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Optimal radiotherapy dose in cervical esophageal squamous cell carcinoma patients treated with definitive concurrent chemoradiotherapy: A population based study

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Abstract

Background: The optimal radiotherapy dose for locally advanced cervical esophageal squamous cell carcinoma (C-ESqCC) treated with definitive concurrent chemoradiotherapy (dCCRT) is unclear. Here, we aimed to compare the survival of those treated with high dose versus standard dose via a population based approach.

Methods: Eligible C-ESqCC patients diagnosed between 2011 and 2017 were identified via the Taiwan Cancer Registry. We used propensity score (PS) weighting to balance observable potential confounders between groups. The hazard ratio (HR) of death and incidence of esophageal cancer mortality (IECM) were compared between high (60–70 Gy) and standard dose (50–50.4 Gy). We also evaluated the outcome in supplementary analyses via alternative approaches.

Results: Our primary analysis consisted of 141 patients in whom covariates were well balanced after PS weighting. The HR of death when high dose was compared with standard dose was 0.65 (95% confidence interval [CI]: 0.4–1.03, $p = 0.07$). The HR of IECM was 0.74 ($p = 0.45$). The HR of OS remained similarly insignificant in supplementary analyses.

Conclusions: We observed a trend in favor of high radiotherapy dose versus standard dose for C-ESqCC treated with dCCRT in this population-based nonrandomized study. Further studies are needed to confirm the findings of the study.

KEYWORDS
cervical esophageal squamous cell carcinoma, definitive concurrent chemoradiotherapy, radiotherapy dose

Chia-Chin Li, Chih-Yi Chen, Ying-Hsiang Chou, Chih-Jen Huang, and Hsiu-Ying Ku contributed equally to this study.

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INTRODUCTION

Esophageal cancer is one of the leading most common cause of cancer mortality worldwide including Taiwan.[1] The most common histology is adenocarcinoma in western countries whereas it is squamous cell carcinoma (SqCC) in Asia.[1,2]

For cervical ESqCC (C-ESqCC), definitive concurrent chemoradiotherapy (dCCRT) is commonly suggested in treatment guidelines, especially in patients with locally advanced disease.[3–6] However, the optimal radiotherapy dose is unknown. For the commonly-seen thoracic EqCC, the standard dose is 50–50.4 Gy at standard fractionation, as suggested by the North American guidelines.[3] This dose has been established by randomized controlled trials (RCTs)[7,8] although it is still debated in the literature[9,10] and in some guidelines.[4,5] For the relatively rare C-ESqCC,[8] "higher doses may be appropriate for tumors of the cervical esophagus" is stated in the North American guidelines.[3] The rationale might be that the treatment for C-ESqCC has been adopted from regimens for esophageal SqCC, as well as head-and-neck SqCC, and therefore 60–70 Gy has been the previously suggested dose.[11,12] Although C-ESqCC was eligible in previous radiotherapy doses in RCTs,[7,8] it accounted for less than 10% of participants[8] and results specific to C-ESqCC have not been reported.[7,8] However, high dose dCCRT has been previously advocated in the literature.[12]

Two comparable effectiveness studies were reported in the above mentioned review paper published in 2020[12] regarding cervical esophageal cancer patients treated with different radiotherapy dose groups and all reported better outcomes in the higher dose group.[13,14] However, both were single institutional studies with sample size less than one hundred. Other studies have also reported higher radiotherapy dose as a better prognostic factor.[15]

Due to the above limitations and uncertainty regarding the optimal radiotherapy dose, our study aimed to compare the survival of high versus standard radiotherapy dose for C-ESqCC patients treated with dCCRT via a population-based approach.

METHODS

Data

We used the Taiwan Cancer Registry (TCR) as the data source in this study. The quality of the TCR is reported to be one of the highest-quality cancer registries in the world.[16,17] Our study was approved by the review committee (National Health Research Institute EC1090502-E).

