Reports of Practical Oncology and Radiotherapy 25 (2020) 271–275

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Provider delay in treatment initiation and its influence on survival outcomes in women with operable breast cancer

Christian H. Flores-Balcázar[a,*], Ma. L. Flores-Luna[b], Cynthia M. Villarreal-Garza[c], Juan E. Bargalló-Rocha[c]

[a] Department of Radiation-Oncology, National Cancer Institute, 22 San Fernando Ave, Section XVI, Tlalpan, Mexico City 14080, Mexico
[b] Department of Epidemiology, National Institute of Public Health, 50 Fray Pedro de Gante, Section XVI, Tlalpan, Mexico City 14080, Mexico
[c] Department of Breast Tumors, National Cancer Institute, 22 San Fernando Ave, Section XVI, Tlalpan, Mexico City 14080, Mexico

ARTICLE INFO

Article history:
Received 14 August 2019
Received in revised form
18 December 2019
Accepted 19 February 2020
Available online 21 February 2020

Keywords:
Timing of cancer treatment
Treatment delay
Breast cancer chemotherapy
Breast cancer surgery
Breast cancer radiotherapy

ABSTRACT

Aim: The goal of this study was to determine whether a delay in starting treatment via surgery or neoadjuvant chemotherapy is related to a decrease in cancer-specific survival (CSS) in women with operable breast cancer (BrCr).
Background: Limited medical infrastructure and a lack of cancer prevention awareness in low- and middle-income countries have caused high BrCr incidence and mortality rates.
Methods: We analyzed a retrospective cohort of 720 women treated at a single center from 2005 to 2012. CSS estimates were obtained by the Kaplan-Meier method. A Cox model of proportional risks was performed to obtain the risk of dying from BrCr. We also obtained the risk according to the category of treatment initiation.
Results: Women with locally advanced stages and without hormone receptor expression were more likely to initiate treatment after 45 days. Patients in Stage IIIA had a 78.1% survival if treatment was initiated before 45 days (95% CI, 0.70–0.84) and 63.6% survival if treatment was started after 45 days (95% CI, 0.44–0.78; $p < 0.001$). Patients in Stage IIIB had a 62.9% survival if treatment was initiated before 45 days (95% CI, 0.53–0.72) and 57.4% survival if treatment started after 45 days (95% CI, 0.31-0.89; $p < 0.001$). Prognostic factors in which lower survival was recognized were Stage IIIA, Stage IIIB, treatment initiation after 45 days, and triple-negative tumors.
Conclusions: The initiation of treatment within the first 45 days of diagnosis of BrCr in women portends better survival compared with those who began treatment longer than 45 days from diagnosis.

1. Background

In recent decades, breast cancer (BrCr) has become a leading cause of cancer death among women worldwide, second to lung cancer.[1] Up to 50% of diagnoses of BrCr and 60% of deaths due to this tumor occur in women living in middle-income countries. BrCr is also the leading cause of cancer death and disability-adjusted life-years for women.[2] The BrCr incidence and mortality rates in these countries are high due to limited medical infrastructure and lack of promotion of cancer prevention and breast self-examination practices.[3,4] Among high-income countries, the average interval for a patient to start cancer treatment is 30–48 days, and up to 60% of patients begin treatment in the first three months after symptoms were discovered. However, in low- to middle-income countries, the interval can range from 165 days in Malaysia to 240 days in Brazil, where < 30% of patients start treatment soon after diagnosis. With respect to the time between the first medical consultation and the start of cancer treatment, Germany's average interval is 15 days—a stark contrast to Brazil, Colombia, Mexico, and Turkey, where this time ranges from 78 days to 240 days.[5] Some studies report an increased range longer than 90 days for starting treatment with decreased survival.[6] The literature uses "total delay" in BrCr care, which is defined as delays greater than three months (approximately 90 days) and is measured from symptoms demonstrated to the date treatment started.[7] Delays are classified into two types of delays: those associated with the patient, and those associated with health services.[8–10] Another indicator of health ser-

Abbreviations: BrCa, breast cancer; CSS, cancer-specific survival; ER, estrogen receptor; HR, hazard ratio; IQR, interquartile range; OR, odds ratio.

