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Breast Cancer

Overall Survival and Related Factors of Patients Undergoing Breast-Conserving Surgery with Boost Through Interstitial Brachytherapy in a Cancer Center in Medellin, Colombia

Liza María González-Hernández[1] Elsa Vásquez-Trespalacios[1] Erika Patricia Gallegos-Téllez[2] Lina María Corrales-Cruz[2] Luis Javier-Gallón[1] Ana María Naranjo[1]

[1] Especialización en Mastología, Posgrados Clínicos. Universidad CES, Medellín, Colombia
[2] Clínica de Oncología Astorga y el Instituto Regional de Oncología (CLINAC), Colombia

Address for correspondence Liza María González-Hernández, MD. Ginecologa y Obstetra, Mastóloga, Calle 10 A # 22-04, Universidad CES, Medellín 50021, Colombia (e-mail: lizamg@gmail.com).

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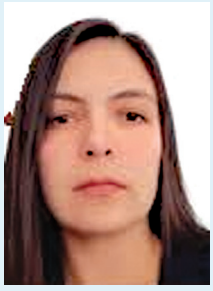
Abstract



Liza María González-Hernández

Patients with breast cancer undergoing conservative surgery require management with radiotherapy to decrease the risk of recurrence. Moreover, the use of tumor bed boost in high-risk patients has shown an absolute reduction in the 10-year local recurrence risk from 23.9 to 13.5%. Therefore, this study aimed to estimate the overall survival of a group of patients undergoing conservative surgery with a boost through interstitial brachytherapy at a cancer center in Medellin, Colombia. A retrospective cohort study was performed, and records from 2014 to 2020 of patients with in situ or infiltrating breast cancer treated with a boost through interstitial brachytherapy were included. Univariate analysis was conducted to characterize the study population; median survival was calculated using the Kaplan–Meier method. Moreover, associations concerning survival were calculated with each of the factors independently. A total of 186 patients were included. Their overall survival was 93.5%, with a median survival of 79 months. The presence of negative hormone receptors, having two or more irradiated fields and having a locally advanced stage were factors associated independently with higher mortality. The overall survival of patients with in situ or infiltrating breast cancer was favorable and correlated with studies regarding intervention with a boost through interstitial brachytherapy and the factors associated with higher mortality, such as having a locally advanced stage.

Keywords

- breast cancer
- brachytherapy
- overall survival
- radiotherapy
- treatment

Introduction

After heart disease, breast cancer is the most frequent and first cause of women's mortality worldwide. In 2020, it had an incidence of 47.8 per 100,000 inhabitants and a mortality of 13.6 per 100,000. Similarly, it was one of the leading causes of cancer mortality in Colombia in the same year. It had an incidence of 48.3 inhabitants per 100,000 and a mortality rate of 13.1 per 100,000 inhabitants.[1]

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Notably, conservative surgery is one of the main treatment options for the surgical treatment of breast cancer. In addition, patients undergoing conservative surgery require radiotherapy, which is fundamental for breast cancer treatment, reducing the risk of local recurrence rate from 26 to 7% in 5 years.[2]

Moreover, since local recurrence occurs mainly at the primary tumor site, a radiotherapy boost is often added to the tumor bed, mainly in high-risk patients. This reinforcement of the tumor bed, also called a boost, can be administered using external radiotherapy or brachytherapy, a radiotherapy technique that uses one or more radioactive sources in the immediate vicinity or inside the tumor. Notably, the radioactive source is always contained in an applicator. Then, it is placed inside the patient, avoiding direct contact with the source, allowing the delivery of an effective dose to the tumor tissue while simultaneously preserving the surrounding healthy tissue and organs at risk, thus minimizing possible side effects. Additionally, the source is administered through multicatheter interstitial brachytherapy, consisting of multiple catheters inserted under local anesthetic in the breast, connected to a delayed loading device that delivers a precise radiation amount to the tumor tissue.[3]