Study population and intervention

We identified C-ESqCC patients diagnosed within 2011–2017 from TCR via the International Classification of Disease for Oncology third edition (ICD-O-3) site and histology codes. We defined locally advanced disease as patients with clinical stage cT2-4N0M0 or cT1-4N1-3M0 by the seventh American Joint Committee on Cancer (AJCC). We only included adult patients age 18–70. We excluded those with multiple treatment records to ensure data quality. We also excluded those with prior cancer(s).

Regarding intervention, we further identified patients treated with dCCRT using external beam intensity-modulated radiotherapy in conventional dose fractionation (1.8–2 Gy/fraction) according to records in TCR then selected those treated with high radiotherapy dose (group A, 60–70 Gy) or standard dose (group B, 50–50.4 Gy). We allowed ± 5% tolerance in RT dose for both groups. We defined dCCRT as patients treated with concurrent systemic therapy and radiotherapy without surgery. These inclusion/exclusion criteria were modified from our clinical and research experiences as well as previous studies.[7,8]

Covariates

We included the following covariates as modified from recent relevant studies and our clinical and research experiences.[7–10,18] Patient demographics (age, gender, residency), patient characteristics (body mass index [BMI], drinking, smoking), disease characteristics (T and N and overall stage), treatment characteristics (peri-CCRT systemic

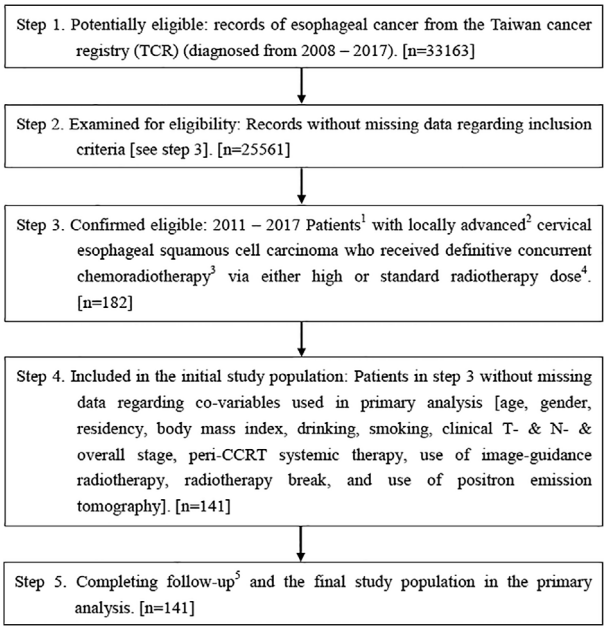

FIGURE 1 STROBE study flowchart and the number of individuals at each stage of the study. 1. We only included those treated (class 1–2) with only one record to ensure data consistency. 2. The Seventh American Joint Committee on Cancer staging clinical stage T2-4N0M0 or T1-4N1-3M0. 3. With concurrent systemic therapy and radiotherapy without surgery. 4. Conventional fractionated external beam radiotherapy dose (high, 60–70 Gy vs. standard, 50–50.4 Gy) at 1.8–2 Gy/fraction, ± 5% tolerance in dose. 5. Without missing information in the TCR and death registry

