



Hypofractionated radiotherapy in breast cancer: a 10-year single institution experience

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ABSTRACT

Background: Moderately post-operative hypofractionated radiotherapy (HYPO-RT) for breast cancer is a safe and effective strategy as seen in large prospective trials. This study aimed to assess overall and disease-free survivals, local control, and acute and late toxicities in patients treated with HYPO-RT.

Materials and methods: Data from patients submitted to post-operative HYPO-RT, with or without boost, were evaluated retrospectively. Demographic, disease, and treatment characteristics were collected.

Results: From March 2009 to December 2016, 393 patients were treated. Breast-conserving surgery was performed in 94.7%, immediate reconstruction after mastectomy in 6 (1.5%). Most patients (91.2%) had initial stage (0 to IIA), and chemotherapy was performed in 42.0%, HYPO-RT was mainly performed in 15 or 16 daily fractions of 267 cGy and 265 cGy, respectively. The median follow-up was 5.7 years. There were 25 deaths (6.4%) and 17 (4.3%) local recurrences. At 5 and 10 years, the overall survival, local control, and disease-free survival were, respectively, 96.0% and 79.3%, 99.2% and 94.9%, 96.6%, and 91.9%. Acute grade 3 or 4 dermatitis was observed in 0.9%. Late grade 1 or 2 occurred in less than 3% of the patients.

Conclusion: HYPO-RT is a safe and effective radiotherapy regimen with excellent disease control and overall survival rates, with low acute and late toxicity rates.

Key words: breast cancer; local treatment; hypofractionated radiotherapy

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Introduction

Moderately hypofractionated radiotherapy (HYPO-RT) for breast cancer is a safe and effective strategy as seen in European, North American, and Chinese randomized trials [1-10]. When compared to conventional 50-50.4 Gy in 25 to 28 fractions, moderate hypofractionation in 15 or 16 fractions has been found to reach similar survival outcomes,

with potentially fewer side effects [1-10]. However, this experience should be validated in countries with different cultures and resource availability. No reports have been identified so far regarding HYPO-RT results in a middle or low-income country environment.

Our hospital is a university general hospital dedicated to the public health system assistance. The Radiotherapy Department is the largest in the

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country, with 10 linear accelerators and one high dose-rate brachytherapy equipment. Around 500 patients come every day for treatment and breast cancer patients comprise about 25% of them. Since 2009, we have been using HYPO-RT for the treatment of breast cancer in a consistent way.

Therefore, this study had the aim to report the 10-year experience of our institution with HYPO-RT regarding local control, overall and disease-free survivals, and acute and late toxicities.

Materials and methods

This is a single institution retrospective cohort study of non-metastatic breast cancer patients submitted to post-operative HYPO-RT, with or without boost. The study was performed in conformity with the Declaration of Helsinki standards, was registered under the number CAAE 08622119.5.0000.0065 and approved by the local ethical committee (NP 3.196.063).

To be eligible for HYPO-RT, patients needed to be at least 50 years old and have been submitted to breast-conserving surgery or mastectomy. Any combination of chemotherapy was allowed, as was the use of hormone therapy and/or anti-Her2 treatment.

Patients with an indication of regional nodal irradiation, alloplastic breast reconstruction, connective tissue diseases, such as systemic lupus erythematosus and scleroderma, bilateral tumors, or large breasts (breast planning target volume, PTV > 1000 cc or tangential fields separation > 20 cm) were to be excluded.

The radiotherapy protocol started with 42.5 Gy in 17 fractions, with or without a boost of 10 Gy in five fractions. After a short period of experience, the protocol was changed and followed the regimens used in the Canadian and START B trials [6, 7]: 40 Gy or 42.5 Gy total dose in 15 or 16 daily fractions, respectively; with or without boost. The boost dose was delivered in five (total dose 10 Gy) or three (total dose 8 Gy) fractions. Indication of boost followed the institutional protocol: patients younger than 60 years, or margins closer than 5 mm.

