research article

Consolidation radiotherapy for patients with extended disease small cell lung cancer in a single tertiary institution: impact of dose and perspectives in the era of immunotherapy

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Background. Consolidation radiotherapy (cRT) in extended disease small cell lung cancer (ED-SCLC) showed improved 2-year overall survival in patients who responded to chemotherapy (ChT) in CREST trial, however results of two meta - analysis were contradictive. Recently, immunotherapy was introduced to the treatment of ED-SCLC, making the role of cRT even more unclear. The aim of our study was to access if consolidation thoracic irradiation improves survival of ED-SCLC patients treated in a routine clinical practice and to study the impact of cRT dose on survival. We also discuss the future role of cRT in the era of immunotherapy.

Patients and methods. We retrospectively reviewed 704 consecutive medical records of patients with small cell lung cancer treated at the Institute of Oncology Ljubljana from January 2010 to December 2014 with median follow up of 65 months. We analyzed median overall survival (mOS) of patients with ED-SCLC treated with ChT only and those treated with ChT and cRT. We also compared mOS of patients treated with different consolidation doses and performed univariate and multivariate analysis of prognostic factors.

Results. Out of 412 patients with ED-SCLC, ChT with cRT was delivered to 74 patients and ChT only to 113 patients. Patients with cRT had significantly longer mOS compared to patients with ChT only, 11.1 months (CI 10.1–12.0) *vs.* 7.6 months (CI 6.9–8.5, $p < 0.001$) and longer 1-year OS (44% *vs.* 23%, $p = 0.0025$), while the difference in 2-year OS was not significantly different (10% *vs.* 5%, $p = 0.19$). The cRT dose was not uniform. Higher dose with 45 Gy (in 18 fractions) resulted in better mOS compared to lower doses 30–36 Gy (in 10–12 fractions), 17.2 months *vs.* 10.3 months ($p = 0.03$) and statistically significant difference was also seen for 1-year OS (68% *vs.* 30%, $p = 0.01$) but non significant for 2-year OS (18% *vs.* 5%, $p = 0.11$).

Conclusions. Consolidation RT improved mOS and 1-year OS in ED-SCLC as compared to ChT alone. Higher dose of cRT resulted in better mOS and 1-year OS compared to lower dose. Consolidation RT, higher number of ChT cycles and prophylactic cranial irradiation (PCI) were independent prognostic factors for better survival in our analysis. For patients who received cRT, only higher doses and PCI had impact on survival regardless of number of ChT cycles received. Role of cRT in the era of immunotherapy is unknown and should be exploited in further trials.

Key words: small cell lung cancer; ED-SCLC; radiotherapy; consolidation radiotherapy; immunotherapy

Introduction

Small cell lung cancer (SCLC) represents only small proportion of lung cancer but is an aggressive disease and unfortunately diagnosed already in advanced stage in majority of patients.[1] In Slovenia 15.3% of lung cancer patients were diagnosed with SCLC in 2014, and majority had metastatic dis-

ease.[2] In recent years, percentage of patients with metastatic disease has slightly increased, but this might only be due to better staging with incorporation of PET/CT and brain MRI.[3,4]

SCLC is highly chemo-sensitive disease and standard treatment for metastatic patients is platinum based chemotherapy (ChT), usually combined with etoposide or irinotecan.[5,6] Almost 75% of the patients have persisting intra-thoracic disease after treatment with ChT and addition of chest radiotherapy (RT) aimed to improve progression free survival (PFS) and overall survival (OS) in those patients.[7] Prospective randomized CREST study suggested survival benefit of added thoracic RT in addition to PCI for ED-SCLC patients who respond to ChT; however, OS at 1-year, which was the primary endpoint of the study, was not significantly improved.[8] Prospective RTOG 0937 study also failed to show 1-year survival benefit, though disease progression was delayed.[9] On the other hand, some retrospective studies showed benefit of consolidation RT (cRT).[10-13] None of the prospective and only rare retrospective studies specifically researched the effect of radiation dose on survival.

In addition, selective patients might benefit from prophylactic cranial irradiation (PCI), which showed increase in overall survival if added to ED-SCLC after ChT.[14] In spite of that, the median overall survival (mOS) of metastatic disease remains poor, ranging from 8 to13 months, with only 5% of patients being alive at 2 years.[15] Recently, immunotherapy with atezolizumab or durvalumab added to ChT without chest irradiation has shown increased mOS in first line treatment of patients with metastatic SCLC, therefore in the future the role of radiotherapy would need to be reconsidered.[16,17]

The aim of our study was to access if cRT improves survival of ED-SCLC patients treated in a routine clinical practice of tertiary single centre and to study the impact of cRT dose on survival. We also discuss whether the cRT still has the role in the treatment of ED SCLC in the era of immunotherapy.

