Thieme

# Treatment and Outcome of Ductal Carcinoma in Situ for the German Federal States Berlin and Brandenburg in the Period 2007–2020

## Duktales Carcinoma in situ: Behandlung und Outcome in den deutschen Bundesländern Berlin und Brandenburg für den Zeitraum 2007–2020



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**Keywords**

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**Schlüsselwörter**

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**ABSTRACT**

**Background**

Ductal carcinoma in situ (DCIS) of the female breast is treated with surgery possibly followed by radiotherapy (RT) and/or adjuvant hormonal therapy despite their known long-term side effects. Since not every DCIS will progress into an invasive breast cancer (IBC), disease progression and de-escalation of treatment is an important topic of current research.

**Methods**

During 2007–2020, 3905 individuals with a DCIS diagnosis were reported to the cancer registry of Brandenburg and Berlin. We selected 3424 women who were cancer-free prior to DCIS diagnosis and without synchronous diagnoses of DCIS or ipsilateral IBC (iIBC). The objective was to describe changes over time in DCIS treatment and risk of developing iIBC by treatment.

**Results**

We observed decreasing proportions of mastectomy, breast-conserving surgery (BCS) with RT, and standard versus hypofractionated RT over time. During a median follow-up of 3.8 years, 105 women developed iIBC. Compared with BCS + RT with standard fractionation (54.9%, 1878/3424, 53 iIBC events), hazard ratios (HR) for iIBC were 0.72 (95% confidence interval [CI] 0.26, 1.99; 4 events) for BCS + hy-

pofractionated RT, 0.70 (95% CI 0.33, 1.41; 11 events) for BCS alone, and 0.83 (95% CI 0.50, 1.37; 26 events) for mastectomy. Analyses were adjusted for DCIS size, grade, residual tumor status and ECOG score.

**Conclusion**
We observed a de-escalation of treatment over time, with fewer mastectomies, less RT, and more hypofractionation of RT. No substantial differences in risk of iIBC were observed between these treatments. There is a need to evaluate DCIS treatment de-escalation in larger cohorts with longer follow-up.

## ZUSAMMENFASSUNG

**Hintergrund**
Ein duktales Carcinoma in situ (DCIS) wird zunächst chirurgisch behandelt, danach erfolgt möglicherweise eine Strahlentherapie und/oder eine adjuvante Hormontherapie trotz der bekannten Langzeitnebenwirkungen. Da aber nicht jedes DCIS sich zu einem invasiven Mammakarzinom weiterentwickelt, ist das Fortschreiten der Erkrankung sowie eine Deeskalation der Behandlung ein wichtiges Thema in der aktuellen Forschung.

**Methoden**
Zwischen 2007–2020 wurden 3905 mit DCIS diagnostizierte Personen dem Krebsregister der Länder Brandenburg und Berlin gemeldet. Insgesamt wurden 3424 Frauen, die vor der Diagnose mit DCIS krebsfrei waren und keine synchrone Diagnose von DCIS oder ipsilateralem invasiven Mammakarzinom hatten, in die Untersuchung aufgenommen. Das Ziel war, die Veränderungen der Behandlung von DCIS im Laufe der Zeit und das Risiko, ein ipsilaterales invasives Mammakarzinom zu entwickeln, zu beschreiben.

**Ergebnisse**
Im Verlauf der Zeit stellten wir einen prozentualen Rückgang an Mastektomien und brusterhaltenden Therapien (BET) mit Strahlentherapie bzw. fraktionierter Strahlentherapie fest. Nach einem mittleren Follow-up von 3,8 Jahren entwickelte sich ein ipsilaterales invasives Mammakarzinom bei 105 Frauen (Endpunkt). Die Hazard Ratios der verschiedenen Behandlungsmethoden für die Entwicklung eines ipsilateralen invasiven Mammakarzinoms wurden verglichen. Im Vergleich mit BET + Strahlentherapie mit regulärer Fraktionierung (54,9%, 1878/3424, 53 Ereignisse) betrugen die Hazard Ratios 0,72 (95%-Konfidenzintervall [KI] 0,26–1,99; 4 Ereignisse) für BET + hypofraktionierte Strahlentherapie, 0,70 (95%-KI 0,33–1,41; 11 Ereignisse) für BET allein und 0,83 (95%-KI 0,50–1,37; 26 Ereignisse) für Mastektomien. Die Analysen wurden adjustiert um die Risikofaktoren DCIS-Größe, Tumorgrad, Resektionsstatus und ECOG-Status.

**Schlussfolgerung**
Wir stellten eine Deeskalation der Behandlung im Laufe der Zeit fest, mit weniger Mastektomien, weniger regulären Strahlentherapien und mehr hypofraktionierten Strahlentherapien. Es gab keine signifikanten Unterschiede zwischen den verschiedenen Behandlungen für das Risiko, ein ipsilaterales invasives Mammakarzinom zu entwickeln. Diese Deeskalation in der Behandlung von DCIS sollte in einem größeren Patientinnenkollektiv mit einem längeren Follow-up evaluiert werden.

## Introduction

Ductal carcinoma in situ (DCIS) is an abnormal proliferation of cells in ducts in the breast without invasive growth into the surrounding tissue [1]. Most women do not have clinical symptoms and most DCIS are found during screening with a mammogram [2]. Therefore, in Germany, the number of diagnoses has increased since the nationwide introduction of biannual mammographic screening for women aged 50–69 years in 2008/2009 [3, 4]. Currently, approximately 6500 women per year are diagnosed with DCIS, which represents about 20% of all abnormalities detected during the population based breast cancer (BC) screening in Germany [5, 6].

Most DCIS will never spread outside the ducts or lobules. However, in some cases DCIS may progress into an invasive BC (IBC) [7]. Since it is unclear which DCIS likely develop into IBC, all women with DCIS receive anti-cancer treatment despite the known long-term side effects of radiotherapy such as cardiovascular disease or second primary tumors [8]. According to current guidelines, DCIS in Germany is treated with surgery with or without radiotherapy (RT) and/or adjuvant hormonal therapy [9]. Identifying women whose DCIS is at low risk for transition to IBC could lead to de-escalation of treatment for such women and significantly reduce the burden of the disease [10, 11]. Different criteria for defining a low-risk DCIS have been proposed using combinations of characteristics such as age at diagnosis, grade, size, estrogen-, progesterone-, HER2-status or the residual tumor free margins [12, 13, 14, 15, 16]. The prevalence of low-risk DCIS ranges from 20.6% to 61.9% across criteria [13, 14, 15]. Therefore, risk-based treatment de-escalation is being investigated in observational studies and randomized controlled trials (RCTs) [17, 18, 19].

