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MINIREVIEWS

Optimal timing of thoracic irradiation for limited stage small cell lung cancer: Current evidence and future prospects

Omer Sager, Ferrat Dincoglan, Selcuk Demiral, Hakan Gamsiz, Bora Uysal, Fatih Ozcan, Onurhan Colak, Esra Gumustepe, Yelda Elcim, Esin Gundem, Bahar Dirican, Murat Beyzadeoglu

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Abstract

Lung cancer is a global health concern as the leading cause of cancer related mortality worldwide. Small cell lung cancer (SCLC) poses a formidable challenge to the treating physicians with the worst prognosis among all lung cancers. However, limited stage SCLC (LS-SCLC) has a relatively better outcome with multimodality management. Efforts have been focused on optimal integration of treatment modalities to achieve an improved therapeutic ratio for patients with LS-SCLC. While chemotherapy and thoracic radiation therapy (TRT) are primary components of initial management for LS-SCLC, there is no consensus on optimal timing of TRT. Within this context, we herein provide a concise overview of current evidence and future prospects regarding the optimal timing of thoracic irradiation for LS-SCLC in light of the literature.

Key Words: Small cell lung cancer; Thoracic irradiation; Limited stage small cell lung cancer; Timing of thoracic radiation therapy; Thoracic radiation therapy

Core Tip: There has been extensive effort to establish optimal timing of thoracic radiation therapy (TRT) in limited stage small cell lung cancer (LS-SCLC) management. While late TRT may have utility for management of LS-SCLC patients who may not tolerate curative-intent upfront chest irradiation due to excessive tumor burden at the outset, early TRT allows for exploiting the synergistic effect of chemoradiotherapy to eradicate as many tumor cells as possible in a shorter timeframe. Admittedly, differences in trial designs, definition of early and late TRT, patient selection criteria, administered chemotherapy regimens, treatment compliance, TRT dose and fractionation may affect treatment outcomes.

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INTRODUCTION

Lung cancer presents a major and global health concern as a leading cause of cancer related mortality worldwide[1,2]. The 2 major histological types of lung cancer include small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). While NSCLC is the most common type, SCLC is typically associated with worse prognosis due to short doubling time and high growth fraction[3-7]. SCLC has been traditionally staged as limited stage SCLC (LS-SCLC) and extensive stage SCLC (ES-SCLC) by the Veterans' Administration Lung Study Group (VALSG) two-stage classification scheme, however, International Association for the Study of Lung Cancer staging with tumor, node, metastasis classification may also be used[8-10]. According to VALSG system, LS-SCLC is defined as disease confined to one hemithorax which can be adequately encompassed in a reasonable radiation portal. ES-SCLC refers to disease extending beyond one hemithorax which can not be encompassed within a tolerable radiation portal and may include presence of malignant pleural or pericardial effusions, contralateral hilar or supraclavicular lymph nodes, and hematogenous metastases[9,10]. While the overall prognosis of SCLC is typically poor, a subgroup of patients with LS-SCLC may have relatively more favorable treatment outcomes[11]. In light of high level evidence from systematic reviews, guidelines, and metaanalyses, current standard management of LS-SCLC includes combination of chemotherapy and thoracic radiation therapy (TRT)[12-16]. While there is consensus on combined modality management for LS-SCLC, controversies remain regarding target volumes, dose fractionation regimens and optimal sequencing of chemotherapy and TRT[17,18]. Herein, we provide a concise overview of current evidence and future prospects regarding the optimal timing of thoracic irradiation for LS-SCLC in light of the literature.