* Corresponding author.
E-mail addresses: christian.floresb@incmnsz.mx (C.H. Flores-Balcázar), mflor@insp.mx (Ma.L. Flores-Luna), cynvg@gmail.com (C.M. Villarreal-Garza), ebargallo@yahoo.com (J.E. Bargalló-Rocha).

https://doi.org/10.1016/j.rpor.2020.02.002
1507-1367/

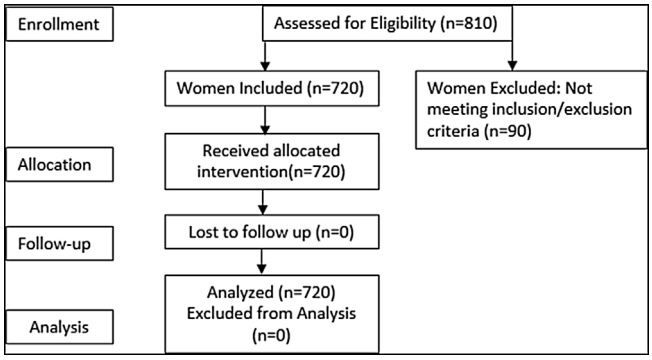

Fig. 1. Flow chart of breast cancer patient enrollment.

vices delay is the interval from diagnosis to initiation of treatment, defined as the time between the histological diagnosis of cancer and the onset of cancer treatment. The latter indicator is the subject of this study.[11] This retrospective study aimed to determine whether a delay in starting treatment via surgery or neoadjuvant chemotherapy is related to a decrease in cancer-specific survival (CSS) of women with operable BrCr treated at our institute.

2. Materials and Methods

A random sample of 810 women was obtained from a large database created to assess treatment delays from 2005 to 2012. A total of 720 women met the inclusion criteria (Fig. 1).

2.1. Data collection and variable definition

The data were extracted from medical records. Our study sample included women older than 18 years with a histopathological diagnosis of ductal and lobular infiltrating cancer. A pathological review was performed for women included in the study. Immunohistochemical assays were used to characterize the BrCr subtypes according to the expression levels of estrogen receptors (ER), progesterone receptors, the transmembrane tyrosine kinase receptor HER2, and the KI67 index value. For triple-negative BrCr determinations of the epidermal growth factor receptor, Actin, cytokeratins 7 and 14, and androgen receptor analyses were performed. Accurate dates of diagnosis and treatment initiation in women with an initial clinical Stage I–IIIB, according to the TNM (tumor, node, metastasis) staging system, were recorded. We excluded men with BrCr, women with cancer in situ, patients operated outside the hospital, women with tumors showing features of inoperability (e.g., extensive breast edema, satellite nodules in the skin, inflammatory cancer, parasternal tumor nodules, confirmed supraclavicular metastases, arm edema, and distant metastases), women with synchronous or metachronous BrCr, women with a history of any other type of cancer except nonmelanoma skin cancer, women in whom the standard treatment had not been granted due to comorbidities that put lives at risk (e.g., morbid obesity, heart disease, and renal failure), and women with metastatic disease at diagnosis. Women with institutional records who had not completed treatment at the hospital or women whose initial treatment took more than seven months for any reason were eliminated. The study was approved by the ethics committee as required by our institution.

We calculated the time between BrCr diagnosis and the onset of treatment for all patients. For CSS survival analysis, the initial event was the date of treatment initiation for BrCr, and the final event was death due to BrCr. Death for other causes was not considered for the analysis. Beside the descriptive analysis of demographic and clinical characteristics, survival estimates were obtained by the Kaplan-Meier method. To evaluate the effect of prognostic factors on the population, survival curves comparisons were performed by a log-rank test. A Cox proportional-hazards model was performed to obtain the risk of dying from BrCr, adjusted by clinical stage, lymphovascular invasion, molecular classification, and categories of delay in treatment. Furthermore, the risk according to category at the initial treatment was obtained. Statistical analysis was performed using STATA Statistical Software Version 14 (StataCorp LP, College Station, TX).

Table 1
Demographic and clinical characteristics of women with operable breast cancer.

