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Comparative effectiveness of simultaneous integrated boost vs sequential intensity-modulated radiotherapy for oropharyngeal or hypopharyngeal cancer patients

A population-based propensity score-matched analysis

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Abstract

There were 2 common radiotherapy dose fractionation strategies in head-and-neck cancer patients (such as oropharyngeal cancer [OPC] or hypopharyngeal cancer [HPC]) treated with radiotherapy: intensity-modulated radiotherapy using simultaneous integrated boost (IMRT-SIB) and sequential IMRT (IMRT-SEQ). There is a lack of high-level clinical evidence to compare IMRT-SIB vs IMRT-SEQ specifically for OPC or HPC patients. The present study investigated the survival outcomes of OPC or HPC patients receiving definite concurrent chemoradiotherapy (CCRT) with either IMRT-SIB or IMRT-SEQ via a population-based propensity score (PS)-based analysis.

The localized stage OPC or HPC patients diagnosed between 2011 and 2015 were identified based on the Health and Welfare Data Science Center database in Taiwan. These patients received definitive CCRT with either IMRT-SIB or IMRT-SEQ. We constructed a PS-matched cohort (1:1 for IMRT-SIB vs IMRT-SEQ) to balance observable potential confounders. We compared the hazard ratio (HR) of death between IMRT-SIB and IMRT-SEQ during the entire follow-up period. We also evaluated other disease outcome or subgroups.

Our study population constituted 200 patients with well balance in observed covariables. The HR of death when IMRT-SIB was compared to IMRT-SEQ was 1.23 (95% confidence interval 0.84–1.80, $P = .29$). The results were similar for other disease outcome or subgroups.

We found the survival outcome might be comparable for those treated with IMRT-SIB vs those treated with IMRT-SEQ.

Abbreviations: 95% CI = 95% confidence interval, HN = head-and-neck, HPC = hypopharyngeal cancer, HR = hazard ratio, HWDC = Health and Welfare Data Science Center, IGRT = image-guided radiotherapy, IMRT = intensity-modulated radiotherapy, IMRT-SEQ = sequential intensity-modulated radiotherapy, IMRT-SIB = intensity-modulated radiotherapy with simultaneous integrated boost, IPCM = incidence of pharyngeal cancer mortality, NHI = National Health Insurance, NPC = nasopharyngeal cancer, OPC = oropharyngeal cancer, OS = overall survival, PS = propensity score, RCT = randomized controlled trials, SA = subgroup analyses, SES = socioeconomic status, SqCC = squamous cell carcinoma, TCR = Taiwan cancer registry.

Keywords: hypopharyngeal cancer, intensity-modulated radiotherapy, oropharyngeal cancer, sequential, simultaneous integrated boost

1. Introduction

Radiotherapy is an important treatment modality of head-and-neck (HN) cancer. Many radiotherapeutic factors were well studied in the past, including the radiation field, the total dose, and overall treatment time. A systematic review published in 2014 had shown that using intensity-modulated radiotherapy (IMRT) reduced the incidence of grade 2 to 4 xerostomia in patients with HN cancer without compromising locoregional control and overall survival (OS), in comparison with conventional technique or three-dimensional radiotherapy.[1] Chemo-

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therapy (especially concurrent chemoradiotherapy [CCRT]) further improves survival in patients with locally advanced HN squamous cell carcinoma (SqCC).[2]

However, there are several different dose-fractionation strategies to perform HN IMRT.[3] Two common strategies are described in this study. The first technique, sequential IMRT (IMRT-SEQ) via conventional dose fractionation, uses usually 180 to 200 cGy to treat all risk regions, and then boost the high-risk region with smaller field thereafter. The other is IMRT with simultaneous integrated boost (IMRT-SIB) via nonconventional dose fractionation, which treats the patients with different dose levels to 2 to 3 planning target volumes at the same time. But the field of radiotherapy is always identical during the whole treatment course.

To compare these 2 techniques, there were several dosimetric studies to compare the dose to the organ at risks when lesions are treated with same coverage.[4–6] However, there is still controversy about which one is better. For other malignancies, the debate over the 2 techniques is also under investigation now.[7–11]

A recently (2019) published meta-analysis reported that for HN cancer patients, there was no significant difference in OS when IMRT-SIB was compared to IMRT-SEQ (hazard ratio [HR] 0.94; $P = .71$).[12] Among the several articles included in this meta-analysis, 3 were randomized controlled trials (RCT) and all 3 focused on nasopharyngeal cancer (NPC). All 3 RCTs reported similar outcome between IMRT-SEQ and IMRT-SIB. Therefore, there is high-level evidence that there was no statistical difference in OS when IMRT-SIB was compared to IMRT-SEQ. Similar results were also seen in the low-level evidence in this systematic review. For example, Tao et al[13] analyzed 107 NPC patients from a single institute and reported no significant difference in 5-year OS (80.9% vs 80.5%, $P = .568$).

