Lung Cancer 100 (2016) 85–89

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Current patterns of care for patients with extensive stage small cell lung cancer: Survey of US radiation oncologists on their recommendations regarding thoracic consolidation radiotherapy

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ARTICLE INFO

Article history:
Received 28 July 2016
Received in revised form 1 August 2016
Accepted 10 August 2016

Keywords:
Extended-stage small cell lung cancer
Thoracic radiation therapy
Survey
Practice patterns

ABSTRACT

Objectives: Current National Comprehensive Cancer Network (NCCN) guidelines recommend thoracic consolidation radiation therapy (TCRT) for patients with Extensive Stage Small Cell Lung Cancer (ES-SCLC) with response to systemic chemotherapy, based on two randomized clinical trials, which varied in patient selection and radiation therapy doses administered. The current pattern of practice among US radiation oncologists is unknown.

Materials and methods: We have surveyed practicing US radiation oncologist via a short online questionnaire. Respondents' characteristics and their self-rated knowledge base were analyzed for association with their treatment recommendations.

Results: We received 473 responses from practicing US radiation oncologists. Over half of respondents were practicing for over 10 years after completing residency training and 70% treated more than 10 lung cancer patients per year. 96% of respondents recommend TCRT for patients with ES-SCLC after systemic chemotherapy. Patient selection and radiation therapy doses vary greatly. High self-rated knowledge of individual clinical trials is associated with lower TCRT recommended doses. Patients treated at academic centers are less likely to receive TCRT than patients treated in private clinics ($p = 0.0101$).

Conclusion: Our analysis revealed that among the respondents, there was a very high adherence to current NCCN guidelines, which recommend TCRT for ES-SCLC patients with clinical response to systemic chemotherapy. The great variability in patient selection and radiation therapy doses is concerning and calls for future clinical trials to standardize treatment approaches and improve treatment outcomes among patients with ES-SCLC. Until such data exists and in light of poor long-term survival of patients with ES-SCLC, the shorter and less toxic regimen of 30 Gy in 10 fractions should be used as the standard of care and the more aggressive regimens studied on clinical protocols.

1. Introduction

Small Cell Lung Cancer (SCLC) is found in 10% of patients with lung cancer and is one of the least curable histological subtypes, with a 5-year survival of approximately 3.5% [1]. It is characterized by rapid growth and early metastases development [2,3]. At the time of diagnosis 70% of patients have extensive-stage SCLC (ES-SCLC), which is initially treated with systemic chemotherapy. For patients with ES-SCLC who respond to chemotherapy current National Comprehensive Cancer Network (NCCN) guidelines [4] recommend thoracic consolidation radiation therapy (TCRT), based on two clinical trials. A Yugoslavian single-institutional randomized trial (Jeremic et al., JCO) showed an overall survival benefit to addition of TCRT of 54 Gy in 36 fractions given twice a day in patients with complete response (CR) in metastatic sites and either CR or partial response (PR) in thorax [5]. A more recent northern European randomized trial (Slotman et al., Lancet) enrolled patients with any clinical response to systemic chemotherapy to 30 Gy of TCRT or no irradiation [6]. The trial failed to show a difference in the primary endpoint – overall survival (OS) at 1 year, but showed a significant improvement in OS at 2 years. Post-hoc analysis revealed that TCRT benefited only patients who had residual disease in thorax (PR) and not patients with CR in thorax [7]. A

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http://dx.doi.org/10.1016/j.lungcan.2016.08.005
0169-5002/

recently published meta-analysis further supports improvement in OS and progression-free survival (PFS) with TCRT in ES-SCLC [8]. Recently a randomized phase II multi-institutional RTOG 0937 trial was closed early due to excessive grade 4 and 5 toxicity in patients randomized to 45 Gy of consolidation radiation to thorax and residual metastatic disease [9].

The current radiation practice patterns in the United States for patients with ES-SCLC are unknown. We designed an online survey to learn how radiation oncologists in the United States counsel patients with ES-SCLC regarding thoracic radiation therapy, what doses they prescribe in various clinical scenarios and what factors influence physicians' clinical recommendations.