COMBINED MODALITY MANAGEMENT FOR LS-SCLC

Addition of TRT to chemotherapy has been shown to improve survival of patients with LS-SCLC as demonstrated by high level evidence[15,16]. In this context, combined modality management with chemotherapy and TRT has been standard treatment for LS-SCLC. Since the mechanism of action is different between these 2 modalities, there is potential for additive and synergistic effects which may lead to improved therapeutic outcomes[18]. SCLC is well known for its propensity to disseminate early in the course of the disease. From this standpoint, it may be feasible to consider the potential of combining 2 different therapeutic modalities for eradication of tumor clonogens to achieve both local and systemic control. In addition to eradication of tumor cells by different mechanisms, synchronous administration of chemotherapy may also play a radiosensitizer role which may enhance the overall effect of combined modality management[18,19].

Main rationale of combined modality management is to eradicate as many tumor cells as possible in a shorter timeframe by exploiting the synergistic effect of chemoradiotherapy. SCLC has tendency for early systemic dissemination, however, there is great potential for achieving good response from chemoradiotherapy given the radiosensitivity and chemosensitivity of tumor cells. Combined modality management may also offer a judicious strategy to overcome accelerated repopulation which is an important cause of treatment failures[18].

OPTIMAL TIMING OF THORACIC IRRADIATION FOR LS-SCLC

Optimal TRT timing in LS-SCLC management has been the subject of several studies, systematic reviews and metaanalyses over the years[20-41]. Selected studies of early and late TRT for LS-SCLC management are summarized in Table 1.

Murray *et al*[20] reported outcomes of a randomized National Cancer Institute of Canada Clinical Trials Group study including 308 eligible patients with LS-SCLC. The study included 155 patients in the early TRT arm (starting in day 22) and 153 patients in the late TRT arm (starting in day 106). Administered chemotherapy regimen included cyclophosphamide, doxorubicin, and vincristine alternating with etoposide and cisplatin, delivered for 3 cycles each every 3 wk. Dose of TRT was 40 Gy delivered in 15 daily fractions over 3 wk. Median progression free survival (PFS) was 15.4 mo in early TRT arm and 11.8 mo in late TRT arm. There was statistically significant improvement in 3 year PFS (26% *vs* 19%, $P = 0.036$), 3 year overall survival (OS) (29.7% *vs* 21.5%, $P = 0.006$), and median survival (21.2 mo *vs* 16 mo, $P = 0.008$) in favor of early TRT[20].

Work *et al*[21] conducted a randomized study of initial *vs* late chest irradiation combined with chemotherapy in LS-SCLC on behalf of the Aarhus Lung Cancer Group from Denmark. A total of 199 consecutive patients were randomly assigned to receive initial chest irradiation or late chest irradiation given 18 wk delayed. There were 99 patients in early TRT arm and 100 patients in late TRT arm all receiving the same 9 cycles of combination chemotherapy including 3 cycles of cisplatin and etoposide and 6 cycles of cyclophosphamide, doxorubicin, and vincristine. Median survival was 10.5 mo in early TRT arm and 12 mo in late TRT arm. Timing of TRT was not found to affect on the incidence of in field recurrences, CNS recurrences, or OS in the study[21]. Inferior outcomes in this study may be partly explained by the reduced chemotherapy doses in the concurrent chemoradiation arm and changing of the TRT schedule from 40 Gy in 20 fractions to 45 Gy in 22 fractions during the study period. Admittedly, initially delivered TRT doses of 40 Gy in 20 fractions may be considered low in comparison with current management standards and may have contributed to inferior outcomes in the study.

Jeremic *et al*[22] reported outcomes of a randomized study on initial *vs* delayed accelerated hyperfractionated TRT and concurrent chemotherapy for LS-SCLC. The study was conducted at the Department of Oncology, University of Kragujevac, Yugoslavia. Out of the total 103 eligible patients, 52 patients were allocated to receive early TRT (starting on day 1) and 51 patients were allocated to receive late TRT (starting on day 43). All patients received a total TRT dose of 54 Gy delivered twice daily fractions of 1.5 Gy. Chemotherapy schedule consisted of concurrent daily carboplatin/etoposide (C/E) (30 mg each) and 4 sequential cycles of cisplatin/etoposide (PE) (30 mg/m^2 and 120 mg/m^2, respectively, on days 1 to 3). Median survival was 34 mo in early TRT arm and 26 mo in late TRT arm, and the Kaplan-Meier 5-year survival rates were 30% *vs* 15%, in favor of early TRT[22].