Patients and methods

We retrospectively reviewed medical records of consecutive patients with SCLC treated at the Institute of Oncology Ljubljana during the five year period, from January 2010 to December 2014. Median follow up was 65 months.

Not all metastatic SCLC patients were referred to our center for treatment; however, during the period studied, we were the only radiotherapy center in the country and all patients that needed irradiation, based on multidisciplinary tumor board decision, were treated at our institution. Only patients who had at least stable disease or regression of disease after chemotherapy were eligible for thoracic consolidation radiotherapy. The decision about the dose was at the discretion of radiation oncologist and based on the volume of the tumor and performance status of the patient since during the time period studied there was no uniform dose suggested in any of the guidelines.

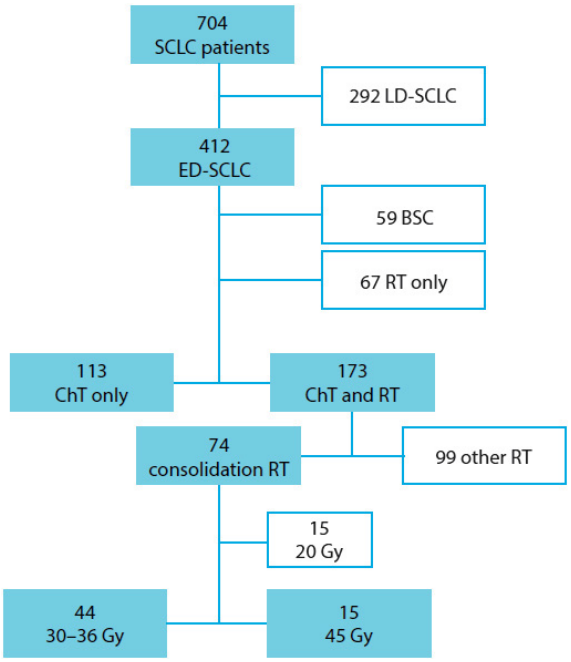

FIGURE 1. Diagram of patients' selection process.

Diagram in Figure 1 outlines the selection process. During 5 year period 704 consecutive patients with SCLC were treated at the Institute of oncology Ljubljana, 412 with extended disease and 292 with locally advanced disease. Among all ED-SCLC patients, 59 (14.3%) were treated with BSC, 67 (16.2%) patients with RT only, 113 (27.4%) with ChT only and 173 (41.9%) with combined ChT and RT. RT was either consolidation RT (cRT), delivered to 74 patients or any other type of RT which included urgent RT, partly concurrent ChT or RT that was prematurely closed due to any reason (99 patents).

The following parameters were recorded: demographic and clinical characteristics, date of diagnosis, TNM stage, treatment characteristics, including chemotherapy and radiation therapy details, metastatic locations and date of death or last follow up.

Chemotherapy

Of Majority (47.5%) of patients received all 6 planned cycles of chemotherapy, 66 patients (35.3%) received less than 4 cycles of ChT. Etoposide with platinum was the most frequent combination (83.8%), the rest received anthracycline based ChT. In the group with cRT were less patients who received 4 ChT cycles or less.

Radiotherapy

Radiotherapy with linear accelerators (photon beam 6-10MV), based on 3D CT-based conformal radiation therapy planning, started after ChT. There was no difference in frequency of patients who started before (29 patients) and after 4 weeks (25 patients) of ChT completion. Prophylactic cranial irradiation was delivered with two opposed lateral fields with the dose of 25 Gy in 10 fractions using 2D planning and 6MV photon beam energy.

Statistical analysis

The primary endpoints in this analysis were mOS, 1-year and 2-year OS of ED-SCLC patients treated with ChT only versus patients treated with ChT and cRT and those receiving higher *vs.* lower dose of cRT. Median OS was calculated from the time of diagnosis to the time of death due to any cause or last follow up visit. Kaplan-Meier (KM) method and log-rank test were used for comparison of survival curves between different groups. Cox proportional hazards algorithm was used for univariate and multivariate analysis. Association between subgroups and clinico-pathological characteristics of patients were tested using chi-square method. All p values reported were based on 2 side hypothesis. The statistical analysis was computed using SPSS v.20 statistical package.

Ethical consideration

This survey was approved by Institutional Ethics Committee and Institutional Review Board in December 2017.

