Radiotherapy and Oncology 190 (2024) 109971

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Comparing the oncologic outcomes of proton therapy and intensity-modulated radiation therapy for head and neck squamous cell carcinoma

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ARTICLE INFO

Keywords:
Proton Therapy
IMRT
HNSCC
Survival
Recurrence
Metastasis

ABSTRACT

Purpose: To compare the oncologic outcomes between proton therapy and intensity-modulated radiation therapy (IMRT) for head and neck squamous cell carcinoma (HNSCC) patients undergoing curative radiotherapy (RT).
Experimental Design: We studied HNSCC patients who underwent curative-intent RT from 2015 to 2019, comparing the oncologic outcomes of proton therapy and IMRT. Our national retrospective HNSCC cohort study involved three institutes with proton therapy and 17 institutes (medical center levels) with IMRT in Taiwan. We utilized the Taiwan Cancer Registry Database to collect medical data for this study. We classified patients into two groups based on treatment method: Group 1 received IMRT, while Group 2 received proton therapy. 3:1 propensity score matching was performed to minimize the impact of potential confounders. Cox proportional hazards models were used to evaluate oncologic outcomes.
Results: This study of 60,485 patients with HNSCC found that proton therapy was associated with better overall and cancer-specific survival and lower locoregional recurrence rates than IMRT. After matching, 982 patients were analyzed, with well-balanced factors. Proton therapy was a significant predictor of all-cause mortality, cancer-specific death, and locoregional recurrence (LRR). Patients who received proton therapy had significantly lower risks of all-cause mortality (adjusted hazard ratio, aHR = 0.43), cancer-specific death (aHR = 0.44), and LRR (aHR = 0.61) than those who received IMRT.
Conclusion: Proton therapy is associated with superior outcomes in terms of overall survival, cancer-specific survival, and locoregional recurrence rates compared to IMRT in patients with HNSCC. These results provide valuable evidence for clinicians and patients in decision-making regarding the choice of radiation therapy for HNSCC.

Abbreviations: RT, radiotherapy; CCRT, concurrent chemoradiotherapy; CCI, Charlson comorbidity index; SD, standard deviation; IQR, interquartile range; AJCC, American Joint Committee on Cancer; N, numbers; Gy, Gray; cGy, centigray; cT, clinical tumor stages; cN, clinical nodal stages; CI, confidence interval; HR, hazard ratio; HNSCC, Head and Neck squamous cell carcinoma; PSM, propensity score matching; LRR, locoregional recurrence; DM, distant metastasis; HNCs, Head and neck cancers; TCRD, Taiwan Cancer Registry Database; NCCN, National Comprehensive Cancer Network; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; RCT, randomized controlled trial; IMRT, intensity-modulated radiation therapy; BMI, body mass index; RBE, relative biological effectiveness; LET, linear energy transfer.

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https://doi.org/10.1016/j.radonc.2023.109971
Received 15 June 2023; Received in revised form 12 October 2023; Accepted 25 October 2023
Available online 30 October 2023

Introduction

Head and neck cancer (HNC) is a major public health issue in Taiwan [1], with betel nut chewing, cigarette smoking, and alcohol use being the leading risk factors [2–10]. Head and neck squamous cell carcinoma (HNSCC) is the most common pathologic type of HNC in Taiwan, and it has a particularly high incidence among economically active individuals, with a median age of 55 years [1–10]. Despite advancements in therapeutics [8–10], the survival rate of HNSCC in Taiwan has remained poor [1], making it a significant clinical challenge. Finding effective treatments to improve oncological outcomes is thus imperative for this relatively young HNSCC population.

Particle therapy, specifically proton therapy, is a specialized form of external beam radiotherapy (RT) that offers unique physical properties to improve the precision of dose delivery [11]. Protons are generated using specialized equipment and are able to reduce the dose to normal tissues due to their unique physical properties [12]. The energy of protons determines their tissue penetration depth and a sharp peak of energy deposition, known as a Bragg peak, allows for more precise dose delivery to the target tissue while reducing radiation to adjoining normal tissue by a factor of 2 to 3 [13–16]. Proton therapy has been shown to be clinically superior to photon therapy in some pediatric populations and in rare situations where normal structures limit conventional photon beam therapy [17–24]. While Intensity Modulated Radiation Therapy (IMRT) also provides highly conformal irradiation dose distribution and precise delivery of high doses to the HNSCC [5,25], the prevalence of HNSCC in areas such as Taiwan calls for comparative studies to evaluate the need for proton therapy in these populations. Given the dismal survival rates for HNSCC in Taiwan, where betel nut chewing and other factors contribute to radioresistance [3,5,7,9,25,26], such studies are crucial to determine the effectiveness and safety of proton therapy compared to IMRT. Understanding the comparative oncologic outcomes of proton therapy versus IMRT would inform treatment decisions and improve survival rates for this aggressive malignancy.

While proton therapy has been evaluated in single-arm studies for breast cancer [27], and randomized trials for esophageal cancer [28], brain glioblastoma [29], and locally advanced non-small cell lung cancer [30], there is still a lack of solid clinical evidence demonstrating its clinical superiority in any adult solid tumor. Further trials are needed to determine the role of protons in oncologic therapy. Moreover, the majority of head and neck cancer studies have focused on proton therapy or IMRT-related toxicities [31,32], rather than on traditional oncologic outcomes such as overall survival, cancer-specific survival, locoregional recurrence, or distant metastasis in comparing proton therapy and IMRT. Given the potential value and benefits of proton therapy for HNSCC, if proven effective, it may be necessary to reevaluate health policies and insurance coverage by the government. Therefore, to address this need, we conducted a real-world database analysis using propensity score matching (PSM) to reduce selection bias and clarify the oncologic outcomes between IMRT and proton therapy for HNSCC patients.

