

Multiple Primary Cancer and Survival after Lumpectomy with or without Radiotherapy for Ductal Carcinoma in Situ: A Propensity Score Matching Case-Control Study

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Abstract

Background: Radiotherapy combined with breast-conserving surgery is widely performed in patients with ductal carcinoma in situ (DCIS). This research was conducted to evaluate the use of radiotherapy to reduce the risk of MPC and mortality in DCIS patients.

Methods: 128,416 patients first diagnosed with DCIS between 1998 and 2015 who received lumpectomy in the Surveillance, Epidemiology, and End Results (SEER) 18 database were included. Information on age, race, year of diagnosis, laterality, pathologic grade, surgery, radiation, estrogen receptor status, progesterone receptor status, tumor size and vital status was extracted. A comparison of lumpectomy alone vs. lumpectomy plus radiotherapy was performed using 1:1 propensity score-based matching.

Results: Of the 128,416 patients with DCIS, 39,039 patients were treated with lumpectomy alone, and 69,377 were treated with lumpectomy and radiotherapy. The adjusted hazard ratio (HR) for death was 0.801 (95%CI: 0.7728-0.8301) and 0.7444 (95%CI: 0.7139-0.7761) for occurrence of MPC in the lumpectomy and radiotherapy vs. lumpectomy alone groups, respectively. Radiotherapy decreased the standardized incidence ratio (SIR) of MPC from 1.36 to 1.34. The incidence rate of a second breast cancer was reduced by 1.83% with radiotherapy (from 5.93% (2,177/36,688) to 4.10% (1,504/36,688)) in the matched cohort.

Conclusion: Lumpectomy plus radiotherapy is associated with a significant reduction in mortality and risk of MPC, mainly second primary BC. Of those patients younger than 40 years, Black women with high-grade tumors were likely to benefit most. Radiotherapy reduced the risk of occurrence rather than the mortality of MPC patients to reduce the overall mortality.

Introduction

Ductal carcinoma in situ (DCIS) is a noninvasive condition in which abnormal cells are found in the lining of a breast duct^[1]. Since the 1970s, multicenter prospective randomized controlled studies on breast-conserving surgery for early breast cancer (BC) patients have shown no significant difference in disease-free and overall survival in such patients compared to those receiving total mastectomy^[2, 3]. In addition, radiotherapy plays an essential role in breast-conserving surgery^[4, 5], resulting in low mortality for patients with DCIS^[6, 7]. While long-term survivors benefit from systemic treatment, the frequency of multiple primary cancer (MPC) diagnosis after BC has been increasing, with MPC becoming one of the leading causes of death^[8].

Multiple primary cancer (MPC) is defined as more than 2 separate original tumors that simultaneously or successively occur in the same or different organs^[9]. Previous studies reported a greater risk of MPC among patients with an initial diagnosis of breast cancer at the age of < 50 years and in Black women with an ER-/PR- status than in Other patients^[10]. A clinical study reported that the use of systemic therapy

did not increase the risk of MPC^[11], while a nested case-control study using the SEER database suggested that radiotherapy (HR = 1.33) was related to the risk of second primary malignancy after BC^[12].

To further study the risk of MPC and mortality in DCIS patients, we conducted a population-based study of women with DCIS using the Surveillance, Epidemiology, and End Results (SEER) database. We extracted data on age and year of diagnosis, laterality, pathologic grade, treatment (surgery and radiation), estrogen receptor (ER) status, progesterone receptor (PR) status, tumor size, MPC and death from BC. We sought to determine whether radiotherapy was associated with a reduced risk of BC death and MPC in this cohort of women and to identify subgroups of women who might benefit the most from radiotherapy.

Materials And Methods

Study Population

SEER 18 Regs Custom Data (with additional treatment fields), Nov 2017 Sub (1973–2015 varying) was used to identify the cohort of women for this study. We selected all female patients with confirmed stage 0 BC coded by the 6th edition breast-adjusted AJCC guidelines^[13]. Among the cases classified as Tis, we excluded those associated with lobular carcinoma in situ, Paget's disease, and an unknown or invasive histology type. We excluded cases with unknown laterality and unknown or no surgical intervention for the primary tumor. We also excluded patients who underwent mastectomy to study those who underwent lumpectomy only. The flow chart of selection is provided in Fig. 1.