Demographic data, disease, and treatment characteristics were collected from patients' charts. Three-year minimum follow-up or until death was required to be included.

Primary outcomes were local control (local disease-free survival), overall (OS) and disease-free survivals (DFS), analyzed from the date of diagnosis. Local control was defined as the absence of disease in the irradiated areas. Recurrences were categorized as local (breast or surgical bed), regional (lymphatic drainage of the axillary, supraclavicular fossa or internal mammary chain), or distant (metastases), and any association of these.

Acute toxicities were considered during and up to 3 months after the end of radiotherapy, and late, thereafter. Toxicities were assessed according to the RTOG criteria [11]. The most severe toxicity presented was reported.

Statistical analysis

Descriptive and frequency analyses were performed with calculation of mean, standard deviation, and median values. Correlations were evaluated by Pearson's chi-square method. The cumulative incidence of local recurrences, OS and DFS were calculated using the Kaplan-Meier method with comparisons between variables made by the Log-rank test. IBM SPSS Statistics Software v.20 (Chicago, Illinois) was used for the analysis with the significance level set at 5% ($p \leq 0.05$).

Results

From March 2009 to December 2015, 393 patients (396 breasts) were treated. Data of demographic and clinical characteristics, as well as systemic treatment, were based on the 393 evaluated patients. All variables related to tumor characteristics and local treatment are described regarding the 396 treated breasts (Tab. 1).

The mean age was 63.9 years (range 34 to 91 years). There were 5.8% ductal carcinoma in situ and all the others comprised invasive tumors. Breast-conserving surgery was performed in 95.7% and immediate reconstruction after mastectomy in six (1.5%) patients, three with autologous and three with alloplastic implants. Most tumors were stage pT1 (60.0%), pN0 or pN1mi (90.2%), "luminal A or B like" (85.4%) pattern. Neoadjuvant or adjuvant chemotherapy was administered in 42.0%, of which 73.3% were anthracycline-based, 35.8% combined with taxanes, and 20.6% with an anti-Her2 drug. Adjuvant hormone therapy was prescribed for 87.5% of the patients. HYPO-RT was delivered in

Table 1. Characteristics of the 393 evaluated patients and 396 treated breasts

Characteristic	N	%
Age (years)		
Mean (\pm standard deviation)	63.9 (\pm 10.8)	
Median	63.7	
Range	34 to 91	
BMI [kg/m²]		
Mean (\pm standard deviation)	28.2 (\pm 5.3)	
Median	27.6	
Range	15.4 to 56.0	
Comorbidities		
Diabetes mellitus	85	21.6
Arterial hypertension	215	54.7
Smoker	90	22.9
Breast side		
Right	213	54.2
Left	177	45.0
Bilateral	3	0.8
Histology*		
Ductal carcinoma in situ	20	5.1
Invasive carcinoma	324	81.8
Invasive lobular carcinoma	20	5.1
Others	32	8.1
Estrogen receptor positive*	349	88.1
Progesterone receptor positive*	306	77.3
HER-2 Positive*	22	5.6
Luminal A or B "like"*	338	85.4
Triple negative*	36	9.1
Clinical stage (AJCC 7th ed)*		
0	23	5.8
I–IIA	235	59.4
IIB–IIIB	138	34.8
Surgery*		
Conservative	375	94.7
Nipple-sparing mastectomy	4	1.0
Modified radical mastectomy	17	4.3
Breast reconstruction	6	1.5

