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ORIGINAL ARTICLE

A National Survey on the Current Status of Radiotherapy in Extensive Stage Small-cell Lung Cancer: Turkish Society of Radiation Oncology Thoracic Oncology Group Study

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OBJECTIVE

We aimed to investigate the current status and use of thoracic radiotherapy (TRT) and prophylactic cranial irradiation (PCI) in extensive-stage small-cell lung cancer (ES-SCLC) patients who responded to chemotherapy (ChT) through a nationwide survey.

METHODS

An electronic survey was created. We invited all the Turkish Society of Radiation Oncology-registered radiation oncologists (ROs).

RESULTS

A total of 101 ROs participated. TRT was routinely recommended to patients who responded to ChT by 76% of ROs. The highest agreement for TRT indication (%94) was in the case of symptomatic residual disease. The most commonly used fractionation scheme was 30 Gy in 10 fractions. There was an increase in the use of 30 Gy in 10 fractions after the publication of the CREST trial. The implementation criteria for TRT were site and number of metastases for 65% and 42% of respondents, respectively. PCI was recommended by 89% routinely. The most commonly (93%) used fractionation scheme was 25 Gy in 10 fractions.

CONCLUSION

This survey highlights the absence of consensus on the eligibility criteria and dosage of TRT in ES-SCLC within the Turkish RO community. The highest agreement for the TRT indication was in patients with symptomatic intrathoracic residual disease. The CREST trial impacted TRT indications and fractionation. There was high consistency in practice in terms of PCI indication, dose, and fractionation.

Keywords: Extensive stage small-cell lung cancer; radiotherapy; survey.

INTRODUCTION

Extensive-stage small-cell lung cancer (ES-SCLC) constitutes almost two-thirds of SCLC patients.[1] Chemotherapy (ChT) combined with immunotherapy has become the new systemic standard of care[2] following the results of two randomized phase III trials.[3,4] Thoracic radiotherapy (TRT) has typically been used

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for palliation. However, intrathoracic residual disease after systemic therapy is of major concern. Intrathoracic control is important to delay disease progression and for symptom control. The role of TRT has been debated during the ChT era, but today, in the immuno-ChT era, it's more debatable.

In 2015, a landmark randomized phase III CREST trial was conducted in 42 hospitals in the UK, Netherlands, and Belgium.[5] Between 2009 and 2012, 498 ES-SCLC patients with confirmed responses to 4–6 cycles of ChT were enrolled. Patients were randomized 1:1 to receive TRT (30 Gy in 10 fractions) or no TRT. All patients received prophylactic cranial irradiation (PCI). At a median follow-up of 24 months, overall survival (OS) at 1 year was not statistically different (33% vs. 28%) between the two groups, with a HR of 0.84 (95% CI 0.69–1.01). In a secondary analysis, OS at 2 years was 13% versus 3%, favoring TRT (p=0.004). Progression was less likely in the TRT group with a 6-month PFS of 24% versus 7% than in the no TRT group (HR: 0.73, 95% CI: 0.61–0.87). These results have raised controversy regarding TRT in ES-SCLC patients.

Because of the paucity of data on the effect of PCI in ES-SCLC, EORTC conducted a randomized trial for the assessment of PCI in 286 ES-SCLC patients with any response to induction ChT.[6] This trial has been criticized for several aspects, for example, the use of non-platinum-based ChT in the first line, the lack of imaging assessment to confirm the absence of brain metastasis at study enrollment, the use of various radiation doses and fractionation in PCI (20–30 Gy in 5–12 fractions), and the lack of follow-up imaging assessment for brain metastasis in no PCI group. Recently, conflicting data on this subject has come from Japan. The recent phase III trial by Takahashi et al.[7] showed no OS benefit with PCI over active magnetic resonance imaging (MRI) surveillance among patients with ES-SCLC, questioning the previously established benefit of PCI for this patient group. Besides, the Japanese trial has a more powerful background, such as cisplatinum-based doublet as first line ChT, the absence of brain metastasis by MRI assessment within 4 weeks at enrollment, and surveillance with MRI in the observation group.

