Reports of Practical Oncology and Radiotherapy 25 (2020) 886–889

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

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

Original research article

Hypofractionated radiation therapy for early breast cancer: Follow up of a new treatment standard

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ARTICLE INFO

Article history:
Received 4 June 2018
Received in revised form 19 May 2020
Accepted 14 August 2020
Available online 25 August 2020

Keywords:
Early breast cancer
hypofrationated whole breast radiation therapy

ABSTRACT

Aim: To assess the oncological outcomes of patients with early breast cancer treated with breast-conserving surgery and adjuvant hypofractionated radiation therapy.
Methods and Material: This retrospective analysis included all patients ≥50 year of age with T1-2 N0 M0 breast cancer treated at our Radiation Oncology Unit between 2008 and 2011. Whole-breast radiation therapy was delivered to a dose of 42.5 Gy in 16 fractions, without boost. The primary outcome was local control.
Results: 212 patients were identified. With a median follow up of 60 months, we found 3% local recurrence and 5.3% regional and/or distant recurrences. At the moment of data analysis, 17 patients had died. Out of 5 local recurrences, 2 had previously had a distant recurrence, both of them died. The other three were still alive at the last follow up. These results are comparable to those observed in Phase III trials that use this fractionation scheme.
Conclusions: The results obtained with this retrospective analysis are comparable to those obtained in large randomized trials. This data also supports the use of hypofractionated radiation therapy in Latin America. Hypofractionated radiation therapy for early breast cancer patients should be the standard adjuvant treatment.

1. Introduction

Breast cancer is the second most common cancer worldwide and the most frequent in women. It occupies the second place of cancer-related mortality in developed countries, and the first place in undeveloped countries (1).

The Early Breast Cancer Trialists' Collaborative Group meta-analysis established the benefit of adjuvant radiation therapy after breast-conserving surgery in reducing locoregional and distant recurrence and breast cancer death (2). This meta-analysis included more than 10,000 women from 17 randomized controlled trials, most of which included treatment to doses around 50 Gy in 2 Gy per fraction, with or without boost to the lumpectomy cavity. One of the major considerations of radiation therapy is related precisely to the number of sessions needed. The treatment consisting of 5 to 7 weeks of daily fractions has been associated in the United States with 30% of patients not receiving adjuvant radiation therapy after breast-conserving surgery (3). This may be related to economic and patient-related issues(4).

Hypofractionation emerged as an attractive alternative based on the observed radiobiology of breast cancer (5,6), which suggests breast cancer has a lower α/β, close to 4, than other tumors such as squamous cell carcinoma. This led to the opening of multiple clinical trials (7–9) assessing the non-inferiority of hypofractionated treatments in terms of overall survival, local control and cosmesis, with up to 10 years of follow up (10–12). The good results obtained in those studies established the recommendation to treat selected patients with breast cancer with hypofractionated whole-breast radiation therapy with doses ranging from 40 Gy to 42.5 Gy according to different guidelines (13,14).

Breast cancer is a leading cause of cancer-related mortality in women globally (15) and also in Chilean women. Since 2005, breast cancer treatment has been guaranteed by law and performed according to national guidelines. Our Radiation Oncology Unit is considered a high-complexity center within the public health system and provides coverage to around 1.5 million people, with over 400 patients treated with adjuvant radiation therapy after breast

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https://doi.org/10.1016/j.rpor.2020.08.013
1507-1367/

cancer surgery in 2016. Hypofractionated whole-breast irradiation was adopted in 2008 as the standard treatment for women over 50 years of age with early, node negative breast cancer. The current report aims to analyze the outcomes of patients treated with hypofractionated whole-breast irradiation between 2008 and 2011.

As the molecular profile currently plays a major role in the prognostic and management of breast cancer (16–18), we attempt to perform an analysis for local recurrence according to molecular profiles.

2. Methods

For this retrospective review we included breast cancer patients treated between 2008 and 2011 in our radiation Oncology Unit. Inclusion criteria were T1-2 N0 M0 tumors, according to the American Joint Committee on Cancer 7th Edition, and age ≥50 years. All patients underwent breast-conserving surgery. All patients were treated with 3D conformal radiation therapy using 6 to 18 MV photons using opposed tangential fields. Fields were conformed using a multileaf collimator and wedges as needed. A hypofractionated whole breast irradiation (HF-WBI) dose of 42.5 Gy in 16 fractions was planned, no nodal irradiation or lumpectomy cavity boost was used. Treatment planning was performed using Varian Eclipse Software. The protocol was reviewed and approved by the local Ethics Committee.

