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FULL PAPER

Safety of image-guided radiotherapy in definitive radiotherapy for localized prostate cancer: a population-based analysis

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Objectives: Image-guided radiotherapy (IGRT) is a recommended advanced radiation technique that is associated with fewer acute and chronic toxicities. However, one Phase III trial showed worse overall survival in the IGRT arm. The purpose of this observational study is to evaluate the impact of IGRT on overall survival.

Methods: We used the Taiwan Cancer Registry Database to enroll cT1-4N0M0 prostate cancer patients who received definitive radiotherapy between 2011 and 2015. We used inverse probability treatment weighting (IPW) to construct balanced IGRT and non-IGRT groups. We compared the overall survival of those in the IGRT and non-IGRT groups. Supplementary analyses (SA) were performed with alternative covariates in propensity score (PS) models and PS approaches. The incidence rates of prostate cancer mortality (IPCM), other cancer mortality (IOCM), and cardiovascular mortality (ICVM) were also evaluated.

Results: There were 360 patients in the IGRT arm and 476 patients in the non-IGRT arm. The median follow-up time was 50 months. The 5-year overall survival was 88% in the IGRT arm and 86% in the non-IGRT arm (adjusted hazard ratio [HR] of death = 0.93; 95% CI, 0.61-1.45; $p = 0.77$). The SA also showed no significant differences in the overall survival between those in the IGRT and non-IGRT arms. Both groups did not significantly differ in terms of IPCM, IOCM, and ICVM.

Conclusions: The overall survival of localized prostate cancer patients who underwent IGRT was not inferior to those who did not.

Advances in knowledge: We demonstrated that the overall survival for prostate cancer patients with IGRT was not worse than those who did not undergo IGRT; this important outcome comparison has not been previously examined in the general population.

INTRODUCTION

Prostate cancer (PC) is a common malignancy and radiotherapy is an important treatment modality.¹ Definitive prostate radiotherapy (DPR) performed via conventional fractionated external beam radiotherapy (CFEBRT) is commonly used for localized PC (LPC).^{1,2} Prostate radiotherapy may even be beneficial for cases of PC with low metastatic burden.³

Daily image-guided radiotherapy (IGRT) is an advanced imaging technique that is employed to ensure localization

of the target position during radiotherapy (in contrast to weekly verification), is the preferred approach as per the treatment guidelines.^{2,4}

However, a randomized controlled trial (RCT) published in 2018 reported significantly worse overall survival (OS) when daily IGRT was compared to weekly verification.⁵ While the findings of this RCT were considered a false positive in the guidelines,⁴ we felt more extensive research was needed because OS was obviously the most important endpoint. Due to the lack of other published RCTs reporting

on the OS associated with this treatment modality,⁴ we aimed to compare the OS for LPC patients treated with DPR via CFEbRT using IGRT versus those without IGRT in this population-based analysis.