However, the literatures were less clear and inconclusive regarding oropharyngeal cancer (OPC) or hypopharyngeal cancer (HPC). Among the non-RCTs in the abovementioned systematic review,[12] none focused specifically on OPC or HPC, whereas 2 single-institution retrospective studies on HN cancer (roughly half of the patients had OPC or HPC) reported similar disease outcome.[14,15] However, one reported lower rate of acute side effect for IMRT-SEQ,[14] whereas the opposite result was reported in the other study.[15]

Since the clinical benefit of IMRT-SIB vs IMRT-SEQ in definitive CCRT for OPC or HPC is unclear and there is a lack of population-based study, we sought to compare IMRT-SIB vs IMRT-SEQ for locally advanced OPC or HPC patients treated with definitive CCRT via a population-based propensity score (PS)-based analysis.

2. Materials and methods

2.1. Data source

The data were obtained from the Health and Welfare Data Science Center (HWDC) database, including the Taiwan cancer registry (TCR), death registry, and reimbursement data for the whole Taiwan population provided by the Bureau of National Health Insurance (NHI). The TCR was established in 1979. The central cancer registry was reformed in 2002 to include details regarding the stage at diagnosis and the first course of treatment. Additional risk factors such as use of alcohol, betel nuts, or smoking were also available since 2011. All recordings in TCR are made by the professional cancer registrar(s) in each hospital in collaboration with relevant physicians, and are further reviewed by the TCR. The excellent quality (97% completeness) of the TCR data has been confirmed.[16] The NHI is a single-payer, compulsory social insurance program that provides insurance coverage to almost all citizens in Taiwan. All of these data were included in the HWDC with personal identifiers removed. This study was approved by the Central Regional Research Ethics Committee, China Medical University, Taichung, Taiwan (CRREC-108-080).

2.2. Study population and design

The study flow chart is depicted in Figure 1, as suggested in the STROBE statement.[17] The study population consisted of locally advanced (nonmetastatic stage III-IV) OPC or HPC patients (SqCC) who were diagnosed between 2011 and 2015 and received definitive CCRT with external beam radiotherapy. CCRT was defined as concurrent systemic therapy with radiotherapy per recording in TCR. The date of diagnosis in the cancer registry was adopted as the index date and the explanatory variable of interest was treatment with IMRT-SIB or IMRT-SEQ. We classified patients as IMRT-SIB or IMRT-SEQ based on the dose range recommended in practice guideline[3] (see footnote in Fig. 1 for definition). Data regarding covariables were also collected to adjust for potential nonrandomized treatment selections (see section 2.3). The survival status of each patient was obtained from the death registry (until December 31, 2017).

2.3. Other explanatory covariables

In this study, our covariables included patient demographics (age, gender, residency region]), patient characteristics (comorbidity, smoking, betel nut chewing, drinking status, socioeconomic status [SES]), disease characteristics (OPC vs HPC, clinical T-stage and N-stage, stage), and treatment characteristics (radiotherapy delivery method [image-guided radiotherapy [IGRT] or non-IGRT], radiotherapy break, and neoadjuvant or adjuvant systemic therapy). The selection and definition of these factors were based on our experiences in clinical care and modified from our previous related studies.[18,19] The covariables were defined as follows. Patient residency region was classified as northern Taiwan or elsewhere. Comorbidity was classified as yes or no via Charlson comorbidity score (excluding existing cancer). SES was classified as high (income greater than minimal wage) or not. T-stage was classified as T1-T2 or T3-T4. N-stage was classified as N0-N1 or N2-N3. Overall stage was classified as III or IV. radiotherapy break was defined as more than 1 week or not. IGRT, neoadjuvant or adjuvant systemic therapy, smoking, betel nut chewing, and drinking status were classified as yes or no.

2.4. Effectiveness assessment

The survival status at the end of the follow-up period was obtained from TCR and the registry of deaths. This information was used to compare the OS as our primary outcome of interest. We also evaluated incidence of pharyngeal cancer mortality (IPCM) according to TCR and death registry.