Gregor *et al*[23] conducted the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group randomized trial of alternating *vs* sequential radiotherapy/chemotherapy in LS-SCLC. A total of 335 eligible patients were randomized to 5 courses of cyclophosphamide, doxorubicin, and etoposide (CDE) chemotherapy followed by TRT and same total dose of chemotherapy and TRT split into 4 courses of 5 daily fractions delivered on days 14 to 21 of the second and subsequent chemotherapy courses. No significant difference was found between the 2 arms in terms of median survival (14 *vs* 15 mo in early *vs* late TRT arms), 1-year survival (60% *vs* 64% in early *vs* late TRT arms), 2 year survival (26% *vs* 23% in early *vs* late TRT arms), and 3-year survival (12% *vs* 15% in early *vs* late TRT arms)[23]. The study failed to confirm the superiority of an alternating schedule of delivery which may be partly explained by hematologic toxicity with this combination of chemotherapy and TRT.

Perry *et al*[24] reported the 10 year update of the experience of the Cancer and Leukemia Group B 8083 study assessing addition of TRT to chemotherapy in LS-SCLC. In the study, a total of 399 patients with LS-SCLC were randomized to receive TRT starting on day 1 (arm I) or day 64 of chemotherapy treatment (arm II), or chemotherapy alone with cyclophosphamide, vincristine, and etoposide (later, doxorubicin). Total TRT dose was 50 Gy delivered in daily fractions of 2 Gy over 5 wk. Median survival was 13.04 mo, 14.54 mo, and 13.58 mo in arm I, arm II, and arm III, respectively with statistical significance ($P = 0.0072$). The authors concluded that the 2 arms including TRT remained to be superior to chemotherapy alone with 10 years of follow-up[24].

Skarlos *et al*[25] conducted the randomized phase II Hellenic Cooperative Oncology Group (HeCOG) study assessing the timing of hyperfractionated TRT (early *vs* late) when given concurrently with chemotherapy. A total of 81 eligible patients with LS-SCLC were randomized to receive hyperfractionated TRT either concurrently with the first cycle of chemotherapy (early TRT group) or with the fourth cycle of chemotherapy (late TRT group). Chemotherapy included carboplatin delivered at an area under the curve of 6 as intravenous infusion followed by etoposide at a dose of 100 mg/m^2 intravenously for 3 consecutive days every 3 wk up to a total of 6 cycles. Overall response rate was 76% in early TRT group and 92.5% in late TRT group. Complete response rate was 40.5% and 56.5% in early and late TRT groups, respectively. Overall median survival was 17.5 and 17 mo, 2 year survival was 36% and 29%, 3 year survival was 22% and 13% in early and late TRT groups, respectively without statistical significance[25].

Table 1 Selected randomized studies of early and late thoracic radiation therapy for limited stage small cell lung cancer management