METHODS AND MATERIALS

Data source

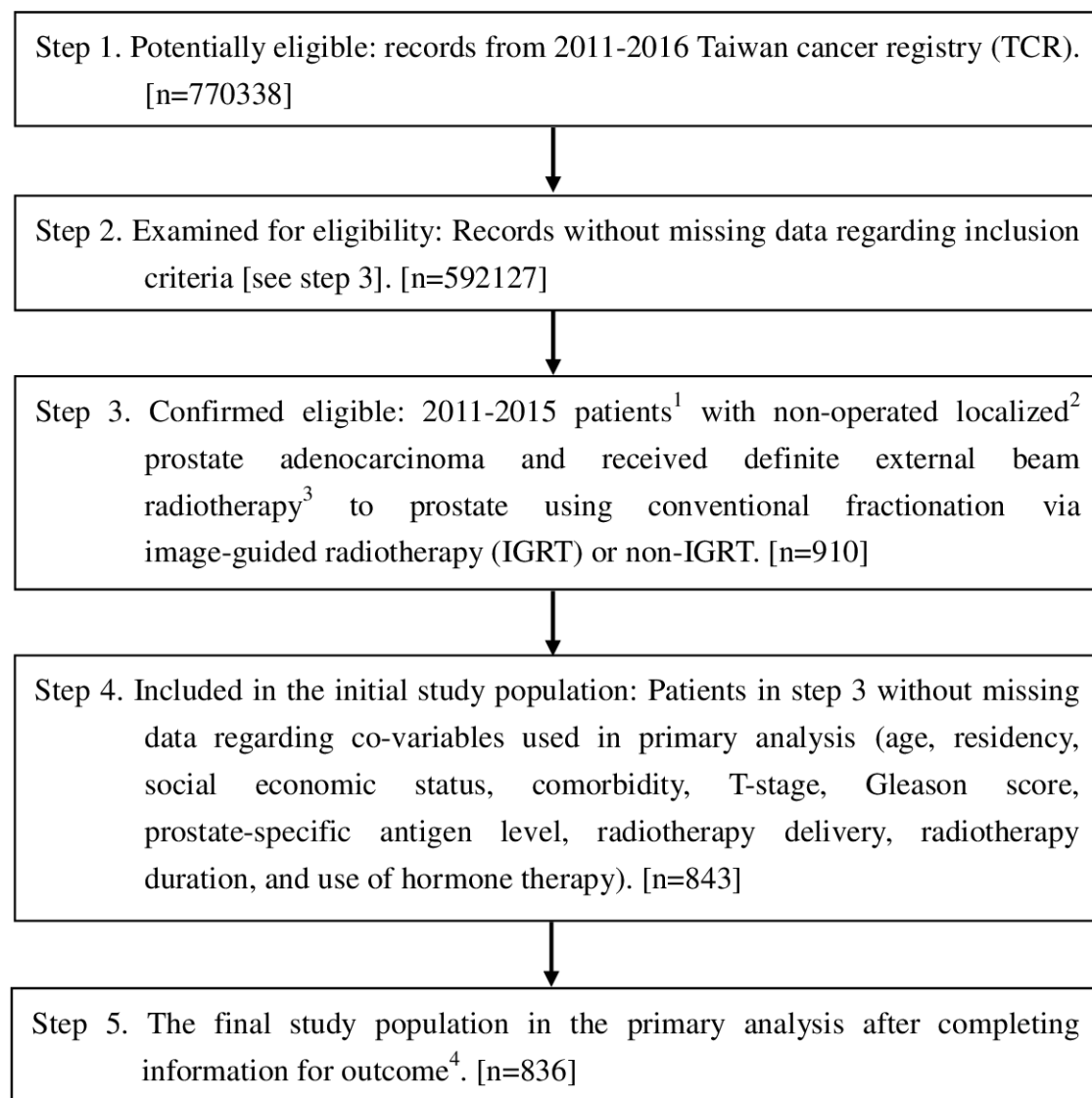
We obtained data with permission from the Health and Welfare Data Science Center (HWDC) database, which includes the Taiwan Cancer Registry (TCR), death registration, and reimbursement data for the entire population of Taiwan provided by the Bureau of National Health Insurance (NHI). Personal identifiers in the HWDC data were removed. The TCR is a high-quality database that provides comprehensive information including patient, disease, and treatment characteristics, as well

as prognostic factor details.⁶ This study was approved by the research ethics committee at our institute (CRREC-108-080).

study population and design

The study flow chart was designed to conform to the STROBE statement and is depicted in Figure 1.⁷ The study population consisted of non-operated localized prostate adenocarcinoma patients (age range: 18–80 years) diagnosed from 2011 to 2015, and who received definitive external beam radiotherapy to the prostate using conventional fractionation via IGRT or non-IGRT. We excluded patients with other cancers, those with nodal or distant metastasis, those with brachytherapy constituting all or part of their treatment, or those treated with elective nodal irradiation. We determined the explanatory variable of interest (IGRT versus non-IGRT), the primary outcome of interest (OS),

