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## No survival benefit with early incorporation of thoracic radiotherapy using daily fractionation in patients with limited-stage small cell lung cancer undergoing chemoradiotherapy in the modern era: A systematic review and meta-analysis

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### Highlights

The early incorporation of thoracic radiotherapy (TRT) is recommended when concurrent chemoradiotherapy (CCRT) is administered for limited-stage small cell lung cancer (LS-SCLC), mainly based on the previous randomized trials using bid-regimen. However, it is controversial if this approach is really beneficial with most commonly used daily fractionated TRT.

This systematic review and meta-analysis demonstrated that the risk of death or progression was not significantly different following late TRT compared with early TRT.

Late TRT was beneficial in terms of alleviating grade 3 or higher esophagitis.

This is the first meta-analysis to support the late incorporation of TRT in managing patients with LS-SCLC undergoing daily fractionated CCRT in the modern era. This approach may not compromise survival and can prevent severe acute toxicities.

### Abstract

#### Background

When concurrent chemoradiotherapy (CCRT) is administered for limited-stage small cell lung cancer (LS-SCLC), the early incorporation of thoracic radiotherapy (TRT) is generally recommended. However, it is controversial if this approach is really beneficial with most commonly used daily fractionated TRT in the modern era.

#### Methods

A systematic literature search was performed using several databases following the PRISMA guidelines from Jan 2000 to Nov 2022. We excluded twice-daily TRT-based studies. The hazard ratio (HR) for survival

following late TRT as a primary effect size was pooled from comparisons within individual studies according to the timing of daily fractionated TRT (early vs. late).

## Results

A total of 10 studies including 10,164 analyzable patients met all inclusion criteria. 'Early' timing usually referred to TRT within 1–2 cycles of concurrent chemotherapy. The pooled results demonstrated that the risk of death was not significantly increased following late TRT compared with early TRT (HR 1.01, 95% CI 0.84–1.20,  $p = 0.94$ ). All sensitivity analysis and planned subgroup analyses showed similar results. In comparison with early TRT, late TRT did not significantly increase the risk of progression (HR 0.94, 95% CI 0.80–1.11,  $p = 0.48$ ). Furthermore, late TRT was beneficial in alleviating grade 3 or higher esophagitis (OR 0.42,  $p = 0.01$ ), but no significant differences was found in pneumonitis (OR 0.62,  $p = 0.38$ ), and neutropenia (OR 0.57,  $p = 0.11$ ). No evidence of publication bias was found.

## Conclusions

This is the first meta-analysis to support the late incorporation of TRT in managing patients with LS-SCLC undergoing daily fractionated CCRT in the modern era. This approach may not compromise survival and can prevent severe acute toxicities. Further prospective studies of the daily fractionated TRT timing are warranted.