Variable	n = 720 (%)
Age at diagnosis	
<45 years	233 (32.4)
≥45 years	487 (67.6)
Age in years, median (SD)	50 (11.8)
Body Mass Index	
Normal	186 (25.8)
Overweight	293 (40.7)
Obesity	241 (33.5)
Hormonal status	
Premenopausal	235 (32.6)
Postmenopausal	485 (67.4)
Clinical stage	
I	90 (12.5)
IIA	157 (21.8)
IIB	190 (26.4)
IIIA	172 (23.9)
IIIB	111 (15.4)
Histology	
Infiltrating ductal	656 (91.1)
Infiltrating lobular	64 (8.9)
Tumor size	
<2.0cm	194 (26.9)
2.1-5.0 cm	278 (38.6)
>5.0 cm	248 (34.5)
Nuclear grade	
Well differentiated	165 (23.0)
Moderately differentiated	261 (36.4)
Poorly differentiated	292 (40.6)
Lymphovascular invasion	
Absent	621 (86.2)
Present	99 (13.8)
Estrogen receptors	
Negative	251 (34.9)
Positive	469 (65.1)
Progesterone receptors	
Negative	213 (29.6)
Positive	507 (70.4)
Molecular classification	
Luminal A	468 (65.0)
Luminal B	39 (5.4)
Her2Neu	67 (9.3)
Triple negative	146 (20.3)
Lymph nodes invasion	
No	232 (32.2)
Yes	488 (67.8)

Abbreviation: SD, standard deviation.

3. Results

The study population consisted of 720 women with BrCr, whose median age was 50 years (range, 27–89), meaning 67.6% of the study participants were older than 45 years. The median time of follow-up was 5.8 years (range, 6 months to 11.5 years). The median time for a patient to start treatment at our institute was 26 days (interquartile range, 1–158 days). Demographic and clinical characteristics are displayed in Table 1.

Of our study sample, 74.2% began treatment 15 days after their admission to the hospital. Most women started treatment between 15 and 30 days from diagnosis confirmation (32.5%). The preferred modality of treatment was neoadjuvant chemotherapy (53.5%),

Table 2
Treatment features of women with breast cancer.

Variables	n = 720 (%)
Delay time for starting	
<15 days	186 (25.8)
15–29 days	234 (32.5)
30–44 days	170 (23.6)
>45 days	130 (18.1)
First treatment performed	
Surgery	318 (44.2)
Neoadjuvant chemotherapy	385 (53.5)
Neoadjuvant hormone therapy	17 (2.3)
Surgery type	
Breast-conserving	118 (16.4)
Mastectomy	602 (83.6)
Adjuvant treatment	
Radiotherapy	222 (30.8)
Chemotherapy	306 (42.5)
Hormone therapy	130 (18.1)
Surveillance	62 (8.6)
Timing of chemotherapy	
Neoadjuvant	385 (54.0)
Adjuvant	306 (31.0)
None	29 (15.0)
Adjuvant radiotherapy	
No	243 (33.8)
Yes	477 (66.2)

which is not surprising given the number of women presenting with locally advanced disease (Table 2).

The 5-year CSS was 83.9%, (95% CI, 0.81–0.86). Women in Stage I had a 5-year CSS of 95.4% (95% CI 0.88–0.98), women in Stage IIA had a CSS of 91.3% (95% CI, 0.85-0.95), those in stage IIB had 89.4% survival (95% CI, 0.84-0.93), patients in Stage IIIA had a 76.1% CSS (95% CI, 0.69–0.82), and 64.3% (95% CI, 0.55–0.73) for Stage IIIB ($p < .001$). The CSS of patients stratified by tumor size was 90.9% (95% CI, 0.8–0.94) when the tumor size was <2 cm, 89.2% (95% CI, 0.85–0.92) in tumors sized 2 cm–4.9 cm, and 71.7% (95% CI, 0.66–0.77) in patients with tumors >5 cm ($p < .001$). Patients categorized as Luminal A had a CSS rate of 88.4% (95% CI, 0.85–0.91); Luminal B patients had a CSS rate of 86.1% (95% CI, 0.69–0.94). Her2Neu and triple-negative patients had 85.1% (95% CI, 0.74–0.92) and 67.5% CSS (95% CI, 0.59–0.75), respectively ($p < .001$). Age at diagnosis, body mass index, hormonal status, histology, nuclear grade, lymphovascular invasion, and expression of ER did not show significant differences between groups. Survival started to decrease at treatment delays of longer than 45 days (Table 3).