Figure 1. STROBE study flowchart and the number of individuals at each stage of the study. ¹We included those treated (class 1-2) with only one record to ensure data consistency. ²The Seventh American Joint Committee on Cancer Staging clinical stage cT1-4N0M0. ³Dose 72–81 Gy ($\pm 10\%$) at 1.8–2 Gy/fraction, as suggested in the guidelines.² ⁴Without missing information in the TCR and the death registry regarding survival status and cause of death. IGRT: image-guided radiotherapy.



and other supplementary outcomes [incidence of PC mortality (IPCM), other cancer mortality (IOCM), and cardiovascular mortality (ICVM)] based on the TCR and the death registry. The date of diagnosis in the TCR was defined as the index date, and OS was calculated from the date of diagnosis to the date of death, or 31 December 2017 (the censoring date of the death registry). The related covariates were collected based on the literature,^{5,8} as well as based on our experiences in clinical care⁹ and TCR studies,^{10–12} to adjust for potential nonrandomized treatment selection (see below).

Other explanatory covariates

Patient demographics (age, residency, socioeconomic status), patient characteristics (comorbidity), disease characteristics [Gleason score, T-stage, and prostate-specific antigen (PSA) level in ng/mL], treatment characteristics [radiotherapy (RT) technique and duration], and the use of hormone therapy were included in the primary analysis. The covariates were defined as follows: Patient residency region was classified as “northern Taiwan” or “non-north”. Socioeconomic status was classified as “higher” (an income greater than minimum wage) or “no higher than minimum wage”. Comorbidity was classified as “with” or “without”, as determined by the Charlson comorbidity index score. Clinical T-stage was classified as “T1–T2” or “T3–T4”. RT technique was classified as “three-dimensional conformal radiotherapy” (3DCRT) or ‘intensity-modulated radiotherapy’ (IMRT). The presumed proper RT duration (in weeks) was calculated as the total fractions divided by 5. If the actual treatment interval (the first day to the last day of radiotherapy) is one week longer than the proper duration, it was defined as prolongation >1 week; otherwise, it would be classified as ≤1 week. The use of hormone therapy was classified as “with” or “without”.

Statistical and supplementary analyses

In the primary analysis (PA), we used the propensity score (PS) method, as advocated in the literature, to balance the measured potential confounders.^{13–16} We evaluated the probability of receiving IGRT (versus non-IGRT) via a logistic regression model, as commonly used in the literature,¹⁷ based on all the above covariates. We used overlap weights in the PS weighting, as suggested in the literature,^{18,19} to balance the differences in covariates between groups. The standardized difference (SDif) was used to assess the balance of covariates between groups.^{9,20,21} We compared the hazard ratio (HR) of death between IGRT and non-IGRT groups during the entire follow-up period using the Cox proportional hazards model in the weighted sample and used the bootstrap method to estimate the 95% confidence interval (95% CI).^{15,22,23} As suggested in the recent literature,²⁴ we also used the E-factor to evaluate the impact of potential unmeasured confounding factor(s) on OS.

In the supplementary analysis (SA), we performed two separate SAs, as suggested by different reviewers during revisions. In the first SA (SA-1), we used PS matched cohort as an alternative approach to compare IGRT versus non-IGRT.¹⁵ We used logistic regression for PS estimation.^{9,17} When estimating the PS in SA-1, we added two equivocal covariates [radiotherapy dose and risk grouping (classified as high versus intermediate/low)], as

considered during the revision, although the RCT had reported a similar OS for high versus low dose,^{25,26} and the components (Gleason score, T-stage, and PSA level) of risk grouping^{27,28} were already included as covariates. We compared the HR of death between IGRT and non-IGRT (1:1 matched) groups during the entire follow-up period via a robust variance estimator.¹⁵ We adopted the subdistribution HR via the clustered Fine–Gray model to evaluate the IPCM, IOCM, and ICVM.²⁹ In the second SA (SA-2), we adopted PS regression as the third approach, in addition to PS weighting or PS matching.^{30,31} We also excluded two covariates (“RT technique” and “RT duration prolongation”) in PS estimation during SA-2. These two covariates were included in the primary analyses because we believed they were the “variables of ambiguous status”, which were “perhaps slightly affected by the treatment, but plausibly standing in as a surrogate for an important covariate that was not measured”.^{10,32,33} After checking the covariate balance, as suggested in the literature,³⁴ we used the Cox regression method, while adjusting this separately estimated PS plus the two excluded covariables (“RT technique” and “RT duration prolongation”) to estimate the effect of IGRT.³⁴ We performed the statistical analyses using SAS 9.4 (SAS Institute, Cary, NC, USA) and R version 3.6.2 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Population

