Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial

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Summary

Background Most patients with extensive stage small-cell lung cancer (ES-SCLC) who undergo chemotherapy, and prophylactic cranial irradiation, have persistent intrathoracic disease. We assessed thoracic radiotherapy for treatment of this patient group.

Methods We did this phase 3 randomised controlled trial at 42 hospitals: 16 in Netherlands, 22 in the UK, three in Norway, and one in Belgium. We enrolled patients with WHO performance score 0–2 and confirmed ES-SCLC who responded to chemotherapy. They were randomly assigned (1:1) to receive either thoracic radiotherapy (30 Gy in ten fractions) or no thoracic radiotherapy. All underwent prophylactic cranial irradiation. The primary endpoint was overall survival at 1 year in the intention-to-treat population. Secondary endpoints included progression-free survival. This study is registered with the Nederlands Trial Register, number NTR1527.

Findings We randomly assigned 498 patients between Feb 18, 2009, and Dec 21, 2012. Three withdrew informed consent, leaving 247 patients in the thoracic radiotherapy group and 248 in the control group. Mean interval between diagnosis and randomisation was 17 weeks. Median follow-up was 24 months. Overall survival at 1 year was not significantly different between groups: 33% (95% CI 27–39) for the thoracic radiotherapy group versus 28% (95% CI 22–34) for the control group (hazard ratio [HR] 0·84, 95% CI 0·69–1·01; p=0·066). However, in a secondary analysis, 2-year overall survival was 13% (95% CI 9–19) versus 3% (95% CI 2–8; p=0·004). Progression was less likely in the thoracic radiotherapy group than in the control group (HR 0·73, 95% CI 0·61–0·87; p=0·001). At 6 months, progression-free survival was 24% (95% CI 19–30) versus 7% (95% CI 4–11; p=0·001). We recorded no severe toxic effects. The most common grade 3 or higher toxic effects were fatigue (11 *vs* 9) and dyspnoea (three *vs* four).

Interpretation Thoracic radiotherapy in addition to prophylactic cranial irradiation should be considered for all patients with ES-SCLC who respond to chemotherapy.

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Introduction

Small-cell lung cancer accounts for 13% of all lung cancers, with the majority presenting at a stage of extensive disease.[1] Chemotherapy is the cornerstone of treatment, and four to six cycles of platinum-based chemotherapy without maintenance treatment is the standard.[2,3] However, survival for extensive stage small-cell lung cancer is poor, and has improved little in recent decades. Results of an analysis done in 2000 showed a 2-year survival of less than 5%.[1] Median time to progression is 4–6 months, and median survival is 7–11 months. Studies investigating other chemotherapeutic drugs, molecularly targeted drugs, or maintenance chemotherapy have not shown improvements.[4,5]

Although most approaches have proven unsuccessful, a notable exception is prophylactic cranial irradiation following response to induction chemotherapy, which provided a survival benefit in a phase 3 trial.[6] In this trial, the incidence of symptomatic brain metastases decreased significantly in the prophylactic cranial irradiation group compared with the control group (15% *vs* 40%), and survival at 1 year improved (27% *vs* 13%).

Intrathoracic tumour control remains a major difficulty for this disease. 75% of patients in the above mentioned study had persisting intrathoracic disease after chemotherapy, and roughly 90% had intrathoracic disease progression within the first year after diagnosis.[6] In a trial done at a single site,[7] patients with extensive stage small-cell lung cancer who had a complete response at distant disease sites, and a complete or partial response locally, were randomly assigned to thoracic radiotherapy with low dose chemotherapy or additional chemotherapy only. The researchers reported a significant improvement in local control and survival following thoracic radiotherapy. Two retrospective analyses[8,9] and one non-randomised phase 2 trial[10] also suggest that thoracic radiotherapy is beneficial for patients. However, the level of evidence to recommend thoracic radiotherapy for patients who do not need immediate symptomatic palliation is low.[3,4,11] We evaluated the role of thoracic radiotherapy in addition to prophylactic cranial irradiation for patients with extensive stage small-cell lung cancer who had responded to chemotherapy.

