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RESEARCH PAPER

Moderately hypofractionated post-operative radiation therapy for breast cancer: preferences amongst radiation oncologists from countries in Latin America and the Caribbean

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ABSTRACT

Background: The safety and effectiveness of moderately hypofractionated post-operative radiation therapy for breast cancer were demonstrated by several trials. This study aimed to evaluate the current patterns of practice and prescription preference about moderately hypofractionated post-operative radiation therapy to assess possible aspects that affect the decision-making process regarding the use of fractionation in breast cancer patients in Latin America and the Caribbean (LAC). We also aimed to identify factors that can restrain the utilization of moderately hypofractionated post-operative radiation therapy for breast cancer.

Materials an methods: Radiation oncologists from LAC were invited to contribute to this study. A 38-question survey was used to evaluate their opinions.

Results: A total of 173 radiation oncologists from 13 countries answered the questionnaire. The majority of respondents (84.9%) preferred moderately hypofractionated post-operative radiation therapy as their first choice in cases of whole breast irradiation. Whole breast plus regional nodal irradiation, post-mastectomy (chest wall and regional nodal irradiation) without reconstruction, and post-mastectomy (chest wall and regional node irradiation) with reconstruction hypofractionated post-operative radiation therapy was preferred by 72.2% 71.1%, and 53.7% of respondents, respectively. Breast cancer stage, and flap-based breast reconstruction were the factors associated with absolute contraindications for the use of hypofractionated schedules.

Conclusion: Even though moderately hypofractionated post-operative radiation therapy for breast cancer is considered a new standard to the vast majority of the patients, its unrestricted application in clinical practice across LAC still faces reluctance.

Key words: breast cancer; radiation therapy; moderately hypofractionated

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Introduction

Breast cancer is the most common malignant tumour in women in Latin America and the Caribbean (LAC) with an estimated 210,100 new cases in 2020 [1]. In general, a multidisciplinary therapeutic approach, which has been correlated to improvement of overall survival rates, comprising surgical oncology, medical oncology and radiation oncology is needed for the optimal management of breast cancer patients [2].

Post-operative radiation therapy (RT) reduces the risk of cancer mortality and loco-regional recurrence rates in most patients who received breast-conserving surgery and mastectomy [3, 4]. Historically, conventional radiation doses with 50 Gy to 50.4 Gy in 25–28 fractions over the course of 5 to 6 weeks were used as a standard scheme. This originates from the traditional radiobiology concept about the doses needed to treat subclinical disease in combination with the historical assumption that breast cancer is less sensitive to changes in the dose per fraction than dose-limiting healthy tissues [5, 6].

The all-purpose engagement of hypofractionation is to decrease the treatment period by shrinking the total number of fractions and offering a therapeutic schedule that is more convenient and optimized for patients. Considering LAC geography and access to cancer care, the benefits of hypofractionation can also be related to increasing patients` access to medical care in case of insufficient capacity, reducing indirect costs related to interruption from work and travelling to the radiation oncology department, and reducing healthcare treatment costs [7–9].

The safety and efficacy of moderately hypofractionated post-operative radiation therapy for breast cancer were demonstrated by at least eight randomised controlled trials that mostly included early-stage patients [10–21]. Several guidelines recommended moderately hypofractionated post-operative whole breast irradiation as the new standard, and its recommendation has become increasingly broad, including not only selected patients with early disease. Currently, although some institutions still have concerns about its generalised application [22], moderately hypofractionated radiation therapy to the breast, chest wall (with/without breast reconstruction), and regional lymph nodes is considered as safe and effective as conventionally fractionated schedules and has been adopted as a treatment option for the vast majority of patients in many centers [8].

In view of the evidence on the benefits of moderately hypofractionated post-operative radiation therapy and presuming there may be differences concerning its application in clinical practice. It is known that many of the problems and difficulties found in LAC countries are common. Drawing a general picture of how moderately hypofractionated post-operative radiation therapy for breast cancer has been performed is important for a global understanding of the subject. Thus, we developed a survey to evaluate the current patterns of practice and to assess possible aspects that affect the decision-making process regarding the use of fractionation in patients with breast cancer in LAC countries. We also aimed to identify factors that can restrain the utilization of moderately hypofractionated post-operative radiation therapy for breast cancer.

