INVESTIGATING THE EFFECTIVENESS OF ADJUVANT THERAPY FOR PATIENTS WITH HORMONE RECEPTOR-POSITIVE DUCTAL CARCINOMA IN SITU

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Abstract

Background

This study compared the recurrence risk of single versus dual adjuvant radiotherapy (RT) and hormonal therapy (HT) following breast-conserving surgery (BCS) in patients with hormone receptor-positive ductal carcinoma in situ (DCIS).

Methods

This retrospective cohort study used the Taiwan Cancer Registry database linking to the Taiwan National Health Insurance data from 2011 to 2016. We compared the recurrence risk between BCS-based regimens in Cox regressions and presented as adjusted hazard ratio (HR) and 95% confidence interval (95%CI).

Results

The 1,836 study cohort with a low-to-intermediate risk of recurrence was grouped into BCS alone (6.1%), BCS+RT (6.2%), BCS+HT (23.4%) and BCS+HT+RT (64.3%) according to the initial treatments. During the follow-up (median: 3.3 years), the highest 5-year recurrence-free survival rate was in BCS+RT (94.1%) group and followed by BCS+HT+RT (92.8%), BCS+HT (87.4%) and BCS alone (84.9%). Of the single adjuvant therapies, RT was more effective than HT. Both BCS+HT (HR: 1.52, 95%CI: 0.99–2.35) and BCS+RT (HR: 1.10, 95%CI: 0.50–2.41) did not significantly increase recurrence risk comparing against the BCS+HT+RT group.
Conclusion

Single adjuvant demonstrated a similar subsequent recurrence risk with dual adjuvant. This study supports the proposition to de-escalate adjuvant treatments in patients with low-to-intermediate risk of DCIS recurrence.

Introduction

Ductal carcinoma in situ (DCIS) is non-invasive and typically curable breast cancer that accounts for approximately 20%–25% of all newly diagnosed breast cancer in the United States and 17%–34% of mammography-detected cases [1–3]. According to the National Comprehensive Cancer Network (NCCN) guideline, treatment options for DCIS include mastectomy alone or breast-conserving surgery (BCS) with whole breast radiation therapy (RT) (with or without radiation boost) and with or without hormone therapy (HT) [4].

Previous clinical trials have shown that both adjuvant RT and HT decrease the reduced the ipsilateral breast tumor recurrence (IBTR) (i.e., either recurrent DCIS or invasive cancer) rate by approximately 50% and 30%, respectively [5–7]. A meta-analysis on four randomized trials found that compared with BCS alone, the adjuvant RT after BCS significantly decreased 15.2% of the ten-year absolute risk of any IBTR (BCS+RT vs. BCS: 12.9% vs. 28.1%; P < 0.00001), despite no significant effect on breast cancer mortality or all-cause mortality [8]. Moreover, a case-series analysis at a single-center in South Korea found that adjuvant HT combining RT with BCS further reduced LR by 30% in 50 women with hormone receptor (HR)-positive (+) DCIS, which is regarded with a low risk of recurrence [9, 10].

Although single (RT only) or dual (RT combining HT) adjuvant therapies have been demonstrated to reduce the LR of DCIS significantly, no significant difference was found in the mortality caused by invasive breast cancer recurrence. Therefore, nowadays, increasing attention has been raised on the de-escalation of dual adjuvant RT and HT following BCS [11] when considering the benefit of controlling local recurrence and the undesirable adverse effects, e.g., RT associated cardiovascular disease and rare malignancies [12, 13] and HT associated thromboembolic events [14]. Besides, adjuvant HT is recommended using consecutively up to five years post-surgery for women with HR-positive DCIS. Adherence to HT was generally suboptimal due to side effects and consequently reduced the treatment effectiveness [15–19]. However, these long-term adverse consequences were generally not measured in randomized controlled trials.

