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A national multicenter study on 1 072 DCIS patients treated with breast-conserving surgery and whole breast radiotherapy (COBCG-01 study)

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Abstract

Background and purpose. Breast-conserving surgery (BCS) and whole breast radiation (RT) with or without endocrine therapy (ET) represent the standard of care for ductal carcinoma in situ (DCIS). The use of adjuvant treatments after surgery is still controversial in this setting. We performed a retrospective multicenter analysis on a series of DCIS patients treated with BCS and adjuvant RT.

Materials and methods. We collected clinical data from nine Italian centers on 1 072 women having a diagnosis of DCIS and treated between 1997 and 2012. We reported on the 5- and 10-year local recurrence (LR) rates, overall survival, and breast cancer specific survival (BCSS) employing the Kaplan-Meier method.

Results. At a median follow-up of 8.4 years, 67 LR (6.3%) and 47 deaths (4.4%) were observed. LR rates at 5 and 10 years were 3.4% and 7.6%, respectively. BCSS rates at 5 and 10 years were 99.7% and 99.1%, respectively. At univariate regression analysis, postmenopausal state (p=0.009), estrogen receptor (ER) (p=0.0001) and progesterone receptor (p=0.018) positivity and ET (p=0.006) were inversely correlated with LR. Final surgical margins (FSM) status <1 mm was significantly correlated with higher LR (p=0.003). At multivariate regression analysis postmenopausal state (p=0.03), and ER positive (p=0.045) maintained the significant favorable feature, while FSM <1 mm (p=0.024) confirmed its negative impact on LR.

Conclusions. Our real-life study pointed out the significant favorable prognostic role of postmenopausal state and ER positive status on LR occurrence. FSM <1 mm was significantly correlated to a higher chance to experience LR.

Keywords. Ductal carcinoma in situ; breast cancer; radiotherapy; multicenter study; prognostic factors.

Introduction

Breast-conserving surgery (BCS) and postoperative whole breast radiotherapy (RT) with or without endocrine therapy (ET) still represent the standard treatment for most ductal carcinomas in situ (DCIS) [1-3].

Generally, RT can halve the risk of local recurrence, compared to BCS only, preventing both ipsilateral in situ and invasive relapse, without a clear benefit in terms of overall survival [4].

The ideal allocation of adjuvant treatments after surgery for DCIS is still controversial, since a consistent and reliable definition of risk categories is still lacking [5,6]. Therefore, tailoring treatment to specific patient's needs, avoiding over- and under-treatment, is still an open issue [7].

While the benefit of ET on DCIS outcome is more controversial [3,8], recently published large studies confirmed the strong evidence in favor of routine postoperative RT after BCS, also considering that omitting radiation seems not to provide a higher breast preservation rate in case of local recurrence (LR) [9,10].

We performed a real-life multicenter national retrospective analysis on a large series of DCIS patients treated with BCS and adjuvant RT at tertiary referral hospitals in Italy, aiming at identifying reliable predictive and prognostic factors.

Materials and methods

Patients

We collected data from nine Italian centers on 1 072 women having a diagnosis of DCIS, treated between 1997 and 2012 with BCS and postoperative RT. Adjuvant ET administration, RT fractionation, and delivery of a boost dose to the tumor bed followed the policy of each Institution.

One center enrolled more than 200 cases (University of Florence), five centers accrued between 100 and 200 patients (Brescia University and Spedali Civili, University Hospital of Modena, Humanitas Cancer Center and Research Hospital, National Cancer Institute of Milan, University of Perugia), and three centers included less than 100 cases (Azienda USL Toscana Centro, University of Turin, Sacro Cuore Don Calabria Hospital).

Radiotherapy schedules (whole breast, tumor bed boost) are summarized in *Table 1*. Hypofractionation regimens were adopted as follow: 42.5 Gy in 16 fractions (University of Perugia, National Cancer Institute of Milan), 44 Gy in 16 fractions (University of Florence, Brescia University and Spedali Civili).

Clinical observation was mostly based on a 6-month clinical examination (years 1 to 5), that became yearly for years 5 to 10 of follow up), together with annual bilateral mammography, A minority of patients lost to clinical follow up within 10 years were contacted by phone, to update the vital status and disease control.

