



Esophageal Cancer Radiotherapy Dose Escalation Meta Regression Commentary: “High vs. Low Radiation Dose of Concurrent Chemoradiotherapy for Esophageal Carcinoma With Modern Radiotherapy Techniques: A Meta-Analysis”

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A Commentary on

High vs. Low Radiation Dose of Concurrent Chemoradiotherapy for Esophageal Carcinoma With Modern Radiotherapy Techniques: A Meta-Analysis

By Sun X, Wang L, Wang Y, Kang J, Jiang W, Men Y and Hui Z (2020) *Front. Oncol.* 10:1222.
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INTRODUCTION

Esophageal cancer is one of the most common and lethal cancers in the world, with 600,000 cases and accounting for 544,000 cause-specific mortalities in 2020 (1). It is typically treated with definitive chemoradiotherapy or with trimodality therapy, but overall survival rates with both approaches remain dismal; the 5-year overall survival (OS) with chemoradiotherapy is only 10–20% (2, 3). Furthermore, high rates of local failure and distant metastases are reported. The search for improving our current management of these patients is urgently needed.

Several studies have, therefore, been initiated, assessing the role of dose escalation for patients receiving definitive radiotherapy (4–7). Success of dose escalation has varied. In particular, seminal trials such as INT 0123 (RTOG 94-05) investigated dose escalation from 50.4Gy to 64.8Gy and

found no OS advantage with higher doses (8). Small sample size, confounding variables and limited statistical power may have limited meaningful conclusions, but impactful prospective dose escalation research thereafter seemed to have stalled.

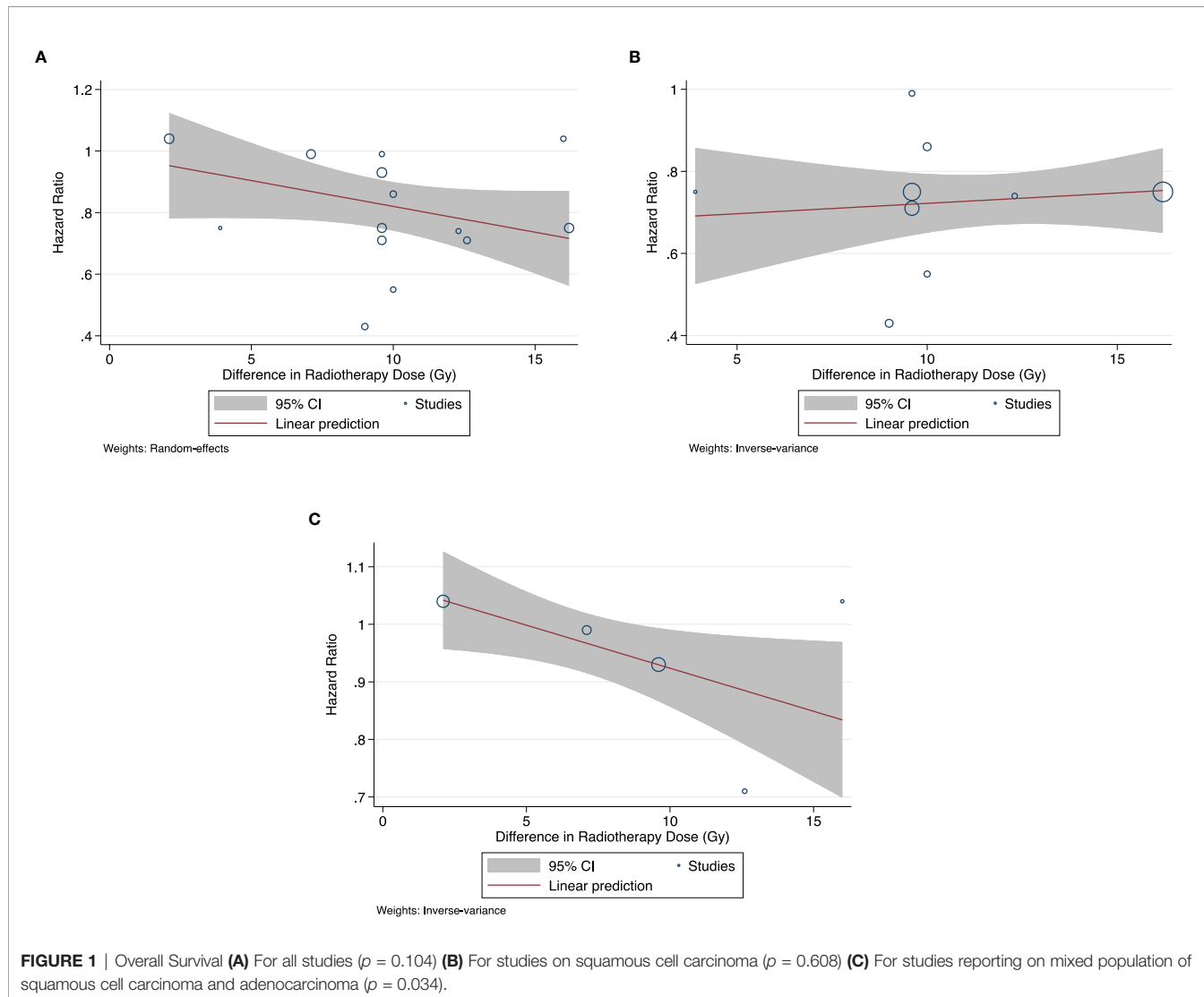
Therefore, methodical meta-analyses are perhaps of greatest help to clinicians to address this question. Sun et al. recently conducted a systematic review and meta-analysis comparing high-dose radiotherapy to standard-dose radiotherapy in the setting of definitive concurrent chemoradiotherapy for esophageal cancer (9). With the pooled sample size across 12 studies and greater statistical power, they reported superior OS and local-regional control rates for patients receiving high-dose radiotherapy, and no difference in distant metastasis rate.

