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Review

Role of thoracic consolidation radiation in extensive stage small cell lung cancer: A systematic review and meta-analysis of randomised controlled trials

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Abstract Extensive stage small cell lung cancer (ES-SCLC) carries a poor prognosis, and the thoracic progression is common. Consolidation radiation to thoracic disease (cRT) could improve progression-free survival (PFS) and overall survival (OS). We conducted an electronic search of PubMed and Embase with no language, year or publication status restrictions and evaluated randomised controlled trials (RCTs) addressing the role of cRT in ES-SCLC. Preferred Reporting of Systematic Reviews and Meta-Analyses guidelines for systematic review and Cochrane methodology for meta-analysis were followed. Effect estimates (hazard ratios [HRs] and confidence intervals [CIs]) and risk ratios were extracted, with a fixed/random-effects model created to estimate treatment effects. I2 statistics and heterogeneity statistics were performed. Comprehensive and systematic search identified 1107 records, after removal of duplicate records screened 922 records, assessed 31 full-text articles for eligibility and 3 RCTs with a total of 690 patients were included. Pooled analysis showed cRT significant improved PFS ($p < 0.0001$) with HR 0.72 (95% CI: 0.61–0.83, I2-0%). In addition, cRT significantly ($p < 0.001$) reduced the risk of thoracic progression as the first site of progression with a relative risk of 0.52 (95% CI: 0.44–0.61, I2-0%). OS analysis showed no significant ($p = 0.36$) benefit with HR of 0.88 (95% CI 0.66–1.18, I2-52%) with cRT. Pooled meta-analysis of 3 randomised controlled studies shows consolidation thoracic radiotherapy (RT)

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offers significant improvement in PFS and reduction in thoracic failures. Further research on subclassification of ES-SCLC (limited vs extensive metastasis), optimise strategy for RT integration (sequential vs concurrent) and optimal RT dose is needed to identify the subset of ES-SCLC likely to have significant OS benefit.

1. Introduction

Lung cancer continues to be a significant health concern worldwide and is projected to be the second common cancer in North America [1]. Small cell lung cancer (SCLC) accounts for 20% of lung cancers and exhibits aggressive behaviour. Extensive stage small cell lung cancer (ES-SCLC) is defined as tumour beyond the confines of the hemithorax, mediastinum and ipsilateral or contralateral supraclavicular nodes and accounts for two-thirds of SCLC [2,3]. Platinum-based chemotherapy (CT) is the cornerstone of treatment of ES-SCLC [4]. Recent evidence suggests the addition of atezolizumab to platinum-based CT resulted in longer (12.3 months vs 10.3 months, p = 0.007) overall survival (OS) [5]. Despite initial high response rates to chemotherapy, early disease progression is typical and expected median survival is 8–12 months [5–7]. Thoracic progression is very common, and approximately 90% of patients develop intrathoracic progression within the first year of diagnosis [8,9]. The second line chemotherapy options in SCLC have not shown much promise, and these progressions eventually lead to death.

SCLC is considered a radiosensitive malignancy, and consolidation radiation to thoracic disease (cRT) could reduce intrathoracic progression and improve progression-free survival (PFS), quality of life (QoL) and OS. Studies from the past era of inferior diagnostic tools, older treatment techniques and use of non-platinum–based chemotherapy showed mixed findings [10–13] with no definitive benefit. In the past two decades, with diagnostic and therapeutic progress, ES-SCLC outcomes have shown promising improvement. Recent randomized controlled trials (RCT) [8,9], prospective studies [14] and reports [15–17] showed that cRT offered survival benefits in ES-SCLC. Prophylactic cranial radiation (PCI) is recommended in ES-SCLC especially for patients achieving complete response (CR), partial response (PR) or stable disease (SD) [4]. However, the recent Radiation Therapy Oncology Group (RTOG) 0937 study evaluated cRT in ES-SCLC in extracranial 1–4 metastasis but showed no survival benefit with cRT [18].

The purpose of this study was to conduct a systematic review and meta-analysis of RCT evaluating the benefit of the addition of cRT in the management of ES-SCLC.

2. Materials and methods

We conducted this systematic review in accordance with Cochrane handbook for systematic reviews of interventions [19]. The quality of evidence was appraised and assessed with Grades of Recommendation, Assessment, Development and Evaluation (GRADE) [20]. Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in the preparation of this manuscript [21].

2.1. Literature search strategy and study selection

We systematically searched literature using the electronic databases Embase and PubMed with no language, year or publication status restrictions. The search was conducted on published literature from inception until June 2018. The reference lists of relevant studies (trials or reviews) and pertinent books were screened to identify potential additional studies. The search was updated on 24th July 2018 to identify any new publications.