Materials and methods

Radiation oncologists who are members of local radiation therapy societies from Argentina, Aruba, Bolivia, Brazil, Chile, Colombia, Dominican Republic, Ecuador, Mexico, Panama, Paraguay, Peru and Uruguay were invited to participate in this study. Between February and March 2022, an invitation email was sent to 1004 radiation oncologists.

We applied the same questionnaires containing 38 questions as used in the European survey study [23]. Questions were organised on a multi-choice setting, allowing multiple answers and also free-text responses. It was not necessary to translate and validate the questionnaire in Portuguese and Spanish as the instrument was applied in its original format in English.

We created an online survey (via *REDCAP*). The participation in the survey was voluntary and respondents did not receive any fee. In the current study, we presented the diverse features of fractionation use in post-operative radiation therapy for breast cancer.

The statistical analyses

The dichotomic and continuous variables were treated as proportions (percentage) and median with standard deviation, respectively. The influence of the following medical aspects in the radiation oncologists' choices to recommend moderately hypofractionated post-operative radiation therapy schedules was investigated: number of breast cancer cases per month, age group, practice setting, years of practice, time dedicated to breast cancer, and academic institution. The treatment (dose to organs at risk, dose inhomogeneity, use of high tangents, regional nodal irradiation, internal mammary node irradiation, flap-based breast reconstruction, and implant-based breast reconstruction) and tumour aspects (breast cancer stage, breast size, tumour side, breast cancer molecular subtype, tumour grade, surgical margins) were tested for association with the decision or contraindication to recommend moderately hypofractionated post-operative. A chi-square test was used in all the analyses. For each subgroup analysis, the odds ratio and 95% confidence interval (CI) were calculated. Statistical significance was defined as a p-value of 0.05. The statistical analysis was performed with the software SPSS version 25.0 and SAS® version 9.4.

Results

A total of 173 radiation oncologists (17.2% of the total number of invitations) answered the questionnaire. Most respondents practiced in Brazil n = 90 (52.0%), Argentina n = 23 (13.2%) and Mexico n = 12 (6.9%) as described in Figure 1.

Only 25 of participants had an academic affiliation (14.4%), and 146 (84.4%) had practiced for at least 5 years since completing residency; 68.8% of the respondents affirmed that they dedicated at least 25% of their clinical time to breast cancer patients, with 54.3% treating 11 or more cases of breast cancer per month.

Discussing the decision to treat breast cancer patients with post-operative radiation therapy in a multidisciplinary tumour board is mostly done only for non-standard cases by 38.1% of the respondents (Supplementary File — Tab. S1).

The majority of respondents (84.9%) preferred moderately hypofractionated post-operative radiation therapy as their first choice in cases

Country	N	%
Argentina	23	13.29
Aruba	1	0.58
Bolivia	6	3.47
Brazil	90	52.02
Chile	7	4.05
Colombia	8	4.62
Dominican Republic	2	1.16
Ecuador	7	4.05
Mexico	12	6.94
Panama	2	1.16
Paraguay	2	1.16
Peru	11	6.36
Uruguay	2	1.16

Figure 1. Number of radiation oncologists and countries that were included

of whole breast irradiation. For whole breast plus regional node irradiation, post-mastectomy (chest wall and regional node irradiation) without reconstruction, and post-mastectomy (chest wall and regional node irradiation) with reconstruction hypofractionated post-operative radiation therapy was preferred by 72.2%, 71.1% and 53.7% of respondents, respectively (Fig. 2). When boost dose to the primary tumour bed is indicated, majority of respondents would offer a hypofractionated schedule (i.e., 3–4 daily fractions of 2.5–3.0 Gy). Simultaneous integrated boost delivery with the photon beam technique was preferred by most radiation oncologists (Supplementary File — Table S2).

Table 2 demonstrates the medical aspects influencing radiation oncologists' choices to recommend moderately hypofractionated post-operative radiation therapy schedules. The main factor influencing the moderate hypofractionated choice was < 50% of time dedicated to breast cancer, odds ratio (OR) 6.98 [95% confidence interval (CI), p = 0.031].

Clinical-pathological and financial aspects influencing the decision of radiation oncologists to recommend moderately hypofractionated post-operative radiation therapy schedules is presented in the Table 3. Of all evaluated features, patients age (p = 0.009), regional nodal irradiation (p = 0.002) and implant-based breast reconstruction (p = 0.031) were the characteristics that significantly impacted on the decision to adopt moderately hypofractionated post-operative radiation therapy.