Methods

Study design and participants

We did this phase 3 randomised controlled trial at 42 hospitals: 16 in Netherlands, 22 in the UK, three in Norway, and one in Belgium. Eligible patients had to satisfy the following criteria: age 18 years or older, WHO performance status 0–2, extensive stage small-cell lung cancer (defined as disease beyond the hemithorax, hilar, mediastinal, and supraclavicular nodes[12]), any response after four to six cycles of standard chemotherapy (platinum etoposide) assessed in accordance with standard local policy, thoracic treatment volume considered treatable using acceptable radiation fields as judged by a radiation oncologist, 6 weeks or less between chemotherapy and randomisation, no clinical evidence of brain, leptomeningeal, or pleural metastases, no previous radiotherapy to brain or thorax, and ability to comply with protocol and follow-up schedules. All participants gave written informed consent according to International Conference on Harmonisation and good clinical practice and national or local regulations. The study protocol was approved by the ethics committee of each participating institution.

Randomisation and masking

We randomly assigned enrolled patients (1:1) centrally by computer to either thoracic radiotherapy plus prophylactic cranial irradiation or prophylactic cranial irradiation only, using minimisation[13] and stratification by institution and presence or absence of intrathoracic disease. Neither patients nor any investigators were masked to treatment allocation.

Procedures

After randomisation, participants gave a clinical history and had a physical examination, chest radiography, and CT scan of their thorax and upper abdomen. A CT or MRI scan of the brain was done for all patients with symptoms suggestive of brain metastases. Other sites of disease were re-evaluated at the discretion of the investigator. Response to chemotherapy was assessed by the local investigators with RECIST 1.1 criteria,[14] with no central review. Patients in both groups were followed up at 6 weeks and 12 weeks, then once every 3 months, then once every 6 months after 1 year. Investigations included at least medical history, physical evaluation, and chest radiography. Toxic effects were recorded according to Common Terminology Criteria for Adverse Events (version 3.0). We also recorded patterns of failure. Treatment for subsequent disease progression was not part of the protocol and was left to each centre's policy, but all such patients were required to be followed up until death.

Prophylactic cranial irradiation was given as 20 Gy in five fractions, 25 Gy in ten fractions, or 30 Gy in ten, 12, or 15 fractions. Each centre had to preselect one prophylactic cranial irradiation scheme for all patients. Treatment was delivered with two opposed lateral fields (4–10 MV). Thoracic radiotherapy was delivered to a dose of 30 Gy in ten fractions. The planning target volume included the post-chemotherapy volume with a 15 mm margin to account for microscopic disease and setup errors. Hilar and mediastinal nodal stations that were considered involved pre-chemotherapy were always included, even in case of response. Both 2D and 3D radiotherapy planning techniques were allowed. For 3D planning, the volume of normal lung tissue, minus planning target volume receiving more than 20 Gy, should be less than 35% and correction for tissue heterogeneity was mandatory. Treatment was delivered with a linear accelerator (4–10 MV) and all fields were treated daily (four or five fractions per week). Prophylactic cranial irradiation and thoracic radiotherapy preferably had to start within 6 weeks, but not later than 7 weeks after chemotherapy, and not within 2 weeks after chemotherapy or if acute grade 2 or higher toxic effects of chemotherapy had not yet resolved.

Outcomes

The primary endpoint was overall survival at 1 year. We also planned to analyse median overall survival and overall survival at 2 years. Secondary endpoints were intrathoracic control, pattern of failure, progression-free survival (median and at 6 months), and toxic effects. We did a post-hoc analysis of overall survival at 18 months. All outcomes were assessed in the intention-to-treat population.

Statistical analysis

Based on the 27% 1-year survival reported in an EORTC study of prophylactic cranial irradiation in a similar group of patients,[5] our study was powered to detect a 10% improvement in overall survival at 1 year from randomisation (hazard ratio [HR] 0·76). Assuming a 5% dropout between randomisation and end of treatment, 483 patients had to be randomly assigned to obtain 80% power against this expected difference (two-sided α=0·05).

We calculated overall survival as time from randomisation to death. We calculated progression-free survival as time from randomisation to progression or death (whichever came first). Patients still alive without progression at the time of analysis were censored. We used the Kaplan-Meier method to estimate survival, and the log-rank two-sided test to compare groups. We summarised compliance to treatment allocation with the following parameters: proportion of patients who completed thoracic radiotherapy, reasons for non-completion, proportion of patients in whom thoracic radiotherapy had to be delayed, and reasons for delays. We tested the interaction of treatment and selected factors with Cox proportional hazard analysis. We calculated the number of patients needed to treat to benefit on the basis of 2-year survival estimates.[15] We deemed a two-sided p value of less than 0·05 as statistically significant.

