Received:
10 December 2017

Revised:
01 March 2018

Accepted:
16 March 2018

<https://doi.org/10.1259/bjr.20170947>

Cite this article as:

Wang Y-C, Li C-C, Chien C-R. Effectiveness of tomotherapy vs linear accelerator image-guided intensity-modulated radiotherapy for localized pharyngeal cancer treated with definitive concurrent chemoradiotherapy: a Taiwanese population-based propensity score-matched analysis. *Br J Radiol* 2018; **91**: 20170947.

FULL PAPER

Effectiveness of tomotherapy vs linear accelerator image-guided intensity-modulated radiotherapy for localized pharyngeal cancer treated with definitive concurrent chemoradiotherapy: a Taiwanese population-based propensity score-matched analysis

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Objective: This study used a population-based propensity score (PS)-matched analysis to compare the effectiveness of tomotherapy-based image-guided intensity-modulated radiotherapy (referred to as T-IMRT) with that of linear accelerator based (referred to as L-IMRT) for clinically localized pharyngeal cancer (LPC, divided into nasopharyngeal cancer and non-nasopharyngeal cancer) with definitive concurrent chemoradiotherapy (CCRT).

Methods: Eligible LPC patients diagnosed between 2007 and 2014 were identified among all citizens in Taiwan from the Health and Welfare Data Science Center database. A PS-matched sample based on the PS estimated from the covariables of interest was constructed to compare the effectiveness of T-IMRT with L-IMRT. In the primary analysis, overall survival (OS) was compared for assessment of effectiveness. We also evaluated freedom from local regional recurrence and pharyngeal cancer-specific survival and performed supplementary analyses.

Results: The study population included 960 patients equally divided into two groups. OS did not differ significantly between the T-IMRT and L-IMRT groups (hazard ratio for death: 0.82, $p = 0.15$, 5-year OS rate: 79 and 74% for T-IMRT and L-IMRT, respectively), and there were no significant differences in the other endpoints or supplementary analyses.

Conclusion: For LPC patients treated with definitive CCRT, we found no significant difference in disease control or survival between the T-IMRT and L-IMRT groups. However, further studies, especially randomized trials or studies focusing on other dimensions, such as quality of life, are needed.

Advances in knowledge: We provide the first population-based study, as well as the largest study, on the clinical effectiveness of T-IMRT compared with L-IMRT in conjunction with CCRT in LPC patients.

INTRODUCTION

Radiotherapy (RT) plays an important role in the treatment of head and neck cancer (HNC).^{1,2} Concurrent chemoradiotherapy (CCRT) significantly improves the outcome of HNC³ and has been widely adopted in treatment guidelines.^{2,4} In contrast to conventional techniques or three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT) can reduce the incidence of Grade 2–4 xerostomia in patients with HNC without compromising loco-regional control or overall survival (OS).⁵ Image-guided (IG)-IMRT may offer further

clinical advantages by increasing the accuracy of radiotherapy delivery.^{2,6}

Tomotherapy is an advanced form of IG-IMRT (referred to as T-IMRT in the following manuscript) administered via a helical delivery method that can be applied to treat complex malignant cancers, such as HNC, with high precision.⁷ A previous dosimetric study showed that T-IMRT led to better tumor coverage and lower normal organ doses in head/neck radiotherapy compared with linear accelerator based IMRT (L-IMRT).⁸ T-IMRT may even meet the

Figure 1. STROBE study flow chart and number of individuals at each stage of the study. ¹: We included only those treated (class 1–2) by any single institution to ensure data consistency. ²: Clinical Stage I–IV and cM0; 2007–2009 staging was conducted according to the 6th American Joint Committee on Cancer Staging, whereas 2010–2014 staging was according to the 7th American Joint Committee on Cancer staging. ³: Classified as NPC (keratinizing squamous cell carcinoma or non-keratinizing carcinoma) or non-NPC (squamous cell carcinoma). ⁴: We included only those treated with external beam radiotherapy but no brachytherapy or radiosurgery. We included those treated with 1.8–2 Gy/fraction ($\pm 10\%$) for 66–74 Gy delivered within 1–2 months. ⁵: Without missing information in the Taiwan Cancer Registry or death registry.

dosimetric requirement for stereotactic radiosurgery.⁹ Excellent outcomes have been reported in many single-arm studies for various disease sites,^{10–12} including HNC.¹³ However, Perrier *et al* reported a higher cost associated with T-IMRT compared with volumetric-modulated arc therapy (VMAT) for patients

with HNC.¹⁴ Moreover, a prolonged treatment time (approximately 25–30 min) influenced the daily workload associated with T-IMRT.^{14–16} In head and neck cancer, the cost per patient of T-IMRT is higher than that of L-IMRT, about \$ 3500–\$ 3700 in Taiwan. In addition, per treatment time in head and neck cancer