Several risk predictive tools have been developed to classify the risk of recurrence into three categories of high, intermediate and low risk based on either the clinicopathological factors (e.g., Van/Nuys prognostic index and system established by Smith et al.) [20, 21] or incorporating genetic factors (e.g., Oncotype DX®) [22]. By incorporating these risk scoring systems and patients’ bio-molecular profiles, there may be a great potential to inform clinical decision-making on de-escalating adjuvant therapies in patients with (HR)-positive (+) DCIS. Nevertheless, these risk scoring tools are needed to be validated in a larger population covering a wide range of ethnicities and socio-diversity. Therefore, this study aimed to investigate the clinical effectiveness of single (RT or HT) and dual (RT and CT) adjuvant therapy following BCS in patients with a low-to-intermediate recurrence risk of DCIS using population-based real-world data. The objectives were to investigate patients’ treatment patterns, compare the effectiveness between different treatment options and investigate factors associated with the risk of recurrence.
Materials and methods

Study design and data sources

This retrospective cohort study used population-level claim-based data from the National Health Insurance (NHI) database, Taiwan Cancer Registry (TCR), and the Breast Cancer Screening Database from 2010 to 2017. In 1995, Taiwan implemented a single-payer NHI system to enhance medical care coverage, which reached over 99.9% of all population in 2014 [23]. The NHI database includes comprehensive claims data for reimbursements on ambulatory, inpatient, emergency, and Chinese medicine visits. The TCR provided archives information on cancer diagnosis, and records additional supplementary information. In 2015, biennial breast cancer screening programs were extended to women aged 45–69 years [24]; accordingly, the Breast Cancer Screening Database provided associated information, such as mammographic results, family history, and menstruation status. The study period was selected for the completion of biomarker information in TCR. This study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-EXEMPT(I)-20180037).

Cohort selection

The study population was adult women (age ≥ 20 years) with newly-diagnosed HR(+) (i.e., estrogen receptor-positive and or progesterone receptor-positive) DCIS and no other concomitant cancers who had undergone BCS as the initial treatment. Patients with DCIS were identified by screening the TCR from 2011 to 2016 for the DCIS-related ICD-O-3 Topography codes C50.x and Morphology codes (8201, 8230, 8500, 8501, 8503, 8507, and 8522). The date of the first DCIS diagnosis was defined as the index date. Patients with ICD-9 codes for other cancers (i.e., 140–208, 230–239) recorded before the index date, HR(−) breast cancer and not undergone BCS as the initial breast cancer management were excluded. Furthermore, we adopted the scoring system proposed by Smith et al. (2006) to stratify the risk of recurrence in the study cohort [21]. A cumulative score was derived from each patient’s age at diagnosis, tumor size, and nuclear grade (Fig 1). Those who had a total score of >3 points were excluded to ensure that the study cohort was at low-to-intermediate risk of recurrence. Excluded patients (i.e., with a high risk of recurrence) were obtained in an additional analysis (S1 Fig). Moreover, as previous studies indicated the premenopausal status as a prognostic factor for DCIS recurrence [25–27], in a sub-analysis, we grouped the study cohort according to the menopausal status [18, 28]. If the information on menstruation status was missing, the age of diagnosis older than 52 years, the median menopausal age in Taiwan [29] was used as a proxy to classify the menopausal status.

Exposure

The initial breast cancer treatments were identified within six months after the DCIS was diagnosed. According to the patients’ initial breast cancer treatments, the study cohort was then grouped into four BCS-based regimens, including BCS alone, BCS+RT, BCS+HT and BCS+HT+RT. Corresponding procedure codes of BCS and RT and prescription codes of HT were used to screen the claims. HT included tamoxifen (ATC code L02BA01), anastrozole (ATC code L02BG03), letrozole (ATC code L02BG04), and exemestane (ATC code L02BG06).

Outcome measure

The study cohort was followed from the index date to the recurrence event, death, or end of the study period (December 31, 2017), whichever occurred first. The primary outcome, any recurrent events (i.e., either recurrent DCIS or invasive cancer), as defined by a proxy of
resuming treatment, i.e., any surgery or chemotherapy records identified in the NHI database after nine months from the index date because the recurrence was not recorded in the claim-based data. The completion of initial breast cancer treatments for DCIS was assumed to be up to nine months following the index diagnosis date. Based on clinical specialists’ experience, the completion of initial breast cancer management typically requires up to 6 months in clinical practice [30]. Moreover, as DCIS is a relatively benign condition, treatment initiation may be delayed for up to three months [31]. The time to LR was also measured to calculate the recurrence-free survival (RFS) rate over time.