We performed a stratified analysis to determine which patients may benefit from treatment within 45 days of diagnosis. Patients in Stage I had a 95.2% survival if treatment was initiated before 45 days (95% CI, 0.86–0.98) and 90.6% if treatment started after 45 days (95% CI, 0.67–0.98). Patients in Stage IIA had a 92.0% survival if treatment was initiated before 45 days (95% CI, 0.86–0.96) and 87.8% if treatment started after 45 days (95% CI, 0.67–0.96). Patients in Stage IIB had an 89.5% survival if treatment was initiated before 45 days (95% CI, 0.83–0.94) and 89.2% if treatment started after 45 days (95% CI, 0.74–0.96). Patients in Stage IIIA had a 78.1% survival if treatment was initiated before 45 days (95% CI, 0.70–0.84) and 63.6% if treatment started after 45 days (95% CI, 0.44–0.78). Patients in Stage IIIB had a 62.9% survival if treatment was initiated before 45 days (95% CI, 0.53–0.72) and 57.4% if treatment started after 45 days (95% CI, 0.31–0.89; Fig. 2).

Prognostic factors in which lower survival was recognized were Stage IIIA (95% CI, 1.9–7.6; hazard ratio [HR], 3.9), stage IIIB (95% CI, 3.4–13.2; HR, 6.7), treatment initiation after 45 days (95% CI, 1.4–2.6; HR, 1.8), and triple-negative tumor status (95% CI, 1.3–2.4; HR, 1.7; Table 4).

Table 3
CSS of women with breast cancer according to treatment initiation before and after 45 Days.

Variable	Calculated survival at 5 years from initial treatment (%)		p-value*
	<45 days 590 (%)[a]	>45 days 130 (%)[a]	
Age at diagnosis (years)			
<45	83.9	81.6	0.434
>45	83.5	84.5	
Body Mass Index			
Normal	84.6	81.3	
Overweight	82.1	79.9	0.058
Obesity	84.5	84.8	
Hormonal status			
Premenopausal	82.3	78.9	0.732
Postmenopausal	84.4	84.3	
Clinical stage			
I	95.2	90.6	
IIA	92.0	87.8	
IIB	89.5	89.2	**<0.001**
IIIA	78.1	63.6	
IIIB	62.9	57.4	
Histology			
Infiltrating ductal	83.6	83.5	0.303
Infiltrating lobular	86.4	75.0	
Tumor size			
<2 cm	92.7	84.3	
2–5 cm	88.2	86.4	**<0.001**
>5 cm	71.6	72.0	
Nuclear grade			
Well differentiated	92.7	90.6	
Moderately differentiated	87.6	80.7	0.162
Poorly differentiated	77.4	78.0	
Lymphovascular invasion			
Absent	84.2	84.9	0.361
Present	81.3	81.4	
Estrogen receptor expression			
Negative	77.1	74.8	0.219
Positive	87.6	87.2	
Progesterone receptor expression			
Negative	79.1	80.1	**<0.001**
Positive	87.4	86.7	
Molecular classification			
Luminal A	88.5	88.0	
Luminal B	86.9	53.3	**<0.001**
Her2 Neu	84.7	62.5	
Triple negative	67.7	66.0	
Lymph node invasion			.001
No	94.5	93.7	**<0.001**
Yes	79.0	75.9	

[a] Kaplan Meier Method.
* Log-Rank Test.

4. Discussion

In recent years, BrCr has been the subject of prevention and early detection campaigns that reinforce the concept of early diagnosis given that cancer diagnosis at advanced stages carries a poor prognosis for survival.[12] Although cancer treatment should be immediate in all cases, no guidelines suggest the acceptable interval between diagnosis and treatment initiation. For over 70 years, research regarding delayed treatment as a prognostic factor for survival in women with BrCr has been contradictory. A meta-analysis in 1999 reported patients treated between the first three to six months of diagnosis had a reduction in five-year survival of 12% (odds ratio [OR], 1.47; 95% CI, 1.42–1.53) compared with women who started treatment within three months of diagnosis and in whom survival decreased 7% (OR, 1.24; 95% CI, 1.17–1.30). Sixty-two percent of the studies included in the meta-analysis were published before 1970, the most recent of which was published in the 1990s.[13] Our findings suggest that patients with BrCr should