Table 1. Patient characteristics for the whole study population

		T-IMRT (n = 480)		L-IMRT (n = 480)		Standardized difference
		Number or mean (SD) ^b	% ^b	Number or mean (SD) ^b	% ^b	
Age	<65 years	418	87.1	431	89.8	0.085
	≥65 years	62	12.9	49	10.2	
Sex	Male	380	79.2	382	79.6	0.010
	Female	100	20.8	98	20.4	
Residence region	North	118	24.6	118	24.6	0.000
	Non-north	362	75.4	362	75.4	
Socioeconomic status	No more than minimum wage	102	21.2	82	17.1	0.106
	Higher	378	78.8	398	82.9	
Comorbidity	With ^a	165	34.4	127	26.5	0.173
	Without	315	65.6	353	73.5	
Cancer history	With	39	8.1	27	5.6	0.099
	Without	441	91.9	453	94.4	
Site	NPC	342	71.3	342	71.3	0.000
	Non-NPC	138	28.7	138	28.7	
Overall stage	I–II	101	21.0	109	22.7	0.040
	III–IV	379	79.0	371	77.3	
T-stage	1–2	274	57.1	275	57.3	0.004
	3–4	206	42.9	205	42.7	
N-stage	0–1	194	40.4	192	40.0	0.008
	2–3	286	59.6	288	60.0	
Period	Early (2007–2009)	30	6.2	34	7.1	0.033
	Recent (2010–2014)	450	93.8	446	92.9	
Induction systemic therapy	With	101	21.0	110	22.9	0.045
	Without	379	79.0	370	77.1	
RT break	≤1 week	450	93.8	459	95.6	0.084
	>1 week	30	6.2	21	4.4	
RT dose (Gy)		70.73 (1.29)		70.86 (1.34)		0.099

L-IMRT, linear accelerator based image-guided intensity-modulated radiotherapy; NPC, nasopharyngeal carcinoma; RT, radiotherapy; SD, standard deviation; T-IMRT, tomotherapy-based image-guided intensity-modulated radiotherapy.

^aCarlson comorbidity score ≥ 1.

^bRounded.

Figure 2. Kaplan-Meier survival curve for the whole study population.

with T-IMRT is about 25 min, just allowing 16 patients within 8 h for irradiation. In addition, a systematic review regarding T-IMRT for cancer treatment reported that “the quality of the included studies was poor”;¹⁷ only two full-length papers (from the same institute) compared T-IMRT with L-IMRT for HNC in that systematic review.^{17–19} Chen *et al* compared 149 patients treated by either T-IMRT or L-IMRT for HNC (non-nasopharyngeal carcinoma, non-NPC) and found no significant difference in 2-year OS.¹⁸ In another study of 30 nasopharyngeal carcinoma (NPC) patients, less xerostomia but no significant difference in 2-year OS was reported.¹⁹ We performed a PubMed search using the keywords “(tomotherapy) AND [(survival) OR (disease-free survival)]” and the search field “Title/Abstract” on January 6, 2018 and found one additional relevant study. Bibault *et al* reported better loco-regional control and cancer-specific

Figure 3. Kaplan-Meier survival curve for the first supplementary analysis (NPC). NPC, nasopharyngeal carcinoma.

Figure 4. Kaplan-Meier survival curve for the second supplementary analysis (non-NPC). NPC, nasopharyngeal carcinoma.

survival, but similar OS, at 18 months in 166 HNC patients from a French multi-institute study treated with T-IMRT compared with VMAT.²⁰

Given the paucity of evidence regarding the clinical effectiveness of T-IMRT via L-IMRT for HNC, we aimed to compare the effectiveness of T-IMRT with L-IMRT for HNC treated with definitive CCRT via a population-based propensity score (PS)-matched analysis.

MATERIALS AND METHODS

Data source

The Health and Welfare Data Science Center (HWDC) database is a set of databases containing complete information regarding the Taiwan Cancer Registry (TCR), death registry and reimbursement data for all citizens in Taiwan (population ~23 million) provided by the Bureau of National Health Insurance (NHI).²¹ The high quality of this cancer registry has been reported previously.²² The NHI is a single-payer, compulsory, social insurance program that provides insurance coverage to the majority of citizens in Taiwan.²³ All of the above data were included in the HWDC with personal identifiers removed.