2.5. Statistical and sensitivity analyses

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and R (version 3.5.1, R Development Core Team, R

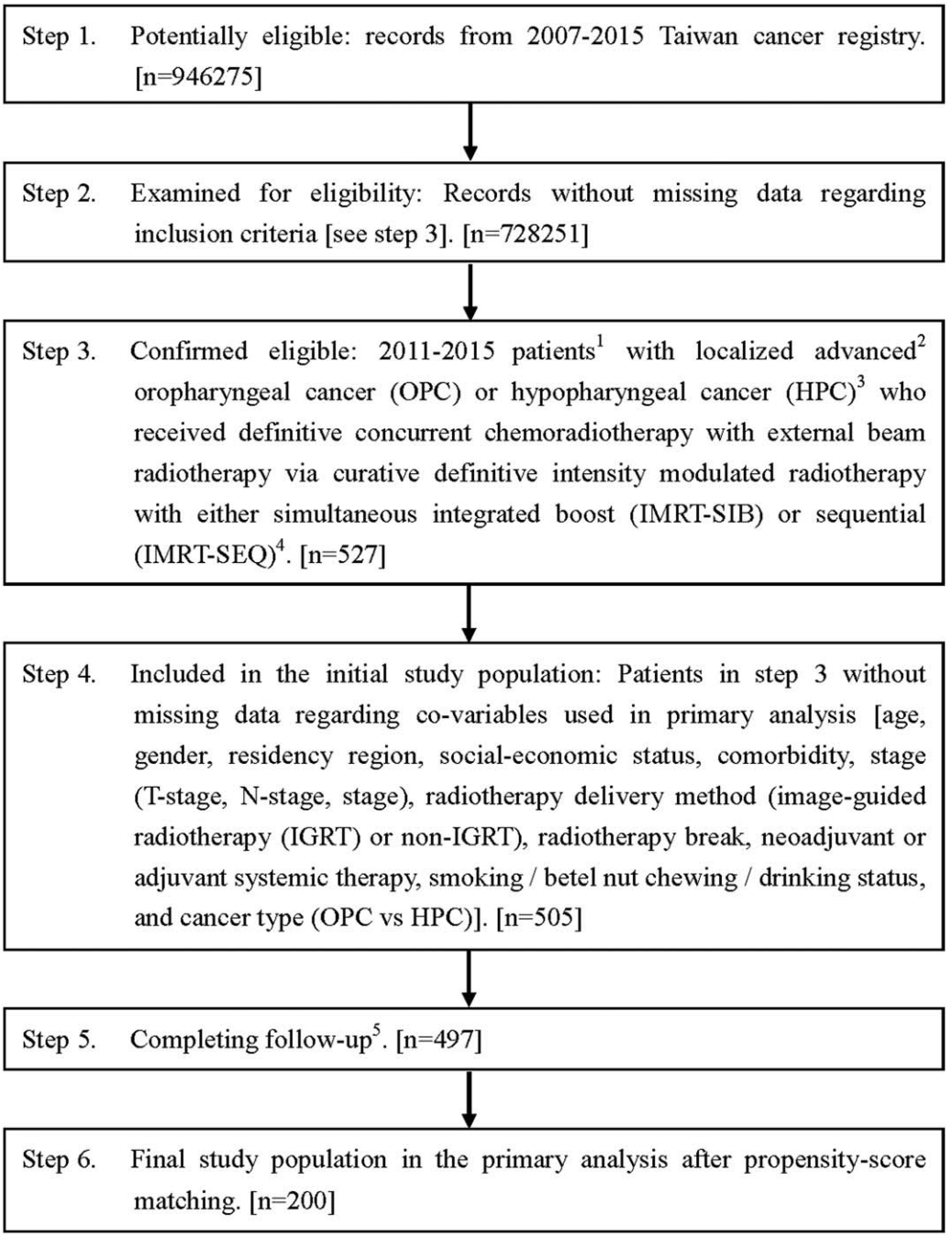

Figure 1. . STROBE study flowchart and the number of individuals at each stage of the study. [1]We only included those treated (class 1–2) by any single institution without synchronous or metachronous cancer to ensure data consistency. [2]Clinical stage III-IV and cM0; by seventh American Joint Committee on Cancer staging. [3]International classification of diseases oncology, third edition, site codes C090-C091, C098-C104, C108-C109 for OPC and C129-C132, C138-C139 for HPC. [4]Simultaneously integrated boost was defined as highest dose 70 Gy with 2 Gy/fraction (Fx) and lower dose 54 to 63 Gy with 1.6 to 1.8 Gy/Fx as well as same Fx for both highest and lower dose, whereas sequential was defined as highest dose 70 Gy with 2 Gy/Fx and lower dose 44 to 50 Gy with 2 Gy/Fx. [5]Without missing information in Taiwan cancer registry and death registry.