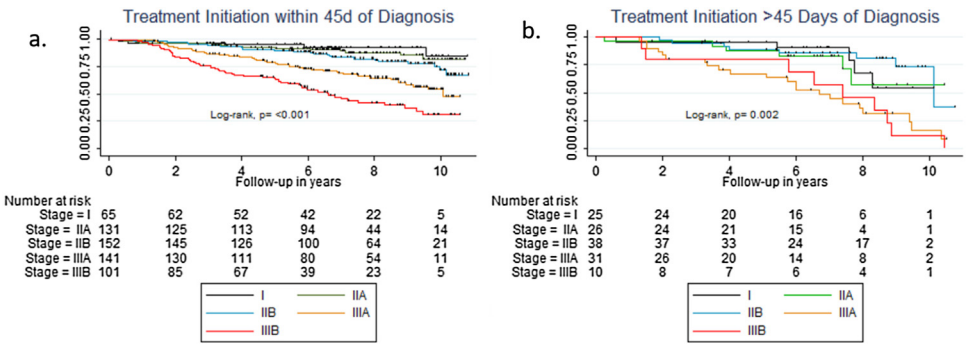

Fig. 2. Kaplan–Meier estimates of cancer-specific survival (CSS) by clinical stage according to treatment initiation within 45 days of diagnosis (a), or after 45 days of cancer diagnosis (b).

Table 4
Prognostic factors in women with breast cancer.

Variable	HR[a]	95% CI	p-value	HR[c]	95% CI	p-value
Clinical stage						
I	1.0[b]			1.0[b]		
IIA	1.1	0.5-2.4	0.728	1.1	0.5-2.5	0.718
IIB	1.5	0.8-3.1	0.243	1.4	0.7-2.9	0.311
IIIA	3.9	2.0-7.5	<0.001	3.9	1.9-7.6	<0.001
IIIB	6.5	3.3-12.6	<0.001	6.7	3.4-13.2	<0.001
Delayed of initial treatment						
<45 days	1.0‡			1.0[b]		
≥45 days	1.6	1.1-2.2	0.006	1.8	1.4-2.6	<0.001
Lymphovascular invasion						
Absent	1.0[b]			1.0[b]		
Present	1.2	0.8-1.7	0.361	1.4	0.90-2.0	0.090
Molecular classification						
Luminal A	1.0[b]			1.0[b]		
Luminal B	1.4	0.8-2.7	0.247	1.7	0.9-3.1	0.106
Her2Neu	1.3	0.8-2.1	0.319	1.3	0.8-2.1	0.361
Triple Negative	1.9	1.4-2.3	<0.001	1.7	1.3-2.4	<0.001

[a] Raw hazard ratio.
[b] Reference Category.
[c] Adjusted hazard ratio for clinical stage, lymphovascular invasion, categories of delay in treatment and molecular classification.

begin treatment preferably within the first 45 days of diagnosis, because survival decreases with delay in treatment initiation, especially in women with tumors in more advanced clinical stages. Recently, Unger-Saldaña et al. conducted a qualitative multicentric study whose objective was the evaluation of the delays in cancer care in women with BrCr.[14] Ninety percent of patients in the study (N = 886) experienced delays in cancer care, while 57% had a delay of longer than six months. For each month of delay in seeking medical care, Unger-Saldaña reported a 1.8% increase in the probability of having a more advanced clinical stage. For each month of delay in care from health services, the likelihood of starting the treatment at a more advanced clinical stage was 1%. Also, for each year of age of the patient, the likelihood of starting treatment at an advanced clinical stage decreased to 0.4%.[14]