Study population and study design

Our study flow chart, according to previous studies,²⁴ is depicted in Figure 1. Our target population was patients with clinically localized pharyngeal cancer (LPC) treated with definitive CCRT in which radiotherapy was delivered via either IG tomotherapy-based IMRT (T-IMRT) or linear accelerator based (*i.e.* non-tomotherapy) IG-IMRT (L-IMRT) during 2007–2014. We included squamous cell carcinoma (SqCC) for oropharynx [International Classification of Diseases Oncology, third edition (ICD-O-3), codes C090–C091, C098–C104 and C108–C109], hypopharynx (ICD-O-3 codes C129–C132 and C138–C139), or pharynx (ICD-O-3 codes C140, C142 and C148) cancers. On the other hand, both keratinizing SqCC (K-SqCC) and

Table 2. Patient characteristics in the first supplementary analysis

		T-IMRT (<i>n</i> = 342)		L-IMRT (<i>n</i> = 342)		Standardized difference
		Number or mean (SD) ^b	% ^b	Number or mean (SD) ^b	% ^b	
Age	<65 years	296	86.6	312	91.2	0.149
	≥65 years	46	13.4	30	8.8	
Sex	Male	250	73.1	251	73.4	0.007
	Female	92	26.9	91	26.6	
Residence region	North	77	22.5	79	23.1	0.014
	Non-north	265	77.5	263	76.9	
Socioeconomic status	No more than minimum wage	68	19.9	52	15.2	0.123
	Higher	274	80.1	290	84.8	
Comorbidity	With ^a	110	32.2	81	23.7	0.190
	Without	232	67.8	261	76.3	
Cancer history	With	15	4.4	12	3.5	0.045
	Without	327	95.6	330	96.5	
Histology	K-SqCC	7	2.0	8	2.3	0.020
	NKC	335	98.0	334	97.7	
Overall stage	I–II	88	25.7	97	28.4	0.059
	III–IV	254	74.3	245	71.6	
T-stage	1–2	214	62.6	214	62.6	0.000
	3–4	128	37.4	128	37.4	
N-stage	0–1	146	42.7	151	44.1	0.029
	2–3	196	57.3	191	55.9	
Period	Early (2007–2009)	19	5.6	23	6.7	0.049
	Recent (2010–2014)	323	94.4	319	93.3	
Induction systemic therapy	With	51	14.9	60	17.5	0.071
	Without	291	85.1	282	82.5	
RT break	≤1 week	322	94.2	332	97.1	0.143
	>1 week	20	5.8	10	2.9	
RT dose (Gy)		70.76 (1.30)		70.92 (1.39)		0.116

K-SqCC, keratinizing squamous cell carcinoma; L-IMRT, linear accelerator based image-guided intensity-modulated radiotherapy; NK, non-keratinizing carcinoma; RT, radiotherapy; SD, standard deviation; T-IMRT, tomotherapy-based image-guided intensity-modulated radiotherapy.

^aCarlson comorbidity Score ≥ 1.

^bRounded.

non-keratinizing carcinoma (NKC) were included for NPC (ICD-O-3 codes C110–C113 and C118–C119),^{25,26} because these LPCs are representative HNCs in which CCRT is used as a curative-intent primary treatment, according to the literature^{18–20} with slight modifications based on our clinical experience. CCRT was defined as concurrent systemic therapy during local regional therapy according to records in the TCR. The date of diagnosis was used as the index date. We then chose the explanatory variable of interest (T-IMRT vs L-IMRT) based on the cancer registry. We also selected other covariables (see next subsection “Other explanatory covariables”) to adjust for

potential non-randomized treatment selection and effectiveness data from the HWDC. Finally, we constructed a PS-matched sample based on the PS estimated using the above covariables to compare the effectiveness of T-IMRT with that of L-IMRT. In the PS analysis, we modeled the use of T-IMRT (vs L-IMRT) as the dependent variable and the covariables as independent variables, and then used the logit of the probability in match, as commonly used in the literature.²⁷ We matched on disease site exactly. This study was approved by the research ethics committee of our institute (CMUH103-REC-005).