The aim of our study was to show real world data indicating de-escalation of treatment for DCIS from two federal states of Germany using cancer registry data of Brandenburg and Berlin. Additionally, we evaluated patient and treatment related determinants of the risk for developing subsequent ipsilateral IBC (iIBC) or contralateral IBC (cIBC).

## Methods

### Patient selection

All residents of Brandenburg and Berlin who were diagnosed with a DCIS (ICD-10: D05.1) and reported to the cancer registry in Berlin from July 2016 and in Brandenburg from January 2007 until December 2020 were selected. Individuals were included for analysis if they:

1. had no previous malignancies other than non-melanoma skin cancer (NMSC),
2. were female,
3. had no lymph node involvement,
4. had no IBC or second DCIS diagnosis in the same month as the initial diagnosis,
5. had available information on the laterality of DCIS and subsequent IBC, if any.

For included women, information on demographic data, DCIS diagnosis and its characteristics, treatment, subsequent cancers and vital status was available. However, for privacy reasons, only month and year of diagnosis were released. Furthermore, if a woman had two DCIS diagnoses within 6 consecutive months, i.e., two synchronous DCIS diagnoses [20], we selected the one with higher iIBC risk defined as higher grade or larger DCIS size (if similar grade) irrespective of laterality. If information on grade and size was missing, we selected a diagnosis with non-missing information on treatment or hormone receptor status. If a woman had a second DCIS diagnosed more than 6 months after the primary diagnosis, i.e., metachronous DCIS diagnoses, information on the second DCIS was not used for descriptive statistics but follow-up ended at the date of the second DCIS diagnosis.

### DCIS treatment

Mastectomy and breast-conserving surgery (BCS) performed within four consecutive months after DCIS diagnosis were considered. If both BCS and mastectomy were performed, the woman was assigned to the mastectomy group. Other surgical procedures were not considered.

If a woman received RT within six months after DCIS diagnosis, she was assigned to RT treatment. The number of fractions was obtained as the intended total dose of RT divided by the intended dose per fraction. A total of 13–17 fractions was considered hypofractionation, 24–28 standard fractionation, and 18–23 was assigned individually in consultation with clinical experts. A woman was considered receiving chemotherapy (CT) if at least one CT dose was administered within six months after DCIS diagnosis. Hormonal therapy was considered if it commenced within two years after DCIS diagnosis and lasted at least six months.

Our main treatment groups of interest were BCS + RT with standard versus hypofractionation, BCS alone, mastectomy and no surgery.

### Endpoints

iIBC was defined as time from DCIS diagnosis to diagnosis of a subsequent IBC in the same breast or death due to IBC. The laterality of IBC as a cause of death was not documented. cIBC was defined similarly, except with IBC in the opposite breast. Overall survival (OS) was the time from DCIS diagnosis to death from any cause. Women were censored at a diagnosis of cancer other than NMSC or IBC, a metachronous DCIS diagnosis, cIBC (for iIBC), iIBC (for cIBC), death from causes other than IBC (except for OS), or at the end of follow-up (December 31, 2020), whichever came first.

### Statistical analyses

Categorical variables were summarized using absolute frequencies and percentages among non-missing observations. Continuous variables were summarized using the mean with standard deviation and the median with the range. Missing information for each variable was reported as a separate category with absolute frequencies and percentages among the total number of observations. Patient and tumor characteristics were compared by treatment groups using chi-square test, Fisher's exact test or ANOVA.

Trends of DCIS diagnoses over time were evaluated separately for patients residing in the federal states of Brandenburg and Berlin. Furthermore, treatment de-escalation over time was investigated by joinpoint regression.

Regarding potential determinants of the survival endpoints missing information ranged from 0 % to 41.3 %. Complete case analyses would have excluded 2729 (79.7 %) women. Therefore, we used multiple imputation (MI) by chained equations. Five imputed datasets were created using a maximum of 30 iterations per imputation. The variables age, year of diagnosis, hormonal therapy, occurrence as well as the cumulative hazard rate of an iIBC, cIBC or OS event, depending on the survival endpoint, were used as covariates with complete information in the imputation models. The cumulative hazard rate was estimated using the Nelson-Aalen estimator. Hormonal and menopausal status were imputed with logistic regression. Grading and residual tumor status were imputed with polytomous logistic regression. For imputation regarding Eastern Cooperative Oncology Group (ECOG) score, RT within BCS + RT group and DCIS size, mean matching was used.

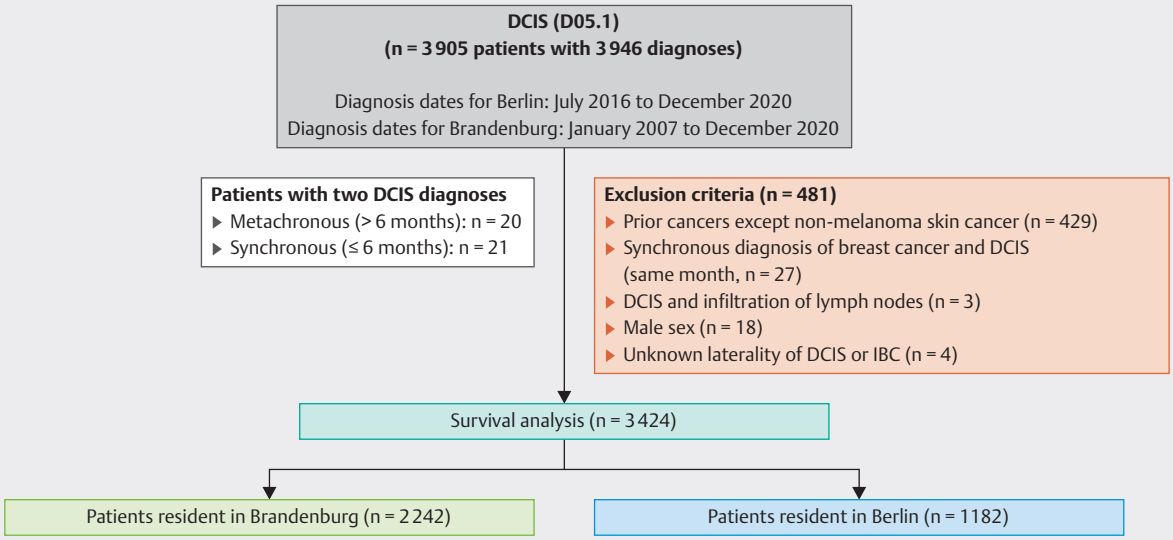
Uni- and multivariable Cox proportional hazards regression was performed for endpoints iIBC, cIBC and OS using age as the time scale and age at DCIS diagnosis as start of follow-up. All patient and tumor characteristics with $p < 0.1$ in univariable Cox regressions were included in the multivariable evaluation of treatment effects. The proportional hazards assumption was evaluated within each imputed dataset by plotting and testing Schoenfeld residuals. No deviation was observed.