We identified 836 eligible LPC patients treated with DPR from 2011 to 2015 via CFEbRT (Figure 1). A total of 360 of these patients were treated with IGRT, whereas 476 were treated without IGRT. These two groups of patients were not all balanced in terms of covariates (only one covariate had an SDif >0.25, while others had an SDif <0.25), but were well balanced (*i.e.* SDif ≤0.25)²¹ after being weighted by overlapping weights (Table 1).^{18,19}

Primary analysis

After a median follow-up of 50 months (range: 4–83 months), 35 and 53 patients were dead in the IGRT and non-IGRT groups, respectively. The 5-year OS rate was 88% [95% confidence interval (95% CI), 83–92] and 86% (95% CI, 81–89) for IGRT and non-IGRT in the unadjusted analysis (log-rank test, $p = 0.56$; Figure 2). After being adjusted by overlapping weights, the HR of death when IGRT was compared to non-IGRT was 0.93 (95% CI, 0.61–1.45; $p = 0.77$). The observed HR of 0.93 for OS could be explained by an unmeasured confounder associated with the selection of treatment (IGRT or non-IGRT) and survival by a risk ratio of 1.28 (E-value)-fold each, but weaker confounding factors could not. The overlapping weight-adjusted OS curve is shown in Figure 3.

Supplementary analysis

In the first SA, we constructed a PS-matched subgroup ($N = 606$; Table 2). The HR of death when IGRT was compared to non-IGRT in this PS-matched analysis was 0.84 (95% CI, 0.51–1.39; $p = 0.50$). The HRs (with a 95% CI) for IPCM, IOCM, and ICVM were 0.21 (95% CI, 0.05–1.00; $p = 0.05$), 0.71 (95% CI, 0.28–1.80; $p = 0.47$), and 1 (95% CI, 0.33–3.1; $p = 0.99$), respectively, when

Table 1. Patient characteristics of the study population in the primary analysis

		IGRT (<i>n</i> = 360; median follow-up = 50 months)		non-IGRT (<i>n</i> = 476; median follow-up = 50 months)		Standardized difference (rounded) ^a	
		Number or mean (SD) ^a	(%) ^a	Number or mean (SD) ^a	(%) ^a	Before PSW	After PSW
Age		72.13 (6.07)		72.58 (5.61)		0.08	≈ 0
Residency	Non-north	162	(45)	134	(28)	0.36	≈ 0
	North	198	(55)	342	(72)		
Socioeconomic status	No more than minimum wage	96	(27)	162	(34)	0.16	≈ 0
	Higher	264	(73)	314	(66)		
Comorbidity	Without	126	(35)	172	(36)	0.02	≈ 0
	With ^b	234	(65)	304	(64)		
T-stage	T1–T2	285	(79)	364	(76)	0.07	≈ 0
	T3–T4	75	(21)	112	(24)		
Gleason score		6.77 (1.02)		6.93 (1.09)		0.16	≈ 0
Prostate-specific antigen level		19.26 (21.85)		20.57 (22.70)		0.06	≈ 0
RT technique	3DCRT	<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>	0.16	≈ 0
	IMRT	<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>		
RT duration prolongation	≤1 week	343	(95)	439	(92)	0.13	≈ 0
	>1 week	17	(5)	37	(8)		
Use of hormone therapy	Without	99	(28)	122	(26)	0.04	≈ 0
	With	261	(72)	354	(74)		

3DCRT, Three-dimensional radiotherapy; IGRT, Image-guided radiotherapy; IMRT, Intensity-modulated radiotherapy; PSW, Propensity-score weighting; RT, Radiotherapy; SD, Standard deviation.