Variables

The SEER data included patient age at diagnosis, race (White, Black, or Other (American Indian/AK Native or Asian/Pacific Islander)), year of diagnosis, laterality, pathologic grade, surgery of the primary site, radiation, estrogen receptor status, progesterone receptor status, tumor size and vital status. We determined 2 time intervals: the time from DCIS to death and the time between the diagnosis of BC and a second primary cancer incidence. We divided all the patients diagnosed with a second primary BC after DCIS into ipsilateral and contralateral groups to compare the laterality of the two primary cancers. Patients eligible for study were categorized into 2 groups: lumpectomy without radiation and lumpectomy with radiation. The groups were compared for the variables above, and differences were evaluated using standardized differences.

Matching

Patients were 1:1 matched for age at diagnosis, race (White, Black, or Other (American Indian/AK Native or Asian/Pacific Islander)), year of diagnosis, laterality, pathologic grade, estrogen receptor status, progesterone receptor status and tumor size. Caliper matching was performed by matching participants

who were within 0.2 times the standard deviation of their propensity score^[14]. A standardized difference of greater than 0.1 was considered a meaningful imbalance between comparison groups.^[15]

Statistical Analysis

Among all participants treated with lumpectomy, we conducted subgroup comparisons by age, race, ER status, PR status, tumor grade, and tumor size (using inverse probability of treatment weighting) to determine the extent to which radiation was associated with decreased risk of death in these various subgroups. The stabilized inverse probability of treatment-weighted estimates were truncated at the 1st and 99th percentiles^[15, 16].

The incidence of second primary cancer was compared to the expected incidence in the general population by calculating standardized incidence ratios (SIRs) and 95% confidence intervals (CIs). SIRs were calculated overall and stratified by clinical parameters. Cumulative survival curves for each patient variable were constructed using the Kaplan-Meier method and were analyzed using the log-rank test in GraphPad Prism 7. Variables with persistent prognostic value were identified by Cox proportional hazards regression, and the associated hazard ratios (HRs) were reported. Statistical analysis was performed using R version 3.6.3 software (<http://www.r-project.org/>).

Results

Baseline Clinical Characteristics

Among the 128,416 patients involved in the cohort, 39,039 patients were treated with lumpectomy alone, and 69,377 were treated with lumpectomy and radiotherapy (Table 1). Radiotherapy was performed with lumpectomy less often in elderly patients (older than 70 years old) than lumpectomy alone (11,927 [30.6%] patients treated with lumpectomy and 12,351 [17.8%] patients treated with lumpectomy plus radiotherapy). Slightly more Black patients and patients of Other races (American Indian/AK Native or Asian/Pacific Islander) received radiotherapy than radiotherapy plus lumpectomy (Black: 7,502 [10.8%] vs. 3,958 [10.1%]; Other races: 7,317 [10.5%] vs. 3,823 [9.8%]). The use of radiotherapy also increased with increasing tumor grade. Radiotherapy was more commonly used when the estrogen receptor status or the progesterone receptor status was positive.

Table 1. Baseline characteristics of patients with ductal carcinoma in situ

Table 1
Baseline characteristics of patients with ductal carcinoma in situ

	N (%)		
Value	Lumpectomy alone	Lumpectomy plus radiotherapy	SMD
Patients	39,039	69,377	
Age at diagnosis, y			
<40	864 (2.2)	1,440 (2.1)	0.303
40–54	11,943 (30.6)	25,388 (36.6)	
55–69	14,305 (36.6)	30,198 (43.5)	
70+	11,927 (30.6)	12,351 (17.8)	
Race			
Black	3,958 (10.1)	7,502 (10.8)	0.093
Other	3,823 (9.8)	7,317 (10.5)	
Unknown	520 (1.3)	343 (0.5)	
White	30,738 (78.7)	54,215 (78.1)	
Year of diagnosis			
1998–2004	13,621 (34.9)	19,920 (28.7)	0.133
2005–2009	11,176 (28.6)	21,669 (31.2)	
2010–2015	14,242 (36.5)	27,788 (40.1)	
Laterality = right	19,033 (48.8)	33,932 (48.9)	0.003
Grade			
I	6,843 (17.5)	7,569 (10.9)	0.35
II	15,056 (38.6)	24,538 (35.4)	
III	10,063 (25.8)	28,295 (40.8)	
Unknown	7,077 (18.1)	8,975 (12.9)	
Estrogen receptor status			
Negative	2,329 (6.0)	7,128 (10.3)	0.314
Positive	20,459 (52.4)	43,114 (62.1)	
Unknown	16,251 (41.6)	19,135 (27.6)	

