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ORIGINAL RESEARCH

Effectiveness of Image-Guided Radiotherapy in Adjuvant Radiotherapy on Survival for Localized Breast Cancer: A Population-Based Analysis

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Purpose: Image-guided radiotherapy (IGRT) is an advanced radiotherapy technique to improve the radiotherapy delivery. We aimed to compare the overall survival (OS) for localized breast cancer (LBC) patient treated with adjuvant conventional fractionated radiotherapy (CFRT) using IGRT vs those without IGRT via a population-based analysis.

Patients and Methods: Eligible LBC patients diagnosed between 2011 and 2013 were identified via the Taiwan Cancer Registry. We used propensity score (PS) weighting to balance observable potential confounders between groups. The hazard ratio (HR) of death and other outcomes were compared between IGRT and non-IGRT. We also evaluated OS in various supplementary analyses.

Results: Our primary analysis included 6490 patients in whom covariates were well balanced after PS weighing. The HR for death when IGRT was compared with non-IGRT was 1.02 (95% confidence interval 0.80–1.31, P = 0.86). There were also no significant differences in the supplementary analyses.

Conclusion: We found that OS of LBC patients treated with adjuvant CFRT was not statistically different between those treated with IGRT versus without IGRT. This was the first study in this regard to our knowledge but randomized controlled trials were needed to confirm our finding.

Keywords: breast cancer, effectiveness, image-guided radiotherapy

Introduction

Breast cancer is one of the leading causes of cancer mortality around the world including Taiwan.[1] Adjuvant radiotherapy (RT) is commonly used for localized breast cancer after breast-conserving surgery (BCS) or mastectomy[2] and can improve local control as well as overall survival.[3]

Image-guided radiotherapy (IGRT) is a strategy using various devices to improve the quality of treatment execution with the potential to improve outcomes.[4–6] In general, IGRT was recommended in the textbook[6] or radiotherapy guideline[7] although its role in breast cancer radiotherapy was less clear and stated as "routine use of daily imaging is not recommended" in the national comprehensive cancer network (NCCN) guideline.[2] IGRT was also usually highly preferred in the setting of radiosurgery or hypofractionated regimens.[5]

However, a randomized controlled trial (RCT) of conventional fractionated radiotherapy (CFRT) for definitive prostate radiotherapy was published in 2018 and reported significantly worse overall survival (OS) for those treated with IGRT.[8] Theoretically, the

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extra-radiotherapy dose due to xray-IGRT may have contributed to the increased risk of other cancer (10% vs 5%) or cardiovascular mortality (6/236 vs 1/234) observed in this study and led to the impaired overall survival.[8] It raised the concern regarding the effectiveness of IGRT in other cancers such as in breast cancer. However, there was no published RCT regarding IGRT's impact on OS for breast cancer to our knowledge.[9] Therefore, the aim of this comparativeness effectiveness research is to investigate the effectiveness of Image-guided radiotherapy in adjuvant conventional fractionated radiotherapy for localized breast cancer patients via a population-based analysis.

Patients and Methods

Data Source

In this retrospective cohort study, the analyzed data with personal identifiers removed were obtained from Health and Welfare Data Science Center (HWDC) database, which included the Taiwan cancer registry (TCR), death registration, and reimbursement data for the whole Taiwan population provided by the Bureau of National Health Insurance (NHI). The TCR is a high-quality database[10] that provides comprehensive information such as patient, disease, and treatment characteristics, and prognostic factor details. This study was approved by the research ethics committee at our institute (CRREC-108-080 by Central Regional Research Ethics Committee China Medical University which waived the requirement to obtain consent from the study participants prior to study commencement).

Study Population and Study Design

The study flowchart as suggested in the STROBE statement[11] was depicted in Figure 1. Our study population consisted of female localized breast cancer patients diagnosed within 2011–2013 who received adjuvant radiotherapy after R0 resection, with external beam radiotherapy using conventional fractionation via image-guided radiotherapy (IGRT) or non-IGRT. We selected this time frame to ensure at least 5 years window for survival measurement. We limited to CFRT instead of hypofractionated radiotherapy (HFRT) because CFRT was recommend for all three scenarios in our study whereas HFRT was not recommended for post-mastectomy chest wall radiotherapy or nodal irradiation.[2] In addition, IGRT was recommended for extreme HFRT in a previous study.[12] The three treatment scenarios included in our study were (A) BCS followed by RT; (B) mastectomy followed by RT; (C) neoadjuvant systemic therapy followed by surgery (BCS or mastectomy) followed by RT. We only included those age within 18−70 years old and excluded those with bilateral breast cancer or previous other cancer. These inclusion/exclusion criteria were based on the clinical trial, treatment guideline, and our clinical experiences.[2,12]