Foundation for Statistical Computing, Vienna, Austria). To overcome the inherent limitations of retrospective studies in the potential imbalance of covariables between treatment groups, several analytic approaches were available in the literature,[20] including the traditional regression method that relied on specific assumptions about the relationship between the covariables and outcome.[20] PS approach was increasingly used in the recent years with modest improvement when compared to traditional Cox regression,[21] so we adopted PS approach in the present study. We did not try the other advocated approach (instrumental variable) due to the difficulty in finding a valid instrument in our study setting.[22] We used PS-matched method as advocated in the literature.[23] We modeled the use of IMRT-SIB (vs IMRT-SEQ) as the dependent variable and the abovementioned covariables as independent variables, and used logistic regression to model the probability of receiving IMRT-SIB. We then used the logit of the

probability as the PS, as commonly used in the literature.[23] Tabulation and standardized differences were used to assess the balance of the covariables.[24] The HR of death between IMRT-SIB vs IMRT-SEQ during the entire follow-up period was compared using Cox model via a robust variance estimator.[23] We further used the E-factor as suggested in the recent (2019) literature to evaluate the impact of potential unmeasured confounder(s) on OS.[25] The sub-distribution HR from the clustered Fine–Gray model was used to evaluate IPCM.[26] We also performed 2 subgroup analyses (SA) for OPC and HPC patients, respectively.

3. Results

3.1. Study population

As shown in Figure 1, 200 eligible patients who received definitive CCRT with external beam radiotherapy between 2011 and 2015 were identified as our primary study population. They were divided into 2 groups: those who received IMRT-SIB (n = 100) and those who received IMRT-SEQ (n = 100). These 2 groups were balanced (standardized differences < 0.25) after matching, although some imbalance existed before matching (Table 1). The median (range) of lower radiotherapy dose in IMRT-SIB was 63

Table 1

Patient characteristics of the study population in the primary analysis.

	Unmatched population (n = 497)					Matched study population (n = 200)				
	IMRT-SIB		IMRT-SEQ			IMRT-SIB		IMRT-SEQ		
	Number or mean (SD)*	%*	Number or mean (SD)*	%*	SDif*	Number or mean (SD)*	%*	Number or mean (SD)*	%*	SDif*
Age	53.67 (9.05)		53.43 (8.05)		0.028	52.04 (8.24)		53.43 (8.05)		0.171
Gender										
Female	21	5	6	6	0.031	5	5	6	6	0.044
Male	376	95	94	94		95	95	94	94	
Residency region										
Non-north	203	51	79	79	0.611	75	75	79	79	0.095
North	194	49	21	21		25	25	21	21	
Socioeconomic status										
Higher than minimal wage	285	72	78	78	0.144	74	74	78	78	0.094
Minimal wage	112	28	22	22		26	26	22	22	
Comorbidity										
Without	259	65	69	69	0.080	69	69	69	69	0
With†	138	35	31	31		31	31	31	31	
T-stage										
T1-T2	166	42	53	53	0.225	49	49	53	53	0.080
T3-T4	231	58	47	47		51	51	47	47	
N-stage										
N0-N1	105	26	18	18	0.204	17	17	18	18	0.026
N2-N3	292	74	82	82		83	83	82	82	
Stage										
III	69	17	14	14	0.093	12	12	14	14	0.060
IV	328	83	86	86		88	88	86	86	
IGRT										
Yes	72	18	40	40	0.496	35	35	40	40	0.103
No	325	82	60	60		65	65	60	60	
Neoadjuvant or adjuvant systemic therapy										
Yes	256	64	39	39	0.527	48	48	39	39	0.182
No	141	36	61	61		52	52	61	64	
Smoking										
Yes	323	81	83	83	0.043	86	86	83	83	0.083
No	74	19	17	17		14	14	17	17	
Betel nut chewing										
Yes	225	57	58	58	0.027	62	62	58	58	0.082
No	172	43	42	42		38	38	42	42	
Drinking										
Yes	309	78	74	74	0.090	80	80	74	74	0.143
No	88	22	26	26		20	20	26	26	
RT break										
≤1 wk	336	85	82	82	0.071	86	86	82	82	0.109
>1 wk	61	15	18	18		14	14	18	18	
Cancer type										
OPC	208	52	47	47	0.108	47	47	47	47	0
HPC	189	48	53	53		53	53	53	53	

HPC = hypopharyngeal cancer, IGRT = image-guided radiotherapy, IMRT = intensity-modulated radiotherapy, OPC = oropharyngeal cancer, RT = radiotherapy, SD = standard deviation, SDif = standardized difference, SEQ = sequential, SIB = simultaneous integrated boost.

