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Radiation Therapy in the Treatment of Small Cell Lung Cancer

Guler Yavas* and Cagdas Yavas

Department of Radiation Oncology, Selcuk University, Turkey

Abstract

Small Cell Lung Cancer (SCLC) represents between 13-15% of all lung cancers; however is the fifth leading cause of cancer death worldwide. SCLC prognosis remains poor despite improvements in diagnosis and treatment over the last 30 years. Patients with SCLC are typically divided into those with Limited Stage (LS) versus Extensive Stage (ES). LS disease is treated with concurrent chemotherapy and thoracic radiotherapy followed by Prophylactic Cranial Irradiation (PCI). For patients with ES-SCLC current approach is using combination chemotherapy with a platinum-based regimen. All the patients who demonstrate response to chemotherapy and have a good performance status with ES-SCLC should receive PCI. The role of thoracic radiotherapy in ES-SCLC was to palliate disease related symptoms. However the recent reports evaluating the role of thoracic radiotherapy in ES-SCLC, have demonstrated that consolidative thoracic radiotherapy is beneficial for selected patients with ES-SCLC who respond to chemotherapy but in whom there is evidence of residual disease within the chest. Recent technical advances in radiation treatment including intensity-modulated radiotherapy, and stereotactic radiotherapy allowed enhancing precise delivery as well as minimizing the radiation related toxicities.

Keywords

Small cell lung cancer, Radiotherapy, Prophylactic cranial irradiation, Limited stage, Extensive stage

Introduction

Lung cancer is the leading cause of cancer-related death in the world, and the second in incidence in both genders; nevertheless, the Small Cell Lung Cancer (SCLC) subtype covers only 13-15% of total lung cancer diagnosis [1]. A decrease in SCLC's incidence has been seen in the last 20 years, probably related to the decrease in tobacco use in occidental countries, since SCLC occurs predominantly in smokers, as well as to the recognition of other subtype: large cell neuroendocrine carcinoma, which before 1990 was considered to be SCLC [1,2].

SCLC is a highly aggressive, undifferentiated neoplasia that originates from the precursors of neuroendocrine cells. SCLC is distinguished from Non-Small Cell Lung Cancer (NSCLC) by its rapid doubling time, high growth fraction, and the early development of widespread metastases [3]. Approximately two-thirds of SCLC patients have clinical evidence of metastasis at diagnosis; most of the remaining third have clinical evidence of extensive involvement of hilar, mediastinal, and sometimes supraclavicular lymph nodes. Although SCLC is initially highly responsive to chemotherapy and radiotherapy, the majority of patients will relapse with broadly resistant disease within few months to a year from initial therapy.

A simple staging system for SCLC was introduced by the Veterans Administration Lung Study Group (VALG) in 1957 for randomized trials in inoperable lung cancer patients [4]. This system classifies patients into the two categories of limited and extensive disease lung cancer, depending in principal on whether all known tumors could be treated within a single radiotherapy portal or not. Limited Stage-Small Cell Lung Cancer (LS-SCLC) is defined as disease that is limited to the ipsilateral hemothorax and regional lymph nodes and can be encompassed in a safe radiotherapy field. However the majority of patients with SCLC have Extensive Stage (ES) disease, with tumor that includes distant metastases, malignant pericardial or pleural effusions, and/or contralateral supraclavicular or contralateral hilar lymph node involvement. VALG staging system is generally ac-

***Corresponding author:** Guler Yavas, MD, Associate Professor in Radiation Oncology, Department of Radiation Oncology, Faculty of Medicine, Selcuk University, Konya, Turkey, Zip code: 42075, Tel: +90-(332)-224-40-85, Fax: +90-(332)-241-60-65, E-mail: guler.aydinyavas@gmail.com

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cepted in SCLC in clinical practice and is usually sufficient for treatment decisions regarding local therapy and carries prognostic information independent whether chemotherapy is used or not [5].