Furthermore, the effectiveness of the boost dose in preventing local recurrence has been demonstrated previously. For instance, in the European Organisation for Research and Treatment of Cancer (EORTC) 22881-10882 Trial, an absolute reduction in the 10-year risk of local recurrence from 23.9 to 13.5% was evident in patients younger than 40 years, and a hazard ratio (HR) for local recurrence of 0.59 (0.46–0.76) in favor of tumor bed boost.[4] Similar results were reported in a 20-year follow-up study, where the HR for local recurrence was 0.65 (0.52–0.81) in favor of tumor bed boosting.[5]

In Colombia, information on patients treated with brachytherapy boost and conservative surgery is scarce, and no scientific articles are related.

Therefore, this study aimed to determine the survival and related factors of patients with breast-conserving surgery taken to tumor bed reinforcement by interstitial brachytherapy at a cancer center in Medellin between 2014 and 2020.

Materials and Methods

A retrospective cohort of patients treated from 2014 to 2020 was studied. Records of patients older than 18 years with infiltrating or in situ breast cancer treated with interstitial brachytherapy boost in a cancer center in the city of Medellin were included.

Selection criteria for interstitial boost include patients under 50 years of age with invasive or in situ carcinoma undergoing breast-conserving surgery and patients older than 50 years with a high risk of local relapse, such as histological grade 3, narrow or positive margins not amenable to further surgery, and negative hormone receptors. Patients with little breast volume, carriers of prostheses or breast expanders and patients with psychiatric disorders such as anxiety or depression, phobia of needles, nonacceptance of the invasive brachytherapy procedure, and consumption of anticoagulant drugs that cannot be suspended were excluded from receiving brachytherapy.

Brachytherapy was administered 2 weeks after completion of external beam radiation therapy. Previously, the surgical bed is identified by reviewing the diagnostic mammography and breast ultrasound images, as well as the evaluation of the simulation tomography in which the clips left by the surgeon for marking the surgical bed were identified. After that, the area to be treated was marked. We proceed to place the metal needles necessary for good coverage of the area to be treated, using a mammary template, and fixing them on templates. The computed tomography of the chest is taken in the treatment position, followed by delimitating the surgical bed to be treated with safety margins, computerized planning, then 800 cGy are administered in a single high-rate fraction of doses with a radioactive source of iridium 192. If there are positive margins, two sessions of 500 cGy are administered with a separation of 8 hours between the two sessions. The needles, templates, and implant were removed, hemostatic compression was applied to the area, bandages were left.

A radiologist expert in ultrasound evaluated all the images and assessed the degree of toxicity commitment in the breast tissue, according to the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) graded as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5). Acute toxicity was defined as less than 6 months and chronic toxicity as more than 6 months.

Patient records with more than 10% of missing data were excluded. Data were taken from the oncology center's database of patients undergoing brachytherapy. It included the clinical history and characteristics of the treatment received, as well as the patients' clinical follow-up and vital status. Additionally, the vital status was verified in the National Civil Registry and the Single Database of Affiliates (ADRES).

Statistical analysis included a univariate analysis that was performed to characterize the study population. The nature of the variables was considered for analysis; for quantitative variables, the Kolmogorov–Smirnov normality test was performed to define whether these variables were presented with averages or medians, and qualitative variables were presented using absolute and relative frequencies. Moreover, the median survival was calculated using the Kaplan–Meier method.

A bivariate analysis was performed using the associations concerning survival, calculating each factor independently. For qualitative variables, the chi-squared test of independence was used. For quantitative variables, the Student's t-test or Mann–Whitney *U*- test (quantitative-qualitative) was used to calculate the odds ratio and 95% confidence intervals (CI) based on binary logistic regression (specific objective 2). Differences in survival according to covariables were calculated with the Log Rank test.