Search terms included 'small cell lung carcinoma OR small cell lung cancer OR SCLC,' AND 'thorax OR thoracic OR extracranial OR chest,' AND 'radiation OR radiotherapy,' AND 'randomised trial OR randomised study OR randomised trial OR randomised study OR RCT.' RCTs evaluating the benefit of the addition of cRT in ES-SCLC treated with platinum-based chemotherapy were eligible for inclusion. We contacted corresponding authors of the included studies for more information, clarifications, if any, and updated information whenever necessary. Two authors (S.R. and Y.L.) independently assessed the eligibility of the included studies, and any disagreement was resolved by discussion.

2.2. Data extraction and analysis

We evaluated OS, disease-free survival, thoracic progressions as the first site of failure (TP) and toxicity. Two authors (S.R. and Y.L.) independently extracted and pooled the outcome data using the Cochrane methodology for meta-analysis. The hazard ratio (HR) with 95% confidence interval (CI) and p-value were recorded. If the HR was not reported in the publication, the authors of the included studies were contacted for

relevant information. If authors could not provide the data, time-to-event data (HR with 95% CI) were extracted from the survival curves (Kaplan–Meier curves were analysed by Engauge Digitizer version 10.7) or with methods using p-value, number of patients randomised to each arm and number of events using the previously reported methods [22–24]. The log HR and its variance were pooled using inverse variance weighted average method (DerSimonian–Laird fixed-effects model) and expressed as a HR or odds ratio, as appropriate, with respective 95% CI and p-value [19,25] Heterogeneity was assessed by I^2 percentage and τ^2 test that expresses the percentage variability of the results related to heterogeneity rather than to the sampling error [26]. Random-effects model was selected if significant statistical heterogeneity ($I^2 > 50\%$) was observed. Begg and Egger funnel plot method was applied to find out any publication biases [27,28]. TP was analysed by pooled risk ratio (RR). The statistical analysis was performed (Y.L. and S.P.) using the statistical software R studio, version 1.1.456 2014-07-11, R.app 1.65(R reference: https://www.r-project.org/).

The analysis, interpretation and reporting of results also included a risk of bias assessment [19]. Included studies were considered to have low, unclear or high risk of bias as per the assessment on the following items: random sequence generation and concealment of allocation (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessors (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias) and any other sources of bias that could influence the quality of the study.

3. Results

Fig. 1 represents the PRISMA flow diagram showing the study selection and inclusion in the present meta-analysis. Our comprehensive and systematic search identified 1107 records. After removal of duplicate records, 922 records were screened. A total of 891 records were excluded with reasons (not SCLC − 497, limited stage − 130, not RCT − 233 and no cRT randomisation 31). A total of 31 full-text articles/abstracts were assessed for eligibility, 28 were excluded with reasons and 3 RCTs were eligible for meta-analysis. A total of 690 patients were included in the analysis.

3.1. Characteristics of the included studies

Details of the included studies are shown in Table 1. Jeremic *et al.* [8] conducted the first RCT (January 1988 to June 1993) addressing the role of RT in ES-SCLC. Eligible patients were treated with three cycles of standard-dose platinum–etoposide (PE) regimen given at 3-week intervals. Patients who achieved a CR at local and distant levels (CR/CR) and those who achieved a PR within the thorax accompanied by CR elsewhere (PR/CR) were randomised to receive accelerated hyperfractionated RT (54 Gy in 36 fractions in 18 treatment days in 3.5 weeks) and concurrent chemotherapy, followed by PCI (25 Gy in 10 fractions over 2 weeks) and then by two additional cycles of PE (group 1) or four additional cycles of PE and PCI (25 Gy in 10 fractions over 2 weeks) (group 2). Eligible patients were treated with three cycles of standard-dose PE regimen given at 3-week intervals. Patients who achieved a CR at local and distant levels (CR/CR) and those who achieved a PR within the thorax accompanied by CR elsewhere (PR/CR) were randomised to receive accelerated hyperfractionated RT (54 Gy in 36 fractions in 18 treatment days in 3.5 weeks) and concurrent chemotherapy, followed by PCI (25 Gy in 10 fractions over 2 weeks) and then by two additional cycles of PE (group 1) or four additional cycles of PE and PCI (25 Gy in 10 fractions over 2 weeks) (group 2). A total of 109 patients were randomised in group 1 and 2. Patients treated with thoracic RT showed a significantly higher OS compared with the no thoracic RT group ($P = 0.041$), and the 1-year survival rates were 65% vs 46%, respectively. Patients treated with cRT had higher first relapse-free survival at 1 year over the no cRT group (56% vs 41%, $p = 0.045$).