**Covariates**

Patients’ demographic (age at diagnosis, year diagnosed), socioeconomic (residential areas of NHI divisions, income rank of NHI registration), lifestyle (obesity, or body mass index of >25, smoking, and alcohol consumption) factors, comorbidity index, medical history (menstruation status, mammography, family history of breast cancer) and tumor features (size, nuclear grade, and histology type) were retrieved. Patients were categorized into three age groups, i.e. 20–50, 51–70, and >70 years. The insurance income ranking was used as a proxy for the monthly income level. Patients’ comorbidities were identified within the preceding year of the index date to calculate the Charlson’s comorbidity index (CCI) score [32] and further categorized into four groups (i.e. 0, 1, 2, and ≥3 points of CCI). Data on mammography results, family history, and menstruation status before the index date were extracted from the Breast Cancer Screening Database.

**Analysis**

The RFS rate was presented in a Kaplan–Meier survival curve and compared the four BCS-based regimens using the log-rank test. The Cox proportional hazards model was used to
analyze the LR risk comparing BCS, BSC+HT, BCS+RT against BCS+RT+HT and adjust for covariates, including residential areas, diagnosed a year, and insurance income rank in the multivariable analysis. The results were adjusted hazard ratios (HRs) and 95% confidence intervals (95%CIs).

Moreover, a sub-analysis was conducted to assess the recurrence rates comparing treatment regimens with or without HT (i.e. BCS±RT+HT vs. BCS±RT) in patients at the pre and post-menopausal status [18, 28]. Furthermore, an additional analysis of the RFS rate was conducted in the groups of patients with a high-risk of recurrence. The Kaplan–Meier survival curve and the log-rank test comparing among the four different BCS-based regimens were presented in S1 Fig.

Data management, computation, and analysis were performed using the SAS software (version 9.4: SAS Institutes, Inc., Cary, NC, US).

Results

Characteristics of the study cohort

During the 6-year inclusion period (2011–2016), 2,911 patients with HR(+) DCIS received BCS as the initial breast cancer management. Of them, 1836 were identified as the low-intermediate-risk cohort and included in the analysis. The median follow-up period was 3.3 years; the mean age (± standard deviation) at diagnosis was 53.6±9.7 years, and 51.4% of the patients were postmenopausal women. The mean tumor size was 9.3±6.9 mm; most patients (86.1%) exhibited a non-comedo-type lump. Most patients had a CCI score of 0 (60.4%), were not obese (72.0%), did not smoke (87.9%), casually drink or did not drink (88.1%) (Table 1). All patients were at low-intermediate-risk of recurrence (scored 1–3 according to Smith et al. (2006) [21]) and a high proportion of patients aged 40–60 years (70.2%) had <16-mm tumor size (88.9%) and low (40.3%) to intermediate (55.8%) nuclear grade (Fig 1).

Characteristics of cohort receiving different BCS-based regimens

Of the four BCS-based initial treatments, most of the study cohort received BCS+HT+RT (64.3%), followed by BCS+HT (23.4%), BCS+RT (6.2%), and BCS alone (6.1%) (Table 1). Compared with the other treatment groups, the BCS alone group (n = 111) had the highest proportion of patients with low nuclear grade tumors (56.8%) (P<0.0001). Moreover, the BCS+RT group reported the largest tumor size of 10.4±7.5 mm (P = 0.0053) and the highest nuclear grade (10.5%). Of patients who received only one adjuvant therapy, the BCS+HT group (n = 430) had older diagnosis age, smaller tumor size, a higher proportion of low nuclear grade and non-comedo-type tumors than the BCS+RT group (n = 114).

Recurrence-free survival rate and associated factors

During the follow-up period, the proportion of patients developed the recurrent was highest in the BCS alone group (11.71%, n = 13), and followed by BCS+HT (7.67%, n = 33), BCS+RT (6.14%, n = 7) and BCS+HT+RT (5.42%, n = 64) groups. Likewise, the BCS alone group had the lowest five-year RFS rate (84.94%) compared with the BCS+HT (87.39%), BCS+RT (94.07%), and BCS+HT+RT (92.78%) groups (log-rank test, P = 0.0315) (Fig 2). Consistently, after adjusting all covariates, the BCS alone group showed significantly higher recurrence risk compared with the BCS+HT+RT group (adjusted HR: 2.05, 95%CI: 1.11–3.78, P = 0.0216). However, there was no significant difference of recurrent rate comparing BCS+HT (adjusted HR: 1.52, 95%CI: 0.99–2.35, P = 0.0582) and BCS+RT (adjusted HR: 1.10, 95%CI: 0.50–2.41, P = 0.8186) groups against the BCS+HT+RT group (Table 2).
Table 1. Baseline characteristics of the study cohort.

