Ductal carcinoma in situ (DCIS) breast cancer treated with 3-week accelerated hypofractionated whole-breast radiation therapy and concomitant boost

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Received: 3 October 2018 / Accepted: 9 January 2019 / Published online: 26 January 2019
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Abstract

Introduction In patients with ductal carcinoma in situ (DCIS), the clinical outcomes with hypofractionated (HF) whole-breast radiation (WBRT), as well as the role of lumpectomy boost, continue to be evaluated. In this paper, we report our experience on DCIS patients treated with HF WBRT with concomitant boost (CB).

Methods Early-stage (DCIS, stages I and II) breast cancer patients were treated on an IRB-approved prospective single-arm study with HF WBRT and CB. This study includes only the DCIS subset of patients prescribed a dose of 40.5 Gy × 2.7 Gy per fraction to WB with CB of 4.5 Gy × 0.3G y per fraction over 15 fractions. A total of 107 breasts in 104 patients met the study criteria.

Results All patients underwent lumpectomy with negative margins. Median age was 59 years. DCIS nuclear grade distribution was 9.3% grade 1, 50.5% grade 2, and 37.4% grade 3. Majority (86%) were ER positive. 41.1% received endocrine therapy. With median follow-up of 74 months (range, 12–158), 5-year actuarial overall survival was 97.2%. At the time of this report, no patient has experienced local relapse. The CTCAE grades 1 and 2 acute skin toxicity was 66.4% and 3.7%, respectively. No patients experienced grade 3 or higher skin toxicity, breast pain, and fatigue.

Conclusion The HF schedule with CB in DCIS patients is well tolerated and associated with excellent clinical outcomes. This schedule affords the benefit of delivering higher dose to the lumpectomy site without protracting overall treatment time.

Keywords Accelerated radiation · Hypofractionated radiation · Concomitant boost · Breast cancer · Whole-breast irradiation · Ductal carcinoma in situ (DCIS)

Introduction

Breast-conserving surgery followed by whole-breast radiation therapy (WBRT) is the preferred treatment option for early-stage breast cancer [1, 2]. Results from several randomized trials that primarily included invasive breast cancer, compared accelerated hypofractionated (HF), and conventional fractionation (CF) 6–7-week course of breast

radiation [3–7]. Reported outcomes note that both HF and CF schedules have comparable therapeutic efficacy and are well tolerated. The inclusion of DCIS patients in these studies was limited, and clinical experience with HF schedules in the treatment of DCIS continues to be evaluated [8–10].

Randomized data also illustrate better local control with lumpectomy cavity boost in addition to WBRT in

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the treatment of early-stage invasive breast cancer [11]. However, there is no level I evidence that helps establish the role of boost in patients with DCIS. A recent retrospective study [12] of 4131 DCIS patients treated with WBRT using either CF or HF radiation schedule, with or without boost, reported statistically significant differences with improved local control when boost to the lumpectomy site was delivered.

Lumpectomy bed boost when prescribed with HF breast radiation schedules is most often delivered sequentially, thus adding to the length of treatment duration. On the other hand, a concomitant boost (CB) to the lumpectomy bed with HF schedules has the added benefit of delivering a tailored differential dose within target without extending treatment duration. In this paper, we report our experience in patients diagnosed with DCIS that underwent breast-conserving surgery and received accelerated HF breast radiation with a CB.

Patients and methods

We completed an IRB-approved single-arm prospective study evaluating the feasibility and toxicity of accelerated HF breast radiation with a CB in patients with early-stage (DCIS, stages I and II) breast cancer [13]. In this paper, we sought to evaluate the clinical outcomes including acute side effects and locoregional failure in patients diagnosed with DCIS who were treated with 3-week accelerated HF WBRT with a CB. The radiation schedule delivered a dose of 40.5 Gy in 2.7 Gy fractions to the whole breast, and a CB of 4.5 Gy in 0.3 Gy per fraction. Accordingly, a total dose of 45 Gy was delivered to the lumpectomy volume and 40.5 Gy to the whole breast over 15 fractions. The details of the radiation therapy schedule, treatment planning, and dosimetry have been described in a prior publication [13].