The explanatory variable of interest [IGRT vs non-IGRT], the primary outcome of interest [overall survival (OS)] and other supplementary outcomes [incidence of breast cancer mortality (IBCM), other cancer mortality (IOCM) and cardiovascular mortality (ICVM)] were determined via the recordings in TCR or the death registry. We adopted OS as the primary outcome of interest because OS was obviously the most important outcome and the negative OS reported in the previous IGRT RCT.[8] We defined the date of diagnosis as the index date and calculated the OS or other endpoints from the index date to the date of death or Dec 31, 2018 [the censoring date of death registry]. We also collected covariates from TCR and reimbursement data to adjust for potential nonrandomized treatment selection [see section "Other explanatory covariates" in Supplementary Material]. The covariates were modified from the literature[12] as well as our experiences in clinical care[13] and TCR studies.[14,15]

Statistical and Supplementary Analyses

In the primary analysis (PA), we adopted the propensity-score (PS) method with a logistic regression model based on the above covariates to balance the measured potential confounders.[16–18] We evaluated the probability of receiving IGRT (vs non-IGRT) and then assessed the balance of covariates between groups (IGRT vs non-IGRT) with the standardized difference.[13,19] During the entire follow-up period, we used the overlap weights[20,21] via a PS weighting approach to compare the hazard ratio (HR) of death between IGRT and non-IGRT groups. The cox proportional hazards model in the weighted sample was used for point estimation, and the bootstrap method was used to estimate the 95% confidence interval (95% CI).[20,22,23] We also compare IBCM, IOCM, and ICVM between groups using the competing risk approach.[24]

In the first to fourth supplementary analyses (SA), we adopted PS matching to construct 1:1 PS matched cohort for four subgroups separately and compared the HR of death between IGRT and non-IGRT groups via a robust variance estimator.[20] In the first supplementary analysis (SA-1), we performed PS matching among the study population of the primary analysis. We also did additional SA (SA-2 – SA-4)

for those received BCS & breast RT (SA-2), BCS & breast plus nodal RT (SA-3), and mastectomy and chest wall plus nodal RT (SA-4). We selected these three SA (SA-2 – SA-4) because these were the three common volumes used for breast cancer radiotherapy.[25–27] In the 5th SA, we used alternative covariate classification [T1, T2, T3, T4 for T-stage and N0, N1, N2, N3 for N-stage] in the PS weighting analyses as suggested during revision. The statistical analyses were performed using the software SAS 9.4 (SAS Institute, Cary, NC).

Results

Study Population in the Primary Analysis

Among 6490 eligible localized breast cancer females received IGRT or non-IGRT between 2011 and 2013 were identified, 1013 patients were treated with IGRT whereas 5477 were treated without IGRT (Figure 1). The patient characteristics are described in Table 1. One covariate [residency] was not balanced before weighting analysis, but all covariates were balanced (standardized differences <0.25) after PS weighting via overlap weights.