Pathology methods

All the specimens were evaluated by expert pathologists dedicated to breast cancer. Estrogen receptor (ER) status and progesterone receptor (PgR) status were assessed; the expression scores were based on the percentages of positive nuclei over the total number of cancer cell nuclei counted. For ER and PgR status, two categories (negative and positive) were considered according to a widely used 10% cut-off values (both ER and PgR) [11]. Positive hormonal status (HS) was defined as positive ER and/or PgR status. Breast cancer was classified according to the histological type and staged following the TNM classification of malignant tumors [12]. Histological tumor grading was assessed according to Elston and Ellis [13]. Final surgical margins (FSM) status was stratified as follow: ≥10 mm, 1 to 9 mm, and <1 mm (0 to 0.9 mm).

Statistical analysis

A descriptive analysis was performed to define the main individual characteristics of both patients and tumors. The survival analysis was carried out in relation to specific events, namely LR (total, DCIS, and invasive) or death (overall and breast cancer specific). We described the 5- and 10-year LR rates (both DCIS and invasive LR), overall survival (OS), and breast cancer specific survival (BCSS). The observation time was measured starting from the date of surgery to the date of LR observation, or date of death or the last follow-up for cases without events.

Survival estimates were calculated according to the Kaplan-Meier method at the end of the follow-up. Differences between groups were evaluated by the log-rank test. Cox proportional regression analysis was used to determine the role of selected parameters on the risk of event occurrence by univariate models, and then by multivariate models including parameters statistically significant at univariate analysis.

The risk of LR was calculated as hazard ratio (HR) with corresponding 95% confidence intervals (95% CI). P-values less than 0.05 were considered statistically significant. All statistical tests were performed using the IBM SPSS Statistics software (Statistical Package for Social Science, version 22).

Results

Patient characteristics

Most of the patients were aged more than 40 years (97.6%) and postmenopausal (72.8%). The median age within the series was 57.2 years (mean 57.7 ±10.0 years). Tumors were mainly sized less than 10 mm (64.3%) and low-grade (G1-2: 64.4%). Whole breast conventional fractionation (50 Gy in 25 fractions) was adopted in 886/1072 patients (82.6%), while hypofractionated RT schedules were used in 186/1072 patients (17.4%). Tumor bed RT boost was delivered in 290/1072 cases (27.1%). Among them 36/290 patients (12.4%) had FSM <1 mm (61% of patients with FSM <1 mm).

ER status was available in 695 cases, and PgR status was available in 694 cases. Among the 557 patients affected by positive HS disease, 279 (50.1%) received adjuvant ET. No data about ET discontinuation and compliance over the 5-year planned treatment was available. Main patient's characteristics are summarized in *Table 1*.

Outcomes

At a median follow-up of 8.4 years (range 4-20 years), 67 LR (6.3%) and 47 deaths (4.4%) were observed. A DCIS LR was observed in 25/67 patients (37.3%) and an invasive LR in 42/67 patients (62.7%). The LR rates according to age (<40, 40-60, >60 years) by Kaplan Meier analysis were 20.5%, 32.2%, and 22.8%, respectively (log rank test p=0.40). We recorded four subsequent distant metastases, all of them after invasive LR. Overall 11/47 deaths (23.4%) were related to BC. We recorded 36 contralateral breast cancers (3.4%). DCIS HS was known for 19 of them and was positive in 13/19 cases (4/13 received previous adjuvant ET).

Mean time to LR was 7 (SD±5) years (5.4 years and 8 years for DCIS and invasive LR, respectively). The LR rates at 5 and 10 years were 3.4% (95% CI 2.3-4.5) and 7.6% (95% CI 6.0-9.2), respectively. LR rate curves (all, DCIS, and invasive) are shown in *Figure 1A-C*.

The OS rates at 5 and 10 years were 98.5% and 97%, respectively; the BCSS rates at 5 and 10 years were 99.7% and 99.1%, respectively.

At univariate regression analysis, postmenopausal status (HR 0.52; 95% CI 0.32-0.85, p=0.009), ER positive status (HR 0.32; 95% CI 0.17-0.60, p=0.0001), PgR positive status (HR 0.46; 95% CI 0.25-0.88, p=0.018), and adjuvant ET (HR 0.39; 95% CI 0.20-0.77, p=0.006) were inversely correlated to LR risk. Conversely, FSM <1 mm on the definitive pathological specimen was directly correlated with LR risk (HR 3.25; 95% CI 1.49-7.08, p=0.003). Both hypofractionated RT (p=0.10) and tumor bed RT boost delivery (p=0.34) showed no significant impact on LR rate.

