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Original article

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

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ABSTRACT

Background: The optimal radiotherapy dose for non-operated localized esophageal squamous cell carcinoma (NOL-ESCC) patients undergoing concurrent chemoradiotherapy (CCRT) is hotly debated.
Methods: We identified eligible patients diagnosed within 2008–2013 from Taiwan Cancer Registry and constructed a propensity score matched cohort (1:1 for high dose (⩾60 Gy) vs standard dose (50–50.4 Gy)) to balance observable potential confounders. We compared the hazard ratio (HR) of death between standard and high radiotherapy dose groups during the entire follow-up period. We performed sensitivity analysis (SA) to evaluate the robustness of our finding regarding potential unobserved confounders & index date definition.
Results: Our study population constituted 648 patients with well balance in observed co-variables. The HR of death when high dose was compared to standard dose was 0.75 (95% confidence interval 0.64–0.88). Our result was sensitive to potential unobserved confounders but robust to alternative index date definition in SA.
Conclusions: We found that higher than standard radiotherapy dose may lead to better survival for NOL-ESCC patients undergoing CCRT.
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Esophageal cancer is one of the common causes of cancer death around the world [1]. The histological type in most of the patients is squamous cell carcinoma [SqCC] although adenocarcinoma is currently more common in Australia, the UK, the USA, and some western European countries [1,2]. For non-operated localized esophageal SqCC [NOL-ESCC], concurrent chemoradiotherapy [CCRT] is the standard of care [3,4]. However, the optimal radiotherapy dose is hotly debated [5] after the publication of the randomized controlled trial [RCT] INT-0123 [6], in that 50.4 Gy was endorsed in the North America guideline [3] in concordant with the INT-0123 whereas 50–60 Gy was acceptable in the European guideline [4]. A recent systematic review [7] had included INT-0123 as the only study relevant to RT dose but an evidence-based review paper still commented "A further dose escalation should be considered as justified" [8]. So, we undertook this retrospective population-based propensity-score matched study to evaluate the survival impact of high dose vs standard dose.

Methods

Data source

The data source comes from Taiwan Cancer Registry (TCR) and death registration in this study. TCR is a high quality cancer registry [9] and provides sufficient information regarding individual demographics, stage of disease, tumor histology, and primary treatment details.

Study population and study design

Our study flow chart was depicted in Fig. 1. The study population consisted of non-operated [ie, surgery was not performed as the primary treatment] localized esophageal squamous cell carcinoma patients who received concurrent chemoradiotherapy with external beam radiotherapy and diagnosed within 2008–2013. In the primary analysis, we adopted the date of diagnosis in the

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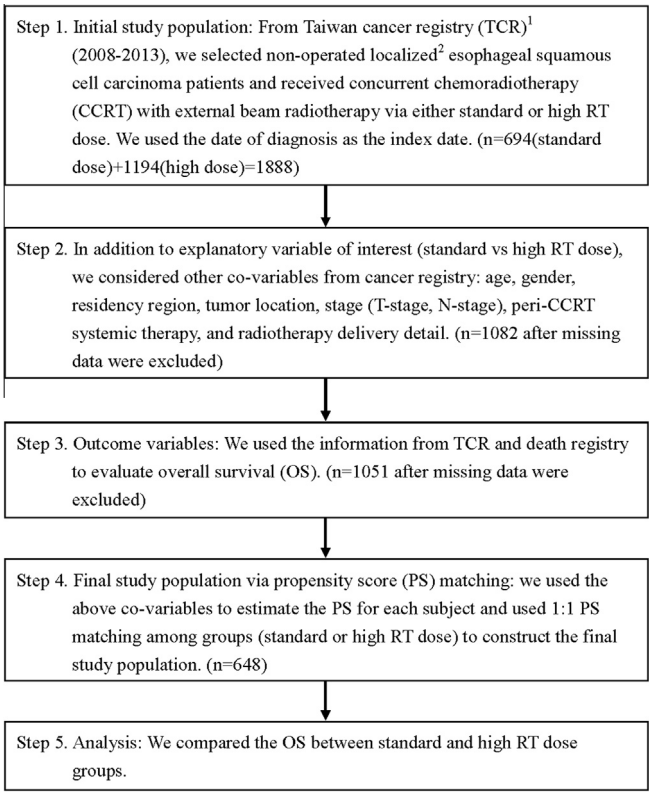