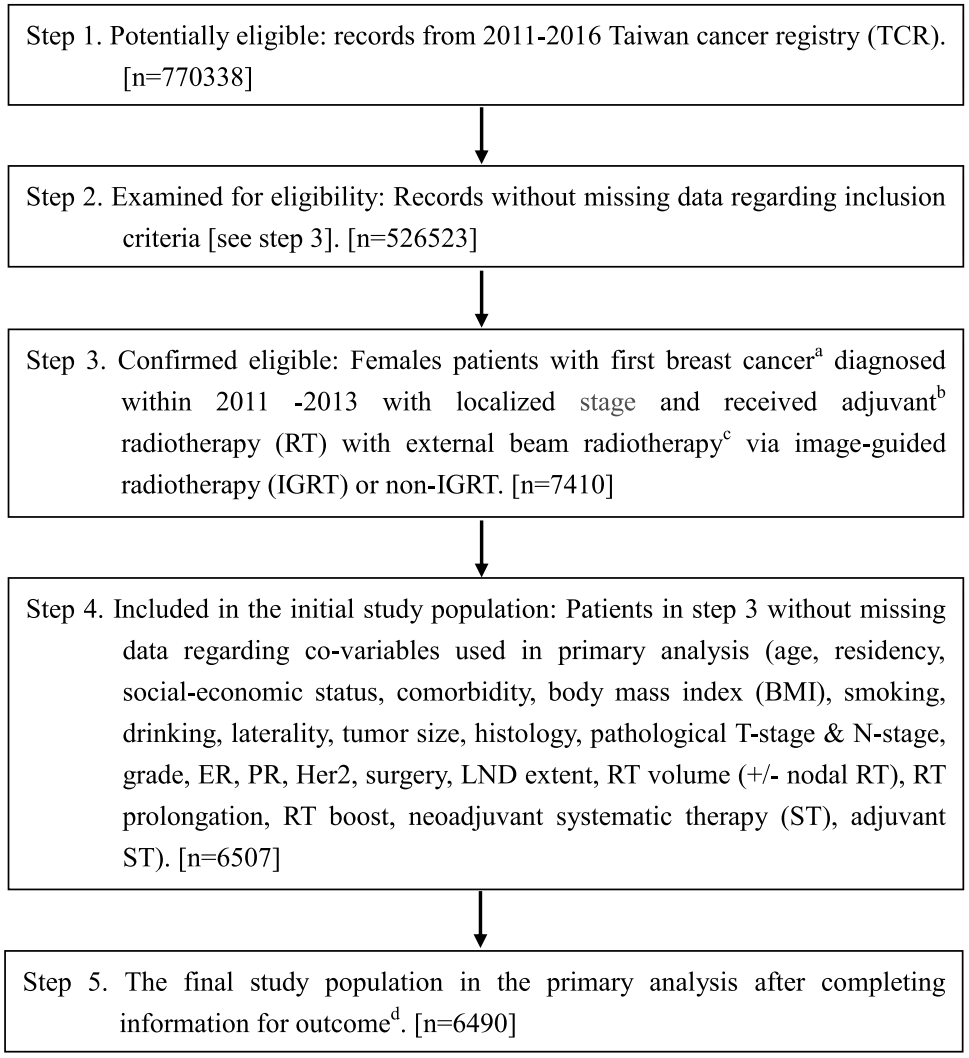

Figure 1 STROBE study flowchart and the number of individuals at each stage of the study.

Notes: [a]We only included those treated (class 1–2) to ensure data consistency. [b]Including three groups per The 7th edition of the American Joint Committee on Cancer staging: (group A) clinical stageT0-3N0-1M0 and pathological staging T1-4N0-3 treated with breast-conserving surgery (BCS); (group B) clinical stage T0-3N0-1M0 and pathological staging T1-4N1-3 treated with mastectomy; (group C) clinical stage T2-4N0-3M0 or T1-4N1-3M0, and pathological staging T0-4N0-3 treated with either BCS or mastectomy. [c]45–66.4 Gy in 1.8–2 Gy/fraction, within ±10% in dose and treatment duration. [d]Without missing information in the TCR and death registry regarding survival status, and cause of death.

Abbreviations: ER, estrogen receptor; Her2, human epidermal growth factor receptor 2; LND, lymph node dissection, expressed as number of pathologically examined lymph nodes; PR, progesterone receptor.

Table 1 Patient Characteristics of the Study Population in the Primary Analysis

		IGRT (n=1013)		Non-IGRT (n=5477)		Standardized Difference[a]	
		Number or Mean (sd)[a]	(%)[a]	Number or Mean (sd)[a]	(%)[a]	Before PSW	After PSW
Age (years)		50.17 (9.11)		50.77 (9.35)		0.065	≈0
Residency	Non-north	762	75	2485	45	0.641	≈0
	North	251	25	2992	55		
Social economic status	No more than minimum wage	215	21	1224	22	0.027	≈0
	Higher	798	79	4253	78		
Comorbidity	Without	730	72	3940	72	0.003	≈0
	With[b]	283	28	1537	28		
BMI		24.19 (4.10)		24.41 (4.24)		0.052	0
Smoking	No	964	95	5195	95	0.014	≈0
	Yes	49	5	282	5		
Drinking	No	979	97	5091	93	0.167	≈0
	Yes	34	3	386	7		
Laterality	Left	508	50	2804	51	0.021	0
	Right	505	50	2673	49		
Tumor size (mm)		24.20 (16.66)		24.32 (16.95)		0.007	0
Histology	IDC	886	87	4763	87	0.015	0
	Others	127	13	714	13		
pT	1–2	951	94	5178	95	0.028	0
	3–4	62	6	299	5		
pN	0–1	816	81	4329	79	0.038	0
	2–3	197	19	1148	21		
Grade	Low	701	69	3675	67	0.045	≈0
	High	312	31	1802	33		
ER	No	184	18	1051	19	0.026	0
	Yes	829	82	4426	81		
PR	No	268	26	1463	27	0.006	0
	Yes	745	74	4014	73		
Her2	No	767	76	4159	76	0.005	0
	Yes	246	24	1318	24		
Surgery	Mastectomy	280	28	1751	32	0.095	0
	BCS	733	72	3726	68		
LND extent (number)		10.82 (9.21)		12.34 (10.43)		0.155	≈0
RT volume	Without	499	49	2659	49	0.014	≈0
	With nodal RT	514	51	2818	51		
RT prolongation	≤ 1 week	943	93	5224	95	0.098	0
	> 1 week	70	7	253	5		
RT boost	No	274	27	1393	25	0.037	≈0
	Yes	739	73	4084	75		
Neoadjuvant ST	No	907	90	4866	89	0.022	≈0
	Yes	106	10	611	11		