Results

We performed two analysis. In our first analysis we included 187 patients, 113 patients treated with Cht only were compared to 74 patients treated with ChT and cRT. Different fractionation schemes were

TABLE 1. Patients' characteristics: chemotherapy only *vs.* chemotherapy with consolidation radiotherapy

		ChT only	ChT with cRT	p
		n (%)	n (%)	
Gender	187 (100)	113 (60.4)	74 (39.6)	
Male	126 (67.4)	81 (71.1)	45 (60.1)	0.12
Female	61 (32.6)	32 (28.9)	29 (39.9)	
Age				
median (range)	63 (42-80)	61 (42-80)	63 (47-80)	0.24
< 65	122 (65.2)	70 (61.9)	52 (70.3)	
> 65	65 (34.8)	43 (38.1)	22 (29.7)	
Number of ChT cycles*				
< 4	66 (35.3)	51 (47.2)	15 (20)	**<0.001**
> 4	113 (60.4)	57 (52.8)	56 (80)	
T stage				0.23
T1–2	32 (17.1)	20(17.7)	12 (16.2)	
T3-4	122 (65.2)	69 (61)	53 (71.6)	
Tx	33 (17.7)	24 (21.3)	9 (12.2)	
N stage				0.56
N0–2	71 (38)	40 (35.4)	31(41.9)	
N3	91(48.7)	56 (49.6)	35 (47.3)	
Nx	25 (13.3)	17 (15)	8 (10.8)	
Metastases location**				
Brain	44 (23.5)	28 (24.8)	16 (21.6)	0.61
Liver	86 (46)	57 (50.4)	29 (39.2)	0.13
Bone	42 (22.5)	28 (24.8)	14 (18.9)	0.34
Adrenal gland	38 (20.3)	23 (20.4)	15 (20.3)	0.98
Other	92 (49.2)	62 (54.9)	30 (40.5)	0.06
Number of metastatic locations				
1	105 (56.1)	55 (48.7)	50 (67.6)	**0.01**
> 2	82 (43.9)	58 (51.3)	24 (23.4)	
PCI				
Yes	41 (21.9)	20 (17.6)	21 (28.4)	0.08
no	146 (78.1)	93 (82.4)	53 (71.6)	

* for 8 patients we were not able to retrieve the exact number of cycles from medical records, percentage of patient is calculated only for those with known number of cycles (179);

** some patients had more than 1 metastatic location, percentages are calculated as part of all patients in a group;

ChT = chemotherapy; cRT = consolidation radiotherapy; PCI = prophylactic cranial irradiation

TABLE 2. Patients' characteristics: higher *vs.* lower dose of radiotherapy

	All	45 Gy	30-36 Gy	p
	n (%)	n (%)	n (%)	
Gender	59	15	44	
Male	35 (60)	6 (40)	29 (65.9)	0.078
Female	24 (40)	9 (60)	15 (34.1)	
Age				
median	62 (42–76)	60 (54–73)	62 (42–76)	0.12
< 65	42 (71.2)	13 (68.7)	29 (65.9)	
> 65	17 (28.8)	2 (13.3)	15 (34.1)	
Number of ChT cycles				
< 4	12 (20.3)	2 (13.3)	10 (22.7)	0.37
> 4	44 (74.6)	13 (68.7)	31 (70.5)	
unknown	3 (5.1)	0 (0)	3 (6.8)	
PS before RT				0.66
0-1	22 (37.3)	5 (33.3)	17 (38.6)	
2–3	7 (11.8))	1 (6.67)	6 (13.6)	
unknown	30 (50.9)	9 (0.6)	21 (47.8)	
T stage				0.15
T1–2	8 (13.6)	4 (26.7)	4 (9.1)	
T3–4	42 (71.2)	8 (53.3)	34 (77.3)	
Tx	9 (15.3)	3 (20)	6 (13.6)	
N stage				0.69
N0–2	24 (40.7)	7 (46.7)	17 (38.6)	
N3	29 (49.2)	6 (40)	23 (52.3)	
Nx	6 (10.1)	2 (13.3)	4 (9.1)	
Metastases location*				
Brain	14 (23.7)	5 (33.3)	9 (20.5)	0.31
Liver	27 (45.7)	6 (40)	21 (47.7)	0.60
Bone	13 (22)	3 (30)	10 (22.7)	0.82
Adrenal gland	15 (25.4)	3 (30)	12 (27.3)	0.57
Other	21 (35.6)	3 (30)	19 (43.2)	0.10
Number of metastatic locations				
1	34 (57.6)	10 (66.7)	24 (54.5)	0.41
> 2	25 (42.4)	5 (33.3)	20 (45.4)	
Timing of RT**				0.15
< 4 weeks after ChT	17 (53.1)	6 (75)	11 (45.9)	
> 4 weeks after ChT	15 (46.9)	2 (25)	13 (54.1)	
PCI				
Yes	17 (28.8)	5 (33.3)	12 (27.3)	0.65

* some patients had more than one metastatic site;

** for 31 missing patients no reliable data of the completion chemotherapy date could be retrieved from the medical records;

Ch =- chemotherapy; Gy = Gray; N = lymph nodes; PS = performance status; RT = radiotherapy; T = tumour

used for cRT. The doses in cRT were not uniform, therefore we divided them into 3 groups: below 30 Gy, 30–36 Gy and 45 Gy. Only 59 patients with doses above 30 Gy were included in our second analysis of dose comparison.