A multivariate analysis was performed using the binary logistic regression statistical method, considering those

significant variables ($p < 0.25$) when evaluated with the outcome, according to the Hosmer–Lemeshow criterion, which allowed estimating the association of the dependent variable with more than two independent variables. The association between covariates and time to event presentation was calculated by COX regression. A p-value of less than 0.05 was considered statistically significant. All analyses were performed using SPSS version 25.

The CES University Human Research Ethics Board endorsed the study and its procedures.

Results

A total of 186 patients were identified from 2014 to 2020. Their average age was 55.4 years. The most frequent histological type was infiltrating ductal carcinoma in 90.3% of cases, followed by ductal carcinoma in situ. ►Table 1 describes the clinical and pathological characteristics and the treatment received by the patients.

The bivariate analysis showed the histopathologic factors associated with more significant mortality, where the presence of negative hormone receptors, having two or more irradiated fields and having a locally advanced stage were highlighted (►Table 2). However, no statistical significance was observed between mortality and the following factors: HER2, histologic grade, Ki67, surgical margin status, and chemotherapy administration ($p > 0.05$).

The time between surgery and the start of radiotherapy had a mean of 118 days ± 9.4. Besides, the mean time among the patients who survived was 121 days ± 94.7 and among those who died was 78 days ± 26.2 with a $p = 0.121$, showing a not statistically significant correlation between time and mortality.

Conversely, the time between the end of radiotherapy and brachytherapy showed a mean of 14.5 days ± 5.2. This period in patients who survived was 14.7 days ± 5.12 and in those who died was 10.4 days ± 5.17, with a $p = 0.05$, indicating a statistically significant difference.

Remarkably, the time between patients who died was shorter than those who survived, which possibly correlated with stage differences. For instance, 75% (9/12 patients) of those who died had a locally advanced stage, while 36.78% (64/174 patients) of those who survived had a locally advanced stage.

Moreover, the overall survival was 93.5%, with a median survival of 79 months and a 95% CI of 76.26 to 81.5 months (►Fig. 1).

Regarding factors associated with time to death, the hormone receptor-positive patients had a median survival of 80.4 months with a 95% CI (78.1–82.8) compared to 73 months with a 95% CI (64.8–80.8) for hormone receptor-negative patients, showing a statistically significant difference ($p = 0.023$).

Concerning stages, patients in early stages had a mean survival of 82 months with a 95% CI (80.1–84.2), compared to patients with locally advanced stages, who had a mean survival time of 74 months, with a 95% CI (68.9–79.9), indicating a statistically significant difference ($p = 0.030$).

Table 1 Clinical characteristics of the analyzed patients

Characteristic	Frequency (%)
Age (mean ± SD)	55.4 ± 10.21
Histology	
Infiltrating ductal carcinoma	168 (90.3%)
Ductal carcinoma in situ	10 (5.4%)
Lobular carcinoma in situ	3 (1.6%)
Other histological subtypes (Mucinous, medullary, and papillary)	5 (2.7%)
Hormone receptors	
Positive hormone receptors	140 (75.3%)
- R Estrogen and progesterone positive	135 (96.4%)
- R Estrogen-positive and progesterone negative	5 (3.6%)
Negative hormone receptors	44 (23.7%)
No information	2 (1.1%)
Her 2	
- Positive	34 (18.3%)
- Negative	142 (76.3%)
- Not applicable (in situ)	4 (2.2%)
- No information	6 (3.2%)
Histological grade	
- 1	29 (15.6%)
- 2	94 (50.5%)
- 3	53 (28.5%)
- No information	10 (5.4%)
Ki67	
- > 20%	78 (41.9%)
- <20%	91 (48.9%)
- Not applicable (in situ)	7 (3.8%)
- No information	10 (5.4%)
Margins	
- Free	54 (29%)
- Negative but < 1cm	129 (69.4%)
- Positives	3 (1.6%)
Stage[a]	
- Early	103 (55.3%)
- Locally advanced	73 (39.2%)
- In situ—0	10 (5.4%)
Chemotherapy treatment	
- Yes	118 (63.4%)
- No	68 (36.6%)
External radiotherapy dose	
- Hypofractionated 4,256 cGy	133 (71.5%)
- Standard dose 5,000 cGy	53 (28.5%)
Irradiated fields	
- Breast	111 (59.7%)
- Breast, supraclavicular fossa	61 (32.8%)
- Breast, supraclavicular fossa, and axilla	14 (7.5%)
Brachytherapy dose	
- 800 cGy	184 (98.9%)
- 1000 cGy	2 (1%)