This study is registered with the Nederlands Trial Register, number NTR1527.

For the **adverse events criteria** see http://ctep.cancer.gov/reporting/ctc.html

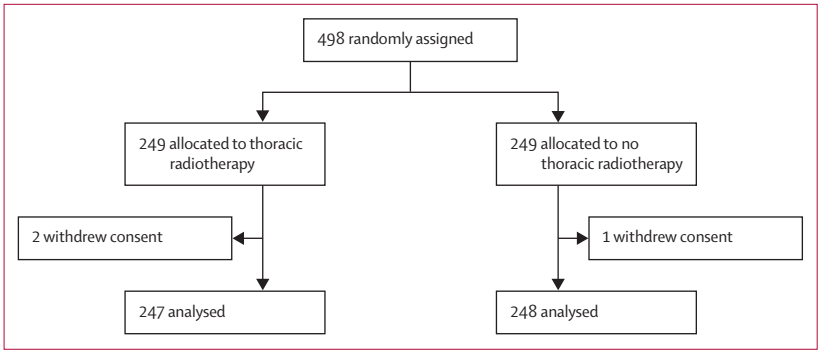

Figure 1: **Trial profile**

	Thoracic radiotherapy group (n=247)	Control group (n=248)
Median age (IQR, years)	63 (58–69)	63 (57–69)
Age <75 years	233 (94%)	226 (91%)
Age ≥75 years	16 (6%)	23 (9%)
Median time to diagnosis (IQR, months)	3·7 (3·2–4·4)	3·7 (3·2–4·4)
Sex		
Men	135 (55%)	136 (55%)
Women	112 (45%)	112 (45%)
WHO performance score		
0	97 (39%)	70 (28%)
1	121 (49%)	155 (63%)
2	29 (12%)	23 (9%)
Response after chemotherapy		
Complete response	12 (5%)	13 (5%)
Partial response	180 (73%)	170 (69%)
Good response	55 (22%)	65 (26%)
Persistent intrathoracic disease	215 (87%)	219 (88%)

Data are median (IQR) or n (%). Data are unavailable for smoking status.

Table 1: **Baseline characteristics**

	Thoracic radiotherapy group (n=247)	Control group (n=248)
Cough (grade 3)	0 (0·0%)	1 (0·4%)
Dysphagia (grade 3)	1 (0·4%)	0 (0·0%)
Dyspnoea (grade 3)	3 (1·2%)	4 (1·6%)
Oesophagitis (grade 3)	4 (1·6%)	0 (0·0%)
Fatigue (grade 3)	11 (4·5%)	8 (3·2%)
Fatigue (grade 4)	0 (0·0%)	1 (0·4%)
Insomnia (grade 3)	3 (1·2%)	2 (0·8%)
Nausea or vomiting (grade 3)	1 (0·4%)	0 (0·0%)
Headache (grade 3)	3 (1·2%)	2 (0·8%)

Table 2: **Grade 3 and higher toxic effects**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 18, 2009, and Dec 21, 2012, we randomly assigned 498 patients (249 in each group; figure 1). The analysis was done in December, 2013; median follow-up was 24 months. 201 patients in the thoracic radiotherapy group died compared with 224 in the control group, with 231 versus 239 progression-free survival events.

The mean interval between start of chemotherapy and randomisation was 15 weeks (range 14–19); the mean interval between diagnosis and randomisation was 17 weeks (16–21). Baseline characteristics were much the same in each group (table 1). 22·9% of patients were over 70 years and 7·8% were over 75 years. The diagnosis of extensive stage disease was based on the presence of distant metastases in 378 patients (76·4%), the extent of intrathoracic disease in 34 patients (6·9%), or both factors in 83 patients (16·8%). No patients had brain, leptomeningeal, or pleural metastases. 230 (46%) of asymptomatic patients underwent a brain CT or MRI according to local policy. After completion of chemotherapy, a CT of the thorax was done for 482 (97%) patients and a brain CT or MRI in 43 (13%) of asymptomatic patients.

