Radiotherapy and Oncology 135 (2019) 74–77

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Consolidative thoracic radiotherapy in stage IV small cell lung cancer: Selection of patients amongst European IASLC and ESTRO experts

Paul Martin Putora [a,b,*], Markus Glatzer [a], Dirk De Ruysscher [x], Corinne Faivre-Finn [f], José Belderbos [c], Benjamin Besse [d,e], Fiona Blackhall [f], Raffaele Califano [g,h,i], Federico Cappuzzo [j], Filippo de Marinis [k], Rafal Dziadiuszko [l], Enriqueta Felip [m], Martin Früh [n,o], Pilar Garrido [p], Cecile Le Pechoux [q], Fiona McDonald [r], Ursula Nestle [s,t], Silvia Novello [u], Mary O' Brien [v], Luis Paz Ares [w], Stephanie Peeters [x], Christoph Pöttgen [y], Sara Ramella [z], Martin Reck [aa], Esther G.C. Troost [ac,ad,ae,af], Paul Van Houtte [ag], Virginie Westeel [ah], Joachim Widder [ai], Francoise Mornex [aj], Ben J. Slotman [ab]

[a] *Department of Radiation Oncology, St. Gallen;* [b] *Department of Radiation Oncology, Bern, Switzerland;* [c] *Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands;* [d] *Institut Gustave Roussy, Villejuif;* [e] *Université Paris Sud, Le Kremlin Bicetre, France;* [f] *Division of Cancer Sciences, University of Manchester & The Christie NHS Foundation Trust Manchester;* [g] *Department of Medical Oncology, The Christie NHS Foundation Trust;* [h] *Department of Medical Oncology, Manchester University Hospital NHS Foundation Trust;* [i] *Division of Cancer Sciences, University of Manchester, Manchester, UK;* [j] *Director Oncology and Hematology Department, AUSL Romagna, Ravenna;* [k] *Division of Thoracic Oncology, European Institute of Oncology, IRCCS, Milan, Italy;* [l] *Department of Oncology and Radiotherapy, Gdansk, Poland;* [m] *Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain;* [n] *Department of Medical Oncology/Hematology, St. Gallen;* [o] *University of Bern, Switzerland;* [p] *Hospital Universitario Ramón y Cajal, Madrid, Spain;* [q] *Comité Pathologie Thoracique, Comité Sarcomes et Tumeurs Mesenchymateuses Gustave Roussy, France;* [r] *Department of Radiotherapy, The Royal Marsden NHS Foundation Trust, London, UK;* [s] *Department of Radiation Oncology, Kliniken Maria Hilf, Moenchengladbach;* [t] *Department of Radiation Oncology, University Hospital Freiburg, Germany;* [u] *Oncology Department, AOU San Luigi, University of Turin, Italy;* [v] *Department of Medicine, The Royal Marsden NHS Foundation Trust, Sutton, UK;* [w] *Hospital Universitario 12 de Octubre, Madrid, Spain;* [x] *Maastricht University Medical Center, Department of Radiation Oncology (Maastro Clinic), School for Oncology and Developmental Biology (GROW), Maastricht, The Netherlands;* [y] *Department of Radiation Oncology, West German Tumor Centre, University of Duisburg-Essen Medical School, Germany;* [z] *Department of Radiation Oncology, Campus Bio-Medico University, Rome, Italy;* [aa] *LungenClinic Airway Research Center North (ARCN), German Center for Lung Research, Grosshansdorf, Germany;* [ab] *Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands;* [ac] *OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus;* [ad] *Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus;* [ae] *Helmholtz-Zentrum Dresden – Rossendorf, Institute of Radiooncology – OncoRay, Dresden;* [af] *German Cancer Consortium (DKTK), Partner Site Dresden, and German Cancer Research Center (DKFZ), Heidelberg, Germany;* [ag] *Department Radiation Oncology, Institut Bordet, Université Libre Bruxelles, Belgium;* [ah] *CHU de Besançon, Besançon, France;* [ai] *Department of Radiotherapy, Comprehensive Cancer Center, Medical University of Vienna, Austria;* [aj] *Service de radiothérapie, CHU Lyon Sud, Hospices civils de Lyon, Pierre-Bénite, France*

ARTICLE INFO

Article history:
Received 28 December 2018
Received in revised form 18 January 2019
Accepted 13 February 2019
Available online 15 March 2019

Keywords:
Small cell lung cancer
Thoracic radiotherapy
Stage IV
Expert opinion
IASLC
ESTRO

ABSTRACT

Background: The role of consolidative thoracic radiotherapy (TRT) in stage IV small cell lung cancer (SCLC) is not uniformly accepted.