	N (%)		
Progesterone receptor status			
Negative	3,914 (10.0)	11,372 (16.4)	0.308
Positive	17,244 (44.2)	35,899 (51.7)	
Unknown	17,881 (45.8)	22,106 (31.9)	
Tumor size, cm			
<2.0	22,195 (56.9)	41,597 (60.0)	0.143
2.0-4.9	4,481 (11.5)	9,951 (14.3)	
≥5.0	1,075 (2.8)	1,572 (2.3)	
Unknown	11,288 (28.9)	16,257 (23.4)	
Abbreviations: SMD, standardized mean difference			

Radiotherapy Reduced The Risk Of Mortality And Mpc

In the matched comparison of patients treated with lumpectomy vs. lumpectomy and radiotherapy, radiotherapy reduced the risk of death (HR = 0.7444, 95%CI: 0.7139–0.7761) (Fig. 2a). In addition, we determined the time interval between the first diagnosis of DCIS and the occurrence of multiple primary cancer (MPC) among the 36,688 propensity-matched pairs. The adjusted HR for MPC in the lumpectomy and radiotherapy vs. lumpectomy alone groups was 0.801 (95%CI: 0.7728–0.8301) (Fig. 2b). Moreover, radiotherapy benefited breast cancer specific survival.(Fig. s1)

Younger Black women and high-grade tumors benefited the most from radiotherapy

Next, we assessed the protective effect of radiotherapy on mortality and MPC incidence in different subgroups using inverse probability of treatment weighting (Fig. 3). All subgroups could benefit from radiotherapy, but the degree of benefit varied among different subgroups. For the risk of MPC, patients younger than 40 years benefited more than elderly patients (0.783 (95%CI: 0.685–0.895) vs. 0.802 (95%CI: 0.776–0.829)). Black women benefited more than White women (0.74 vs. 0.823). The HR was 0.898 for patients with grade I tumors, 0.806 for patients with grade II tumors, and 0.793 for patients with high-grade tumors (grade III). The subgroup containing Black women younger than 40 years with high-grade tumors benefited more than other subgroups in terms of mortality (Fig. 3b). The only difference was that ER-positive patients benefited more than ER-negative in terms of a reduced risk of MPC (0.777 vs. 0.798), but the opposite was true in terms of mortality (0.65 vs. 0.555).

Effect of radiotherapy on the standardized incidence ratio differed by tumor type

Next, we calculated and compared the standardized incidence ratios (SIRs) among DCIS patients treated with lumpectomy vs. lumpectomy plus radiotherapy (Fig. 4). The rates of MPC that occurred at all sites among those treated with radiation (lumpectomy plus radiotherapy SIR = 1.34, 95%CI: 1.32–1.39; lumpectomy alone SIR = 1.36, 95%CI: 1.34–1.38) were lower than those among patients treated with other therapies, while both SIRs were higher than those for the general female population in the SEER database. The SIRs varied across different types of second primary cancer. For second BC, which accounted for the largest proportion of second primary cancer, the SIR was 2.11 (95%CI: 2.06–2.17) for patients treated with radiation and 2.19 (95%CI: 2.13–2.24) for patients treated without radiation. Radiotherapy had a protective effect on reducing the SIRs in patients with kidney, renal pelvis (1.18 to 1.14), colon and rectal cancer (0.83 to 0.82), while the SIRs were higher in patients with oral cavity, pharynx cancer or splenic flexure cancer.

Radiotherapy reduced both contralateral and ipsilateral second breast cancer incidence

The incidence rate of second breast cancer was reduced by 1.83% with radiotherapy (from 5.93% (2,177/36,688) to 4.10% (1,504/36,688)) in the matched cohort. The incidence rate of contralateral second primary breast cancer incidence rate was reduced from 0.06% with radiotherapy (from 2.45% (901/36,688) to 2.39% (879/36,688)). The reduction was greater when the second breast cancer occurred ipsilaterally (from 3.48% (1,276/36,688) to 1.7% (625/36,688)).