TABLE 1 Patient characteristics of the study population in the primary analysis

	Group A (high dose) ($n = 114$)		Group B (standard dose) ($n = 27$)		Standardized difference (rounded)[a]	
	Number or mean (SD)[a]	(%)[a]	Number or mean (SD)[a]	(%)[a]	Before PSW	After PSW
Age (year)	53.98 (7.29)		54.52 (6.66)		0.077	≈0
Gender						
Female	13	(11)	1	(4)	0.295	≈0
Male	101	(89)	26	(96)		
Residency						
Non-north	72	(63)	16	(49)	0.080	≈0
North	42	(37)	11	(41)		
BMI	21.25 (3.73)		21.43 (4.02)		0.047	≈0
Drinking						
No	16	(14)	3	(11)	0.088	≈0
Yes	98	(86)	24	(89)		
Smoking						
No	15	(13)	4	(15)	0.048	≈0
Yes	99	(87)	23	(85)		
T stage						
1–2	13	(11)	4	(15)	0.101	≈0
3–4	101	(89)	23	(85)		
N stage						
0–1	60	(53)	13	(48)	0.090	≈0
2–3	54	(47)	14	(52)		
Overall stage						
2	18	(16)	5	(19)	0.072	≈0
3	96	(84)	22	(81)		
Peri-CCRT systemic therapy						
No	73	(64)	19	(70)	0.135	≈0
Yes	41	(36)	8	(30)		
Use of IGRT						
No	84	(74)	14	(52)	0.464	≈0
Yes	30	(26)	13	(48)		
Radiotherapy break						
No	91	(80)	22	(81)	0.042	≈0
Yes	23	(20)	5	(19)		
Use of PET						
No	30	(26)	13	(48)	0.464	≈0
Yes	84	(74)	14	(52)		

Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiotherapy; IGRT, image-guided radiotherapy; PET, positron emission tomography; PSW, propensity-score weighting; SD, standard deviation.
[a]Rounded.

therapy, use of image-guided radiotherapy [IGRT], radiotherapy break) and the use of positron emission tomography (PET) were defined as follows. Patient residency region was classified as "northern Taiwan" or "non-north".[9,18] Smoking, drinking and the use of PET or IGRT were classified as yes or no. The details of IGRT (such as 2D or 3D) was not available in TCR. The clinical T stage was classified as "1–2" versus "3–4". The clinical N stage was classified as "0–1" or "2–3". Overall staging was grouped as 2 versus 3. Those patients who received pre- or post-CCRT systemic therapy was classified as "yes" for "peri-CCRT systemic therapy" (induction or adjuvant or both) whereas those without were classified as "no". Those patients with radiotherapy prolongation of more than one week were classified as "yes" for "radiotherapy break," whereas those without were classified as "no".

Statistical and supplementary analyses

The primary outcome of interest was overall survival (OS). We also evaluated the impact of intervention (high vs. standard dose) on incidence of esophageal cancer mortality (IECM). We adopted a propensity score (PS) approach and used PS weighting (PSW) as the framework for analyses as advocated in the literature.[19–22] We estimated the probability of receiving a high radiotherapy dose (vs. standard dose) with a logistic regression model based on all the above covariates, and then assessed the balance of covariates between groups after PSW using overlap weight[23] via the standardized difference (SDif) rather than the chi-square or *t*-test.[19,20] We compared the hazard ratio (HR) of death between the group A and group B groups during the entire follow-up period via Cox proportional hazards model in the weighted sample for point estimation and used the bootstrap method to estimate the 95% confidence interval (95% CI).[24–26] We used E-value to assess the robustness of our finding regarding potential unmeasured confounder(s) as suggested in the literature[27] because a PS approach is only be valid under the assumption of no unmeasured confounder(s). We took a competing risk approach to compare IECM between groups.[28] We performed two supplementary analyses (SA) using alternative analytic approaches. We did SA-1 via using PS matching (PSM) by constructing a 1:1 matched cohort and performed the analyses as described in the literatures.[24,29] We did SA-2 by using Cox regression method as suggested by the reviewer during revision. We used software SAS 9.4 (SAS Institute) and R version 3.6.2 (R Development Core Team) for statistical analyses.

RESULTS

Study population

We identified 141 patients (114 for group A and 27 for group B) as our primary study population as shown in Figure 1.[30] We achieved covariate balance after PSW although some imbalance was seen before PSW as shown in Table 1. After a median follow-up of 19 months (range 3–102) with 21 months (range 3–102) for group A, as well as 13 months (range 3–50) for group B, death was observed in 82 patients in group A and in 23 patients in group B. The median follow-up was 61 months (range 29–102) for survivors.

