



Consolidation thoracic radiotherapy after chemoimmunotherapy in ES-SCLC: A multicentric retrospective analysis

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ABSTRACT

Background: The CREST trial established the benefit of consolidative thoracic radiotherapy (TRT) following first line (1L) chemotherapy in extensive-stage small cell lung cancer (ES-SCLC), demonstrating improved 2-year overall survival (OS). However, the role of TRT in the chemoimmunotherapy (CT-IO) era remains unclear, as TRT was excluded from registrational trials.

Methods: This retrospective study analysed consecutive patients (pts) with ES-SCLC treated with 1L CT-IO between January 2020 and January 2024 across 4 centres. Pts without radiological progression (PD) at their first post-treatment assessment were included. Intrathoracic recurrence rates, progression-free survival (PFS), and OS were compared between pts who received TRT and those who did not.

Results: 336 pts were identified, with 111 (33.0 %) receiving TRT. Pts who received TRT had a lower rate of intrathoracic PD compared to those who did not (40.5 % vs 57.8 %, $p = 0.003$). Among those with intrathoracic PD despite TRT, only 21 (24.1 %) experienced PD within the radiation field. With a median follow-up of 31.3 months, pts who received TRT showed improved PFS (HR 0.89, $p = 0.363$) and OS (HR 0.82, $p = 0.142$), although not statistically significant. Multivariate analysis identified baseline liver metastases (LM) and stable disease after CT-IO as independent predictors of shorter PFS. Subgroup analysis revealed a longer PFS for pts receiving higher TRT doses (≥ 45 Gy vs < 45 Gy) and those without LM.

Conclusions: In this series, TRT following 1 L CT-IO significantly improved intrathoracic control, although it did not translate into significantly better survival outcomes. Prospective trials are warranted to evaluate the impact of TRT on quality of life and survival.

1. Introduction

Small-cell lung cancer (SCLC) represents 13–15 % of all lung malignancies. Its hallmarks include neuroendocrine features and highly

aggressive biology, with rapid growth and early widespread diffusion. Therefore, more than 65 % of newly diagnosed SCLC cases present as extensive stage (ES-SCLC) [1].

Over the last few decades, platinum-based chemotherapy has been

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the backbone of treatment for this malignancy. Immunotherapy has been the most recent and significant practice-changing advancement, based on the results of two trials, CASPIAN and IMpower-133, which tested either durvalumab or atezolizumab plus chemotherapy vs chemotherapy alone, respectively [2,3].

Despite these developments, disease control remains a major challenge. Morphologically, 75 % of patients have residual thoracic disease after first-line treatment, with most experiencing intrathoracic relapse or progression within the first year, despite systemic progression being the dominant pattern [1,4]. This presents significant challenges for effective tumour control, as uncontrolled thoracic disease can impair quality of life and cause severe morbidity, including complication such as superior vena cava obstruction, lung infections and respiratory distress.

Considering the ‘radiosensitivity’ of SCLC, radiotherapy has therefore been employed to improve local control and overall survival (OS) [5]. In the pre-immunotherapy era, the CREST trial established the benefit of consolidative thoracic radiotherapy (TRT) in ES-SCLC [4]. Patients responding to chemotherapy who received TRT, and prophylactic cranial irradiation (PCI) demonstrated a 2-year OS of 13 % compared to 3 % in those receiving PCI alone ($p = 0.004$). Notably, a subgroup analysis identified significant improvements in OS, progression-free survival (PFS), and intrathoracic disease control among patients with residual thoracic disease undergoing TRT [6]. In the immunotherapy era, TRT was not allowed in the registration trials which led to the approval of durvalumab and atezolizumab in addition to platinum/etoposide as first-line treatment for ES-SCLC. Therefore, since the introduction of immune-checkpoint blockade in ES-SCLC, the benefits of TRT are uncertain [2,3].

Small retrospective studies have investigated the addition of TRT to standard chemo-immunotherapy treatment, generally showing a benefit in survival outcomes [7–12]. However, the role of consolidative radiotherapy remains controversial in the immunotherapy era, due to the absence of randomized studies evaluating its clinical efficacy and safety in this context. Furthermore, in the non-small cell lung cancer (NSCLC) setting, radiation-induced lymphopenia was shown to abrogate the benefits of consolidative immunotherapy [13].

The current ESMO and ASTRO guidelines conditionally recommend TRT for patients with ES-SCLC who respond to chemotherapy and immunotherapy but have residual thoracic disease [14,15]. The recommended dose is 30 Gy in 10 fractions, though a dose of 45 Gy in 15 fractions could be considered for well-selected, fit patients. The strength of this recommendation is conditional and based on expert opinion. Similarly, National Comprehensive Cancer Network (NCCN) guidelines recommend TRT as an option for selected patients, during or before maintenance immunotherapy, but highlights the lack of definitive clinical data to support routine use [16]. The uncertainty underlying these recommendations likely reflects the unknown magnitude of benefit associated with TRT.

This multicentric retrospective study aimed to evaluate the impact of consolidative TRT on local recurrence, PFS and OS in ES-SCLC patients treated with chemo-immunotherapy.