Table 4 shows the absolute contraindications for the use of moderately hypofractionated post-op-

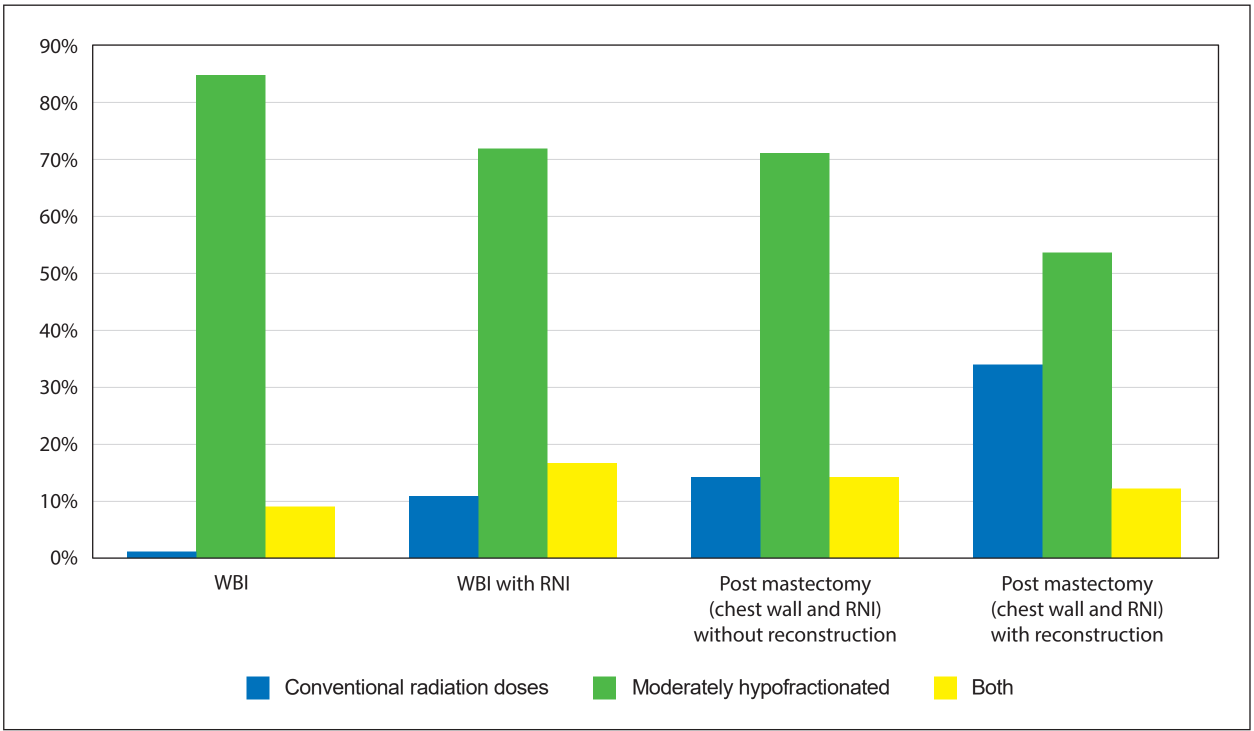

Figure 2. Radiation oncologists and their fractionation preference. WBI — whole breast irradiation; RNI — regional nodal irradiation

erative radiation therapy schedules as reported by radiation oncologists. The two most important factors for not indicating hypofractionation were breast cancer stage (p = 0.036), and flap-based breast reconstruction (p = 0.04).

Discussion

To the best of our knowledge, this is the first study to assess the LAC radiation oncologists' preferences related to the use of moderately hypofractionated post-operative radiation therapy in breast cancer patients. A total of 173 radiation oncologists corresponding to 13 countries responded to the survey which made it possible to understand the treatment profile that has been carried out in these countries. The results of our study showed that moderately hypofractionated post-operative radiation therapy had been used not only for selected early-stage breast cancer patients, but also in cases after mastectomy and when regional nodal irradiation is needed. In other words, despite the greater tendency to use moderately hypofractionated post-operative radiation therapy for patients that do not need regional nodal irradiation, it is observed that the hypofractionation has been gaining ground in clinical practice, even when regional nodal irradiation is needed or after mastectomy with or without reconstruction.