The second and the largest RCT Dutch Chest Radiotherapy in Extensive stage (CREST) disease [9] was conducted in 42 hospitals in the UK, Netherlands and Belgium. Between 2009 and 2012, 498 ES-SCLC patients with ECOG 0–2 and confirmed response to 4–6 cycles of PE chemotherapy were enrolled. Patients were randomised 1:1 to receive cRT (30Gy/10Fr) or no cRT. All patients received PCI (25Gy/10Fr, 20Gy/5Fr, 30Gy/10-12-15Fr). The primary endpoint of the study was 1 year OS, and analysis was conducted with an intention to treat basis. At a median follow up of 24 months, OS at 1 year was not statistically different (33% - cRT vs. 28% - no cRT) between two groups with the HR of 0.84 (95% CI 0.69–1.01). In a secondary analysis, OS at 2 years was 13% vs 3% favouring cRT ($p = 0.004$). Progression was less likely in the cRT group with 6 months PFS 24% vs 7% than in the no cRT group (HR = 0.73, 95% CI: 0.61–0.87).

The recent RCT by the NRG–RTOG 0937 [18] group evaluated the role of thoracic RT in ES-SCLC. This study included ES-SCLC with one to four extracranial metastases with a complete or partial response to 4–6 cycles of platinum-based chemotherapy. From March 2010 to February 2015, a total of 97 patients were randomised to receive PCI + cRT vs. PCI alone. However, 11 patients were ineligible, and, of the 86 patients randomised, 44 received cRT (thoracic disease and other extracranial metastasis) and 42 received no cRT. All patients received PCI (25Gy/10FR). The study was closed prematurely as it crossed futility margins for

