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Retrospective cohort study assessing clinical outcomes of patients with extensive-stage small cell lung cancer treated with and without consolidative thoracic radiotherapy at the Princess Margaret Cancer Centre

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ABSTRACT

Objectives Most patients with small cell lung cancer present with extensive-stage (ES-SCLC) disease. An international randomised trial demonstrated a survival benefit in patients treated with consolidative thoracic radiotherapy (cTRT). We report our institutional experience with this regimen.

Methods A retrospective review was conducted on patients with ES-SCLC who were candidates for cTRT at our institution between 2013 and 2022. The patients included in our study had biopsy-proven ES-SCLC, received ≥4 cycles of chemotherapy and achieved complete response, partial response or stable disease as per Response Evaluation Criteria in Solid Tumors V.1.1. Overall survival, progression-free survival (PFS) and recurrence patterns were compared between patients who received cTRT and those who did not. For patients who received cTRT, treatment tolerability was assessed.

Results We identified 123 patients with ES-SCLC who received ≥4 cycles of chemotherapy and were candidates for cTRT. Of those, 49 patients received cTRT, and 74 patients did not. From the end of chemotherapy, the control group had a median OS of 0.6 years with a 1- and 2-year OS of 23.5% and 11.0%. Within the cTRT group, the median OS was 0.9 years with a 1- and 2-year OS of 46.7% and 26.3%. Within the control group, the median PFS was 0.2 years compared with 0.4 years within the cTRT group. Intrathoracic failures in the cTRT group were lower compared with the control group (16.3% vs 29.7%). cTRT was well tolerated with no grade 3+ toxicities.

Conclusion The improved clinical outcomes of cTRT for patients with ES-SCLC were comparable to the reported the Chest Radiotherapy Extensive-Stage Small Cell Lung Cancer Trial (CREST) outcome, with a low rate of side effects in our study cohort.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our study provides a real-life analysis, outside of a clinical trial setting, of the impacts of treating patients with extensive-stage small cell lung cancer with consolidative thoracic radiotherapy.
⇒ We provide a robust analysis of the patient population's treatment-related toxicity.
⇒ Our study provides a focused analysis of treatment outcomes in the absence of immunotherapy, facilitating better correlation of outcomes and symptoms.

BACKGROUND

Small cell lung cancer (SCLC) comprises 15% of all lung cancer diagnoses worldwide and is the most aggressive subtype of lung cancer.[1] The 5-year survival rate for patients with SCLC is only 7% compared with the 28% 5-year survival rate for non-SCLC.[2 3] Patients with SCLC are often pragmatically stratified into limited-stage and extensive-stage (ES) at diagnosis.[4 5] Most patients with SCLC are diagnosed with ES disease (60–75%), which is clinically defined as tumour or metastases extending outside the hemithorax or that is not encompassable within a tolerable radiotherapy (RT) portal.[6–8] As of 2023, patients with ES-SCLC had a median survival of 13 months and an overall 5-year survival of 5%.[2 9 10] As of 2018, the standard of care for patients with ES-SCLC consists of combination chemoimmunotherapy. However, most of these studies did not include consolidative thoracic radiotherapy (cTRT).[9 11]

In 1999, Jeremic *et al* evaluated the use of concurrent chemotherapy and thoracic RT for patients with ES-SCLC and reported preliminary evidence showcasing an overall survival (OS) benefit.[12] Further interest in

cTRT was garnered in 2015, following the publication of the European Organisation for Research and Treatment of Cancer Phase III CREST trial that demonstrated a survival benefit for patients with ES-SCLC at the secondary 2-year endpoint of 14% with cTRT compared with 3% without cTRT.[13] cTRT also improved local control with less intrathoracic progression when treated with cTRT (43.7% vs 79.8%). However, how the results of this study can be applied to clinical practice and the associated real-life impact has not been reported. Previously, in 2011, we reported that cTRT was well tolerated in 19 patients with ES-SCLC treated from 2005 to 2009.[14] Therefore, we sought to review and update our institutional experience with cTRT for patients with ES-SCLC since the publication of the 2015 CREST study. Here, we report our real-world institutional outcomes associated with treating patients with ES-SCLC diagnosed between 2013 and 2022. We analysed potential candidates for the CREST-like cTRT approach, comparing those who received cTRT with patients who were also potential candidates but did not receive cTRT.