In our study, the factors that most affected the decision to utilize moderately hypofractionated post-operative radiation therapy in clinical practice were percentage of time dedicated to breast cancer, regional nodal irradiation, implant-based breast reconstruction, and patient's age. Moreover, breast cancer stage, and flap-based breast reconstruction were factors more commonly associated with absolute contraindications for the use of hypofractionated schedules. These findings are similar to the European study which, by evaluating the responses of 412 radiation oncologists from 44 countries, demonstrated that many factors can affect the decision to use hypofractionation in clinical practice [23]. It is important to recognise that the clinical application of the moderately hypofractionated post-operative radiation therapy differs across the globe, with rates ranging from 34.5% to 95% [24–29]. Previous authors reported breast laterality and volume, younger age, breast cancer stage, triple-negative tumour, and radiation plan inhomogeneity as factors related to lower hypofractionation utilization [26–28, 30].

Table 1. Participants' characteristics

Characteristics	N	%
Age group (years)		
< 35	25	14.4
35–45	84	48.5
46–60	38	22
61–70	22	12.7
> 70	4	2.3
Years in practice		
< 5 years	27	15.6
5–10 years	36	20.8
11–20 years	63	36.4
>20 years	46	26.6
Number of breast cancer patients treated per month		
< 5	6	3.4
5–10	72	41.8
11–20	55	31.9
> 20	39	22.6
Number of radiation oncologists treating breast cancer patients in participant's place of work		
1	13	7.5
2	29	16.7
3	43	24.8
4	21	12.1
> 5	66	38.1
Other	1	0.5
Percentage of clinical time dedicated to breast cancer patients		
< 25%	54	31.2
25–50%	85	49.1
51–75%	25	14.5
> 75%	9	5.2

Note: The absolute numbers and percentages correspond to the total response obtained in each item

Numerous prospective randomised trials have studied several features of hypofractionated irradiation in breast cancer patients. Primarily, these studies with almost 8000 patients have demonstrated that hypofractionation is as safe and effective as conventional fractionation. Nevertheless, most of these studies involved mostly patients with early-stage disease who received breast-conserving therapy. Most patients underwent whole breast radiation therapy without regional nodal irradiation [12, 15–18, 20]. Therefore, the utilization of moderately hypofractionated post-operative radiation therapy is not globally adopted in patients who received mastectomy or need regional nodal irradiation due to overconcern about toxicity related to the treatment [8].

Some experts advocate that the use of moderate hypofractionation for regional nodal irradiation must be evaluated with attention until outcomes of other clinical trials are available due to the long-term side effects of this treatment, especially regarding heart and lung functions [31]. Furthermore, there could be unease related to the fact that chemotherapy was used in 14%, 11%, 35%, 22% of patients in the OCOG trial [14, 15], START A [17, 18] and START B [16, 17], respectively, and most patients received a non-standard chemotherapy regimen. Nonetheless, standard chemotherapy (anthracycline and taxane-based) schedules were used in the Chinese trial [19] and the Shaitelman et al. [32] study with suitable side effects outcomes. Although these trials [19, 32] had a shorter follow-up, current evidence of using conventional dose radiation therapy after breast-conserving surgery and mastectomy (with or without regional nodal irradiation) comes from randomized trials that mostly used a non-standard chemotherapy regime as well [3, 4]. Moreover, the START trials' data demonstrated that the rates of ischemic heart disease and lung fibrosis were remarkably low (less than 2%) [33]. Even though these values can be higher than those noticed by other authors using modern diagnostic instruments, patients rarely developed symptoms consistent with pulmonary and cardiac side effects that required medical intervention [34-37].

The treatment-related side effects are possibly more associated with the radiation therapy technique than the dose scheme used. The estimated absolute risks for second cancer or heart disease (with cardiac mortality) from modern radiation therapy were very low compared to older therapies [38]. Thus, the hypothesis of contemporary homogeneously delivered volume-based radiation therapy techniques can be applied to understanding that treatment effects should be undistinguishable regardless of the target volumes. Data from prospective and retrospective studies also showed that hypofractionated post-mastectomy radiation therapy with or without regional nodal irradiation is safe, with low rates of side effects and suitable local control results [22, 37, 39–48].