|                          | Total (N = 1836) | BCS alone (n = 111, 6.1%) | BCS+HT (n = 430, 23.4%) | BCS+RT (n = 114, 6.2%) | BCS+HT+RT (n = 1181, 64.3%) | p value |
|--------------------------|------------------|--------------------------|------------------------|------------------------|-----------------------------|---------|
| **Follow-up period (Years)** |                  |                          |                        |                        |                             |         |
| Mean ±SD                 | 3.5 ±1.7         | 3.5 ±1.8                 | 3.3 ±1.7               | 3.8 ±1.7               | 3.5 ±1.7                    | 0.0254  |
| Median (Q1, Q3)†         | 3.3 (2.1–4.8)    | 3.3 (1.9–5.0)            | 3.0 (1.9–4.6)          | 3.7 (2.5–5.2)          | 3.4 (2.2–4.9)               |         |
| **Age of diagnosis**     |                  |                          |                        |                        |                             |         |
| Mean ±SD                 | 53.6 ±9.7        | 52.6 ±11.5               | 55.0 ±10.8             | 52.7 ±10.3             | 53.3 ±8.9                   | 0.0053  |
| Median (Q1, Q3)†         | 52.0 (47–61)     | 51.0 (45–61)             | 54.0 (47–63)           | 52.0 (46–61)           | 52.0 (47–60)                |         |
| **Age ranks (%)**        |                  |                          |                        |                        |                             |         |
| 20–50 y/o                | 785 (42.8)       | 55 (49.6)                | 168 (39.1)             | 52 (45.6)              | 510 (43.2)                  | <0.0001 |
| 51–70 y/o                | 979 (53.3)       | 47 (42.3)                | 231 (53.7)             | 57 (50.0)              | 644 (54.5)                  |         |
| >70 y/o                  | 72 (3.9)         | 9 (8.1)                  | 31 (7.2)               | 5 (4.4)                | 27 (2.3)                    |         |
| **Diagnosed year (%)**   |                  |                          |                        |                        |                             |         |
| 2011                     | 212 (11.6)       | 14 (12.6)                | 48 (11.2)              | 19 (16.7)              | 131 (11.1)                  | 0.0255  |
| 2012                     | 249 (13.6)       | 21 (18.9)                | 41 (9.5)               | 13 (11.4)              | 174 (14.7)                  |         |
| 2013                     | 290 (15.8)       | 18 (16.2)                | 70 (16.3)              | 19 (16.7)              | 183 (15.5)                  |         |
| 2014                     | 328 (17.9)       | 19 (17.1)                | 68 (15.8)              | 26 (22.8)              | 215 (18.2)                  |         |
| 2015                     | 387 (21.1)       | 15 (13.5)                | 101 (23.5)             | 25 (21.9)              | 246 (20.8)                  |         |
| 2016                     | 370 (20.2)       | 24 (21.6)                | 102 (23.7)             | 12 (10.5)              | 232 (19.6)                  |         |
| **Characteristics of tumor** |                |                          |                        |                        |                             |         |
| Tumor size (mm)          |                  |                          |                        |                        |                             |         |
| Mean ±SD                 | 9.3 ±6.9         | 7.5 ±5.1                 | 9.0 ±7.9               | 10.4 ±7.5              | 9.5 ±6.6                    | 0.0053  |
| Grade (%)                |                  |                          |                        |                        |                             |         |
| Low                      | 739 (40.3)       | 63 (56.8)                | 195 (45.4)             | 37 (32.5)              | 444 (37.6)                  | <0.0001 |
| Intermediate             | 1025 (55.8)      | 45 (40.5)                | 221 (51.4)             | 65 (57.0)              | 694 (58.8)                  |         |
| High                     | 72 (3.9)         | 3 (2.7)                  | 14 (3.3)               | 12 (10.5)              | 43 (3.6)                    |         |
| Histology (%)            |                  |                          |                        |                        |                             |         |
| Comedo type              | 256 (13.9)       | 9 (8.1)                  | 43 (10.0)              | 16 (14.0)              | 188 (15.9)                  | 0.0057  |
| None-comedo type         | 1580 (86.1)      | 102 (91.9)               | 387 (90.0)             | 98 (86.0)              | 993 (84.1)                  |         |
| **Screening data**       |                  |                          |                        |                        |                             |         |
| Family history (%)       |                  |                          |                        |                        |                             |         |
| Negative                 | 1119 (61.0)      | 55 (49.6)                | 251 (58.4)             | 70 (61.4)              | 743 (62.9)                  | 0.0076  |
| Positive                 | 98 (5.3)         | 4 (3.6)                  | 17 (4.0)               | 9 (7.9)                | 68 (5.8)                    |         |
| Missing                  | 619 (33.7)       | 52 (46.9)                | 162 (37.7)             | 35 (30.7)              | 370 (31.3)                  |         |
| Menstruation status (%)  |                  |                          |                        |                        |                             |         |
| Premenopausal            | 892 (48.6)       | 56 (50.5)                | 187 (43.5)             | 59 (51.8)              | 590 (50.0)                  | 0.1128  |
| Postmenopausal           | 944 (51.4)       | 55 (49.6)                | 243 (56.5)             | 55 (48.3)              | 591 (50.0)                  |         |
| Suspect malignancy (%)   |                  |                          |                        |                        |                             |         |
| Negative                 | 375 (20.4)       | 18 (16.2)                | 89 (20.7)              | 21 (18.4)              | 247 (20.9)                  | 0.0114  |
| Positive                 | 842 (45.9)       | 41 (36.9)                | 179 (41.6)             | 58 (50.9)              | 564 (47.8)                  |         |
| Missing                  | 619 (33.7)       | 52 (46.9)                | 162 (37.7)             | 35 (30.7)              | 370 (31.3)                  |         |
| **CCI (%)**              |                  |                          |                        |                        |                             |         |
| 0                        | 1109 (60.4)      | 72 (64.9)                | 254 (59.1)             | 66 (57.9)              | 717 (60.7)                  | 0.8754  |
| 1                        | 413 (22.5)       | 25 (22.5)                | 101 (23.5)             | 26 (22.8)              | 261 (22.1)                  |         |
| 2                        | 188 (10.2)       | 8 (7.2)                  | 50 (11.6)              | 13 (11.4)              | 117 (9.9)                   |         |
| ≥3                       | 126 (6.9)        | 6 (5.4)                  | 25 (5.8)               | 9 (7.9)                | 86 (7.3)                    |         |
| **Lifestyle**            |                  |                          |                        |                        |                             |         |
| Obesity (%)†             |                  |                          |                        |                        |                             |         |