(*Continued*)

Table 1 (Continued).

		IGRT (n=1013)		Non-IGRT (n=5477)		Standardized Difference[a]	
		Number or Mean (sd)[a]	(%)[a]	Number or Mean (sd)[a]	(%)[a]	Before PSW	After PSW
Adjuvant ST	No	21	2	129	2	0.019	0
	Yes	992	98	5348	98		

Notes: [a]Rounded. [b]Modified Carlson comorbidity score ≥1.

Abbreviations: BCS, breast-conserving surgery; BMI, body mass index; ER, estrogen receptor; IDC, infiltrating ductal carcinoma; Her2, human epidermal growth factor receptor 2; IGRT, image-guided radiotherapy; LND, lymph node dissection; PSW, propensity-score weighting; PR, progesterone receptor; RT, radiotherapy; sd, standard deviation; ST, systemic treatment.

Primary Analysis

After a median follow-up of 76 months [range 5–96 months], death was observed for 74 patients in the IGRT group and 401 patients in the non-IGRT group. The overlap weights adjusted OS curve was shown in Figure 2. The 5-year OS rates for two groups were 94.35% [IGRT] and 94.64% [non-IGRT]. The PS weighting adjusted HR of death when IGRT was compared to non-IGRT was 1.02 [95% confidence interval (95% CI) 0.80–1.31, P = 0.86]. The results were also not significantly different for IBCM [HR = 1.02, P = 0.94], IOCM [HR = 1.43, P = 0.51] and ICVM [HR = 0.65, P = 0.66].

Supplementary Analyses (SA)

In the SA-1 to SA-4, covariates were also balanced after PS matching [Table S1–S4]. There were also no statistically significant difference for OS when IGRT was compared to non-IGRT [SA-1: HR = 1.08, P = 0.64; SA-2: HR = 0.57, P = 0.09; SA-3: HR = 1.04, P = 0.91; SA-4: HR = 1.07, P = 0.77]. In SA-5 when alternative covariate classification was used,