Before the introduction of immunotherapy in ES-SCLC patients in our country, these recent trials on TRT and PCI in ES-SCLC patients raised controversy regarding the implementation of TRT and PCI, which led us to investigate the current status and use of TRT and PCI in ES-SCLC patients who responded to ChT by a nationwide survey in our community.

MATERIALS AND METHODS

An electronic questionnaire comprising 33 multiple-choice questions and one open-ended question was developed following a review of the current literature. The first part was composed of demographic questions, the following parts mainly focused on the staging investigations, eligibility criteria, preferred fractionation schemes for TRT and PCI in ES-SCLC patients with any response to ChT, use of TRT in different clinical scenarios (symptomatic residual thoracic disease, asymptomatic residual thoracic disease, and no residual thoracic disease), and future research questions, respectively.

The study received approval from the Tepecik Training and Research Hospital Ethics Board in May 2019. An electronic survey was created. We invited all the Turkish Society of Radiation Oncology (TROD)-registered radiation oncologists (ROs) to answer a survey, addressing their use of TRT and PCI for patients with ES-SCLC. An e-mail with the link to the survey to participate was distributed among TROD members through TROD in July 2019. Electronic informed consent was obtained from each participant online before the survey commencement. The responses were collected in September 2019 and then analyzed using descriptive statistics. A copy of the questionnaire has not been included in this article, but the full version is available upon request.

RESULTS

Demographics

A total of 101 ROs participated. The respondents predominantly practiced at a university hospital (42%). The percentages of ROs practicing in research and training hospitals, private hospitals, and public hospitals were 38%, 15%, and 5%, respectively. The number of SCLC patients treated per month was between 10 and 50 in 46%, <10 in 44%, and 50 or more in 9% of participants.

Staging Investigations

The routine staging investigations performed before ChT were PET/CT and cranial MRI in 100% and 82%, respectively. After ChT, PET/CT and cranial MRI were used by 99% and 53% of participants for restaging, respectively.

TRT

TRT was routinely recommended to patients who responded to ChT by 76% of ROs. The preferred fractionation schemes are shown in Figure 1.

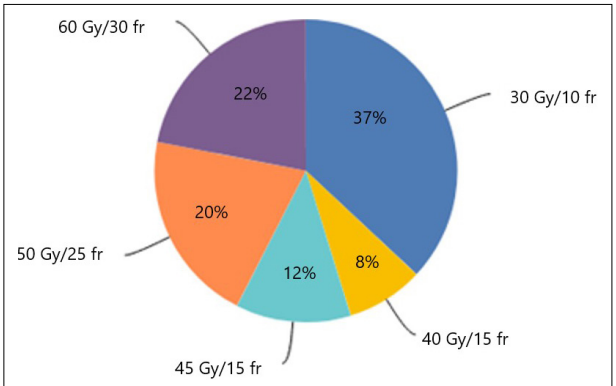

Fig. 1. Thoracic RT fractionation schemes.

Table 1 Thoracic RT fractionation schemes according to different scenarios

Dose/ fractionation scheme	Symptomatic residue (%)	Asymptomatic central residue (%)	Asymptomatic non-central residue (%)
10 fr/30 Gy	33	33	25
15 fr/40 Gy	9	7	5
15 fr/45 Gy	17	17	9
25 fr/50 Gy	9	14	19
30 fr/60 Gy	30	27	41
Other	2	2	1

RT: Radiotherapy.

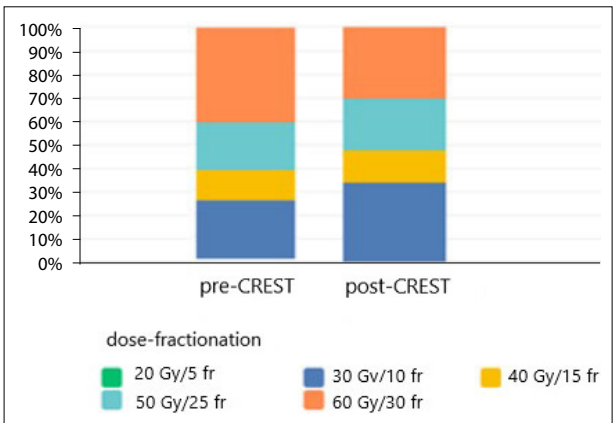

Fig. 2. The preferred thoracic RT fractionation schemes before and after CREST study.