Methods: We obtained a list of 13 European medical oncologists from the International Association for the Study of Lung Cancer (IASLC) and 13 European radiation oncologists from the European Society for Therapeutic Radiation Oncology (ESTRO). The strategies in decision making for TRT in stage IV SCLC were collected. Decision trees were created representing these strategies. Frequencies of recommending TRT were analysed for various parameter combinations based on the objective consensus methodology.

Results: The factors associated with the recommendation for TRT included fitness of the patient, limited extrathoracic tumour burden, initial bulky thoracic disease and response to chemotherapy. The highest consensus for TRT was in fit patients with limited extrathoracic tumour burden and initial bulky disease with either a complete extrathoracic response or partial thoracic response (92% recommend TRT). For these patients the recommendations were the same for medical and radiation oncologists. In the setting of partial response (intra- and extra-thoracically) without initial bulky thoracic disease radiation oncologists were more likely to recommend TRT than medical oncologists. For unfit patients or for patients with poor overall response to chemotherapy, the majority did not recommend TRT.

Conclusion: European radiation and medical oncologists specializing in lung cancer recommend TRT in selected patients with stage IV SCLC and restrict its use primarily to fit patients who responded to chemotherapy with limited extrathoracic tumour burden.

* Corresponding author at: Dept. of Radiation Oncology, Kantonsspital St. Gallen, 9007 St. Gallen, Switzerland.
E-mail address: paul.putora@kssg.ch (P.M. Putora).

https://doi.org/10.1016/j.radonc.2019.02.010
0167-8140/

As a standard of care, patients with stage IV SCLC receive four to six cycles of palliative chemotherapy (platinum/etoposide). The Impower 133 trial has shown improvement of progression-free survival (PFS) and overall survival (OS) when adding atezolizumab to carboplatin/etoposide and this regimen may become a new standard of care in suitable patients [1].

The most recent and largest randomized European CREST trial [2] investigated the role of TRT (10×3 Gy) in addition to PCI in stage IV patients with any response after chemotherapy. The primary endpoint of OS improvement at 1 year was not met. The 1-year OS was 28% in the control arm and 33% in the TRT group (HR 0.84, 95% CI 0.69–1.01, $p = 0.066$). The 1-year OS in the control group was similar to the experimental arm in the previous study comparing PCI after chemotherapy to chemotherapy alone (27%) [3]. An analysis of patients with residual disease after chemotherapy (one of the stratification factors) revealed an OS benefit for this group of patients but not in patients with a complete response in the thorax after chemotherapy [2].

An unplanned exploratory subgroup analysis demonstrated that patients with less than four distant metastases and a good response of distant metastases after chemotherapy, but persistent thoracic disease, benefitted most from thoracic radiotherapy [4].

A recent European survey showed that after publication of the CREST trial [2], thoracic radiotherapy (TRT) was used in 85% of the surveyed centres [5]. Although other prospective [6] and retrospective studies [7,8] also showed benefit in local control and survival, some still question the benefit of TRT.

Given the discussion on the role of TRT in routine clinical practice, understanding how clinical experts approach a problem is of interest [9]. Collecting decision making patterns directly from clinical experts provides valuable insights into decision making, especially in determining which decision criteria are most relevant in clinical practice, as these may not be recorded in clinical trials, databases or health records [10,11].

We performed a decision-making analysis on the role of TRT in the setting of stage IV SCLC amongst experts from the International Association for the Study of Lung Cancer (IASLC) and the European Society for Therapeutic Radiation Oncology (ESTRO). The results for PCI in this setting are reported separately [12], in this analysis the decision for or against TRT is considered indenpendent of the indication for PCI, and the decision criteria for or against TRT are therefore defined independent of PCI.

Methods

In order to avoid specialty bias [13,14] we collected decision patterns from European medical oncologists (provided by IASLC) as well as European radiation oncologists (provided by ESTRO) from a broad range of countries.

ESTRO and IASLC provided a list of 13 European experts each. The experts are amongst the authors of this manuscript representing various countries in Europe (Austria, Belgium, France, Germany, Italy, Netherlands, Poland, Spain, Switzerland and the United Kingdom). Each expert was asked the following question by email: "Under which circumstances would you recommend thoracic radiotherapy/or PCI for stage IV SCLC? Please describe any disease or patient characteristics relevant for your decision."