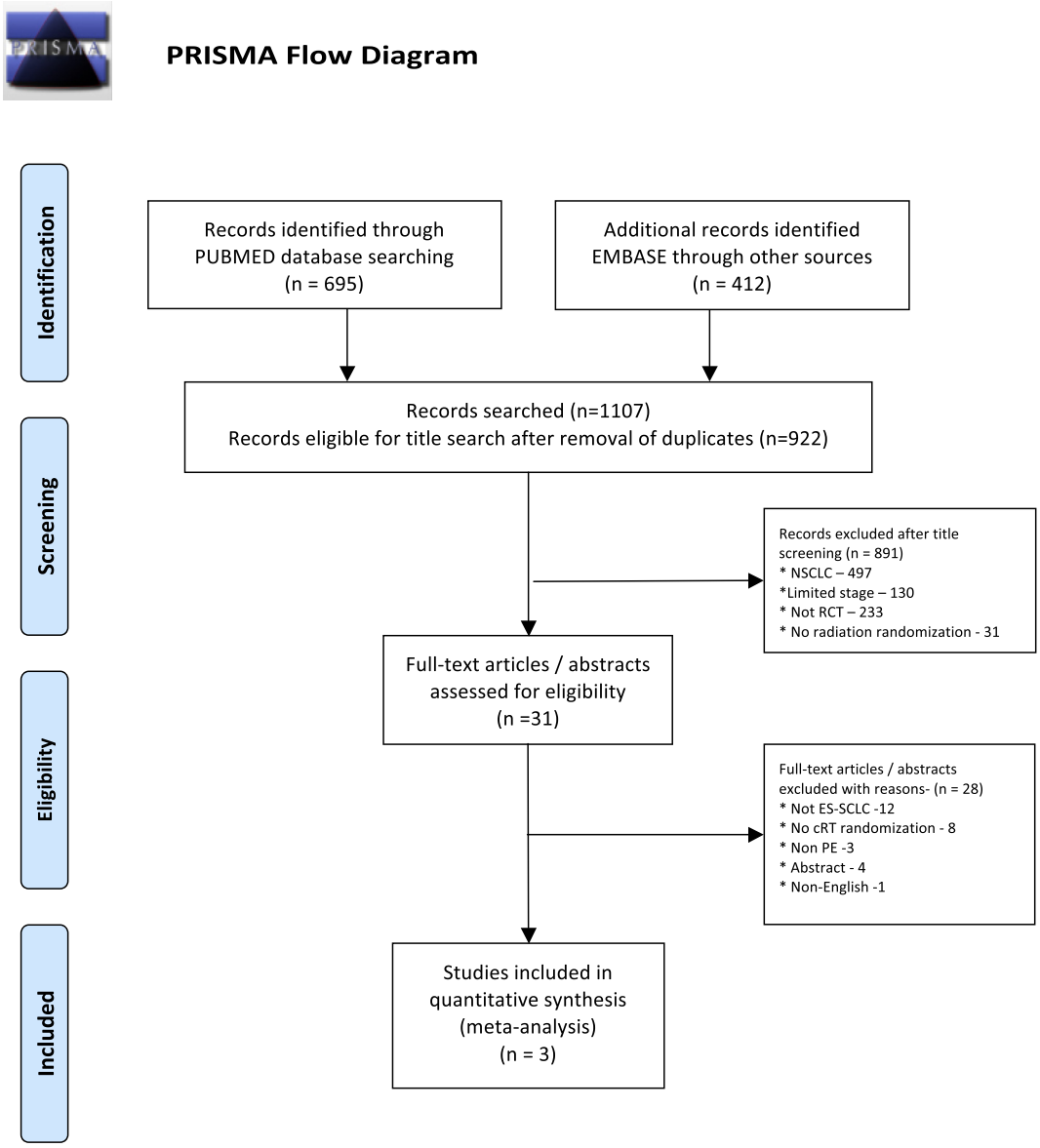

Fig. 1. PRISMA 2009 flow diagram. PRISMA, Preferred Reporting of Systematic Reviews and Meta-Analyses; PE, platinum–etoposide; ES-SCLC, extensive stage small cell lung cancer; cRT, consolidation radiation to thoracic disease; NSCLC, non-small cell lung cancer.

OS at the planned interim analysis. The study failed to show any significant (p = 0.21) difference in 1 year OS (50.8% - PCI + cRT vs. 60.1%-PCI alone). Progression rate at 1 year was 79.6% for PCI vs. 75% for PCI + cRT, and time to tumour progression was significantly better with PCI + cRT (HR-0.53, 95% CI 0.32–0.87). There were only two and four deaths without progression with the PCI group and PC + cRT group, respectively. Median PFS was 2.9 months (95% CI: 2.4–3.7) for PCI and 4.9 months (95% CI: 3.4–6.0) for PCI + cRT (p = 0.0148). HR and 95% CI were extracted for PFS with recommended methods using p-value, the number of patients randomised to each arm and the number of events. Extracted PFS HR was 0.56 (95% 0.35–0.89). A detailed assessment of the quality of the evidence is shown in Tables 2 and 3.

3.2. Meta-analysis synthesised findings

3.2.1. Overall survival

All 3 studied reported OS outcomes, and meta-analysis of OS included 346 and 344 patients in the cRT group and no cRT group, respectively [8,9,18]. The pooled HR with random effects model for OS was 0.88 (95% CI 0.66–1.18, I^2-52%) and was not significant (p = 0.35) for the difference between groups receiving cRT vs. no cRT (Fig. 2-a and Table 3). On performing the sensitivity analysis for studies using sequential approach

Table 1
Details of the included studies.

Study	Country	RCT design	Period	Study size (cRT vs no cRT)	cRT approach	cRT	CT	PCI approach PCI		Endpoints
Gore *et al.* (2017)	US	Ph II	March 2010 –February 2015	42/44	Sequential (post CT)	45Gy/15Fr	4 to 6 cycles of platinum based CT	Concurrent with cRT	25Gy/10Fr	OS, Progression rate, and Toxicity
Slotman *et al.* (2015)	Netherlands, UK and Belgium	Ph III	February 2009 - December 2012	247/248	Sequential (post CT)	30Gy/10Fr	4 to 6 cycles of PE	Concurrent with cRT	30Gy/12Fr, 25Gy/10Fr, 20Gy/5Fr	OS, PFS, and Toxicity
Jeremic *et al.* (1999)	Yugoslavia	Ph III	January 1988–June 1993	55/54	Concurrent with CT	54Gy/36Fr/18 days	3 cycles of PE	Sequential (post cRT)	25Gy/10Fr	OS, LC, DMFS and PFS

CT, chemotherapy; cRT, consolidation radiation; PCI prophylactic cranial radiation; OS, overall survival; PFS progression-free survival; DMFS, distant metastasis–free survival; LC, local control; Gy, gray; Fr, fractions; ph, phase; PE, platinum etoposide.

cRT, two studies including 291 patients in the cRT group and 290 patients with the no cRT group were analysed [9,18]. Our findings (Fig. 2-b) suggest cRT with sequential approach did not offer significant OS benefit ($p = 0.11$) and the pooled HR with random effects model was 1.03 (95% CI 0.62–1.71, $I^2 = 68\%$). Overall quality of evidence was high, and inverted funnel does not show any publication bias (Fig. 3-a).

3.2.2. Progression-free survival

Pooled analysis of [8,9,18] PFS included 346 and 344 patients in the cRT group and no cRT group, respectively. The pooled HR with fixed effects model for progression was 0.72 (95% CI: 0.61–0.83, $I^2 = 0\%$) and significantly in favour of cRT ($p < 0.0001$) over the no cRT group (Fig. 2-c and Table 3). Sensitivity analysis for cRT using sequential approach (Fig. 2-d), included two studies with 291 patients in the cRT group and 290 patients with the no cRT group [9,18]. Findings suggest cRT with sequential approach offered significant PFS benefit ($p = 0.004$) and the pooled HR with fixed effects model was 0.71 (95% CI 0.60–0.83, $I^2 = 8\%$). Overall quality of evidence was high, and inverted funnel does not suggest publication bias (Fig. 3-b).