Primary analysis

The overlap weights adjusted OS curve are shown in Figure 2. The one/two/three/four-year OS rates for both groups were 59%, 48%, 38% and 32% (group A) and 59%, 42%, 23% and 7% (group B), respectively. When group A (high dose) was compared to group B (standard dose), the HR of death was 0.65 (95% confidence interval [95% CI]: 0.4–1.03, $p = 0.07$). The observed HR of 0.65 for OS could be explained by an unmeasured confounder that was associated with both selections of treatment (group A vs. B) and outcome (live vs. death) by a risk ratio of 2.03 (E-factor) fold each, but weaker confounding could not. The HR of IECM was 0.74 (95% CI: 0.33–1.64, $p = 0.45$).

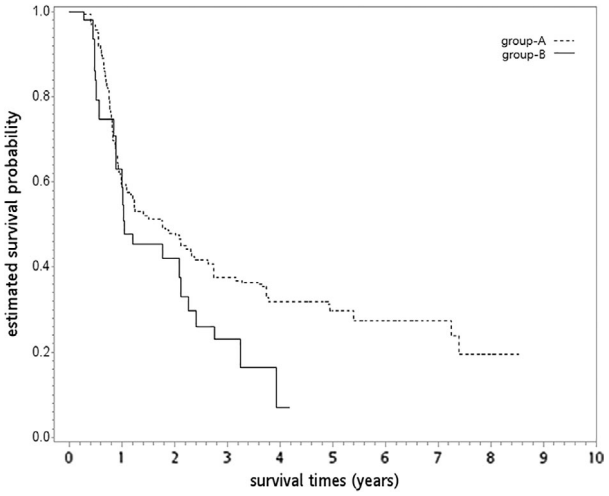

FIGURE 2 The overlap weight-adjusted overall survival curve (in years) in the primary analysis

Supplementary analyses

In SA-1 (PSM), imbalance (SDif > 0.25)[31] was observed for three covariates (gender, use of IGRT, use of PET) before PSM, whereas only one covariate (use of PET) remained imbalanced after PSM, as shown in Tables 1 and 2. When group A (high dose) was compared to group B (standard dose), the HR of death was 0.63 (95% CI: 0.34–1.16, $p = 0.13$). The OS curve for the PSM cohort is shown in Figure 3. The HR of IECM was 0.66 (95% CI: 0.35–1.23, $p = 0.19$).

In SA-2 (Cox regression), we found group A (high dose) was associated with insignificantly lower HR of death (0.72, 95% CI: 0.43–1.21, $p = 0.21$) when compared with group B (standard dose) (Table 3). Because three covariates (gender, use of IGRT, use of PET) were imbalanced between groups before PS analyses, we also performed univariate and multivariate analyses as suggested by the reviewer during revision and found the results remained insignificant in multivariate analyses (HR of death 0.66, 95% CI: 0.41–1.07, $p = 0.09$) (Tables S1 and S2).

DISCUSSION

In this population-based nonrandomized study on C-ESqCC patients treated with definitive concurrent chemoradiotherapy, there was a trend in favor of high radiotherapy dose versus standard dose with borderline significance ($p = 0.06$) in the

TABLE 2 Patient characteristics of the study population in the supplementary analysis

