The Breast 41 (2018) 89–92

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Local control in young women with early-stage breast cancer treated with hypofractionated whole breast irradiation

Kathy Rock [a, c], Sylvia Ng [a], Louise Murray [a], Jie Su [b], Anthony Fyles [a], C. Anne Koch [a, *]

[a] Department of Radiation Oncology, Princess Margaret Cancer Centre/University of Toronto, ON, Canada
[b] Department of Biostatistics, Princess Margaret Cancer Centre/University of Toronto, ON, Canada
[c] Department of Radiation Oncology, Cork University Hospital, Cork, Ireland

ARTICLE INFO

Article history:
Received 2 March 2018
Received in revised form
27 May 2018
Accepted 7 July 2018
Available online 11 July 2018

Keywords:
Breast cancer
Hypofractionation
Breast conserving therapy
Young women
Local control

ABSTRACT

Objective: To compare local control (LC) in young women with early-stage breast cancer (BC) treated with hypofractionated (HF) whole breast irradiation (WBI) vs conventional fractionation (CF) following breast-conserving surgery (BCS).
Materials and Methods: Women <50 years with pT1-2N0 BC following BCS treated with WBI, CF (50Gy/25 fractions) or HF (42.4Gy/16 fractions) followed by a tumor bed boost (10–16Gy/5–8 fractions) from 2009 to 2013 were identified from an institutional database. Median follow-up was 5.2 years (range 0.3–8.4). Kaplan-Meier analysis was used to estimate 5-year LC. Logistic regression identified factors associated with receipt of CF vs HF WBI.
Results: Of 270 eligible women, 227 (84%) were treated with HF and 43 (16%) with CF WBI. A tumor bed boost of 10 Gy/5 fractions was given in 97% of patients, 53% received adjuvant chemotherapy and 94% (225/239) with estrogen-positive disease received endocrine therapy. Median age was 45 years (range 30–49) in HF and 40 years (range 19–49) in the CF group. The 5-year LC rate was 99.3% (95% CI 97.9–100%, $p = 0.495$) in the HF and 97.5% (95% CI 92.8–100%) in the CF group. On univariate analysis, age ≤ 40 years or triple negative BC was associated with a decreased likelihood of receiving HF WBI. Only age remained significant on multivariate analysis [OR 2.82 (95% CI 1.45–5.48, $p = 0.002$)].
Conclusions: HF WBI was associated with excellent LC rates in this study cohort, comparable to CF WBI. However, CF WBI was more likely to be recommended to women <40 years.

1. Introduction

Following breast-conserving surgery (BCS), adjuvant whole breast irradiation (WBI) lowers the 5-year relative risk of ipsilateral breast tumor recurrence by approximately 70% and confers a 5% absolute improvement in 15-year overall survival [1]. Historically, the commonly used WBI fractionation schedule was 'conventional' fractionation of 50 Gy in 25 fractions delivered over 5–6 weeks. More recent studies have used a larger dose per fraction (hypofractionation, >2 Gy per fraction) delivered over a shorter period of time. Multiple large randomized clinical trials (Canadian and UK Standardization of Breast Radiotherapy (START) trials) compared hypofractionated (HF) to conventionally fractionated (CF) WBI and found comparable patient outcomes at ten years in eligible women of all ages [2,3].

HF WBI is rapidly becoming the standard of care for appropriately selected patients, but there has been some heterogeneity in the uptake [4,5]. For example in Canada while there was earlier adoption of HF WBI compared to the US [6–8], younger women continued to receive CF WBI at the discretion of the radiation oncologist at many centres [8]. Indeed, the 2011 ASTRO evidence-based guideline on fractionation for WBI permitted but did not endorse the use of HF WBI in women under 50 years of age [9,10].

The aim of this study was to investigate local control (LC) in women less than 50 years of age with pT1-2N0 breast cancer treated with HF WBI following BCS, as compared with CF WBI. Factors associated with the choice of CF versus HF were also elucidated.

* Corresponding author. FRCPC Princess Margaret Cancer Centre 610 University Ave Toronto, ON M5G 2M9, Canada.
E-mail address: anne.koch@rmp.uhn.ca (C.A. Koch).

https://doi.org/10.1016/j.breast.2018.07.002
0960-9776/

2. Methods

2.1. Study population

he institutional research ethics board approved the study. A retrospective cohort was established from a prospectively collected institutional database. The study period was between September 2009 and December 2013. Criteria for inclusion were as follows: women <50 years at the time of starting WBI, BCS, pathological stage T1-2N0 according to 7th edition TMN [11], either sentinel lymph node biopsy or axillary dissection, node negative (isolated tumor cells were permitted), invasive ductal, tubular or lobular carcinoma. Exclusion criteria included previous history of BC (ipsilateral or contralateral), neoadjuvant chemotherapy, mastectomy, bilateral BC, any other known malignancy or known BRCA1 or BRCA2 carriers at time of diagnosis.

Adjuvant WBI was delivered on weekdays by either HF (42.4 Gy in 16 fractions) or CF (50 Gy in 25 fractions). Both RT fractionation schedules were permitted as per institutional guidelines and were at the discretion of the treating radiation oncologist. In the majority of patients a sequential boost to the tumor bed of 10–16 Gy in 5–8 fractions followed WBI, as per group policy for women <50 years of age. Diagnostic and pathological information, radiotherapy details, information on systemic therapy, date of last follow-up visit and most recent diagnostic imaging were collected from the patient's electronic patient record.