2. Materials and methods

2.1. Study design and patient selection

We retrospectively identified consecutive patients with histologically or cytologically diagnosed ES-SCLC treated with first-line chemo-immunotherapy between January 2020 and January 2024 at four European institutions: The Christie NHS Foundation Trust (Manchester, UK), Fondazione Policlinico A. Gemelli (Rome, Italy), Istituto Tumori Giovanni Paolo II (Bari, Italy) and Ospedale San Luigi Gonzaga (Orbassano, Italy), with The Christie as the coordinating site. Patients were eligible if they had no progression on the first assessment CT scan following the initiation of treatment. 396 patients were screened and

336 (84.8 %) were included in the analysis, with 111 (33 %) receiving consolidative TRT and 225 not receiving TRT.

2.2. Treatment and radiotherapy parameters

All patients received platinum-based doublet chemotherapy combined with either durvalumab or atezolizumab. Radiotherapy was delivered using intensity-modulated techniques, virtual simulation or parallel pair techniques with shielding of organs at risk. The gross tumour volume included the residual primary tumour after chemo-immunotherapy (CT-IO) treatment and the positive lymph nodes before CT-IO. The clinical target volume (CTV) was defined as the gross tumour volume with a margin of 5 mm and positive lymph nodes. The planning target volume was expanded from the CTV with a margin of 5–8 mm. Dose selection was based on clinical factors and local institutional protocols.

2.3. Endpoints and assessments

The primary endpoint was intrathoracic control rate in patients who received TRT vs those who did not. Local recurrence was defined as the proportion of patients experiencing intrathoracic disease progression. Secondary endpoints were PFS, defined as the time from treatment initiation to documented progression or death, and OS, defined as the time from treatment initiation to death from any cause. Exploratory endpoints encompassed subgroup analyses based on radiotherapy dose, presence of liver metastases, and best response to induction therapy. Radiological responses were assessed by local radiologists and/or investigators.

2.4. Statistical analysis

All statistical analyses were performed using R (v4.4.0) and IBM SPSS Statistics (v29). Descriptive statistics compared patient characteristics between the TRT and non-TRT groups. Patients who were lost to follow-up or had not experienced the event by the study cut-off were censored; their data were right-censored at the last date of available follow-up, ensuring that survival estimates accounted for these observations within a Kaplan–Meier analysis. Kaplan–Meier curves were generated to describe PFS and OS. Comparisons were made using Cox proportional-hazards models, and effect estimates were expressed as hazard ratios (HR) with 95 % confidence intervals. Proportional-hazards (PH) assumptions were evaluated using scaled Schoenfeld residuals. When the global test indicated non-proportionality ($p \leq 0.05$), we calculated the restricted mean survival time (RMST) up to a truncation time (τ) corresponding to the 95th percentile of follow-up.

Propensity-score matching (PSM) was performed in R. A logistic model including gender, dichotomised ECOG (0–1 vs ≥ 2), liver and brain metastases, age, and PCI generated propensity scores. One-to-one nearest-neighbour matching with caliper 0.2 (SD of the logit-PS) was applied. Balance was assessed via standardised mean differences and visualised in a Love plot; SMDs < 0.10 were considered acceptable. Survival in the matched cohort was analysed with Cox models or, when PH was violated, RMST.

Multivariate Cox regression analyses were performed to identify independent prognostic factors of survival. A p value < 0.05 was considered statistically significant. Additional exploratory subgroup analyses were conducted to examine the associations between radiotherapy dose (X vs X), liver metastasis status (X vs X), and the best response to induction therapy (X vs X) with survival outcomes.

As a sensitivity analysis for the primary endpoint, intrathoracic progression was modelled in the propensity-matched cohort using a conditional Cox proportional-hazards model stratified by matched pair (equivalent to a conditional logistic regression).

2.5. Ethical considerations

This study was registered and approved as a service evaluation by 4 participating sites, with the coordinating centre being The Christie NHS Foundation Trust in Manchester (UK) (Reference: project number 4228). Patient data were anonymized to ensure confidentiality, and the requirement for informed consent was waived due to the retrospective nature of the study.

3. Results

3.1. Patients' characteristics

336 were included in the analysis, with 111 (33 %) receiving consolidative TRT. Of these evaluable patients, 39.0 % were current smokers and 59.2 % were former smokers. The TRT group included 111 (33.0 %) patients, while the control group included 225 patients. The median number of chemo-immunotherapy cycles was 4 in both groups, the majority (n = 243; 73.5 %) of patients received atezolizumab, while 87 (25.9 %) patients received durvalumab, and 2 (0.6 %) patients received pembrolizumab. Baseline characteristics—including age, sex, performance status, and metastatic profile—were similar between groups, except for a significantly lower proportion of liver metastases in the TRT group (25.2 % vs 42.2 %, p = 0.002) (Table 1). Of the patients who received TRT, 82 (73.9 %) were treated with 30 Gy, 3 (2.7 %) with lower doses, and 23 (21.3 %) with doses higher than 30 Gy (range 45–60 Gy). Patients who received TRT were also more likely to receive PCI: 32.4 % (n = 36) vs 12.9 % (n = 29), respectively (p < 0.001).

