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(Article begins on next page)

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

3

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31

32 **Abstract**

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

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

40 **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
41 years were 3.4% and 7.6%, respectively. BCSS rates at 5 and 10 years were 99.7% and 99.1%, respectively. At univariate
42 regression analysis, postmenopausal state ($p=0.009$), estrogen receptor (ER) ($p=0.0001$) and progesterone receptor
43 ($p=0.018$) positivity and ET ($p=0.006$) were inversely correlated with LR. Final surgical margins (FSM) status <1 mm
44 was significantly correlated with higher LR ($p=0.003$). At multivariate regression analysis postmenopausal state ($p=0.03$),
45 and ER positive ($p=0.045$) maintained the significant favorable feature, while FSM <1 mm ($p=0.024$) confirmed its
46 negative impact on LR.

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

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

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63 **Introduction**

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

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

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

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

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

76

77 **Materials and methods**

78 *Patients*

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

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

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

89 Clinical observation was mostly based on a 6-month clinical examination (years 1 to 5), that became yearly for years 5 to
90 10 of follow up), together with annual bilateral mammography, A minority of patients lost to clinical follow up within 10
91 years were contacted by phone, to update the vital status and disease control.

92

93 *Pathology methods*

94 All the specimens were evaluated by expert pathologists dedicated to breast cancer. Estrogen receptor (ER) status and
95 progesterone receptor (PgR) status were assessed; the expression scores were based on the percentages of positive nuclei
96 over the total number of cancer cell nuclei counted. For ER and PgR status, two categories (negative and positive) were
97 considered according to a widely used 10% cut-off values (both ER and PgR) [11]. Positive hormonal status (HS) was
98 defined as positive ER and/or PgR status. Breast cancer was classified according to the histological type and staged
99 following the TNM classification of malignant tumors [12]. Histological tumor grading was assessed according to Elston
100 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
101 mm).

102

103 *Statistical analysis*

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

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

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

116

117 **Results**

118 *Patient characteristics*

119 Most of the patients were aged more than 40 years (97.6%) and postmenopausal (72.8%). The median age within the
120 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-
121 2: 64.4%). Whole breast conventional fractionation (50 Gy in 25 fractions) was adopted in 886/1072 patients (82.6%),
122 while hypofractionated RT schedules were used in 186/1072 patients (17.4%). Tumor bed RT boost was delivered in
123 290/1072 cases (27.1%). Among them 36/290 patients (12.4%) had FSM < 1 mm (61% of patients with FSM < 1 mm).

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

127

128 *Outcomes*

129 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
130 was observed in 25/67 patients (37.3%) and an invasive LR in 42/67 patients (62.7%). The LR rates according to age
131 (<40, 40-60, >60 years) by Kaplan Meier analysis were 20.5%, 32.2%, and 22.8%, respectively (log rank test p=0.40).

132 We recorded four subsequent distant metastases, all of them after invasive LR. Overall 11/47 deaths (23.4%) were related
133 to BC. We recorded 36 contralateral breast cancers (3.4%). DCIS HS was known for 19 of them and was positive in 13/19
134 cases (4/13 received previous adjuvant ET).

135 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
136 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
137 invasive) are shown in *Figure 1A-C*.

138 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
139 99.1%, respectively.

140 At univariate regression analysis, postmenopausal status (HR 0.52; 95% CI 0.32-0.85, p=0.009), ER positive status (HR
141 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
142 0.39; 95% CI 0.20-0.77, p=0.006) were inversely correlated to LR risk. Conversely, FSM <1 mm on the definitive
143 pathological specimen was directly correlated with LR risk (HR 3.25; 95% CI 1.49-7.08, p=0.003). Both hypofractionated
144 RT (p=0.10) and tumor bed RT boost delivery (p=0.34) showed no significant impact on LR rate.

145 At multivariate regression analysis post-menopausal status (HR 0.40; 95% CI 0.18-0.92, p=0.03; *Figure 2*), and positive
146 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
147 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
148 multivariate analyses results are summarized in *Table 2*.