Kaplan-Meier curves for iIBC by treatment were used to illustrate survival until iIBC occurrence, and 5-year survival probabilities were calculated for each treatment group.

Cumulative incidence of iIBC by DCIS treatment was estimated using the Aalen-Johansen estimator with death in the absence of IBC as a competing event [21].

As sensitivity analyses, treatment effects on iIBC were evaluated using Cox proportional hazard models with follow-up time as the time scale and a Fine and Gray model with death in the absence of IBC as a competing event.

$P < 0.05$ was considered statistically significant. No correction for multiple testing was applied. Joinpoint regression was performed using Joinpoint Regression Program version 5.0.2 [22]. All




▶ **Fig. 1** Flowchart of the selection of patients with at least one diagnosis of DCIS in the breast in the Clinical-epidemiological Cancer Registry Brandenburg-Berlin. DCIS, ductal carcinoma in situ; IBC, invasive breast cancer.

other statistical analyses were performed using the statistical software R version 4.3.1 [23]. Multiple imputation was conducted using the MICE package version 3.16.0 [24] and cumulative incidence was obtained using the CMPRSK package version 2.2–11 [25].

## Results

### Patient characteristics

Analyses included 3424 women (▶ **Fig. 1**) of whom 2995 (87.5 %) were ≥ 50 years of age at the time of DCIS diagnosis. The median age was 59 (range 25–94 years). Half of DCIS were diagnosed between 2017 and 2020 (50.5 %, 1728/3424). The majority of DCIS were of low or moderate grade (65.4 %, 1968/3007) and were residual tumor-free after surgery (97.4 %, 2963/3041). The majority of women had an ECOG score of 0 or 1 (88.8 %, 1835/2067), i.e., normal functional capacity with no or minor restrictions (▶ **Table 1**).

### DCIS treatment

Of 3424 patients, 1878 (54.9 %) were treated with BCS + RT, 669 (19.5 %) with mastectomy, 617 (18.0 %) with BCS alone, 110 (3.2 %) with hormonal therapy, and 4 (0.1 %) with CT. No surgical treatment was reported for 260 patients (7.6 %). Hypofractionated RT was used for 14 % (230/1604) of patients with known fractionation.

Of 3424 women, 543 (15.9 %) were above 70 years of age at time of diagnosis. Among patients who underwent BCS + RT, only 11.1 % were above 70 years of age at the time of diagnosis compared with 23.8 % for BCS alone and 17.9 % for mastectomy, respectively. Tumors treated with BCS alone were more often of low grade (32.8 %) than in the group BCS + RT (20.4 %) and mastectomy (17.0 %), respectively. Average tumor size was 5.3 cm among patients with mastectomy compared with 2.4 cm for BCS + RT and 1.8 cm for BCS alone. Patients with mastectomy had more often hormone receptor negative tumors (25.8 %) than BCS + RT (16.5 %) and BCS alone (11.2 %). Mastectomy patients were also more often premenopausal (30.7 %) than those treated with BCS + RT (17.6 %) or BCS alone (17.6 %).

Over the years, the number of new DCIS diagnoses was stable in both federal states and roughly proportional to the size of the female population. The proportion of patients treated with mastectomy among all patients treated surgically varied between 15–30 %. The data indicate a non-significant decrease by 0.4 percentage points per year (pp/yr, ▶ **Fig. 2a**). The proportion of patients treated with BCS + RT among all patients treated with BCS increased between 2007 and 2011 by 4.4 pp/yr (95 % CI 0.6, 8.3) and then decreased by 3.5 pp/yr (95 % CI 2.4, 4.6) to about 60 % in 2020 (▶ **Fig. 2b**). The proportion of standard fractionation among all patients was rather constant between 2007 and 2015 (decrease by 0.4 pp/yr) and decreased significantly by 7.0 pp/yr thereafter (95 % CI 5.2, 8.8) to about 60 % in 2020 (▶ **Fig. 2c**).

### Ipsilateral invasive breast cancer

During a median follow-up of 3.8 years (interquartile range [IQR] 1.9–8.0 years), 105 women were assigned to an iIBC event. Of those, 72 had a diagnosis of iIBC during follow-up and 33 women died due to IBC without a prior recorded IBC diagnosis (online Supplementary Table **S1**). Multivariable adjusted hazard ratios (HR) were reduced among women with a DCIS of less than 1 cm compared with 2.5 cm or more (HR 0.45, 95 % CI 0.24, 0.87) and were increased for women with an ECOG score of 2 or more compared with less (HR 1.93, 95 % CI 1.19, 3.13). Women with residual tumor after surgery were at increased risk compared to others (HR 3.20, 95 % CI 1.43, 7.18) (▶ **Table 2**).