Ref.	Period	Number of patients	Age	Performance status	Timing of RT (start of TRT) (d)	RT dose fractionation schedule	Chemotherapy Schedule	PCI	Survival	*P* value
Murray *et al*[20], 1993, National Cancer Institute of Canada Clinical Trials Group Study	1985-1988	Total number of patients 308; 155 patients in early TRT group; 153 patients in late TRT group	Median age 61.8 yr in early TRT group; Median age 61.6 yr in late TRT group	ECOG 0-1 87% in early TRT group; ECOG 0-1 90% in late TRT group	Day 22 in early TRT group; Day 106 in late TRT group	40 Gy/2.67 Gy daily RT (hypofractionation)	Platinum based chemotherapy	86% of patients received PCI (2.5 Gy × 10 fractions)	Median survival 21.2 mo in early TRT group; 2-yr survival 40% in early TRT group; 3-yr survival 29.7% in early TRT group; Median survival 16 mo in late TRT group; 2-yr survival 34% in late TRT group; 3-yr survival 21.6% in late TRT group	0.006 in favor of early TRT
Work *et al*[21], 1997, Aarhus Lung Cancer Group Study	1981-1989	Total number of patients 199; 99 patients in early TRT group; 100 patients in late TRT group	Age range 36-70 yr in early TRT group; Age range 36-69 yr in late TRT group	KPS 80-100 82% in early TRT group; KPS 80-100 80% in late TRT group	Day 1 in early TRT group; Day 120 in late TRT group	40-45 Gy/2 Gy daily (conventional fractionation) split course RT over 7 wk	Platinum based chemotherapy	All early RT patients received PCI; 58% of late RT patients received PCI	Median survival 10.5 mo in early TRT group; 2-yr survival 20.2% in early TRT group; 3-yr survival 13.1% in early TRT group; Median survival 12 mo in late TRT group; 2-yr survival 19% in late TRT group; 3-yr survival 12% in late TRT group	Not statistically significant
Jeremic *et al*[22], 1997, University of Kragujevac, Yugoslavia study	1988-1992	Total number of patients 103; 52 patients in early TRT group; 51 patients in late TRT group	Age range 40-67 yr in early TRT group; Age range 44-66 yr in lateTRT group	KPS 90-100 52% in early TRT group; KPS 90-100 47% in late TRT group	Day 1 in early TRT group; Day 43 in late TRT group	54 Gy 1.5 Gy BID (hyperfractionation)	Platinum based chemotherapy	All patients with complete or partial response received PCI (2.5 Gy × 10 fractions)	Median survival 34 mo in early TRT group; 2-yr survival 71.2% in early TRT group; 3-yr survival 48.1% in early TRT group; Median survival 26 mo in late TRT group; 2-yr survival 52.9% in late TRT group; 3-yr survival 39.2% in late TRT group	0.027 in favor of early TRT
Gregor *et al*[23], 1997, EORTC Lung Cancer Co-operative Group Study	1989-1995	Total number of patients 335	Median age 61 yr (range: 33-75 yr)	ECOG 0-1 in 311 patients	Day 42 in early TRT group; Day 91 in late TRT group	12.5 Gy/2.5 Gy daily (1 wk on, 3 wk off) × 4 in early TRT group (hypofractionation); 50 Gy/2.5 Gy daily in late TRT group (hypofractionation)	No platinum based chemotherapy	PCI was not a formal part of the study, however, all patients with complete response were eligible	Median survival 14 mo in early TRT group; 2-yr survival 26% in early TRT group; 3-yr survival 12% in early TRT group; Median survival 15 mo in late TRT group; 2-yr survival 23% in late TRT group; 3-yr survival 15% in late TRT group	Not statistically significant
Perry *et al*[24], 1998, Cancer and Leukemia Group B (CALGB) study	1981-1984	Total number of patients 270; 125 patients in early TRT group; 145 patients in late TRT group	Age range 32-79	ECOG 0-1 86% in early TRT group; ECOG 0-1 87% in late TRT group	Day 1 in early TRT group; Day 64 in late TRT group	50 Gy/2 Gy daily conventionally fractionated RT over 5 wk	No platinum based chemotherapy	All patients received PCI (3 Gy × 10 fractions)	Median survival 13.04 mo in early TRT group; 2-yr survival 24% in early TRT group; 3-yr survival 7.2% in early TRT group; Median survival 14.54 mo in late TRT group; 2-yr survival 31.7% in late TRT group; 3-yr survival 13.8% in late TRT group	0.0072 in favor of lateTRT
Skarlos *et al*[25], 2001, Hellenic	1993-1999	Total number of patients 81; 42	Age range 40-76 yr in early	ECOG 0-1 76% in early TRT group;	Day 1 in early TRT	45 Gy 1.5 Gy BID (hyperfractionation)	Platinum based chemotherapy	All patients with complete or near	Median survival 17.5 mo in early TRT group; 2-yr survival 36% in	Not statistically significant