3.2.3. Thoracic progression as the site of first progression

Of the included 3 studies, 2 studies reported information on thoracic progression as the first site of disease progression [9,18]. Analysis conducted with 291 patients in the cRT group and 290 patients in the no cRT arm (Fig. 2-e and Table 3) showed significantly ($p < 0.001$) lower risk of thoracic progression as the first site of progression with the relative risk of 0.52 (95% CI: 0.44–0.61, $I^2 = 0\%$).

3.2.4. Toxicity

CREST study reported grade III or higher toxic effects occurred in 26 patients in the cRT group and 18 patients in the no cRT group ($p = 0.28$) [9]. In the RTOG 0937 study, two groups showed no significant difference ($p = 0.24$) in grade III or higher adverse events

Table 2
Assessment of the quality of the evidence.

Criteria	Jeremic *et al.*	Slotman *et al.*	Gore *et al.*
Random sequence generation	Unclear risk	Low risk	Low risk
Allocation concealment	Unclear risk	Low risk	Low risk
Blinding of participants and personnel	Low risk	Low risk	Low risk
Blinding of outcome assessment	Low risk	Low risk	Low risk
Incomplete outcome data	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk
Other bias	Low risk	Low risk	Low risk
Overall quality	Low risk	Low risk	Low risk

Table 3
Consolidation RT compared with no consolidation RT for outcomes.

Patient or population: Outcomes
Setting: Extensive stage small cell lung cancer
Intervention: Consolidation RT
Comparison: No Consolidation RT

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No Consolidation RT	Risk difference with Consolidation RT
Overall survival	690 (3 RCTs)	⊕⊕⊕◯ MODERATE	**HR 0.88** (0.66–1.18)	70 per 100	**8 fewer per 100** (24 fewer to 11 more)
Progression-free survival	690 (3 RCTs)	⊕⊕⊕⊕ HIGH	**HR 0.72** (0.62–0.84)	89 per 100	**9 fewer per 100** (14 fewer to 5 fewer)
Thoracic progression as the first site of progression	581 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 0.52** (0.44–0.61)	73 per 100	**35 fewer per 100** (41 fewer to 29 fewer)

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: confidence interval; **RR**: risk ratio; **HR**: hazard ratio; **RT**, radiotherapy.
GRADE Working Group grades of evidence: **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

(no cRT n = 10 [23.8%] vs. cRT n = 16 [36.4%]) [18]. Grade III or higher toxicity attributed to therapy was reported in four patients treated with PCI (9.5%) and 11 treated with PCI. cRT (25%). Jeremic *et al.* reported acute grade III and IV toxic events in the cRT group that were less frequent (88/55) than those in the group 2 (145/54) [8]. There was no difference combined late grade III and IV (3/55 vs 0/54, p = 0.082) toxicity