Radiation Therapy (RT) plays a fundamental role in the management and care of patients with SCLC [6]. The current standard approach for LS-SCLC consist of combination chemotherapy with four cycles of a platinum-based regimen in conjunction with concurrent thoracic RT, followed by Prophylactic Cranial Irradiation (PCI) for patients who demonstrate an objective therapeutic response. The addition of thoracic RT and PCI improves both local control and overall survival [6,7]. The standard care for ES-SCLC was combination chemotherapy with a platinum-based regimen. The role of RT in ES-SCLC was only for palliative purpose historically. However in a phase III trial, Slotman and colleagues demonstrated that PCI increases overall survival in patients with ES-SCLC who have response to chemotherapy [8]. The importance of thoracic RT in ES-SCLC was demonstrated in two phase III randomized trials [9,10]. Both of these studies suggested that consolidation chest RT, after chemotherapy for ES-SCLC improved Local Control (LC) which may influence Overall Survival (OS). Therefore for patients with ES-SCLC who have had a favorable response to chemotherapy but in whom there is evidence of residual disease within the chest identified on Computed Tomography (CT), thoracic RT should be considered. The purpose of the present review is to report the role of the RT in the management of SCLC by the light of the novel publications.

Limited stage disease

The role of thoracic radiotherapy in the limited stage disease: Approximately only 5% of SCLC patients present as T1-2N0-1 M0 disease; and these have shown to have a more favorable long term prognosis, with a 5-year OS of 50% [11]. LS-SCLC is a potentially curable disease when it is aggressively and rapidly treated with concomitant chemo-radiotherapy [1]. Although the current guidelines of the National Comprehensive Cancer Network (NCCN) [12], and the American College of Chest Physicians (ACCP) [13] are not identical; both recommend that only patients with clinical stage I disease (T1-2 N0) should be considered for surgery. It has been demonstrated in a retrospective studies that in patients with stage I SCLC (T1-2 N0 M0) that undergo lobectomy, and with confirmed lack of mediastinal and supraclavicular involvement, long-term OS is 40-60% [1,14]. On the other hand, it was demonstrated that patients with node involvement do not benefit from excisional treatment; and therefore this modality should not be offered to patients with N1-3 disease [15]. It is mandatory to offer four cycles of cisplatin-based adjuvant chemotherapy after lobectomy. In cases where pathologic analysis of mediastinal nodes sampling is positive for malignant disease (N1 or N2) and a complete lymphadenectomy has not been performed, postoperative mediastinal RT should be considered [1].

In a randomized study Murray and colleagues demonstrated that thoracic RT was superior to surgery [16]. However this study was performed in 1960; and active chemotherapeutic agents had not been discovered yet and; long-term survivors were few. In 1980 the active chemotherapy agents against SCLC was introduced. In that years there was a trend suggesting that RT might not be needed in SCLC [7,17]. However, subsequent studies demonstrated high rates of local recurrence without thoracic RT, thus supporting its role in optimal care of LS-SCLC [17]. Two large meta-analyses have suggested that the addition of thoracic RT provides absolute survival benefit of 5% at 2 and 3 years, respectively for patients treated with chemo-radiotherapy [18,19]. One meta-analysis, which included 11 randomized studies, found that the addition of thoracic RT was associated with an absolute improvement in local control of 23 percent (two-year local control rate 47 versus 24 percent) [19]. Another meta-analysis of 13 randomized trials (including the same 11) found that the use of combined chemotherapy and thoracic RT resulted in an absolute survival benefit of 5.4 percent at three years [18]. The survival benefit associated with the use of thoracic RT outside of clinical trials was confirmed in a more recent review from the National Cancer Data Base [20].

The optimal dose and fractionation scheme for concurrent chemoradiation for LS-SCLC is an area of active investigation. SCLC is highly radiosensitive suggesting that hyperfractionation could be employed to reduce late normal tissue toxicity**.** The current standard of care for the dose and fractionation of thoracic RT is based on the randomized phase III Intergroup 0096 study [21], which compared 45 Gy/1.8 Gy per fraction in 25 fractions over 5 weeks once-daily to 45 Gy/1.5 Gy per fraction BID in 30 fractions over 3 weeks. In both treatment methods thoracic RT started with the first cycle of four planned cycles of concurrent cisplatin + etoposide (PE). Twice-daily treatment beginning with the first cycle of chemotherapy significantly improved survival as compared with concurrent once-daily radiotherapy ($P = 0.04$ by the log-rank test). After a median follow-up of almost 8 years, the median survival was 19 months for the once-daily group and 23 months for the twice-daily group. The rate of local failure was 36% in the group receiving twice-daily RT ($P = 0.06$). In fact, twice-daily regimen has been poorly adopted by physicians. Therefore the most active area of clinical research in thoracic RT in LS-SCLC concerns its optimal total dose and fractionation [6]. Two contemporary phase III randomized trials are addressing the question of whether a higher total dose of thoracic RT will result in an improvement in OS: CONVERT (concurrent once daily versus twice daily radiotherapy) [22]; and North America (CALGB 30610/RTOG 0538) [23]. The