Methods

Study population

We included patients with HNSCC who underwent curative-intent RT between January 1, 2015, and December 31, 2019, as recorded in the Taiwan Cancer Registry Database (TCRD). The follow-up period extended from the index date (i.e., date of initiation of RT) to December 31, 2021. The TCRD contains comprehensive information related to cancer, including clinical staging, smoking status, treatment modalities, pathologic data, and differentiation grade [9,33–36]. The study protocols were meticulously scrutinized and received ethical clearance from the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Inclusion and exclusion criteria

The focus of this study was on HNSCC, which encompasses squamous cell carcinoma in the oral cavity, oropharynx, hypopharynx, larynx, nasal cavity, and paranasal sinuses. All enrolled patients with HNSCC received standard curative-intent RT using either IMRT or proton therapy. Our national retrospective HNSCC cohort study involved three institutes with proton therapy and 17 institutes (medical center levels) with IMRT in Taiwan. Medical centers typically boast higher academic standings and greater healthcare resources [37]. As a result, the control arm (IMRT group) was exclusively composed of patients treated at medical centers, with hospitals outside this designation omitted. In Taiwan, the designation of being a medical center represents the highest level of hospital classification recognized by the Taiwan Ministry of Health and Welfare, with no higher tier in their evaluation [37]. Additionally, all patients in our study received treatment between 2015 and 2019, with follow-up data available until December 31, 2020. This means that all cases included in our analysis originated within the past five years, constituting a cohort of recently diagnosed HNSCC cases. Furthermore, it's worth noting that all radiotherapy treatments in our study involved the use of Image-Guided Radiotherapy to ensure precise radiation delivery.

To eliminate any potential bias from surgical outcomes on survival, we specifically selected patients who did not undergo surgery and received curative RT as their primary treatment. Our study aimed to compare the oncologic outcomes of proton therapy and IMRT for HNSCC patients receiving curative RT. The proton therapy regimen in the study was 6996 cGy in 33 fractions. The therapeutic approaches for patients with curative HNSCC were based on the National Comprehensive Cancer Network (NCCN) guidelines [38], which included concurrent chemoradiotherapy (CCRT), induction chemotherapy followed by CCRT, sequential chemotherapy and RT, or RT alone. These approaches were chosen based on each patient's individual tolerance and the standard protocols established by the NCCN guidelines and cancer committees within each hospital. The treatment protocols for HNSCC were closely monitored by the Taiwan National Health Research Institutes' Cancer Evaluation and various cancer committees within each hospital. Any deviation from the established guidelines resulted in severe penalties and disqualification of the cancer treatment hospital from meeting the required standards.

We classified the patients into two groups based on their treatment method: Group 1 received IMRT, while Group 2 received proton therapy. Moreover, we evaluated the oncologic outcomes (including all-cause mortality, cancer-specific death, locoregional recurrence [LRR], and distant metastasis [DM]) associated with proton therapy.

Propensity score matching and covariates

To minimize the impact of potential confounders when comparing all-cause mortality in patients with and without proton therapy, we performed 3:1 PSM with a caliper of 0.1 for a range of variables known to influence oncologic outcomes in HNSCC patients undergoing curative-intent RT (see Table 1) [39,40], including age, sex, cancer type, clinical stage, degree of differentiation, p16 status, urbanization level, income level, treatment modality, use of immune therapy, smoking history, betel nut chewing history, alcohol use, body mass index (BMI), and presence of comorbidities. Cox proportional hazards models were used to evaluate the impact of proton therapy on all-cause mortality, cancer-specific death, LRR, and DM. To account for clustering within matched sets, we used robust sandwich estimators [40]. Multivariate Cox regression analyses were conducted to calculate hazard ratios (HRs) for the aforementioned oncologic outcomes for HNSCC patients treated with IMRT or proton therapy. All-cause mortality was the primary endpoint in both groups, with cancer-specific death, LRR, and DM

Table 1
Comparison of Characteristics in Head and Neck Squamous Cell Carcinoma Patients Undergoing IMRT or Proton Therapy before and after PSM.