DISCUSSION

We commend the authors for a thorough and informative study that helps to inform radiation dosing for non-operable patients.

However, there exists heterogeneity in their analyses that are worth commenting on and reanalyzing. This may or may not be accounted for by the degree of dose escalation in individual studies. Specifically, the magnitude of dose escalation may be an effect-modifier. To address this possible moderator variable, we conducted a meta-regression of study results, as identified by Sun et al. (9). Meta-regression is a meta-analytic method that specifically accounts for possible confounders to reveal the true effect of the variables of interest.

We included all 12 studies (4–7, 10–17) in our meta-regression. The difference in median dose of patients receiving high-dose and standard-dose radiotherapy was noted, per each study. Study data on OS, local-regional failure rate and distant metastasis rate were extracted, and cross-validated with that reported by Sun et al. (9). All studies reported on OS and were analyzed; stratified analyses by patient population (squamous cell carcinoma, and both squamous cell carcinoma and adenocarcinoma patients) were also conducted. Six studies (5, 6, 13–16) reported on local-regional failure and distant



metastasis failure rates and were analyzed. A random-effects weighting was used for meta-regression when heterogeneity was high ($I^2 > 50$); a fixed-effects weighting was used for low heterogeneity ($I^2 < 50$). P-values less than 0.05 were considered statistically significant. All analyses were conducted using Stata 16.1 (StataCorp, College Station, TX, USA).

There exists a trend for improved OS, with greater dose escalation (**Figure 1**; $p = 0.104$). Among studies only reporting on squamous cell carcinoma patients, OS did not improve with greater dose escalation ($p = 0.608$). In studies reporting on a mixed population of squamous cell carcinoma and adenocarcinoma patients, OS significantly improved with greater radiotherapy dosage ($p = 0.034$). Local failure rate and distant metastasis rate remain unchanged regardless of the degree of dose escalation varied (**Appendix 1**).

It is important to mention that in all analyses other than the OS analysis of all studies, there is only one study where dose escalation was in excess of 14 Gy. This sole datapoint, likely an influential point, makes it difficult to attain enough statistical power for this analysis. Nevertheless, this analysis suggests that dose escalation may be an effective strategy to improve the currently poor outcome of esophageal cancer patients and should be further explored.

Lastly, landmark trials such as the INT 0123 (RTOG 94-05) trial (8) that established lower doses of 50.4 Gy as standard have been criticized as less applicable to modern radiotherapy (18). Furthermore, 7 out of 11 patients who died in the high dose arm received 50.4 Gy or less. We eagerly await the results of the now-completed ARTDECO randomized phase III trial of dose escalation in a more modern cohort of esophageal cancer patients. Additionally, with the increasing use of advanced radiotherapy techniques such as intensity-modulated radiation therapy, proton therapy and MR-guided radiotherapy (19) today,

the risk-benefit ratio of dose escalation may be further improved. Furthermore, with increasing consideration for using smaller radiation fields and/or omission of elective nodal irradiation for esophageal cancer (20), dose escalation may become safer and more widely utilized in the future.

In summary, we fully support prospective assessment of dose escalation for non-operable esophageal cancer, and the findings by Sun et al. (9) and our updated analysis in this commentary should be updated as additional data emerge, including studies using advanced radiation modalities and smaller radiation fields.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2021.700300/full#supplementary-material>

Supplementary Appendix 1 | (A) Local-Regional Failure Rate ($p = 0.426$) **(B)** Distant Metastasis Rate ($p = 0.837$).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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