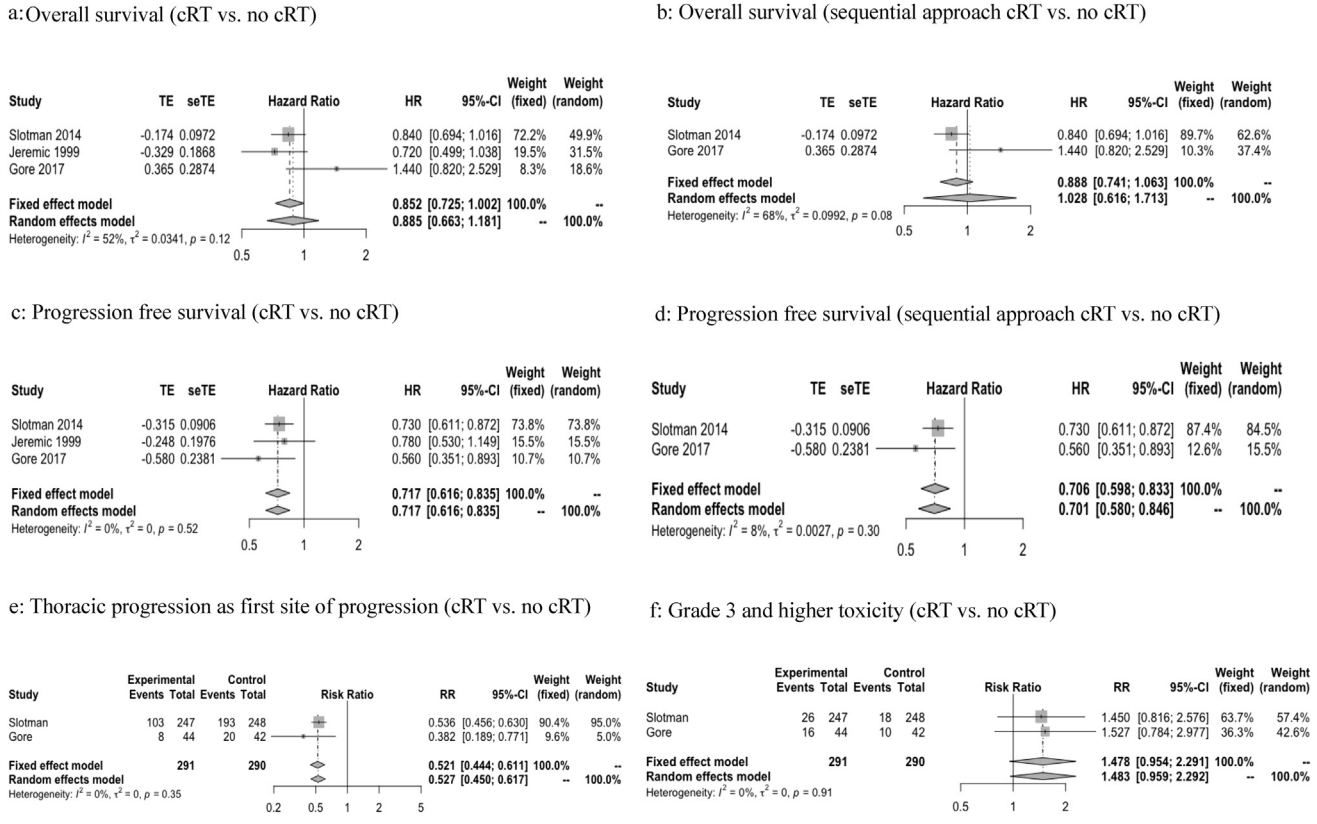

Fig. 2. Pooled analysis showing Forest plot of cRT versus no cRT. (a) Forest plot of cRT versus no cRT for overall survival; (b) Forest plot of sequential approach cRT versus no cRT for overall survival; (c) Forest plot of cRT versus no cRT for progression-free survival; (d) Forest plot sequential approach cRT versus no cRT for progression-free survival; (e) pooled analysis showing risk ratio of thoracic progression as the first site of progression with cRT versus no cRT; (f) pooled analysis showing risk ratio of grade III and higher toxicity (cRT vs. no cRT) cRT, consolidation radiation to thoracic disease; HR, hazard ratio; CI, confidence interval.

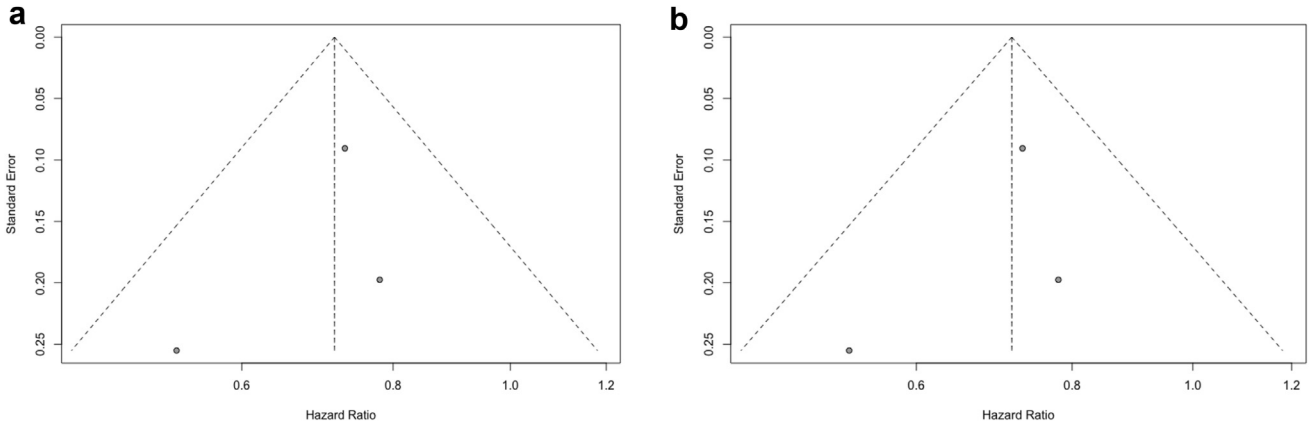

Fig. 3. Inverted funnel plots (a) studies reporting overall survival and (b) studies reporting progression-free survival.

between the two groups. The study did not report on the cumulative number of patients having any grade or higher toxicity. Pooled analysis of two studies (Fig. 2-f), reporting number of individuals showed no significant difference ($p = 0.08$) in the risk of grade III or higher toxicity between two groups (RR 1.48; 95% CI: 0.96–2.29, $I^2 = 0\%$) [9,18].