	Before propensity scores matching					**After propensity scores matching**				
	IMRT		**Proton**		***P Value***	**IMRT**		**Proton**		***P value***
	N = 60,209		**N = 276**			**N = 735**		**N = 247**		
	N	%	N	%		N	%	N	%	
Age(mean ± SD)	54.79 ± 11.67		55.33 ± 12.84		0.450	56.44 ± 14.11		55.01 ± 12.75		0.157
	54.00 (47.00,62.00)		55.00 (47.00,64.00)		0.345	55.00 (47.00,64.00)		55.00 (46.00,64.00)		0.569
Age group, years-old					0.496					0.978
<45	12,663	21.03 %	60	21.74 %		167	22.72 %	56	22.67 %	
45–55	20,229	33.60 %	85	30.80 %		220	29.93 %	76	30.77 %	
56–65	16,990	28.22 %	75	27.17 %		196	26.67 %	67	27.13 %	
>65	10,327	17.15 %	56	20.29 %		152	20.68 %	48	19.43 %	
Sex					<0.001					0.780
Male	52,942	87.93 %	214	77.54 %		568	77.28 %	193	78.14 %	
Female	7,267	12.07 %	62	22.46 %		167	22.72 %	54	21.86 %	
Cancer types					<0.001					0.953
Oral cavity	23,541	39.10 %	43	15.58 %		90	12.24 %	32	13.00 %	
Oropharynx	28,740	47.73 %	190	68.84 %		545	74.15 %	182	73.68 %	
Hypopharynx and larynx	6,087	10.11	28	10.14		68	9.52 %	23	9.31	
Nasal cavity and paranasal sinuses	1,841	3.06 %	15	5.43 %		32	4.35 %	10	4.05 %	
AJCC clinical stage					<0.001					0.657
I	4,450	7.39 %	42	15.22 %		128	17.41 %	34	13.77 %	
II	8,631	14.34 %	52	18.84 %		122	16.60 %	45	18.22 %	
III	10,915	18.13 %	57	20.65 %		142	19.32 %	54	21.86 %	
IVA	24,945	41.43 %	79	28.62 %		232	31.56 %	74	29.96 %	
IVB	11,268	18.71 %	46	16.67 %		111	15.10 %	40	16.19 %	
cT stage					<0.001					0.073
cT1	10,449	17.7 %	67	24.28 %		199	27.07 %	59	23.89 %	
cT2	16,152	26.83 %	69	25.00 %		201	27.35 %	59	23.89 %	
cT3	9,267	15.39 %	56	20.29 %		112	15.24 %	54	21.86 %	
cT4	24,341	40.43 %	84	31.25 %		223	30.34 %	75	30.36 %	
cN stage					<0.001					0.265
0	18,424	30.60 %	95	34.42 %		225	30.61 %	79	31.98 %	
1	11,754	19.52 %	77	27.90 %		209	28.44 %	74	29.96 %	
2	25,461	42.28 %	74	26.82 %		195	26.53 %	65	26.32 %	
3	4,570	7.59 %	41	10.87 %		106	14.42 %	29	11.74 %	
Differentiation					<0.001					0.841
I (well differentiated)	6,845	11.37 %	14	5.07 %		28	3.81 %	12	4.86 %	
II (moderately differentiated)	36,387	60.43 %	199	72.10 %		506	68.84 %	172	69.64 %	
III (poorly differentiated)	16,977	28.20 %	63	22.83 %		201	27.35 %	63	25.51 %	
p16 positive	7,358	12.22 %	61	22.11 %	<0.001	169	22.99 %	57	23.08 %	0.885
Urbanization					<0.001					0.921
Rural	27,257	45.27 %	58	13.77 %		162	22.04 %	56	22.67 %	
Urban	32,952	54.73 %	218	71.74 %		573	77.96 %	191	77.33 %	
Income levels (NTD)					<0.001					0.884
<22,000	9,044	15.02 %	9	3.26 %		26	3.54 %	8	3.24 %	
22,001–40,000	36,224	60.20 %	26	9.42 %		69	9.34 %	24	9.72 %	
>40,000	14,941	24.82 %	241	87.32 %		640	87.07 %	215	87.04 %	
Treatment modality					<0.001					0.492
CCRT	40,141	66.67 %	195	70.65 %		460	62.59 %	168	68.02 %	
Induction chemotherapy + CCRT	8,929	14.83 %	11	3.99 %		37	5.03 %	11	4.45 %	
Sequential chemotherapy and RT	9,166	15.22 %	12	4.35 %		52	7.07 %	11	4.45 %	
RT alone	4,973	8.26 %	58	21.01 %		186	25.31 %	57	23.08 %	
Immune therapy	2,402	3.99 %	52	18.84 %	<0.001	106	14.42 %	35	14.17 %	0.801
Cigarette Smoking	48,510	80.57 %	139	50.36 %	<0.001	410	55.78 %	126	51.01 %	0.426
Betel nut Chewing	40,069	66.55 %	95	34.42 %	<0.001	253	34.42 %	84	34.01 %	0.764
Alcohol use	43,364	72.07 %	122	44.20 %	<0.001	365	49.66 %	110	44.53 %	0.376
BMI					<0.001					0.603
<18.5	10,174	16.90 %	10	3.62 %		23	3.13 %	8	3.24 %	
18.5–23	26,020	43.22 %	112	40.58 %		308	41.90 %	104	42.11 %	
24–26	15,052	24.95 %	96	34.78 %		244	33.20 %	85	34.41 %	
≥27	8,963	14.89 %	58	21.01 %		160	21.77 %	50	20.24 %	
Coexisting Comorbidities										
CCI Score (mean ± SD)	0.72 ± 1.12		0.55 ± 0.93		0.017	0.56 ± 1.24		0.55 ± 0.90		0.529
	0.00 (0.00,1.00)		0.00 (0.00,1.00)		0.051	0.00 (0.00,1.00)		0.00 (0.00,1.00)		0.275
CCI Score	60,209		276		0.119					0.696
0	38,737	64.34 %	190	68.84 %		490	66.67 %	168	68.02 %	
≥1	21,472	35.66 %	86	31.16 %		245	33.33 %	79	31.98 %	
Diabetes	12,438	20.66 %	60	21.74 %	0.658	167	22.72 %	54	21.86 %	0.780
Hypertension	22,285	37.01 %	107	38.77 %	0.547	284	38.64 %	92	37.25 %	0.697
Hyperlipidemia	13,168	21.87 %	92	33.33 %	<0.001	216	29.39 %	77	31.17 %	0.596
Chronic kidney disease	2,135	3.55 %	14	5.07 %	0.172	43	5.85 %	13	5.26 %	0.731
Cardiovascular diseases	9,852	16.36 %	54	19.57 %	0.152	138	18.78 %	48	19.43 %	0.820
RT dose (cGy), mean ± SD	7000 ± 512.48		6896.95 ± 553.58			6996 ± 553.58		6889.96 ± 582.75		
Median (Q1, Q3)	7000 (6600,7400)		6996.00 (6996.00,6996)			6996 (6600,7400)		6996.00 (6996.00,6996)		