At multivariate regression analysis post-menopausal status (HR 0.40; 95% CI 0.18-0.92, p=0.03; *Figure 2*), and positive ER status (HR 0.35; 95% CI 0.13-0.98, p=0.045; *Figure 3*) confirmed their significant favorable effect on LR risk, while FSM <1 mm (HR 3.3; 95% CI 1.17-9.28, p=0.024; *Figure 4*) confirmed its negative impact on LR. Univariate and multivariate analyses results are summarized in *Table 2*.

Focusing on the impact of adjuvant ET among the HS positive group of patients (279 out of 557), no significant effect was observed in terms of all LR (p=0.34), DCIS LR (p=0.92), invasive LR (p=0.25), and OS (p=0.81).

No parameter statistically affected OS and BCSS rates (data not shown).

Discussion

Our experience represents one of the largest published national multicenter analyses on DCIS patients treated with BCS followed by postoperative radiation, with or without ET. Adjuvant RT after BCS led to a low rate of LR over time, below 8% at 10 years. This is a lower rate than that observed in the population-based Munich Cancer Registry, which described a cumulative incidence of ipsilateral in-breast tumor recurrence of 13.6% at 10 years [14], but similar to what reported in the SEER database (11%) [15], NSABP-B17 trial (8%) [1], or in the EORTC 10853 trial (8%) [16].

Interestingly, we observed a relatively high rate of invasive LR (over 60%), compared to the commonly reported rate of 50% [16,17]. We do not have any specific explanation for this finding, apart from observing that few series reported rates of invasive LR close to 60%, such as the MD Anderson Cancer Center series used to externally validate the Memorial Sloan Kettering Cancer Center nomogram for DCIS (57% rate of invasive recurrence) [18]. Other series reported an even higher invasive LR rate such as in Vidali et al (63%) [19], which is a retrospective analysis on a population treated in Italy, and in Shaitelman et al (76%) [20]. Main recently published studies on DCIS receiving postoperative whole breast radiotherapy [14,19,21-23] were reported in *Table 3*.

The assessment of FSM width could be affected by several biases: whole organ sectioning, radiological-pathological correlations of mastectomy specimens, technical limitations including excessive compression for specimen radiography, surface ink tracking deeper into specimen portions, tumor-to-ink distance on any slide not being representative of the entire specimen [24]. Therefore, the ideal FSM threshold is still strongly debated.

In our series the FSM status resulted as the most relevant predictive factor for LR, similarly to several published studies. The risk for LR was shown to be more than 3-time higher for patients with FSM <1 mm (HR 3.3; 95%CI 1.17-9.28, p=0.024). In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial [25], the annual rate for ipsilateral breast LR after surgery alone was 8.1% in patients with positive FSM compared to 3.3% in patients without, and it was reduced after whole breast RT to 2.7% and 1.2%, respectively.

Van Zee et al [26], found no difference in LR risk between ≤2 mm margins and wider resection in patients receiving whole breast RT. Conversely, a meta-analysis published in 2016 compared specific FSM width thresholds (2, 3, 5, and 10 mm) with negative margins (defined as >0 mm or 1 mm). The odds of LR and the 10-year probability of recurrences were much lower in case of the wider margins [27]. Indeed, the Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus guidelines on FSM for BCS treated with whole-breast RT in DCIS, recommend the use of a 2-mm margin as the standard for an adequate FSM, since it is associated with lower rates of LR and has the potential to decrease re-excision rates, to improve cosmetic outcomes, and to decrease health care costs [28].

However, clinical judgment should always determine which patients having negative margin would require re-excision. In carefully selected patients with close (< 2 mm) or focally/minimally involved margins, re-excision was avoided with satisfactory local control achieved by increasing the radiation dose to the tumor bed to at least 66 Gy [29].

The risk assessment for LR should include the following: residual calcifications on post-excision mammography, extent of DCIS close to the margin, cosmetic impact assessment, comorbidity, and overall patient expectation [1,30].

In our experience inadequate FSM confirmed its strong negative impact on LR rate, independently of the use of a RT boost to the tumor bed. However, no definitive conclusions on the RT boost role could be drawn from this study, since its use was heterogeneous and not strictly related to the FSM status. Indeed, it is well-known that tumor bed RT boost is able to reduce but not fully overcome the negative impact of an inadequate FSM status on LR rate [23,31-36].