* Rounded.

† Charlson comorbidity score ≥ 1.

(56–63) Gy (all by 35 fractions), whereas the median (range) of lower radiotherapy dose and fractions in IMRT-SEQ was 50 (44–50) Gy and 25 (22–25) fractions.

3.2. Primary analysis

After a median follow-up period of 33 months (range 3–84) (median 45 and range 24–84 for the survivors), 90 deaths were observed (47 for IMRT-SIB vs 43 for IMRT-SEQ). There was no statistical significance when IMRT-SIB was compared to IMRT-SEQ (HR for death 1.23, 95% confidence interval [CI] 0.84–1.80, $P=.29$]. The observed HR of 1.23 for OS could be explained by an unmeasured confounder that was associated with both selections of SIB/SEQ and live/death by a risk ratio of 1.58 (E-factor) fold each, but weaker confounding could not do so. The OS curve is shown in Figure 2. The 5-year OS rates were 47% in IMRT-SIB vs 54% in IMRT-SEQ. There were no statistical differences for IPCM (HR 1.40, 95% CI 0.89–2.21, $P=.14$, Fig. 3).

3.3. Subgroup analyses

In the first SA for OPC, well-balanced covariables were seen after PS-matching (Table 2). The HR for death when IMRT-SIB was compared with IMRT-SEQ was 1.39 (95% CI 0.87–2.20; $P=.17$). In the second SA for HPC, well-balanced covariables were seen after PS matching (Table 3). The HR for death when IMRT-SIB was compared with IMRT-SEQ was 1.11 (95% CI 0.65–1.89; $P=.71$).

4. Discussion

4.1. Synopsis of key findings

To the best of our knowledge, we provided the first population-based study specifically for OPC or HPC patients treated with definitive CCRT using either IMRT-SIB or IMRT-SEQ. We found the survival outcome might be comparable for those treated with IMRT-SIB vs those treated with IMRT-SEQ.