The primary endpoint was local control, defined by means of local recurrence from the date of surgery until development of recurrence within the breast. Regional and distant recurrence were also analyzed from the moment of surgery until development of regional nodal recurrence or distant metastases, respectively. Information was retrieved until the last follow-up visit by reviewing clinical records from the Radiation Oncology Unit or Breast Pathology Unit, aiming at the most updated information. Patients were censored at last follow-up visit if no evidence of recurrent disease (by means of clinical, histological or imaging studies) or if they died without evidence of recurrent disease. Overall survival was defined as the time from date of breast surgery to the date of death from any cause. Survival analysis was performed using the Kaplan-Meyer method and log rank test.

Molecular classification was performed using immunohistochemistry techniques, when available according to local practice. Confirmatory c-erbB2 FISH was not performed routinely for equivocal 2+ or 3+ c-erbB2 immunohistochemistry in the period of time included in this study. Patients were classified into molecular subtypes using Hormone receptor and Her2 immunohistochemistry information when possible.

2.1. Results

A total of 212 patients were treated with hypofractionated whole breast radiation therapy between 2008 to 2011. All patients were female with a median age of 69.3 years (RIQ 63-74), 99% of whom were post-menopausic. Pathological and molecular features are described in Table 1. We were able to classify 70.7% of identified patients into molecular subtypes: 101 (67.3%) corresponding to Luminal patients, 42 (28%) Her2 and 7 (4.7%) who were Triple negative breast cancer subtype. Staging according to AJCC 7 and the prognostic AJCC 8 staging system was performed for patients whose data is available as detailed in Table 2.

2.2. Treatment

All patients were surgically managed with breast-conserving surgery (BCS). The management of axillary nodes was axillary dissection in 84.3%, sentinel lymph node 15.7% and not performed in 2 in-situ patients. A median of 14 (IQR 11-18) nodes were removed when axillary dissection was performed and a median of 3 (IQR 2-4) in sentinel lymph node cases. No patient presented metastatic lymph nodes.

Thirty-four patients received adjuvant chemotherapy, 29 (85.3%) patients received AC, 2 (5.9%) CMF, one (2.9%) FAC and two (5.9%) received AC plus Trastuzumab. Hormonotherapy was received by 164 (83.5%) patients, mainly Tamoxifen, as per local clinical guidelines. No patient received neoadjuvant treatment.

Table 1
Pathological and molecular tumor features.

Tumor characteristic	num – (%)
Tumor Size	**(n-%)**
Tis	2 (0.94%)
T1	145 (68.4%)
T2	65 (30.66%)
Tumor grade	
G1	51 (24%)
G2	96 (45.2%)
G3	20 (10.6%)
Unknown	45 (21.2%)
Estrogen receptor	
Positive	171 (80.6%)
Negative	34 (16%)
Unknown	7 (3.3%)
Progesterone receptor	
Positive	138 (65%)
Negative	59 (27.8%)
Unknown	15 (7%)
Her2 status	
Positive	42 (19.8%)
Negative	108 (50.9%)
Unknown	62 (29.2%)
Lymph-vascular space invasion (LVSI)	
Present	58 (27.3%)
Absent	121 (57%)
Unknown	33 (15%)

Table 2
AJCC 7 and 8 stages.

AJCC 7 Staging	
0	1 (0.4%)
IA	145 (68.3%)
IIA	65 (30.6%)
Unknown	1 (0.4%)
AJCC 8 Pronostic staging	
0	2 (0.9%)
IA	43 (20%)
IB	44 (20.7%)
IIA	18 (8.4%)
IIB	2 (0.9%)
IIIA	8 (3.7%)
Unknown	95 (44.8%)

2.3. Follow-Up

With a median follow up of 60 months (CI95% 9-91%), we found 3% local recurrence, which corresponds to 5 local recurrences, all of them in the same breast quadrant as the primary lesion. 5.5% of regional and/or distance relapses was observed during this follow-up period. At five years, overall survival was 88.7% IC95% (82.3-92.9%), freedom from local recurrence 95.8% IC95% (90.2-98.2%) and disease free survival 84.3% IC95% (77.1-89.4%).