(*continued on next page*)

Table 1 (*continued*)

	Before propensity scores matching					After propensity scores matching				
	IMRT		Proton		*P Value*	IMRT		Proton		*P value*
	N = 60,209		N = 276			N = 735		N = 247		
	N	%	N	%		N	%	N	%	
RT fraction, mean ± SD	35 ± 2.52		32.57 ± 2.64			33 ± 2.64		33 ± 2.78		
Median (Q1, Q3)	35.00 (33.00,37.00)		33.00 (33.00,33.00)			33.00 (33.00,37.00)		33.00 (33.00,33.00)		
Follow-up, Years (mean ± SD)	3.91 ± 3.48		2.72 ± 2.01		<0.001	2.61 ± 2.09		2.85 ± 2.06		0.119
Follow-up, Years; Median (Q1,Q3)	3.55 (0.97,3.34)		2.32 (1.83,3.03)		<0.001	2.38 (0.82,3.67)		2.35 (1.94,3.21)		0.223
Outcomes										
All-cause Death	33,370	55.42 %	64	23.19 %	<0.001	308	41.90 %	59	23.89 %	<0.001
Cancer Death	29,779	49.46 %	58	21.01 %	<0.001	272	37.01 %	53	21.46 %	<0.001
Metastasis	13,548	22.50 %	59	21.38 %	0.655	170	23.13 %	56	22.67 %	0.429
Locoregional Recurrence	12,610	20.93 %	36	13.04 %	0.001	149	20.27 %	30	12.15 %	<0.001

Abbreviations: RT, radiotherapy; CCRT, concurrent chemoradiotherapy; CCI, Charlson comorbidity index; SD, standard deviation; IQR, interquartile range; AJCC, American Joint Committee on Cancer; N, numbers; Gy, Gray; cGy, centigray; cT, clinical tumor stages; cN, clinical nodal stages; PSM, propensity score matching; IMRT, intensity-modulated radiation therapy; NTD, New Taiwan Dollars.

considered secondary endpoints. Comorbidities were identified using ICD-9-CM or ICD-10-CM codes for main diagnoses in inpatient records or outpatient visits occurring at least twice within one year. Continuous variables were presented as means ± standard deviations, where appropriate. Through this rigorous statistical approach, we aimed to provide a reliable assessment of the oncologic outcomes of IMRT and proton therapy in patients with HNSCC undergoing curative RT.

Statistical analysis

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) after controlling for confounding variables. Statistical significance was set at $P < 0.05$ for a two-tailed Wald test. We used the Kaplan-Meier method to estimate overall survival, cancer-specific survival, LRR, and DM, and assessed between-group differences using the stratified log-rank test, stratified according to matched sets [41].

Results

We identified a total of 60,485 patients diagnosed with HNSCC between 2015 and 2019 who underwent either standard IMRT (60,209 patients) or proton therapy (276 patients, representing 0.46 % of the cohort) before PSM (Table 1). Patients receiving proton therapy were more likely to be female, diagnosed in more recent years (2015–2019), have more cancer types of oropharyngeal, nasal cavity, or paranasal sinus cancer, have early stages of the disease (including early clinical stages, early cT, and early cN), have moderate differentiation, be p16 positive, live in urban areas, have higher income levels, receive more RT alone, more immune therapy, have lower rates of smoking history, lower rates of alcohol and betel nut use, lower Charlson comorbidity index scores, and more hyperlipidemia than those in the IMRT group. After performing PSM, 982 patients (735 in the IMRT group and 247 in the proton therapy group) were eligible for further analysis, and their characteristics are summarized in Table 1. Age, sex, cancer type, clinical stage, degree of differentiation, p16 status, urbanization level, income level, treatment modality, immune therapy use, smoking history, betel nut use, alcohol use, BMI, and presence of coexisting comorbidities were well-balanced between the two groups (all *P*-values > 0.05). Following PSM, crude rates of all-cause mortality (41.90 % versus 23.89 %), cancer-specific death (37.01 % versus 21.46 %), and LRR (20.27 % versus 12.15 %) were significantly higher in the IMRT group compared to the proton therapy group (Table 1).

Double robust Cox regression modeling analysis revealed that proton therapy was a significant predictor of all-cause mortality, cancer-specific death, and LRR (Table 2). Both univariate and multivariate Cox regression analyses demonstrated that HNSCC patients who received curative-intent RT with proton therapy had better overall survival, cancer-specific survival, and lower locoregional recurrence rates compared to those who received IMRT. In the multivariate Cox regression analysis, the adjusted hazard ratios (aHRs) for all-cause mortality for HNSCC patients receiving proton therapy compared to IMRT were 0.43 (95 % confidence interval [CI], 0.32–0.57; $P < 0.001$). Similarly, the aHRs (95 % CIs) for cancer-specific death, LRR, and DM for HNSCC patients receiving proton therapy were 0.44 (95 % CI, 0.33–0.59; $P < 0.001$), 0.61 (95 % CI, 0.33–0.88; $P = 0.009$), and 0.85 (95 % CI, 0.72–2.01; $P = 0.490$), respectively, in the multivariate Cox regression analysis.