Characteristic	N	%
Pathological stage (AJCC 7th ed)*		
0	22	5.6
I–IIA	339	85.6
IIB–IIIB	35	8.8
pT stage*		
pTis	22	5.6
pT0–T2	367	92.6
pT3–T4	7	1.8
pN stage*		
pN0	331	83.6
pN1mi	26	6.6
pN1a	34	8.6
pN2a	4	1.0
pN3a	1	0.2
Chemotherapy		
None	228	58.0
Neoadjuvant	16	4.1
Adjuvant	149	37.9
Hormone therapy	344	87.5
Radiotherapy fractionation		
15 fractions	161	40.6
16 fractions	147	37.1
17 fractions	88	22.3
Additional radiotherapy fields*		
Supraclavicular/axillary	13	3.3
Internal mammary	1	0.3
Boost	110	27.8
Tangential fields separation [cm]*		
Mean (\pm standard deviation)	18.0 (\pm 2.9)	
Median	17.8	
Range	8.5 to 27.0	
PTV [cc]*		
Mean (\pm standard deviation)	915.6 (\pm 368.5)	
Median	868.8	
Range	211.9 to 2402.8	

N — number; BMI — body mass index; PTV — planning target volume; *Data regarding the number of treated breasts

15 or 16 fractions in 77.3%, with boost indicated in 110 (27.8%) breasts. The boost was prescribed mostly in five fractions of 2 Gy, and a small percentage (7.3%) in 3 fractions of 2.67 Gy. Fourteen (3.5%) cases received irradiation of the lymphatic drainage, only one including the internal mammary chain (first three intercostal spaces).

Dosimetric data could be retrieved for 343 patients treated with three-dimensional conformal radiotherapy. The others were treated with a conventional two-dimensional technique. The tan-

gential fields separation ranged from 8.5 to 27 cm (mean = 18.0 ± 2.9 cm; median = 17.7 cm), and the breast PTV from 211.9 to 2402.8 cc (mean = 915.6 cc and median = 868.8 cc). The institutional protocol defines the optimal coverage as 95% of the volume receiving at least 95% of the prescribed dose. However, 90% coverage of the PTV with 90% of the prescribed dose is accepted as a small protocol deviation. Hot spots of 115% are allowed with less than 50% of the PTV receiving more than 110% of the prescribed dose. All patients achieved the

dosimetric goals while complying with the organs at risk dose constraints, with three-dimensional conformal radiotherapy using a forward-planned modulated field-in-field technique to homogenize the dose distribution.

The median follow-up was 5.7 years (1 to 10.9 years). The survival analyses considered the total number of patients (393), regarding the higher risk tumor in the bilateral cases; and local control, the number of treated breasts/chest walls (396). There were 25 (6.4%) deaths and 17 (4.3%) recurrences in the period. The OS rates at 5 and 10 years were, respectively, 96.0% and 79.3% (mean = 10.0 ± 0.2 years) (Fig. 1). DFS was 96.6% and 91.9% at 5 and 10 years, respectively (Fig. 2). Local control was 99.2%