Table 2. Medical aspects influencing the decision of radiation oncologists to recommend moderately hypofractionated post-operative radiation therapy schedules

Characteristics	Hypofractionation (n = 146)		Other (n = 27)		OR (95% CI)	p-value
	N	%	N	%		
Patients number at clinic						
≥ 10 patients	81	44.5	12	52	1.35 (0.57–3.16)	0.488
< 10 patients	65	55.5	13	48		
% Time dedicated to breast cancer						
≤ 50%	114	78	25	96	6.98 (1.10–53.70)	**0.031**
> 50%	32	22	1	4		
Age group						
≤ 45 years	95	65	13	50	1.86 (0.81–4.32)	0.143
> 45 years	51	35	13	50		
Setting practice						
Public	89	61	16	61.5	0.97 (0.41–2.30)	0.955
Private	57	39	10	38.5		
Academic hospital						
No	123	84	24	92.3	0.44 (0.08–2.00)	0.283
Yes	23	16	2	7.7		
Timing working as radiation oncologist						
< 10years	54	37	9	38.4	1.11 (0.46–2.66)	0.817
≥ 10years	92	63	17	61.6		
Number of radiation oncologists at the service						
1	9	6.3	4	13	0.36 (0.10–1.20)	0.110
> 1	132	93.7	27	87		
Academic institution						
Yes	23	15.7	2	7.7	0.44 (0.09–2.90)	0.283
No	123	84.3	24	92.3		

Note: The absolute numbers and percentages correspond to the total response obtained in each item. OR — odds ratio; CI — confidence interval

Many patients undergo implant and autologous breast reconstruction before and after RT [49]. Several studies demonstrated that radiation therapy might lead to post-operative increase of capsular contracture rates and infection. In some situations, this could result in the removal of the implant [50–53]. Interestingly, besides the fact that implant-based reconstruction significantly affected the decision for choosing the fractionation scheme, flap-based reconstruction was a categorical contraindication for the higher dose per fraction schedule in most responses. In our opinion, this finding reflects a higher fear of complications with irradiation of reconstructed breasts with higher doses per fraction, mainly with autologous tissue that, however, should be demystified. And, if there are any concerns, they should be mostly related to implant-based reconstruction. It is important to highlight that none of the published randomized phase III trials that formally compared the results of moderate hypofractionation to conventionally fractionated irradiation [13, 15–19] included patients with implant and autologous breast reconstruction. On the other hand, all of these trials showed that most breast side effects that could be strongly associated with radiation-related toxicities in implant and autologous breast reconstruction (skin retraction, fibrosis and breast shrinkage) were lower or, at least, equal in patients who underwent hypofractionation. A retrospective experience from a Korean group [2] demonstrated that there were no differences in late effects regarding the timing and type of breast reconstruction related to both radiation therapy fractionation schemes. Additionally, there is no randomized phase III trial that validated the use of a conventional radiation dose after breast reconstruction. Historically, the conventional dose has been empirically used

Table 3. Clinical-pathological and financial aspects influencing the decision of radiation oncologists to recommend moderately hypofractionated post-operative radiation therapy schedules

Characteristics	Hypofractionation		Other		OR (95% CI)	p-value
	N	%	N	%		
Age	114	78.0	12	54	3.01 (1.2–7.2)	0.009
Breast cancer stage	111	76.0	19	73	1.10 (0.4–3.3)	0.747
Breast size	111	76.0	18	69	1.41 (0.56–3.21)	0.461
Tumour side (right or left)	135	92.5	23	88	1.60 (0.41–6.19)	0.491
Breast cancer molecular subtype	131	89.7	22	85	1.59 (0.41–5.23)	0.444
Tumor grade	126	86.3	22	84	1.15 (0.35–3.5)	0.819
Surgical margins	123	84.2	22	84	0.97 (0.31–3.01)	0.962
Dose to organs at risk	104	71.2	20	77	0.74 (0.27–1.98)	0.551
Dose inhomogeneity	115	78.8	19	73	1.37 (0.52–3.51)	0.519
Use of high tangents	140	95.9	25	96	0.93 (0.10–8.00)	0.950
Regional nodal irradiation	105	71.9	13	50	2.56 (1.1–6.00)	0.002
Internal mammary node irradiation	105	71.9	19	73	0.94 (0.36–2.40)	0.903
Flap-based breast reconstruction	126	86.3	23	88	0.82 (0.22–3.00)	0.766
Implant-based breast reconstruction	136	93.1	21	65	3.24 (1.1–10)	0.031
Financial issues/reimbursement	100	68.5	20	77	0.65 (0.24–1.73)	0.389

Note: The absolute numbers and percentages correspond to the total response obtained in each item. OR — odds ratio; CI — confidence interval

when breast reconstruction techniques were described [54, 55]. Over the past decades, in clinical practice, once the treatment was performed with conventional doses, there was a simple incorporation of reconstructive surgeries in this scenario. Thus, the available medical evidence of using hypofractionation or conventional fractionated irradiation can be considered equivalent in patients with breast reconstruction.