Chemotherapy consisted of a platinum etoposide combination for 488 (99%) patients, with seven patients receiving other platinum-based regimens. Nine patients did not receive or stopped prophylactic cranial irradiation (six had disease progression, two had deterioration of general health, and one patient refused), six in the thoracic radiotherapy group and three in the control group. In the thoracic radiotherapy group, seven patients did not receive and six did not complete thoracic radiotherapy, because of disease progression (n=5), deterioration of general condition (n=3), patient refusal (n=4), or treatment-related toxic effects (n=1). The mean interval between last chemotherapy and prophylactic cranial irradiation was 32 days. Prophylactic cranial irradiation was delivered as 20 Gy in five fractions for 300 patients (62%), 25 Gy in ten fractions for 105 patients (22%), 30 Gy in ten fractions for 65 patients (14%), and 30 Gy in 12–15 fractions for 15 patients (3%). For 240 (88%) patients in the thoracic radiotherapy group, thoracic radiotherapy was combined with prophylactic cranial irradiation. Thoracic radiotherapy was started 1 week before prophylactic cranial irradiation for five (2%) patients, and thoracic radiotherapy was started for 13 patients (5%) within 7 days or less or on average 1 week after prophylactic cranial irradiation for all other patients (n=235, 98%). Grade 3 or higher toxic effects occurred in 26 patients in the thoracic radiotherapy group and 18 patients in the control group (p=0·28, table 2).

Overall survival at 1 year was 33% (95% CI 27–39) in the thoracic radiotherapy group versus 28% (95% CI 22–34) in the control group: the difference between groups was not significant (HR 0·84, 95% CI 0·69–1·01, p=0·066; figure 2). Median overall survival was 8 months in both groups. At 18 months, survival was 16% versus 9% (p=0·03). At 2 years, survival was 13% (95% CI 9–19) in the thoracic

radiotherapy group and 3% (95% CI 2–8) in the control group (p=0·004). The number of patients needed to treat to avoid one death was 10·6 (95% CI 6·1–42·5).

Median survival was significantly different between patients in whom diagnosis of extensive stage disease was on the basis of intrathoracic disease only (11·8 months), distant metastases (7·5 months), or both factors (8·3 months; p<0·0001). We recorded no significant differences in overall survival in subgroups divided by presence of intrathoracic disease at randomisation, sex, age, response to chemotherapy, WHO performance score, or extent of disease (ie, whether extensive stage disease was diagnosed on the basis of distant metastases, volume of intrathoracic tumour, or both (figure 3).

Progression was less likely in the thoracic radiotherapy group than in the control group (HR=0·73, 95% CI 0·61–0·87, p=0·001; figure 4). Progression-free survival at 6 months was 24% (95% CI 19–30) for the thoracic radiotherapy group and 20% (95% CI 16–26) in the control group (p=0·001). Median progression-free survival was 4 months for the thoracic radiotherapy group and 3 months for the control group. In a test for interaction of factors with treatment, there was no significant difference in the effect of thoracic radiotherapy on progression-free survival for presence of intrathoracic disease at randomisation (p=0·11), sex (p=0·12), age (p=0·19), response to chemotherapy (p=0·92), WHO performance score (p=0·94), and extent of disease (p=0·78).

Isolated intrathoracic progression was rarer in the thoracic radiotherapy group (n=49, 19·8%) than in the control group (n=114, 46·0%, p<0·0001). Intrathoracic progression either with or without progression elsewhere occurred in 108 (43·7%) in the thoracic radiotherapy group versus 198 (79·8%) in the control group (p<0·0001). Brain metastases occurred in 24 (9·7%) versus 13 (5·2%; p=0·09), and disease progression at other sites occurred in 149 (60·3%) versus 100 (40·3%; p<0·0001). Table 3 shows patterns of progression. We considered progression occurring at different organ sites within 30 days as simultaneous progression. The thorax was the first site of disease progression for 103 (41·7%) patients in the thoracic radiotherapy group versus 193 (77·8%) in the control group (p=0·009).

Discussion

The addition of thoracic radiotherapy to prophylactic cranial irradiation for patients with extensive stage small-cell lung cancer did not improve survival at 1 year. However, 2-year overall survival was significantly improved and progression-free survival was significantly greater. Furthermore, we report an almost 50% reduction in intrathoracic recurrences. These positive results are consistent with findings from studies of patients with locally advanced non-small-cell lung cancer showing that improved local control leads to improved survival.[16]