Cooperative Oncology Group (HeCOG) study		patients in early TRT group; 39 patients in late TRT group	TRT group; Age range 38-79 yr in late TRT group	ECOG 0-1 85% in late TRT group	group; Day 56 in late TRT group			complete response received PCI (1.5 Gy BID × 6)	early TRT group; 3-yr survival 22% in early TRT group; Median survival 17 mo in late TRT group; 2-yr survival 29% in late TRT group; 3-yr survival 13 % in late TRT group	
Takada *et al*[26], 2002, Japan Clinical Oncology Group (JCOG) Study	1991-1995	Total number of patients 228; 114 patients in early TRT group; 114 patients in late TRT group	Age range 39-74 yr in early TRT group; Age range 30-74 yr in late TRT group	ECOG 0-1 95% in both early and late TRT groups	Day 2 in early TRT group; Day 85 in late TRT group	45 Gy 1.5 Gy BID (hyperfractionation)	Platinum based chemotherapy	All patients with complete response received PCI (4 Gy × 6)	Median survival 27.2 mo in early TRT group; 2-yr survival 54.4% in early TRT group; 3-yr survival 29.8% in early TRT group; Median survival 19.7 mo in late TRT group; 2-yr survival 35.1% in late TRT group; 3-yr survival 20.2% in late TRT group	0.097 in favor of early concurrent TRT but not statistically significant

TRT: Thoracic radiation therapy; PCI: Prophylactic cranial irradiation.

Takada *et al*[26] reported the results of the Japan Clinical Oncology Group phase III study 9104 assessing concurrent *vs* sequential TRT in combination with cisplatin and etoposide for LS-SCLC. Total dose of TRT was 45 Gy delivered in twice daily fractions of 1.5 Gy over 3 wk. Patients were randomized to sequential or concurrent TRT arms. All patients received 4 cycles of cisplatin plus etoposide every 3 wk in the sequential arm or 4 wk in the concurrent arm. TRT was started on day 2 of the first cycle of chemotherapy in concurrent arm and after the fourth cycle in the sequential arm. Concurrent TRT conferred improved survival compared to sequential TRT (P = 0.097, not statistically significant). Median survival was 19.7 mo *vs* 27.2 mo in the in the sequential and concurrent TRT arms, respectively. The 2, 3, and 5 year survival rates were were 35.1%, 20.2%, and 18.3% *vs* 54.4%, 29.8% and 23.7% for patients receiving sequential *vs* concurrent TRT, respectively[26].

While all these randomized studies have addressed sequencing of chemotherapy and TRT in multimodality management of LS-SCLC, there are several critical points to consider in interpretation of the results from the perspective of TRT timing. Trial designs and protocols, patient selection criteria, definition of early and late TRT, administered chemotherapy regimens and compliance, TRT doses and fractionation schemes, follow up durations and outcome measures show significant diversities which emphasizes the need for vigilance in interpretation of the results. Administered TRT dose and treatment delivery techniques, dose and content of chemotherapy regimens in some of these studies may be considered inadequate and outdated as compared to current treatment standards.

There have also been more recent studies and metaanalyses addressing timing of TRT in LS-SCLC. Huncharek and McGarry[27] conducted a metaanalysis of timing of chest irradiation in combined modality treatment of LS-SCLC. Eight randomized trials including 1574 patients were analyzed, and 60% relative benefit was found in 2 year OS for early TRT which increased to 81% when only trials using cisplatin/etoposide based chemotherapy were included[27].

Bayman *et al*[28] assessed impact of early *vs* late TRT on survival for patients with LS-SCLC. A total of 70 consecutive patients receiving chemoradiotherapy for LS-SCLC were retrospectively analyzed. Administration of TRT was either after 1 to 2 cycles of chemotherapy (early TRT) or after 3 to 6 cycles of chemotherapy (late TRT). At a median follow-up duration of 2 years, late TRT was found to provide

improved response rate[28].