Abbreviation: SD, standard deviation.
[a]Early stage: IA, IB, and IIA; Locally advanced: IIB to IIIB.

Additionally, the COX regression showed that other factors associated with time to death were negative hormone receptors, locally advanced stages, and having two or more irradiated fields (►Table 3).

Table 2 Factors associated with mortality in patients undergoing brachytherapy

Status/Factor	Alive (%)	Dead (%)	OR (95% CI)	*p*-Value
Positive HR	95.7	4.3	3.5 (1.07–11.5)	0.028
Negative HR	86.4	13.6		
RT standard dose	93.5	6.5	5.7 (1.6–19.9)	0.002
Hypofractionated	97.0			
Irradiated fields				
1	97.3	2.7	4.9 (1.28–18.78)	0.013
Two or more	88.0	12.0		
Stage				
In situ		10.0	0.79 (0.08–6.99)	0.020
Early	98.1	1.9	0.14 (0.02–0.67)	
Locally advanced	87.7	12.3	Ref	

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; RT, radiotherapy.

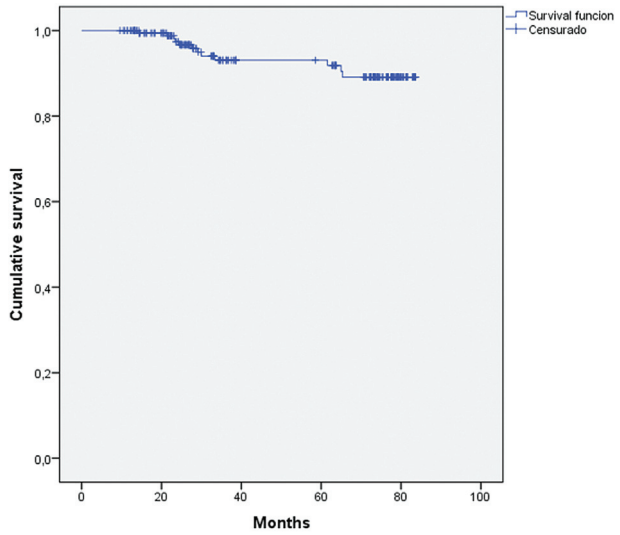

Fig. 1 Survival function of patients undergoing brachytherapy.

Noticeably, five patients presented relapse with metastasis to bone and brain, and only one survived until the evaluation of the results.

Toxicity Events

Acute toxicity was recorded for 26 patients (13.9%): 21 grade 1 events and 5 grade 2 events.

Chronic toxicity was recorded for six (3.2%) patients: five grade 1 event and one grade 2 events, and acute and chronic toxicity were recorded for six patients (3.2%). All the acute and chronic toxicity events consisted of dermatitis or fibrosis.

Discussion

This study showed an overall survival of 93.5% at 5 years of patients treated with conservative surgery and boost brachytherapy from 2014 to 2020. The mean age of the patients was 55 years, and 33% (61) patients were younger than 50 years.

Comparatively, Guinot et al[6] reported patients younger than 45 years with similar clinical and treatment characteristics, indicating a prevalence of negative hormone receptors of 23%, while we found a prevalence of 23.7%. Additionally, Her2 was positive in 18.3% of our patients versus 20% of theirs. Also, all their patients had early clinical stages T1 and T2, while we found 55.3% in the early stages. Furthermore, those patients received a dose of external radiotherapy between 4,600 and 5,000 cGy (standard dose), while in our study, the hypofractionated dose (4,256 cGy) was applied to 71.5% of patients. Possibly because Guinot et al's study was performed between 1999 and 2007, and the hypofractionation clinical trials were not published until 2008.[7] Moreover, single brachytherapy dose was 700 cGy in 90% of the patients, while according to our study, it was 800 cGy in 98.9%. Furthermore, the elapsed difference between radiotherapy and brachytherapy was no more than 2 weeks, as was the mean of our study (2 weeks).