Fig. 1. Study flow chart. [1]: We only included those treated (class 1–2) by any single institution to ensure data consistency. [2]: 6th American Joint Committee on Cancer staging clinical stage 2–4a (2008–2009) or 7th stage 2–3 (2010–2013).

cancer registry as the index date as commonly used in registry-based studies [10,11]. We decided the explanatory variable of interest (delivered RT dose: 50–50.4 Gy (standard) vs ⩾60 Gy (high)). We also collected co-variables for adjustment of potential non-randomized treatment selection (see next section). The survival statuses of cancer patients were obtained from the death registry (follow-up until Dec 31th, 2014). Then we constructed a propensity-score (PS) matched sample based on estimated PS with the above co-variables, and performed the survival analysis to evaluate the effect of RT dose.

Other explanatory covariables

In this study, we included patient demographic (age, gender, residency region), disease characteristics (tumor location, clinical T-stage and N-stage), and treatment characteristics including use of peri-CCRT systemic therapy and RT delivery factors (3D conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT); image-guided radiotherapy (IGRT) or non-IGRT; radiotherapy break). The selection and definition of these factors were based on our experiences in clinical care and prior related studies [3,12–15]. The definitions of our co-variables were as follows. Age was classified ⩾65 year old or not. Patient residency region was classified as northern Taiwan or elsewhere. T-stage was classified as T1–T2 or T3–T4. N-stage was classified as positive [N1M0 or N0-1M1a (2008–2009); N1–N3 (2010–2013)] or negative. Tumor location was classified as cervical vs others since higher dose might be considered for cervical esophageal cancer [3]. Peri-CCRT systemic therapy [i.e., induction or consolidative in additional to CCRT] was classified as with yes or no External beam radiotherapy delivery was classified as 3D conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT) as well as IGRT or non-IGRT. The interval of radiotherapy break was classified as >1 week or ⩽1 week.

Effectiveness assessment

We obtained the survival status in the end of follow-up according to death registry. We used this information to compare the overall survival (OS) of patients between standard and high RT dose groups.

Statistical & Sensitivity Analysis [SA]

Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC) except STATA 12.1 [StataCorp LP, College Station, TX USA] in matching. Tabulation and standardized difference were used to assess the balance of covariates between PS-matched groups. We compared the hazard ratio of death between standard and high RT dose groups during the entire follow-up period using a robust variance estimator [16]. Under the assumption of "no unmeasured confounder", the probability of receiving either treatment should be the same after PS matching. However, if there was an unmeasured confounder which was associated with both treatment selection and outcome, then the true probability of receiving treatment might be differed for a factor [labeled as Γ] even after PS matching. Therefore, we undertook the 1st sensitivity analysis [SA-1] as suggested in the literature [16] to assess the extreme statistical significance of the treatment effect that would be observed had this unmeasured confounder had been accounted for, at various levels of Γ. Therefore, the robustness of our result could be tested at various levels of violation of the "no unmeasured confounder" assumption. We did another sensitivity analysis [SA-2] to examine the impact of alternative index date definition [date of start of treatment rather than date of diagnosis in the primary analysis].This study was approved by Research Ethics Committee, National Health Research Institutes [EC1041006-E].

Results

Identification of the study population

As revealed in Fig. 1, 1888 cancer patients who received CCRT with external beam radiotherapy among groups (standard or high RT dose) were identified as the initial study population. After exclusion of missing data and using PS matching method, the final study population included 648 patients. The patient characteristics were described in Table 1. Well balance in covariables and small standardized differences (<0.25) were seen for all covariables [17].

Clinical outcomes

For the entire follow-up period, the hazard ratio (HR) of death when high RT dose was compared to standard dose was 0.75 (95% confidence interval 0.64–0.88). The 5-year overall survival rate was 22% for high RT dose vs 14% for standard RT dose. The Kaplan–Meier survival curve for OS is shown in Fig. 2.

Sensitivity analysis

In SA-1 regarding the potential impact of some unmeasured confounder[s], we found that if there was an unmeasured binary confounder that increases the odds of high RT dose (vs standard RT dose) for 4% instead of zero, our conclusion that high dose was more effective would remain statistically significant ($p = 0.049$). However, if there was an unmeasured binary confounder that increases the odds of high dose for at least 4.5%, then the observed effectiveness of high dose might be no longer

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