Compared with BCS + RT with standard fractionation, risks of iIBC were not significantly different for BCS + hypofractionated RT

▶**Table 1** Characteristics of female patients diagnosed with DCIS in Berlin and Brandenburg in the period 2007–2020 by treatment groups breast-conserving surgery (BCS) plus radiotherapy (RT), BCS alone, mastectomy and no surgery.

| **Characteristic** at diagnosis | **BCS + RT** (N = 1878) | **BCS alone** (N = 617) | **Mastectomy** (N = 669) | **No surgery** (N = 260) | **Total** (N = 3424) | **P value**** |
|---|---|---|---|---|---|---|
| Age (year) | | | | | | < 0.001 |
| ▪ Mean (SD) | 59.3 (8.9) | 62.2 (11.0) | 58.0 (12.4) | 61.8 (12.4) | 59.8 (10.4) | |
| ▪ Median [Min, Max] | 59 [28, 85] | 62 [29, 91] | 57 [25, 94] | 60 [25, 89] | 59 [25, 94] | |
| ▪ < 40 | 28 (1.5%) | 5 (0.8%) | 41 (6.1%) | 6 (2.3%) | 80 (2.3%) | |
| ▪ 40–49 | 162 (8.6%) | 46 (7.5%) | 115 (17.2%) | 26 (10.0%) | 349 (10.2%) | |
| ▪ 50–59 | 808 (43.0%) | 217 (35.2%) | 214 (32.0%) | 88 (33.8%) | 1327 (38.8%) | |
| ▪ 60–69 | 671 (35.7%) | 202 (32.7%) | 179 (26.8%) | 73 (28.1%) | 1125 (32.9%) | |
| ▪ ≥ 70 | 209 (11.1%) | 147 (23.8%) | 120 (17.9%) | 67 (25.8%) | 543 (15.9%) | |
| Year of diagnosis* | | | | | | < 0.001 |
| ▪ 2007–2011 | 516 (27.5%) | 92 (14.9%) | 173 (25.9%) | 13 (5.0%) | 794 (23.2%) | |
| ▪ 2012–2016 | 538 (28.6%) | 122 (19.8%) | 181 (27.1%) | 61 (23.5%) | 902 (26.3%) | |
| ▪ 2017–2020 | 824 (43.9%) | 403 (65.3%) | 315 (47.1%) | 186 (71.5%) | 1728 (50.5%) | |
| Laterality | | | | | | 0.957 |
| ▪ Left | 950 (50.6%) | 315 (51.1%) | 336 (50.2%) | 131 (50.4%) | 1732 (50.6%) | |
| ▪ Right | 928 (49.4%) | 302 (48.9%) | 333 (49.8%) | 129 (49.6%) | 1692 (49.4%) | |
| Size (cm) | | | | | | < 0.001 |
| ▪ Mean (SD) | 2.40 (1.80) | 1.80 (1.81) | 5.25 (3.12) | 2.64 (2.65) | 2.91 (2.49) | |
| ▪ Median [Min, Max] | 2.0 [0, 15.8] | 1.2 [0, 11.5] | 5.00 [0, 20.0] | 2.00 [0, 14.0] | 2.20 [0, 20.0] | |
| ▪ < 1.0 | 307 (19.8%) | 170 (38.6%) | 26 (4.7%) | 24 (30.8%) | 527 (20.1%) | |
| ▪ 1.0 – < 2.5 | 609 (39.3%) | 159 (36.1%) | 80 (14.5%) | 20 (25.6%) | 868 (33.2%) | |
| ▪ ≥ 2.5 | 634 (40.9%) | 111 (25.2%) | 444 (80.7%) | 34 (43.6%) | 1223 (46.7%) | |
| ▪ Missing | 328 (17.5%) | 177 (28.7%) | 119 (17.8%) | 182 (70.0%) | 806 (23.5%) | |
| Grading | | | | | | < 0.001 |
| ▪ Low | 342 (20.4%) | 179 (32.8%) | 100 (17.0%) | 41 (20.8%) | 662 (22.0%) | |
| ▪ Moderate | 741 (44.2%) | 234 (42.9%) | 234 (39.7%) | 97 (49.2%) | 1306 (43.4%) | |
| ▪ High | 592 (35.3%) | 133 (24.4%) | 255 (43.3%) | 59 (29.9%) | 1039 (34.6%) | |
| ▪ Missing | 203 (10.8%) | 71 (11.5%) | 80 (12.0%) | 63 (24.2%) | 417 (12.2%) | |
| Hormonal Status | | | | | | < 0.001 |
| ▪ Positive | 965 (83.5%) | 309 (88.8%) | 302 (74.2%) | 88 (88.9%) | 1664 (82.8%) | |
| ▪ Negative | 190 (16.5%) | 39 (11.2%) | 105 (25.8%) | 11 (11.1%) | 345 (17.2%) | |
| ▪ Missing | 723 (38.5%) | 269 (43.6%) | 262 (39.2%) | 161 (61.9%) | 1415 (41.3%) | |
| Menopausal status | | | | | | < 0.001 |
| ▪ Premenopausal | 247 (17.6%) | 79 (17.6%) | 150 (30.7%) | 17 (19.5%) | 493 (20.3%) | |
| ▪ Postmenopausal | 1157 (82.4%) | 369 (82.4%) | 338 (69.3%) | 70 (80.5%) | 1934 (79.7%) | |
| ▪ Missing | 474 (25.2%) | 169 (27.4%) | 181 (27.1%) | 173 (66.5%) | 997 (29.1%) | |
| Residual status | | | | | | < 0.001 |
| ▪ Residual tumor | 30 (1.6%) | 27 (4.7%) | 21 (3.3%) | – | 78 (2.4%) | |
| ▪ Tumor-free | 1789 (98.4%) | 551 (95.3%) | 623 (96.7%) | – | 2963 (89.8%) | |
| ▪ No surgery | – | – | – | 260 (100%) | 260 (7.9%) | |
| ▪ Missing | 59 (3.1%) | 39 (6.3%) | 25 (3.7%) | – | 123 (3.6%) | |