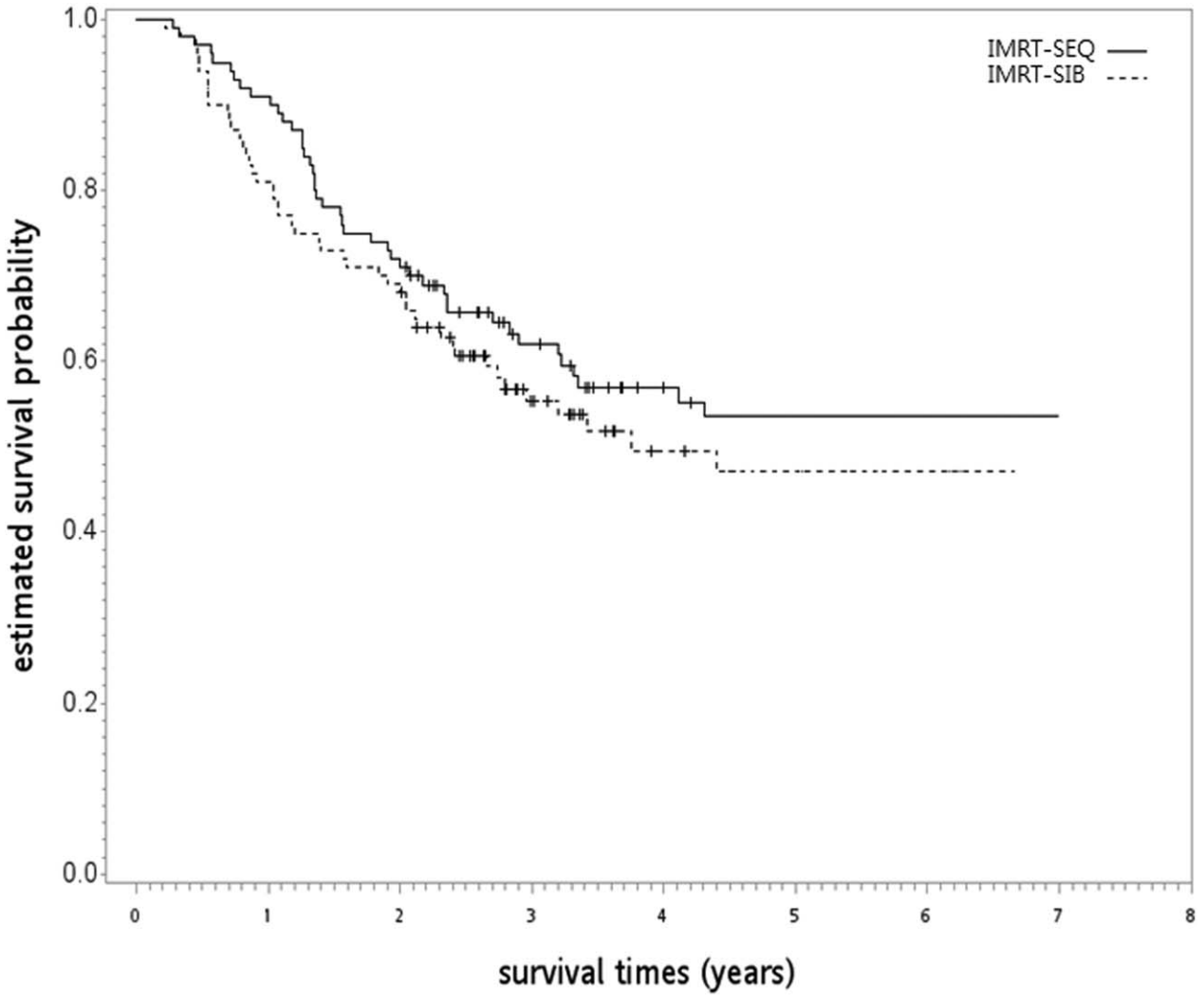

Figure 2. . Overall survival in the primary analysis.

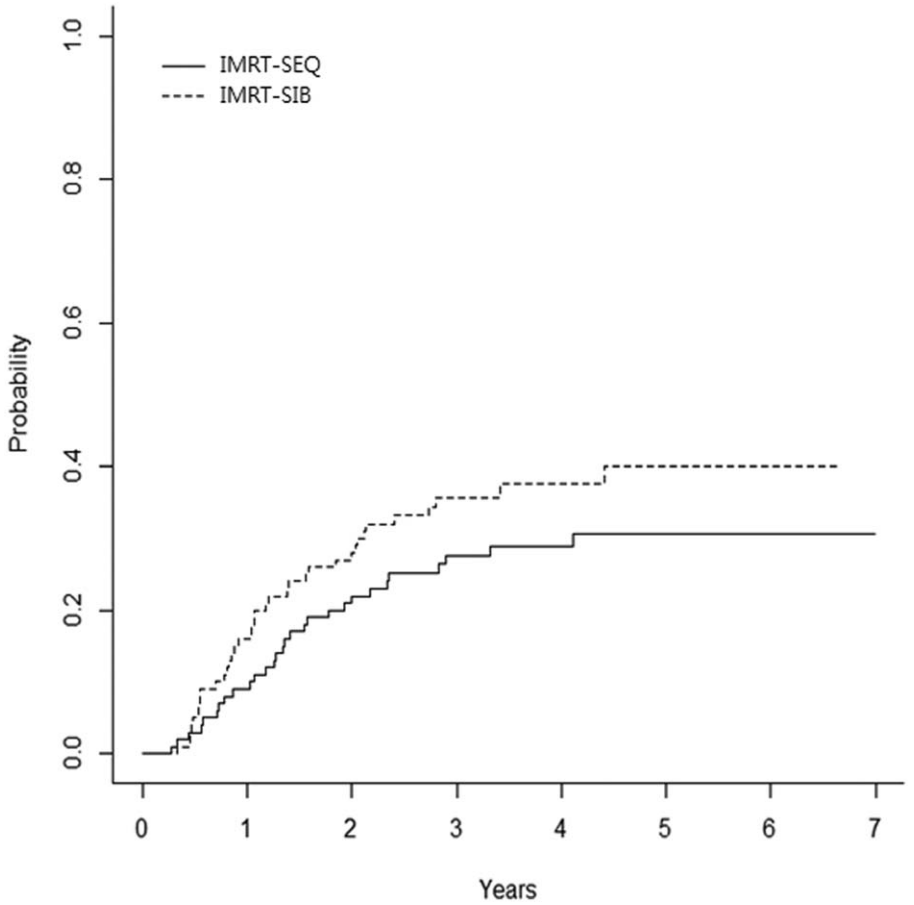

Figure 3. . Incidence of pharyngeal cancer mortality in the primary analysis. IMRT-SEQ = sequential intensity-modulated radiotherapy, IMRT-SIB = intensity-modulated radiotherapy with simultaneous integrated boost.

4.2. Clinical applicability of the study

IMRT-SIB technique was developed after the clinical implementation of IMRT. The dose/fractionation of IMRT-SIB was assumed to be at least as effective as the conventional fractionation (ie, IMRT-SEQ) based on radiobiological modeling. However, clinical evidence was needed to confirm this assumption. Our study provides real-world rationale for clinical implementation of IMRT-SIB, although it utilizes nonconventional dose fractionation. However, we should be aware that our observation was interesting but inconclusive with limitations mentioned in section 4.4. Furthermore, our cases were staged by the seventh American Joint Committee on Cancer (AJCC) and its implication for current patients (staged by eighth AJCC) is unsure.

