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Which patients with ES-SCLC are most likely to benefit from more aggressive radiotherapy: A secondary analysis of the Phase III CREST trial

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Highlights

- Additional analysis of patients in CREST trial on Thoracic radiotherapy in ES-SCLC
- OS and PFS were significantly better in patients with 2 or fewer metastases
- OS was significantly worse if liver and/or bone metastases were present
- Future studies on (extra)thoracic radiotherapy in ES-SCLC should focus on patients with 2 or fewer metastases.

Abstract

Introduction: In ES-SCLC patients with residual intrathoracic disease after first-line chemotherapy, the addition of thoracic radiotherapy reduces the risk of intrathoracic recurrence, and improves 2-year survival. To identify patient subgroups for future trials investigating higher dose (extra)thoracic radiotherapy, we investigated the prognostic importance of number and sites of metastases in patients included in the CREST trial.

Materials/Methods: Additional data on sites and numbers of metastases were collected from individual records of 260 patients from the top 9 recruiting centers in the randomized CREST trial (53% of 495 study patients), which compared thoracic radiotherapy (TRT) to no TRT in ES-SCLC patients after any response to chemotherapy. All patients received prophylactic cranial irradiation.

Results: The clinical characteristics and outcomes of the 260 patients analyzed here did not differ significantly from that of the other 235 patients included in the CREST trial, except that fewer patients had a WHO=0 performance status (24% vs 45%), and a higher proportion had WHO=2 (15% vs 5%; p<0.0001). No distant metastases were recorded in 5%, 39% had metastases confined to one organ, 34% to two, and 22% to three or more organ sites. Metastases were present in the liver (47%), bone (40%), lung (28%), extrathoracic (non-supraclavicular) lymph nodes (19%), supraclavicular nodes (18%), adrenals (17%) and other sites (12%). The OS (p=0.02) and PFS (p=0.04) were significantly better in patients with 2 or fewer metastases, with OS significantly worse if liver (p=0.03) and/or bone metastases (p=0.04) were present.

Discussion: This analysis of patients recruited from the top 9 accruing centers in the CREST trial suggests that future studies evaluating more intensive thoracic and extra-thoracic radiotherapy in ES-SCLC should focus on patients with fewer than 3 distant metastases.

Key-words: Thoracic radiotherapy, extensive stage, small cell lung cancer, metastases

Introduction

Most patients with extensive stage small cell lung cancer (ES-SCLC) have persistent intrathoracic tumor after completing chemotherapy, and will experience intrathoracic failure as the first site of progression [1]. In the CREST trial, we demonstrated that a relatively low dose of thoracic radiotherapy (TRT) was able to reduce the

risk of intrathoracic progression from nearly 80 to 44% [2]. Furthermore, thoracic radiotherapy was associated with a non-significant benefit in overall survival at 1 year (33 vs. 27 %; p=0.066). The difference in overall survival at 2 years was statistically significant (13% vs 3%; p=0.004), although the study was not powered to detect a survival difference at this landmark. A stratification factor in the CREST trial was presence or absence of intrathoracic disease after chemotherapy, and a subsequent analysis demonstrated a statistically significant overall survival benefit in patients with residual intrathoracic disease after chemotherapy [3,4].

As the risk of intrathoracic disease progression after TRT was 44%, and as side-effects of TRT were minimal in the CREST trial, a higher TRT dose merits consideration. The predominant sites of relapse in patients receiving both prophylactic cranial irradiation (PCI) and TRT within the CREST trial, was outside the brain and thorax [2], and radiotherapy to extra-thoracic metastases has been considered as well. A study exploring the latter was closed prematurely due to toxicity and futility, and although a significant benefit was seen in local control, no benefit in overall survival was observed [5].

In order to identify patient groups that are most likely to benefit from inclusion into future studies evaluating aggressive radiotherapy strategies, we studied the prognostic importance of metastatic load (numbers, sites).

Materials/Methods

The CREST study was a phase 3 randomized controlled trial which enrolled 495 patients from 42 hospitals, mainly in the Netherlands and the United Kingdom. Eligible patients had to be 18 years or older, have WHO performance status 0-2, ES-SCLC, any response after 4-6 cycles of platinum-based chemotherapy without evidence of disease progression at any site [2]. Patients with brain, leptomeningeal or pleural metastases were excluded from the trial. Patients were randomized to receive PCI with TRT (30 Gy in 10 fractions) or PCI only. Due to limited funding for data management, it was decided to limit this study to the top 9 of the 42 recruiting centers in the CREST trial (7 Dutch and 2 UK centers) which had accrued a total of 260 patients (53% of 495 study patients). We obtained ethics and IRB approval to collect the additional data . and analyzed the individual patient records for details on anatomical location and numbers of distant metastases.
Characteristics of the 260 patients included in this analysis were compared with the 235 CREST patients who were not selected. Differences in progression-free survival (PFS) and overall survival (OS) for patients with and

without metastases in ipsilateral lung, contralateral lung, supraclavicular lymph nodes, distant lymph nodes (i.e. outside thorax and supraclavicular fossa), adrenal glands, liver, bone, and other sites were compared using the log-rank test and Cox proportional hazard analysis was used to calculate hazard ratios with 95% confidence intervals. A separate analysis of the effect of TRT was only performed for liver metastases and bone metastases in this additional study because of the small number of patients in the other subgroups.