▶Table 1 continued

| Characteristic at diagnosis | BCS + RT (N = 1878) | BCS alone (N = 617) | Mastectomy (N = 669) | No surgery (N = 260) | Total (N = 3424) | P value** |
|---|---|---|---|---|---|---|
| Chemotherapy | | | | | | 0.823 |
| ▪ No | 1876 (99.9%) | 616 (99.8%) | 668 (99.9%) | 260 (100%) | 3420 (99.9%) | |
| ▪ Yes | 2 (0.1%) | 1 (0.2%) | 1 (0.1%) | 0 (0%) | 4 (0.1%) | |
| Hormonal therapy | | | | | | 0.025 |
| ▪ No | 1805 (96.1%) | 607 (98.4%) | 646 (96.6%) | 256 (98.5%) | 3314 (96.8%) | |
| ▪ Yes | 73 (3.9%) | 10 (1.6%) | 23 (3.4%) | 4 (1.5%) | 110 (3.2%) | |
| Radiotherapy | | | | | | < 0.001 |
| ▪ No | 0 (0%) | 617 (100%) | 603 (90.1%) | 209 (80.4%) | 1429 (41.7%) | |
| ▪ Yes | 1878 (100%) | 0 (0%) | 66 (9.9%) | 51 (19.6%) | 1995 (58.3%) | |
| Radiotherapy type | | | | | | 0.837 |
| ▪ Hypofractionation | 230 (14.3%) | – | 6 (12.0%) | 14 (33.3%) | 250 (14.7%) | |
| ▪ Standard fractionation | 1374 (85.7%) | – | 44 (88.0%) | 28 (66.7%) | 1446 (85.3%) | |
| ▪ Missing | 274 (14.6%) | – | 16 (24.2%) | 9 (17.6%) | 299 (15.0%) | |
| ECOG score | | | | | | 0.317 |
| ▪ 0–1 | 1153 (89.3%) | 269 (89.1%) | 349 (86.6%) | 64 (90.1%) | 1835 (88.8%) | |
| ▪ ≥ 2 | 138 (10.7%) | 33 (10.9%) | 54 (13.4%) | 7 (9.9%) | 232 (11.2%) | |
| ▪ Missing | 587 (31.3%) | 315 (51.1%) | 266 (39.8%) | 189 (72.7%) | 1357 (39.6%) | |

BCS = breast conserving surgery; ECOG Score = Eastern Cooperative Oncology Group performance status; RT = radiotherapy
% of non-missing categories are among all patients with non-missing values, % of missings are among all patients.
* Percentages cannot be used to assess trends since DCIS cases from Berlin were included from 2016 on.
** P values were only calculated among surgery groups (BCS + RT, BCS alone and mastectomy).

(HR 0.72, 95% CI 0.26, 1.99), BCS alone (HR 0.70, 95% CI 0.35, 1.41) and mastectomy (HR 0.83, 95% CI 0.50, 1.37). Women without reported surgery had a two-fold non-significantly increased risk (HR 1.99, 95% CI 0.99, 3.99). The majority of women with no reported surgery were diagnosed in recent years 2017–2020 (71.5%, 186/260) and were older than 60 years (53.8%, 140/260). Results were similar when all women with BCS + RT were used as the reference group (data not shown).

Kaplan-Meier iIBC-free survival probabilities at 5 years for women with BCS and RT with standard fractionation were 97.6% (95% CI 96.6, 98.4), for BCS and hypofractionated RT 95.1% (95% CI 87.0, 98.2), for BCS alone 97.8% (95% CI 95.4, 98.9), for mastectomy 95.7% (95% CI 93.3, 97.3), and for no surgery 92.0% (95% CI 85.6, 95.6) (▶ **Fig. 3**).

Cumulative incidence of iIBC at 10 years was 7.5% (95% CI 4.8, 10.9%) after mastectomy, 6.0% (95% CI 4.5, 7.8%) after BCS + RT, 5.2% (95% CI 2.3, 9.8%) after BCS alone, and 7.8% (95% CI 3.9, 13.2%) for women with no reported surgery (▶ **Fig. 4**).

## Contralateral invasive breast cancer and overall survival

During a median follow-up of 3.8 years (IQR 2.0–8.2 years), 94 women were assigned to a cIBC event. Of those, 61 had a diagnosis of cIBC during follow-up plus the same 33 deaths as above due to IBC without a recorded prior IBC diagnosis. In total, 152 women died due to any cause. HRs for OS and cIBC were about 2-fold (95% CI 1.36, 2.77) and 3-fold (95% CI 1.97, 4.90) significantly elevated for women with an ECOG score above one compared with ECOG ≤ 1, respectively (data not shown).

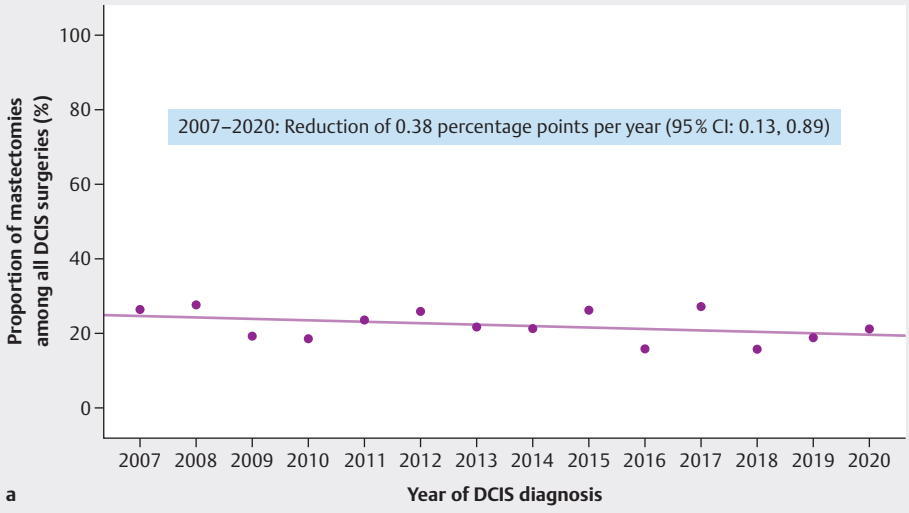
Compared with BCS + RT with standard fractionation, risks of cIBC were not significantly different for BCS + hypofractionated RT (HR 1.51, 95% CI 0.64, 3.54), BCS alone (HR 1.19, 95% CI 0.63, 3.54) and mastectomy (HR 0.97, 95% CI 0.55, 1.71). Women without reported surgery had a two-fold non-significantly increased risk (HR 2.08, 95% CI 0.99–4.90).