Within the five patients that relapsed locally, two had a simultaneous distance relapse, both finally died; meanwhile, the other three were still alive at the moment of this analysis. Of the 17 patients that ultimately died, two had previously a local recurrence and five had a regional or distant recurrence previous to death.

Local recurrences were also analyzed according to molecular subtypes (Fig. 1). Two occurred in hormone receptor positive

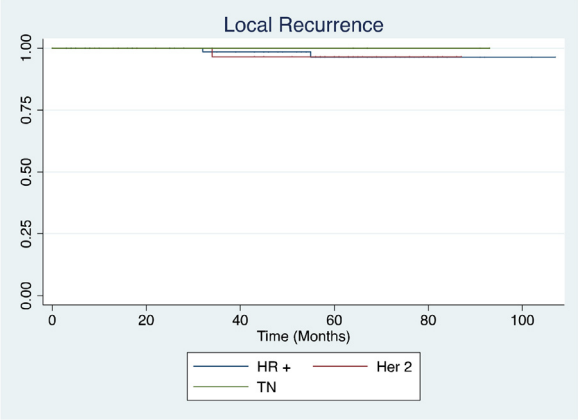

Fig. 1. Kaplan Meier curves for local recurrence, incidence according to molecular profile (time in moths). HR+ (Hormone receptor positive)

patients, one in her2 and the two remaining were not classified because of missing molecular profile data.

In an exploratory analysis for overall survival, no differences were found within molecular subtypes (p = 0.57) or tumor grade (p = 0.95).

An analyses of recurrence pattern regarding AJCC 7 and AJCC 8 staging systems were not performed on account of the very low incidence of local and regional and distant recurrences.

2.4. Discussion

Our local recurrence rate of 3%, with a median follow-up of 5 years, is close to local control rates reported in prospective randomized trials. Wheelan et al. reported a 5-year local recurrence-free survival of 97.2% in the group with the HF-WBI regimen. At 10 years, local-relapse rate for this group was 6.2% (10). When comparing 2 HF-WBI schedules studied at the Royal Marsden Hospital (RMH) and Gloucestershire Oncology Centre (GOC) in the UK(19), local-recurrence rate at 5 years was 9.1% (95% CI 6.4-11.7) in the 39 Gy in 13 fractions group, and 7.1% (95% CI 4.6-9.5) in the 42.9 Gy in 13 fractions group. Local control was significantly improved in the 42.9 Gy group. This relapse rate may seem high compared to our report, but the inclusion criteria in the RMH-GOC study allowed women with more advanced stage disease to be included. Similar inclusion criteria where considered in the UK START trials (11), although RT scheme was different and boost to the tumor bed was allowed. Reported rates of local recurrence at 5 years in UK START A were 3.2 (95% CI 1.9-4.5) in the 41.6 Gy in 13 fractions group, and 4.6% (95% CI 3.0-6.2) in the 39 Gy in 13 fractions group. The UK START B (8)(9) trial used a treatment schedule closer to the Canadian protocol (7) and ours. The rate of local recurrence at 5 years was 2.0% (95% CI 1.1-2.8) in the HF-WBI. Comparison of regional and distant control is difficult due to the difference in reporting methods and systemic management. Hormone therapy and chemotherapy were used more frequently in our report than in other node-negative population (10).

Some considerations must be made regarding our analysis. We did not assess cosmesis or quality of life in our cohort because these issues are not evaluated during follow-up visits at our institution with a properly standardized instrument. Evidence from international trials suggests that there is no difference in cosmetic outcomes with HF-WBI. The immunohistochemistry study performed in our center between 2008 and 2011 did not include evaluation of Ki 67, and patients with equivocal HER-2 were not further evaluated with FISH. This clinical information is currently considered when managing patients with breast cancer, but it is not clear if local adjuvant therapy should be tailored according to this, because the relationship between radiosensitivity and molecular subtype is not completely understood (20). In our data base, no evidence of interaction between immunohistochemical profile and local relapse was found.

3. Conclusion

Our local recurrence rate obtained using HF-WBI for early breast cancer patients is similar to those obtained in large randomized trials.

Our data supports that a hypofractionated radiation scheme can be used safely and with equivalent oncological outcomes in a Latin American Cancer center.

This information is valuable as shorter treatments reduce costs, a key issue in limited resource centers.

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