Results

The characteristics of the patients are provided in Table 1. Their median age was 63 years and 52% were male. At randomization, 4% of patients had a CR after chemotherapy, 69% a PR and 27% a 'good response'. Details on response evaluation have been described previously [2]. Patients were classified as having a 'good response' if their tumor regressed, but less than was required to qualify for a PR according to RECIST criteria, or if not all sites of initial disease could be evaluated according to RECIST criteria after completion of chemotherapy. Residual intrathoracic disease post-chemotherapy was identified in 89% of patients. The clinical characteristics of the 260 patients analyzed were not significantly different from the 235 other patients in the CREST trial, with the exception that fewer patients had a World Health Organization (WHO) performance status= 0 (24% vs 45%) and a higher proportion were WHO=2 (15% vs 5%; overall: $p<0.0001$). Patients in the analysis had a similar PFS (3.5 months), but a trend towards inferior OS, when compared to the non-selected patients (median 7.4 vs 8.1 months; $p=0.06$).

No distant metastases were recorded in 13 patients (5.0%), in whom the diagnosis of ES-SCLC was based only on the extent of the intrathoracic tumor. In 59 patients (22.7%), there were 1-2 metastases and 188 patients (72.3%) had 3 or more metastases. In 102 patients (39.2%), the metastases were confined to one organ, in 88 (33.8%) to two, and in 57 (21.9%) to three or more organs. The predominant sites of metastasis were the liver (46.5%), bone (39.6%), lung (28.5%), distant lymph nodes (19.2%), supraclavicular nodes (17.7%), and adrenal glands (16.9%) [Table 2].

Progression-free survival was superior in the absence of bone metastases ($p=0.01$), and showed a favorable trend in the absence of liver metastases ($p=0.06$). Overall survival (OS) was significantly worse if liver metastases (Figure 1a; $p=0.03$) were present. Patients with bone metastases also had significantly worse OS

(Figure 1b; p=0.04) . For other metastatic sites, no differences in PFS or OS were observed.

Regardless of the administration of TRT, both OS (Figure 3; HR 1.43 (95%CI = 1.07-1.92); p=0.02) and PFS (HR=1.35 (95%CI = 1.02-1.78); p=0.04) were significantly better in patients with up to 2 metastases, compared to those with 3 or more distant metastases (Figure 1c). Survival of patients with 0, compared to 1 or to 2 distant metastases did not differ significantly.

Univariate analysis revealed no significant differences in PFS between patients diagnosed with liver metastases who received (n=69) and not received TRT (n=52; Table 3). In patients without liver metastases, those receiving TRT (n=63) had significantly longer PFS compared to those who did not receive TRT (n=52; HR=1.74' p=0.001). In patients with bone metastases, PFS was significantly longer in patients receiving TRT (n=50) than in to those who did not (n=53; HR 1.60; p=0.02). In patients without bone metastases, the difference in PFS did not reach statistical significance (HR=1.36; p=0.06).

In patients with 0-2 distant metastases, TRT led to a statistically significant benefit in PFS (n=61; HR=2.02; p=0.003). In patients with more than 2 distant metastases, the difference in PFS was statistically significant (HR1.25; p=0.14).

The differences in OS between patients without liver metastases who received and not received TRT was not statistically significant (HR=1.38; p=0.08), probably due to small numbers. Only for patients with 2 or fewer distant metastases, there was a trend for improved OS (HR=1.55; p=0.09)

In a multivariate analysis of PFS, including WHO Performance status (0,1,2), TRT (yes/no), liver metastases (yes/no), bone metastases (yes/no), and number of metastases (0-2 vs >2), the following factors were statistically significant: TRT (HR =1.48 (95%CI=1.15-1.91); p=0.002) and absence of bone metastases (HR=1.36 (95%CI=1.04-1.78); p=0.02). A multivariate analysis for OS did not identify significant factors associated with survival.

Discussion

This secondary analysis of patients recruited from the top 9 centers accruing to the CREST trial suggests that future studies evaluating more intensive thoracic and extrathoracic radiotherapy in ES-SCLC could focus on patients with a low burden of disease.