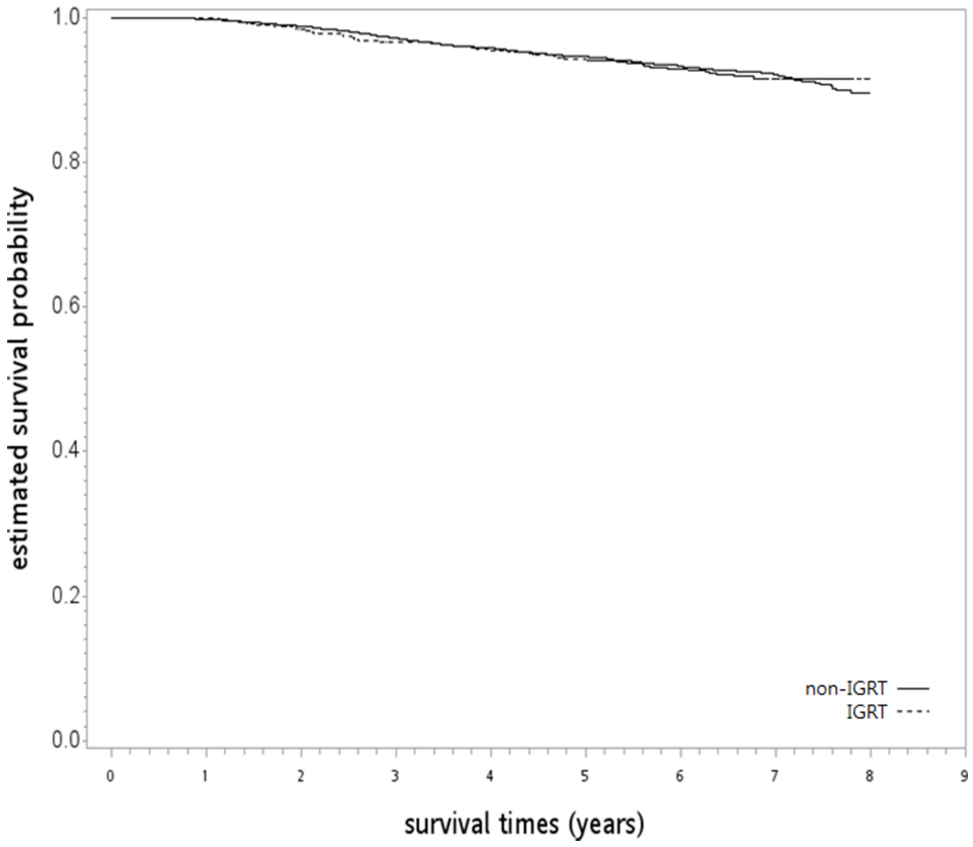

Figure 2 The overlap weights adjusted overall survival curve (in years) in the primary analysis.

covariates were balanced after PS weighting [Table S5] and similar results were seen [HR = 1.01, P = 0.95].

Discussion

In this population-based analysis, we found that the use of image-guided radiotherapy in adjuvant conventional fractionated radiotherapy for localized breast cancer patients did not lead to worse overall survival or other outcomes. This was the first study in this regard to our knowledge.

As we mentioned in the above introduction section, IGRT was advocated in the field of breast radiation oncology in general[4,28,29] but not recommended by the current NCCN guideline.[2] One study for 174 breast cancer patients treated with adjuvant whole breast CFRT after BCS had stated "Extensive set-up errors were found in more than half patients undergoing conventional fractionated radiotherapy and IGRT was advocated for these patients".[30] However, when we searched in Pubmed using "((IGRT) OR (Image-guided Radiation Therapy) OR ((image*) AND (guid*) AND ((radiotherapy) OR (radiation therapy)))) AND survival AND (breast cancer)" in Dec 2020, we did not found studies comparing survival outcomes of breast adjuvant CFRT via IGRT vs non-IGRT, although IGRT was advocated in some HFRT studies.[31,32]

The motivation of our study was the negative survival impact of IGRT on prostate cancer radiotherapy along with the higher risk of secondary cancer and cardiovascular mortality reported in the recent RCT.[8] Our results revealed that IGRT in adjuvant CFRT for localized breast cancer patients did not lead to worse overall survival or other outcomes. So it might be safe to use IGRT (usually via x-ray) regardless of the theoretical concern in cardiovascular disease or secondary cancer,[33,34] at least for selected patients with significant setup errors. However, it should be noted the radiotherapy setting and technique in prostate cancer radiotherapy in that RCT[8] was different vs the one for breast cancer in the current study [curative/definitive vs preventive/adjuvant]. Furthermore, our results should also be interpreted with caution given its non-randomized nature. However, there was no published RCT to our knowledge.[9] We further searched in clinical trials registry [https://clinicaltrials.gov/] in Dec 2020 using keywords "(image-guided radiation therapy) OR (image-guided radiotherapy) OR (IGRT) | breast cancer" but did not find ongoing RCT as well. Therefore, our study would be a reasonable tentative evidence to guide the use of IGRT for breast cancer patients treated with adjuvant CFRT, whereas the role of IGRT in HFRT deserves further study.

There were some limitations of our study to be addressed below. Firstly, the treatment [IGRT] was not randomly given so the impact of potentially unobserved confounders could not be eliminated although we had used PS methods to adjust for observable ones. Furthermore, the treatment [IGRT] in our study was not homogeneous but the detail could not be clarified with certain due to data limitation in HWDC. Secondly, the minimal potential follow-up in our study [5 year] may not be long enough to capture some long term effects which had been reported in some HFRT studies.[35] Thirdly, other potential covariables [such as systemic therapy details] or outcomes [such as patient reported outcome or quality of life] might also be relevant but were not investigated in our study due to data limitation.

Conclusion

Our non-randomized population-based study found that the overall survival of localized breast cancer patients treated with adjuvant CFRT was not statistically different between those treated with IGRT versus without IGRT. This was the first study in this regard to our knowledge but randomized controlled trials were needed to confirm our finding.

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Disclosure

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support from the Health Data Science Center at the China Medical University Hospital, during the conduct of the study. The authors declare that there are no other conflicts of interest.

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