Table 3. Patient characteristics in the second supplementary analysis

		T-IMRT (<i>n</i> = 138)		L-IMRT (<i>n</i> = 138)		Standardized difference
		Number or mean (SD) ^b	% ^b	Number or mean (SD) ^b	% ^b	
Age	<65 years	122	88.4	119	86.2	0.065
	≥65 years	16	11.6	19	13.8	
Sex	Male	130	94.2	131	94.9	0.032
	Female	8	5.8	7	5.1	
Residence region	North	41	29.7	39	28.3	0.032
	Non-north	97	70.3	99	71.7	
Socioeconomic status	No more than minimum wage	34	24.6	30	21.7	0.069
	Higher	104	75.4	108	78.3	
Comorbidity	With ^a	55	39.9	46	33.3	0.136
	Without	83	60.1	92	66.7	
Cancer history	With	24	17.4	15	10.9	0.188
	Without	114	82.6	123	89.1	
Overall stage	I–II	13	9.4	12	8.7	0.025
	III–IV	125	90.6	126	91.3	
T-stage	1–2	60	43.5	61	44.2	0.015
	3–4	78	56.5	77	55.8	
N-stage	0–1	48	34.8	41	29.7	0.109
	2–3	90	65.2	97	70.3	
Period	Early (2007–2009)	11	8.0	11	8.0	0.000
	Recent (2010–2014)	127	92.0	127	92.0	
Induction systemic therapy	With	50	36.2	50	36.2	0.000
	Without	88	63.8	88	63.8	
RT break	≤1 week	128	92.8	127	92.0	0.027
	>1 week	10	7.2	11	8.0	
RT dose (Gy)		70.63 (1.26)		70.70 (1.20)		0.056

L-IMRT, linear accelerator based image-guided intensity-modulated radiotherapy; RT, radiotherapy; SD, standard deviation; T-IMRT, tomotherapy-based image-guided intensity-modulated radiotherapy.

^aCarlson comorbidity Score ≥ 1.

^bRounded.

Other explanatory covariables

We referred to available data and our clinical and research experience for other explanatory covariables.^{28–31} Accordingly, we included patient demographic factors (age, sex and residence region), patient characteristics (socioeconomic status, comorbidity and cancer history), disease characteristics [disease site and stage, histology (only for NPC)], treatment (induction systemic therapy, RT dose and RT break) and time period. Age was classified as < or ≥65 years. Comorbidity was defined as a modified Carlson comorbidity Score ≥1, as used in our previous NHI cancer study.³¹ Socioeconomic status was classified as high (income greater than minimum wage) or not. Cancer history was defined as with or without pharyngeal cancer before the index date. The residence of the patient was classified as northern Taiwan or elsewhere. Disease site was classified as NPC or

non-NPC. Stage was classified as T1–2 vs T3–4 for T-stage, N0–1 vs N2–3 for N-stage and Stage I–II vs III–IV for overall stage. Histology (only for NPC) was classified as K-SqCC vs NKC. Induction systemic therapy was classified as with or without. RT break was classified as ≤1 or >1 week. Time period was classified as early (2007–2009) or recent (2010–2014, to match the change in staging since 2010).

Effectiveness assessment

OS was used as our primary endpoint to assess effectiveness. We obtained survival status according to the national death registry (censored on December 31, 2016). We also evaluated freedom from local regional recurrence and pharyngeal cancer-specific survival according to the TCR and death registry.

Table 4. Patient characteristics in the third supplementary analysis

		T-IMRT (<i>n</i> = 437)		L-IMRT (<i>n</i> = 437)		Standardized difference
		Number or mean (SD) ^c	% ^c	Number or mean (SD) ^c	% ^c	
Age	<65 years	380	87.0	397	90.9	0.124
	≥65 years	57	13.0	40	9.1	
Sex	Male	353	80.8	360	82.4	0.041
	Female	84	19.2	77	17.6	
Residence region	North	118	27.0	119	27.2	0.005
	Non-north	319	73.0	318	72.8	
Socioeconomic status	No more than minimum wage	106	24.3	92	21.0	0.077
	Higher	331	75.7	345	79.0	
Comorbidity	With ^a	138	31.6	132	30.2	0.030
	Without	299	68.4	305	69.8	
Cancer history	With	35	8.0	35	8.0	0.000
	Without	402	92.0	402	92.0	
Site	NPC	306	70.0	306	70.0	0.000
	Non-NPC	131	30.0	131	30.0	
Overall stage	I–II	82	18.8	90	20.6	0.046
	III–IV	355	81.2	347	79.4	
T-stage	1–2	225	51.5	241	55.2	0.073
	3–4	212	48.5	196	44.8	
N-stage	0–1	171	39.1	171	39.1	0.000
	2–3	266	60.9	266	60.9	
Period	2007	<i>b</i>	<i>b</i>	<i>b</i>	<i>b</i>	0.059 ^b
	2008	<i>b</i>	<i>b</i>	<i>b</i>	<i>b</i>	
	2009	27	6.2	27	6.2	
	2010	67	15.3	52	11.9	
	2011	49	11.2	59	13.5	
	2012	87	19.9	97	22.2	
	2013	136	31.1	105	24.0	
	2014	66	15.1	92	21.1	