149 Focusing on the impact of adjuvant ET among the HS positive group of patients (279 out of 557), no significant effect
150 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).

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

152

153 **Discussion**

154 Our experience represents one of the largest published national multicenter analyses on DCIS patients treated with BCS
155 followed by postoperative radiation, with or without ET. Adjuvant RT after BCS led to a low rate of LR over time, below
156 8% at 10 years. This is a lower rate than that observed in the population-based Munich Cancer Registry, which described
157 a cumulative incidence of ipsilateral in-breast tumor recurrence of 13.6% at 10 years [14], but similar to what reported in
158 the SEER database (11%) [15], NSABP-B17 trial (8%) [1], or in the EORTC 10853 trial (8%) [16].

159 Interestingly, we observed a relatively high rate of invasive LR (over 60%), compared to the commonly reported rate of
160 50% [16,17]. We do not have any specific explanation for this finding, apart from observing that few series reported rates
161 of invasive LR close to 60%, such as the MD Anderson Cancer Center series used to externally validate the Memorial
162 Sloan Kettering Cancer Center nomogram for DCIS (57% rate of invasive recurrence) [18]. Other series reported an even
163 higher invasive LR rate such as in Vidali et al (63%) [19], which is a retrospective analysis on a population treated in
164 Italy, and in Shaitelman et al (76%) [20]. Main recently published studies on DCIS receiving postoperative whole breast
165 radiotherapy [14,19,21-23] were reported in *Table 3*.

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

170 In our series the FSM status resulted as the most relevant predictive factor for LR, similarly to several published studies.
171 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,
172 p=0.024). In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial [25], the annual rate for
173 ipsilateral breast LR after surgery alone was 8.1% in patients with positive FSM compared to 3.3% in patients without,
174 and it was reduced after whole breast RT to 2.7% and 1.2%, respectively.

175 Van Zee et al [26], found no difference in LR risk between ≤ 2 mm margins and wider resection in patients receiving
176 whole breast RT. Conversely, a meta-analysis published in 2016 compared specific FSM width thresholds (2, 3, 5, and
177 10 mm) with negative margins (defined as >0 mm or 1 mm). The odds of LR and the 10-year probability of recurrences
178 were much lower in case of the wider margins [27]. Indeed, the Society of Surgical Oncology-American Society for
179 Radiation Oncology-American Society of Clinical Oncology Consensus guidelines on FSM for BCS treated with whole-
180 breast RT in DCIS, recommend the use of a 2-mm margin as the standard for an adequate FSM, since it is associated with
181 lower rates of LR and has the potential to decrease re-excision rates, to improve cosmetic outcomes, and to decrease
182 health care costs [28].