4. Discussion

Poor prognosis associated with the treatment of SCLCs continues to be an ongoing challenge. Majority of SCLC present with extensive stage disease, and CT continues to be the mainstay of therapy in ES-SCLC [4]. Thoracic cRT is recommended for ES-SCLC patients, especially with CR or PR [4]. We performed the meta-analysis of RCT's evaluating role of cRT to thoracic disease in ES-SCLC.

Our meta-analysis shows cRT provides a significant PFS benefit in ES-SCLC. The pooled HR for progression was 0.72 (95% CI: 0.61–0.83, $I^2 = 0\%$), significantly in favour of cRT ($p < 0.0001$) with no heterogeneity within the included studies. This finding is consistent with all 3 individual studies showing benefits with PFS. Typically, intrathoracic disease is likely to the site of the first progression [8,9]. The present meta-analysis shows the addition of cRT offered a significant reduction in the rate of thoracic progression as the first site of progression with relative risk of 0.52 (95% CI: 0.44–0.61, $I^2 = 0\%$). Our meta-analysis shows, cRT to thoracic disease offers 48% reduction in thoracic progression as the first site of failure and 28% reduction in PFS. Addition of sequential approach cRT did not show a significant increase in the risk of grade III or higher side toxicity.

Our meta-analysis showed no statistically significant OS benefit with cRT in ES-SCLC with pooled HR 0.88 (95% CI 0.66–1.18, $I^2 = 54\%$, $p = 0.36$). Sensitivity analysis for cRT using sequential approach showed no significant OS difference ($p = 0.11$), and the pooled HR was 1.03 (95% CI 0.62–1.71, $I^2 = 68\%$). Slotman *et al.* [9] showed, at 2 years OS, improvement was noted with cRT and, at the predefined endpoint of 1 year, there was no significant OS difference (33% - thoracic RT vs. 28% - no thoracic RT) between the 2 groups. The RTOG 0937 [18] study crossed the futility boundary for OS and closed prematurely at planned interim analysis before meeting accrual target. OS significantly exceeded the expected value in both the groups and no OS benefit with cRT.

Previous meta-analysis by Palma et al included 2 of the 3 studies and showed CRT improved OS (HR, 0.81; 95% CI, 0.69–0.96; $P = 0.014$) and PFS (HR, 0.74; 95% CI, 0.64–0.87, $P < .001$) [17]. In this updated meta-analysis, we showed cRT significantly reduced thoracic progression as the first site of failure and improved PFS benefit, however, did not offer significant OS benefit. To the best of our knowledge, we present the first meta-analysis report showing these findings.

It is tempting to seek potential explanations and assess the differences in the included studies. The studies had significant treatment differences in terms of patient population, duration of palliative CT (3 vs. 4–6 cycles), radiation approach (concurrent vs. sequential), radiation doses, use of concurrent chemotherapy, duration of total treatment and use of PCI (concurrent vs. sequential) [8,9,18]. For example, sequential cRT (4–6 cycles of chemotherapy followed by cRT) was used in CREST and RTOG 0937; however, concurrent cRT was used in the pivotal study by Jeremic *et al.* [8,9,18] It is plausible that with concurrent approach, aggressive cRT with concurrent CT in a shorter overall treatment time has led to faster improvement in local control which, in turn, may have led to faster improvement in the OS in Jeremic *et al.* study. Aggressive hyperfractionated approach (54Gy/36Fr/BID) compared with lesser doses of cRT (30Gy/10Fr/2weeks or 45Gy/15Fr/3weeks) could also be a potential contributing factor to the survival differences noted. Confounding effect related to the inherent difference in the population included in the individual

studies could not be excluded. To highlight, the CREST study had more unfavourable patients (ECOG 0–2 10% vs 0%) than the Jeremic *et al.* study [8,9]. Similarly, there were some imbalances in the two groups in RTOG 0937 that could potentially contribute to the lack of OS benefit, despite improvements in thoracic control [18].

Although cRT significantly reduced thoracic failures, increased failures in other organ were noted. CREST study showed other sites failures only were noted in 36% of patients receiving cRT compared with 8% in the no cRT group. Similarly, in RTOG 0937 study, failures at any new sites at any time were higher in patients receiving cRT (61% vs. 31%). This could probably contribute to a lack of significant OS benefit and perhaps highlights the need for better systemic therapy.