^aRounded at the second.

^bModified Charlson comorbidity score ≥1.

^cThe exact numbers were not reported because of a Health and Welfare Data Science Center (HWDC) database center policy to avoid numbers in single cells (≤2).

IGRT was compared to non-IGRT (Figure 4a–4c). In the second SA, we found all covariates were well balanced between the two groups (weighted standardized difference <0.1)^{21,34} and the HR of death when IGRT was compared to non-IGRT in this PS-regression analysis was 0.93 (95% CI, 0.60–1.43; *p* = 0.73).

DISCUSSION

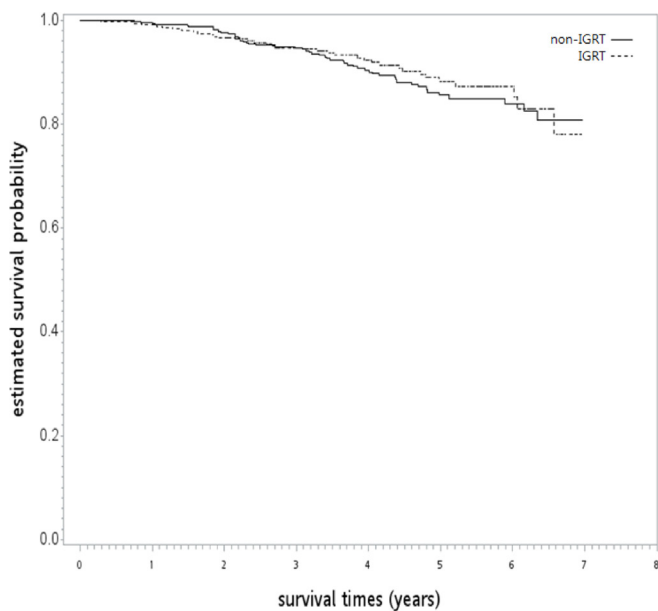
Our study is the first to use a real-world population database to investigate the impact of IGRT on PC patients' OS. To our knowledge, our study was the largest to evaluate the effect of IGRT on the number of enrolled patients.^{35,36} With balanced baseline characteristics of the IGRT and non-IGRT arms, the OS was not significantly different. This result implicates the safety of adding IGRT to standard DPR for PC.

In our study, the crude 5-year OS rate was 88 and 86% for IGRT and non-IGRT, respectively. After balancing the baseline covariates with IPW, the HR of death with IGRT was 0.93 (95% CI, 0.61–1.45). A statistically significant difference was not noted. Our 5-year OS was comparable to that of the IGRT group in a

French Phase III trial (83%).⁵ In the French trial, there were more second primary malignancy- and cardiovascular-related deaths in the IGRT arm. However, most second primary malignancies at that trial occurred shortly after radiation, and they mostly originated from the radiation fields. The relationship between the extra events and daily IGRT was not compatible with most carcinogenesis studies due to irradiation. In the first SA of our study, we used the well-advocated PS-matching method to evaluate the OS between the IGRT group and non-IGRT group. In line with the literature,¹⁸ covariate balancing was better with PS weighting than with PS matching. However, the OS was still not significantly different between the two groups. Similar results were seen in SA-2 as well.