(Continued)

Table 4. (Continued)

		T-IMRT (<i>n</i> = 437)		L-IMRT (<i>n</i> = 437)		Standardized difference
		Number or mean (SD) ^c	% ^c	Number or mean (SD) ^c	% ^c	
Induction systemic therapy	With	97	22.2	102	23.3	0.027
	Without	340	77.8	335	76.7	
RT break	≤1 week	408	93.4	416	95.2	0.079
	>1 week	29	6.6	21	4.8	
RT dose (Gy)		70.85 (1.35)		70.80 (1.30)		0.045

L-IMRT, linear accelerator based image-guided intensity-modulated radiotherapy; NPC, nasopharyngeal carcinoma; RT, radiotherapy; SD, standard deviation; T-IMRT, tomotherapy-based image-guided intensity-modulated radiotherapy.

^aCarlson comorbidity Score ≥ 1.

^bThe exact case numbers of 2007 and 2008 were not reported due to HWDC policy (no reporting of cases ≤ 2), but the total numbers in 2007–2008 were the same (*n* = 5) between tomotherapy and IG-IMRT; the standardized difference for year was calculated as a continuous variable.

^cRounded.

Statistical analysis

Tabulation and standardized differences were used to assess the balance of covariates between the PS-matched groups. We obtained the hazard ratio (HR) for the event via Cox proportional hazards models with a robust variance estimator, as performed previously.²⁷ We calculated the E-factor to evaluate the robustness of our findings regarding potential unmeasured confounder(s), as described previously.³² We also performed supplementary analyses according to disease site (NPC vs non-NPC). To consider the potential impact regarding the temporal incidences of applying these two techniques, we performed a third supplementary analysis by categorizing the treatment period into individual years (2007, 2008, ..., 2014) instead of 2007–2009 vs 2010–2014, as in the primary analysis. The Kaplan–Meier method was used to calculate the survival curve. SAS 9.4 (SAS Institute, Cary, NC) and STATA 11 (Stata Corp. LP, College Station, TX) were used for all statistical analyses.

RESULTS

Identification of the study cases

As revealed in [Figure 1](#), 2130 clinical LPC patients who were treated with either T-IMRT or L-IMRT were identified as the initial study population. After exclusion of those patients with missing data and with no match by PS, the final study population included 960 patients. The characteristics of these patients are described in [Table 1](#). A good balance among the covariables and small standardized differences (≤0.25)³³ for all covariables were seen.

Effectiveness

After a median follow-up of 41 months (range: 3–111 months), death was observed in 201 patients (82 in the T-IMRT and 119 in the L-IMRT groups). OS did not differ significantly between the T-IMRT and L-IMRT groups [HR for death: 0.82, 95% confidence interval (CI) (0.63–1.07), *p* = 0.15]. The observed HR (0.82) could be explained by an unmeasured confounder that was associated with both the selection of T-IMRT/L-IMRT and alive/dead by a risk ratio of 1.56-fold each; however, this would not be the case with weaker confounding. The 5-year OS rates for T-IMRT and L-IMRT were 79 and 74%, respectively. The Kaplan–Meier survival curve is depicted in [Figure 2](#). There were no significant differences in freedom from local regional recurrence [HR: 0.82, 95% CI (0.62–1.08), *p* = 0.15] or pharyngeal cancer-specific survival [HR: 0.76, 95% CI (0.55–1.05), *p* = 0.09].

Supplementary analyses

In the first supplementary analysis of patients with NPC, a good balance in covariables was achieved ([Table 2](#)). OS did not differ significantly between groups [HR for death: 0.85, 95% CI (0.54–1.34), *p* = 0.49]. The Kaplan–Meier survival curve is depicted in [Figure 3](#). In the second supplementary analysis of patients with non-NPC, a good balance in covariables was achieved ([Table 3](#)). OS did not differ significantly [HR for death: 0.78, 95% CI (0.54–1.13), *p* = 0.19]. The Kaplan–Meier survival curve is depicted in [Figure 4](#). In the third supplementary analysis, we constructed another PS-matched population (*n* = 874) categorizing time period into individual years and achieved a good

balance among covariables (Table 4). OS did not differ significantly [HR for death: 0.99, 95% CI (0.77–1.26), $p = 0.91$].

DISCUSSION

In this population-based PS-matched analysis, we found that for patients with LPC treated with definitive CCRT, OS did not differ significantly between T-IMRT and L-IMRT treatments. To our knowledge, this is the first population-based study, as well as the largest study, regarding this issue.