The extent and location of metastatic disease could have a significant prognostic impact. In a secondary analysis, Slotman *et al.* evaluated prognostic importance of number and sites of metastases in patients included in the CREST study [29]. In this analysis of 260 patients from 9 centres, regardless of the administration of cRT, both OS (HR 1.43; 95% CI 1.07–1.92; p = 0.02) and PFS (HR = 1.35; 95% CI 1.02–1.78; p = 0.04) were significantly better in patients with up to 2 metastases, than in those with 3 or more distant metastases. Jeremic *et al.* study, in contrast, included over 90% of patients with less than 2 metastases and did show OS benefit with cRT [8]. The RTOG trial did focus on the oligometastatic subset with 1–4 metastasis, and 17 (40%) patients had 1 metastasis in the cRT group compared with 14 (32%) in the no cRT group [18]. Ineffective RT dose and schedule, advanced age, and an imbalance in disease burden in the two groups could possibly contribute to lack of survival advantage with consolidative RT in this trial. With OS significantly exceeded both groups, Gore et al [18] suggested that perhaps a more appropriate treatment for this patient population with low volume systemic disease could have been early RT concurrent with cycle three or four of CT in patients with a favourable response to cycles one and two of CT followed by PCI, similar to the Jeremic *et al.* study.

Nevertheless, in view of poor response and low survival rates to second line treatment options [30], PFS continues to be a meaningful objective in ES-SCLC. We support use of cRT in ES-SCLC to be considered on a case-by-case basis. Patients with response to CT, residual intrathoracic disease and limited extrathoracic disease to might be at a higher risk of intrathoracic progression. Use of cRT in this population may yield maximum benefit and would be appropriate.

Further research is needed to identify the subgroup of ES-SCLC patients who are more likely to derive an OS benefit for cRT. Despite the adoption of the Union for International Cancer Control/American Joint Committee on Cancer TNM system for SCLC, the Veterans Administration Lung Study Group (VALSG) classification is limited and extensive SCLC is still commonly used terminology [31,32]. In today's era of modern imaging, the extensive stage could vary from limited metastatic disease to disseminated metastatic disease, and VALSG classification limits our ability to stage these patients systematically. Systematic use of TNM is preferred, and its wider application should be supported. It would be preferred to incorporate this wisdom and refine treatment as per disease bulk [33]. Future studies evaluating optimal treatment combination, number of chemotherapy before cRT, dose fractionation, concurrent vs sequential approach and timing of PCI may help to address unanswered questions and help tailor treatment approaches.

4.1. Limitations and strengths

Our study has several limitations. This systematic review was focused on RCT, and we excluded non-randomised and retrospective studies. Included studies were limited to published English literature; however, this is unlikely to significantly impact our findings [34,35]. Reporting bias is an important limitation; we made no attempt to seek out unpublished studies. The most important limitation is that the current meta-analysis is based on summary data and not individual patient data. We were unable to assess the impact of patient factors (age, performance status, gender, etc), the extent of extensive disease and response to CT (CR/PR/SD), as the required information was not available from all trials. Differences related to heterogeneity of patients, treatment and follow-up factors might also have limited the findings. None of the studies have reported QoL or cost-effectiveness of treatment intensification, precluding any such estimation in the meta-analysis. For the present meta-analysis, two of the included studies did not report grade I–II toxicities [9,18]. Thus, pooled outcome of G1-2 toxicities could not be reported in the present study.

Despite the limitations, our systematic review and meta-analysis include comprehensive search in accordance with Cochrane guidelines. The quality of evidence was appraised and graded using the GRADE system [20], and PRISMA guidelines [21,36] were used for the preparation of the manuscript.

In summary, we present a systematic review and meta-analysis of RCT evaluating cRT in ES-SCLC. Thoracic cRT offers significant PFS improvement, a significant reduction in thoracic progression as the first site of progression, however, did not show significant OS benefit. We support use of cRT in ES-SCLC to be considered on a case-by-case basis. Patients with response to CT, residual intrathoracic disease and limited extrathoracic disease to might be at a higher risk of intrathoracic progression. Use of cRT in this population may yield maximum benefit and would be appropriate. Further research to identify the subset of ES-SCLC likely to have significant OS benefit is needed.

Strategies focussing on subclassification of ES-SCLC (limited vs extensive metastasis) optimise strategy for RT integration (sequential vs concurrent), and optimal RT dose might be helpful.

5. Conclusion

Our meta-analysis of 3 randomised controlled studies shows consolidation thoracic RT offers significant improvement in PFS and reduction in thoracic failures. Use of cRT in ES-SCLC should be considered on a case-by-case basis. Further research to identify the subset of ES-SCLC likely to have significant OS benefit is needed.

Conflict of interest statement

None declared.

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