The initial responses were collected and checked for redundancies, ambiguities or missing answers to specific criteria combinations. An iterative bilateral approach with each expert individually was used to finalize the individual decision trees as described previously [12,15]. The individual decision trees were anonymized and used for analysis to obtain information on areas of consensus or dissent based on the objective consensus methodology [16] which is based on a quantitative comparison of treatment recommendation from each expert for every single possible combination of parameters. Additionally, criteria precluding TRT that were used by less than 3 experts were omitted from the decision tree analysis. Criteria that were removed were: previous irradiation to the area or pre-existing thoracic disease that precludes radiotherapy. General criteria, such as the capacity to give informed consent were also excluded, as they were considered universal.

Six decision criteria were initially evaluated, these included fitness of the patient (fit: yes, no), age (age: young, old), thoracic response to chemotherapy (thoracic: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD)), and extrathoracic response to chemotherapy (extrathoracic: CR, PR, SD, PD), initial bulky thoracic disease (iBTD: yes, no), limited extrathoracic tumour burden (LETTB: yes, no). As age was only used by two participants, it was excluded in the final analysis. Specific cut-off values for fitness or age were not defined. Similarly, strict definitions for LETTB and iBTD were not defined as they represented a range of answers (for LETTB e.g.: "max. 3 metastases", "no hepatic metastases" or "few small metastases"). Differences in the proportion of experts who recommended TRT amongst radiation and medical oncologists were tested using two-sided chi-squared tests for equality of proportions with continuity correction.

Results

Five decision criteria were implemented in this analysis. Multiple participants stated e.g. the presence of "extensive extrathoracic disease", "limited number of metastases" or "maximum of 3 metastases"; these criteria were grouped into the binary criterion "limited extrathoracic tumour burden" (LETTB). Several participants selected the presence of significant intrathoracic disease or bulky thoracic disease before chemotherapy – this was summarized as initial bulky thoracic disease (iBTD). Response to chemotherapy was categorized into intrathoracic and extrathoracic response. Fitness was also selected as a decision criterion. Age criterion was only selected by only two medical oncologists as a contraindication to TRT, this criterion was therefore not included in the overall analysis.

Fig. 1 displays detailed results based on input from all participating experts. TRT was recommended by the majority in fit patients with limited extrathoracic tumour burden and good response to chemotherapy (CR, PR). Initial bulky thoracic disease was associated with a slightly higher rate of recommending TRT. This was true for both medical and radiation oncologists, with a higher proportion of radiation oncologists recommending TRT when the thoracic response was partial. In patients with thoracic CR after chemotherapy, the proportion of medical oncologists recommending TRT was higher but not statistically significant. TRT was not recommended in unfit patients and patients with progressive disease by most oncologists. In patients with significant extrathoracic disease, TRT was only recommended in case of CR and PR in the thorax in patients otherwise fit and with initial bulky thoracic disease (majority of 54%).

The recommendation to deliver RT after good response and limited extrathoracic disease burden was the same between radiation oncologists and medical oncologists (Table 1). The strongest consensus for TRT was in fit patients with limited extrathoracic disease burden, intrathoracic partial remission and extrathoracic good response (CR, PR).

Discussion

In spite of two international randomized phase III trials, there is no clear consensus as to which patients should be offered TRT in stage IV SCLC after chemotherapy.