As might be expected from treatment of metastatic extensive stage small-cell lung cancer, overall survival was much the same in both groups during the first 9 months, but a significant difference in favour of the thoracic radiotherapy emerged at 2 years. 1 year survival for patients who received prophylactic cranial irradiation only was similar to that of patients who received only this treatment in an EORTC study[6] (27·1% versus 27·6%), suggesting that our findings are representative and applicable to patients with extensive stage small-cell lung cancer. We measured median survival and 2 year survival from the time of randomisation, which was about 4 months after the start of chemotherapy. As such, our

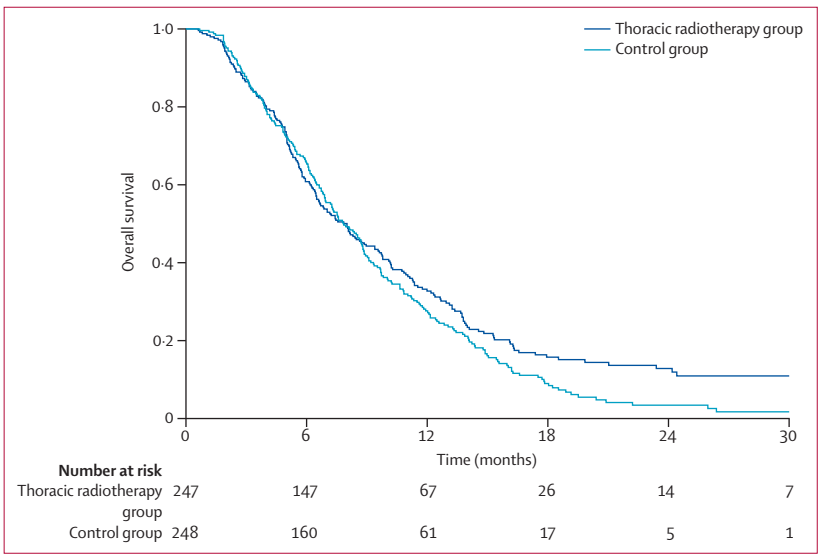

Figure 2: **Kaplan-Meier curves for overall survival**

	Thoracic radiotherapy Events/patients	Control Events/patients	Hazard ratio (CI)*	p value
Intrathoracic disease				0·35
Yes	175/213	195/215	0·80 (0·61–1·05)	
No	26/34	29/33	1·09 (0·54–2·18)	
Sex				0·06
Men	115/135	122/136	1·01 (0·72–1·41)	
Women	86/112	102/112	0·68 (0·46–1·00)	
Age (years)				0·58
36–70	152/193	170/189	0·82 (0·61–1·09)	
71–85	49/54	54/59	0·96 (0·58–1·60)	
Response to chemotherapy				0·58
CR	10/13	12/13	1·38 (0·45–4·22)	
PR	148/179	153/170	0·81 (0·60–1·10)	
Good response	43/55	59/65	0·76 (0·45–1·28)	
WHO performance status				1·00
0	74/97	65/70	0·85 (0·55–1·32)	
1	101/121	136/155	0·84 (0·60–1·18)	
2	26/29	23/23	0·83 (0·39–1·78)	
Extensive disease based on				0·86
Intrathoracic disease	11/19	9/15	0·68 (0·20–2·31)	
Distant metastases	161/190	172/188	0·87 (0·66 –1·16)	
Both	29/38	43/45	0·89 (0·48–1·65)	
Total	**201/247**	**224/248**	**0·84 (0·69–1·02)**	

Figure 3: **Overall survival at 1 year in subgroups**

*CI is 99% for subgroups, 95% for total. CR=complete response. PR=partial response.