Figs. 1 and 2 display Kaplan-Meier survival curves for overall survival, cancer-specific survival, locoregional recurrence, and metastasis among the PSM-matched IMRT and proton therapy groups who underwent curative RT for HNSCC. The overall survival curve for patients receiving proton therapy was superior to that of those receiving IMRT (Fig. 1A, $P < 0.001$). At 2 years, the overall survival rates for HNSCC patients who received proton therapy and IMRT were 86.08 % and 68.92 %, respectively. The 2-year cancer-specific survival rates were 88.22 % and 70.03 % for proton therapy and IMRT in HNSCC patients (Fig. 1B, $P < 0.001$). Furthermore, HNSCC patients receiving IMRT had significantly higher cumulative rates of locoregional recurrence than those receiving proton therapy, as evidenced by the log-rank test (Fig. 2A, $P = 0.001$ for LRR). However, there were no significant differences in distant metastasis between the IMRT and proton therapy groups for HNSCC patients (Fig. 2B).

Discussion

In recent years, charged particles and heavy ions have been increasingly used for HNC, especially for those requiring high doses adjacent to critical organs at risk, such as the skull base, or in the reirradiation setting [31,32,42–45]. Proton therapy provides better dosimetric sparing of normal organs or structures for well-defined and relatively small lesions [31,32]. However, whether this dosimetric advantage translates into clinical benefit for patients is still uncertain, and there are significant uncertainties about the biologic effectiveness of these particles as well as the accuracy of predicting dose deposition [31,32]. Additionally, the benefits of using proton therapy compared to IMRT for newly diagnosed HNSCC patients without recurrence or metastasis and who have never received radiation therapy are still uncertain. In a retrospective study of 292 patients with nonmetastatic oropharyngeal carcinoma, curative-intent RT employing IMPT demonstrated a substantial reduction in acute toxicity compared to IMRT. The research findings indicated minimal chronic adverse effects and positive oncologic outcomes, including a low 2-year locoregional recurrence rate of only 5 %. However, it's important to note that this study lacks

Table 2
Cox Proportional Regression Analysis of All-Cause Death, Cancer-Specific Death, Locoregional Recurrence, and Metastasis for IMRT versus Proton Therapy for Propensity Score Matching Head and Neck Squamous Cell Carcinoma Patients.

	Crude HR(95 %CI)		*P Value*	Adjusted HR(95 %CI)*		*P Value*
All-Cause Death						
IMRT (ref.)	1.00	–	–	1.00	–	–
Proton	0.52	(0.39,0.68)	<0.001	0.43	(0.32,0.57)	<0.001
Cancer-Specific Death						
IMRT (ref.)	1.00	–	–	1.00	–	–
Proton	0.53	(0.39,0.7)	<0.001	0.44	(0.33,0.59)	<0.001
Locoregional recurrence						
IMRT (ref.)	1.00	–	–	1.00	–	–
Proton	0.71	(0.23,0.89)	0.002	0.61	(0.33,0.88)	0.009
Distant Metastasis						
IMRT (ref.)	1.00	–	–	1.00	–	–
Proton	0.84	(0.71,1.98)	0.377	0.85	(0.72,2.01)	0.490

Abbreviations: CI, confidence interval; HR, hazard ratio; HNSCC, Head and Neck squamous cell carcinoma; MRT, intensity-modulated radiation therapy; ref., reference group.

* Adjustment for potential confounding factors listed in Table 1, such as age, sex, cancer type, clinical stage, degree of differentiation, p16 status, urbanization level, income level, treatment modality, smoking history, betel nut chewing history, alcohol use, body mass index, and presence of coexisting comorbidities.