183 However, clinical judgment should always determine which patients having negative margin would require re-excision.
184 In carefully selected patients with close (< 2 mm) or focally/minimally involved margins, re-excision was avoided with
185 satisfactory local control achieved by increasing the radiation dose to the tumor bed to at least 66 Gy [29].
186 The risk assessment for LR should include the following: residual calcifications on post-excision mammography, extent
187 of DCIS close to the margin, cosmetic impact assessment, comorbidity, and overall patient expectation [1,30].
188 In our experience inadequate FSM confirmed its strong negative impact on LR rate, independently of the use of a RT
189 boost to the tumor bed. However, no definitive conclusions on the RT boost role could be drawn from this study, since
190 its use was heterogeneous and not strictly related to the FSM status. Indeed, it is well-known that tumor bed RT boost is
191 able to reduce but not fully overcome the negative impact of an inadequate FSM status on LR rate [23,31-36].
192 Randomized data are upcoming, including the multicentric BONBIS French study to evaluate the impact of a localized
193 16 Gy boost after BCS [37], and the Australian-led Breast International Group (BIG) 03-07/Trans-Tasman Radiation
194 Oncology Group (TROG) 07.01 phase III trial evaluating lumpectomy boost after whole-breast RT. The results of TROG
195 trial will clarify also the role of hypofractionated RT in DCIS patients, a still debated issue. However, a meta-analysis of
196 observational studies published in 2015 [38], showed the hypofractionation as a safe option for DCIS patients, and our
197 analysis seems to confirm this data, despite our small sample size.
198 In a multicenter collaborative effort at three Canadian institutions (440 patients), excellent local control for DCIS
199 undergoing BCS treated with hypofractionated RT using 42.5 Gy in 16 fractions was shown [39].
200 Moreover, Offersen and colleagues have recently the updated results of the DBCG HYPO trial [40], confirming the
201 efficacy and safety of hypofractionation for DCIS treatment, with a low LR risk.
202 Adjuvant ET after BCS demonstrated a significant benefit only in selected patients and is not currently accepted as a
203 standard of care for HS positive DCIS, due to the potential overtreatment and toxicity profile [3,8]. The UK/ANZ DCIS
204 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
205 beneficial only in the subgroup of patients with positive margins (24%).
206 Almost half of our treated patients had positive HS, and around half of them received adjuvant ET. Although our results
207 showed an independent protective role for postmenopausal status and positive ER status, the use of adjuvant ET seemed
208 not to impact on patient survival outcomes. Thus, a positive HS disease seems to be an intrinsic biological protective
209 factor. Indeed, it has been reported by several published experiences the possible negative impact on outcome of a negative
210 HS [41-44], while older age and postmenopausal status seemed to be associated with better prognosis [45].
211 However, we have to take into account study limitations while interpreting our results, mainly related to the retrospective
212 nature of the analysis. A median follow-up close to 8 years is probably too short to allow any definitive conclusions on
213 impact of treatment on OS and BCSS. Moreover, we should consider the different practice among centers on the

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

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

221

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227 0113. Meattini I, Pasinetti N, Meduri B, et al. DCIS treated with breast conservative surgery and radiotherapy: a national
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230

231 **References**

232 [1]. Wapnir IL, Dignam JJ, Fisher B, Mamounas EP, Anderson SJ, Julian TB, et al. Long-term outcomes of invasive
233 ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J*
234 *Natl Cancer Inst* 2011;103:478–88.

235 [2]. EORTC Breast Cancer Cooperative Group; EORTC Radiotherapy Group, Bijker N, Meijnen P, Peterse JL,
236 Bogaerts J, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results
237 of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853d a study by the EORTC
238 Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *J Clin Oncol* 2006;24:3381–7.

239 [3]. Cuzick J, Sestak I, Pinder SE, Ellis IO, Forsyth S, Bundred NJ, et al. Effect of tamoxifen and radiotherapy in
240 women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. *Lancet Oncol*
241 2011;12:21–9.

242 [4]. Early Breast Cancer Trialists’ Collaborative Group (EBCTCG), Correa C, McGale P, Taylor C, Wang Y, Clarke
243 M, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst*
244 *Monogr* 2010;2010:162–77.