3.2. Efficacy

3.2.1. Intrathoracic disease control

No significant differences were observed in the overall rate of disease progression between patients treated with thoracic radiotherapy (TRT) and those who were not (78.4 % vs 82.8 %, respectively; p = 0.329). However, the TRT group demonstrated a significantly lower intrathoracic recurrence rate compared to the non-TRT group (40.5 % vs 57.8 %, respectively; p = 0.003), as shown in Fig. 1. The reduced risk of intrathoracic progression was maintained in the multivariate analysis (Table 2). Among patients receiving TRT who experienced disease progression, only 21 (24.1 %) had progression within the radiation field.

As a sensitivity analysis, we performed 1:1 propensity-score matching (104 pairs; n = 208) on key baseline covariates (gender, ECOG performance status [0–1 vs ≥ 2], liver metastases, CNS metastases, age, and PCI). In this matched cohort, conditional Cox regression stratified by matched pair confirmed that TRT was associated with a significantly lower hazard of intrathoracic progression (HR = 0.44, 95 % CI: 0.25–0.77; p = 0.004).

3.2.2. Survival outcomes

The median follow-up of right-censored patients was 31.3 months (95 % CI 25.6–37.0). By study cut-off, 18 patients (16.2 %) in the TRT group and 32 patients (14.2 %) in the non-TRT group remained alive without progression. In the entire study cohort, the median PFS was 6.6 months. Patients who received TRT had a significantly longer PFS (8.1 (95 % CI: 7.1–9.2), vs 6.1 months (95 % CI: 5.7–6.6), p = 0.010). The Schoenfeld residual test demonstrated violation of the PH assumption for the TRT variable (global χ^2 = 7.96, p = 0.005); therefore, RMST was used as the primary effect measure. Up to τ = 29.2 months, patients who received TRT had an RMST of 10.9 months compared with 9.0 months in the non-TRT group, yielding an absolute gain of 1.9 months (95 % CI: 0.0–3.7, p = 0.046) and an RMST ratio of 1.21 (95 % CI: 1.01–1.44). These findings support the benefit of TRT despite non-proportional hazards. By the same cut-off date, 33 patients (29.7 %) in the TRT group and 42 patients (18.7 %) in the non-TRT group were alive. Similarly, OS was significantly improved in the TRT cohort (13.5 months

Table 1
Clinical characteristics of patients who received TRT vs those who did not receive TRT.

Characteristic	Overall (N = 336)	TRT group (N = 111)	No TRT group (N = 225)	p
Age at treatment start (years) (median [IQR])	66 (60–72)	64 (58–71)	66 (60–72)	0.160
Sex				0.178
Male (n, %)	181 (53.9)	54 (48.6)	127 (56.4)	
Female (n, %)	155 (46.1)	57 (51.4)	98 (43.6)	
Performance status				0.316
ECOG 0–1 (n, %)	318 (94.6)	107 (96.4)	211 (93.8)	
ECOG 2–3 (n, %)	18 (5.4)	4 (3.6)	14 (6.2)	
COPD				0.759
Grouped T				0.205
T1–T2 (n, %)	85 (25.3)	29 (26.1)	56 (24.9)	
T3–T4 (n, %)	208 (61.9)	63 (56.8)	145 (64.4)	
Unknown	43 (12.8)	19 (17.1)	24 (10.7)	
Grouped N				0.154
N0–N1 (n, %)	36 (10.7)	9 (8.1)	27 (12.0)	
N2–N3 (n, %)	247 (73.5)	79 (71.2)	168 (74.7)	
Unknown	53 (15.8)	23 (20.7)	30 (13.3)	
Yes (n, %)	76 (22.6)	24 (21.6)	52 (23.1)	
No (n, %)	260 (77.4)	87 (78.4)	173 (76.9)	
Brain metastases				0.645
Present (n, %)	62 (18.5)	19 (17.1)	43 (19.1)	
Absent (n, %)	273 (81.5)	92 (82.9)	181 (80.4)	
Unknown (n, %)	1 (0.3)	0 (0.0)	1 (0.4)	
Liver metastases				0.002
Present (n, %)	123 (36.6)	28 (25.2)	95 (42.2)	
Absent (n, %)	213 (63.4)	83 (74.8)	130 (57.8)	
Response to Ch-IO				0.026
Complete/partial response (n, %)	296 (88.1)	104 (93.7)	192 (85.3)	
Stable disease (n, %)	40 (11.9)	7 (6.3)	33 (14.7)	
Intrathoracic residual disease (n, %)				0.095
Yes	269 (80.1)	87 (78.4)	182 (80.9)	
No	15 (4.5)	2 (1.8)	13 (5.8)	
Unknown	52 (15.5)	22 (19.8)	30 (13.3)	
ICI				0.114
Atezolizumab (n, %)	247 (73.5)	89 (80.2)	158 (70.2)	
Durvalumab (n, %)	87 (25.9)	22 (19.8)	65 (28.9)	
Pembrolizumab (n, %)	2 (0.6)	0 (0.0)	2 (0.9)	
PCI				< 0.001
Yes (n, %)	65 (19.3)	36 (32.4)	29 (12.9)	
No (n, %)	268 (79.8)	75 (67.6)	193 (85.8)	
Unknown (n, %)	3 (0.9)	0 (0.0)	3 (1.3)	

Abbreviations: Ch-IO, Chemoimmunotherapy; COPD, Chronic Obstructive Pulmonary Disease; ECOG, Eastern Cooperative Oncology Group; ICI, Immune Checkpoint Inhibitor; IQR, Interquartile Range; n, Number of patients; OS, Overall Survival; PFS, Progression-Free Survival; PD-1, Programmed Cell Death Protein 1; PCI, Prophylactic Cranial Irradiation; TRT, Thoracic Radiotherapy.