Patient characteristics

Baseline characteristics of 187 patients, divided to those with ChT only and those who also received cRT are presented in Table 1. The two groups were balanced regarding gender, age, T and N stage and metastatic locations. However, lower number of patients received 4 or less cycles of ChT and had 2 or more metastases present at diagnosis in ChT plus cRT group.

Table 2 present baseline characteristics of 59 patients who received > 30 Gy cRT, comparing those with higher dose (45 Gy) cRT and lower dose (30–36 Gy). In summary, median age was 63 years, more than half were men. Majority of patients were younger than 65 years. Unfortunately, reliable PS could not be retrieved from medical records for half of the patients and more than 10% of patients had PS 2-3 before cRT. Non-significantly more patients had larger tumors (T3-4) and more extended lymph node disease (N3) in the group treated with lower dose RT. For more than 10% of patients with central tumors, the size of tumor (T) or nodal status could not be determined. Fifty-eight percent of patients had one metastatic site. The most frequent site of metastases were liver. Less than third of patients had PCI.

Survival data

Median OS of patients who had either BSC or RT only was poor, 1.86 and 2.42 months, respectively. Patients who had any form of additional chest irradiation (173 patients) had significantly better mOS than 113 patients with ChT only (9.9m *vs.* 7.6m, p = 0.002).

Consolidation RT was delivered to 74 patients. Those patients had significantly longer mOS compared to 113 patients with ChT only as presented in Figure 2, 11.1 months (CI 10.1–12.0) *vs.* 7.6 months (CI 6.9–8.5), p < 0.001. They also had significantly longer 1-year OS (44% *vs.* 23%, p = 0.0025), but non significantly longer 2-year OS (10% *vs.* 5%, p = 0.19).

Univariate survival analysis (UVA) for patients with or without cRT included the following variables: cRT, gender, age, number of ChT cycles, T and N stage, metastatic location, number of meta-

static locations and PCI. Presence of cRT, female gender, number of ChT cycles (4 or less and more than 4) and PCI were significant in univariate analysis and were tested in multivariate analysis (MVA) (Table 3). Except for gender, they were all independent predictors of better survival.

In the group of 59 patients irradiated with cRT ≥ 30 Gy patients irradiated with 45 Gy had better mOS compared to patients irradiated with doses 30–36 Gy, 17.2 months *vs.* 10.3 months, p = 0.03. (Figure 3) Patients with higher dose of consolidation RT had significantly longer 1-year OS (68%) than those with lower dose (30%), p = 0.01, but non-significantly longer 2-year OS (18% *vs.* 5%, p = 0.11).

In the group of patients with cRT, we made another analysis. We included gender, age categories, PS before RT, RT dose, T and N stage, metastatic locations, number of ChT cycles, number of metastatic lesions, PCI and timing of RT in UVA. Statistically significant predictors of longer mOS were PCI irradiation and higher RT dose. Both were analyzed in MVA (Table 4) and remained independent predictors of improved survival. (PCI HR = 0.51, 95% CI 0.27–0.96; higher RT dose HR = 0.47, 95% CI 0.25–0.87).

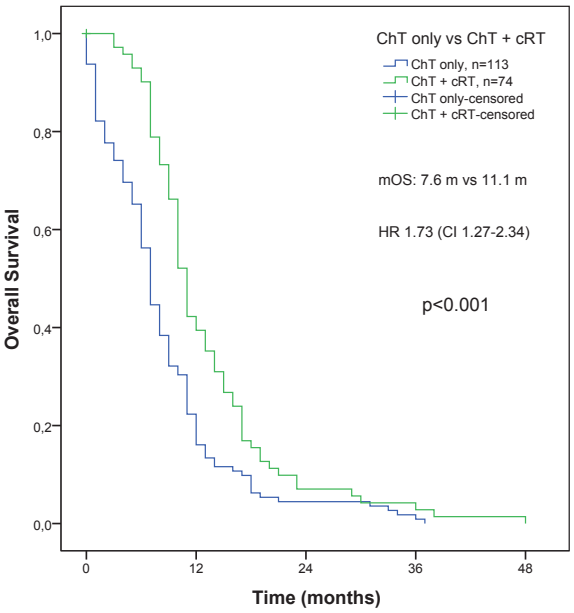

FIGURE 2. Overall survival of patients treated with chemotherapy (Cht only) *vs.* chemotherapy and consolidation radiotherapy (ChT + cRT).