(Continued)
Sub-analysis

For post-menopausal patients, 40 (4.80%) and 10 (9.09%) recurrence events were identified from the groups receiving regimens with HT (BCS±RT+HT, n = 834) and without HT (BCS±RT, n = 110), respectively (Fig 3A). In comparison, 57 (7.34%) and 10 (8.70%) recurrent events were identified from regimens with (n = 777) and without HT (n = 115), respectively in pre-menopausal patients (Fig 3B). In the post-menopausal group, the 5-year RFS was significantly higher in patients who received HT than those without HT (93.42% vs. 87.73%). On the contrary, there was no difference between these regimens in the pre-menopausal patients.

Discussion

This population-based study investigated evidence that may inform an ongoing debate on de-escalating treatments of DCIS, particularly in patients with low-to-intermediate recurrence risk. Similar to the previous literature, this study found that the recommended treatment regimen (BCS+HT+RT) resulted in a significantly lower risk of recurrent than the regimen of BCS alone without any adjuvant therapy in patients with HR(+)-DCIS, i.e., low-to-intermediate recurrence risk. However, combining BCS with dual adjuvant therapies acquired no additional benefits than single adjuvant therapy. The recurrent risk of both BCS+RT or BCS+HT regimen was comparable to BCS+HT+RT. Moreover, the five-year RFS rate was higher in the BCS+RT group than in the BCS+HT+RT group. Compared to the addition of HT to BCS, the addition of RT might be more critical to reduce the subsequent recurrence risk. Furthermore,
dominating advantage of single over dual adjuvant therapies was not observed in patients with a high risk of recurrence (S1 Fig). Therefore, these results support the proposition to de-escalate adjuvant treatments in patients with low-to-intermediate risk of DCIS recurrence.