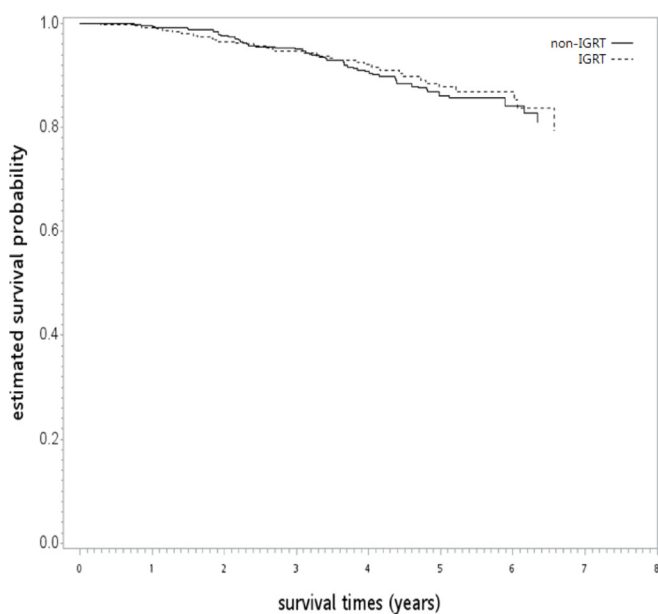
In addition, the mortality rate due to the second primary malignancy (IOCM) in the IGRT arm was not significantly different from that of the non-IGRT arm (*p* = 0.17). In the French trial, more cardiovascular-related deaths were also observed; our SA-1 showed a larger risk of cardiovascular-related deaths in the IGRT arm, but this did not reach statistical significance (HR = 2.39;

Figure 2. Kaplan-Meier overall survival curve (in years) in the primary analysis. IGRT: image-guided radiotherapy.



95% CI, 0.63–9.03; $p = 0.20$). The most commonly found studies related to radiotherapy and cardiovascular events examine the effects of thoracic irradiation, such as in cases of Hodgkin disease or breast cancer. More cardiovascular events were noted between surgery and radiotherapy on PC patients.³⁷ In addition, the duration and regimen of hormone treatment³⁸ might serve as potential confounders of the cardiovascular events. However, the interaction between these systemic agents and IGRT was not known. Furthermore, the results on the secondary endpoints (such as ICVM or IOCM) must be interpreted with caution

Figure 3. The overlapping weight-adjusted overall survival curve (in years) in the primary analysis. IGRT: image-guided radiotherapy.



because the comorbidity assessment we used (the Charlson comorbidity score) is a general composite score that may not be specific for these endpoints.

Overall, it has been shown that IGRT can provide margin reduction³⁹ and fewer radiotherapy-related side-effects in PC and other malignancies,^{40,41} although one prospective study showed no differences in patient-reported outcomes.⁸ Precise dose delivery with IGRT is advocated, which might be of benefit when attempting to ensure better tumor control. As IGRT offers benefits associated with decreasing toxicity, the additional cost was thought to be acceptable.⁴² The French Phase III trial showed better biochemical and clinical progression-free survival in the daily IGRT group. One retrospective study also demonstrated the benefit of biochemical failure with IGRT in the high-risk group.³⁶ In our study, we could not evaluate the difference in biochemical failure between the IGRT and non-IGRT arms given the lack of laboratory exam results in the database. However, the HR of PC mortality with IGRT was 0.41 (95% CI, 0.11–1.60) in SA-1. Patients with IGRT may be treated with higher biologically effective doses to the prostate; however, it was also shown that dose escalation to PC patients yields better biochemical-free survival, but does not lead to better OS.^{25,26} This might be due to the positive therapeutic effects of salvage hormone treatment.

There are several obvious limitations in our study. First, this study is a non-randomized retrospective study; as such, there might be unmeasured confounders between the two groups. We used the PS methods to ensure baseline covariate balance and to avoid the risks associated with model misspecification. For the potentially unmeasured confounders, we further used the E-factor to measure the strength of our results. The OS outcomes of other RCTs are also forthcoming and eagerly awaited.⁸ Second, due to the fact that the data were derived from real-world practice and obtained from most hospitals in Taiwan, it was noted that there are no unified protocols for contouring, treatment, or IGRT technique. In TCR, IGRT was simply coded as 'with' or 'without' in the item "external beam radiotherapy", without further detail regarding IGRT technique. Therefore, the intervention (IGRT) was actually heterogeneous (including but not limited to radio-opaque fiducial markers, cone beam computed tomography, and megavoltage computed tomography in tomotherapy), and imaging dose was not the same between techniques,⁴ which can be a confounding factor for OS, IOCM, or ICVM. However, there was no universal preferred IGRT technique to our knowledge.