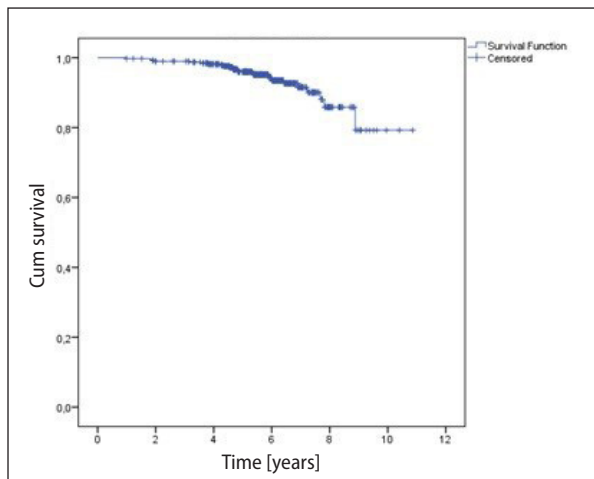


Figure 1. Overall survival (393 patients) — 25 events. Mean = 10.05 ± 0.19 years

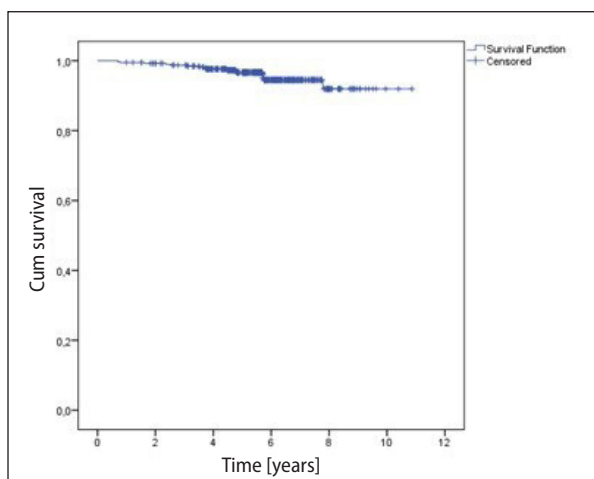


Figure 2. Disease-free survival (393 patients) — 17 events. Mean = 10.04 ± 0.12 years

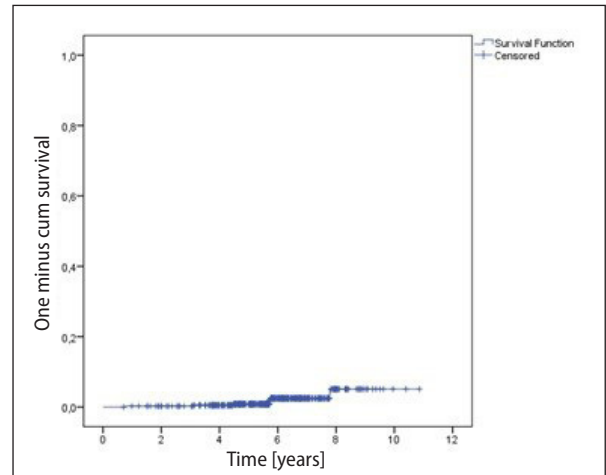


Figure 3. Local control (396 breasts) — seven events. Mean local disease-free survival = 10.6 ± 0.14 years

and 94.9% at 5 and 10 years, respectively (Fig. 3). Recurrences were local in seven (1.8%) breasts, regional in only one (0.3%), and nine (2.3%) patients presented distant metastases. Distant metastases were more likely to occur in the more advanced stages (IIB–IIIB 8.6% vs. I–IIA 1.7%; $p < 0.0001$). Local recurrences occurred in a median of 5.7 years, while any recurrence in a median of 3.7 years.

We also compared the initial HYPO-RT schedule of 17 fractions ($BED_{Gy3} = 77.9$ Gy) (88 patients, 22.3%) with the 15 or 16 fractions schedules ($BED_{Gy3} = 76.9$ Gy and 77.7 Gy, respectively) (308 patients, 77.7%). No differences were found between the schedules in all the analyzed outcomes nor between the boost and no-boost subgroups. (Supplementary File — Figure S1 and S2).

Acute grade 3 or 4 radiodermatitis occurred in 0.9% (3 breasts) of the patients, with most (62.8%) presenting with grade 2. Late toxicities were reported as fibrosis (2.8%), pain (1.5%), and hyperchromia (2.8%), all grade 2 or less. No internal organ-related toxicity was observed.

Discussion

Radiotherapy is one of the cornerstones in the treatment of breast cancer, regarding both local control and survival [12, 13]. Breast cancer is the worldwide leading cancer in women and the second cause of death due to cancer in this population [14]. The classic radiotherapy schedule of 25 to 28 daily fractions has been successful over time. However, it is time-consuming and the reduction of patients'

daily visits to the hospital would be welcome. This has been achieved with the moderate hypofractionated regimens proposed by several clinical trials [1–9]. The population included in the pioneer studies [1–5] was mainly comprised of patients aged 50 years or more, with low-risk tumors and no chemotherapy combined. Also, patients with indication of regional nodal irradiation were either excluded or underrepresented in those early trials.