4.3. Comparisons with other studies (Table 4)

Presently, all RCTs for NPC reported similar OS as mentioned in the systematic review and meta-analysis,[12] similar to what we found for OPC or HPC. There were no fully published journal articles specifically for OPC or HPC to our knowledge, although similar OS had also been reported in 2 single-institution studies for HN cancer patients,[14,15] and similar OS had also been reported in a single-institution study for OPC in another conference paper.[27] In additional, IMRT-SEQ was reported to be associated with better OS when used in adjuvant radiotherapy for oral cavity cancer patients in another conference paper.[28]

4.4. Strengths and weaknesses of the study

There were some limitations to our study. First, our study is an observational study, and there might exist some unidentified (due to data limitation in HWDC) confounding factors (such as human papillomavirus status, or systematic or radiation therapy detail) for patient's survival. The treatment groups between prospective randomized studies are homogenous except the treatment but may not be so in retrospective studies (such as our study). Although we used the PS method to diminish the potential imbalance in observable covariables, the 2 groups in our study may still not be similar regarding unmeasured potential confounders. Therefore, one prospective trial with enough follow-up period is warranted to resolve this issue. However, when we searched for phase 3 trials via "Simultaneous Integrated Boost Phase 3" at https://clinicaltrials.gov in September 2019, we found that SIB vs conventional fractionation had been investigated in various tumors such as glioma (NCT01507506), breast cancer (NCT02474641, NCT01322854, NCT02440191), and rectal cancer (NCT01224392), but there is no new ongoing relevant trial for OPC or HPC. Second, there lacks the comprehensive dosimetric comparison between IMRT-SIB and IMRT-SEQ among these patients. Third, treatment-related toxicity such as osteoradionecrosis[29] was a potential differentiating factor between SEQ and SIB and maybe the more clinically relevant question when comparing these 2 techniques. Unfortunately, our population-based analysis was unable to explore these toxicity differences due to data limitation.

Table 2

Characteristics of the OPC patient in the first subgroup analysis.

	IMRT-SIB (n = 47)		IMRT-SEQ (n = 47)		
	Number or mean (SD)*	%*	Number or mean (SD)*	%*	SDif*
Age	52.34 (8.08)		53.81 (7.80)		0.185
Gender					
Female	†	†	†	†	0.072
Male	†	†	†	†	
Residency region					
Non-north	34	72	36	77	0.098
North	13	28	11	23	
Socioeconomic status					
Higher than minimal wage	36	77	37	79	0.051
Minimal wage	11	23	10	21	
Comorbidity					
Without	33	70	32	68	0.046
With‡	14	30	15	32	
T-stage					
T1-T2	23	49	23	49	0
T3-T4	24	51	24	51	
N-stage					
N0-N1	6	13	8	17	0.120
N2-N3	41	87	39	83	
Stage					
III	5	11	7	15	0.128
IV	42	89	40	85	
IGRT					
Yes	15	32	18	38	0.134
No	32	68	29	62	
Neoadjuvant or adjuvant systemic therapy					
Yes	19	40	16	34	0.132
No	28	60	31	66	
Smoking					
Yes	37	79	34	72	0.149
No	10	21	13	28	
Betel nut chewing					
Yes	26	55	23	49	0.128
No	21	45	24	51	
Drinking					
Yes	32	68	30	64	0.090
No	15	32	17	36	
RT break					
≤1 wk	38	81	37	79	0.053
>1 wk	9	19	10	21	

IGRT = image-guided radiotherapy, IMRT = intensity-modulated radiotherapy, RT = radiotherapy, SD = standard deviation, SDif = standardized difference, SEQ = sequential, SIB = simultaneous integrated boost.

* Rounded.

† The 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).

‡ Charlson comorbidity score ≥ 1.

Table 3

Characteristics of the HPC patient in the second subgroup analysis.