METHODS

Study design and participants

This was a retrospective cohort study of patients diagnosed with ES-SCLC at our tertiary cancer centre between January 2013 and December 2022. The patients included in our study were aged ≥18 years, biopsy-proven ES-SCLC with Eastern Cooperative Oncology Group (ECOG) performance status 0–3, received at least four cycles of chemotherapy,and had complete medical records. Patients with only complete response (CR), partial response (PR) or stable disease (SD) as per the Response Evaluation Criteria in Solid Tumors V.1.1 were included.[15] Since immunotherapy became available in our jurisdiction in the latter half of 2021, it was administered to only three patients during the study period who met all other inclusion criteria. Consequently, patients treated with immunotherapy were excluded from this study.

Patient and public involvement

There was no patient involvement in preparing the study design or conducting the study. Results of this study will be appropriately disseminated to educate patients treated at our institution to inform their medical decisions surrounding treatment.

Treatment definitions

Radiation details, including dose fractionation and technique, were abstracted. cTRT was defined as those receiving at least 30 Gy to the thorax either delivered concurrently or within 10 weeks of completing first-line chemotherapy. A time period of 10 weeks from the end of chemotherapy was chosen to maintain the consolidative nature of RT similar to the CREST study, which initiated cTRT within 6–7 weeks after chemotherapy.

Variables and outcomes

Patients were staged as per the American Joint Committee on Cancer tumour, node, metastases (TNM), 8th edition. Patients were followed with a clinic visit and imaging generally every 3–4 months after treatment as per the treating oncologist. Imaging and imaging reports of the thorax, abdomen, brain (either CT or MRI), including PET-CT or bone scans, when available, were reviewed. Clinical history, smoking history in pack-years (py) and physical examination were noted.

First-line therapy chemotherapeutic agents, number of cycles and timing relative to cTRT were abstracted. Prophylactic cranial irradiation (PCI) for patients without baseline brain metastasis was at the discretion of the treating physicians, and available details were collected. Acute radiation-associated side effects were reviewed and recorded according to the Common Terminology Criteria for Adverse Events V.5. Intrathoracic disease recurrence was defined as patients with disease recurrence or progression in lung parenchyma or mediastinum. Extrathoracic disease progression or recurrence was identified in individual organ sites. The study cohort was divided into two groups: those receiving cTRT and those not receiving cTRT (control). Those included in the control group were theoretically eligible for cTRT but did not undergo the treatment, for various reasons, including but not limited to the patient declining cTRT, the radiation oncologist not recommending cTRT or some patients not being formally referred for RT opinion. The objectives of this study were to report the OS, progression-free survival (PFS) and patterns of disease recurrence for patients with cTRT and examine the impact of cTRT on the outcomes of interest compared with control.

Statistical analysis

The study population was summarised descriptively. The patient characteristics at baseline were compared between the cTRT and controls groups using χ^2 or Fisher's exact test for categorical variables, and Student's t-test or Wilcoxon rank sum test for continuous variables. Radiation-associated toxicity outcomes were examined descriptively for patients with cTRT. The OS was calculated from the end of first-line chemotherapy to the date of death or last follow-up. The PFS was calculated from the end of first-line chemotherapy to first progression or death, or last follow-up if alive without progression. The OS and PFS rates were then estimated using the Kaplan-Meier method and compared between cTRT and control groups using the log-rank test. We examined the association of OS and PFS with treatment and the patient characteristics using univariate Cox proportional hazard models (UVA). Multivariable Cox proportional hazard models were further conducted to determine the association of OS/PFS, with the treatment adjusted for risk factors and potential confounders. Data management and all statistical analyses were performed using SAS 9.4 (SAS Institute Inc, North Carolina, USA). A two-sided p value of <0.05 was considered statistically significanct.

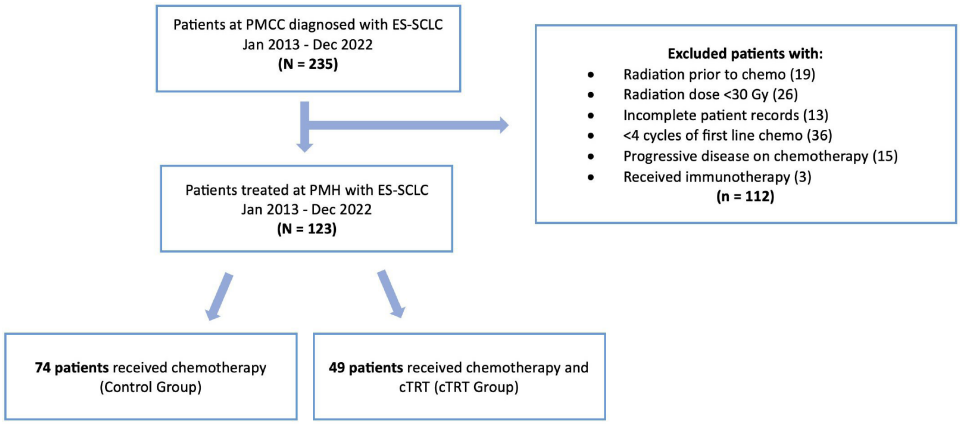

Figure 1 Study design outlining exclusion criteria used for the selection of patients treated at Princess Margaret Cancer Centre (PMCC) within the control group and consolidative thoracic radiotherapy (cTRT) groups. ES-SCLC, extensive-stage small cell lung cancer.