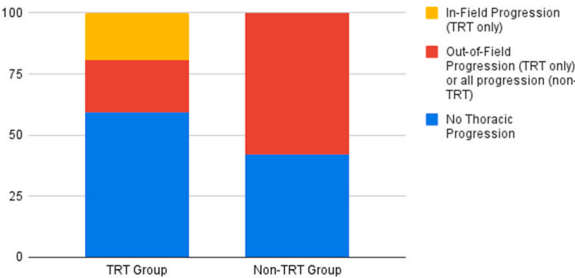


Fig. 1. Rate and location of thoracic recurrence in patients who underwent thoracic radiotherapy (TRT group) and those who did not (non-TRT group).

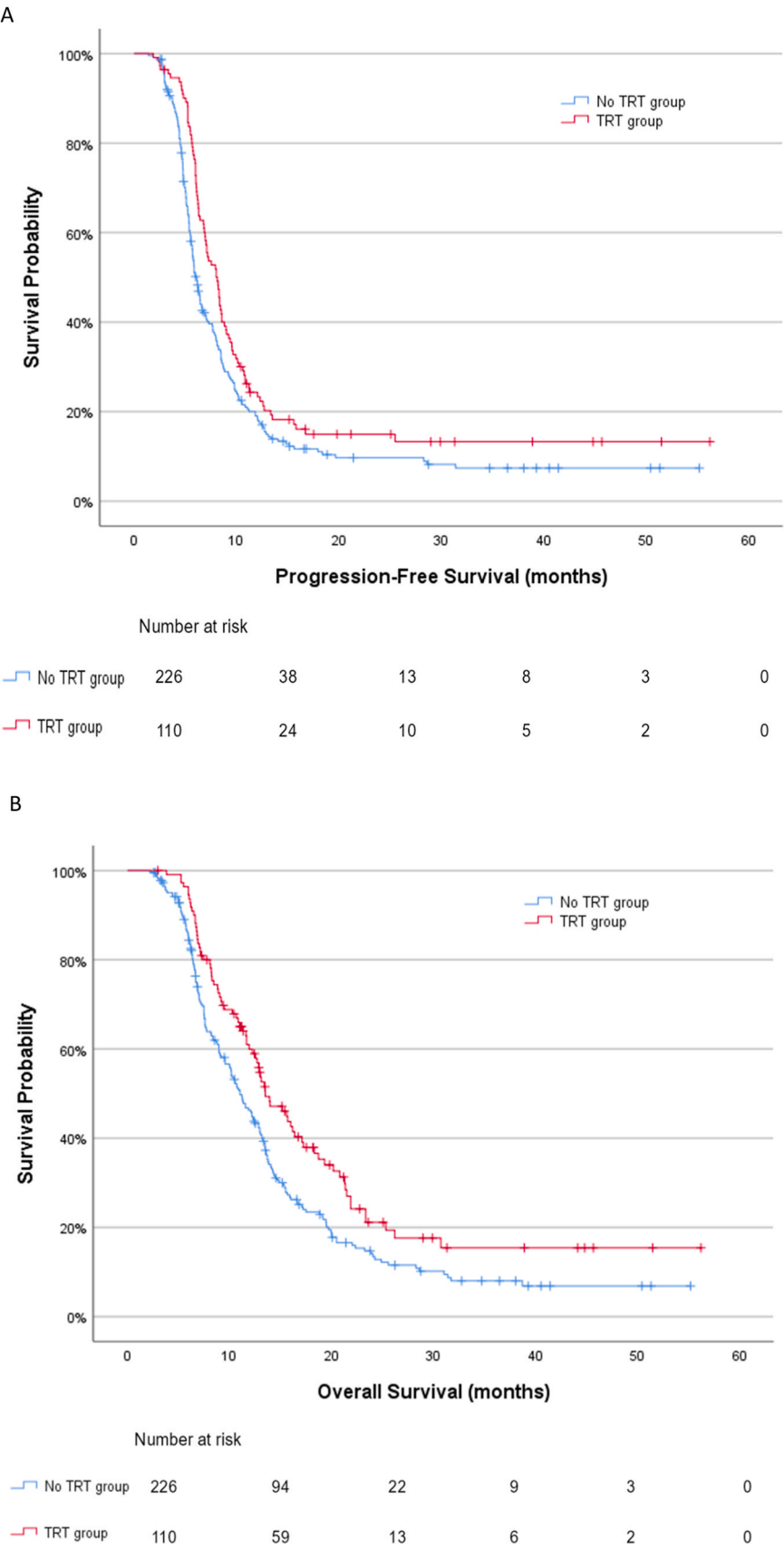


Fig. 2. Kaplan–Meier survival curves examining the association between consolidative thoracic radiotherapy (TRT) and (A) progression-free survival, and (B) overall survival.

Table 2

Multivariate analysis of factors associated with intrathoracic control.