Guinot et al[6] selected a group of young patients since they have an increased risk of local recurrence, and one of the indications for boost is being younger than 50 years old.[8] Moreover, the overall survival of these patients at 5 years was 92.1%, like our study. They also evidenced in the univariate and multivariate analysis a higher risk of death and distant metastasis in patients with negative hormone receptors with an HR of 5.9 (2.2–15.8; $p < 0.00$). Similarly, we found the same factors related to death, with an HR of 3.42 (1.10–10.63; $p = 0.039$) in the univariate analysis and an HR of 3.89 (0.55–27-59; $p = 0.173$), with no statistical significance.

Polgár et al described a cohort of 100 patients with early-stage breast cancer from 1995 to 2007 who received a boost with high dose rate brachytherapy after breast-conserving surgery and whole breast irradiation.[9] In this group, the local recurrence rate was 7%, and distant metastasis was 15%, with survival at 8 years of 80.4%, lower than in our study. However,

Table 3 Univariate and multivariate Cox model for factors associated with time to death

Variable	Univariate		Multivariate	
	HR 95%(CI)	*p*-Value	HR 95%(CI)	*p*-Value
Receptors (negative/positive)	3.42 (1.10–10.63)	0.039	3.89 (0.55–27.59)	0.173
Ki67 (<20%/≥20%)	0.60 (0.14–2.52)	0.487	1.13 (0.15–11.04)	0.801
Her2 (negative/positive)	1.41 (0.29–6.70)	0.661	2.54 (0.20–31.48)	0.466
Stage: In situ-Early/locally advanced	0.16 (0.035–0.75)	0.03	0.47 (0.24–0.90)	0.024
RT dose (standard/hypofractionated)	2.78 (0.82–9.30)	0.09	1.65 (0.11–23.54)	0.71
Histological grade (low/intermediate-high)	1.17 (0.25–5.54)	0.837	1.39 (0.37–5.10)	0.62
Surgical margins (negative/positive)	0.22 (0.02–1.75)	0.153	0.90 (0.11–7.42)	0.99
Age, coefficient	0.023	0.425	1.07 (0.97–1.18)	0.152
Time between the termination of RT and start of brachytherapy, coefficient	−0.125	0.015	0.90 (0.76–1.08)	0.277
Irradiated fields (breast + axilla or supraclavicular fossa)	0.50 (0.26–0.97)	0.041	0.34 (0.10–1.0)	0.06

Abbreviations: CI, confidence interval; HR, hazard ratio; RT, radiotherapy.

our follow-up was shorter at 6.5 years, and the available treatments used were more advanced than in other studies, that is, a chemotherapy regimen-based on cyclophosphamide, methotrexate, and fluorouracil. Nevertheless, these methods are not standard.

Furthermore, we have found no local studies using the same intervention. However, Ramírez et al[10] described a large part of our population concerning baseline characteristics. For instance, conservative surgery was used in 57.3% of cases, positive hormone receptors in 77%, and radiotherapy in 80% of patients. Additionally, they had an overall survival rate of 97%, while in our study, it was 93.5% at 5 years. However, Ramírez et al did not clearly describe whether the patients were taken to tumor bed boost and the radiotherapy technique[10] This report also showed that overall survival is lower in hormone receptor-negative patients by 88.5 versus 98.9% for hormone receptor-positive ($p < 0.001$). Similarly, we found an overall survival of 86.4% for hormone receptor-negative patients and 95.7% for hormone receptor-positive patients ($p = 0.023$).