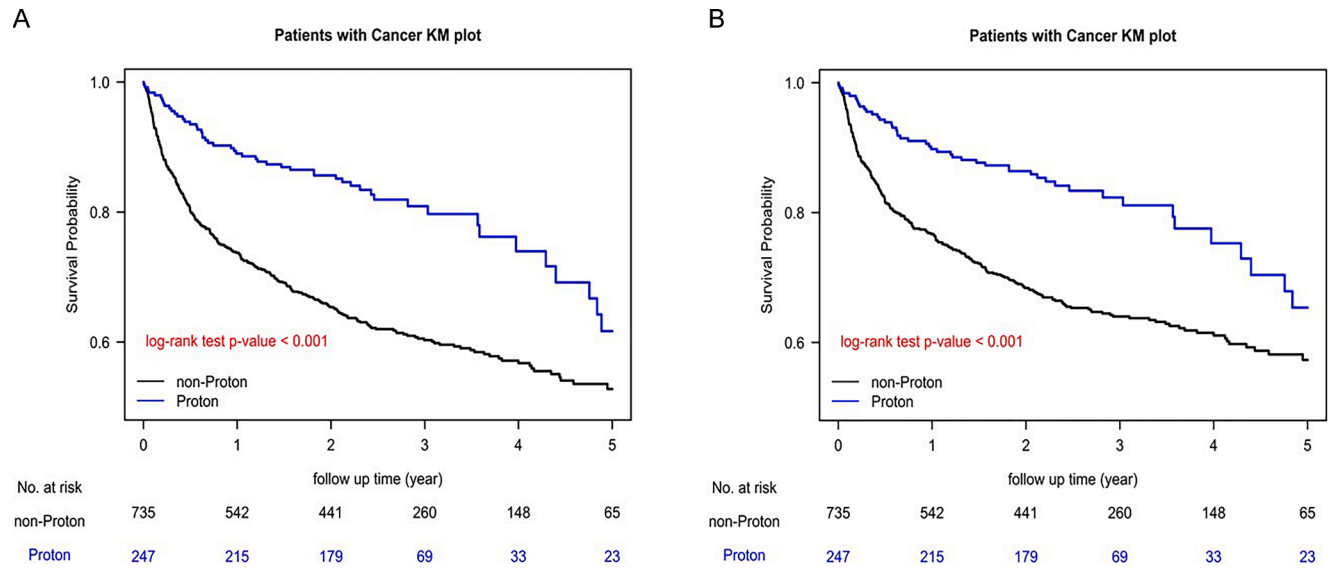

Fig. 1. Kaplan-Meier Curves for Overall and Cancer-Specific Survival for IMRT and Proton Therapy in Head and Neck Squamous Cell Carcinoma. (1A) Overall Survival. (1B) Cancer-Specific Survival.

detailed data on various factors, such as degree of differentiation, urbanization level, income status, betel nut consumption history, alcohol use, BMI, the presence of comorbidities, and other oncologic parameters [46]. A small sample size randomized clinical trial (NCT01893307) has indeed been conducted, comparing IMRT and proton therapy for patients with oropharyngeal tumors [47]. This trial has been completed, and we are currently awaiting the release of its results. However, as of now, there is a lack of data to compare the oncologic outcomes between IMRT and proton therapy for first-diagnosed HNSCC without recurrence and metastasis. Our study is the first PSM cohort study to compare the oncologic outcomes of IMRT and proton therapy in HNSCC. It is pertinent to acknowledge a previous study conducted at MD Anderson, although lacking PSM utilization. This earlier research concentrated on a matched cohort of oropharynx cancer patients, primarily exploring the effects of IMPT on reducing dependency on feeding tubes and mitigating severe weight loss without compromising clinical outcomes [48]. Our findings imply improved overall survival, cancer-specific survival, and reduced locoregional recurrence rates in HNSCC patients treated with proton therapy compared to those receiving standard IMRT (Table 2, Figs. 1, and 2). Notably, no significant differences in metastasis were observed between HNSCC patients undergoing proton therapy and those treated with IMRT. It is essential to acknowledge that this study is retrospective, and despite the utilization of PSM, the cohort remains highly unbalanced, with PSM mitigating only a portion of the inherent imbalances.

Despite the increasing use of proton therapy for head and neck cancer patients, RCTs comparing its efficacy and toxicity with other radiotherapy techniques, such as IMRT, are scarce [47]. This preference largely arises from the ability of proton therapy to minimize radiation exposure to critical structures, reducing side effects and improving treatment outcomes, especially in cases where tumors are in proximity to such structures [31,32,42–45,49]. Despite potential initial cost considerations, the long-term benefits in terms of enhanced quality of life and reduced healthcare expenses make proton therapy an attractive option. The primary limitation hindering the conduct of a RCT in the context of proton therapy is the accessibility to proton treatment, mainly driven by financial constraints and insurance coverage. This financial burden significantly contributes to the challenges associated with carrying out an RCT to address the question of proton therapy's efficacy [12,31,32,42–45,49,50]. Another reason for the sparsity of RCTs in Proton Beam therapy is the lack of centers and limited accessibility across the globe. As a result, the majority of evidence available is derived from retrospective studies [31,32,42–45], which have inherent limitations and potential sources of bias. The ongoing RCT comparing

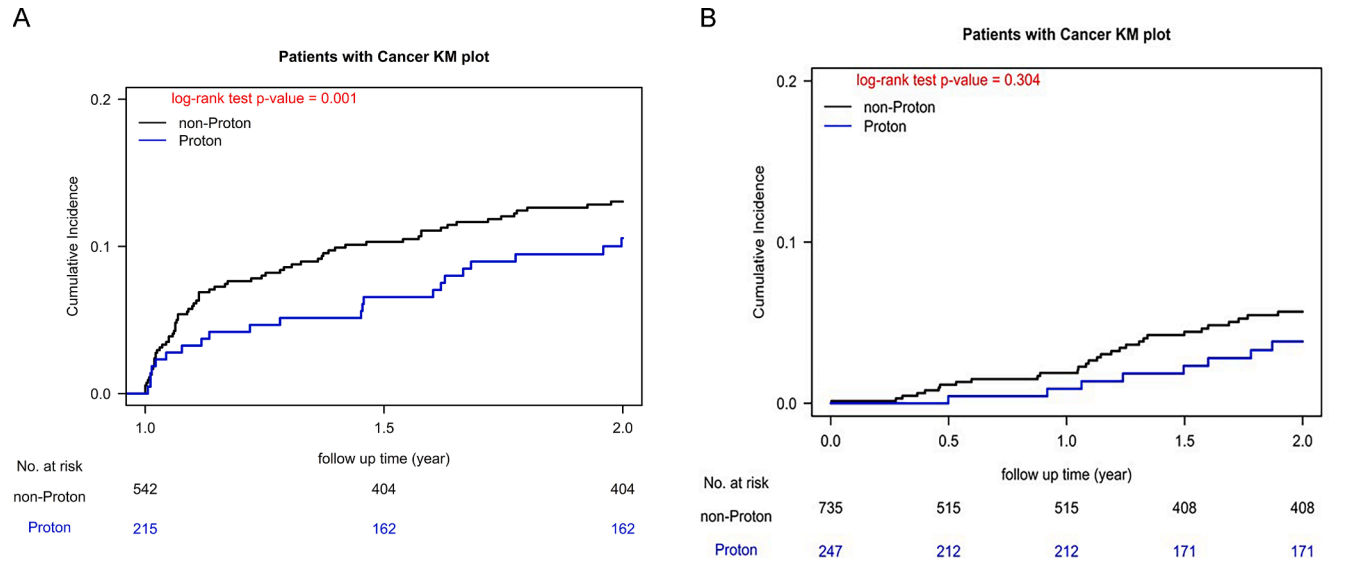

Fig. 2. Kaplan-Meier Curves for Cumulative Incidence of Locoregional Recurrence and Distant Metastasis between IMRT and Proton Therapy in Head and Neck Squamous Cell Carcinoma. (2A) Locoregional Recurrence. (2B) Distant Metastasis.