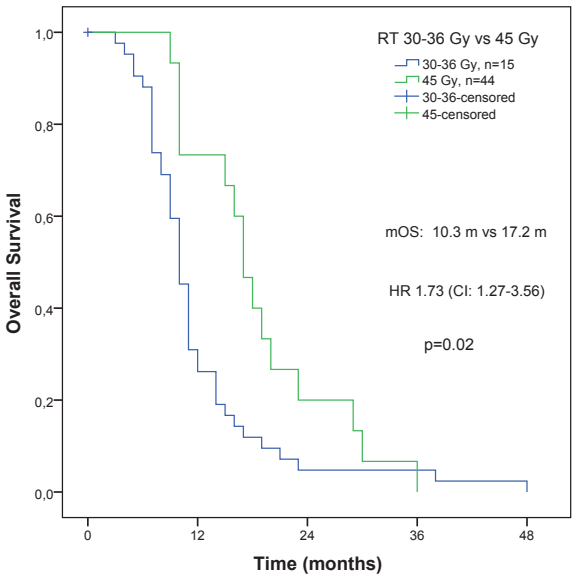

FIGURE 3. Overall survival of patients treated with higher (45 Gy) *vs.* lower (30-36 Gy) dose of irradiation.

Discussion

Thoracic irradiation has never been considered such an important part of ED-SCLC treatment as chemotherapy. Since the pivotal study of Jeremic *et al.* two decades ago, who were the first to show importance of RT in ED SCLC, only lately introduction of modern RT techniques with less toxicity rose interest again for the use of RT.[18]

Survival of patients with chemotherapy only and those who also had consolidation radiotherapy

Our analysis showed that cRT significantly improved mOS compared to patients who had ChT only, 11.1 months *vs.* 7.6 months. Those patients also had significantly longer 1-year OS (44% *vs.* 23%) and non-significantly longer 2-year OS (10% *vs.* 5%). Apart from cRT, independent predictors of survival were also PCI and higher number of ChT cycles delivered. Unfortunately, the response to ChT could not be included to our analysis, as due to retrospective nature of this study the response to ChT was not uniformly evaluated.

How results of our study compares to others is presented in Table 5. In a retrospective study of 119 patients by Zhu *et al.*, survival results were much better than in our analysis, with mOS of 17 months for patients in ChT plus cRT group and 9.3 months for those with ChT only, and 2-year OS of 35% and 17%, respectively. They delivered higher cRT dose (range 40–60 Gy) and had comparable mOS (17.2 months) as our group of patients irradiated with 45

TABLE 3. Univariate and multivariate analysis of overall survival for patients with cRT vs no cRT (n = 187)

	p	Univariate analysis HR (95% CI)	p	Multivariate analysis HR (95% CI)
cRT	**< 0.001**	**1.73 (1.27–2.34)**	**0.01**	**1.52 (1.10–2.09)**
no				
yes				
Gender	**0.042**	**1.17 (1.00–1.37)**	0.68	1.03 (0.87–1.21)
Male				
Female				
Age	0.25	1.19 (0.88–1.62)		
> 65				
< 65				
Number of cycles received	**< 0.001**	**3.23 (2.33–4.47)**	**< 0.001**	**3.11 (2.22–4.35)**
< 4				
> 4				
T stage	0.98	1.00 (0.67–1.50)		
T1, 2				
T3, 4				
N stage	0.16	1.08 (0.96–1.22)		
N0-2				
N3				
Metastases location				
Brain no/yes	0.61	0.91 (0.64–1.29)		
Liver no/yes	0.40	1.13 (0.84–1.52)		
Bone no/yes	0.75	0.94 (0.67-1.33)		
Adrenal gland no/yes	0.62	1.09 (0.76–1.57)		
Other no/yes	0.18	1.21 (0.90–1.63)		
Number of metastatic locations	0.68	1.06 (0.79–1.42)		
1				
> 2				
PCI	**< 0.001**	**0.49 (CI 0.32–0.76)**	**0.015**	**1.59 (1.09–2.32)**
No				
Yes				

cRT = consolidation radiotherapy; N = lymph nodes; PCI = prophylactic cranial irradiation; T = tumour