Moreover, we found that tumor stage was another factor associated with time to death, where patients in the early stages had a survival of 98.1% and those with locally advanced stages of 87.7% ($p = 0.030$). Likewise, Ramírez et al found that patients with locally advanced stages had variable survival between 86.3 and 100%. However, this finding was not statistically significant ($p = 0.009$).[10]

The effectiveness of this additional dose in the prevention of local recurrence has been demonstrated in several trials, such as in the EORTC 22881-10882 Trial, where 2,661 patients were enrolled in the boost arm, and all patients received 50 Gy of whole breast irradiation and a boost dose of 16 Gy to the tumor bed after microscopically complete lumpectomy. In addition, 63% of patients received the boost dose with eight fractions of external electron radiotherapy, 29% were treated with eight fractions with a tangential field, and 9% with interstitial brachytherapy with iridium 192 at a dose of 10 Gy per 24 hours. During the 5-year follow-up, local recurrences were 4.8% in patients who received a boost with electrons, 4% in the case of a tangential field, and 2.5% for brachytherapy. However, there was no statistically significant difference.[11]

Interestingly, Kindts et al[12] compared the administration of boost between brachytherapy and external radiotherapy concerning local recurrence, in which an overall local recurrence rate of 2.2% was observed at 10 years, and there were no significant differences concerning the technique administered, thus concluding that the reduction in the risk of local recurrence is not influenced by the boost technique applied. However, despite there are no differences between techniques, brachytherapy has shown more benefits comparatively. Although external electron beam boost generally involves the skin and subcutaneous vessels, interstitial brachytherapy represents a more conformal technique, which offers the advantage of lower rates of late side effects, particularly cutaneous telangiectasia, and cutaneous fibrosis.[13] In addition, Terheyden et al[14] showed lower exposure of organs at risk by comparing boost dosimetric data between external beam radiotherapy. Specifically, 10 Gy photons in five fractions versus interstitial brachytherapy with 10 Gy in one fraction showed no difference in left-sided cancers concerning the maximum dose to the heart, while the maximum dose to the other organs at risk was significantly lower in the brachytherapy group (D_{max} lung 47.12 vs. 87.7% [$p < 0.01$]; rib 61.17 vs. 98.5, [$p < 0.01$]; skin 57.1 vs. 94.75%, [$p < 0.01$]). Thus, reducing radiation exposure to organs at risk could reduce long-term side effects.

Nevertheless, the aesthetic outcome of brachytherapy can be a controversial aspect. For example, Roy et al[15] compared external beam radiotherapy with interstitial brachytherapy, finding an excellent cosmetic outcome in 80% of patients with external beam radiotherapy versus 50% in brachytherapy with a statistically significant difference ($p = 0.024$). However, the radiation dose in brachytherapy was 15 Gy in three fractions with 6 hours difference. Conversely, we

found a dose of 8Gy in 98.9% of the patients. Moreover, Shaitelman et al[16] evaluated multicatheter interstitial brachytherapy for partial breast irradiation and reported a cosmetic outcome among 23 studies from 56 to 95.7%. In addition, Polgár et al[9] described late radiation effects and excellent/good cosmetic results in 56.1% and severe skin side effects in 8%.

Remarkably, our literature search did not deliver recent or regional information on this topic. However, we had limitations such as the use of patient records and follow-ups given to different centers, and we could not access a relapse record of this cohort, so we could not evaluate the specific mortality due to breast cancer but report all causes.

Since brachytherapy boost is sometimes avoided because of its cosmetic outcome, and most studies are retrospective for using it in accelerated partial irradiation, additional studies with more evidence on brachytherapy boost are required to evaluate cosmetic outcomes, quality of life, and long-term follow-up in this group of patients.

Conclusion

The overall survival for the patients was 93.5%, which is considered good and correlates with similar intervention studies. Moreover, the main factor associated with higher mortality was a locally advanced stage.

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Conflict of Interest

None declared.

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