IMRT and proton therapy for oropharyngeal cancer has several limitations, including a small sample size and a lack of adjustment for important confounding factors, such as comorbidities, degree of differentiation, urbanization level, smoking history, alcohol use, nutrition status, and the presence of coexisting comorbidities [47]. Additionally, the study has other shortcomings, including choices related to the primary endpoint and varying access to proton therapy among participants. Nevertheless, due to the inherent nature of an RCT, it is expected to provide the most robust evidence to date, surpassing retrospective real-world data, especially in the context of significant disparities in access to proton therapy. The use of PSM in our study comparing IMRT and proton therapy for HNSCC offers several benefits in situations where RCTs are not feasible or ethical. PSM can balance the distribution of potential confounders between the two treatment groups, reducing the impact of selection bias and increasing the internal validity of the study [39,40,51]. This allows for a more accurate estimation of treatment effects and can help to address some of the limitations of non-randomized studies [39,40,51]. However, it is important to acknowledge that PSM does not fully eliminate the potential for unmeasured confounding, and the results should be interpreted with caution [39,40,51]. In addition, PSM may not be able to account for all possible confounding factors, which could impact the treatment effect estimates [39,40,51]. Therefore, the results obtained from PSM analyses should be interpreted with caution and ideally confirmed with other study designs, such as RCTs or prospective cohort studies. Previous reports have highlighted the advantages of proton therapy for HNSCC, demonstrating reduced toxicity and improved irradiation dosimetry distribution attributable to the Bragg effect [31,32,42–45,49]. These factors may have contributed to the observed oncologic benefits, such as longer overall survival, enhanced cancer-specific survival, and a decreased number of locoregional recurrences. However, it's essential to recognize that our follow-up period is relatively short, which is insufficient to account for potential late effects of radiation. While improved dosimetry theoretically leads to reduced toxicity, it may not entirely explain the observed survival benefits within this limited follow-up period. For a comprehensive assessment of oncologic advantages, such as prolonged overall survival, enhanced cancer-specific survival, and decreased locoregional recurrences, more extended follow-up is necessary.

The mechanisms underlying the improved oncologic outcomes of proton therapy for HNSCC can be divided into two categories: physical and radiation biological characteristics of proton and photon therapy [14,15]. In Taiwan, local recurrence is the predominant cause of treatment failure in curative-intent RT for HNSCC [3], which may be attributed to the high prevalence of betel nut chewing among Taiwanese HNSCC patients [3,5,7,9,25,26]. Betel nut chewing has been shown to cause overexpression of epidermal growth factor receptor and a high frequency of p53 mutations, both of which may contribute to radiation resistance [3,5,7,9,25,26]. Hence, better local control is crucial for relatively radiation-resistant HNSCC to achieve improved survival [3,5,25,26,52]. Proton therapy offers advantages not only in terms of its physical properties but also in radiobiology [13], particularly for HNSCC, which is relatively resistant to radiation [26]. Proton therapy and photon (IMRT) have distinct physical and radiobiological characteristics when used to treat HNSCC [13]. Proton therapy employs a Bragg peak that enables a higher radiation dose to be delivered to the tumor site with minimal dose to adjacent normal tissues, resulting in a higher therapeutic ratio compared to IMRT [13]. In contrast, IMRT delivers a relatively uniform dose throughout the tissue, leading to greater exposure of normal tissues to radiation and thus more RT-related toxicities compared with proton therapy [31,32,42–45,49]. Furthermore, the relative biological effectiveness (RBE) of proton therapy depends on the energy of the protons used and the type of tissue being irradiated [13]. Protons have a higher linear energy transfer (LET) than IMRT [13], which means that they deposit their energy over a shorter distance, causing more damage to the DNA within the HNSCC [13]. This can result in a higher RBE for protons, meaning that they can be more effective at killing relatively radiation-resistant cancer cells like HNSCC compared to IMRT [13]. Other particle beams, such as carbon ions with higher LET, are being investigated for other indications, such as salivary gland tumors (which are even more resistant to irradiation) [53].

This study has several limitations. Firstly, it is based on an Asian population in Taiwan, and generalizing these findings to non-Asian populations should be done cautiously. Second, while PSM was used to control for confounders, it may not address all unmeasured variables, potentially introducing selection bias. Moreover, despite efforts to minimize residual confounding [54], especially related to PSM's caliper distance [39,40], some concerns may persist. Third, the relatively short follow-up duration limits assessments of long-term outcomes like late toxicity and secondary malignancies. However, the observed divergence in survival curves within the initial one to two years suggests that proton therapy's benefits are likely to endure with longer follow-up. Nevertheless, a more extended follow-up period is crucial for conclusive long-term survival assessments. Fourth, the sample size and follow-up duration may not detect small but clinically meaningful differences. Fifth, the

use of alternative data sources for toxicity assessments, such as medication reimbursement records, may lack the precision required to evaluate radiation-induced toxicities comprehensively. Thus, detailed toxicity data are unavailable in this analysis. Sixth, the proton therapy group's unique characteristics were addressed through PSM, and the comparatively lower survival rates in the IMRT group can be attributed to a higher proportion of advanced or inoperable cancer types. Lastly, while comorbid conditions were verified by the Taiwan Cancer Registry Administration, conducting large-scale randomized controlled trials to obtain precise, population-specific data on disease occurrence and treatment safety is warranted, although it presents logistical challenges.