Gy.[10] Study by Yee *et al.* included only 33 patients, all with PCI and cRT (40 Gy), but their reported mOS of 8.3 months is lower than ours.[11] Another small retrospective study of 19 patients with cRT 40 Gy in 15 fraction reported mOS 14 months with 1-year and 2-year OS 58% and 14%.[12] Difference in the results of these studies show that survival benefit could not be attributed to RT only, but also to the increased chances of those patients who remained in a better shape and fitter at the time of disease progression to receive subsequent lines of chemotherapy. Data from SEER analysis on almost 7000 patients also provide evidence that radiotherapy for thoracic lesion and any metastatic sites could significantly improve the OS, except for brain metastasis.[13]

Three prospective randomized trials researched impact of RT on survival in ED SCLC.[8,9,18] Trial by Jeremic *et al.* differs in many ways from more recently reported studies. They used accelerated hyperfractionation (54 Gy in 36 fractions) with concomitant ChT after 3 cycles of induction ChT and additional 2 cycles after RT in one group or after 5 cycles of ChT in another, both groups also eligible for PCI. They studied combined modality treatment rather than cRT. The reported mOS was excellent for those who received RT early (17 months) as compared to those who received late RT (6–8 months).[18] Another concern regarding hyperfractionated RT is that is delivered twice daily (BID) and is technically challenging for patients with bilateral mediastinal lesions, which represented the majority in our population. Further, patients selected for combined modality treatment, which incorporates BID RT must have excellent performance status and baseline pulmonary function. In our study more than 10% of patients had PS 2-3 before cRT and unfortunately in more than half of patients PS could not be reliably retrieved from medical records.

Phase III EORTC study (CREST) included patents with PS 0–2 without brain and pleural metastases. Responders after 4–6 cycles of ChT and residual disease in the thorax were treated with irradiation of 30 Gy in 10 fractions.[8] Contrary to our results, no benefit was shown for added RT after ChT regarding mOS, which reported to be 8 months in both groups and for 1-year OS (33% for ChT with cRT *vs.* 28% for ChT group only). However, they reported significant difference in 2-year OS 13% *vs.* 3% (p = 0.004). It should, however, be noted that mOS was calculated from the randomization while mOS from diagnosis (as calculated in our analysis) was 12 months.

More aggressive thoracic irradiation was given in RTOG 0937 trial with 45 Gy in 15 fractions.[9] Reported median OS (15.8 months) was better than anticipated and much better than in CREST and our study. Unlike all other studies, they reported better mOS for ChT only group (15.8 months) than for ChT plus RT group (13.8 months), though the difference was not statistically significant. 1-year OS was similar, surprisingly higher for ChT only than for ChT plus cRT group (60.1% *vs.* 50.8%).

Two meta-analyses were published. The first, published by Palma *et al.* in 2015 included 2 studies with 604 patients, while the second published in 2019 by Rathod *et al.* added also 86 patients from prematurely closed RTOG 0937 data.[19,20] First meta-analysis found increased OS (p = 0.01), while the second failed to show improvement in overall survival by adding cRT to ChT, (p = 0.36).

Effect of consolidation radiotherapy dose on survival

We found that patients who had been irradiated with higher dose (45 Gy in 18 fractions) had better mOS compared to those who received lower doses 30–36 Gy (in 10–12 fractions), 17.2 months *vs.* 10.3 months. Patients with higher dose of cRT had better 1-year OS (68%) than those with lower dose (30%) and also better 2-year OS (18% *vs.* 5%).

Not many studies looked into dose difference for cRT. In retrospective study including 306 patients of whom 170 received cRT, those with higher RT dose (BED > 50 Gy) had longer 2y-OS, 32.3% *vs.* 17% (p < 0.001), respectively.[21] In recently published retrospective analysis of National Cancer Database that included 3280 patients they also reported that patients treated with the dose at least 45 Gy had better survival; 1-year OS was 58.1% and 2-year OS was 25.2% compared to 43.8% and 15.1% for lower dose.[22] Our results for 1-year OS compare favorable, but 2-year OS data are lower, suggesting our subsequent treatments were not as effective.

In CREST study, cRT dose used was 30 Gy in 10 fractions. The relative high intrathoracic failure rate of 42% indicated that this dose might be insufficient to eliminate all the residual disease. In additional analysis from CREST study, for patients with complete intrathoracic response no benefit of TRT was observed. They concluded that TRT should be offered to patients with a good or partial response after chemotherapy, but not to those without residual disease in the thorax. It appears that the greater the volume of the residual disease in the thorax is, the higher dose is needed to eliminate the tumor.