The length of follow-up was calculated from the date of diagnosis (initial diagnostic biopsy or if unavailable date of BCS) to the date of the most recent imaging or clinical review in which disease status was recorded. The final margin status for both invasive carcinoma and ductal carcinoma in situ (DCIS) was recorded as positive (tumor on inked margin), <2 mm or $\geq$ 2 mm [12].

2.2. Outcome measures

The primary outcome was any local recurrence (LR) of invasive or in situ carcinoma anywhere in the treated breast. The date of LR was based on histological confirmation in all patients. Secondary outcomes included regional (RR) or distant recurrences (DR) or development of a contralateral BC.

2.3. Statistical analyses

Patient characteristics were compared using a *t*-test for continuous variables and chi-square test for discrete covariates where appropriate. Kaplan-Meier analysis was used to estimate the 5-year local, regional, and distant control rates and development of contralateral BC. Binary logistic regression was used to investigate factors associated with choice of fractionation schedule. Univariate analysis investigated the impact of age (>40 vs. $\leq$ 40), triple negative breast cancer (TNBC), tumor size, grade, lymphovascular invasion (LVI) and year of treatment on the choice of fractionation schedule. Factors that were found to be significant on univariate analysis were investigated on multivariate analysis. Statistical analyses were carried out using SAS 9.4 (SAS Institute, Carey, NC, USA) and R 3.1.2.

3. Results

3.1. Patient characteristics

Two hundred and seventy eligible women treated with adjuvant WBI following BCS were analyzed, 227/270 (84%) and 43/270 (16%) received HF and CF WBI respectively. The median age for the whole cohort was 44 years (range: 19–49); 45 (30–49) and 40 (19–49) in the HF and CF group, respectively ($p < 0.01$). Median follow-up was 5.2 years (range 0.3–8.4) for all patients, 5.1 years (0.3–8.3) in HF group and 5.9 years (0.7–8.4) in CF group. The clinical and pathological characteristics were similar across both groups, apart from age and triple negative receptor status (Table 1).

Most patients (94%) had invasive ductal carcinoma, 34% had grade 3 disease, 16% had LVI, 89% had estrogen-receptor (ER) positive disease and 8% of patients had TNBC. Of the 239 with ER positive tumors, 225 (94%) received endocrine therapy. Over half of

Table 1
Patient, tumor and treatment characteristics in the hypofractionation (HF) and conventional fractionation (CF) groups.

Characteristic	Hypofractionation (n = 227)	Conventional fractionation (n = 43)	p value
Median age, range (years)	45 (30–49)	40 (19–49)	<0.01
Histology			
IDC	211 (93%)	43 (100%)	0.656
ILC	8 (3.5%)	–	
Others (IMC, tubular, solid papillary carcinoma)	8 (3.5%)	–	
Multifocal			
Yes	31 (13.5%)	5 (12%)	0.209
No	195 (86%)	37 (86%)	
Unknown	1 (0.5%)	1 (2%)	
Mixed invasive/in situ carcinoma			
Yes	166 (73%)	33 (77%)	0.1713
No	61 (27%)	10 (23%)	
Median tumor size, range (cm)	1.7 (0.09–5)	1.6 (0.4–4)	0.626
Grade			
1	53 (23%)	6 (14%)	0.121
2	99 (44%)	17 (40%)	
3	74 (32.5%)	19 (44%)	
Unknown	1 (0.5%)	1 (2%)	
LVI			
Yes	36 (16%)	7 (16%)	0.653
No	175 (77%)	32 (74%)	
Unknown	16 (7%)	4 (10%)	
Estrogen receptor			
+	203 (89%)	36 (84%)	0.204
–	24 (11%)	7 (16%)	
Progesterone receptor			
+	191 (84%)	32 (74%)	0.085
–	35 (15.5%)	11 (26%)	
Unknown	1 (0.5%)		
HER2/neu			
+	32 (14%)	6 (14%)	1.00
–	192 (85%)	36 (84%)	
Unknown	3 (1%)	1 (2%)	
TNBC	15 (7%)	7 (16%)	0.034
Adjuvant chemotherapy			
Yes	117 (51.5%)	28 (65%)	0.072
No	110 (48.5%)	15 (35%)	
Boost			
10/5	221 (97.5%)	41 (95%)	0.219
12.5/5	1 (0.5%)	0	
16/8	3 (1%)	0	
No boost	2 (1%)	2 (5%)	
Invasive final margin			
Positive	4 (2%)	1 (2.5%)	0.193
<2 mm	45 (19%)	4 (9%)	
≥2 mm	172 (76%)	37 (86%)	
Unknown	6 (3%)	1 (2.5%)	
DCIS final margin			
Positive	9 (4%)	0 (0%)	0.558
<2 mm	29 (13%)	5 (12%)	
≥2 mm	118 (52%)	24 (56%)	
Unknown	10 (4%)	4 (9%)	
N/A	61 (27%)	10 (23%)	

Abbreviations: IMC = invasive mammary carcinoma, LVI = lymphovascular invasion, TNBC = triple negative breast cancer, DCIS = ductal carcinoma in situ, N/A = not applicable.