Researchers have used various intervals to explain the impact of treatment delay in cancer survival. Smith et al. and Redondo et al. found no significant differences in survival for a treatment delay of 30 days.[15,16] Because of their findings, we chose 45 days as the threshold for treatment delays. We stratified patients by clinical stage at diagnosis to analyze the effect of treatment delay on survival. The lack of stratification in other studies may explain why those studies failed to show a significant decrease in survival. Although the delay in treatment initiation decreased survival in women with early disease, this decrease was not significant. However, survival decreased significantly in patients with locally advanced disease. Our study suggests a delayed start of treatment longer than 45 days increases the risk of dying from cancer. Two studies from Korea reported similar results; both studies used national records and insurance data (which could present errors in data collection).[17,18] Shin et al. suggest the risk of dying from BrCr doubles in women for whom surgery is delayed more than 12 weeks.[17] Yun et al. suggested that in hospitals with a high volume of patients, a delay longer than four weeks from diagnosis increases the risk of death 1.6 times.[18] Our study's use of electronic records derived from a single institution offered more detailed clinicopathologic information and excluded patients with major delays of six months who may have ignored their diagnosis, rejected standard treatment, or chosen alternative treatment outside the institution. McLaughlin et al. reported the extended time between histologic confirmation and initiation of treatment decreased the survival of patients in more advanced clinical stages but not in women with tumors in clinical Stage I.[19] McLaughlin used a Cox proportional hazards model to adjust for the clinical stage to assess overall survival and specific survival for BrCr. They found that while the delay in treatment did not affect overall survival (p = 0.37) or specific survival (p = 0.49) among patients with early BrCr, a delay to start treatment >60 days for patients with advanced clinical disease was associated with a lower overall survival (HR, 1.66; 95% CI, 1.00–2.77; p = 0.05) and a decrease in specific survival for BrCr (HR, 1.85; 95% CI 1.04–3.27, p = 0.04).[19] Delays between surgery and adjuvant radiotherapy may be due to a lack of linear accelerators and trained personnel. However, existing knowledge regarding adjuvant radiotherapy delay after surgery is poor, and some authors suggest the implementation of satellite units for decentralizing radiotherapy services, reducing delays and radiotherapy treatment interruptions.[20,21] A recent Mexican study

found a statistical decrease in disease-specific survival in women with locally advanced BrCr receiving radiotherapy after a delay >60 days.[22]

Given our study's retrospective nature, it is not without limitations and biases. Our findings cannot be generalized to all populations; it is geared towards a specific group of women in whom treatment should start in the first 45 days of diagnosis confirmation (i.e., women with Stage IIIA disease and more advanced stages, triple-negative molecular category, and lymphovascular invasion). Identifying specific factors that contributed to the delayed initiation of treatment would have been helpful (e.g., multiple biopsies, breakdown of mammography or computed tomography equipment, and a long waiting list in operating rooms) in addition to cultural and socioeconomic factors related to the patient. Another limitation was the size of the sample—a larger sample should have been selected for the analysis of each clinical stage.

5. Conclusions

The initiation of treatment within the first 45 days of diagnosis of BrCr in women is associated with better survival compared with those who began treatment longer than 45 days from diagnosis. Any study that aims to analyze the effect of a delay in starting treatment faces the ethical dilemma of not being able to randomize subjects by delay categories in a prospective trial; so, when retrospective studies are conducted, they open an area of opportunity for further research to dictate a policy for patients with cancer to be treated in a timely manner. While our study design may prohibit generalizations for other populations, our findings should encourage other institutions to create their own data given the growing waiting lists for treatment initiation in cancer centers worldwide.

Financial disclosure

None declared.

Conflict of interest

None declared.

Acknowledgements

None declared.