A total of 107 breasts in 104 patients, 3 having bilateral DCIS, are the subjects of this analysis. Table 1 summarizes the patient characteristics. The distribution of nuclear grade notes that majority patients had grade 2, and 37.4% had nuclear grade 3. The ER status was known for 95.3% of patients. Among those patients, 90.2% were estrogen receptor positive. 41.1% of patients received endocrine therapy.

For clinical assessment, patients were examined weekly during treatment, and then 1 week and 8 weeks after therapy to score the acute toxicity as per the National Cancer Institute/Common Terminology Criteria for Adverse Events (CTCAE). The highest acute toxicity score observed was recorded. All patients were followed at scheduled intervals by the multidisciplinary physician team. Ipsilateral mammogram every 6 months for the first 2 years, followed by annual imaging thereafter, was obtained. Documentation of recurrence required biopsy confirmation.

Table 1 Patient characteristics

Median age in years (range)	59 years (37 years–85 years)
DCIS nuclear grade	
1	10 patients
2	54 patients
3	40 patients
Unknown	3 patients
ER receptor status	
Negative	10 patients
Positive	92 patients
Unknown	5 patients
PR receptor status	
Negative	20 patients
Positive	81 patients
Unknown	6 patients
Endocrine therapy	
Yes	44 patients
No	54 patients
Unknown	9 patients

ER, estrogen receptor; PR, progesterone receptor

Statistical considerations

Follow-up time was calculated from the date of diagnosis to the most recent electronic medical record entry or death for each patient. A minimum period of 12 months of follow-up was required for analysis. Kaplan-Meier overall survival analysis was performed using the follow-up time. Statistical analysis was performed using SPSS, version 22 (IBM Corp, Armonk, NY).

Results

Patients underwent breast-conserving surgery with documented negative margins of resection (≥ 2 mm). All patients completed the prescribed radiation treatment regimen described above. The median follow-up is 74 months (range, 12–158 months). The 5-year actuarial survival is 97.2% (Fig. 1). At the time of this report, all patients remain without evidence of local breast cancer recurrence at last follow-up.

The CTCAE toxicity observed weekly during treatment, and then at 1 week and 8 weeks after therapy, was noted. The incidence of acute skin toxicity observed was as follows: grade 0 in 29.9%, grade 1 in 66.4%, grade 2 in 3.7%. No patients experienced grade 3 or 4 CTCAE skin toxicity, treatment-related breast pain, hematologic toxicity, and fatigue.

Fig. 1 Kaplan-Meier survival curve

Discussion

The reduced treatment time in a HF schedule results in less disruption to the patients' lives and reduces health-care costs, thus promoting high-value medical care [14–16]. Despite growing evidence in favor of HF, studies note that the CF radiation schedule is still the most commonly prescribed schedule for patients with DCIS in the USA [17, 18]. The role of boost in the treatment of DCIS is variably supported: ASTRO guidelines provide a “conditional” recommendation based on moderate evidence that a tumor bed boost be used for DCIS patients who are less than or equal to 50 years old, high grade, or with close (< 2 mm) or positive margins [16]. Further, the role of boost for patients diagnosed with DCIS is being studied in ongoing randomized trials [19, 20]. Retrospective data support improved local control rates in DCIS patients when boost was delivered in addition to WBRT [12].

Moran et al. [12] reported a study on 4131 patients with DCIS. In this study, patients were treated either with CF or HF schedules and with or without sequential boost. The analysis compared outcomes among the patients receiving boost versus no boost. At follow-up intervals of 5 years, 10 years, and 15 years, the study noted significantly lower ipsilateral breast local recurrence rates in the patients receiving boost radiation. The estimated absolute benefit of boost was reported as 3.6% at 15 years (HR, 0.70; 95% CI, 0.54–0.92) [12].