Our finding of no significant difference in OS between the two treatments is compatible with those of previous studies.^{18–20} Thus, considering that our study was population-based and the case number much larger, our results strengthen this observation and represent an interesting complement to the existing knowledge.

In our study, the dosimetric benefit of T-IMRT,⁸ although numerically higher, did not result in an obvious benefit in disease control or survival compared with L-IMRT. This may be because the dosimetric benefit was only “slightly better”.⁸ Similar scenarios (dosimetric merit did not lead to improved “hard” disease outcome via T-IMRT) have been observed in studies evaluating other disease sites.^{34,35} However, because of a lack of data availability, we did not investigate the potential benefits of reduced side effects or improved quality of life. These endpoints may be even more important than OS when comparing T-IMRT and L-IMRT.

There were also several limitations to our study. First, like all non-randomized studies, we cannot exclude the possibility of unmeasured confounders, although we used PS matching to balance observable variables. However, data on some potential confounders, such as nutritional status, viral status (such as Epstein–Barr virus or human papillomavirus), systemic therapy regimen, other forms of IMRT such as VMAT, or dosimetric detail, were not available. In addition, our point estimate (HR

0.82 for OS) was in favor of T-IMRT, although the difference was not significant, and the E-factor was only 1.56.³² Therefore, a randomized control trial is eagerly awaited. However, when we searched <https://clinicaltrials.gov/> using “Intervention/Treatment tomotherapy; Applied Filters Phase 3” in January 2018, we did find randomized control trials that had compared T-IMRT with conventional RT or 3DCRT for prostate and cervical cancers (NCT00326638 and NCT01279135). However, there is no ongoing randomized control trial comparing T-IMRT with other forms of radiotherapy for HNC. Therefore, we believe our study is valuable, because it used a registry, as performed in the literature, regarding RT technology assessment.³⁶ Second, while the sample size of our study was much larger than the largest found in the literature (960 in our study vs 166 in the literature), it was still moderate,²⁰ which may have limited our statistical power. Third, we did not investigate the impact of side effects or quality of life, as mentioned above.

CONCLUSIONS

For LPC patients treated with definitive CCRT, we found no significant difference in disease control or survival between the T-IMRT and L-IMRT groups. However, further studies, especially randomized trials or studies focusing on other dimensions, such as quality of life, are needed.

ACKNOWLEDGMENTS

The data analyzed in this study was provided by the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare, Executive Yuan, Taiwan. The authors thank “Textcheck Inc.” for editorial assistance. The corresponding author would like to thank Dr Ji-An Liang, Dr Ming-Hsui Tsai, Dr Chang-Fang Chiu, Dr Shwn-Huey Shieh, Dr Tzung-chi Huang, Dr Ching-Yun Hsieh, Dr Ming-Yu Lein for their help.

FUNDING

This work was supported by China Medical University Hospital (DMR-105–151 and CRS-106–040 to C.R.C.).

REFERENCES

- Grégoire V, Langendijk JA, Nuyts S. Advances in radiotherapy for head and neck cancer. *J Clin Oncol* 2015; **33**: 3277–84. doi: <https://doi.org/10.1200/JCO.2015.61.2994>
- National Comprehensive Cancer Network. National comprehensive cancer network guideline for head and neck cancers, version 2. 2017. Available from: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf [cited 2017 Oct 5].
- Pignon JP, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009; **92**: 4–14. doi: <https://doi.org/10.1016/j.radonc.2009.04.014>
- Nibu KI, Hayashi R, Asakage T, Ojiri H, Kimata Y, Kodaira T, et al. Japanese clinical practice guideline for head and neck cancer. *Auris Nasus Larynx* 2017; **44**: 375–80. doi: <https://doi.org/10.1016/j.anl.2017.02.004>
- Marta GN, Silva V, de Andrade Carvalho H, de Arruda FF, Hanna SA, Gadia R, et al. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. *Radiother Oncol* 2014; **110**: 9–15. doi: <https://doi.org/10.1016/j.radonc.2013.11.010>
- Bujold A, Craig T, Jaffray D, Dawson LA. Image-guided radiotherapy: has it influenced patient outcomes? *Semin Radiat Oncol* 2012; **22**: 50–61. doi: <https://doi.org/10.1016/j.semradonc.2011.09.001>
- Kupelian P, Langen K. Helical tomotherapy: image-guided and adaptive radiotherapy. *Front Radiat Ther Oncol* 2011; **43**: 165–80. doi: <https://doi.org/10.1159/000322420>
- Zhang X, Penagaricano J, Moros EG, Corry PM, Yan Y, Ratanatharathorn V. Dosimetric comparison of helical tomotherapy and linac-IMRT treatment plans for head and neck cancer patients. *Med Dosim* 2010; **35**: 264–8. doi: <https://doi.org/10.1016/j.meddos.2009.08.001>
- Soisson ET, Mehta MP, Tomé WA. A comparison of helical tomotherapy to circular collimator-based linear-accelerator radiosurgery for the treatment of brain metastases. *Am J Clin Oncol* 2011; **34**:

