Radiotherapy and Oncology 123 (2017) 10–14

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

The effect of post-mastectomy radiation in women with one to three positive nodes enrolled on the control arm of BCIRG-005 at ten year follow-up

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ARTICLE INFO

Article history:
Received 10 November 2016
Received in revised form 25 February 2017
Accepted 1 March 2017
Available online 22 March 2017

Keywords:
Radiation therapy
1–3 positive nodes
Breast cancer
Mastectomy

ABSTRACT

Background and purpose: We evaluated the effect of post-mastectomy radiation (PMRT) in 1–3 positive lymph nodes (LN) in patients who received uniform modern systemic therapy.
Materials and methods: Cohort study using individual data collected for 1,649 node-positive women who received doxorubicin/cyclophosphamide with sequential docetaxel in 2000–2003 on the control arm of BCIRG-005. All women underwent mastectomy or lumpectomy and axillary LN dissection. PMRT was given at investigator's discretion.
Results: A total of 523 women with 1–3 positive LN underwent mastectomy and 39% (206/523) received PMRT. With a median follow-up of 10 years, PMRT improved loco-regional control (LRC) from 91% to 98% ($p = 0.001$) but had no effect on overall survival (OS) (84% vs. 86%, $p = 0.9$). On multivariate analysis, PMRT improved local control (LC) (hazard ratio, 0.14; 95% CI, 0.03–0.62; $p = 0.01$) and LRC (hazard ratio, 0.15; 95% CI, 0.04–0.50; $p = 0.002$). PMRT did not significantly impact OS on multivariate analysis (hazard ratio, 0.91; 95% CI, 0.55–1.51; $p = 0.7$). Results remained consistent with the use of propensity score analysis.
Conclusions: In this cohort of patients with N1 disease treated with modern systemic therapy, PMRT improves LRC but has no effect on OS. The rates of OS were excellent, irrespective of adjuvant radiation.
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The role of post-mastectomy radiation (PMRT) in women with one to three positive lymph nodes in the setting of modern systemic therapy is controversial. A meta-analysis of clinical trials performed in 1964–1986 demonstrated that PMRT reduced 10-year local regional failure (20% vs. 4%) and 20-year breast cancer mortality (50% vs. 42%) in women with one to three positive nodes [1]. However, the applicability of these findings to the current era is questionable given the inconsistent use of hormonal therapy, the small number of patients who received anthracycline-containing regimens, and the lack of taxane-based chemotherapy during the era in which these trials were conducted.

Indeed, more recent single-institution series have reported excellent outcomes in patients treated in 1990–2007 with 1–3 positive nodes who do not receive PMRT [2–5]. The patients included in these studies typically received both a more consistent use of hormone therapy and chemotherapy that was generally doxorubicin- or taxane-based. At a median follow-up of 6–7 years, these studies reported very low 5–10 year local regional recurrence rates of approximately 5%.

The recently published PMRT consensus guideline update discusses that PMRT unambiguously reduces the risk of LRF and breast cancer mortality for patients with T1–2 breast cancer and one to three positive LN. However, the panel recognizes that "some subsets of these patients are likely to have such a low risk of LRF that the absolute benefit of PMRT is outweighed by its potential toxicities [6]." This subset is likely to include those patients who receive modern systemic therapy which has led to significant improvements in local regional control. Therefore, in our study, we evaluated the effect of radiation therapy in a cohort of node positive women who received uniform combination anthracycline- and taxane based chemotherapy in an era of modern surgical and radiation techniques at a long-term follow up of 10 years.

Materials and methods

We analyzed individual patient data of 1649 women treated on the control arm of BCIRG-005 (accrual 2000–2003) with doxorubicin/cyclophosphamide and sequential docetaxel (AC>T) collected

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http://dx.doi.org/10.1016/j.radonc.2017.03.001
0167-8140/

from Project Data Sphere®. BCIRG-005 is an international, multicenter, phase III study that randomized women to concomitant docetaxel (TAC) vs sequential docetaxel (AC>T) [7].

Patient eligibility for BCIRG-005 included women ages 18–70 with a Karnofsky performance status of ≥80% and with operable, histologically confirmed, invasive adenocarcinoma of the breast (T1–3, clinically N0-1, M0) without HER2 amplification. Patients were required to have mastectomy or breast-conserving surgery with negative margins. Patients received axillary lymph node dissection with a minimum of 6 lymph nodes removed and at least one axillary lymph node involved with disease. For those patients who underwent a mastectomy, adjuvant radiation was given at investigator's discretion.

Adjuvant hormonal therapy with tamoxifen or aromatase inhibitor was given to patients with hormone positive disease. Patients on the control arm received AC>T with doxorubicin 60 mg/m^2 as an intravenous (IV) bolus and cyclophosphamide 600 mg/m^2 IV on day 1 every 3 weeks for four cycles, followed by four cycles of docetaxel 100 mg/m^2 IV every 3 weeks. Patients were subsequently observed for relapse and survival every 3 months for the first 2 years, every 6 months for years 3–5, and then annually for years 6–10.