Variable	Odds Ratio (95 % CI)	p-value
Thoracic Radiotherapy	0.49 (0.28–0.85)	0.011
Age (per 1-year increase)	0.98 (0.96–1.01)	0.254
Gender (male vs female)	0.80 (0.48–1.34)	0.402
ECOG PS (≥ 2 vs 0–1)	2.00 (0.59–6.81)	0.269
Liver metastases (yes vs no)	0.87 (0.52–1.48)	0.608
CNS metastases (yes vs no)	0.40 (0.20–0.80)	0.009
Response to induction (SD/PR vs CR)	0.81 (0.17–3.85)	0.791

Abbreviations: CI = confidence interval; CR = complete response; PR = partial response; SD = stable disease; PS = performance status.

(95 % CI: 11.1–15.9) vs 11.0 months (95 % CI: 9.7–12.4), $p = 0.004$). The Schoenfeld residual test demonstrated no violation of the PH assumption for OS (global $\chi^2 = 1.59$, $p = 0.21$). The 1-year OS rate was 55 % in the TRT group compared to 41 % in the non-TRT group, and the 2-year OS rates were 21 % and 12 %, respectively.

In the univariate analysis of PFS and OS, the presence of liver metastases ($p < 0.001$) and response to induction chemoimmunotherapy ($p < 0.001$) were identified as significant prognostic factors.

For the multivariate analysis, variables with a p value < 0.10 in the univariate analysis were included [Table 3](#). The multivariate analysis revealed that the presence of baseline liver metastases and failure to achieve a partial or complete response after completion of chemoimmunotherapy were independently associated with shorter PFS. Regarding OS, in addition to the presence of liver metastases and lack of response to treatment, an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3 was also significantly associated with shorter survival.

3.2.2.1. Propensity-matched cohort. After 1:1 nearest-neighbour matching on gender, ECOG (0–1 vs ≥ 2), liver and CNS metastases, age, and PCI, 208 patients (104 per arm) remained. Balance was excellent, with all standardised mean differences below 0.10 ([Supplementary Fig. 1](#)).

For PFS, the PH assumption continued to be violated (global $\chi^2 = 5.07$, $p = 0.024$), so we compared restricted mean survival times up to $\tau = 31.37$ months. Patients who received TRT had an RMST of 10.46 months vs 10.33 months in the control group (absolute difference 0.13 months; 95 % CI: – 2.18 to 2.44; $p = 0.912$), indicating no meaningful gain. The matched Cox model yielded HR = 0.90 (95 % CI: 0.67–1.21; $p = 0.50$), consistent with the RMST analysis. For OS, proportional hazards held (global $\chi^2 = 0.10$, $p = 0.75$). The matched Cox analysis showed a non-significant difference with a HR of 0.85 (95 % CI: 0.62–1.16; $p = 0.31$).

Table 3

Multivariable Cox regression model of OS and PFS in SCLC patients treated with anti-PD(L)1 immunotherapy, who underwent consolidative thoracic radiotherapy.

	PFS				OS			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	HR (95 %CI)	P value	HR (95 %CI)	P value	HR (95 %CI)	P value	HR (95 %CI)	P value
TRT	0.72 (0.57–0.93)	0.011	0.89 (0.69–1.15)	0.363	0.68 (0.52–0.88)	0.004	0.82 (0.62–1.07)	0.142
Age	1.01 (1.00–1.03)	0.088	1.01 (0.99–1.02)	0.396	1.01 (1.00–1.02)	0.120		
Gender (male vs female)	1.02 (0.81–1.28)	0.539			0.99 (0.77–1.26)	0.923		
ECOG PS (≥ 2 vs 0–1)	1.35 (0.83–2.21)	0.054	1.46 (0.88–2.40)	0.141	1.55 (0.95–2.53)	0.082	1.93 (1.17–3.18)	0.010
Liver metastases (Yes vs No)	1.98 (1.55–2.53)	< 0.001	1.93 (1.51–2.48)	< 0.001	1.89 (1.48–2.43)	< 0.001	2.04 (1.57–2.64)	< 0.001
Brain metastases (Yes vs No)	0.89 (0.66–1.21)	0.457			0.84 (0.60–1.16)	0.185		
Response to induction Ch-IO (CR/PR vs SD)	0.51 (0.36–0.71)	< 0.001	0.49 (0.35–0.70)	< 0.001	0.47 (0.33–0.67)	< 0.001	0.40 (0.28–0.58)	< 0.001

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; Ch-IO, chemo-immunotherapy; CR/PR, complete response and partial response; SD, stable disease.

3.3. Exploratory subgroup analyses

3.3.1. Radiotherapy dose

The radiotherapy dose was recorded in 108 out of 111 (97.2 %) patients who received TRT. Among them, the majority (73.9 %) received a standard RT dose (~30 Gy in 10 fractions), while 23 (21.3 %) patients received higher-dose of TRT (45–60 Gy). We did not find significant differences in terms of local recurrence rates (41.2 % vs 39.1 %, $p = 0.859$). Patients who received higher-dose TRT experienced significantly longer median PFS compared to those who received the standard 30 Gy dose (9.6 months vs 8.0 months; HR 0.50, $p = 0.016$). Similarly, OS was improved in the higher-dose group (20.2 vs 13.1 months, HR 0.45, $p = 0.013$).