RESULTS

Patient characteristics

Between January 2013 and December 2022, 262 consecutively treated patients with ES-SCLC at our institute were identified. Of these, 123 patients (M:F=46:77) were eligible for our study (figure 1). The median age was 66.2 years (range: 46.1–89.5 years), and most had an ECOG score of 0–1 at diagnosis (78.8%). Median follow-up was 0.6 years (range: 0.01–10.7 years) for the entire cohort. Smoking history was recorded in 122 patients (99%), with a median of 45 py (range 4–120 py). At baseline, 23 (18.7%) and 47 (38.2%) patients had brain and liver metastases, respectively. The advanced T category (T3–T4) was seen in 66 patients (53.6%), and most (93.4%) patients had mediastinal lymph node involvement. Metastatic disease was present in 113 patients (97.8%; table 1). Of the entire cohort (n=123), 49 (39.8%) were treated with cTRT, while 74 (60.1%) were not treated with cTRT (figure 1). 45 (91.8%) and 67 (90.5%) patients underwent brain imaging at diagnosis in the cTRT and control groups, respectively. There were 7 (14.3%) and 16 (21.6%) patients in the cTRT and control groups with brain metastasis at diagnosis, respectively. A statistical difference was observed between the two groups. 13 (26.53%) and 34 (45.95%) patients had liver metastasis at diagnosis in the cTRT and control groups, respectively ($p<0.05$). No other differences in baseline characteristics between the two groups were observed.

Chemotherapy and radiation treatment

All 123 patients were treated with at least four cycles, with a maximum of six cycles of first-line chemotherapy. Of these patients, 94 (76.4%) had PR, 23 (18.7%) SD while only 6 (4.8%) had CR to first-line chemotherapy. Platinum-based agents (cisplatin/carboplatin) were used in 116 (94.3%) while only 7 (5.7%) patients received treatment with non-platinum-based agents, including single-agent etoposide or cyclophosphamide, doxorubicin and vincristine as first-line chemotherapy. The use of platinum agents (93.2% vs 95.9%, p=0.9) and response to first-line chemotherapy (95.9% vs 93.8%, p=0.89) were balanced between the control and cTRT groups (table 1). All patients in the cTRT group (n=49, 39.8%) received cTRT during or after completion (within 10 weeks) of first-line chemotherapy. Of patients receiving cTRT, four (8.2%) were treated concurrently and 45 (91.8%) were treated sequentially. The most common RT regimen in the cTRT group was 30 Gy in 10 fractions over 2 weeks (n=42, 85.7%), followed by 40 Gy in 15–16 fractions over 3 weeks (n=6, 12.4%), and one patient (2.0%) was treated with 45 Gy in 30 fractions two times per day. Within the cTRT group (n=49), 29 (59.1%) patients underwent radiation using three-dimensional conformal radiation therapy, and 20 (40.9%) patients were treated with intensity-modulated radiation therapy or volumetric-modulated arc therapy. With respect to RT treatment volumes, most patients were treated similarly to the CREST-defined target definitions, where postchemotherapy parenchymal residual lung cancer along with the prechemotherapy disease involved hilar and/or mediastinal lymph node regions were targeted with cTRT. 45 (91.8%) and 67 (90.5%) patients underwent brain imaging at diagnosis in the cTRT and control groups, respectively. There were 7 (14.3%) and 16 (21.6%) patients in the cTRT and control groups with brain metastasis at diagnosis, respectively.

Radiation-associated side effects

The most common toxicity in the cTRT group was grade 1 (n=25, 54.4%) and grade 2 (n=7, 15.2%) oesophagitis. Grade 1 pneumonitis after cTRT was observed in only one patient (table 2).