- 245 [5]. Silverstein MJ. The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ
246 of the breast. *Am J Surg* 2003;186:337-43.
- 247 [6]. Sagara Y, Freedman RA, Vaz-Luis I, Mallory MA, Wong SM, Aydogan F, et al. Patient Prognostic Score and
248 Associations With Survival Improvement Offered by Radiotherapy After Breast-Conserving Surgery for Ductal
249 Carcinoma In Situ: A Population-Based Longitudinal Cohort Study. *J Clin Oncol* 2016;34:1190-6.
- 250 [7]. Groen EJ, Elshof LE, Visser LL, Rutgers EJT, Winter-Warnars HAO, Lips EH, et al. Finding the balance
251 between over- and under-treatment of ductal carcinoma in situ (DCIS). *Breast* 2017;31:274-83.
- 252 [8]. Allred DC, Anderson SJ, Paik S, Wickerham DL, Nagtegaal ID, Swain SM, et al. Adjuvant tamoxifen reduces
253 subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP
254 protocol B-24. *J Clin Oncol* 2012;30:1268-73.
- 255 [9]. Barbour S, Moore J, Dunn N, Effeney R, Harden H, McCarthy A, et al. Patterns of care for ductal carcinoma in
256 situ of the breast: Queensland's experience over a decade. *Breast* 2017;35:169-76.
- 257 [10]. Rakovitch E, Nofech-Mozes S, Hanna W, Sutradhar R, Gu S, Fong C, et al. Omitting radiation therapy after
258 lumpectomy for pure DCIS does not reduce the risk of salvage mastectomy. *Breast* 2018;37:181-6.
- 259 [11]. Hammond ME, Hayes DF, Wolff AC, Mangu PB, Temin S. American Society of Clinical Oncology/College of
260 American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone
261 receptors in breast cancer. *J Oncol Pract* 2010;6:195-7.
- 262 [12]. Sobin L, Gospodarowicz M, Wittekind C, eds. *TNM Classification of Malignant Tumors*. 7th ed. Hoboken, NJ:
263 John Wiley and Sons; 2009.
- 264 [13]. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer: I. The value of histological grade in breast
265 cancer: experience from a large study with long-term follow-up. *Histopathology* 1991;19:403-10. *Histopathology*
266 2002;41:151-2, discussion 152-3.
- 267 [14]. Corradini S, Pazos M, Schönecker S, Reitz D, Niyazi M, Ganswindt U, et al. Role of postoperative radiotherapy
268 in reducing ipsilateral recurrence in DCIS: an observational study of 1048 cases. *Radiat Oncol* 2018;13:25.
- 269 [15]. Warren JL, Weaver DL, Bocklage T, Key CR, Platz CE, Cronin KA, et al. The frequency of ipsilateral second
270 tumors after breast-conserving surgery for DCIS: a population-based analysis. *Cancer* 2005;104:1840-8.
- 271 [16]. Donker M, Litière S, Werutsky G, Julien JP, Fentiman IS, Agresti R, et al. Breast-conserving treatment with or
272 without radiotherapy in ductal carcinoma In Situ: 15-year recurrence rates and outcome after a recurrence, from the
273 EORTC 10853 randomized phase III trial. *J Clin Oncol* 2013;31:4054-9.

- 274 [17]. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Correa C, McGale P, Taylor C, Wang Y, Clarke
275 M, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst*
276 *Monogr* 2010;2010:162-77.
- 277 [18]. Yi M, Meric-Bernstam F, Kuerer HM, Mittendorf EA, Bedrosian I, Lucci A, et al. Evaluation of a breast cancer
278 nomogram for predicting risk of ipsilateral breast tumor recurrences in patients with ductal carcinoma in situ after local
279 excision. *J Clin Oncol* 2012;30:600-7.
- 280 [19]. Vidali C, Caffo O, Aristei C, Bertoni F, Bonetta A, Guenzi M, et al. Conservative treatment of breast ductal
281 carcinoma in situ: results of an Italian multi-institutionalretrospective study. *Radiat Oncol* 2012;7:177.
- 282 [20]. Shaitelman SF, Wilkinson JB, Kestin LL, Ye H, Goldstein NS, Martinez AA, et al. Long-term outcome in
283 patients with ductal carcinoma in situ treated with breast-conserving therapy: implications for optimal follow-up
284 strategies. *Int J Radiat Oncol Biol Phys* 2012;83:e305-12.
- 285 [21]. Rakovitch E, Narod SA, Nofech-Moses S, Hanna W, Thiruchelvam D, Saskin R, et al. Impact of boost radiation
286 in the treatment of ductal carcinoma in situ: a population-basedanalysis. *Int J Radiat Oncol Biol Phys* 2013; 86:491-7.
- 287 [22]. Alvarado R, Lari SA, Roses RE, Smith BD, Yang W, Mittendorf EA, et al. Biology, treatment, and outcome in
288 very young and older women with DCIS. *Ann Surg Oncol* 2012;19:3777-84.
- 289 [23]. Cutuli B, Wiezzane N, Palumbo I, Barbieri P, Guenzi M, Huscher A, et al. Breast-conserving treatment for ductal
290 carcinoma in situ: Impact of boost and tamoxifen on localrecurrences. *Cancer Radiother* 2016;20:292-8.
- 291 [24]. Faverly DR, Burgers L, Bult P, Holland R. Three dimensional imaging of mammary ductal carcinoma in situ:
292 clinical implications. *Semin Diagn Pathol* 1994;11:193-8.
- 293 [25]. Fisher ER, Costantino J, Fisher B, Palekar AS, Redmond C, Mamounas E. Pathologic findings from the National
294 Surgical Adjuvant Breast Project (NSABP) Protocol B-17. Intraductal carcinoma (ductal carcinoma in situ). The National
295 Surgical Adjuvant Breast and Bowel Project Collaborating Investigators. *Cancer* 1995;75:1310-9.
- 296 [26]. Van Zee KJ, Subhedar P, Olcese C, Patil S, Morrow M. Relationship Between Margin Width and Recurrence of
297 Ductal Carcinoma In Situ: Analysis of 2996 Women Treated With Breast-conserving Surgery for 30 Years. *Ann Surg*
298 2015;262:623-31.
- 299 [27]. Marinovich ML, Azizi L, Macaskill P, Irwig L, Morrow M, Solin LJ, et al. The Association of Surgical Margins
300 and Local Recurrence in Women with Ductal Carcinoma In Situ Treated with Breast-Conserving Therapy: A Meta-
301 Analysis. *Ann Surg Oncol* 2016;23:3811-21.
- 302 [28]. Morrow M, Van Zee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, et al. Society of Surgical
303 Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on