Radiotherapy reduced the risk of occurrence of MPC rather than the mortality of MPC patients to reduce the overall mortality

To elucidate the association between radiotherapy and the prognosis of patients with only one primary cancer, KM curve analyses were performed. MPC patients had a higher risk of death than patients with only one primary cancer, and the HR was 1.944 (95%CI: 0.848–2.045) (Fig. 5a). Radiotherapy reduced the risk of death in only the group of patients with one primary cancer (Fig. 5c), and no statistically significant reduction in the risk of death was found in the MPC group between patients treated with lumpectomy alone vs. those treated with lumpectomy plus radiotherapy.

Discussion

Our study is the first to characterize the risk of MPC and death in DCIS patients in a large population using propensity score matching analysis. Among those with DCIS treated with lumpectomy, the majority of patients received radiotherapy, and these patients were middle-aged and elderly and were more likely to

have high-grade disease, ER-positive status, PR-positive status and smaller tumor size than those who did not undergo radiation (Table 1). These factors were accounted for in the matched analysis, and propensity scoring was used to balance the baseline characteristics between the groups (eTable 1). Therefore, we believe that the reductions in the risk of death and MPC are a result of the radiotherapy.

In the present study, the incidence of a second primary breast, kidney, renal pelvis and thyroid cancer as well as leukemia after DCIS increased, similar to previous studies^[17,18]. As previously established, this increased risk of MPC is partially attributable to genetic and environmental influences. Importantly, we found that radiotherapy could reduce the risk of MPC by 20%, and several reports support our conclusion. Kaire Innos et al^[19] concluded that the use of radiation therapy appears to be protective against the occurrence of subsequent ipsilateral invasive cancer after studying California Cancer Registry data on 23,547 women with DCIS first diagnosed in 1988–1999. Carolyn J. Kushner et al^[20] studied a dataset comprising 755 women with DCIS (n = 135) or stage I-II breast carcinoma (n = 620) and found that high-dose radiotherapy (> 63 Grays) was not associated with a significantly increased risk of SMN. William Beaumont Hospital^[21] reported that the overall 10-year and 15-year rates of second malignancy among the surgery and radiotherapy (S + RT) and surgery alone cohorts were 14.2% and 24.2%, and 16.4% and 22.6%, respectively (p = 0.668). The 15-year second contralateral BC rate was 14.2% in the S + RT cohort and 10.3% in the surgery alone cohort (p = 0.439). There are several possible underlying mechanisms: 1) There is statistical evidence of departure from a linear dose-response, with a downward curvature seen at high doses, likely resulting from radiation-induced cell sterilization^[22]. 2) High-dose radiation may suppress estrogen production by relevant target cells, as well as androgen production by other cells (with androgen having the potential to be converted peripherally into estrogen)^[23]. 3) Previously hidden tumor-associated antigens, stress proteins and danger-associated molecular patterns will be exposed after radiotherapy^[24]. The exposure of antigens might activate antitumor immunity^[25] and stimulate tumor cell killing.

In addition, we sought to identify those individuals who would benefit the most from radiotherapy. Lumpectomy combined with radiotherapy reduced the risk of both ipsilateral and contralateral second BC compared with lumpectomy alone. Among patients younger than 40 years, Black women with high-grade tumors were likely to benefit most. An interesting finding in our study is that patients with a negative ER status benefited more in terms of mortality, while ER-positive patients benefit slightly more in terms of the risk of MPC. Although data from endocrine therapy use are not included in the SEER database, it is likely that some ER-positive patients received hormone treatment combined with radiotherapy; thus, the mortality benefit from radiation appeared artificially low. In addition, the IDEAL trial (BOOG 2006-05) found that adjuvant endocrine therapy did not have a statistically significant effect on either overall survival or distant recurrence but reduced the risk of MPC (HR = 0.39, 95%CI: 0.19–0.81, log-rank p = 0.01)^[26]. Considering the benefit of reducing the risks of mortality and MPC, we recommend that patients undergo radiotherapy whether receiving endocrine therapy or not.