These inclusion criteria are almost identical to those of the phase II randomized trial on consolidative extra-cranial radiotherapy which was closed recently (NRG-RTOG0937). In this study, all responding patients were randomized between PCI plus consolidative radiotherapy to the thorax and 1-4 other extra-cranial sites of disease, or PCI only. The primary endpoint was overall survival and the accrual target was 154 patients. The study was closed early after an interim analysis of 86 patients who were entered over a 5 year period. The results have been presented in abstract form only [5], and reveal an imbalance between the study groups, with more adverse prognostic factors (advanced age, worse performance status, fewer CR, and more metastases) in the experimental arm, although only the difference in age reached statistical significance. The use of TRT and radiotherapy to extra-thoracic sites was associated with significantly longer progression-free survival. However, no significant difference in overall survival was observed. The risk of intrathoracic recurrence was reduced from 83 to 26%, and recurrence rates in treated metastases decreased from 78 to 42% [5]. In the experimental arm more toxicity was observed, including one death due to lung toxicity.

One of the limitations of the present study is that data was collected only from the top-accruing centers. However, we believe that the observed imbalance between treatment arms compared to the full CREST dataset, probably did not influence our conclusions. In addition, the smaller numbers of patients in certain subgroups (e.g. metastatic sites), make statistical comparisons difficult. For example, the beneficial effect of TRT observed in patients with bone metastases could be attributable to the lower frequency of liver metastases in this subgroup, with total numbers being too small to address this question adequately. The new UICC staging for lung cancer proposes a subdivision into a single metastasis in one organ versus multiple metastases in one or more organs [6,7]. We did not observe a difference between patients with 0-1 versus to 2 metastatic sites, a finding that could reflect small patient numbers.

The significant reduction in the risk of metastases in the brain [1], thorax [2,5] and extra-thoracic disease sites [5] demonstrates that radiotherapy is effective in ES-SCLC and this might translate into improved OS in patients

with a limited disease load. Our findings suggest that future studies should focus on patients with less than 3 metastases.

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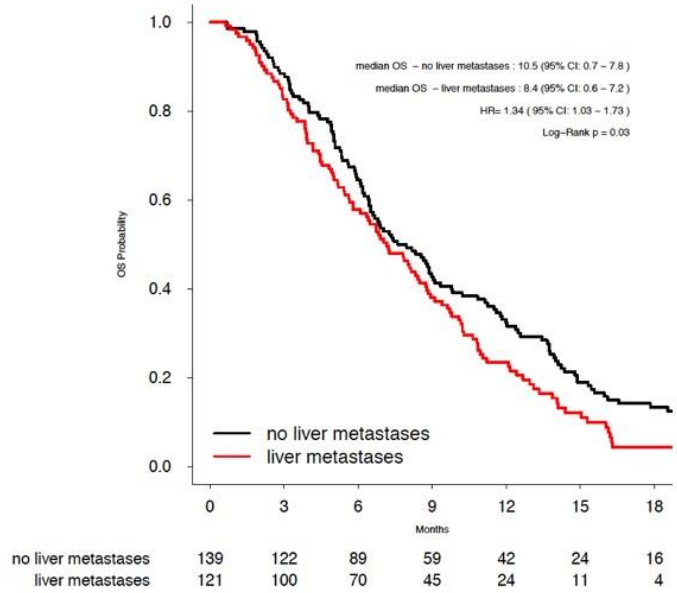
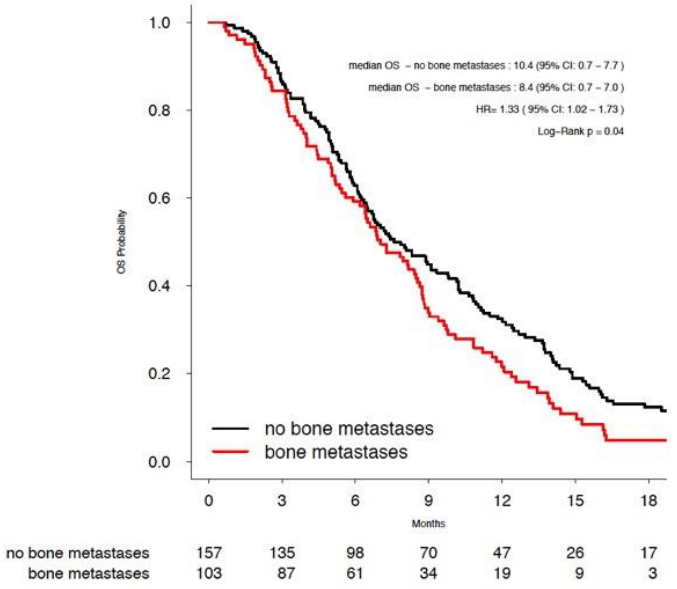
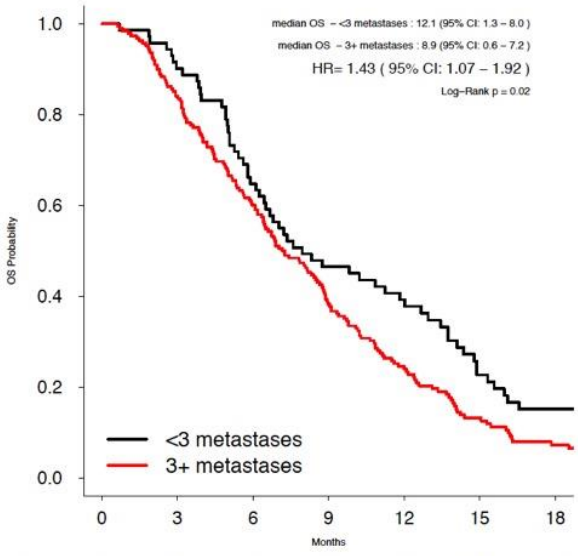
Figure legends