	Group A (high dose) ($n = 27$)		Group B (standard dose) ($n = 27$)		
	Number or mean (SD)[a]	(%)[a]	Number or mean (SD)[a]	(%)[a]	Standardized difference (rounded)[a]
Age (year)	54.41 (5.54)		54.52 (6.66)		0.018
Gender					
Female	1	(4)	1	(4)	0
Male	26	(96)	26	(96)	
Residency					
Non-north	18	(67)	16	(59)	0.154
North	9	(33)	11	(41)	
BMI	21.06 (3.39)		21.43 (4.02)		0.100
Drinking					
No	3	(11)	3	(11)	0
Yes	24	(89)	24	(89)	
Smoking					
No	3	(11)	4	(15)	0.110
Yes	24	(89)	23	(85)	
T stage					
1–2	3	(11)	4	(15)	0.110
3–4	24	(89)	23	(85)	
N stage					
0–1	12	(44)	13	(48)	0.074
2–3	15	(56)	14	(52)	
Overall stage					
2	4	(15)	5	(19)	0.100
3	23	(85)	22	(81)	
Peri-CCRT systemic therapy					
No	21	(78)	19	(70)	0.170
Yes	6	(22)	8	(30)	
Use of IGRT					
No	17	(63)	14	(52)	0.226
Yes	10	(37)	13	(48)	
Radiotherapy break					
No	23	(85)	22	(81)	0.100
Yes	4	(15)	5	(19)	
Use of PET					
No	9	(33)	13	(48)	0.305
Yes	18	(67)	14	(52)	

Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiotherapy; IGRT, image-guided radiotherapy; PET, positron emission tomography; PSW, propensity-score weighting; SD, standard deviation.
[a]Rounded.

primary analyses (PSW), although significance ($p = 0.03$) was observed in the supplementary analysis (PSM). To the best of our knowledge, this is the first population based study in C-ESqCC.

Single arm studies[12,32] have previously investigated the effect of radiotherapy in cervical esophageal cancer. Furthermore, as mentioned previously, some single institutional studies have also reported the radiotherapy dose effect on these patients.[13,14] McDowell et al. reported that a high dose (analyzed as a continuous variable) was associated with a borderline improved OS (HR 0.97, $p = 0.075$).[14] Kim et al. also reported that a high dose (≥59.4 Gy) was associated with reduced risk of death with HR 0.88 when compared to low dose (<59.4 Gy).[13] We further searched PubMed in January 2021 using the keywords "(cervical esophageal cancer) AND (squamous cell carcinoma) AND ((radiation therapy dose) OR (radiotherapy dose))" and found no additional relevant studies. The findings in our study

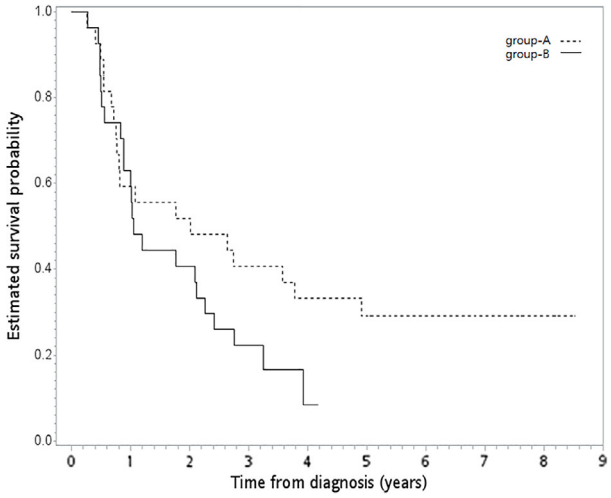

FIGURE 3 The overall survival curve (in years) in the supplementary analysis (SA-1)

TABLE 3 Hazard ratio of death in SA-2 (Cox regression)

	HR[a]	95% CI[a]	*p*-value[a]
Dose	0.72	0.43–1.21	0.21
Age (year)	1.01	0.99–1.04	0.33
Gender	0.87	0.38–2.00	0.75
Residency	0.91	0.60–1.37	0.64
BMI	0.87	0.82–0.93	<0.0001
Drinking	1.67	0.75–3.68	0.21
Smoking	1.18	0.5–2.79	0.71
T stage	1.87	0.79–4.44	0.16
N stage	1.97	1.20–3.24	0.01
Overall stage	0.79	0.35–1.77	0.56
Peri-CCRT systemic therapy	0.75	0.49–1.15	0.19
Use of IGRT	0.74	0.46–1.17	0.19
Radiotherapy break	1.83	1.07–3.15	0.03
Use of PET	0.68	0.44–1.06	0.09

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; CCRT, concurrent chemoradiotherapy; HR, hazard ratio; IGRT, image-guided radiotherapy; PET, positron emission tomography; SA, supplementary analysis.
[a]Rounded.