Previous UK/ANZ DCIS trial indicated the effectiveness of single adjuvant therapy when investigated the risk of any breast cancer event occurred in patients with locally excised DCIS comparing BCS+HT versus BCS alone (HR: 0.71, 95%CI: 0.57–0.87) or BCS+RT versus BCS alone (HR: 0.41, 95%CI: 0.30–0.57). When comparing the dual and single adjuvant therapies, this trial demonstrated that single adjuvant RT did not incur a significantly higher risk than dual therapy (BCS+RT+HT vs. BCS+RT, HR: 0.99, 95%CI: 0.61–1.59), but single adjuvant HT seems to have a higher risk of recurrence compared to dual therapy (BCS+RT+HT vs. BCS +HT, HR: 0.44, 95%CI: 0.32–0.60) [16].

In line with the consensus guideline that RT was recommended as an adjuvant method to reduce recurrence risk [33], our study found BCS+RT resulted in a significantly lower 5-year recurrence rate than BCS alone (6.14% vs. 11.71%). These results were similar to a previous

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**Fig 2. Kaplan Meier plot of cumulative recurrence-free survival among BCS-based regimens.** Abbreviations: BCS, breast-conserving surgery; HT, hormone therapy; RT, radiation therapy; RFS, recurrence-free survival.

![Kaplan Meier plot](https://doi.org/10.1371/journal.pone.0262934.g002)
Table 2. Univariate and multivariable adjusted hazard ratios of covariates for breast cancer recurrence.

| Characteristic                  | Univariate HR | P value  | Adjusted HR† | P value |
|---------------------------------|---------------|----------|--------------|---------|
| **BCS-based regimen**           |               |          |              |         |
| BCS+HT+RT                       | 1.00          |          | 1.00         |         |
| BCS alone                       | 2.20 (1.21–3.99) | 0.0097  | 2.05 (1.11–3.78) | 0.0216  |
| BCS+HT                          | 1.50 (0.98–2.28) | 0.0598  | 1.52 (0.99–2.35) | 0.0582  |
| BCS+RT                          | 1.06 (0.48–2.31) | 0.8892  | 1.10 (0.50–2.41) | 0.8186  |
| **Age ranks**                   |               |          |              |         |
| 20–50 y/o                       | 1.00          |          | 1.00         |         |
| 51–70 y/o                       | 0.60 (0.42–0.88) | 0.0083  | 0.73 (0.38–1.39) | 0.3335  |
| >70 y/o                         | 0.88 (0.35–2.18) | 0.7769  | 0.73 (0.23–2.30) | 0.5889  |
| **Characteristics of tumor**    |               |          |              |         |
| Tumor size                      |               |          |              |         |
| Low                             | 1.00          |          | 1.00         |         |
| Intermediate                    | 0.87 (0.61–1.26) | 0.4716  | 1.03 (0.70–1.52) | 0.8756  |
| High                            | 0.42 (0.10–1.72) | 0.2268  | 0.60 (0.14–2.55) | 0.4843  |
| **Histology**                   |               |          |              |         |
| Non-comedo type                 | 1.00          |          | 1.00         |         |
| Comedo type                     | 1.24 (0.68–2.26) | 0.4753  | 1.19 (0.64–2.22) | 0.5906  |
| **Screening data**              |               |          |              |         |
| Menopausal status               |               |          |              |         |
| Premenopausal                   | 1.00          |          | 1.00         |         |
| Postmenopausal                  | 0.69 (0.48–0.99) | 0.0435  | 0.91 (0.47–1.75) | 0.7801  |
| Previously suspected as malignancy‡ | 1.00          |          | 1.00         |         |
| Negative                        | 1.00          |          | 1.00         |         |
| Positive                        | 1.65 (0.86–3.15) | 0.1312  | 1.75 (0.89–3.45) | 0.1072  |
| **Family history§**            |               |          |              |         |
| Negative                        | 1.00          |          | 1.00         |         |
| Positive                        | 0.33 (0.08–1.34) | 0.1216  | 0.38 (0.09–1.57) | 0.1816  |
| **CCI**                         |               |          |              |         |
| 0                               | 1.00          |          | 1.00         |         |
| 1                               | 0.96 (0.60–1.52) | 0.8448  | 1.14 (0.71–1.83) | 0.5938  |
| 2                               | 1.31 (0.76–2.26) | 0.3261  | 1.55 (0.89–2.70) | 0.1259  |
| ≥3                              | 0.99 (0.47–2.05) | 0.9697  | 1.46 (0.68–3.12) | 0.3321  |
| **Lifestyle**                   |               |          |              |         |
| Smoking                         |               |          |              |         |
| Negative                        | 1.00          |          | 1.00         |         |
| Positive                        | 1.00 (0.57–1.75) | 0.9910  | 1.20 (0.51–2.85) | 0.6741  |
| Alcohol consumption             |               |          |              |         |
| Negative                        | 1.00          |          | 1.00         |         |
| Positive                        | 0.94 (0.53–1.67) | 0.8293  | 0.81 (0.33–1.98) | 0.6395  |
| Obesity§,§                       |               |          |              |         |
| Negative                        | 1.00          |          | 1.00         |         |
| Positive                        | 0.67 (0.39–1.14) | 0.1378  | 0.70 (0.40–1.21) | 0.2002  |