TABLE 4. Univariate and multivariate analysis of overall survival for higher *vs.* lower dose of consolidation radiotherapy

	p	Univariate analysis	p	Multivariate analysis
		HR (95% CI)		HR (95% CI)
Dose	**0.023**	**0.49 (0.27–0.90)**	**0.018**	**0.47 (0.25–0.87)**
45 Gy				
30-36 Gy				
Gender	0.17	1.4 (0.86–2.27)		
Male				
Female				
Age	0.38	1.25 (0.75–2.09)		
> 65				
< 65				
PS before RT	0.089	1.94 (0.90–4.18)		
2–3				
0–1				
Number of ChT cycles	0.065	1.78 (0.96–3.31)		
< 4				
> 4				
T stage	0.34	0.72 (0.37–1.40)		
T1–2				
T3–4				
N stage	0.28	1.32 (0.79–2.20)		
N0–2				
N3				
Metastases location				
Brain da/ne	0.52	1.2 (0.68–2.11)		
Liver da/ne	0.39	1.22 (0.76–1.92)		
Bone da/ne	0.46	1.24 (0.70–2.21)		
Adrenal gland da/ne	0.98	0.99 (0.59–1.67)		
Other	0.84	0.95 (0.58–1.56)		
Number of metastatic locations	0.43	0.82 (0.51–1.33)		
1				
> 2				
Timing of RT	0.71	1.13 (0.59–2.16)		
< 4 weeks after ChT				
> 4 weeks after ChT				
PCI	**0.04**	**0.56 (CI 0.32–0.97)**	**0.037**	**0.51 (0.27–0.95)**
Yes				
No				

ChT = chemotherapy; cRT = consolidation radiotherapy; N = lymph nodes; PS = performance status; RT = radiatiotherapy; T = tumour

TABLE 5. Trials of consolidation radiotherapy (cRT) in extended disease small cell lung cancer (ED-SCLC)

Author/Trial, reference	Publication year	Type of study	Patients -years enrolled	Number of patients	Patient selection	Thoracic irradiation dose scheme	mOS	1-year OS	2-year OS
Jeremic[18]	1999	P	1988–1993	109	ED-SCLC with CR at metastatic sites and at least PR in thorax	54 Gy in 36 fractions, BID	17 m *vs.* 11 m* P = 0.041	65% *vs.* 46% P ≤ 0.05	38% *vs.* 28% P ≤ 0.05
Slotman (CREST)[8]	2015	P	2009–2012	495	ED-SCLC with any response to ChT	30 Gy in 10 fractions	8 m *vs.* 8 m	33% *vs.* 28% P = 0.066	13% *vs.* 3% P = 0.004
Gore (RTOG 0937)[9]	2017	P	2010–2016	97	ED-SCLC (1-4 extracranial m., any response to ChT	40 Gy in 15 fractions	15.8 m *vs.* 13.8 m P = 0.21	50.8% *vs.* 60.1% P = 0.21	NR
Zhu[10]	2011	R	2003–2006	119	ED-SCLC	40–60 Gy	17 m *vs.* 9.3 m P = 0.014	NR	35% *vs.* 17%
Giuliani[12]	2011	R	2005–2009	19	ED-SCLC with minimal metastatic disease	36–45 Gy	14 m	58%	14%
Yee[11]	2012	R	2008–2009	32	ED-SCLC	40 Gy in 15 fractions	8.3 m	NR	NR
Zhan[13] (SEER database)	2018	R	2010–2012	6812	ED-SCLC from SEER database	Different, not reported	9 m *vs.* 7 m; P < 0.001 8 m *vs.* 6 m for polymetastases P < 0.05	NR	NR
Stanic	2020	R	2010–2014	187	ED-SCLC	30–45 Gy	11.1 m *vs.* 7.6 m P < 0.001	44% *vs.* 23% P = 0.0025	10% *vs.* 5% P = 0.19

* group 1 CR/PR and RT *vs.* group 2 CR/PR, no RT;

BID = twice daily; ChT = chemotherapy; CR = complete response; ED-SCLC = extended disease small cell lung cancer; m = months; mOS = median overall survival; NR-not reported; OS = overall survival; P = prospective; PR = partial response; R = retrospective

However, dose restrictions to the organs at risk and consequent toxicity limit the actual received dose.

Number of metastases was not predictive factor for survival in our analysis. Contrary to that, in recent retrospective publications it was shown that tumor burden of metastatic disease should be taken into account when treating ED SCLC patients, since those with ≥2 metastases had significantly worse outcome than those with only one metastasis.[23,24]

No difference of timing was found in our survival analysis if RT started before or after 4 weeks after ChT completion. In RTOG 0937 trial and one retrospective Chinese study also no difference was found in survival for patients who received RT early or late.[9,25] On the contrary, meta-analysis for limited SCLC, showed that earlier or shorter RT brings 7.7% advantage in 5-year survival.[26]