Clinical outcomes

Of the 123 patients, 30 (24.4%) were alive, while 93 (75.6%) had died at last follow-up. Median OS for the control group (0.6 (95% CI 0.4 to 0.9) years) was significantly shorter compared with the cTRT group (0.9 (95% CI 0.7 to 1.4) years, p=0.014). The rate of OS at 1 and 2 years was 23.5% (14.5% to 38.0%) and 11% (5% to 24.3%) in the control group and 46.7% (34.3% to

Table 1 Comparison of patient baseline characteristics between the control (n=74) and cTRT (n=49) groups

	Control (n=74)	cTRT (n=49)	Total (n=123)	P value
Median age (years), median (IQR)	66.1 (51.0–82.9)	68.1 (46.1–89.5)	66.2 (46.1–89.5)	0.48
Sex, n (%)				0.21
Male	43 (58.11%)	34 (69.39%)	77 (62.60%)	
Female	31 (41.89%)	15 (30.61%)	46 (37.40%)	
Smoking status, n (%)				0.68
Never	6 (8.22%)	3 (6.12%)	9 (7.38%)	
Former	45 (61.64%)	34 (69.39%)	79 (64.75%)	
Current	22 (30.14%)	12 (24.49%)	34 (27.87%)	
T stage, n (%)				0.62
T1	7 (9.46%)	5 (10.20%)	12 (9.76%)	
T2	21 (28.38%)	16 (32.65%)	37 (30.08%)	
T3	11 (14.86%)	8 (16.33%)	19 (15.45%)	
T4	28 (37.84%)	19 (38.78%)	47 (38.21%)	
Tx	7 (9.46%)	1 (2.04%)	8 (6.50%)	
N stage, n (%)				0.57
N0	1 (1.35%)	3 (6.12%)	4 (3.25%)	
N1	5 (6.76%)	4 (8.16%)	9 (7.32%)	
N2	28 (37.84%)	21 (42.86%)	49 (39.84%)	
N3	37 (50.00%)	20 (40.82%)	57 (46.34%)	
Nx	3 (4.05%)	1 (2.04%)	4 (3.25%)	
M stage, n (%)				0.08
M0	3 (4.05%)	6 (12.24%)	9 (7.32%)	
M1	71 (95.95%)	42 (85.71%)	113 (91.87%)	
Mx	0 (0.00%)	1 (2.04%)	1 (0.81%)	
Eastern Cooperative Oncology Group at diagnosis, n (%)				0.97
0	9 (13.04%)	6 (12.24%)	15 (12.71%)	
1	46 (66.67%)	31 (63.27%)	77 (65.25%)	
2	12 (17.39%)	10 (20.41%)	22 (18.64%)	
3	2 (2.90%)	2 (4.08%)	4 (3.39%)	
Chemotherapy characteristics				
Number of cycles, n (%)				0.045
4	42 (56.76%)	22 (44.90%)	64 (52.03%)	
5	11 (14.86%)	3 (6.12%)	14 (11.38%)	
6	21 (28.38%)	24 (48.98%)	45 (36.59%)	
Chemo drug, n (%)				0.87
Cisplatin	38 (51.35%)	27 (55.10%)	65 (52.85%)	
Carboplatin	31 (41.89%)	20 (40.82%)	51 (41.46%)	
Other	5 (6.75%)	2 (4.08%)	7 (5.70%)	
Response after chemotherapy, n (%)				0.89
Stable disease	14 (18.92%)	9 (18.37%)	23 (18.70%)	
Partial response	57 (77.03%)	37 (75.51%)	94 (76.42%)	
Complete response	3 (4.05%)	3 (6.12%)	6 (4.88%)	

Continued

Table 1 Continued

	Control (n=74)	cTRT (n=49)	Total (n=123)	P value
Radiation characteristics, n (%)				
Median dose		30 Gy		
Median fractionation		10 fractions		
Range of dose		30–45 Gy		
Brain metastasis at diagnosis, n (%)	16 (21.62%)	7 (14.29%)	23 (18.70%)	0.31
Liver metastasis at diagnosis, n (%)	34 (45.95%)	13 (26.53%)	47 (38.21%)	0.03*

Patient characteristics were compared between two groups, cTRT and control, using χ^2/Fisher's exact tests for categorical variables and Wilcoxon rank sum test for continuous variables.
*p<0.05; **p<0.01.
cTRT, consolidative thoracic radiotherapy.

63.5%) and 26.3 (15.7% to 44.1%) in the cTRT group (figure 2A). On UVA analysis, no statistically significant associations of OS with sex, smoking status, age, response to chemotherapy, ECOG performance score, TNM classification at diagnosis, liver metastases at diagnosis or brain metastases at diagnosis were observed (table 3). However, the receipt of cTRT treatment was significantly associated with improved OS (figure 2A; HR 0.59, 95% CI 0.39 to 0.90, p=0.015).