3.3.2. Baseline liver metastases

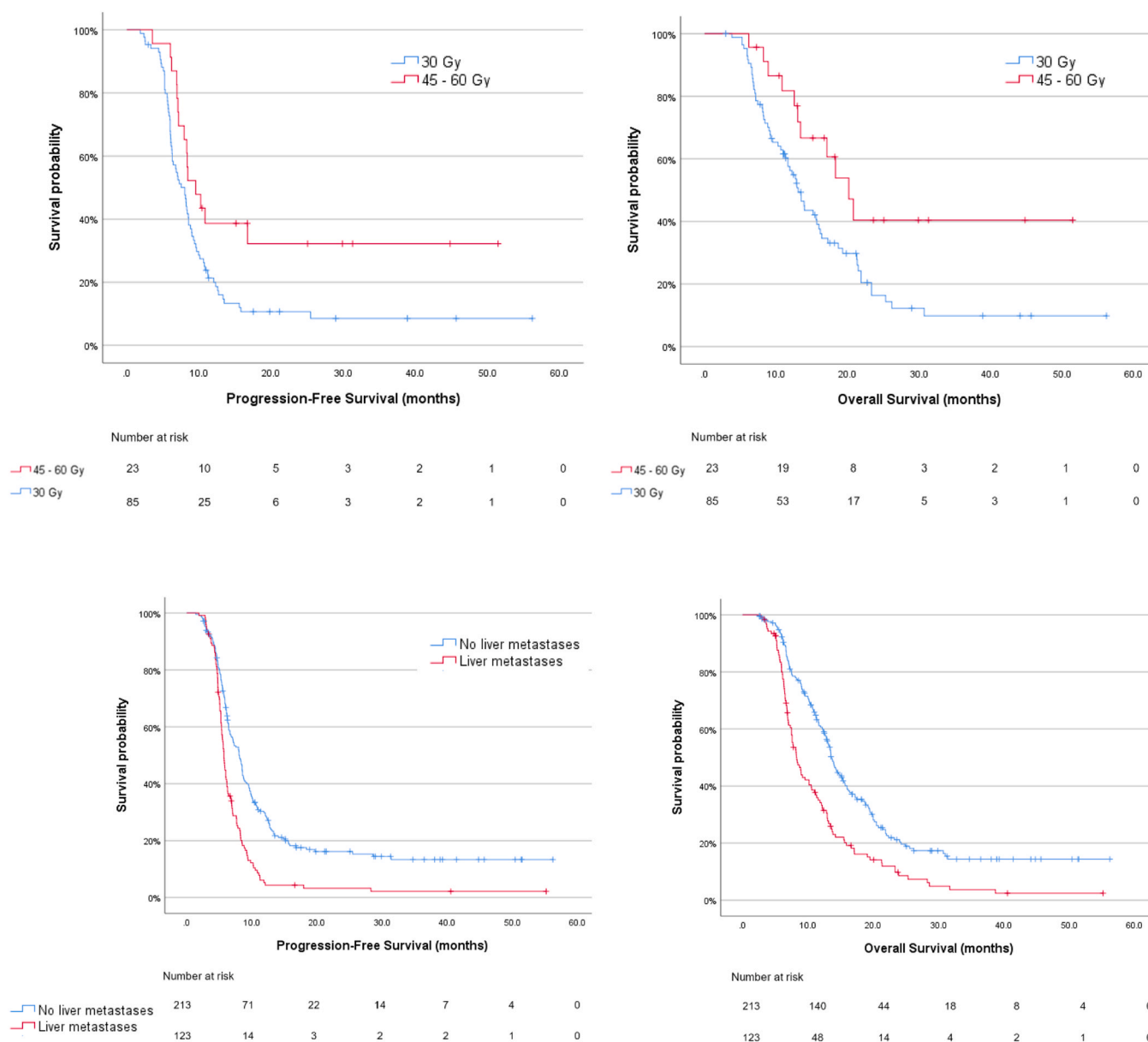
The efficacy of TRT appeared to be influenced by the presence of baseline liver metastases. Among patients with liver metastases ($n = 123$), the local recurrence rate was not significantly different between those who received TRT and those who did not (53.6 % vs 56.8 %, respectively; $p = 0.759$). In contrast, among patients without liver metastases, TRT was associated with a significantly lower local recurrence rate (36.1 % vs 58.5 %; $p = 0.001$).

The median PFS in patients with baseline liver metastases was 6.3 vs 5.6 months for the TRT group and non-TRT group, respectively. In patients without liver metastases, the median PFS was longer, at 8.6 months in the TRT group versus 7.1 months in the non-TRT group. Similarly, when evaluating OS, significant differences were observed in patients without liver metastases (OS was 15.7 vs 13.3 months for the TRT group and non-TRT group, respectively). In contrast, among patients with liver metastases, OS was 8.4 months in the TRT group and 7.7 months in the non-TRT group ($p = 0.035$).

3.3.3. Response to induction: PR/SD vs CR

We also assessed the efficacy of TRT in patients who achieved a complete response (CR to induction chemoimmunotherapy ($n = 14$; 4.2 %) compared to those whose best response was stable disease (SD) or partial response (PR) ($n = 322$; 95.8 %). In the PR/SD group, TRT was associated with a significantly lower intrathoracic recurrence rate compared to no TRT (41.1 % vs 58.9 %; $p = 0.003$). Among patients with CR, TRT substantially reduced the local recurrence rate (25.0 % vs 40.0 %; $p = 0.597$).