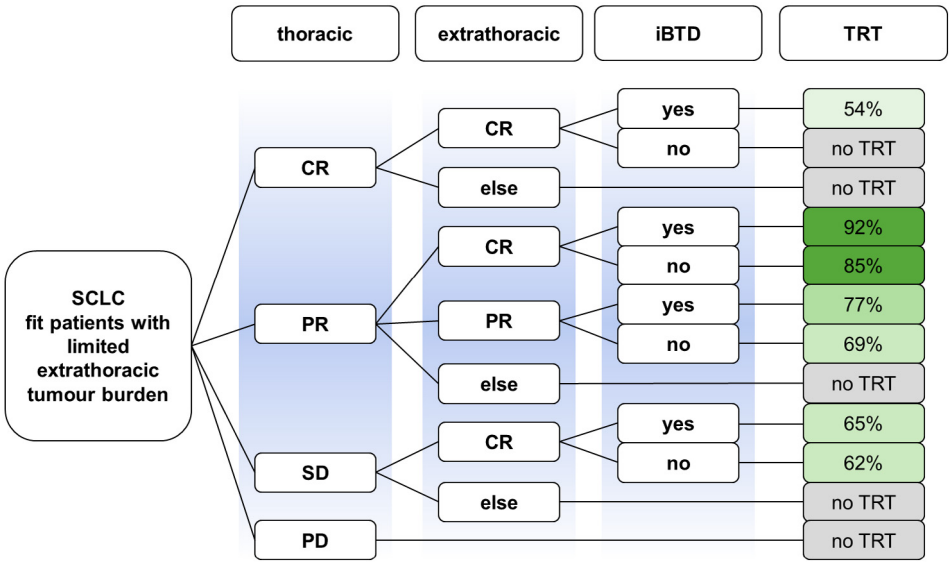

Fig. 1. Decision trees showing the use of thoracic radiotherapy (TRT) in stage IV SCLC amongst medical and radiation oncologists (thoracic and extrathoracic refers to response to chemotherapy in these respective locations, CR-complete response, PR-partial response, SD-stable disease, PD-progressive disease). iBTD – initial bulky thoracic disease.

Table 1
Recommendations for TRT in fit patients with limited extrathoracic tumour burden, based on overall response to chemotherapy and initial bulky thoracic disease. IASLC – medical oncologists, ESTRO – radiation oncologists.

Thoracic response	Extrathoracic response	Initial bulky disease	IASLC	ESTRO	*p*-value
CR	CR	Yes	62% (8/13)	46% (6/13)	0.69
CR	CR	No	46% (6/13)	38% (5/13)	1
CR	PR	Yes	54% (7/13)	46% (6/13)	1
CR	PR	No	38% (5/13)	38% (5/13)	1
PR	CR	Yes	92% (12/13)	92% (12/13)	1
PR	CR	No	77% (10/13)	92% (12/13)	0.59
PR	PR	Yes	62% (8/13)	92% (12/13)	0.16
PR	PR	No	46% (6/13)	92% (12/13)	**0.013**

bold *p*-value was statistically significant.

This patterns-of-decision analysis shows that in fit patients with good response to chemotherapy, with limited extrathoracic tumour burden, the majority of medical and radiation oncology experts would recommend TRT in stage IV SCLC. There was variation in the definition of «limited extrathoracic tumour burden», however for comparability a single term (LETTB) was used. In our survey the definition of LETTB represented answers like "max. 3 metastases" (based on the CREST subgroup analysis [4]), "no hepatic metastases" or "few small metastases" without a specific numerical cut-off. To date, little information exists to elucidate varying prognosis amongst patients with different sites or numbers of metastases from lung cancer.

Generally, there was an agreement between medical and radiation oncologists. In the setting of CR within the thorax and PR outside of the thorax, medical oncologists were marginally more likely to recommend TRT. In patients with intra- and extrathoracic partial response, radiation oncologists were more likely to recommend TRT than medical oncologists. This may be explained by a higher proportion of radiation oncologists being convinced by the CREST subgroup analysis [4], in which the presence or absence of intrathoracic tumour after completion of chemotherapy was a stratification factor. The analysis revealed that the difference in 1 yr OS between patients with residual intrathoracic tumour after chemotherapy was statistically significantly favouring the TRT arm [17].

Age was not considered in the analysis, however it was selected as a criterion precluding TRT by two medical oncologists. The general consensus was that age should not be considered a significant decision criterion independent of fitness. This is supported by the CREST trial, in which no significant difference in outcome was reported between patients below or above the age of 70. It should be noted that around 10% of included patients had a WHO performance score 2, and 8% of patients were over 75 years.

Response to chemotherapy was a significant factor influencing the recommendation to offer consolidative TRT. CR and PR were typically associated with a recommendation to offer TRT. The ratio of intrathoracic to extrathoracic disease is one of the main driving factors when considering TRT. The results are based on decision trees populated by experts in the field of SCLC. Although participating experts were selected by IASLC and ESTRO, both unaware of the study objective, from a range of countries representing different practices and health-care systems, a difference in results with a different selection of experts cannot be excluded and a strict definition of the term expert was not defined. Whilst it cannot be excluded, a higher number of experts would probably not significantly change the identified trends as the criteria selected and the trends identified were rather homogeneous. However, the specific percentages for majorities would quite possibly be a bit different with a different set of experts. At the time this survey was done the commonly used treatment regime was carboplatin/etoposide. How the addition of atezolizumab will change the implementation of TRT is not currently answered and needs further investigation. We phrased the study question openly in order to avoid suggesting specific parameters or cut-off values. Despite

this, a set of decision criteria were identified which seem to represent the relevant decision criteria for most experts in this setting, we believe future trials and guidelines should take the identified criteria into account. Whilst majorities were identified in this analysis, this manuscript does not represent a clinical guideline.