110 (92.4%) out of 123 patients had disease progression, of which 46 (41.8%) were in the cTRT group and 64 (58.2%) in the control group. Median PFS for the control group (0.2 (95% CI 0.2 to 0.3) years) was shorter compared with the cTRT group (0.4 (95% CI 0.4 to 0.7) years, p=0.0001) (figure 2B). The 1-year PFS rates for the control and cTRT groups were 3.7% (1% to 14.3%) and 17.5% (9.4% to 32.5%), respectively. On UVA, no association of PFS with covariates was seen (table 3), except for chemotherapy response with HR 1.61 (95% CI 1.00 to 2.58, p<0.049), and the receipt of cTRT treatment with HR 0.48 (95% CI 0.32 to 0.72, p<0.001).

On multivariable analysis, consistent with UVA, cTRT had improved OS (HR 0.53, 95% CI 0.31 to 0.90, p=0.019) and PFS (HR 0.46, 95% CI 0.31 to 0.69, p<0.001) compared with the control patients, after adjustment for potential confounders and risk factors.

Table 2 Toxicities experienced by patients who received both chemotherapy and cTRT (n=55)

	CTRT
Oesophagitis	
Grade 1	25 (54%)
Grade 2	7 (15%)
Grade 3+	0
Pneumonitis	
Grade 1	1 (2%)
Grade 2	0
Grade 3+	0

cTRT tolerability was determined using incidence and grade of oesophagitis and radiation pneumonitis as per Common Terminology Criteria for Adverse Events V.5.
cTRT, consolidative thoracic radiotherapy.

Patterns of disease failure

30 patients (24.4%) developed intrathoracic disease progression after treatment with or without associated extrathoracic progression (table 4). There were numerically fewer intrathoracic failures in the cTRT group (n=8, 16.3%) compared with the control group (n=22, 29.7%); however, this was not statistically significant (p=0.09). Patients with recurrence involving bone, non-mediastinal lymph nodes, pleura and other organ sites excluding the brain and liver were grouped as 'other sites' of failures. There were 27 patients each in the cTRT and control groups with other sites of disease progression. Isolated or combined liver progression was seen in 20 (27%) and 9 (18.4%) patients in the cTRT and control groups, respectively. Overall, 27 patients had progressive disease in the brain with or without associated extracranial progression, of which 10 patients (20.4%) were in the cTRT group and 17 patients (22.9%) in the control group. Of these, isolated brain failures were in 9 (18.4%) and 14 (18.9%) patients in the cTRT and control groups, respectively. Although the use of PCI was higher in the cTRT group (51% vs 21.6%, p<0.001), the proportion of patients with progressive brain failures was equal in both groups and may suggest that prolonging thoracic disease control by cTRT increases the time-dependent risk of developing progressive brain metastases.

DISCUSSION

In this real-world study, we report the outcomes of patients with ES-SCLC who were potential candidates for cTRT treated at our tertiary cancer centre. Our study cohort comprised patients diagnosed with ES-SCLC, treated at a single tertiary cancer centre, predominantly representing patients from urban and suburban communities. The demographic composition of our sample (age, functional status and stage) is consistent with recent demographic trends in the literature.[16] The results of