References

1. DeSantis CE, Ma J, Gaudet MM, et al. Breast cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(6):438–451, http://dx.doi.org/10.3322/caac.21583.
2. Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. *JAMA Oncol*. 2017;3(4):524–548, http://dx.doi.org/10.1001/jamaoncol.2016.5688.
3. Villarreal-Garza C, Aguila C, Magallanes-Hoyos M, et al. Breast cancer in young women in Latin America: an unmet, growing burden. *Oncologist*. 2013;18(12):1298–1306, http://dx.doi.org/10.1634/theoncologist.2013-0321.
4. Villarreal-Garza C, Lopez-Martinez EA, Muñoz-Lozano JP, Unger-Saldaña K. Locally advanced breast cancer in young women in Latin America. *Ecancermedicalscience*. 2019;13:894, http://dx.doi.org/10.3332/ecancer.2019.894.
5. Unger-Saldaña K. Breast cancer early diagnosis in developing countries. *World J Clin Oncol*. 2014;5(3):465–477, http://dx.doi.org/10.5306/wjco.v5.i3.465.
6. Olivotto IA, Bancej C, Goel V, et al. Waiting times from abnormal breast screen to diagnosis in 7 Canadian provinces. *CMAJ*. 2001;165:277–283.
7. Unger-Saldaña K, Infante-Castañeda C. Delay of medical care for symptomatic breast cancer: a literature review. *Salud Publica Mex*. 2009;51(Suppl 2):S270–85, http://dx.doi.org/10.1590/s0036-36342009000800018.
8. Bright K, Barghash M, Donach M, de la Barrera MG, Schneider RJ, Formenti SC. The role of health system factors in delaying final diagnosis and treatment of breast cancer in Mexico city, Mexico. *Breast*. 2011;20(Suppl 2):S54–9, http://dx.doi.org/10.1016/j.breast.2011.02.012.
9. Knaul F, Bustreo F, Ha E, Langer A. Breast cancer: why link early detection to reproductive health interventions in developing countries? *Salud Publica Mex*. 2009;51(Suppl 2):s220–7, http://dx.doi.org/10.1590/s0036-36342009000800012.
10. Barber MD, Jack W, Dixon JM. Diagnostic delay in breast cancer. *Br J Surg*. 2004;91(1):49–53, http://dx.doi.org/10.1002/bjs.4436.
11. Facione NC. Delay versus help seeking for breast cancer symptoms: a critical review of the literature on patient and provider delay. *Soc Sci Med*. 1993;36:1521–1534, http://dx.doi.org/10.1016/0277-9536(93)90340-a.
12. Dianatinasab M, Fararouei M, Mohammadianpanah M, Zare-Bandamiri M. Impact of social and clinical factors on diagnostic delay of breast cancer: a cross-sectional study. *Medicine (Baltimore)*. 2016;95(38):e4704, http://dx.doi.org/10.1097/MD.0000000000004704.
13. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. *Lancet*. 1999;353(9159):1119–1126, http://dx.doi.org/10.1016/s0140-6736(99)02143-1.
14. Unger-Saldaña K, Miranda A, Zarco-Espinosa G, Mainero-Ratchelous F, Bargalló-Rocha E, Miguel Lázaro-León J. Health system delay and its effect on clinical stage of breast cancer: multicenter study. *Cancer*. 2015;121(13):2198–2206, http://dx.doi.org/10.1002/cncr.29331.
15. Smith ER, Adams SA, Das IP, Bottai M, Fulton J, Hebert JR. Breast cancer survival among economically disadvantaged women: the influences of delayed diagnosis and treatment on mortality. *Cancer Epidemiol Biomarkers Prev*. 2008;17:2882–2890, http://dx.doi.org/10.1158/1055-9965.EPI-08-0221.
16. Redondo M, Rodrigo I, Pereda T, et al. Prognostic implications of emergency admission and delays in patients with breast cancer. *Support Care Cancer*. 2009;17(5):595–599, http://dx.doi.org/10.1007/s00520-008-0513-2.
17. Shin DW, Cho J, Kim SY, et al. Delay to curative surgery greater than 12 weeks is associated with increased mortality in patients with colorectal and breast cancer but not lung or thyroid cancer. *Ann Surg Oncol*. 2013;20:2468–2476, http://dx.doi.org/10.1245/s10434-013-2957-y.
18. Yun YH, Kim YA, Min YH, et al. The influence of hospital volume and surgical treatment delay on long-term survival after cancer surgery. *Ann Oncol*. 2012;23:2731–2737, http://dx.doi.org/10.1093/annonc/mds101.
19. McLaughlin J, Anderson R, Ferketich A, Seiber E, Balkrishnan R, Paskett E. Effect on survival of longer intervals between confirmed diagnosis and treatment initiation among low-income women with breast cancer. *J Clin Oncol*. 2012;30:4493–4500, http://dx.doi.org/10.1200/JCO.2012.39.7695.
20. Arenas M, Gomez D, Sabater S, Rovirosa A, Biete A, Colomer J. Decentralisation of radiation therapy. Is it possible and beneficial to patients? Experience of the first 5 years of a satellite radiotherapy unit in the province of Tarragona, Spain. *Rep Pract Oncol Radiother*. 2014;20(2):141–144, http://dx.doi.org/10.1016/j.rpor.2014.10.008.
21. Arenas M, Sabater S, Gascón M, et al. Quality assurance in radiotherapy: analysis of the causes of not starting or early radiotherapy withdrawal. *Radiat Oncol*. 2014;9:260, http://dx.doi.org/10.1186/s13014-014-0260-0.
22. Flores-Balcázar CH, Flores-Luna L, Villarreal-Garza C, Mota-García A, Bargalló-Rocha E. Impact of delayed adjuvant radiotherapy in the survival of women with breast cancer. *Cureus*. 2018;10(7):e3071, http://dx.doi.org/10.7759/cureus.3071.