In our study PCI was independent predictor of better survival, although only 21.9% of patients received one. Our previous publication, focused on impact of PCI on survival in patients with LD-SCLC, also showed that only low number of patients (6%) actually received PCI in routine clinical setting, nevertheless OS was improved with PCI.[27] As our analysis is retrospective, this reflects real clinical situation. However, the reason why such a low number of patients actually received PCI is unclear. PCI as independent predictor of survival was reported also in retrospective study by Xu *et al*.[21] PCI in ED-SCLC was studied in EORTC conducted prospective study that showed reduced incidence of symptomatic brain metastases and improved 1-year OS (27% *vs.* 13.3%, HR 0.68, p = 0.003). That study, however, was highly criticized due to the insufficient imaging prior to PCI.[9] Japanese prospective study evaluated 224 patients with ED-SCLC who performed MRI prior to randomization to PCI or observation with MRI.[28] The study was terminated prematurely due to lower rate of brain metastases in PCI arm (40%) *vs.* MRI observation only (64%), but they found no significant difference in 1-year OS. None of our patients had MRI prior to PCI and only one third had CT evaluation, indicating that imaging in routine

clinical practice should improve. In CREST study PCI dose was not uniform (20–30 Gy in 5–15 fractions) with unusual hypofractionated dose (20 Gy in 5 fraction) used in majority of patients (62%).[8] It was delivered concurrently with thoracic irradiation in 88% of patients, while other studies used sequential approach and uniform dose of 25 Gy in 10 fractions.[9,18] Difference in pre-PCI imaging and dose delivered as well as timing of PCI show diversified approach on this not fully researched area.[29]

Consolidation radiotherapy and immunotherapy

Immunotherapy (IT) has been successfully incorporated into the treatment of metastatic non-small cell lung cancer (NSCLC) either as combination of ChT and IT or as mono-IT and lately also in stage III as consolidation treatment after concomitant chemoradiotherapy.[30-39]

Recently, two randomized studies confirmed efficacy of IT also for the treatment in ED-SCLC. IMpower 133 study was the first to show improved OS in patients treated with atezolizumab combined with ChT (12.3 months) as compared to ChT plus placebo (10.3 months). 1-year OS rate was 51.7% in the atezolizumab group and 38.2% in the placebo group.[16] Consolidation RT was not permitted, while patients could have PCI. The same criteria about cRT and PCI were also applied in CASPIAN study with durvalumab.[17] Again, IT combination showed increased results, mOS in ChT-IT arm was 13 months and 10.3 months in ChT only arm and 1-year OS was 54% *vs.* 40%, respectively. Though PCI was allowed in the non IT group, only 8% of patients received it. If the inclusion of immunotherapy would prove to reduce the incidence of brain metastases in ES-SCLC considerably in future trials as suggested from present studies, then PCI and consequently neurotoxic sequels could be omitted in the future. The decision about skipping cRT might be more challenging. Survival data from current studies has not shown superior survival in first line treatment with ChT-IT in ED-SCLC compared to studies with ChT and cRT. Could cRT be combined with IT during the consolidation phase? First reported data indicate that the combination is tolerable, however trials are still ongoing and safety as well as survival results are expected in the future.[40] As previously reported, the use of thoracic RT may enhance the effect of IT by influencing the immune system and its interactions with cancer cells and tumors, recruiting anti-tumor immune cells, increasing the exposure of tumor antigens, and improving cross-presentation of these antigens to the adaptive immune system.[41-43]

Beside retrospective nature of our analysis we should acknowledge several other limitations of our research. The irradiation dose was not specified by the protocol or any other department regulation and the decision was under the discretion of treating physician. Larger tumors (T3-4, N3) were more frequently irradiated with lower dose, but this does not necessarily mean that larger tumors would not be feasible to the treatment with larger doses. Unfortunately, we were not able to retrieve reliable information about PS before RT in half of patients, reflecting real clinical practice. This would be valuable information as treatment decision in clinical practice is greatly influenced by PS and consequently might influence survival data. Due to the fact that not all patients were treated with ChT in our institution, PS before ChT could not be included in UVA and MVA. Also, the response to initial Cht as one of the main prognostic factors of cRT efficacy according to the published data, is missing, since not all the patients were treated at our institution. However, all the patients were discussed at the MTB before the treatment which at least partially reduces this shortcoming.

Conclusions

Our analysis has shown that cRT improved mOS as compared to ChT alone of the ED-SCLC patients treated at our institution. Consolidation RT, higher number of ChT cycles and profilactic cranial irradiation (PCI) were independent prognostic factors for better survival. For patients who received cRT, only higher doses and PCI had impact on survival regardless of number of ChT cycles received. Whether cRT and PCI will still be players in the era of immunotherapy is unknown and will be shown in further trials.

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