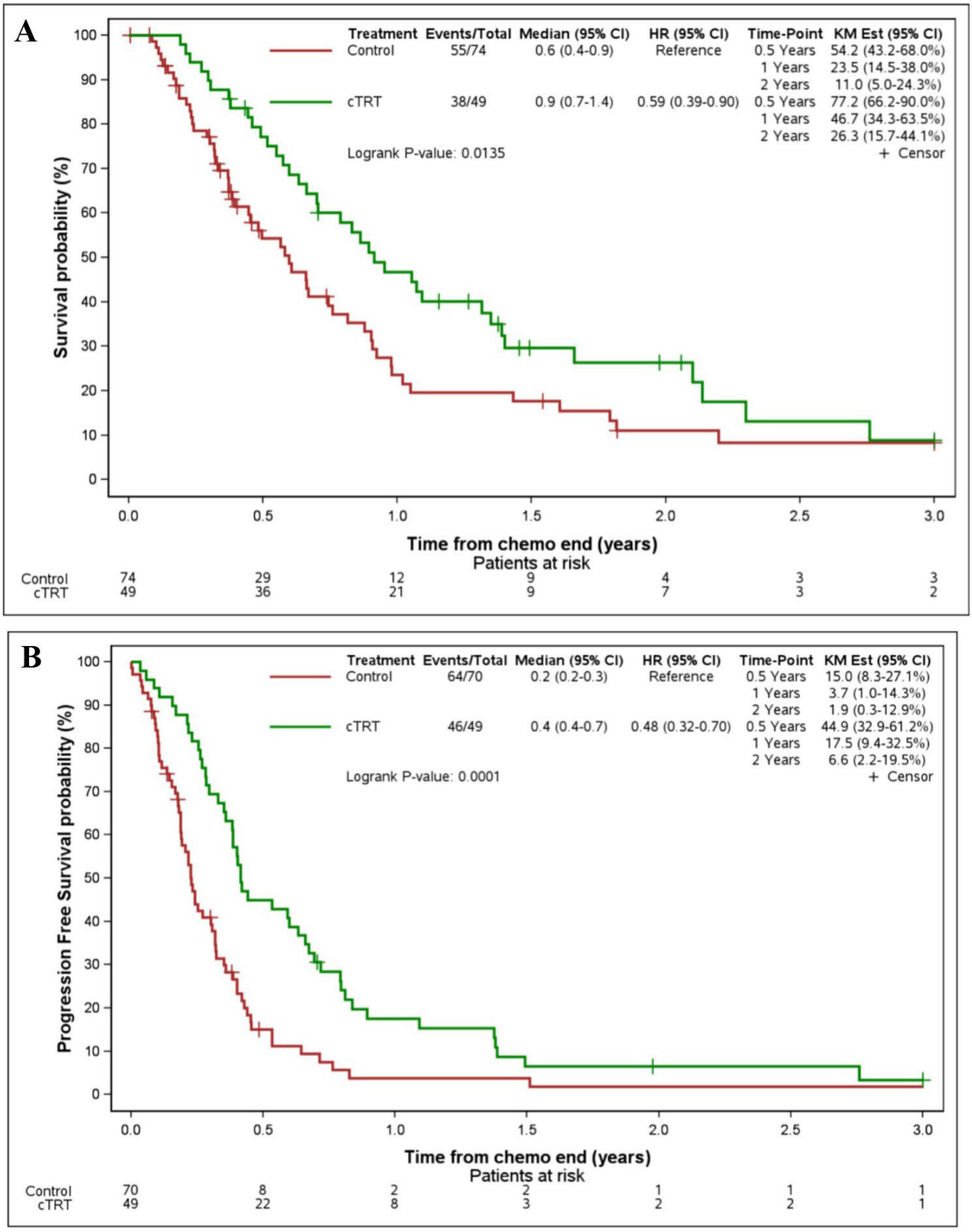

Figure 2 Comparison of Kaplan Meier (KM) survival curves between two groups: consolidative thoracic radiotherapy (cTRT) and control. A log-rank test was used for the comparisons. (A) Overall survival (OS)—the median OS for control (0.6 years) was shorter compared with cTRT+chemotherapy (0.9 years) (p=0.0135). (B) Progression-free survival (PFS)—the median PFS for control (0.2 years) was shorter compared with cTRT+chemotherapy (0.4 years) (p=0.0001).

Table 3 Univariate analysis comparing the impact of clinical characteristics on OS and PFS

	Endpoint: OS		Endpoint: PFS	
	HR (95% CI)	P value	HR (95% CI)	P value
Median age (years)	1.00 (0.98 to 1.03)	0.86	1.02 (0.99 to 1.04)	0.103
Sex				0.83
Male	Ref		Ref	
Female	1.18 (0.78 to 1.80)	0.43	0.96 (0.64 to 1.43)	
Smoking status				
Never	Ref		Ref	
Former	0.89 (0.38 to 2.06)	0.78	1.32 (0.61 to 2.88)	0.48
Current	0.83 (0.34 to 2.01)	0.67	0.90 (0.39 to 2.09)	0.81
T stage				
T1	Ref		Ref	
T2	1.65 (0.81 to 3.38)	0.17	1.40 (0.69 to 2.84)	0.35
T3	1.39 (0.63 to 3.08)	0.42	1.36 (0.64 to 2.89)	0.43
T4	1.89 (0.94 to 3.82)	0.08	1.74 (0.88 to 3.45)	0.11
Tx	2.56 (0.86 to 7.60)	0.09	2.70 (1.01 to 7.19)	0.047
N stage				
N0	Ref		Ref	
N1	1.81 (0.47 to 7.03)	0.39	2.99 (0.80 to 11.13)	0.10
N2	1.60 (0.49 to 5.20)	0.44	1.97 (0.61 to 6.36)	0.26
N3	1.71 (0.53 to 5.53)	0.37	1.79 (0.56 to 5.78)	0.33
Nx	3.51 (0.70 to 17.61)	0.13	2.43 (0.40 to 14.74)	0.33
M stage				0.73
M0	0.74 (0.32 to 1.70)	0.48	1.13 (0.57 to 2.24)	
M1	Ref		Ref	
Eastern Cooperative Oncology Group at diagnosis				0.88
0/1	Ref		Ref	
2/3	0.87 (0.51 to 1.50)	0.63	1.04 (0.65 to 1.67)	
Chemotherapy characteristics				
Number of cycles, per cycle increase	1.10 (0.89 to 1.36)	0.38	0.94 (0.77 to 1.14)	0.53
Chemo drug				
Cisplatin	Ref		Ref	
Carboplatin	0.95 (0.61 to 1.46)	0.81	1.07 (0.73 to 1.59)	0.72
Other	0.95 (0.41 to 2.20)	0.90	1.99 (0.85 to 4.65)	0.11
Response after chemotherapy				
Partial response/complete response	Ref		Ref	
Stable disease	1.00 (0.60 to 1.67)	0.99	1.61 (1.00 to 2.58)	0.049
Brain metastasis at diagnosis (yes vs no)	1.06 (0.60 to 1.86)	0.84	1.08 (0.66 to 1.77)	0.76
Liver metastasis at diagnosis (yes vs no)	1.16 (0.76 to 1.77)	0.50	1.09 (0.74 to 1.59)	0.68
Treatment: consolidative thoracic radiotherapy vs control	0.59 (0.39 to 0.90)	0.015	0.48 (0.32 to 0.70)	<0.001