2. Methods

2.1. Survey instrument development

The study was approved by the OHSU institutional review board. The online survey was developed with the REDCap software licensed by the Oregon Clinical and Translational Research Institute (OCTRI) for use by the Oregon Health and Science University (OHSU). The survey contained 22 potential questions regarding respondent demographics, thoracic consolidation radiation therapy practices (TCRT), prophylactic cranial irradiation therapy (PCI), and use of memantine with PCI. Branching logic was used to tailor the questions based on previous responses, so that most respondents did not see all 22 questions. Respondents self-rated their knowledge of three landmark trials for patients with ES-SCLC: Yugoslavian single-institutional randomized trial (Jeremic et al., JCO, which revealed improvement in overall survival for patients with complete response at distant sites and either complete or partial response in thorax, with addition of accelerated hyperfractionated RT to concurrent chemotherapy) [5], the northern European randomized trial NTR1527 (Slotman et al., Lancet, which showed improved OS at 2 years with addition of TCRT to patients with clinical response to chemotherapy) [6], and the RTOG 0937 trial (closed to accrual due to excessive toxicity in consolidation RT arm) [9]. Based on the response selection for the first two – Yugoslavian and European – trials, we have assigned a score of 0 ("Do not know this study"), 1 ("I know the main conclusion, but don't know the details of the trial and would not be able to quote the numbers") or 2 ("I have read the article and feel comfortable discussing the results"). Based on the response selection for the closed RTOG 0937 trial we assigned a score of 0 ("I am not familiar with this study"), 1 ("I am familiar with this study, but did not know it was closed to accrual due to toxicity early this year"), 2("I am familiar with this study and know that it was closed to accrual due to toxicity") and 3 ("I am familiar with this study and my institution enrolled patients on this study when it was open"). These individual scores were summed to obtain a knowledge score (KS) between 0 and 7, with 0 representing the least familiarity and 7 representing the expert level of knowledge. KS approached a normal distribution with a mean value of 3.81 (SD 1.86). The respondents were analyzed by three groups: low knowledge (KS 0–2), intermediate knowledge (KS 3–4), and high knowledge (KS 5–7).

2.2. Data collection

The data sample was collected through two internet-based, anonymized surveys of radiation oncologists in the United States. The survey was initially sent to 6967 potential participants from a developed database of radiation oncologists compiled through the American Society for Radiation Oncology (ASTRO) directory. These participants were then contacted through email using the REDCap tool and invited to take the survey. The invitation contained instructions on participation, contact information for questions, and usage of results. E-mail invitations were originally sent on September 7th, 2015. Participants who had requested to be removed due to non-applicability were not sent a reminder email, whereas potential respondents who did not complete the survey were contacted with a reminder email on September 15th, 2015 to maximize response rate.

Table 1
Characteristics of Radiation Oncologists who completed the survey.

	Number of respondents (%)
Number of years after completion of residency training	
Currently in residency training	37 (7.82%)
0–2	45 (9.51%)
3–5	67 (14.16%)
6–10	73 (15.43%)
over 10	251 (53.07%)
Number of lung cancer patients treated over the past 12 months	
0	17 (3.59%)
<5	42 (8.88%)
5–10	85 (17.97%)
>10	329 (69.56%)
Practice setting	
Academic Center	205 (43.34%)
Private Practice	268 (56.66%)
Practice region	
Central	116 (24.52%)
Northern	115 (24.31%)
Pacific	94 (19.87%)
Southern	103 (21.78%)
Western	45 (9.51%)

2.3. Statistical analysis

Respondents were characterized by years since residency completed, number of lung cancer patients treated in the past year, practice setting, region of practice, and the knowledge base, as discussed above. These five variables were analyzed for correlation with respondent treatment recommendations. Chi Square analysis was used to examine the correlations between characteristics and knowledge base with treatment questions. Cochran-Armitage test of trend was used to evaluate the trend in change for ordinal categorical variables. A p-value < 0.05 was considered statistically significant. SAS 9.4 (NY, Cary) was used for statistical analysis.

3. Results

3.1. Survey respondents

The survey was sent to 6967 email addresses, some of which could likely belong to the same individuals, as both personal as well as institutional email addresses were used. We received 499 failed/undeliverable automatic responses, 55 non-applicable/ineligible responses and 497 completed responses, among which 24 were from non-radiation oncologists, thus excluded from analysis. Characteristics of 473 radiation oncologists who completed the survey are summarized in Table 1. Over half of respondents were practicing for over 10 years after completing residency training, and 70% treated more than 10 lung cancer patients per year. Respondents self-rated on their knowledge of three landmark trials for patients with ES-SCLC, as described in Methods. Distribution of respondents was split with 25% in the low knowledge, 37% in the intermediate knowledge, and 38% in the high knowledge categories.

Table 2
Self-rated knowledge of landmark clinical trials in ES-SCLC and background of survey respondents.