	IMRT-SIB (n = 53)		IMRT-SEQ (n = 53)		
	Number or mean (SD)*	%*	Number or mean (SD)*	%*	SDif*
Age	51.77 (8.44)		53.09 (8.33)		0.157
Gender					
Female	†	†	†	†	0
Male	†	†	†	†	
Residency region					
Non-north	41	77	43	81	0.093
North	12	23	10	19	
Socioeconomic status					
Higher than minimal wage	38	72	41	77	0.130
Minimal wage	15	28	12	23	
Comorbidity					
Without	36	68	37	70	0.041
With‡	17	32	16	30	
T-stage					
T1-T2	26	49	30	57	0.152
T3-T4	27	51	23	43	
N-stage					
N0-N1	11	21	10	19	0.047
N2-N3	42	79	43	81	
Stage					
III	7	13	7	13	0
IV	46	87	46	87	
IGRT					
Yes	20	38	22	42	0.077
No	33	62	31	58	
Neoadjuvant or adjuvant systemic therapy					
Yes	29	55	23	43	0.228
No	24	45	30	57	
Smoking					
Yes	49	92	49	92	0
No	4	8	4	8	
Betel nut chewing					
Yes	36	68	35	66	0.040
No	17	32	18	34	
Drinking					
Yes	48	91	44	83	0.224
No	5	9	9	17	
RT break					
≤1 wk	48	91	45	85	0.173
>1 wk	5	9	8	15	

IGRT = image-guided radiotherapy, IMRT = intensity-modulated radiotherapy, RT = radiotherapy, SD = standard deviation, SDif = standardized difference, SEQ = sequential, SIB = simultaneous integrated boost.

* Rounded.

† The 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).

‡ Charlson comorbidity score ≥ 1.

In conclusion, we provided the first clinical evidence regarding IMRT-SIB vs IMRT-SEQ specifically for OPC or HPC patients treated with definitive CCRT. We found the survival outcome might be comparable for those treated with IMRT-SIB vs those treated with IMRT-SEQ. However, this result should be interpreted with caution given the nonrandomized study design. A prospective study would be needed for further evaluation.

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Author contributions

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Formal analysis: Chia-Chin Li, Chun-Ru Chien.

Table 4

Studies to compare IMRT-SIB and IMRT-SEQ in head-and-neck cancer.

	Disease	Number	Technical	OS	DFS or PFS	ICSM	Study population	Study type	Paper type	Note
Jiang L et al[12]										
SIB vs SEQ	Mixed†	576 vs 473	Various	HR 0.94	HR 1.03	NA	All single-institution studies	Systematic review	Journal	Five of the 7 included studies were NPC specific. The other 2 studies were by Vlacich et al[14] and Spiotto et al[15] in this table
Vlacich et al[14]										
SIB	Mixed†	141	69.3 and 56.1 Gy over 33 Fx	69.3% (4 yr)	63% (4 yr)	NA	Single institution	Retrospective cohort	Journal	66% OPC or HPC
SEQ		68	50.4 Gy/24 Fx + boost 18.9 Gy/9 Fx	76.3% (4 yr)	69% (4 yr)	NA				
Spiotto et al[15]										
SIB	Mixed†	134	Mainly 66,, 60, and 54 Gy over 30 Fx	66.9% (2 yr)	54.5% (2 yr)	NA	Single institution	Retrospective cohort	Journal	SIB: 38% OPC or HPC; SEQ: 44% OPC or HPC
SEQ		120	2 Gy/Fx daily or 1.2 to 1.5 Gy/Fx bid; median high/intermediate/low dose =71/51/50 Gy	71.1% (2 yr)	60.4% (2 yr)					
Shah et al[27]										
SIB vs SEQ	OPC	Total 183	NA	$P=.6$	$P=.59$	NA	Single institution	Retrospective cohort	Conference	All OPC
Hsieh et al[28]										
SIB	Oral cavity	63	Dose/Fx = 2/1.8/1.52 for high/intermediate/low	Reference	NSD	NA	NA	Retrospective cohort	Conference	Adjuvant radiotherapy
SEQ		119	Low: 46 Gy/23 Fx; intermediate: 60 Gy/30 Fx	HR 0.492*						
Present study										
SIB	OPC or HPC	100	See footnote 4 in Figure 1	47% (5 yr)	NA	HR 1.4, $P=.14$	Population based (Taiwan)	Retrospective cohort	Journal	OPC 47% and HPC 53% in both SIB and SEQ
SEQ		100	See footnote 4 in Figure 1	54% (5 yr)						

DFS = disease-free survival, Fx = fraction, HPC = hypopharyngeal cancer, HR = hazard ratio, ICSM = incidence of cancer-specific mortality, IMRT = intensity-modulated radiotherapy, NA = not applicable or available, NPC = nasopharyngeal cancer, NSD = no significant differences, OPC = oropharyngeal cancer, OS = overall survival, PFS = progression-free survival, SEQ = sequential, SIB = simultaneous integrated boost.

* $P<.05$.

† Including but not limited to OPC or HPC.

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