According to different scenarios, TRT use ratios after any response to ChT were as follows: In case of symptomatic residual disease, asymptomatic central residual disease, and asymptomatic non-central residual disease, 94%, 85%, and 77%, respectively. Thoracic RT fractionation schemes according to different scenarios are shown in Table 1.

An upper age limit and performance status, mostly ECOG 2, were applied for the selection of patients for TRT by 16% and 71% of participants, respectively. The metastatic site was used as an implementation criterion for TRT by 64% of respondents. These metastatic sites and their usage rates as a criterion were as follows: Leptomeningeal 58%, cranial 26%, pleural 12%, diffuse hepatic 1%, diffuse bone 1%, and multiple sites 2%. Besides, the number of metastases was used as a selection criterion by only 42% of ROs. One to two metastases, two to five, and more than five metastases were considered an upper limit for TRT by 41%, 58%, and 1% of participants, respectively. Consolidative RT for asymptomatic metastases was a common practice in 37% of participants.

After the publication of the CREST study, which randomized ES-SCLC patients to PCI only vs. PCI and TRT in ES-SCLC patients, 57% of the respondents mentioned an increase, and 5% mentioned a decrease in their TRT indications. On the other hand, 38% reported no change. The effect of this study on dose-fractionation schemes can be seen in Figure 2.

PCI

In patients who had any response to ChT, 89% of ROs recommended PCI routinely. The most commonly (93%) used fractionation scheme was 25 Gy in 10 fractions. An upper age limit and performance status, mostly ECOG 2, was applied for the selection of patients for PCI by 14% and 68% of participants, respectively. The publication of phase III Japanese trial randomizing PCI and close surveillance with cranial MRI in ES-SCLC patients did not have an implication on PCI indications in 86% of respondents.

Future Research

When asked which research subject was important for the future, increasing the dose of TRT, SABR/conventional RT to metastatic sites, early start of TRT even concurrent with ChT if possible, and adding immunotherapy to TRT were implicated by 31%, 74%, 40%, and 46% of respondents, respectively.

DISCUSSION

The aim of our study was to understand the current status and use of TRT and PCI in ES-SCLC patients who responded to ChT among members of TROD.

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There was a wide variation in our community in terms of TRT dose fractionation schedules, which is in line with the literature.[8,9] Although the largest trial recommended 30 Gy/10 fractions,[5] the greatest survival benefit from the randomized data was shown by Jeremic et al.[10] where the highest dose of radiation was delivered several retrospective studies have shown that a higher dose of thoracic radiation is correlated with a greater OS benefit in ES-SCLC.[11] A total of 30 Gy in 10 fractions was the most commonly used (37%) regimen among our participants. While the most preferred fractionation scheme was 30 Gy in 10 fractions for symptomatic residue and asymptomatic central residue, 60 Gy in 30 fractions was the preferred scheme for asymptomatic non-central residue. The reason for the discrepancy between the doses in asymptomatic central and peripheral tumors is unknown.