Compared with BCS + RT with standard fractionation, risks of OS were not significantly different for BCS + hypofractionated RT (HR 0.72, 95% CI 0.22, 2.30), BCS alone (HR 0.68, 95% CI 0.40, 1.16) and mastectomy (HR 1.06, 95% CI 0.69, 1.63). Women without reported surgery had a significantly increased risk (HR 2.16, 95% CI 1.22–3.84).

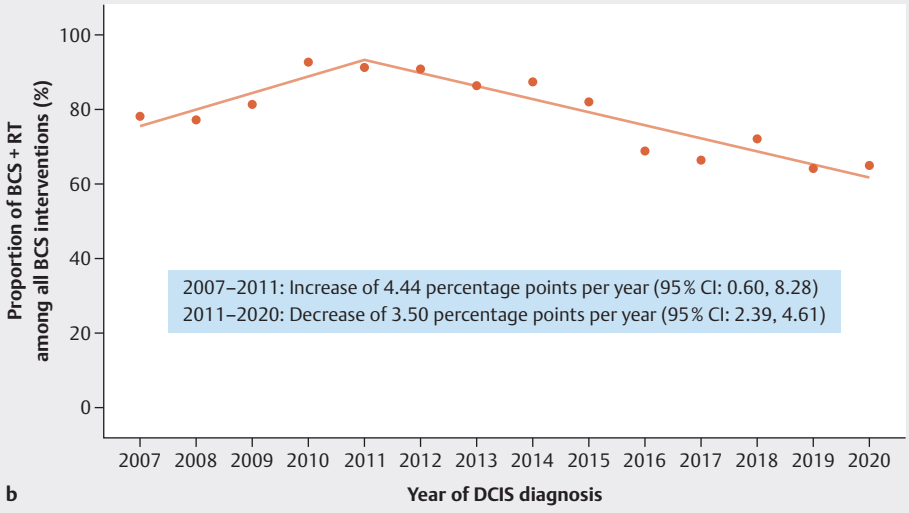
These results of cIBC and OS are not shown in the tables.

## Sensitivity analyses

Similar results were obtained with follow-up time as the time scale or with a Fine and Gray model using death in the absence of IBC as a competing event (data not shown).




a

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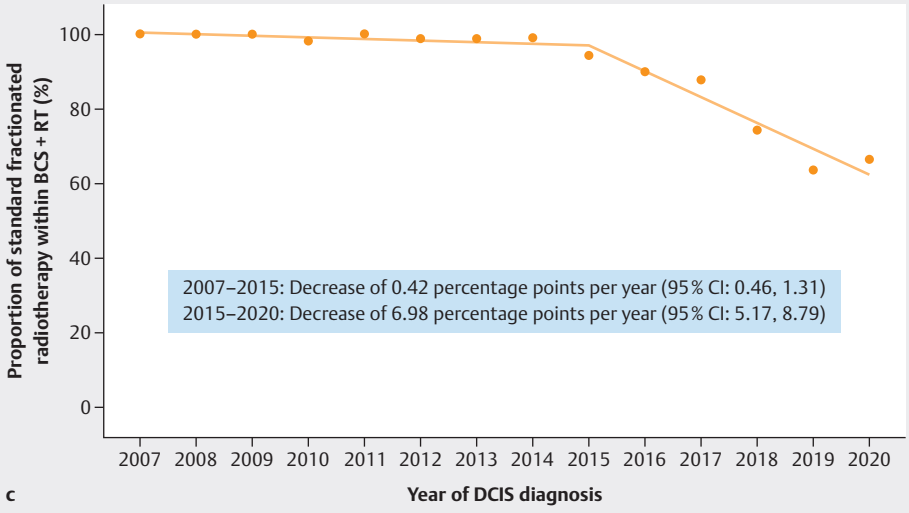



c

▶ **Fig. 2** Treatment de-escalation in the period 2007–2020 in Berlin and Brandenburg for 3424 women diagnosed with DCIS. BCS = breast conserving surgery; DCIS = ductal carcinoma in situ; RT = radiotherapy.

▶**Table 2** Univariable and multivariable Cox regression for time to ipsilateral invasive breast cancer (iIBC) among 3424 women with DCIS diagnosed in the period 2007–2020 in Berlin and Brandenburg.

| Characteristic | | Number of women* | Number of iIBC* events | Crude HR (95% CI) | Adjusted HR (95% CI) |
|---|---|---|---|---|---|
| Follow-up (years), Median [IQR] | | 3.80 [1.88, 8.04] | | | |
| Diagnosis period | 2007–2011 | 794 | 46 | 0.96 (0.57, 1.63) | |
| | 2012–2016 | 902 | 37 | 1.16 (0.68, 1.99) | |
| | 2017–2020 | 1728 | 22 | 1.00 | |
| Grading | Low | 738 | 22 | 1.11 (0.65, 1.91) | 1.26 (0.73, 2.18) |
| | Moderate | 1509 | 34 | 1.00 | 1.00 |
| | High | 1177 | 49 | 1.69 (1.08, 2.63) | 1.53 (0.97, 2.40) |
| DCIS size (cm)** | < 1.0 | 671 | 12 | 0.43 (0.23, 0.80) | 0.45 (0.24, 0.87) |
| | 1.0 – < 2.5 | 1121 | 29 | 0.65 (0.42, 1.01) | 0.69 (0.44, 1.10) |
| | ≥ 2.5 | 1632 | 64 | 1.00 | 1.00 |
| Hormone receptor status | Positive | 2857 | 82 | 1.00 | |
| | Negative | 567 | 23 | 1.34 (0.84, 2.15) | |
| Menopausal status | Premenopausal | 787 | 28 | 0.57 (0.27, 1.19) | |
| | Postmenopausal | 2637 | 77 | 1.00 | |
| Residual tumor status | Residual tumor | 78 | 7 | 3.03 (1.38, 6.66) | 3.20 (1.43, 7.18) |
| | Tumor-free | 3086 | 87 | 1.00 | 1.00 |
| | No surgery | 260 | 11 | 2.26 (1.16, 4.38) | 1.99 (0.99, 3.99) |
| Treatment modality | BCS + RT | | | | |
| | ▪ Hypofractionation | 282 | 4 | 0.77 (0.28, 2.13) | 0.72 (0.26, 1.99) |
| | ▪ Standard Fractionation | 1596 | 53 | 1.00 | 1.00 |
| | BCS alone | 617 | 11 | 0.71 (0.36, 1.40) | 0.70 (0.35, 1.41) |
| | Mastectomy | 669 | 26 | 1.10 (0.68, 1.78) | 0.83 (0.50, 1.37) |
| | No surgery | 260 | 11 | 2.05 (1.03, 4.08) | 1.99 (0.99, 3.99) |
| Hormonal therapy | No | 3314 | 100 | 1.00 | |
| | Yes | 110 | 5 | 0.75 (0.30, 1.85) | |
| ECOG Score | 0–1 | 3065 | 81 | 1.00 | 1.00 |
| | ≥ 2 | 359 | 24 | 1.84 (1.14, 2.97) | 1.93 (1.19, 3.13) |