- 388–94. doi: <https://doi.org/10.1097/COC.0b013e3181e9c0ee>
10. Tomita N, Soga N, Ogura Y, Hayashi N, Kageyama T, Ito M, et al. High-dose radiotherapy with helical tomotherapy and long-term androgen deprivation therapy for prostate cancer: 5-year outcomes. *J Cancer Res Clin Oncol* 2016; **142**: 1609–19. doi: <https://doi.org/10.1007/s00432-016-2173-9>
 11. Nagai A, Shibamoto Y, Yoshida M, Inoda K, Kikuchi Y. Intensity-modulated radiotherapy using two static ports of tomotherapy for breast cancer after conservative surgery: dosimetric comparison with other treatment methods and 3-year clinical results. *J Radiat Res* 2017; **58**: 529–36. doi: <https://doi.org/10.1093/jrr/rrw132>
 12. De Bari B, Jumeau R, Bouchaab H, Vallet V, Matzinger O, Troussier I, et al. Efficacy and safety of helical tomotherapy with daily image guidance in anal canal cancer patients. *Acta Oncol* 2016; **55**: 767–73. doi: <https://doi.org/10.3109/0284186X.2015.1120886>
 13. Zhang X, Du L, Zhao F, Wang Q, Yang S, Ma L. A phase II clinical trial of concurrent helical tomotherapy plus cetuximab followed by adjuvant chemotherapy with cisplatin and docetaxel for locally advanced nasopharyngeal carcinoma. *Int J Biol Sci* 2016; **12**: 446–53. doi: <https://doi.org/10.7150/ijbs.12937>
 14. Perrier L, Morelle M, Pommier P, Boisselier P, Coche-Dequeant B, Gallocher O, et al. Cost analysis of complex radiation therapy for patients with head and neck cancer. *Int J Radiat Oncol Biol Phys* 2016; **95**: 654–62. doi: <https://doi.org/10.1016/j.ijrobp.2016.02.013>
 15. Winkler C, Duma MN, Popp W, Sack H, Budach V, Molls M, et al. Protection of quality and innovation in radiation oncology: the prospective multicenter trial QUIRO of DEGRO: evaluation of time, attendance of medical staff, and resources during radiotherapy with tomotherapy. *Strahlenther Onkol* 2014; **190**: 950–6. doi: <https://doi.org/10.1007/s00066-014-0615-3>
 16. Bijdekerke P, Verellen D, Tournel K, Vinh-Hung V, Somers F, Bieseman P, et al. TomoTherapy: implications on daily workload and scheduling patients. *Radiation Oncol* 2008; **86**: 224–30. doi: <https://doi.org/10.1016/j.radonc.2007.10.036>
 17. Yang ZX, Shen JT, Li YP, Zhao K, Shi CH, Xiao Y, et al. Helical tomotherapy for cancer treatment: a rapid health technology assessment. *J Evid Based Med* 2014; **7**: 192–218. doi: <https://doi.org/10.1111/jebm.12109>
 18. Chen AM, Marsano J, Perks J, Farwell G, Luu Q, Donald PJ, et al. Comparison of IMRT techniques in the radiotherapeutic management of head and neck cancer: is tomotherapy “better” than step-and-shoot IMRT? *Technol Cancer Res Treat* 2011; **10**: 171–7. doi: <https://doi.org/10.7785/ctrt.2012.500192>
 19. Chen AM, Yang CC, Marsano J, Liu T, Purdy JA. Intensity-modulated radiotherapy for nasopharyngeal carcinoma: improvement of the therapeutic ratio with helical tomotherapy vs segmental multileaf collimator-based techniques. *Br J Radiol* 2012; **85**: e537–e543. doi: <https://doi.org/10.1259/bjr/23807619>
 20. Bibault JE, Dussart S, Pommier P, Morelle M, Huguet M, Boisselier P, et al. Clinical outcomes of several IMRT techniques for patients with head and neck cancer: a propensity score-weighted analysis. *Int J Radiat Oncol Biol Phys* 2017; **99**: 929–37. doi: <https://doi.org/10.1016/j.ijrobp.2017.06.2456>
 21. Ministry of Health and Welfare. The health and welfare data science center database. 2017. Available from: <http://dep.mohw.gov.tw/DOS/np-2497-113.html> [cited 2017 Sep 28].
 22. Chiang CJ, You SL, Chen CJ, Yang YW, Lo WC, Lai MS. Quality assessment and improvement of nationwide cancer registration system in Taiwan: a review. *Jpn J Clin Oncol* 2015; **45**: 291–6. doi: <https://doi.org/10.1093/jjco/hyu211>