Univariate survival analysis was conducted to assess the association of OS and PFS with each characteristic.
OS, overall survival; PFS, progression-free survival.

Table 4 Patterns of disease progression in patient cohorts treated with and without cTRT

Site	Control (n=74)	cTRT (n=49)	Total (n=123)
Thorax only	5 (6.7%)	2 (4.1%)	7 (5.7%)
Thorax+liver	9 (12.2%)	3 (6.1%)	12 (9.7%)
Thorax+brain	2 (2.7%)	--	2 (1.6%)
Thorax+brain+liver	--	1 (2%)	1 (0.8%)
Thorax+other sites	6 (8.1%)	2 (4.1%)	8 (6.5%)
Any thorax	*22 (30%)*	*8 (16%)*	*30 (24%)*
Brain+liver	3 (4%)	1 (2%)	4 (3.2%)
Liver only	8 (10.8%)	4 (8.2%)	12 (9.8%)
Brain only	14 (18.3%)	9 (18.4%)	23 (18.7%)
Other sites only	27 (36.5%)	27 (55.1%)	54 (43.9%)

cTRT, consolidative thoracic radiotherapy.

our study are likely generalisable to patients receiving care at tertiary cancer sites, and less so to rural communities and populations with limited access to specialised oncology care. We evaluated the utilisation of cTRT with or after first-line chemotherapy for patients who received at least four cycles and did not have progressive disease. We found that the receipt of cTRT was associated with a significant improvement in both OS (1-year OS 46.7% vs 23.5%) and PFS (1-year PFS 17.5% vs 3.7%). This was consistent on multivariate analysis confirming receipt of cTRT was associated with higher OS (HR 0.59, 95% CI 0.39 to 0.90) and PFS (HR 0.46, 95% CI 0.31 to 0.69). There was also a non-significant trend towards higher intrathoracic control (16.3% vs 29.7%, p=0.09) in patients receiving cTRT. By effectively controlling disease spread within the thoracic region, cTRT may have contributed to prolonged thoracic disease control and delayed the onset of progressive and distant metastases. At our institution, the use of cTRT increased from a previously reported 9% over 2005–2009 to 23.4% of consecutively diagnosed patients with ES-SCLC in the current study over a period of 2013–2022.[14] This increased utilisation of cTRT over time was likely attributed to the CREST trial results, which identified a significant improvement in PFS and 2-year OS for patients receiving both cTRT (30 Gy/10 fractions) and PCI with any response to chemotherapy. In another study that included cTRT, RTOG 0937 did not show OS and PFS benefit at 1 year for cTRT with extrathoracic RT to oligometastases (45 Gy/15 fractions). Notably, the RTOG 0937 differed from the CREST trial by including radiation to extrathoracic oligometastatic disease in addition to intrathoracic disease. There was excess toxicity in the trial, with 36% of patients in cTRT having grade 3+ toxicity with one death attributed to radiation-induced pneumonitis, which exceeded lung constraints. The trial was closed prematurely following a futility analysis, which indicated an improbable likelihood of achieving a survival advantage. The contrasting results between CREST and RTOG 0937 support the balancing act of optimising the therapeutic ratio of RT doses and target selection in the context of cTRT. Of note, our study did not identify grade 3+ adverse events attributable to thorax-only cTRT, likely due to the lower doses delivered to most patients (n=42, 85.7%) who received 30 Gy/10 fractions and the omission of concurrent extrathoracic radiation. Grade 2 oesophagitis (15%) was the most common side effect observed. Our study provides real-world data with practice patterns and outcomes of patients who are potential candidates for cTRT, and their outcomes based on receipt of cTRT compared with those who did not receive cTRT.