304 Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Ductal Carcinoma In Situ. *Ann Surg Oncol*
305 2016;23:3801-10.

306 [29]. Monteau A, Sigal-Zafrani B, Kirova YM, Fourchette V, Bollet MA, Vincent-Salomon A, et al. Ductal carcinoma
307 in situ of the breast with close or focally involved margins following breast-conserving surgery: treatment with reexcision
308 or radiotherapy with increased dosage. *Int J Radiat Oncol Biol Phys* 2009;75:1021-8.

309 [30]. Vos EL, Siesling S, Baaijens MHA, Verhoef C, Jager A, Voogd AC, et al. Omitting re-excision for focally
310 positive margins after breast-conserving surgery does not impair disease-free and overall survival. *Breast Cancer Res*
311 *Treat* 2017;164:157-67

312 [31]. Moran MS, Zhao Y, Ma S, Kirova Y, Fourquet A, Chen P, et al. Association of Radiotherapy Boost for Ductal
313 Carcinoma In Situ With Local Control After Whole-Breast Radiotherapy. *JAMA Oncol* 2017;3:1060-8.

314 [32]. Omlin A, Amichetti M, Azria D, Cole BF, Fournier P, Poortmans P, et al. Boost radiotherapy in young women
315 with ductal carcinoma in situ: a multicentre, retrospective study of the Rare Cancer Network. *Lancet Oncol* 2006;7:652-
316 6.

317 [33]. Wong P, Lambert C, Agnihotram RV, David M, Duclos M, Freeman CR. Ductal carcinoma in situ--the influence
318 of the radiotherapy boost on local control. *Int J Radiat Oncol Biol Phys* 2012;82:e153-8.

319 [34]. Wai ES, Lesperance ML, Alexander CS, Truong PT, Culp M, Moccia P, et al. Effect of radiotherapy boost and
320 hypofractionation on outcomes in ductal carcinoma in situ. *Cancer* 2011;117:54-62.

321 [35]. Meattini I, Livi L, Franceschini D, Saieva C, Meacci F, Marrazzo L, et al. Role of radiotherapy boost in women
322 with ductal carcinoma in situ: a single-center experience in a series of 389 patients. *Eur J Surg Oncol* 2013;39:613-8.