Randomized data are upcoming, including the multicentric BONBIS French study to evaluate the impact of a localized 16 Gy boost after BCS [37], and the Australian-led Breast International Group (BIG) 03-07/Trans-Tasman Radiation Oncology Group (TROG) 07.01 phase III trial evaluating lumpectomy boost after whole-breast RT. The results of TROG trial will clarify also the role of hypofractionated RT in DCIS patients, a still debated issue. However, a meta-analysis of observational studies published in 2015 [38], showed the hypofractionation as a safe option for DCIS patients, and our analysis seems to confirm this data, despite our small sample size.

In a multicenter collaborative effort at three Canadian institutions (440 patients), excellent local control for DCIS undergoing BCS treated with hypofractionated RT using 42.5 Gy in 16 fractions was shown [39].

Moreover, Offersen and colleagues have recently the updated results of the DBCG HYPO trial [40], confirming the efficacy and safety of hypofractionation for DCIS treatment, with a low LR risk.

Adjuvant ET after BCS demonstrated a significant benefit only in selected patients and is not currently accepted as a standard of care for HS positive DCIS, due to the potential overtreatment and toxicity profile [3,8]. The UK/ANZ DCIS trial did not find a benefit in the use of tamoxifen in RT group [3], and in the NSABP B-24 protocol [8] tamoxifen was beneficial only in the subgroup of patients with positive margins (24%).

Almost half of our treated patients had positive HS, and around half of them received adjuvant ET. Although our results showed an independent protective role for postmenopausal status and positive ER status, the use of adjuvant ET seemed not to impact on patient survival outcomes. Thus, a positive HS disease seems to be an intrinsic biological protective factor. Indeed, it has been reported by several published experiences the possible negative impact on outcome of a negative HS [41-44], while older age and postmenopausal status seemed to be associated with better prognosis [45].

However, we have to take into account study limitations while interpreting our results, mainly related to the retrospective nature of the analysis. A median follow-up close to 8 years is probably too short to allow any definitive conclusions on impact of treatment on OS and BCSS. Moreover, we should consider the different practice among centers on the

application of hypofractionated schedule or boost to the tumor bed, the missing information about compliance/adherence for ET, and the so-called 'healthy user effect' which is a well-established source of sampling bias in observational studies dealing with early-stage breast cancer patients [46].

In conclusions, our study pointed out the significant favorable predictive role of the postmenopausal and positive ER status with respect to LR occurrence. FSM <1 mm was the most relevant independent risk factor for LR. Prospective data are needed to investigate the benefit of adjuvant therapy for DCIS and to better define a reliable risk-groups stratification. Undoubtedly, a strong cooperation with breast surgeons in a multidisciplinary setting is highly recommended.

Acknowledgments

Partial data presented on this paper have been presented as poster presentation at the 11th European Breast Cancer Conference (EBCC) Barcelona 2018 (cited as "Ductal carcinoma in situ treated with breast conservative surgery and radiotherapy: A national multicentre experience". DOI10.1016/S0959-8049(18)30392-7), and as selected oral communication at the 37th European SocieTy for Radiation Oncology (ESTRO) Congress Barcelona 2018 (cited as "E37-0113. Meattini I, Pasinetti N, Meduri B, et al. DCIS treated with breast conservative surgery and radiotherapy: a national multicentre experience"). We would like to acknowledge Livia Marrazzo (Medical Physics, Careggi University Hospital) for the English revision.

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Figure captions

Figure 1. LRFS Kaplan-Meier curves: all LR (**Figure 1A**), DCIS LR (**Figure 1B**), and invasive LR recurrence rates (**Figure 1C**).

Figure 2. LR recurrence rate curves comparing premenopausal (**dotted line**) to postmenopausal status (**solid line**; HR 0.40; 95% CI 0.18-0.92, p=0.03).

Figure 3. LR recurrence rate curves comparing estrogen receptor (ER) negative (**dotted line**) to ER positive status (**solid line**; HR 0.35; 95% CI 0.13-0.98, p=0.045).

Figure 4. LR recurrence rate curves stratified by final surgical margins (FSM) status: ≥10 mm (**dashed line**), 1 to 9 mm (**dotted line**), and <1 mm (**solid line**; HR 3.3; 95%CI 1.17-9.28, p=0.024).