Despite the limitations, our study has significant strengths. To our knowledge, this is the first and largest comparative study to evaluate the detailed oncologic outcomes of proton therapy and IMRT for HNSCC patients, including overall survival, cancer-specific survival, locoregional recurrence, and distant metastasis. We used a well-designed PSM approach with a real-world database, which eliminated any bias between the two groups and provided a homogenous sample (Table 1). Furthermore, the TCRD was linked with Taiwan's National Cause of Death Database, which enabled us to perform a lifelong follow-up of most patients. Given the magnitude and statistical significance of the observed effects, it is unlikely that the limitations have affected our conclusions. Thus, our study provides valuable insights into the oncologic outcomes of proton therapy and IMRT for HNSCC patients and can serve as a basis for future studies.

Conclusion

After carefully evaluating the oncologic outcomes of proton therapy and IMRT for patients with HNSCC, our study indicates that proton therapy may be associated with improved overall survival, cancer-specific survival, and fewer occurrences of locoregional recurrence. The findings suggest that proton therapy has significant therapeutic advantages compared to IMRT in treating HNSCC. These results provide important insights into the potential effectiveness of proton therapy for HNSCC patients and could serve as a basis for further clinical trials and investigations in this field.

Research in context:

Evidence before this study:

Previous studies have shown that proton therapy has dosimetric advantages over IMRT in sparing normal organs and tissues, especially for small and well-defined lesions. However, the clinical benefits of proton therapy over IMRT for HNSCC patients have not been fully explored, and there is a lack of comparative studies assessing the oncologic outcomes of proton therapy and IMRT in HNSCC patients. To our knowledge, no previous studies have investigated the long-term survival and recurrence rates of HNSCC patients treated with proton therapy compared to those treated with IMRT using a well-matched propensity score matching approach.

Added value of this study:

This nationwide retrospective cohort study is the first and largest to compare the detailed oncologic outcomes of proton therapy and IMRT for HNSCC patients, including overall survival, cancer-specific survival, locoregional recurrence, and distant metastasis. Using a well-designed propensity score matching approach, the study eliminates potential bias and provides a homogeneous sample. The study's results demonstrate that proton therapy is associated with superior outcomes in terms of overall survival, cancer-specific survival, and locoregional recurrence rates compared to IMRT in patients with HNSCC.

Implications of all the available evidence:

The findings of this study provide valuable evidence for clinicians and patients in making informed decisions regarding the choice of radiation therapy for HNSCC. The results suggest that proton therapy may be a better treatment option than IMRT for HNSCC patients undergoing curative RT. However, further studies are needed to investigate the long-term efficacy of proton therapy compared to IMRT, as well as the potential cost-effectiveness and quality of life outcomes associated with proton therapy. Future research may also explore the use of proton therapy in combination with other treatment modalities, such as chemotherapy or immunotherapy, for HNSCC patients.

Condensed Abstract

This study is the first and largest comparative cohort study to evaluate the detailed oncologic outcomes of proton therapy and IMRT for HNSCC patients, including overall survival, cancer-specific survival, locoregional recurrence, and distant metastasis. Using a well-designed propensity score matching (PSM) approach with a real-world database, the study eliminated any bias between the two groups and provided a homogenous sample. Additionally, the TCRD was linked with Taiwan's National Cause of Death Database, which enabled lifelong follow-up of most patients. The study results demonstrate superior overall survival, cancer-specific survival, and lower locoregional recurrence rate for HNSCC patients receiving proton therapy compared to those receiving standard IMRT. However, there was no significant difference in metastasis between HNSCC patients receiving proton therapy and those receiving IMRT. The study provides valuable insights into the oncologic outcomes of proton therapy and IMRT for HNSCC patients and can serve as a basis for future studies.

Ethics approval and consent

The study protocols were reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Financial Support

Lo-Hsu Medical Foundation, LotungPoh-Ai Hospital, supports Szu-Yuan Wu's work (Funding Number: 10908, 10909, 11001, 11002, 11003, 11006, and 11013).

Availability of data and material

Data analyzed during the study were provided by a third party. Requests for data should be directed to the provider indicated in the Acknowledgments.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Lo-Hsu Medical Foundation, LotungPoh-Ai Hospital, supports Szu-Yuan Wu's work (Funding Number: 110908, 10909, 11001, 11002, 11003, 11006. The data sets supporting the study conclusions are included in the manuscript. We used data from the National Health Insurance Research Database and Taiwan Cancer Registry database. The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. The data used in this study cannot be made available in the manuscript, the supplemental files, or in a public repository due to the Personal Information Protection Act executed by Taiwan's government, starting in 2012. Requests for data can be sent as a formal proposal to obtain approval from the ethics review committee of the appropriate governmental department in Taiwan. Specifically, links regarding contact info for which data requests may be sent to are as follows: http://nhird.nhri.org.tw/en/Data_Subsets.html#S3 and http://nhis.nhri.org.tw/point.html.

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