Respondents characteristics	Self-rated high knowledge of landmark clinical trials	p-value
Number of years since residency training		<0.0001
Resident	46%	
0–2	67%	
3–5	55%	
6–10	44%	
>10	26%	
Practice Setting		<0.0001
Academic	54%	
Private	26%	
Number of lung cancer patients treated per year		0.0143
0	13%	
<5	36%	
5–10	31%	
>10	42%	

Table 3
Recommendation of survey respondents to administer TCRT based on response to systemic chemotherapy in thorax and metastatic disease sites.

Clinical scenario after chemotherapy for ES-SCLC	% of respondents recommending TCRT[a]
CR in thorax and CR in metastatic sites	52%
CR in thorax and PR in metastatic sites	17%
PR in thorax and CR in metastatic sites	78%
PR in thorax and PR in metastatic sites	34%

Abbreviations: CR—complete response; PR—partial response.
[a] Percentages in table do not add up to 100%, as respondents could select more than one clinical scenario for recommending consolidation thoracic RT.

3.2. Relationship exists between knowledge base and certain respondent characteristics

Geographic region was not associated with self-rated knowledge ($p = 0.4349$). There was a correlation between increased number of lung cancer patients treated and self-rated knowledge base ($p = 0.0143$). Respondents practicing in academic centers had a higher self-rated knowledge of the three landmark trials ($p < 0.0001$), with 54% of respondents from academic institutions rating themselves at a high level of knowledge vs 26% of respondents from private practices. Experience – defined as the number of years since completion of residency training – was highly associated with knowledge of the three landmark trials ($p < 0.0001$), with the highest self-rated knowledge among recent graduates and the lowest knowledge among physicians >10 years out of residency (Table 2).

3.3. Most respondents recommend thoracic consolidation radiotherapy

18 out of 473 respondents (3.8%) recommended against TCRT regardless of the clinical scenario. 15 out of these 18 respondents cited insufficient evidence to recommend TCRT for patients with ES-SCLC. The remaining 96% of respondents recommended TCRT, with the breakdown by clinical scenario as shown in Table 3. Survey allowed respondents to pick the following TCRT doses: 30, 45, 50, 54, 60, 63 and 66 Gy. During the analysis, the responses were grouped into four categories: 30 Gy, 45 Gy, 50 or 54 Gy, and 60 or more Gy. Fig. 1 shows the distribution of recommended doses by survey respondents for each of the four clinical scenarios. Among 248 respondents, who have recommended TCRT for more than one clinical scenario, 153 (62%) did not alter the TCRT dose based on change in clinical scenario.

Table 4
Estimated proportion of patients in respondent's practice who received TCRTRT.

Estimated percentage of patients receiving TCRT in respondent's practice	Number of respondents (Percentage)
<10%	42 (9%)
10–40%	71 (16%)
41–80%	129 (29%)
>80%	201 (45%)

3.4. Relationship exists between recommended thoracic consolidation RT dose and knowledge of individual published clinical trials

Among our respondents, 39% had high self-rated knowledge of Yugoslavian trial and 47% had high self-rated knowledge of European trial. When responses were dichotomized into two groups – a minimum of 54 Gy of thoracic RT for any clinical scenario vs a maximum of 50 Gy for any clinical scenario – knowledge of Yugoslavian trial was strongly associated with recommended doses. 47% of respondents with low knowledge and 29% of respondents with high knowledge of Yugoslavian trial recommend a minimum dose of 54 Gy ($p < 0.0001$). When responses were dichotomized into two different groups – maximum dose of 30 Gy for any clinical scenario vs any higher dose of RT – 20% of respondents with low knowledge and 45% of respondents with high knowledge of northern European trial recommend a maximum dose of 30 Gy ($p < 0.0001$).

3.5. Trend exists between recommended thoracic consolidation RT dose and knowledge of closed RTOG 0937 clinical trial

Among our respondents, 36% had high self-rated knowledge of the RTOG 0937 clinical trial. There was a non-significant trend towards recommending lower thoracic RT doses among respondents with high self-rated knowledge of RTOG 0937 trial. When responses were dichotomized into two different groups – maximum dose of 30 Gy for any clinical scenario vs any higher dose of RT – 29% of respondents would not increase the RT dose beyond 30 Gy with low self-rated knowledge of the RTOG trial vs 37% of respondents with high self-rated knowledge ($p = 0.0845$). When responses were dichotomized into maximum dose of 45 Gy vs any higher dose of RT – 49% of respondents with low knowledge of RTOG trial would not increase TCRT dose beyond 45 Gy with low knowledge and 58% of respondents with high knowledge of RTOG 0937 ($p = 0.0828$).