In the European guidelines, there were four types of techniques recommended for IGRT of PC.⁴ Even in the NCCN guidelines, there are also several techniques recommended for daily prostate localization.² In addition, the coding details regarding the radiotherapy parameters in TCR were modified from the National Cancer Database.⁴³ A previous validation study showed good accuracy in the details of radiotherapy and chemotherapy treatment.⁴⁴ Third, due to the lack of laboratory data and imaging data, we could not compare the biochemical failure survival between the IGRT and non-IGRT groups. However, this is not an obstacle for our primary endpoint, OS.

Table 2. Patient characteristics of the PS-matched subgroup in this supplementary analysis

		IGRT (<i>n</i> = 303; median follow-up = 51 months)		non-IGRT (<i>n</i> = 303; median follow-up = 50 months)		Standardized difference (rounded) ^a
		Number or mean (SD) ^a	(%) ^a	Number or mean (SD) ^a	(%) ^a	
Age		72.22 (6.04)		72.25 (5.62)		0
Residency	Non-north	115	(38)	122	(40)	0.05
	North	188	(62)	181	(60)	
Socioeconomic status	No more than minimum wage	88	(29)	91	(30)	0.02
	Higher	215	(71)	212	(70)	
Comorbidity	Without	108	(36)	110	(36)	0.01
	With ^b	195	(64)	193	(64)	
T-stage	T1–T2	229	(76)	233	(77)	0.03
	T3–T4	74	(24)	70	(23)	
Gleason score		6.80 (1.05)		6.79 (1.01)		0.01
Prostate-specific antigen level		19.54 (22.27)		19.87 (21.64)		0.02
RT technique	3DCRT	<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>	0
	IMRT	<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>	
RT duration prolongation	≤1 week	287	(95)	282	(93)	0.07
	>1 week	16	(5)	21	(7)	
Use of hormone therapy	Without	81	(27)	81	(27)	0
	With	222	(73)	222	(73)	
Radiotherapy dose		76.77 (2.34)		76.65 (2.12)		0.06
Risk grouping	Intermediate/low	106	(35)	105	(35)	0.01
	High	197	(65)	198	(65)	

3DCRT, Three-dimensional radiotherapy; IGRT, Image-guided radiotherapy; IMRT, Intensity-modulated radiotherapy; PS, Propensity score; RT, Radiotherapy; SD, Standard deviation.

^aRounded at the second.

^bModified Charlson comorbidity score ≥1.

^cThe exact numbers were not reported because of a Health and Welfare Data Science Center (HWDC) database center policy to avoid numbers in single cells (≤2).

In addition, the similar OS rates imply the safety of using IGRT in daily practice. The lack of comparison of biochemical failure-free survival in the two groups could not explain the effectiveness of IGRT, as the previous French trial showed the efficacy of tumor control with IGRT.⁵ Fourth, in our study, the median follow-up time was 50 months, which might be relatively short for PC control and the development of a secondary malignancy. However, the benefit of PC control and the difference in the OS were statistically significant after a similar follow-up (median: 4.1 years) in the French trial.⁵ The lack of a notable difference in OS in comparable follow-up studies showed the safety of IGRT administration and indicated that a longer follow-up time is necessary to further observe this trend.

Fifth, the choice of covariates included in the PS model may be a limitation of our study. Theoretically, only the true confounders were needed for the PS model, whereas the risk factors without