Therefore, in 2009, after the first five-year follow-up results of this moderately hypofractionated schedule were published, we started treating patients with this strategy in our Hospital.

This study reports our experience with median follow-up of 5.7 years in a large single-institution cohort from a Latin-American middle-income country. As can be seen in Table 1, the indication of the hypofractionated scheme became more flexible during the study period, with the inclusion of patients with bilateral tumors, and an indication of lymphatic irradiation.

When comparing the patients treated in our cohort with those included in the Canadian [6] and United Kingdom [7] trials, we observed an older population selected in our cohort, but the most relevant aspect was the use of chemotherapy, which was allowed and administered in 42% of the patients. According to more modern regimens, anthracyclines were used in most of the patients that received chemotherapy, with the use of taxanes and anti-Her2 drugs reported as well (Tab. 2). No statistically significant impact in any of the outcomes, including complications, and the use or not of chemotherapy was observed. However, the use of neoadjuvant chemotherapy, prescribed in more advanced diseases, was associated with worse survival outcomes, as expected.

Our data demonstrated that local recurrence was low and comparable to the results of published prospective randomized clinical trials for early breast cancer [6, 7, 9] (Tab. 2). Moreover, overall complication rates were also low, as expected. At first, we were more conservative, establishing restrictions related to the breast size and tangential field separation. However, later on, with a better acquaintance with the fractionation schedule and using 3D planning, these restrictions were no longer an issue, so long as the breast dose homogeneity was kept within the institutional protocol recommendations. The same strategy was used in the Danish trial [9],

where the primary endpoint was the occurrence of breast induration. There were no restrictions regarding the breast size, and the late toxicity was very low and comparable with the conventional fractionation arm. Nevertheless, a limitation of our study was the scarceness of data to evaluate grades 1 or 2 adverse effects, which are not always specified in the charts.

Consensus recommendations for the use of HYPO-RT were first published by the American Society of Therapeutic Radiation Oncology (ASTRO) in 2011 [15] when we were already using HYPO-RT for breast cancer (these recommendations were further updated in 2018 [16] with more flexible criteria).

When analyzing Table 1, most treated patients followed the 2011 guidelines, except for the chemotherapy, prescribed in almost half of the patients in our cohort. And also 21% received an anti-Her2 drug, not available at the time of recruitment of the first trials on hypofractionation and not considered in the guidelines.

Comparing our results with the long-term publications of the Canadian and START B trials [6, 7], on which we based our choice of HYPO-RT schedule, our patient selection was more restrictive than the original ones, although with a few deviations such as the amount of combined chemotherapy used, the treatment of a few patients with breast reconstruction and some with an indication of regional nodal irradiation (Tab. 2).

The local recurrence rate in our cohort was low, and comparable with that observed in those studies, with a very low rate of significant early and late complications. Probably, the use of more modern radiotherapy techniques, better chemotherapy regimens, and even the better patient staging that can be achieved with the currently available imaging exams could have contributed to our better results.

With a median follow-up of 5.7 years, the survival analyses were by what was expected for this low-risk population. There was an early death at 12 months follow-up in a 34-year-old patient with a fast-growing locally advanced disease (stage IIIC) due to clinical complications after local recurrence.

In 2018, the Brazilian Society of Radiotherapy (*Sociedade Brasileira de Radioterapia — SBRT*) published recommendations for hypofractionated whole-breast irradiation [17], with a high agreement (100%) among the experts on indicating this

Table 2. Comparison of the present study with the trials from which we chose the HYPO-RT schedule for breast cancer [6, 7]. Comparison with a more recently published trial that aimed to evaluate the toxicity is also presented [9]. The numbers refer to the hypofractionated arm of each study