A metaanalysis by Pijls-Johannesma *et al*[29] used a different definition for early TRT as starting within 30 days of chemotherapy initiation. Seven randomized trials were included in the metaanalysis, and no statistically significant difference was found in 2-year OS rates (P = 0.18). However, a statistically significant survival improvement was observed in favor of early TRT when the only trial using non-platinum based chemotherapy was excluded (P = 0.01). The authors emphasized that the results should be interpreted with caution given the potential influence of patient selection, systemic treatment, and compliance rates[29].

American Radium Society Thoracic Appropriate Use Criteria Committee reported consensus recommendations for LS-SCLC[30]. The panel reaffirmed that early delivery of TRT was supported by high level evidence and suggested that it was appropriate for TRT to be incorporated in combined modality management of LS-SCLC no later than second cycle of chemotherapy[30].

Sun *et al*[35] conducted aphase III trial of concurrent TRT with either first or third cycle chemotherapy for LS-SCLC. TRT dose was 52.5 Gy in 25 daily fractions of 2.1 Gy delivered over 5 wk. Chemotherapy consisted of 4 cycles of etoposide/cisplatin which was delivered every 21 d. Median OS and PFS did not significantly differ between early and late TRT arms. Also, significantly lower rate of neutropenic fever was observed in the late TRT arm which could be partly explained by relatively smaller postchemotherapy TRT treatment volumes[35].

De Ruysscher *et al*[36] assessed impact of earlier or later TRT and shorter or longer TRT in LS-SCLC by conducting an individual patient data metaanalysis on behalf of the RadioTherapy Timing in SCLC (RTT-SCLC) Collaborative Group. Importance of using individual patient data was emphasized. Data from 9 trials including 2305 patients were available for the analysis. Median follow-up duration was 10 years. OS was not significantly effected by earlier or shorter *vs* later or longer TRT when all trials were analyzed together. Nevertheless, earlier or shorter TRT resulted in improved OS when trials including similar proportion of patients in both arms with respect to chemotherapy compliance were analyzed. Absolute gain in 5-year OS was 7.7% with earlier or shorter TRT when trials with similar chemotherapy compliance in both arms were analyzed, albeit with a higher incidence of severe acute esophagitis[36].

Wong *et al*[37] examined the National Cancer Data Base to evaluate practice patterns and survival for TRT timing in association with chemotherapy for non metastatic SCLC. A total of 8391 patients were included, and early TRT was found to improve survival compared to late TRT particularly when hyperfractionated TRT was used. Multivariate analysis revealed that hyperfractionated TRT was associated with reduced mortality[37].

Zhao *et al*[38] assessed effects of TRT timing and duration on PFS in LS-SCLC. A total of 197 patients receiving chemoradiotherapy for LS-SCLC were retrospectively analyzed. Early and short TRT was found to be correlated with longer PFS on univarite analysis. The study confirmed that early and short TRT had a positive prognostic role in LS-SCLC particularly for patients receiving hyperfactionated TRT and etoposide/cisplatin chemotherapy[38].

Results of a survey among 309 US Radiation Oncologists on timing of TRT with chemotherapy in LS-SCLC by Farrell *et al*[39] revealed that adherence to guidelines was excellent. When delivering TRT concurrently with chemotherapy, 71%, 25%, and 4% of participants preferred beginning TRT in cycle 1, cycle 2, cycle 3 or later of chemotherapy, respectively[39].

Hu *et al*[40] compared standard hyperfractionated TRT with hypofractionated TRT in combination with concurrent chemotherapy for LS-SCLC in a retrospective study. Analysis of patients enrolled in 2 independent prospective studies revealed that both hyperfractionated and hypofractionated TRT delivered with concurrent EP chemotherapy may confer good locoregional control and OS. The authors concluded that early commencement of TRT and utilization of a short course TRT schedule should be considered[40].