Several studies have pointed out the relationship between recurrence and mortality and the benefit of radiation. In RTOG 9804, a good-risk subset of patients with mammographically detected low- or intermediate-grade DCIS, measuring less than 2.5 cm with margins ≥ 3 mm, the ipsilateral local failure rate was decreased significantly with the addition of radiotherapy^[6]. In 2018, Vasily Giannakeas et al studied 140,366 patients with DCIS diagnosed between 1998 and 2014 in the SEER 18 database. The adjusted HR for mortality associated with radiotherapy (based on 29,465 propensity-matched pairs) was 0.77 (95% CI: 0.67–0.88; $P < 0.001$)^[27]. A recent population-based cohort study observed that the rate of ipsilateral invasive BC for women undergoing breast-conserving surgery with no record of radiotherapy was higher than that for women receiving radiotherapy (adjusted rate ratio 1.43, 95% confidence interval 1.05 to 1.96), and the mortality from BC between the various treatment groups was similar^[28]. In our study, we found that radiotherapy could reduce the risk of death, and the HR was 0.744 (95%CI: 0.7139–0.7761) among the cohort. However, the reduction in death only occurred in the patients with only one primary cancer, and radiotherapy did not have a statically significant effect among the MPC patients. We further compared mortality and found that the occurrence of MPC led to a higher risk of death than no occurrence of MPC. Therefore, radiotherapy reduced the risk of MPC rather than the death associated with MPC and thereby reduced overall mortality.

Limitations

Our study has several limitations. First, this is a retrospective study from the SEER database rather than a prospective cohort study, so inherent selection biases may undermine its external validity. Second, similar to other SEER database studies, this study lacks specific information on chemotherapy and hormone treatment. Third, the treatments for patients were not assigned at random. In addition, cases with some unknown variables were excluded; thus, the results may not include all patients with DCIS.

Conclusion

Among patients with DCIS, treatment with lumpectomy plus radiotherapy was associated with a significant reduction in mortality and risk of MPC, mainly second primary BC. Among patients younger than 40 years, Black women with high-grade tumors were likely to benefit most. The effect of the sequence of radiation and surgery and the form of radiotherapy should be explored in future studies.

Declarations

Author Contributions: Conceptualization, Yitong Li.; methodology, Yitong Li and Wenjun Yi.; data curation, Yitong Li.; writing—original draft preparation, Yitong Li; writing—review and editing, Wenjun Yi.; visualization and supervision, Wenjun Yi. All authors have read and agreed to the published version of the manuscript.