DCIS = Ductal carcinoma in situ; ECOG Score = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; iIBC = ipsilateral invasive breast cancer; IQR = interquartile range

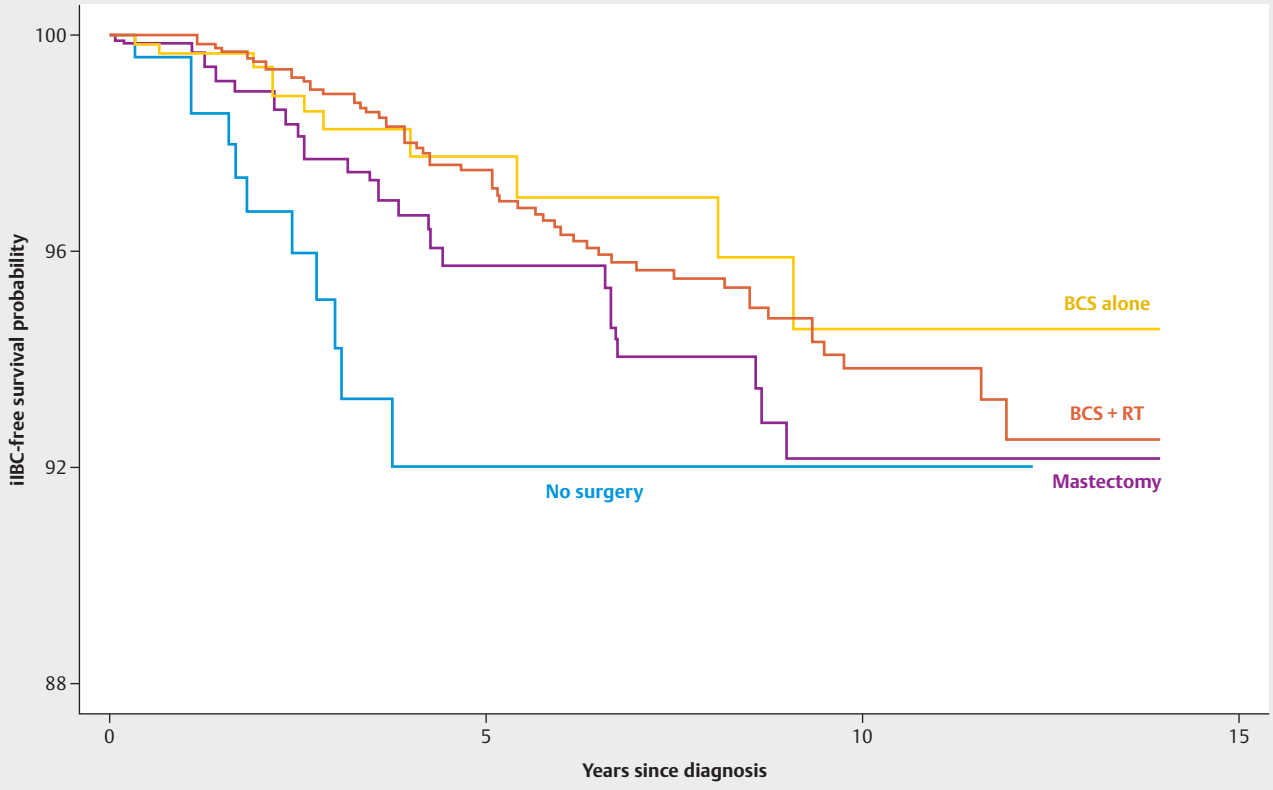
* Median value across 5 imputed datasets

** P value of continuous size: 0.064 for univariable testing, 0.189 for multivariable testing

## Discussion

During the last two decades, women living in Brandenburg and Berlin who were diagnosed with DCIS were mostly treated with BCS and RT with standard fractionation. Since about 2011, the proportion of patients treated with RT after BCS decreased, and the proportion of hypofractionated RT increased since about 2015. We found no evidence of poorer tumor control with the observed de-escalation, which reduces side effects of RT and is more convenient to patients.

Our data are consistent with previous studies. The majority of women in our study were postmenopausal and had small DCIS with negative residual status after resection which is consistent with what other studies found [11, 23, 24]. As already observed by Byng et al. [13] and Schiza et al. [12], we also found increased risks for larger DCIS size and for positive residual tumor after surgery. Although we did not observe significant differences in iIBC risk between BCS + RT and mastectomy, the direction of the effect is comparable with studies which showed a significant benefit of mastectomy [8, 13]. However, while we found a non-significantly decreased risk after BCS alone compared with BCS + RT, previous




▶ **Fig. 3** Survival probability for iIBC by treatment for 3424 women diagnosed with DCIS in the period 2007–2020 in Berlin and Brandenburg. BCS = breast conserving surgery; iIBC = ipsilateral invasive breast cancer; RT = radiotherapy.

studies reported a protective effect of additional RT after BCS [13, 26, 27].