PFS was also improved with TRT. In patients who achieved PR/SD, median PFS was 8.0 months in the TRT group compared to 5.9 months in the non-TRT group. In patients with CR, the median PFS was 13.5 months with TRT vs 12.9 months without TRT ($p = 0.031$). Overall survival followed a similar trend, with patients achieving PR/SD demonstrating a median OS of 13.5 months with TRT compared to 10.7 months without TRT. Among patients with CR, TRT was associated with a median OS of 13.5 months compared to 14.9 months in the non-TRT group.



3.4. Treatment post-progression

Overall, 267 (81.9 %) patients experienced disease progression following the initiation of first-line chemoimmunotherapy. Among them, 165 (61.3 %) patients received at least one subsequent line of systemic therapy. The likelihood of receiving second-line treatment did not significantly differ between patients who had received TRT and those who had not, with 64.7 % ($n = 55$) of the TRT group and 60.4 % ($n = 110$) of the non-TRT group receiving further therapy ($p = 0.504$).

The most commonly used second-line regimens included rechallenge with carboplatin plus etoposide ($n = 76$, 28.1 %), vincristine, adriamycin, and cyclophosphamide (VAC) combination ($n = 30$, 11.1 %), topotecan ($n = 25$, 9.3 %), and irinotecan ($n = 22$, 8.1 %).

4. Discussion

To the best of our knowledge, this is the largest retrospective multicentric study to investigate and to demonstrate a significant improvement for intrathoracic disease control rates in patients with ES-

SCLC treated with chemo-immunotherapy who went on to receive consolidation thoracic TRT. This study also highlights factors associated with benefit from TRT.

In recent years, the most promising development in the treatment of ES-SCLC has been the addition of immunotherapy to standard platinum-based first-line chemotherapy, based on the CASPIAN and IMpower133 trials. However, neither study permitted consolidation TRT. While both immunotherapy and TRT could individually benefit patients with ES-SCLC, evidence supporting the use of TRT in this setting remains insufficient. In addition, the optimal dose, timing of radiotherapy and the characteristics of patients most likely to benefit remain unclear.

In the pre-chemoimmunotherapy era, the phase III CREST trial did not demonstrate a statistically significant improvement in 1-year overall survival with consolidative TRT (33 % vs 28 %; HR 0.84) [4]. Conversely, a secondary analysis of the trial showed a reduction in intrathoracic recurrence (HR 0.73; $p = 0.001$) and a benefit in PFS (HR 0.73) and 2-year OS (13 % vs 3 %; $p = 0.004$). Similarly, a systematic review and meta-analysis of 12 studies, conducted in 2021 and comprising a total of 936 patients in the TRT group and 1059 patients in

the non-TRT group, found that consolidative TRT significantly improved OS (HR 0.65), PFS (HR 0.64) and local recurrence-free survival (HR 0.38; $p < 0.00001$) [17]. In the post-chemo-immunotherapy era, the largest retrospective study evaluating local recurrence rates in patients who underwent TRT was conducted by Li et al. and included 100 patients. This study confirmed a reduction in intrathoracic progression in patients who received TRT (20.0 % vs 55.9 %, $p = 0.003$) [12]. Our results are consistent with the findings of this study and with prospective trials conducted in the pre-chemo-immunotherapy era [4,6,17]. Given these heterogeneous results and the paucity of evidence on local control after chemo-IO, we chose intrathoracic recurrence rate as our primary endpoint to evaluate the locoregional benefit of TRT, independent of competing risks from distant failures.

In contrast with our study, most retrospective studies have only focused on the correlation between consolidative TRT and survival outcomes. Notably, the largest study published to date included 276 patients and demonstrated significant differences in PFS ($p = 0.014$) and OS ($p = 0.009$) between the TRT and non-TRT group [9]. Interestingly, patients with liver metastases did not derive clinical benefit from TRT. In our study, although we observed statistically significant improvements in PFS and OS in the univariable analysis, the multivariable analysis did not confirm these findings. Furthermore, after propensity-score matching, the survival advantage of TRT was attenuated and no longer statistically significant, underscoring the influence of baseline prognostic factors on treatment allocation. The lack of statistical significance for PFS (HR 0.363) and OS (HR 0.142) may be due to the inclusion of patients with liver metastases ($n = 123$), who did not seem to benefit from TRT [18].

Building upon our findings and the consistent observation across studies that not all patients with ES-SCLC benefit from TRT, we conducted a further exploratory analysis based on the presence or absence of liver metastases. Patients without liver metastases had lower rates of local recurrence and significantly improved survival outcomes, compared to those with liver metastases. These findings suggest that patients with liver metastases derive limited benefit from TRT in terms of intrathoracic disease control and survival outcomes. A possible explanation is that liver metastases may impair the systemic efficacy of immunotherapy through macrophage-mediated T-cell elimination [19]. A recent pivotal study has introduced a new classification based on transcription factors, identifying a subgroup of patients with inflamed tumours who are more likely to respond to immunotherapy [20]. It is plausible that patients with liver metastases represent a biologically distinct, "cold" disease subtype, for whom intensified approaches, including TRT, may not be beneficial [19].