In conclusion, experts from both IASLC and ESTRO, representing European radiation and medical oncologists specializing in lung cancer, recommend consolidative TRT in selected patients with stage IV SCLC and restrict its use primarily to fit patients, who responded to chemotherapy.

Conflict of interest

All authors have no conflict of interest related to this manuscript.

References

[1] Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379:2220–9.
[2] Slotman BJ, van Tinteren H, Praag JO, Knegjens JL, El Sharouni SY, Hatton M, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 2015;385:36–42.
[3] Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007;357:664–72.
[4] Slotman BJ, Faivre-Finn C, van Tinteren H, Keijser A, Praag J, Knegjens J, et al. Which patients with ES-SCLC are most likely to benefit from more aggressive radiotherapy: a secondary analysis of the Phase III CREST trial. Lung Cancer 2017;108:150–3.
[5] Haslett K, De Ruysscher D, Dziadziuszko R, Guckenberger M, Pechoux CL, Nestle U, et al. Short communication: management of patients with extensive-stage small-cell lung cancer treated with radiotherapy: a survey of practice. Cancer Treat Res Commun 2018;17:18–22.
[6] Jeremic B, Shibamoto Y, Nikolic N, Milicic B, Milisavljevic S, Dagovic A, 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 1999;17:2092-.
[7] Zhu H, Zhou Z, Wang Y, Bi N, Feng Q, Li J, et al. Thoracic radiation therapy improves the overall survival of patients with extensive-stage small cell lung cancer with distant metastasis. Cancer 2011;117:5423–31.
[8] Giuliani ME, Atallah S, Sun A, Bezjak A, Le LW, Brade A, et al. Clinical outcomes of extensive stage small cell lung carcinoma patients treated with consolidative thoracic radiotherapy. Clin Lung Cancer 2011;12:375–9.
[9] Putora PM, Oldenburg J. Swarm-based medicine. J Med Internet Res 2013;15:e207.
[10] Rothermundt C, Bailey A, Cerbone L, Eisen T, Escudier B, Gillessen S, et al. Algorithms in the first-line treatment of metastatic clear cell renal cell carcinoma-analysis using diagnostic nodes. Oncologist 2015;20:1028–35.
[11] Glatzer M, Panje CM, Siren C, Cihoric N, Putora PM. Decision making criteria in oncology. Oncology 2018:1–9.
[12] Putora PM, Glatzer M, et al. Prophylactic cranial irradiation in stage IV small cell lung cancer: selection of patients amongst European IASLC and ESTRO experts. Radiother Oncol 2019;133:163–6.
[13] Rich AL, Tata LJ, Free CM, Stanley RA, Peake MD, Baldwin DR, et al. Inequalities in outcomes for non-small cell lung cancer: the influence of clinical characteristics and features of the local lung cancer service. Thorax 2011;66:1078–84.
[14] Fowler Jr FJ, McNaughton Collins M, Albertsen PC, Zietman A, Elliott DB, Barry MJ. Comparison of recommendations by urologists and radiation oncologists for treatment of clinically localized prostate cancer. J Am Med Assoc 2000;283:3217–22.
[15] Panje CM, Glatzer M, von Rappard J, Rothermundt C, Hundsberger T, Zumstein V, et al. Applied swarm-based medicine: collecting decision trees for patterns of algorithms analysis. BMC Med Res Method 2017;17:123.
[16] Putora PM, Panje CM, Papachristofilou A, Dal Pra A, Hundsberger T, Plasswilm L. Objective consensus from decision trees. Radiat Oncol 2014;9:270.
[17] Slotman BJ, van Tinteren H, Praag JO, Knegjens JL, Sharouni SYE, Hatton M, et al. Radiotherapy for extensive stage small-cell lung cancer – authors' reply. Lancet 2015;385:1292–3.