(a trend of reduced risk of death for high dose) was in line with these studies.[13,14]

The interpretation of our study appears straightforward due to the general belief that C-ESqCC should be treated more like other head-and-neck SqCC.[12] However, it should be noted that the survival difference within median follow-up (around one and a half year) was not obvious (see Figure 2 and subsection "Primary analysis" in results). Our study should also be interpreted with caution given its non-randomized nature and borderline statistical significance. However, when we searched the trial registry [https://clinicaltrials.gov/] in March 2021, we did not find any relevant RCT specific for C-ESqCC. Therefore, we believe that our study provides useful evidence regarding radiotherapy for C-ESqCC while we await the results of more studies on this subject.

There were also limitations in our study. First,as in all nonrandomized studies, potential unmeasured confounder(s) such as patient social economic status, bodyweight loss or performance status, biomarkers, precision in staging work-up, use of supportive care (such as nasogastric tube or enterostomy), chemotherapy regimen details, or radiotherapy tolerability or techniques (such as target delineation and elective nodal region) were not available due to data limitation, although we had used a PS approach to balance observed covariates and reported E-value to assess the potential impact of potential unmeasured confounder(s). Although guidelines within individual institutions are encouraged by the government, there was a lack of general guidelines, so the treatment selection (high vs. standard radiotherapy) was at the discretion of the treating radiation oncologists (i.e., not randomly assigned). Second, the use of salvage therapy (especially surgery) may have impacted our primary endpoint (OS) but could not be evaluated due to data limitation in TCR. Finally, other endpoints, such as pattern of failure or quality of life in addition to OS used in our study, might also be relevant, but these were not investigated due to concern with regard to data availability.

In conclusion, we observed a trend in favor of high radiotherapy dose versus standard dose for C-ESqCC treated with dCCRT in this population-based nonrandomized study. Further studies (especially RCT) are needed to confirm our findings.

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CONFLICT OF INTERESTS

All authors declare there are no conflicts of interest.

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REFERENCES

1. Lagergren J, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. Lancet. 2017;390:2383–96.
2. Chien CR, Lin CY, Chen CY. Re: incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. J Natl Cancer Inst. 2009;101:1428–9.
3. National Comprehensive Cancer Network Guidelines for Esophageal and Esophagogastric Junction Cancers, version 5.2020 [free