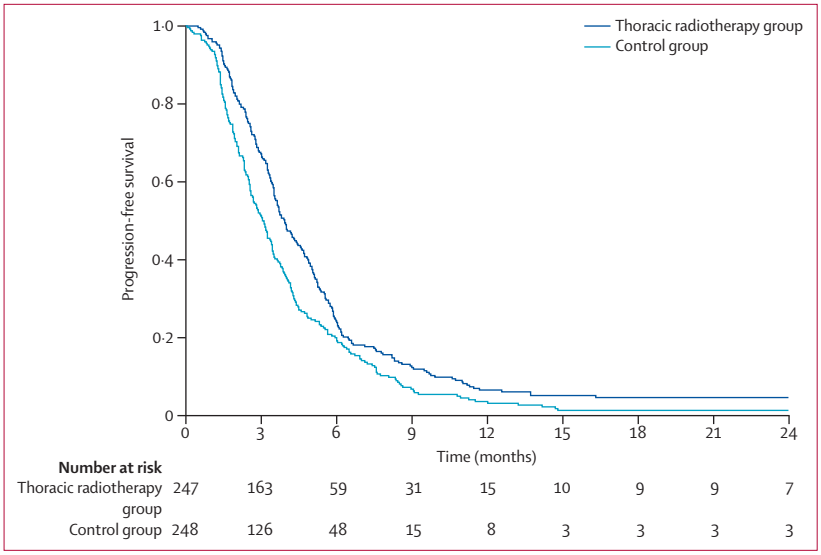

Figure 4: **Kaplan-Meier curves for progression-free survival**

	Thoracic radiotherapy group (n=247)	Control group (n=248)
Any site	213 (86·2%)	223 (89·9%)
Thorax only	49 (19·8%)	114 (46·0%)
Thorax and brain	5 (2·0%)	3 (1·2%)
Thorax and other sites	50 (20·2%)	77 (31·0%)
Thorax, brain, and other sites	4 (1·6%)	4 (1·6%)
Brain only	10 (4·0%)	6 (2·4%)
Brain and other sites	5 (2·0%)	0 (0·0%)
Other sites only	90 (36·4%)	19 (7·6%)

Progression occurring at different organ sites within 30 days was considered as occurring simultaneously.

Table 3: **Recurrences**

findings have to be considered in the context of other trials for extensive stage disease[17–19] that reported survival of 8·1–10·6 months, measured from diagnosis. Median survival in our trial was 8 months from randomisation and about 12 months from diagnosis, but, since only responding patients were included, comparison with other studies is difficult.

Thoracic radiotherapy was well tolerated and we recorded no severe acute or late toxic effects. Compliance was high, with 95% of patients completing protocol-specified thoracic radiotherapy without interruption, and just one patient stopped thoracic radiotherapy before completion because of treatment-related toxic effects. By contrast with the EORTC study of prophylactic cranial irradiation, which used an inclusion age limit of 75 years, we used no age restrictions. 8% of patients were older than 75 years, making the findings of our study more applicable to the general population of patients with extensive stage small-cell lung cancer.

At present, standard treatment for patients with extensive stage small-cell lung cancer consists of four to six cycles of platinum-based chemotherapy, followed by prophylactic cranial irradiation for responding patients.[2,3] Although 70–85% of patients respond after chemotherapy, with a complete response in up to 25% of cases, almost all patients relapse.[4] Furthermore, response and survival after second-line chemotherapy is very poor and the use of systemic treatments in the past two decades has done little to improve ouctomes.[2] By contrast, radiotherapy has survival advantages in both limited and extensive stage small-cell lung cancer.[20,21] Prophylactic cranial irradiation improves survival of patients with extensive stage small-cell lung cancer.[6] Although most patients have persistent intrathoracic disease after chemotherapy, thoracic radiotherapy is generally not considered because of the spread of disease outside the thorax, and is reserved for palliation of symptoms.

The use of thoracic radiotherapy for extensive stage small-cell lung cancer was investigated previously in a single-institution randomised study including 210 patients, done between 1988 and 1993, which suggested a benefit of thoracic radiotherapy for extensive stage disease (panel).[7] Initial treatment consisted of three cycles of cisplatin-etoposide, and 206 patients were fully assessable for toxic effects and survival. Only 109 patients from two favourable subgroups, namely those with complete response at both local and distant levels (n=55), and those with partial response within the thorax accompanied by complete response elsewhere (n=54), were considered for enrolment. Patients were randomly assigned to thoracic radiotherapy (54 Gy in 36 fractions delivered twice per day concurrently with chemotherapy, or chemotherapy alone).[7] Patients who received thoracic radiotherapy had both higher median survival (17 months *vs* 11 months) and 5-year survival (9·1% *vs* 3·7%) than did those who did not receive thoracic radiotherapy. These survival rates are the highest of any reported in a randomised study of the disease, and result from selection of a favourable patient population. By contrast, only 5% of patients in our study had a complete response recorded at the time of randomisation.