Our results show an increase in the use of TRT in ES-SCLC after the publication of the CREST trial.[5,12] Furthermore, there was an increase in the use of 30 Gy in 10 fractions and a decrease in the use of 60 Gy in 30 fractions, suggesting the CREST trial has changed the daily practice. Indeed, the CREST trial had a great impact across Europe; it has increased the use of TRT. Besides, the dose and fractionation of that trial have been widely adopted.[8]

A major concern about TRT is which patients with ES-SCLC are most likely to benefit from consolidative TRT.[13] This has been evaluated by secondary analysis of the CREST trial.[12] Of the 495 patients included in the intent-to-treat analysis, 434 had residual intrathoracic disease at baseline, and 61 patients had no residual intrathoracic disease. In the trial, patients were stratified by the presence or absence of intrathoracic disease after ChT. Since residual intrathoracic disease was a stratification factor, there were no differences in patient characteristics between the two groups. The analysis demonstrated a statistically significant OS benefit in patients with residual intrathoracic disease who received TRT (hazard ratio 0.81, 95% CI 0.66–1.00, p=0.044). No such benefit for TRT was seen in patients without residual intrathoracic disease, suggesting that the presence of residual intrathoracic disease after ChT is a factor that should be considered in patient selection.[12] Similarly, in our survey, the highest agreement for TRT was in patients with symptomatic intrathoracic residual disease.

At that point, it would be appropriate to add that, in the era of immunotherapy, there is no certain idea whether TRT could play a positive role for patients with ES-SCLC or not. Since ChT combined with immunotherapy has become the new systemic standard of care treatment following the results of two randomized phase III trials investigating anti-PD-L1 (atezolizumab-IMpower133 or durvalumab-CASPIAN) in addition to ChT in ES-SCLC,[4,3] the role of PCI and TRT in this setting has become more controversial. Since TRT was not allowed both in the IMpower133 and CASPIAN trials, we have to wait for the safety and efficacy of thoracic chemoradiation with immunotherapy until the results of the upcoming NRG oncology phase III study (LU005) of chemoradiation±atezolizumab in the LS-SCLC setting (NCT03811002).

The number and site of metastases are also important concerns for TRT indications in ES-SCLC patients. In the CREST trial, regardless of the administration of TRT, both OS (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 two metastases, compared to those with three or more distant metastases.[12] In contrast to this finding, less than half of our respondents mentioned that they use the number of metastases as a patient selection criterion. Besides, two to five metastases were mostly considered an upper limit for TRT.

In a secondary analysis of the CREST trial, the presence of bone (p=0.04) and liver metastases (p=0.003) was significantly associated with worse OS.[12] However, our participants used mostly leptomeningeal, cranial, and pleural metastases as an exclusion criterion for TRT indication.

There was high consistency in practice in our community in terms of PCI indication, total dose, and fractionation, which was a similar finding by Haslett et al.[8] Although the Japanese trial[7] questioning the previously established benefit of PCI has fueled a great debate over the role of PCI worldwide[14] it has not had a great impact on our community. This might be the result of concerns about differences in ethnicity and the absence of a cost-effectiveness study in our country. Recently, the cost-effectiveness of MRI surveillance versus PCI has been reported by Kim et al.[15] and PCI was not found to be cost-effective compared with MRI surveillance alone, owing to the neurocognition decline effect of PCI based on available evidence.

The routine clinical practice mostly differed among ROs in routine staging procedures, especially after ChT in terms of cranial MRI. However, this finding is in line with the literature.[8]

Limitations of the Study

The limitations of this survey warrant consideration. As a result of volunteer response bias, the results may not be broadly representative of the views of all ROs in our country and may not be generalizable to other countries. Moreover, the limitations on the scope of response options due to the design of the survey limit our comprehensive understanding of the perceptions of respondents. Besides, at the time of our survey, IMpower-133 had just been released and CASPIAN had not yet been published. Therefore, if we had done a similar survey in the current period, we might have encountered different results.

CONCLUSION

The aim of our study was to understand the current status and use of TRT and PCI in ES-SCLC patients with any response to ChT. This survey highlights the absence of consensus on the eligibility criteria, dose-fractionation scheme of TRT, and staging procedures within our radiation oncology community. There was an impact from the CREST trial in terms of TRT indications and fractionation. The highest agreement for TRT was in patients with symptomatic intrathoracic residual disease. There was high consistency in practice in our community in terms of PCI indication and dose-fractionation scheme. There were no major changes in the use of PCI for patients with ES-SCLC following the publication of the Japanese trial by Takahashi et al.[7]

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