3.6. Receipt of thoracic consolidation RT was more common in non-academic centers

443 respondents estimated the frequency at which their patients underwent TCRT, as detailed in Table 4. 201 respondents (45%) estimated the majority of their patients undergoing TCRT. Patients treated at academic centers were less likely to receive TCRT than patients treated in private practices ($p = 0.0101$). When respondents were dichotomized into two groups based on thoracic RT dose recommendations (low dose: 30–45 Gy vs high dose: 54 Gy or more), there was no association between frequency of receiving TCRT by patients and the respondents' TCRT dose recommendation ($p = 0.2934$).

4. Discussion

The use of thoracic consolidation radiation therapy for patients with ES-SCLC with clinical response to systemic chemotherapy is

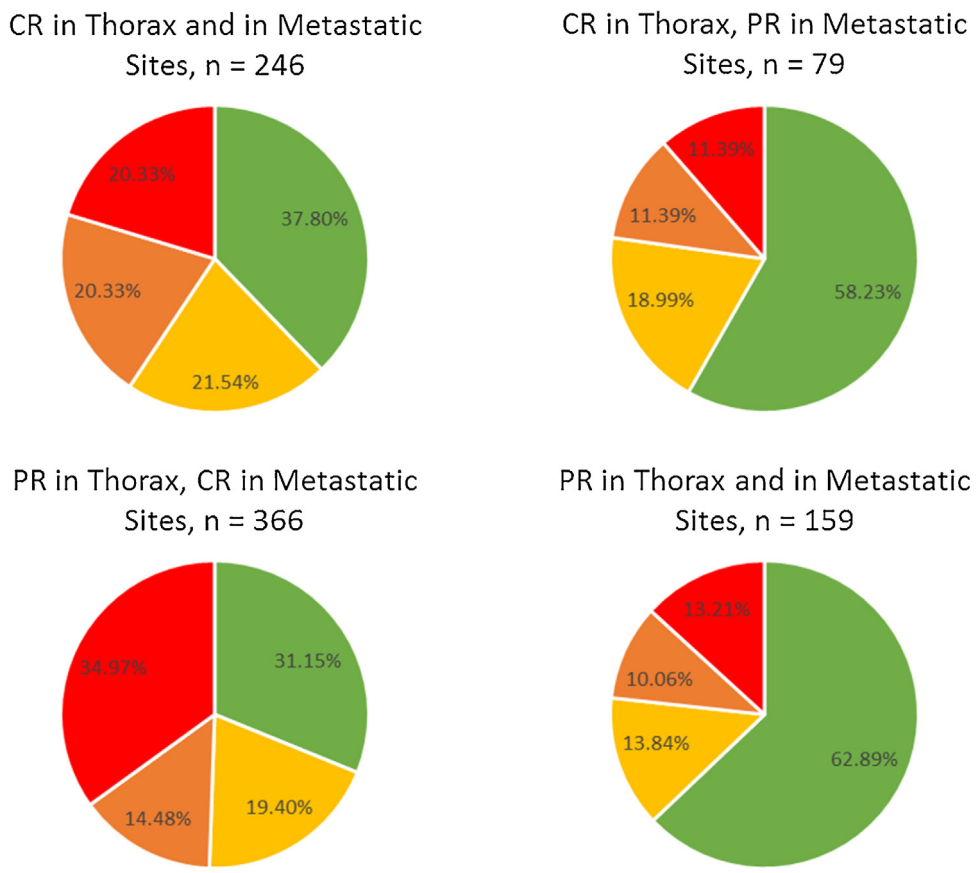

Fig. 1. Distribution of recommended radiation therapy doses by survey respondents for each of the four clinical scenarios. Colors: green—30 Gy; yellow—45 Gy, orange—50 or 54 Gy, red—60 Gy and over. Abbreviations: CR = complete response; PR = partial response (to systemic chemotherapy).