Even though there is high level evidence to support the use of hypofractionation-based radiation therapy for breast cancer and its use may have significant financial benefits, it fails to be widely adopted in many countries [56]. This might be explained by the fact that the adoption of shorter treatment regimens may have significant implications on health economics, resulting in a financial loss depending on the reimbursement arrangement [57]. While in countries like the Netherlands and the United Kingdom (where reimbursement is independent from the number of fractions) hypofractionated breast irradiation is used by most centres for nearly all patients (except in the case of re-irradiation and concomitant chemoradiation); in more reimbursement-driven models with payment per fraction, including Germany, France, the United States, there is a lot of reluctance towards applying hypofractionation in daily practice [57]. Despite the reimbursement issue being an important factor for the adoption of hypofractionation in clinical practice in many countries, our study showed that this factor is considered in a limited number of respondents.

Our study has some limitations, most notably limited sampling and respondent availability. Even though the survey participants offer some perception about moderately hypofractionated post-operative radiation therapy clinical practice for breast cancer patients in LAC, the responders are self-selected. So, the results would not be robustly representative, illustrating a lack of radiation oncology community representation. However, most responders (54.5%) declared that they treated at least 11 breast cancer patients per month, and the great majority (96.6%), at least five patients per month (Tab. 1). So, the sample seems to represent a community with experience in breast cancer treatment. In addition, the ones that dedicate less time of their clinical practice to breast cancer are those that would choose other fractionation scheme rather than the hypofractionated one (Tab. 2). Therefore, our study can positively stimulate radiation oncologists in their reflections and decision-making on whether or not to

Table 4. Absolute contraindications for the use of moderately hypofractionated post-operative radiation therapy schedules as reported by radiation oncologists

Characteristics	HYPO		Other		OR (95% CI)	p-value
	N	%	N	%		
Age	139	95.2	20	76.9	2.62 (0.62–10.7)	0.176
Breast cancer stage	142	97.3	23	88.5	4.63 (1.07–22)	0.036
Breast size	139	95.2	25	96.1	0.79 (0.08–6.74)	0.832
Breast side (right or left)	145	99.3	26	100	1.83 (0.07–46)	0.672
Breast cancer molecular subtype	144	98.6	25	96.1	2.88 (0.25–33)	0.374
Tumor grade	4	2.7	20	76.9	6.00 (0.90–44.6)	0.05
Surgical margins	141	96.6	23	88.5	3.68 (0.82–16.8)	0.07
Dose to organs at risk	117	80.1	19	73.1	1.49 (0.51–3.87)	0.415
Dose inhomogeneity	121	82.9	22	84.6	0.88(0.27–2.79)	0.827
Use of high tangents	144	98.6	26	100	1.09 (0.05–23.4)	0.548
Regional nodal irradiation	136	93.1	22	84.6	2.47 (0.71–8.58)	0.143
Internal mammary node irradiation	124	84.9	22	84.6	1.02 (0.32–3.26)	0.967
Flap-based breast reconstruction	139	95.2	21	80.7	3.14 (1.07–11.3)	0.04
Implant-based breast reconstruction	124	84.9	23	88	0.73 (0.20–2.66)	0.638
Financial issues/reimbursement	143	97.9	25	96.1	1.91 (0.19–19)	0.577

Note: The absolute numbers and percentages correspond to the total response obtained in each item. OR — odds ratio; CI — confidence interval

accept hypofractionated breast radiation therapy in their daily clinical practice, in order to take the road towards higher convenience for the patients and less societal costs. The adoption of hypofractionation in emerging countries is not just a subject of cost-effectiveness but one of entrance to improved medical health assistance and patient survivorship [58, 59].

Conclusion

In conclusion, even though moderately hypofractionated post-operative radiation therapy for breast cancer is considered a new standard to many patients. Its unrestricted and wide application in clinical practice across LAC still faces some reluctance, especially when regional nodal irradiation is needed or after mastectomy with or without reconstruction.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by G.N.M., G.A.V. and R.G.deJ. The first draft of the manuscript was written by Gustavo Nader Marta and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethical approval

The study was approved by the Brazilian Ethical Review Authority (CAAE: 52076121.7.0000.5336; number: 5.081.397).

Conflict of interest

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