Study	OCOG ⁶	START B ⁷	DBCG ⁹	HC-FMUSP
Accrual period	1993-96	1999-2001	2009-14	2009-15
Type of study	Prospective randomized	Prospective randomized	Prospective randomized	Retrospective cohort
N	1234 (two arms)	2215 (two arms)	1854 (two arms)	392 (single cohort)
RT	16 fractions	15 fractions	15 fractions	15 or 16 fractions (17 fractions 23%)
Age ≥ 50 years	76%	79%	89%	90%
DCIS	–	–	13%	5.8%
HT	41%	87%	37%	87%
CT	11%	22%	42%	42%
Anthracycline-based	59.1%	(CMF 28.6%)	NA	73%
Taxane	(9 patients)	(19 patients)	NA	36%
Anti-Her2 drug	–	–	9%	21%
RNI	–	7%		4% (IMC: 1 patient)
Boost	–	43%	23%	28%
Breast size	–	74% “medium”	Median CTV 635 cc	78% (TFS ≤ 20 cm) 64% (PTV ≤ 1000 cc)
Median follow-up	12 years	9.9 years	7.3 years	5.7 years
5-year local recurrence	2.2%	2.8%	1.0%	0.8%
10-year local recurrence	7.4%		3.0% (9-year)	5.1%

N — number of patients; RT — radiotherapy; HT — hormone therapy; CT — chemotherapy; CMF — cyclophosphamide, methotrexate, fluorouracil; RNI — Regional nodal irradiation; IMC — internal mammary chain; TFS — tangential fields separation; CTV — clinical target volume; PTV — breast planning target volume; NA — non-available.

schedule for almost all patients older than 40 years, with low-risk disease, and an indication of a breast only irradiation. Despite the scarcity of evidence available regarding association with neoadjuvant chemotherapy or anti-HER2 drugs, above 90% of the experts would treat these patients with hypofractionated schedules. These recommendations came to corroborate our experience.

Existing data confirm that moderately hypofractionated RT for breast cancer is efficient, convenient, and safe for all indications, target volumes, and techniques [18], even for advanced stages as seen in the prospective randomized trial from Beijing published in 2019 [8]. The trial included 820 pT3–4 pN2–3 post-mastectomy breast-cancer patients, who were randomized to receive post-mastectomy RT of the chest wall and selected nodal irradiation (supraclavicular and level 3 axillary) with 50 Gy in 25 fractions in five weeks or 3-week hypofractionation, 43.5 Gy in 15 fractions

(EDQ2 = 50 Gy). The 5-year loco-regional relapse rates were 8.1% and 8.3% for the conventional dose and hypofractionation groups, respectively, resulting in a non-significant absolute difference of 0.2% (90% CI: –3.0–2.6) and a hazard ratio of 1.10 (90%CI: 0.72–1.69; $p < 0.001$ for non-inferiority). There were no significant differences between the groups in acute and late toxicities, except that fewer patients in the hypofractionated radiotherapy group had grade 3 acute skin toxicity than in the conventional fractionated radiotherapy group [14 (3%) of 401 patients vs. 32 (8%) of 409 patients; $p < 0.0001$].

At our institution, after this initial experience, HYPO-RT has been indicated since April 2019 for all patients with breast cancer who need adjuvant radiotherapy, irrespective of age, associated treatments, breast reconstruction, or regional node irradiation. We hope to report our results in a near future.

Currently, even shorter schedules are under consideration for radiotherapy for selected patients with breast cancer. The 5-year results of the FAST-FORWARD trial, delivering 26 Gy in 5 consecutive daily fractions of 5.2 Gy are promising and provocative and may be used as a treatment option for selected patients [19].

Conclusion

HYPO-RT is a safe and effective radiotherapy regimen with excellent disease control, overall survival rates, and low toxicity. We believe that our results may be translated to other centers with similar cultural, social, and economic environments. Since 2019, it has become the standard treatment schedule for all breast cancer patients in the institution in the adjuvant setting.

Conflict of interest

None declared.

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