supported by the current NCCN guidelines, but patient selection and radiation therapy doses are not well defined in the literature. Yugoslavian single-institutional trial selected patients with CR in distant sites and either PR or CR in thorax and randomized them to either thoracic accelerated hyperfractionated radiotherapy (54 Gy in 36 fractions administered twice a day) or additional cycles of chemotherapy with no radiation. This was a small study with 55 patients in the first group and 54 patients in the second group, and yet it showed improvement in median survival time (17 vs 11 months) and 5-year overall survival (9.1% vs 3.7%, $p = 0.041$). Although acute high-grade toxicity was higher in non-RT arm, mostly due to hematological toxicities from additional systemic chemotherapy, patients randomized to 54 Gy of RT developed radiation-induced esophagitis, with 20% experiencing grade 3 and 7% experiencing grade 4 acute esophageal toxicities. A more modern northern European trial conducted at 42 hospitals randomized 498 patients with any clinical response to systemic chemotherapy to either TCRT of 30 Gy in 10 fractions or no radiation. With a median followup of 24 months, the study failed to detect a predetermined survival benefit at 1 year, but did show in a secondary analysis a survival advantage at 2 years (13% vs 3%, $p = 0.004$). There was an improvement in 6 months progression free survival (24% vs 7%, $p = 0.001$) and no Grade 4 and 5 acute toxicities related to 30 Gy of thoracic RT. Although any patient with clinical response to systemic therapy was eligible, the post-hoc analysis, reported as a correspondence – showed that in patients with residual intrathoracic disease, the OS was significantly longer in the TCRT group (HR 0.81, 95% CI 0.66–1.00, $p = 0.044$). No such benefit for TCRT was observed in patients without residual intrathoracic disease. RTOG 0937 randomized Phase II clinical trial investigating the benefit of consolidative extra-cranial irradiation to 45 Gy for ES-SCLC closed early in February 2015 due to high rate of grade 4 and 5 toxicities in the consolidation arm, however the results are unpublished and the treatment arms may have been unbalanced, contributing to the outcomes.

Our survey analysis, based on responses from 473 practicing radiation oncologists in the United States, shows that 96% of physicians recommend TCRT, and few patients end up not receiving the treatment. Only 18 physicians in our survey do not recommend TCRT, arguing that the clinical evidence supporting this NCCN recommended therapy is insufficient. This finding is critical for the ongoing and future clinical trials in patients with ES-SCLC. A large international randomized phase III trial (NCT02538666) of Programmed cell death protein 1 (PD-1) immunotherapy in patients with ES-SCLC after completion of systemic chemotherapy allows prophylactic cranial irradiation (PCI), but specifically excludes TCRT. Our thoracic multi-disciplinary team approached the sponsoring company with request to amend the protocol, arguing that the NCCN-supported standard of care – thoracic consolidation RT – is a widely accepted and practiced treatment paradigm, based on the results of our survey We argued that if PD-1 therapy proves to be beneficial in patients with ES-SCLC, the debate will ensue over the relative merits of PD-1 therapy vs TCRT and physicians may start combining PD-1 therapy with TCRT in the absence of robust safety data.

Despite the almost universal recommendation among radiation oncologists in the United States, patient selection greatly varies, and there is little consensus on appropriate radiation therapy doses. Based on our survey, the most likely patient in US to receive TCRT is one who achieved complete response (CR) in metastatic sites and only partial response (PR) in thorax – with 78% of our respondents recommending TCRT in this setting. This scenario is indeed sup-

ported by inclusion criteria of the Yugoslavian trial and the post-hoc analysis of the northern European trial. 17% of respondents recommend TCRT in the setting of PR in metastatic sites and CR in thorax – which is not supported by the clinical evidence.

Recommended doses for TCRT span from 30 Gy to over 60 Gy. We observed a relationship between knowledge of individual clinical trials and recommended radiation therapy doses. Knowledge of the Yugoslavian trial was associated with higher likelihood of recommending doses less than 54 Gy, and the knowledge of northern European trial was associated with higher chance that respondents recommended the maximum dose of 30 Gy. We also observed a trend towards lower TCRT recommended doses and knowledge of the closed RTOG 0937 clinical trial. It appears that physicians with high self-rated knowledge of these landmark studies tend to prescribe lower TCRT doses. We also observed that respondents with high self-rated knowledge of these trials tended to practice in academic centers, specialize in thoracic malignancies and have completed the residency training in the not so distant past.