For this cohort analysis, we selected women who underwent mastectomy and who were found to have one to three positive nodes on pathology. Primary outcomes analyzed included local control (LC), loco-regional control (LRC), distant metastasis (DM), and overall survival (OS). LC is defined as freedom from isolated local failure which includes the scar, ipsilateral breast, ipsilateral anterior chest wall, and skin or soft tissue within the local area. LRC is defined as freedom from isolated local regional failure which included local failures and the ipsilateral axillary lymph node, ipsilateral supraclavicular nodes, ipsilateral internal mammary lymph node, ipsilateral infraclavicular lymph node, and skin or soft tissue within the regional area. Of note, the original dataset classified supraclavicular failures as distant metastasis and were therefore reclassified to regional failures for these analyses. Endpoints were measured from the date of random assignment. Statistical analysis of categorical data was performed with X^2 test. Survival curves were plotted using the Kaplan–Meier method, and survival analysis was completed using log-rank test and Cox proportional hazards model using SPSS statistical software. Covariates included the use of radiation therapy, age, grade, number of positive nodes, T stage, and estrogen receptor status. A propensity score match was performed using the "nearest-neighbor" method found within the *MatchIt* package available in R [8]. A two-sided test of less than 0.05 was regarded as significant.

Results

Among the 1649 patients treated in the control arm of BCIRG-005, 955 women underwent mastectomy and 523 women had one to three positive lymph nodes. The eligible patients included in this analysis (n = 523) had a median follow up of 10 years (IQR: 5.9–10.8 years). Among the women with one to three positive lymph nodes, 39% patients (206/523) received PMRT. Among those who received PMRT, 71% (146/206) received nodal irradiation with a supraclavicular field, and 27% (56/206) received irradiation to ipsilateral internal mammary nodes. Table 1 shows baseline characteristics. Women receiving PMRT were significantly younger, were more likely to have three positive lymph nodes, and had more advanced T stage than patients who did not receive PMRT.

PMRT significantly improved 10-year LC (99% vs. 94%, log rank p = 0.006) when compared with patients who did not receive PMRT (Fig. 1). Advanced T stage (T3 vs. T1–2), number of lymph nodes involved (2–3 vs. 1), age (<40 vs. ≥40), estrogen receptor status, and grade (poorly differentiated vs. moderately and well differentiated) were not predictive of LC on log-rank test. In multivariate models, PMRT was the only prognostic factor significantly associated with improved LC (hazard ratio, 0.14; 95% CI, 0.03–0.62; p = 0.01).

Table 1
Patient and disease baseline characteristics.

	PMRT (n = 206) n (%)	No PMRT (n = 317) n (%)	X2 test
Age			0.023
<40	40 (19)	37 (12)	
≥40	166 (81)	280 (88)	
Premenopause	116 (56)	176 (56)	0.8
Grade			0.8
Well Diff	19 (9)	20 (6)	
Mod Diff	103 (50)	140 (44)	
Poorly Diff	71 (34)	97 (31)	
Unknown	13 (6)	60 (19)	
# LNs positive			0.019
1	81 (39)	161 (51)	
2	77 (37)	108 (34)	
3	48 (23)	48 (15)	
LN involved			0.07
>20%	47 (23)	51 (16)	
T stage			<0.001
T1	60 (29)	130 (41)	
T2	115 (56)	176 (56)	
T3	30 (15)	11 (3)	
ER			0.06
Positive	163 (79)	228 (72)	
Negative	42 (20)	89 (28)	
PR			0.4
Positive	139 (67)	203 (64)	
Negative	60 (29)	107 (34)	

PMRT significantly improved 10-year LRC (98% vs. 91%, log rank p = 0.001) which was consistent on MVA (hazard ratio, 0.15, 95% CI 0.04–0.50; p = 0.002) (Fig. 2). Age ≤ 40 (hazard ratio, 0.36; 95% CI, 0.15–0.89; p = 0.03) was also significantly associated with LRC on MVA. These results remained consistent when chest wall only PMRT was excluded in this comparison. With exclusion of chest wall only PMRT, the 10-year LRC for PMRT vs. no PMRT was 99% vs 91% (log rank p = 0.002), which was consistent on MVA (hazard ratio, 0.07; 95% CI 0.01–0.53, p = 0.01). Of note, the number of lymph nodes involved, the number of lymph nodes sampled, and radiation field (SCV and IMN vs. chest wall alone) were not significantly associated with local regional failure.

PMRT had no statistically significant impact on 10-year DM (20% vs. 17%, log rank p = 0.7) or OS (86% vs. 84%, log rank p = 0.9) when compared with patients who did not receive PMRT on log-rank test or multivariate analysis (Fig. 3). Predictors of DM on univariate analysis included estrogen receptor negative tumors, age ≤ 40, and poorly differentiated histology. Age ≤ 40 remained significantly associated with DM on multivariate analysis (hazard ratio, 0.31; 95% CI, 0.19–0.50; p < 0.001). PMRT had no effect on 10-year OS (86% vs. 84%, log rank p = 0.9). Predictors of OS on univariate analysis included estrogen receptor negative tumors, age ≤ 40, poorly differentiated histology, and T stage. Age (hazard ratio, 0.38; 95% CI, 0.22–0.64; p < 0.001) and high grade (hazard ratio, 0.56; 95% CI, 0.34–0.95; p = 0.03) remained significant on multivariate analysis.

A 1:1 propensity score matched cohort was created and all patients with T3 disease were excluded to control for unbalanced clinical characteristics which included T stage, age (<40 years old), and number of positive lymph nodes. In matched patients, PMRT (n = 175) showed a benefit in 10-year LC (99% vs. 93%, log-rank p = 0.003) and 10-year LRC (96% vs 91%, log-rank p = 0.035) when compared with patients who did not receive PMRT