Similar to our study, there are few data published on the treatment of DCIS with HF radiation and CB [8–10]. Cante et al. [10] reported on 104 patients with DCIS treated with

45 Gy $\times$ 20 fractions with a daily CB of 0.25 Gy per fraction. At a median follow-up of 48 months, they reported excellent local control with no local recurrence observed. Guenzi et al. [8] reported their experience on 113 patients with DCIS that were treated using HF regimens with a dose-adjusted concomitant boost to surgical margins: One HF schedule delivered 46 Gy in 20 fractions, and the second HF schedule delivered 39 Gy in 13 fractions. With a median follow-up of 30.5 months, they observed one local recurrence. Ciervide et al. [9] published their experience on 86 patients with DCIS treated on HF schedule of 40.5 Gy in 15 fractions and a daily CB of 0.5 Gy per fraction. At a median follow-up of 60 months, they observed 3 local recurrences. Relative to these reports, our study has the longest median of 74 months and supports the favorable outcomes when treating DCIS patients with HF and CB. Comparable to other published data, we also observed low rates of early skin toxicity (Table 2). It is noteworthy that in most studies delivering concomitant boost, the total boost dose per fraction to the lumpectomy is additive to the whole-breast dose per fraction. Hence, in these studies including our own, the concomitant boost dose ranges from 4.5 to 7.5 Gy. This is in contrast to a sequential boost where the dose generally ranges from 10 to 16 Gy delivered in 2 Gy fractions, and the dose to the lumpectomy volume is delivered after the dose to the whole breast [19, 20].

The long natural history of DCIS with expected late local breast relapses warrants long-term follow-up of alternative radiation schedules. There are two randomized trials ongoing that will evaluate the role and optimal schedule of boost in patients with DCIS. In the French BONBIS trial, the radiation

Table 2 Comparison of results from prospective studies of patients with DCIS treated with hypofractionated RT with a concomitant boost

Study	<i>n</i>	Median age (years)	DCIS nuclear grade 1/2/3 (%)	ER + (%)	Endocrine therapy (%)	Median follow-up (months)	# recurrences	Early skin toxicity grade 0/1/2/3/4 (%)
Ciervide et al. 2012 [9]	86 ^a	56.4	18/35/46	63	43	38.87	3 ^a	Not available
Guenzi et al. 2013 [8]	113 ^b	67 ^b	21.2/59.3/19.5 ^b	81.4 ^b	9.7 ^b	30.5 ^b	1 ^b	Fractionation scheme 1: 34.1/56.1/9.8/0/0 Fractionation scheme 2: 68.1/31.9/0/0/0
Cante et al. 2014 [10]	103	62.1 (mean)	23/48/25	83	14	48	0	35/54/9/2/0
Berlin et al. (current study)	107	59	9.3/50.5/37.4	86	41.1	74	0	29.9/66.4/3.7/0/0

^a Results specific to the “boost” group of this study, total *n* of 145, with *n* of 86 in boost group

^b Authors reported two different HF schedules both with CB. Values correspond to overall *n* of 113 patients from both HF schedules

protocol is 50 Gy to the WB, with and without a sequential boost dose of 16 Gy [19]. The anticipated completion date of the study is 2029. The Australian TROG 07.01 trial includes 4 arms: a HF “shorter” schedule (16 fractions to 42.5 Gy) and a CF schedule (25 fractions to 50 Gy), each with and without a sequential boost dose of 10Gy [20]. This study is expected to complete in 2024. While data from level I evidence is awaited, observations to date from single-arm studies suggest that HF and CB are well tolerated and effective for treatment of DCIS with the added benefit of shorter overall treatment time.

Conclusions

Hypofractionated radiation schedules are rapidly being adopted as standard of care for treatment of invasive breast cancer. There is accumulating body of data that suggest favorable outcomes of HF with CB for the treatment of patients with DCIS. This schedule is both well tolerated and delivered in a manner that does not protract overall treatment time. Randomized trials evaluating the benefit of boost for patients with DCIS are ongoing and results are slated for release several years from now [19, 20].

Compliance with ethical standards

Funding No funding was received for this study.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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