Our results are broadly in line with retrospective[8,9] and non-randomised[10] studies of thoracic radiotherapy. In a retrospective review of 215 patients with extensive stage small-cell lung cancer, 19 patients received consolidative thoracic radiotherapy.[8] In this favourable subset of patients with one or two metastatic sites, locoregional failure was reported in 26% at 1 year and 39% at 2 years.[8] Investigators of another retrospective study including 119 patients did a multivariate analysis and reported an improvement in median survival for patients receiving thoracic radiotherapy.[9] In a prospective non-randomised phase 2 study of patients with extensive stage small-cell lung cancer given four cycles of platinum-based chemotherapy, subsequent consolidative thoracic radiotherapy delivered as 40 Gy in 15 daily fractions was well tolerated, and only five of 32 patients developed a symptomatic chest recurrence.[10]

Our results must be considered in the context of the strengths and weakness of the study design. A planning

Panel: Review in context

Systematic review

We searched PubMed and the Cochrane Library databases without language restrictions for studies published between Jan 1, 1990 and Jan 1, 2014, with the terms "small cell lung cancer", "extensive", and "radiotherapy" or "radiation therapy". We also searched clinical trial registers (ClinicalTrials.gov and WHO International Clinical Trials Registry Platform) for ongoing trials and searched reference lists of relevant publications. We excluded retrospective studies and found one published randomised trial.[7] This trial showed a survival benefit for patients with extensive stage small-cell lung cancer given thoracic radiotherapy in combination with chemotherapy, in a highly selected group of patients with a complete response outside the thorax and a partial or complete response in the thorax.

Interpretation

Our findings suggest that the addition of thoracic radiotherapy after any response to chemotherapy in patients with extensive stage small-cell lung cancer leads to a significant reduction in intrathoracic recurrence and, despite the lack of a significant benefit in overall survival at 1 year, there were significant improvements in overall survival at 2 years and progression-free survival at 6 months.

CT scan of the thorax was only mandatory in case of large volume disease, which could have resulted in suboptimum doses of radiation delivered to some patients. However, the prescribed dose of 30 Gy in ten fractions is often delivered using opposed anterior and posterior fields, with low likelihood of missing the target. More than 40% of patients who received thoracic radiotherapy had an intrathoracic recurrence, which might suggest that even higher doses of radiation, as assessed in previous studies,[7–10] might be more efficacious. A dose of 30 Gy in ten fractions is an accepted high palliative dose in lung cancer and is associated with few toxic effects.[22] The effect of thoracic radiotherapy on overall survival in this study opens the way for further studies assessing higher doses of radiation and using advanced delivery techniques. However, many patients in our study had extrathoracic disease progression within the first year after treatment. A fractionation scheme of 30 Gy in ten fractions, or 40 Gy in 15 fractions, seems to offer a good balance between expected benefit, risk of side-effects, and burden of treatment in this vulnerable group of patients with a poor prognosis.

A limitation of this study was the absence of patient-reported outcomes. Evaluation of quality of life in these patients is challenging, and reported quality of life might reflect the disease more than the treatment itself. However, future studies of higher, potentially more toxic, radiation doses might benefit from studying patient-reported outcomes.

Almost all patients had a diagnostic CT scan of the thorax to assess response to chemotherapy, but detailed restaging of other sites of disease was not mandated to assess response, because detailed re-staging after chemotherapy is not standard practice for extensive stage small-cell lung cancer. The use of a practical minimum requirement of at least a response within the thorax, even if not meeting the formal criteria for a partial response, can be easily implemented in clinical practice. We think that this approach, previously used in the EORTC prophylactic cranial irradiation study,[6] might make the study results more generalisable to daily clinical practice. Indeed such a pragmatic study led to changes in routine practice within a few months of the study's publication.[23]

Because many patients have progression outside the thorax and brain despite thoracic radiotherapy, the addition of radiotherapy to sites of extrathoracic disease might also merit investigation.[11] Such an approach is being investigated by the Radiation Therapy Oncology Group in a phase 2 study (ClinicalTrials.gov number NCT01055197). In this study, prophylactic cranial irradiation and thoracic radiotherapy are combined with radiotherapy to up to four extrathoracic metastases. Furthermore, molecularly targeted drugs that might be combined with radiotherapy are being investigated.[5]

For the present, our results show that thoracic radiotherapy improves long-term survival. Therefore, thoracic radiotherapy should be considered for patients with extensive stage small-cell lung cancer who have responded to chemotherapy.

Contributors

BJS, HvT, AK, CF-F, and SS designed the study, collected, analysed, and interpreted data, and wrote the report. JOP, JLK, SYES, and MH collected and interpreted data and wrote the report.

Declaration of interests

We declare no competing interests.

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