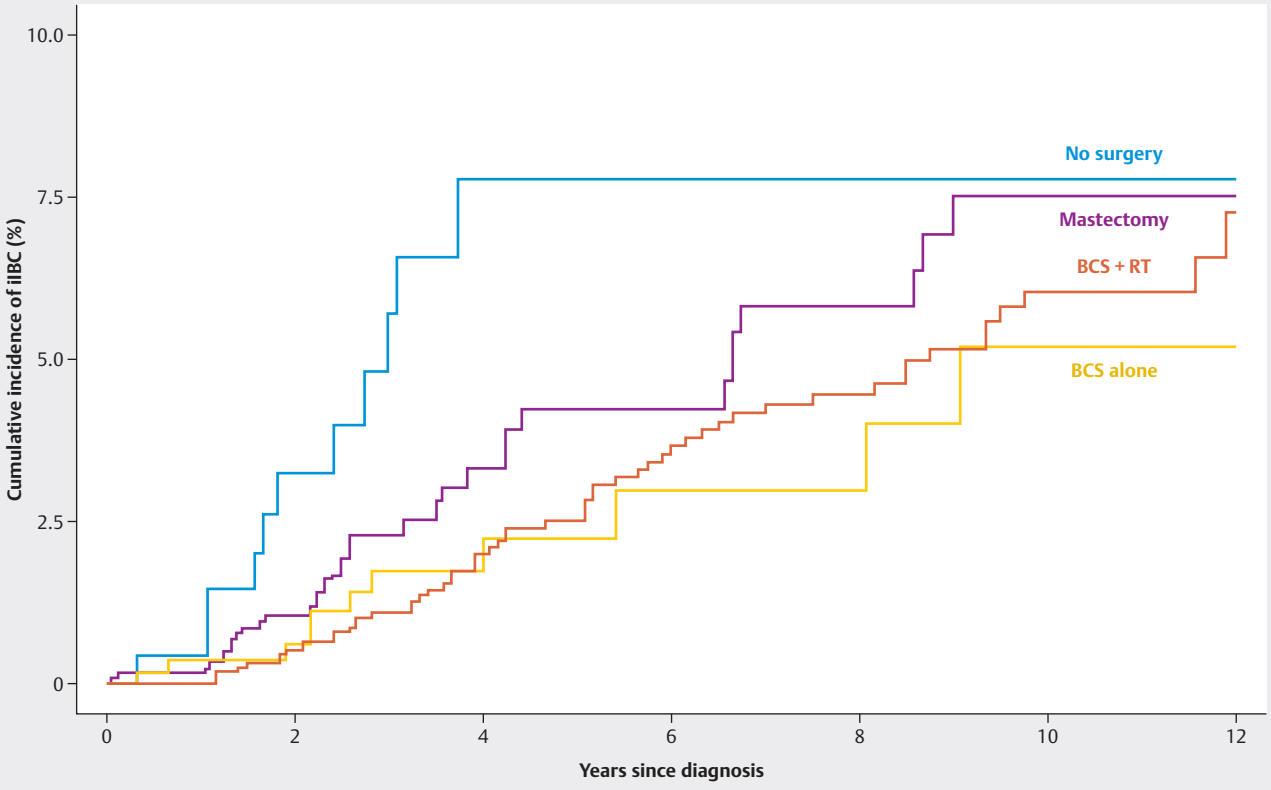
We observed a relatively high incidence of iIBC following mastectomy. This may be partly due to the fact that 134 of the 669 women with mastectomy (and 13 of the 26 women with iIBC in this group) underwent a subcutaneous mastectomy. This procedure is less invasive for the patients and facilitates breast reconstruction but may leave a larger amount of glandular tissue than a radical mastectomy.

De-escalation of DCIS treatment is an important topic of current research. The notion that a proportion of DCIS will never progress to IBC motivated attempts to identify low-risk DCIS [7]. Ongoing randomized trials evaluate whether treatment de-escalation is safe for low-risk DCIS [28, 29]. If so, this would offer substantial gains in quality of life for many patients by reducing, for example, the side effects of RT.

A limitation of our study is the small number of iIBC events due to the small size of the cohort and relatively short follow-up. The unexpectedly high proportion of women without surgical treatment is not explained by differences in age, DCIS size, grading or ECOG status compared to other women. It is possible that some surgeries might not have been reported to the registry when data were extracted. Most importantly, potential confounding by indication is a concern in this non-randomized study. For example, it is possible that more aggressive treatment was given to women with better health status and/or younger age at diagnosis. However, in multivariable analysis, we adjusted for age and ECOG score to control indication bias. We did perform many statistical tests, which can increase the risk of type I errors. Except for the main objectives, these p-values are exploratory and should be interpreted with caution.

Our study has several strengths. We show, for the first time, real world data indicating de-escalation of treatment for DCIS. Nevertheless, the proportion of mastectomies was relatively stable and the majority of patients still receives RT after BCS. In addition, previous studies did not control potential indication bias due to general health status. We were able to adjust for ECOG status by multiple imputation of missing values for about 40 % of patients. The fact that we found no substantial confounding lends credibility to earlier studies for which this information was not available.

In summary, our data show a trend to less RT after BCS and in favor of hypofractionated vs. standard fractionated RT with no evidence of poorer oncological outcome. Larger studies are needed with sufficient information to control potential indication bias of risk estimates from non-randomized data. With such data, the selection of low-risk DCIS might be improved so that treatment can be safely de-escalated.




▶ **Fig. 4** Cumulative incidence of iIBC by treatment for 3424 women diagnosed with DCIS in the period 2007–2020 in Berlin and Brandenburg. BCS = breast conserving surgery; iIBC = ipsilateral invasive breast cancer; RT = radiotherapy.

## Supplementary Material

**Supplementary Table S1:** Types of events and reasons for censoring by treatment in the analyses with time to ipsilateral IBC as endpoint.

## Contributors' Statement

Sandy Burmeister performed all statistical analyses of the data and drafted the manuscript. Michael Hauptmann and Katarzyna Jóźwiak contributed to the conception of the study, provided overall supervision and coordination of the manuscript preparation. Andre Buchali, Christiane Richter-Ehrenstein, Christine Holmberg, Anne von Rüsten, Constanze Schneider contributed to the interpretation of the results. All authors provided critical feedback in all aspects of the study and they reviewed and approved the final version of the manuscript.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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