In selecting doses for TCRT, it is important to note the significant differences in the treatment characteristics of the two published studies and the closed RTOG trial. The study by Jeremic et al. targeted gross disease +2 cm, the ipsilateral hilum, the mediastinum, and bilateral supraclavicular fossae. 54 Gy was delivered in 36 fractions over 18 days (1.5 Gy BID) and was prescribed to a point. The study by Slotman et al. targeted post-chemotherapy volumes +1.5 cm and areas of pre-chemotherapy lymphadenopathy to a dose of 30 Gy in 10 fractions (4–5 fractions per week) using either 2D or 3D techniques. RTOG 0937 targeted areas of residual primary and metastatic disease. 45 Gy at 3 Gy/day was prescribed, but 30–40 Gy in 10 fractions was allowed. 3D planning was required. These data do not give direct guidance as to the appropriate dose to select for TCRT. However, in light of poor long term survival of these patients, the more palliative (and less toxic) dose of 30 Gy in 10 fractions is attractive in the authors' opinion. We would argue that the use of higher doses – more toxic, more costly and more time consuming to patients – would be best studied in a clinical trial setting. We would also endorse TCRT in the setting of very good systemic response to chemotherapy, so that improved disease control in thorax is clinically meaningful for patients.

The greatest limitation of our study is a sample size of 473 responses, and findings may not be representative of other radiation oncologists who chose not to participate in the survey. Recall bias may misrepresent actual treatment recommendations. A patterns of care analysis using National Cancer Data Base or Surveillance, Epidemiology, and End Results data could substantiate our analysis of physicians' opinions with data on actual uptake of TCRT in the United States. No free text response was allowed in order to simplify the survey design and analysis. We did not query as to whether respondents functioned primarily as thoracic radiotherapy leaders for their respective programs, and another survey targeting specifically these physicians is in the analysis phase by our colleagues at the University of Pennsylvania. We are unable to ascertain whether there are financial conflicts which may influence decisions on whether to administer TCRT or not, and how many fractions of TCRT to offer to patients with ES-SCLC.

5. Conclusion

The goal of this study was to broadly sample US radiation oncologists in their approach to patients with ES-SCLC after clinical response to systemic chemotherapy. We saw an almost universal adherence to the current NCCN guidelines, recommending TCRT. However, appropriate selection of patients and radiation therapy doses are not well defined. Future clinical trials must address this question and define the appropriate treatment strategies for patients with ES-SCLC. Until such time, a more conservative approach with a shorter treatment of 30 Gy in 10 fractions, leading to fewer treatment-related toxicities, should be a preferred treatment recommendation. Ongoing and future clinical trials should incorporate TCRT, given its widespread application in the United States. Finally, survey of medical oncologists is forthcoming, which will show which patients are referred to radiation oncologists for consideration of TCRT, as this may dramatically skew what patients are seen in radiation oncology departments.

Conflict of interest

None.

Acknowledgment

OHSU REDCap is supported by grant 1 UL1 RR024140 01.

References

[1] U. Lassen, K. Osterlind, M. Hansen, P. Dombernowsky, B. Bergman, H.H. Hansen, Long-term survival in small-cell lung cancer: posttreatment characteristics in patients surviving 5–18+ years—an analysis of 1,714 consecutive patients, J. Clin. Oncol. 13 (5) (1995) 1215–1220.
[2] C.L. Hann, C.M. Rudin, Management of small-cell lung cancer: incremental changes but hope for the future, Oncology 22 (13) (2008) 1486–1492.
[3] D.M. Jackman, B.E. Johnson, Small-cell lung cancer, Lancet 366 (9494) (2005) 1385–1396.
[4] NCCN Clinical Practice Guideliens in Oncology, National Comprehensive Cancer Network http://www.nccn.org.
[5] B. Jeremic, Y. Shibamoto, N. Nikolic, B. Milicic, S. Milisavljevic, A. Dagovic, et al., Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study, J. Clin. Oncol. 17 (7) (1999) 2092–2099.
[6] B.J. Slotman, H. van Tinteren, J.O. Praag, J.L. Knegjens, S.Y. El Sharouni, M. Hatton, et al., Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial, Lancet 385 (9962) (2015) 36–42.
[7] B.J. Slotman, H. van Tinteren, J.O. Praag, J.L. Knegjens, S.Y. El Sharouni, M. Hatton, et al., Radiotherapy for extensive stage small-cell lung cancer—authors' reply, Lancet 385 (9975) (2015) 1292–1293.
[8] D.A. Palma, A. Warner, A.V. Louie, S. Senan, B. Slotman, G.B. Rodrigues, Thoracic radiotherapy for extensive stage small-cell lung cancer: a meta-analysis, Clin. Lung Cancer 17 (4) (2016) 239–244.
[9] TO: investigators participating in RTOG 0937: a randomized phase II study comparing prophylactic cranial irradiation alone to prophylactic cranial irradiation and consolidative extra-cranial irradiation for extensive disease small cell lung cancer (ED-SCLC) [press release], NRG Oncol. 2015 (February 27) (2015).