Furthermore, in the multivariable analysis, we demonstrated that, alongside patients with good performance status, those who achieved a partial or complete response to induction chemo-immunotherapy benefit more from TRT. Interestingly, patients who achieved a complete response (CR) to induction treatment appeared to benefit from TRT in terms of reduced local recurrence rates, although this did not translate into a survival advantage. Conversely, Slotman et al. [21] conducted an additional analysis of the CREST trial, comparing patients with and without residual intrathoracic disease, and found no benefit in terms of PFS, OS or intrathoracic recurrence in the subgroup without intrathoracic disease. Although our sample size is very small ($n = 14$), it would be valuable to further explore and validate these findings.

Lastly, determining the optimal radiation dose for TRT is essential. Our exploratory analysis showed that different dose fractionation schemes had no significant impact on intrathoracic PD status but were associated with better survival outcomes, likely influenced by patient selection, as those who receive a higher dose tend to be younger and with less comorbidities. In the pre-chemo-immunotherapy era, a retrospective analysis from the USA National Cancer Database, which included 3280 patients, found that a TRT dose of 45 Gy or more was independently associated with longer survival [22]. Similarly, another retrospective study of 492 patients, 244 of whom received TRT, reported

that higher radiation doses were linked to improved survival and disease control [23]. Since combining TRT with immunotherapy may increase the incidence of adverse events and increase the risk of lymphopenia, careful patient selection and thoughtful consideration are essential when determining the most appropriate dose-fractionation schedule for TRT. Based on the findings from our study, we can hypothesize that patients who achieve a partial response to systemic therapy and do not have liver metastases may represent a subset with a more favourable prognosis, in whom intensified local radiotherapy could be crucial to eradicating residual cancer cells. Therefore, an individualized treatment strategy may be beneficial in this population, allowing the identification of patients likely to derive the most benefit from TRT and ensuring that benefits outweigh potential risks.

The ongoing RAPTOR trial (NCT 04402788) is evaluating the benefit of TRT in patients with ES-SCLC. The study is randomizing patients to receive either standard immunotherapy maintenance or maintenance with consolidative radiation to up to five thoracic and/or extrathoracic sites [24] and is due to complete enrolment in 2027. Meanwhile, the TREASURE trial, which assessed the benefit of TRT in patients without brain metastases, recently closed recruitment due to a higher-than-expected incidence of grade 5 adverse events, the specifics of which have not been disclosed [25].

Our study has several limitations. First, as a retrospective analysis, it is subject to potential selection bias and unmeasured confounding, thereby precluding definitive causal inference. Although we conducted a multicentre study to diversify both the patient population and the treatment approaches, the findings should be interpreted with caution. Second, the retrospective design led to some heterogeneity within the study population, including variations in immune checkpoint inhibitors, radiation doses, and, most notably, an uneven distribution of liver metastases. These baseline imbalances limit the applicability and generalizability of our findings to broader ES-SCLC populations. Finally, data on the timing of TRT were not analysed, as they were not available for the entire cohort of patients.

5. Conclusions

This study represents the largest retrospective study to date evaluating the impact of consolidative thoracic radiotherapy in patients with ES-SCLC receiving first-line chemo-immunotherapy. Our findings suggest that consolidative radiotherapy reduces the risk of intrathoracic recurrence and may contribute to improved clinical outcomes. Notably, patients without liver metastases and those with a good response to first-line therapy appear to derive the greatest benefit, highlighting a subgroup that may warrant exploration of higher radiotherapy doses. Further prospective studies are needed to better define the role of consolidative radiotherapy and its toxicity profile in the era of immunotherapy.

CRedit authorship contribution statement

Yvonne Summers: Visualization, Validation, Supervision. **Gerard Walls:** Project administration, Formal analysis, Data curation. **Giam-paolo Tortora:** Project administration, Methodology, Investigation. **Ornella Cantale:** Investigation, Data curation. **Maria Antonietta Gambacorta:** Project administration, Methodology, Investigation. **Clara Chan:** Formal analysis, Data curation. **Sara Polidori:** Investigation, Data curation. **Emilio Bria:** Writing – review & editing, Visualization, Validation, Supervision, Project administration. **Mariantonietta Di Salvatore:** Investigation, Data curation. **Fiona Blackhall:** Project administration, Methodology, Investigation. **Luca Boldrini:** Visualization, Validation, Supervision. **Silvia Novello:** Validation, Supervision. **Ana Parreira:** Formal analysis, Data curation. **Domenico Galetta:** Investigation, Formal analysis, Data curation. **Antonella Martino:** Investigation, Formal analysis, Data curation. **Federico Monaca:** Writing – review & editing, Writing – original draft, Investigation, Data

curation, Conceptualization. **Corinne Faivre-Finn**: Writing – review & editing, Visualization, Validation, Supervision, Project administration. **Emanuele Vita**: Project administration, Methodology, Investigation. **Raffaele Califano**: Writing – review & editing, Visualization, Validation, Supervision, Project administration. **Vito Longo**: Investigation, Formal analysis, Data curation. **Igor Gomez-Randulfe**: Writing – review & editing, Software, Formal analysis, Data curation.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2025.115592](https://doi.org/10.1016/j.ejca.2025.115592).

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