Abbreviations: BCS, breast-conserving surgery; HT, hormonal therapy; RT, radiation therapy

†The multivariable analysis was adjusted by the covariates, including residential areas, diagnosed a year, and insurance income rank.

‡We created another category for the missing data and adjusted them in the regression model.

§Obesity was defined as a body mass index of >25 according to the Health Promotion Administration.

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study that synthesized data from randomized controlled trials and reported BCS+RT with a significantly lower 5-year ipsilateral breast event rate than BCS alone (7.6% vs. 18.1%, \( P < 0.0001 \)) in all patients with DCIS [34]. The slight differences observed may be attributed to the different study cohorts; our study included only an HR(+) low-to-intermediate risk population, previously determined to have a low recurrence risk [10]. Moreover, the results of a large matched cohort study also support the effectiveness of single adjuvant RT. Giannakeas et al. reported that the 15-year mortality was lower with BCS+RT than with BCS alone in patients with DCIS (1.74% vs. 2.33%) [35].

Nevertheless, the effectiveness of single adjuvant HT is less conclusive. Our study found the recurrent event rate of single adjuvant HT (BCS+HT) was significantly lower than BCS alone (7.67% vs. 11.71%) but slightly higher than BCS+RT+HT (7.67% vs. 5.42%; HR: 1.52, 95%CI: 0.99–2.35). These results echoed with the UK/ANZ DCIS trial results, and the discrepancy in effect size might be because our study only focused on the HR(+) and low-to-intermediate risk instead of all DCIS patients with BCS. In addition, the NSABP B-24 trial also reported that patients with HR(+) DCIS who received BCS+RT+tamoxifen showed a significant reduction in any breast cancer event while compared to BCS+RT (HR: 0.58, 95%CI: 0.415–0.81) [15]. The difference between the NSABP B-24 trial and our study (HR: 1.52, 95%CI: 0.99–2.35) might be because our study only included a cohort with low-to-intermediate risk.