registration required]. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed January 25, 2021.
4. Kitagawa Y, Uno T, Oyama T, Kato K, Kato H, Kawakubo H, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 2. Esophagus. 2019;16:25–43.
5. Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D. ESMO Guidelines Committee. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v50–7.
6. Shah MA, Kennedy EB, Catenacci DV, Deighton DC, Goodman KA, Malhotra NK, et al. Treatment of locally advanced esophageal carcinoma: ASCO guideline. J Clin Oncol. 2020;38:2677–94.
7. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (radiation therapy oncology group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol. 2002;20:1167–74.
8. Xu YJ, Zhu WG, Liao ZX, Kong Y, Wang WW, Li JC, et al. A multicenter randomized prospective study of concurrent chemoradiation with 60 Gy versus 50 Gy for inoperable esophageal squamous cell carcinoma. Zhonghua Yi Xue Za Zhi. 2020;100:1783–8.
9. Chen CY, Li CC, Chien CR. Does higher radiation dose lead to better outcome for non-operated localized esophageal squamous cell carcinoma patients who received concurrent chemoradiotherapy? A population based propensity-score matched analysis. Radiother Oncol. 2016;120:136–9.
10. Li CC, Fang HY, Lin CY, Shen WC, Chien CR. Outcomes of localized esophageal squamous cell carcinoma patients treated with definitive concurrent chemoradiotherapy using either standard or high radiotherapy dose: a retrospective study controlling for organ at risk dose. Anticancer Res. 2019;39:511–7.
11. Hoeben A, Polak J, Van De Voorde L, Hoebers F, Grabsch HI, de Vos-Geelen J. Cervical esophageal cancer: a gap in cancer knowledge. Ann Oncol. 2016;27:1664–74.
12. Kwong DLW, Chan WWL, Lam KO. Radiotherapy for cervical esophageal squamous cell carcinoma. Methods Mol Biol. 2020;2129:295–305.
13. Kim TH, Lee IJ, Kim JH, Lee CG, Lee YC, Kim JW. High-dose versus standard-dose radiation therapy for cervical esophageal cancer: retrospective single-institution study. Head Neck. 2019;41:146–53.
14. McDowell LJ, Huang SH, Xu W, Che J, Wong RKS, Brierley J, et al. Effect of intensity modulated radiation therapy with concurrent chemotherapy on survival for patients with cervical esophageal carcinoma. Int J Radiat Oncol Biol Phys. 2017;98:186–95.
15. Zhao L, Zhou Y, Mu Y, Chai G, Xiao F, Tan L, et al. Patterns of failure and clinical outcomes of definitive radiotherapy for cervical esophageal cancer. Oncotarget. 2017;8:21852–60.
16. 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.
17. Chiang CJ, Wang YW, Lee WC. Taiwan's Nationwide cancer registry system of 40 years: past, present, and future. J Formos Med Assoc. 2019;118:856–8.
18. Kuo YH, Fang HY, Lin YS, Lein MY, Yang CY, Ho SC, et al. Effectiveness of image-guided radiotherapy for locally advanced esophageal squamous cell carcinoma patients treated with definitive concurrent chemoradiotherapy. Thorac Cancer. 2020;11:113–9.
19. Webster-Clark M, Stürmer T, Wang T, Man K, Marinac-Dabic D, Rothman KJ, et al. Using propensity scores to estimate effects of treatment initiation decisions: state of the science. Stat Med. 2021;40:1718–35.
20. Goetghebeur E, Cessie S, De Stavola B, Moodie EE, Waernbaum I. Formulating causal questions and principled statistical answers. Stat Med. 2020;39:4922–48.
21. Lalani N, Jimenez RB, Yeap B. Understanding propensity score analyses. Int J Radiat Oncol Biol Phys. 2020;107:404–7.
22. Booth CM, Karim S, Mackillop WJ. Real-world data: towards achieving the achievable in cancer care. Nat Rev Clin Oncol. 2019;16:312–25.
23. Mao H, Li L, Greene T. Propensity score weighting analysis and treatment effect discovery. Stat Methods Med Res. 2019;28:2439–54.
24. 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.
25. Cole SR, Hernán MA. Adjusted survival curves with inverse probability weights. Comput Methods Programs Biomed. 2004;75:45–9.
26. Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. Stat Med. 2016;35:5642–55.
27. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-value to assess the potential effect of unmeasured confounding in observational studies. JAMA. 2019;321:602–3.
28. Bolch CA, Chu H, Jarosek S, Cole SR, Elliott S, Virnig B. Inverse probability of treatment-weighted competing risks analysis: an application on long-term risk of urinary adverse events after prostate cancer treatments. BMC Med Res Methodol. 2017;17:93.
29. Austin PC, Fine JP. Propensity-score matching with competing risks in survival analysis. Stat Med. 2019;38:751–77.
30. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–7.
31. 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.
32. Kumabe A, Zenda S, Motegi A, Onozawa M, Nakamura N, Kojima T, et al. Long-term clinical results of concurrent chemoradiotherapy for patients with cervical esophageal squamous cell carcinoma. Anticancer Res. 2017;37:5039–44.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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