Chemotherapy remains the mainstay of treatment, and despite some evidence for cTRT the application of cTRT is heterogeneous. The use of cTRT in ES-SCLC has been investigated in three phase III randomised controlled trials (RCTs) and one meta-analysis leading to practice guidelines recommendations.[12 13 17–20] A meta-analysis showed no OS improvement (pooled HR 0.88, 95% CI 0.66 to 1.18); however, it identified a significant improvement in PFS (pooled HR 0.72, 95% CI 0.61 to 0.83) and decreased intrathoracic progression with the addition of cTRT as a sequential approach. Patients within these trials with different responses (SD, PR to CR) to first-line chemotherapy were included. There was heterogeneity among the three RCTs, including different cTRT dose, sequence and starting point of survival estimates (date of diagnosis, commencement or end of chemotherapy). These differences among these trials with respect to eligibility criteria and various cTRT dosing schedules and differences related to the role of extrathoracic radiation likely contribute to the fact that cTRT is not consistently applied. Our 1-year survival rates for the cTRT and control group of 46.7% and 23.5%, respectively, parallel those reported in the CREST study (33% and 28%, respectively), with 1-year OS favouring the cTRT group.

A key limitation of our study inherent to all real-world studies is the retrospective, non-randomised nature of patient selection which likely contributes to some of the improved OS observed. For example, there was a significantly higher number of patients with liver metastasis at baseline in the control group compared with the cTRT

group (45.9% vs 26.5%, p=0.03). While we controlled for clinical variables where possible, there are assuredly confounding variables that are not fully captured. Nonetheless, on multivariate analysis, our study showed that cTRT was associated with improved OS (HR 0.53, 95% CI 0.31 to 0.90, p=0.019) and PFS (HR 0.46, 95% CI 0.31 to 0.69, p<0.001).

Moreover, the retrospective nature of this study entails that details are gathered from chart review and interpreted in the context of our research question. As a result, there is the potential for information bias associated with interpretation based on available record keeping. For example, patient toxicities were graded retrospectively using documented details when real-time classification was not recorded in the patient's chart. Similarly, available patient records did not always fully capture the reason for why patients did not receive cTRT in the context of our non-cTRT group.

Finally, IMpower133, CASPIAN and KEYNOTE-604 have demonstrated the efficacy of immunotherapy in combination with first-line chemotherapy; however, these studies generally excluded cTRT or only a small minority of patients with cTRT were enrolled. Given our study time period, we are unable to comment on the efficacy of chemoimmunotherapy in conjunction with cTRT. Separately, a study conducted by Gross *et al* included patients receiving chemoimmunotherapy (n=26) or chemotherapy without immunotherapy (n=137) and assessed the impact of cTRT. This study reported that cTRT improved OS only on UVA analysis (p=0.02).[20] This trend persisted on multivariate analysis of OS but was not independently significant (p=0.06).[21] Gross *et al* also reported no detected difference in PFS.[21] A multi-institutional study, Longo *et al*, reported on 120 patients with ES-SCLC who received chemoimmunotherapy, of which 59 also received cTRT. Propensity score matching was performed, and PFS with cTRT was significantly longer (p=0.00013), with a trend towards improved OS (p=0.12) per Kaplan-Meier analysis of the entire probability curves.[22] Another multicentre study examined 276 patients who received chemoimmunotherapy, focusing on 197 patients after propensity score matching, of which 99 received cTRT. PFS and OS were reported to be significantly different (p=0.014 and 0.009, respectively).[23] Overall, these findings are intriguing, and additional studies are warranted to define the role of and the potential OS benefit of cTRT that we observed in patients treated at our institution over the past 10 years as we are in the chemoimmunotherapy era.[9 11 24]

CONCLUSION

We report real-world data from 2013 to 2022, demonstrating the addition of cTRT in patients with ES-SCLC without progressive disease after first-line chemotherapy is associated with improved OS and PFS, and decreased intrathoracic progression with tolerable side effects. A future study of how to optimally integrate and define the benefit of cTRT with first-line chemoimmunotherapy is warranted.

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