 23. National Health Insurance Administration, Ministry of Health and Welfare. Universal health coverage in Taiwan. 2017. Available from: https://www.nhi.gov.tw/Resource/webdata/21717_1_UniversalHealthCoverage-2.pdf [cited 2017 Jul 15].
 24. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg* 2014; **12**: 1495–9. doi: <https://doi.org/10.1016/j.ijsu.2014.07.013>
 25. Ou SH, Zell JA, Ziogas A, Anton-Culver H. Epidemiology of nasopharyngeal carcinoma in the United States: improved survival of Chinese patients within the keratinizing squamous cell carcinoma histology. *Ann Oncol* 2007; **18**: 29–35. doi: <https://doi.org/10.1093/annonc/mdl320>
 26. National Cancer Institute. ICD-O-3 SEER site/histology validation list. 2018. Available from: <http://seer.cancer.gov/icd-o-3/> [cited 2018 Jan 15].
 27. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med* 2014; **33**: 1242–58. doi: <https://doi.org/10.1002/sim.5984>
 28. Li CC, Chen CY, Chien CR. Comparative effectiveness of image-guided radiotherapy for non-operated localized esophageal squamous cell carcinoma patients receiving concurrent chemoradiotherapy: a population-based propensity score matched analysis. *Oncotarget* 2016; **7**: 71548–55. doi: <https://doi.org/10.18632/oncotarget.12250>
 29. Hsia TC, Tu CY, Fang HY, Liang JA, Li CC, Chien CR. Cost and effectiveness of image-guided radiotherapy for non-operated localized lung cancer: a population-based propensity score-matched analysis. *J Thorac Dis* 2015; **7**: 1643–9. doi: <https://doi.org/10.3978/j.issn.2072-1439.2015.09.36>
 30. Chien CR, Lin HW, Yang CH, Yang SN, Wang YC, Kuo YC, et al. High case volume of radiation oncologists is associated with better survival of nasopharyngeal carcinoma patients treated with radiotherapy: a multifactorial cohort analysis. *Clin Otolaryngol* 2011; **36**: 558–65. doi: <https://doi.org/10.1111/j.1749-4486.2011.02405.x>
 31. Chien CR, Pan IW, Tsai YW, Tsai T, Liang JA, Buchholz TA, et al. Radiation therapy after breast-conserving surgery: does hospital surgical volume matter? A population-based study in Taiwan. *Int J Radiat Oncol Biol Phys* 2012; **82**: 43–50. doi: <https://doi.org/10.1016/j.ijrobp.2010.09.025>
 32. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med* 2017; **167**: 268–74. doi: <https://doi.org/10.7326/M16-2607>
 33. Garrido MM, Kelley AS, Paris J, Roza K, Meier DE, Morrison RS, et al. Methods for constructing and assessing propensity scores. *Health Serv Res* 2014; **49**: 1701–20. doi: <https://doi.org/10.1111/1475-6773.12182>
 34. Yeung R, McConnell Y, Warkentin H, Graham D, Warkentin B, Joseph K, et al. Intensity-modulated radiotherapy (IMRT) vs helical tomotherapy (HT) in concurrent chemoradiotherapy (CRT) for patients with anal canal carcinoma (ACC): an analysis of dose distribution and toxicities. *Radiat Oncol* 2015; **10**: 92. doi: <https://doi.org/10.1186/s13014-015-0398-4>
 35. Hsieh CH, Shueng PW, Hsiao SM, Wei MC, Wu WY, Sun HD, et al. Helical tomotherapy provides efficacy similar to that of intensity-modulated radiation therapy with dosimetric benefits for endometrial carcinoma. *Oncotargets Ther* 2012; **5**: 245–53. doi: <https://doi.org/10.2147/OTT.S35958>
 36. van Loon J, Grutters J, Macbeth F. Evaluation of novel radiotherapy technologies: what evidence is needed to assess their clinical and cost effectiveness, and how should we get it? *Lancet Oncol* 2012; **13**: e169–e177. doi: [https://doi.org/10.1016/S1470-2045\(11\)70379-5](https://doi.org/10.1016/S1470-2045(11)70379-5)