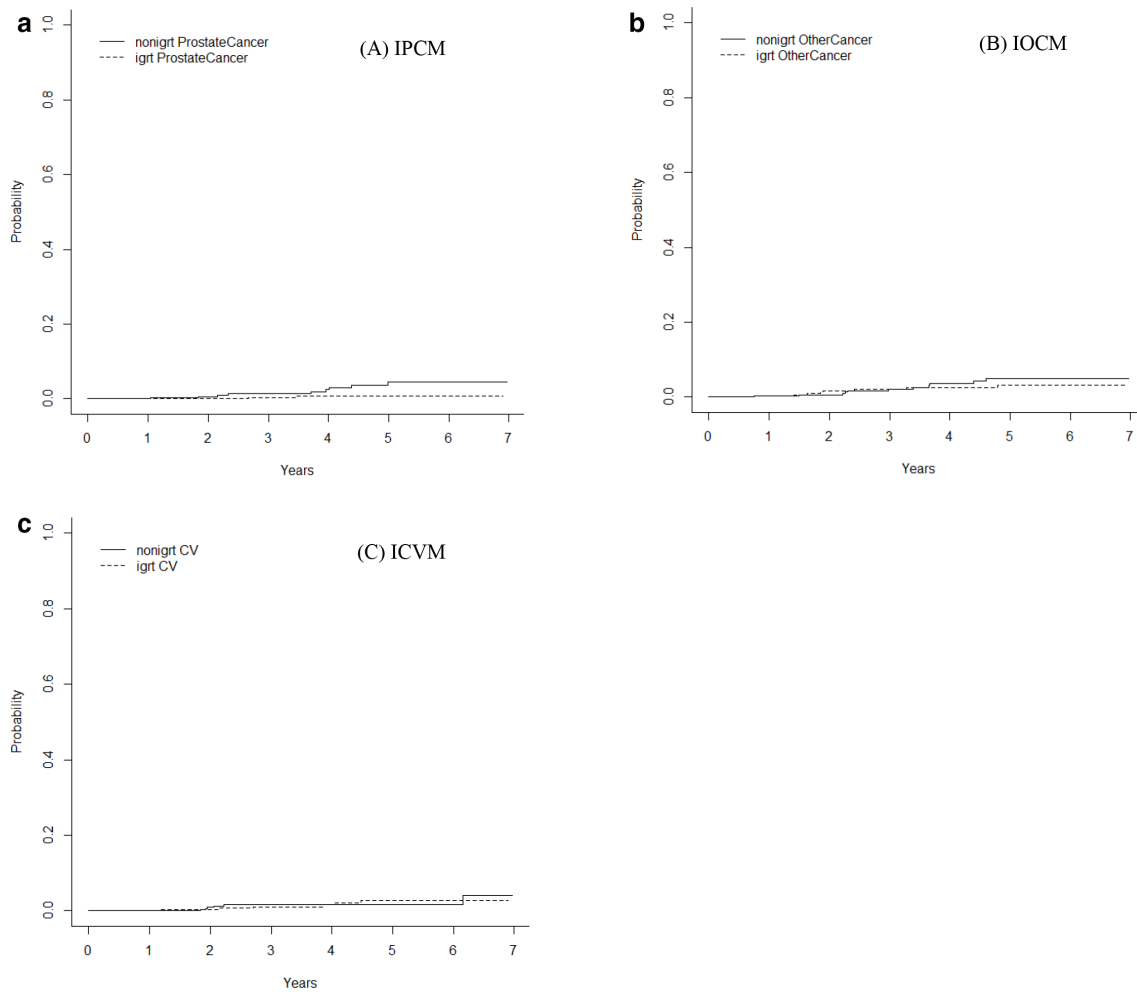
an association to IGRT may be skipped in the PS model.⁴⁵ However, the optimal practical approach for covariate selection in the PS model was debated in the literature.^{9,21,45} Therefore, we performed two SAs to examine the robustness of our findings, as they pertained to the different covariates included in the PS model.

The final limitation relates to the accessibility of IGRT for our study population (*i.e.* reflecting a non-zero probability assumption for the PS method). This cannot be definitively confirmed due to data limitations. However, to our knowledge, all of the radiotherapy departments in Taiwan possessed the ability to perform IGRT in accordance with the literature.⁴

CONCLUSION

Our study showed how adding IGRT to radical radiotherapy in PC has no obvious impact on OS. Further, IGRT does not

Figure 4. Estimated cumulative incidence for (a) the incidence rates of prostate cancer mortality (IPCM), (b) the incidence rates of other cancer mortality (IOCM), and (c) the incidence rates of cardiovascular mortality (ICVM).



increase the risk of death due to other malignancies or cardiovascular events. However, the follow-up period was modest (median: 50 months), and the results related to other cancer- or cardiovascular-related mortality should be interpreted with caution. Further studies are needed to clarify our findings.

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