323 [36]. Stokes WA, Amini A, Jackson MW, Plimpton SR, Kounalakis N, Kabos P, et al. Patterns of Fractionation and
324 Boost Usage in Adjuvant External Beam Radiotherapy for Ductal Carcinoma in Situ in the United States. *Clin Breast*
325 *Cancer* 2017 Jun 29. pii: S1526-8209(17)30286-0. doi: 10.1016/j.clbc.2017.06.009. [Epub ahead of print]

326 [37]. Azria D, Cowen D, Bourgier C, de la Lande B, Gourgou-Bourgade S, Z. Douadi Gaci Z, et al. Phase III
327 randomized French multicentric study to evaluate the impact of a localized 16-Gy boost after conservative surgery and a
328 50-Gy whole-breast irradiation in breast ductal carcinoma in situ (the BONBIS trial). *Journal of Clinical Oncology* 2011
329 29:15_suppl, TPS131-TPS131. DOI: 10.1200/jco.2011.29.15_suppl.tps131.

330 [38]. Nilsson C, Valachis A. The role of boost and hypofractionation as adjuvant radiotherapy in patients with DCIS:
331 a meta-analysis of observational studies. *Radiother Oncol* 2015;114:50-5.

332 [39]. Hathout L, Hijal T, Théberge V, Fortin B, Vulpe H, Hogue JC, et al. Hypofractionated radiation therapy for
333 breast ductal carcinoma in situ. *Int J Radiat Oncol Biol Phys* 2013;87:1058-63.

- 334 [40]. Offersen BV, Jacobsen EH, Nielsen MH, Krause M, Stenbygaard L, Mjaaland I, et al. OC-0142: Hypo- vs
335 normofractionated radiation of early breast cancer in the randomised DBCG HYPO trial. *Radiother Oncol* 2016;119:S64-
336 S65. DOI: [https://doi.org/10.1016/S0167-8140\(16\)31391-3](https://doi.org/10.1016/S0167-8140(16)31391-3).
- 337 [41]. Meattini I, Saieva C, Bastiani P, Martella F, Francolini G, Lo Russo M, et al. Impact of hormonal status on
338 outcome of ductal carcinoma in situ treated with breast-conserving surgery plus radiotherapy: Long-term experience from
339 two large-institutional series. *Breast* 2017;33:139-44.
- 340 [42]. Zhou W, Jirström K, Amini RM, Fjällskog ML, Sollie T, Lindman H, et al. Molecular subtypes in ductal
341 carcinoma in situ of the breast and their relation to prognosis: a population-based cohort study. *BMC Cancer* 2013;13:512.
- 342 [43]. Kerlikowske K, Molinaro AM, Gauthier ML, Berman HK, Waldman F, Bennington J, et al. Biomarker
343 Expression and Risk of Subsequent Tumors After Initial Ductal Carcinoma In Situ Diagnosis. *J Natl Cancer Inst*
344 2010;102:627-37.
- 345 [44]. Gennaro M, De Santis MC, Mariani L, Lo Vullo S, Cappelletti V, Agresti R, et al. Ten-year results of applying
346 an original scoring system for addressing adjuvant therapy use after breast-conserving surgery for ductal carcinoma in
347 situ of the breast. *Breast* 2017;35:63-8.
- 348 [45]. Poulakaki N, Makris GM, Battista MJ, Böhm D, Petraki K, Bafaloukos D, et al. Hormonal receptor status, Ki-
349 67 and HER2 expression: Prognostic value in the recurrence of ductal carcinoma in situ of the breast? *Breast* 2016;25:57-
350 61.
- 351 [46]. Giordano SH, Kuo YF, Duan Z, Hortobagyi GN, Freeman J, Goodwin JS. Limits of observational data in
352 determining outcomes from cancer therapy. *Cancer* 2008;112:2456-66.

353

354 **Figure captions**

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

357 **Figure 2.** LR recurrence rate curves comparing premenopausal (**dotted line**) to postmenopausal status (**solid line**; HR
358 0.40; 95% CI 0.18-0.92, p=0.03).

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

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