Figure 1. Overall survival of patients with and without liver metastases (a), with an without bone metastases (b), and 0-2 versus 3 or more metastases (c).







<3 metastases	72	64	46	33	27	15	10
3+ metastases	188	158	113	71	39	20	10

Table 1. Patient characteristics of selected from top accruing centers and non-selected patients.

		selected patients (n=260)	non-selected patients (n=235)	significance
Age	median (years)	63	63	NS
Sex	Male	136 (52.3%)	135 (57.4%)	NS
	Female	124 (47.7%)	100 (42.6%)	
WHO performance score	0	62 (23.8%)	105 (44.7%)	
	1	179 (68.8%)	118 (50.2%)	p<0.0001
	2	71 (27.3%)	12 (5.1%)	
Response	CR	10 (3.8%)	16 (6.8%)	
	PR	179 (68.8%)	170 (72.3%)	NS
	'Good response'	71 (27.3%)	49 (20.9%)	
Intrathoracic disease	No	28 (10.8%)	34 (14.5%)	NS
	Yes	232 (89.2%)	201 (85.5%)	
Interval diagnosis to start of chemotherapy	median (days)	3	3	NS
Interval start chemotherapy to randomization	median (days)	96	100	NS
Interval last chemotherapy to radiotherapy	median (days)	31	34	NS

Table 2. Overall survival and progression-free survival.

				Overall survival (HR; 95% CI)	Significance	Progression-free survival (HR; 95% CI)	p-value
		n	n (%)				
Ipsiateral lung	No	202		1.18	p=0.29	0.96	p=0.77
	Yes	58	(22.3%)	(0.87-1.59)		(0.71-1.28)	
Contralateral lung	No	244		1.04	p=0.89	0.99	p=0.99
	Yes	16	(6.2%)	(0.62-1.71)		(0.60-1.65)	
Supraclavicular nodes	No	214		0.81	p=0.23	1.01	p=0.97
	Yes	46	(17.7%)	(0.58-1.14)		(0.73-1.37)	
Extrathoracic (non-supraclavicular) lymph nodes	No	210		1.00	p=0.98	0.96	p=0.93
	Yes	50	(19.2%)	(0.73-1.39)		(0.72-1.34)	
Adrenal glands	No	216		0.72	p=0.06	0.98	p=0.89
	Yes	44	(16.9%)	(0.51-1.02)		(0.70-1.36)	
Liver	No	139		1.34	**p=0.03**	1.27	p=0.06
	Yes	121	(46.5%)	(1.03-1.73)		(0.99-1.63)	
Bone	No	157		1.33	**p=0.04**	1.39	**p=0.01**
	Yes	103	(39.6%)	(1.02-1.73)		(1.08-1.79)	
Other sites	No	229		0.84	p=0.39	0.86	p=0.46
	Yes	31	(11.9%)	(0.56-1.26)		(0.59-1.27)	

Table 3. Effect of thoracic radiotherapy and site and number of metastases.

	Progression free survival HR (95% CI); p-value	Overall survival HR (95% CI); p-value
Liver metastases		
present	1.22 (0.75-1.76) p=0.28	0.90 (0.62-1.31) p=0.57
absent	1.74 (1.23-2.46) p=0.001	1.38 (0.96-1.98) p=0.08
Bone metastases		
present	1.60 (1.08-2.38) p=0.02	0.94 (0.63-1.41) p=0.76
absent	1.36 (0.98-1.87) p=0.06	1.19 (0.85-1.65) p=0.32
Number of metastases		
0-2	2.02 (1.24-3.28) p=0.003	1.55 (0.93-2.58) p=0.09
>2	1.25 (0.93-1.66) p=0.14	0.94 (0.70-1.27) p=0.69