Hasan *et al*[41] evaluated optimal timing of TRT in LS-SCLC with daily fractionation using the National Cancer Database (NCDB). Trends in timing of TRT in LS-SCLC treated with daily fractionation, the significance of 30 day window to start TRT in this patient population, as well as optimal duration and completion times of TRT were assessed. Three and 5-year actuarial survival rates were 32.7% and 22.9% *vs* 28% and 18.4% when TRT was initiated within 30 d and beyond 30 d of chemotherapy, respectively (P < 0.001). Multivariable analysis revealed that commencement of TRT beyond 30 d of chemotherapy was associated with reduced survival[41].

To summarize, the literature includes conflicting results regarding the optimal timing of TRT in multimodality management of LS-SCLC. Different results between the studies may be partly explained by differences in trial designs, definition of early and late TRT, patient selection criteria, administered chemotherapy regimens, treatment compliance, TRT dose and fractionation.

CONCLUSION

There has been extensive effort to establish optimal timing of TRT in LS-SCLC management. The debate continues despite the accumulating data from randomized studies, systematic reviews, and metaanalyses. While late TRT may have utility for management of LS-SCLC patients who may not

tolerate curative-intent upfront chest irradiation due to excessive tumor burden at the outset, early TRT allows for exploiting the synergistic effect of chemoradiotherapy to eradicate as many tumor cells as possible in a shorter timeframe. Admittedly, differences in trial designs, definition of early and late TRT, patient selection criteria, administered chemotherapy regimens, treatment compliance, TRT dose and fractionation may affect treatment outcomes.

It appears that thorough individualized patient assessment gains critical importance in decision making for optimal TRT timing in combined modality management of LS-SCLC. Nevertheless, early TRT may be suggested to overcome accelerated repopulation and improve treatment outcomes particularly when compliance with chemotherapy is high. Future trials should focus on optimal TRT dose and fractionation, incorporation of immunotherapy approaches, adaptive TRT strategies and contemporary image guidance techniques to improve the toxicity profile of radiation delivery.

Article highlights

Lung cancer presents a major and global health concern as a leading cause of cancer related mortality worldwide. While chemotherapy and TRT are primary components of initial management for LS-SCLC, there is no consensus on optimal timing of TRT.

While several randomized studies have addressed sequencing of chemotherapy and TRT in multimodality management of LS-SCLC, there are several critical points to consider in interpretation of the results from the perspective of TRT timing. Trial designs and protocols, patient selection criteria, definition of early and late TRT, administered chemotherapy regimens and compliance, TRT doses and fractionation schemes, follow up durations and outcome measures show significant diversities which emphasizes the need for vigilance in interpretation of the results.

While late TRT may have utility for management of LS-SCLC patients who may not tolerate curative-intent upfront chest irradiation due to excessive tumor burden at the outset, early TRT allows for exploiting the synergistic effect of chemoradiotherapy to eradicate as many tumor cells as possible in a shorter timeframe. It appears that thorough individualized patient assessment gains critical importance in decision making for optimal TRT timing in combined modality management of LS-SCLC. Nevertheless, early TRT may be suggested to overcome accelerated repopulation and improve treatment outcomes particularly when compliance with chemotherapy is high.

Future trials should focus on optimal TRT dose and fractionation, incorporation of immunotherapy approaches, adaptive TRT strategies and contemporary image guidance techniques to improve the toxicity profile of radiation delivery.

FOOTNOTES

Author contributions: Sager O, Dincoglan F, Demiral S, Gamsiz H, Uysal B, Ozcan F Colak O and Gumustepe E played significant role in data acquisition, interpretation of data, reviewing and writing of the manuscript; Elcim Y, Gundem E and Dirican B worked on checking the manuscript for important intellectual content; Beyzadeoglu M took part in designing, reviewing and writing of the manuscript and checking the manuscript for important intellectual content; all authors have read and approved the final manuscript.

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