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Figures

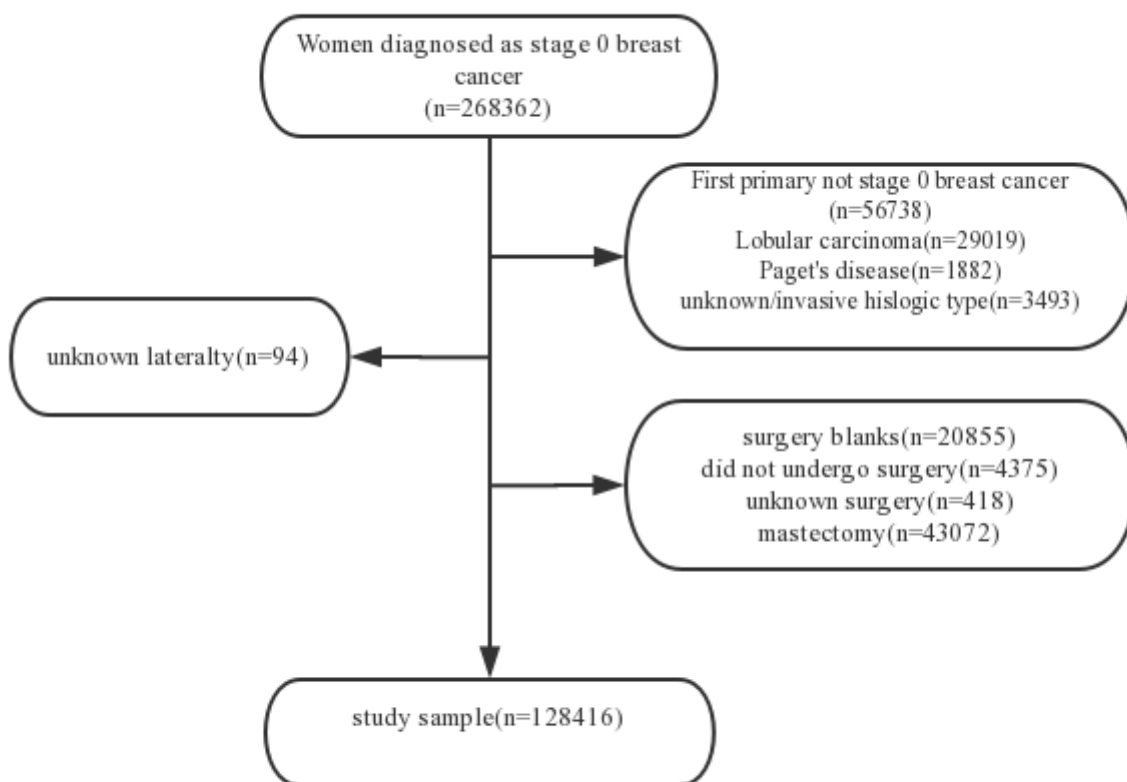


Figure 1

Flow chart for the selection of study samples

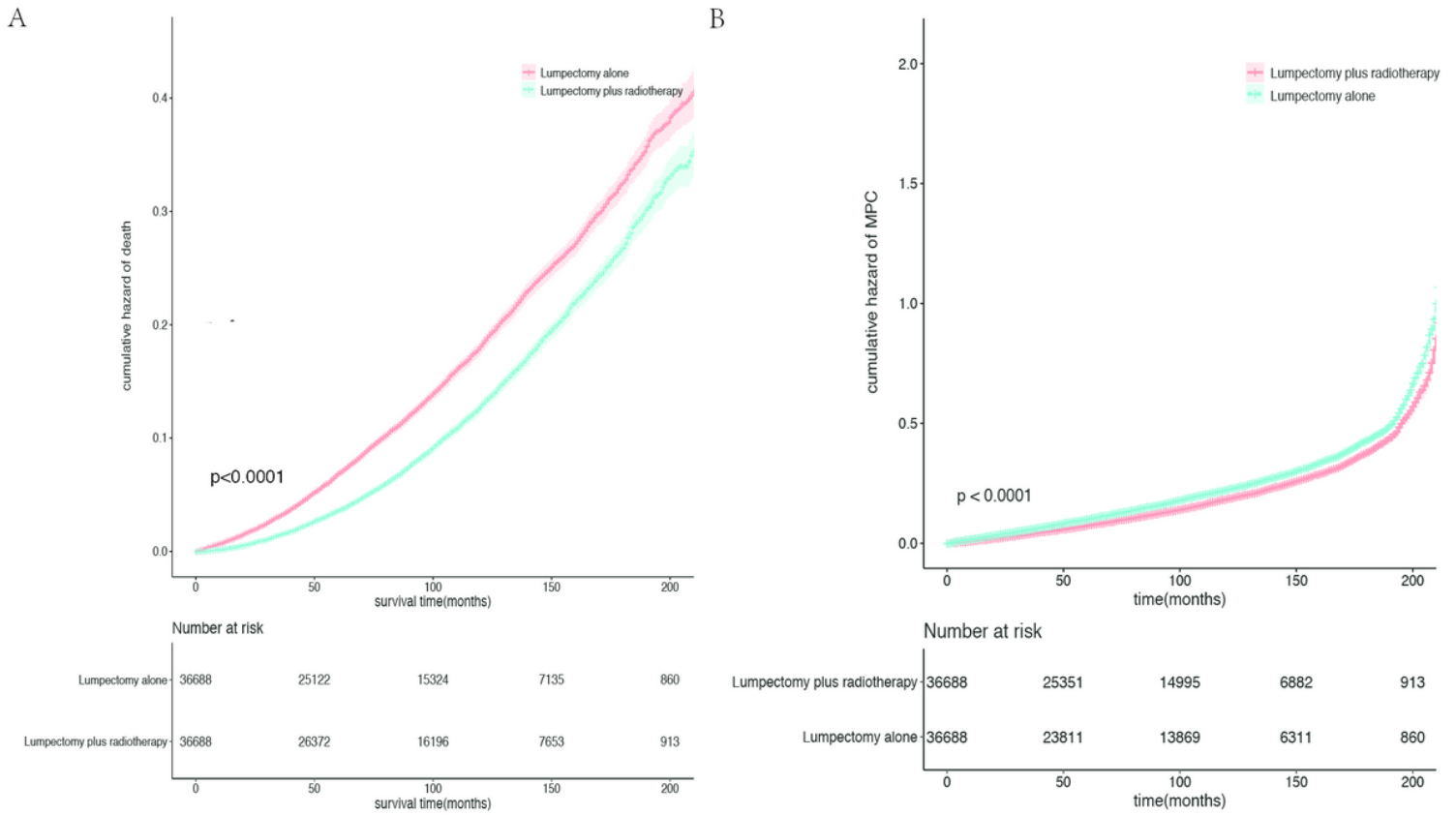


Figure 2

Kaplan-Meier curves of the cumulative hazard of death (A) and the cumulative hazard of multiple primary cancer (B) for DCIS patients (all $p < 0.0001$, log-rank test)