This study adopted the scoring system for recurrence risk from Smith et al. (2006) using clinicopathological factors, as the information is available in the TCR database [21]. Single adjuvant RT benefited patients in either the low-to-intermediate-risk or high-risk groups. In the low-to-intermediate risk group, the absolute reduction of 5-year recurrence rate associated with RT was 9.2% (BCS+RT vs. BCS: 5.9% vs. 15.1%) (Fig 2); in the high-risk group, the corresponding reduction was 10.4% (BCS+RT vs. BCS: 15.5% vs. 25.9%) (S1 Fig). However, histological evaluation has been criticized by the high inter-observer variability and many grading/classification systems variations.
Notably, an increasing number of molecular tools, such as molecular phenotypes and genes information, are being used to de-escalate treatment components in patients with a low recurrence risk identified by expanding multi-gene expression profiling techniques. In addition to these clinicopathological factors, molecular diagnostics may offer a path to determine DCIS subtypes for de-escalating therapy in future precision medicine. For instance, Solin et al. created a specific panel of the Oncotype DX DCIS score (DS), calculated from seven cancer-related genes and five reference genes, that predicts LR risk after performing BCS alone on low-risk patients [36, 37]. Furthermore, Rakovich et al. also demonstrated that RT reduced the 10-year LR risk in patients with a low-risk (BCS+RT vs. BCS: 5.0% vs. 10.6%) and high-risk (BCS+RT vs. BCS: 12.6% vs. 25.4%) of recurrence based on the DS score. The absolute reduction associated with RT was greater in the high-risk than low-risk group (12.8% vs. 5.6%) [38], similar to our finding.

In addition to the clinical effectiveness, adherence to treatments, adverse effects and patient preferences also influence de-escalating adjuvant therapies. A systemic review found that the prevalence of HT adherence ranged from 41 to 72% over periods greater than four years among breast cancer survivors. The discontinuation (i.e., non-persistence) rate ranged from 31 to 73% measured at the end of five years of HT treatment. Side effects were negatively associated with adherence and/or persistence [39]. The CANTO study investigated patient-reported outcomes in a French prospective clinical cohort of stage I-III breast cancer patients. Two years after the breast cancer diagnosis, 15.9% and 21.0% of patients who received adjuvant HT and RT did not return to work [40]. Moreover, in our subgroup analysis, in the post-menopausal group, treatment regimens with adjuvant HT exhibited a higher 5-year RFS than those without HT. That was not observed in the premenopausal group. One of our previous studies also resonated that older age (≥50 years) was associated with adherence to HT [41].

As the first study to focus on patients with HR(+) DCIS in a Taiwanese population, the results can inform the de-escalating therapeutic strategy in patients with low-to-intermediate risk of recurrence. To compare the single and dual adjuvant therapies in this Asian population, we selected a representative cohort with HR positivity [42], i.e., a relatively high percentage of HR(+) patients. Furthermore, this study pioneered DCIS investigation in a low-to-intermediate risk local population categorized by risk scores compared with other studies. Because the risk score was a significant predictor of breast cancer recurrence [21], selecting a similar low-intermediate risk cohort was necessary to address the effectiveness of de-escalated treatment.

We acknowledge several limitations of this study. First, for the completion of biomarker information, only patients diagnosed after 2011 were included; besides, our dataset was available 2010–2017, resulting in a shorter follow-up period. However, the reported peak for breast cancer recurrence in patients with DCIS was between the first and second years after diagnosis [43]; our study findings could reference clinicians for considering the interventions during this period. Second, we lacked confirmed ipsilateral breast tumor recurrence and margin information from our database; therefore, we used any surgery or chemotherapy records identified in the NHI database after nine months from the index date as our surrogate definition of recurrence. However, the reason for some patients receiving an indication of a second surgery may be owing to positive margins or other causes and not because of DCIS recurrence. Consequently, the biological behavior may not be so aggressive. Finally, regarding the adherence to HT, our previous study [41] indicated the proportion of non-adherence to adjuvant HT in the whole HT prescribed period was slightly lower (15.6%) in breast cancer women who have prescribed HT while compared to most of the other published observational studies range from 12% to 59% depending on the definition of each study [39].

In conclusion, in an Asian population of non-high-risk HR(+) DCIS, the combination of dual adjuvant therapies showed no significant additional benefits and was associated with unnecessary escalation. Simultaneously, the undesirable adverse effects of combined dual
Adjuvant therapies and patient quality of life should be considered during individual decision-making. The present study provided information to help clinicians avoid specific adjuvant treatments in patients with low-intermediate risk HR(+) DCIS. We believe that the results from the ongoing active surveillance trials, genomic prognostic testing, molecular biomarkers, and artificial intelligence tools will be helpful to provide more targeted, personalized treatment options for women with DCIS.

Supporting information

S1 Fig. Kaplan Meier plot of cumulative recurrence-free survival among BCS-based regimens in a high-risk group. Abbreviations: BCS, breast-conserving surgery; HT, hormone therapy; RT, radiation therapy.

(TIF)

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