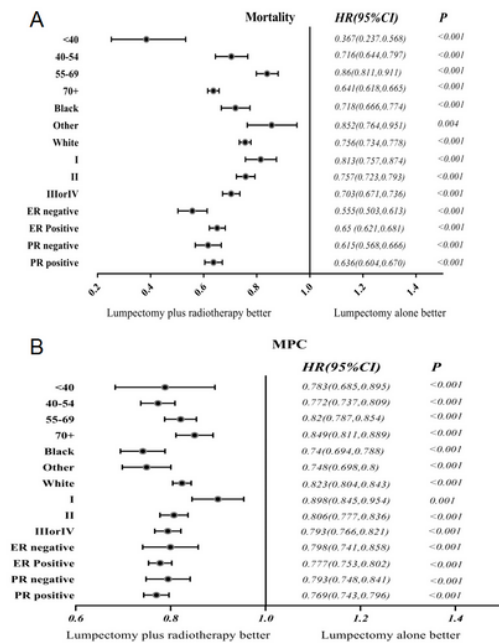


Figure 3

Hazard ratios for mortality (A) and the risk of multiple primary cancer (B) in various subgroups

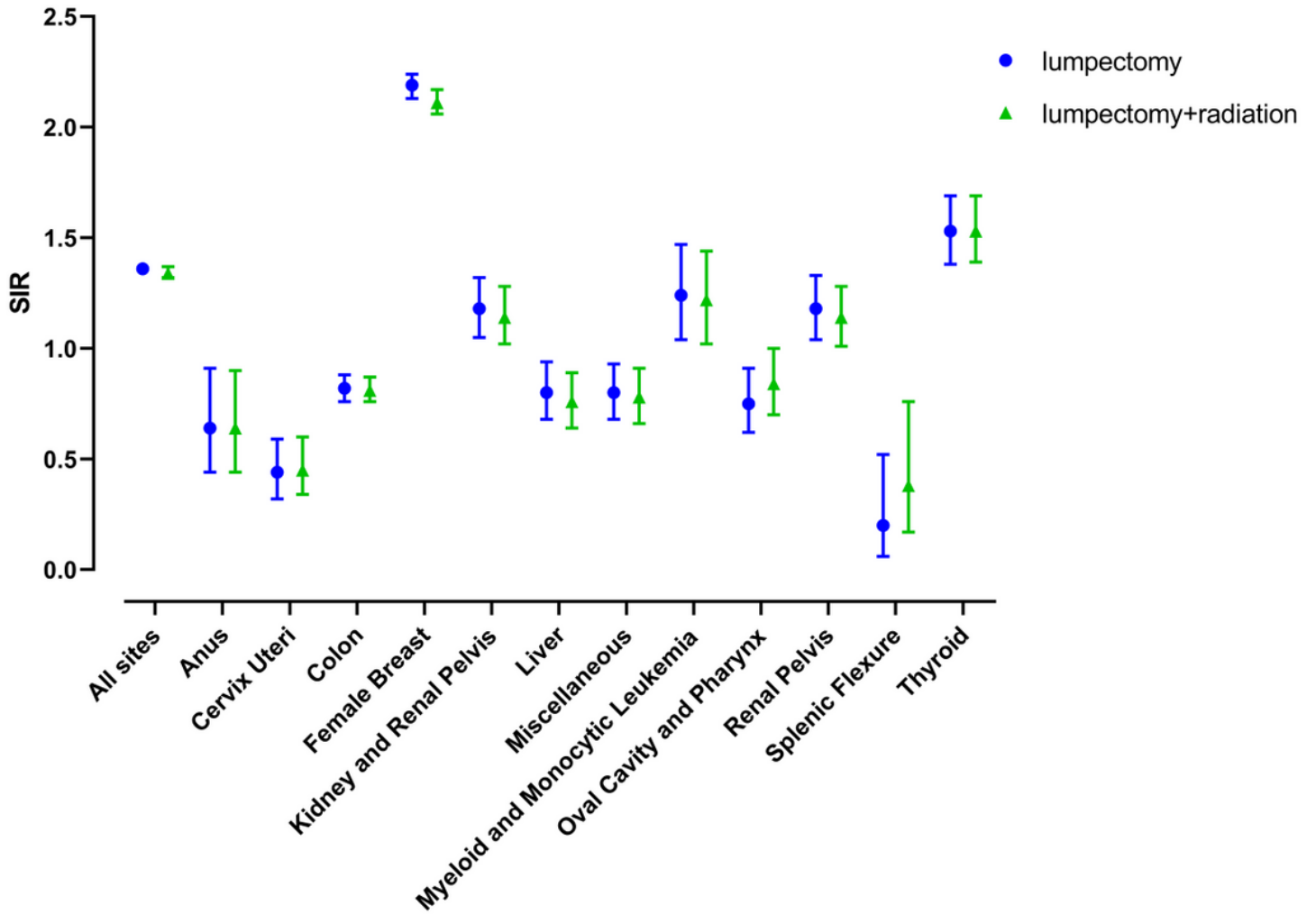


Figure 4

Standardized incidence ratios (SIRs) of second primary cancer after DCIS for patients treated with lumpectomy or lumpectomy plus radiation coded by "site recode B ICD-O-3/WHO 2008" showing a significant difference ($p < 0.05$) compared with those for the general population

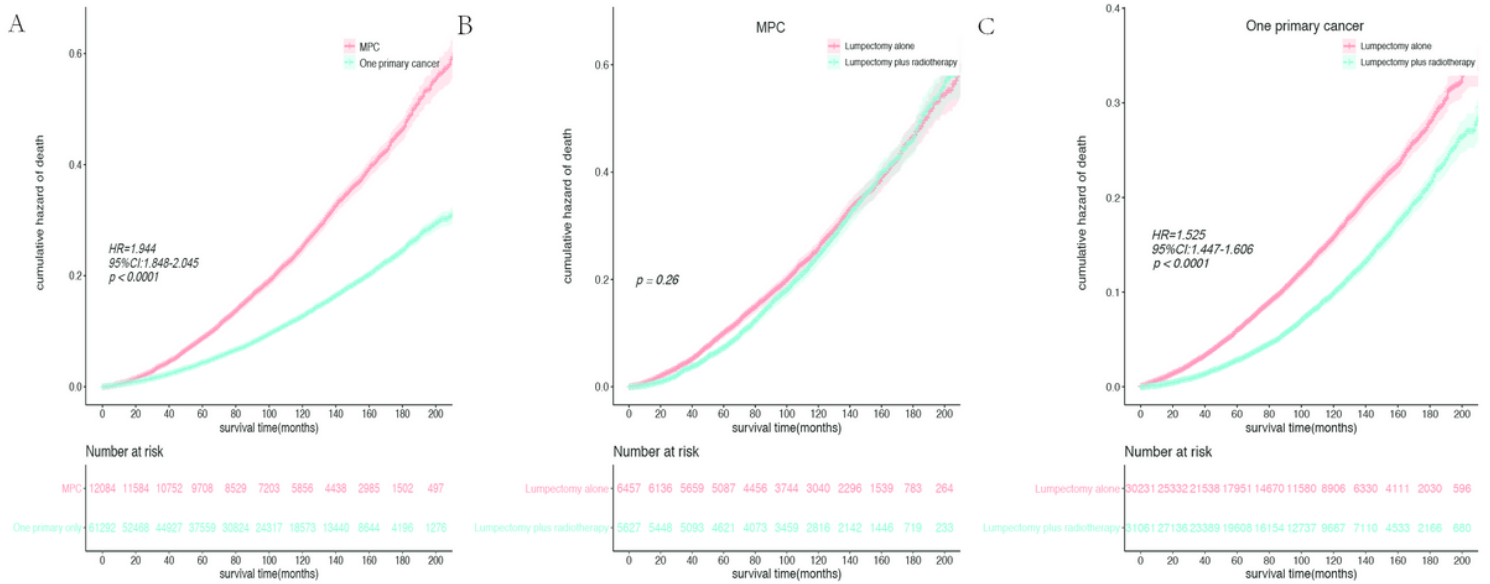


Figure 5

KM curves of patients overall (A); in the MPC group (B) and in the only one primary cancer group (C).

Supplementary Files

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