primary end-point of both studies is an improvement in OS. In CONVERT trial patients were randomized to 45 Gy/1.5 Gy BID in 30 fractions or to 66 Gy in 33 once-daily fractions, both starting with the second cycle of PE [22]. In North America trial the standard arm of 45 Gy/1.5 Gy BID was compared with either 70 Gy/2 Gy once-daily over 7 weeks or 61.2 Gy/1.8 Gy once-daily over 16 days followed by 1.8 Gy twice-daily for 9 days [23]. All schedules had RT administered with concurrent PE starting at cycle 1 or 2. In March 2013 61.2 Gy arm was closed after a series of planned interim analyses by the Data Safety and Monitory Board to determine the feasibility of dropping one of the experimental arms. Because in 61.2 Gy arm there were three on-study deaths compared to the 70 Gy arm; which had none [6].

Hyperfractionated thoracic RT has also been delivered as a split course treatment with alternating regimens of chemotherapy and thoracic RT. In a pilot study by the Eastern Cooperative Oncology Group (ECOG), thoracic RT consisting of 1.5 Gy given twice daily over five continuous days was delivered after the first, second, and third cycles of etoposide and cisplatin (EP) chemotherapy [24]. The two-year progression-free survival for this series was 47 percent. The Groupe Lyonnais d'Oncologique Thoracique reported the results of a similar hyperfractionated thoracic RT schedule alternating with chemotherapy in the treatment of 76 patients [25]. The median survival for this group was 14 months, and the one-year disease-free survival was 42 percent. In summary, the optimal dose and fractionation approach for SCLC remains to be defined. An ongoing intergroup effort (CALGB 30610, RTOG 0538, NCT00632853) seeks to determine the optimal radiation schedule.

Historically, thoracic RT treatment volumes included all gross disease present at the time of initial diagnosis (prechemotherapy volume), as well as prophylactic inclusion of adjacent uninvolved nodal regions. However the Southwest Oncology Group (SWOG) performed a randomized trial, in which 191 patients with LS-SCLC who had a partial response or stable disease following induction chemotherapy were randomly assigned to thoracic RT fields that included either the prechemotherapy or the postchemotherapy tumor volumes [26]. There weren't any statistically significant differences with respect to the patterns of failure or median survival between the two regimens. There was no apparent difference in severe drug-related toxicity or severe radiation pneumonitis between the thoracic RT groups. However, the frequency of severe complications related to myelosuppression was higher for patients treated with wide field thoracic RT. SWOG trial is the only randomized trial to date addressing the specific question of treatment volume. Despite some uncertainty, the use of limited field thoracic RT is the current standard of care. Specifically, the treatment volume should include all gross disease present at the time of radiation planning (postchemotherapy volume), and all nodal regions involved at the time of initial diagnosis (prechemotherapy volume). PET scans should be obtained for staging if RT is planned for patients with suspected LS-SCLC.

Thoracic RT is routinely delivered early and concurrent with, rather than late or sequential to chemotherapy if patient's condition is appropriate. Because three major meta-analyses showed that the early administration of thoracic RT is associated with improved survival [27-29]. The addition of thoracic RT integrated with EP chemotherapy during cycle 1 or 2 is the current standard of care for patients with LS-SCLC. Although there are conflicting data regarding the optimal timing of thoracic RT relative to chemotherapy, the studies that employed standard EP chemotherapy delivered with minimal dose reduction all showed a clear benefit for early thoracic RT.

The role of prophylactic cranial radiotherapy in the limited stage disease: The value of PCI was demonstrated in a meta-analysis of seven randomized trials that included 987 patients who achieved a complete remission with chemotherapy and received PCI between 1977 and 1995 [30]. In this meta-analysis Auperin and colleagues reported that PCI yields a 25.3% decreased incidence of brain metastases at 3 years ($P < 0.001$) and that overall and disease-free survivals are increased in PCI group by 5.4% ($P = 0.01$) and 8.8% ($P < 0.001$) respectively at 3 years. After the publication of this meta-analysis PCI became standard of care in LS-SCLC patients who has complete response to concurrent chemo-radiotherapy.

In patients with LS-SCLC who have a good response to initial therapy, PCI both decreases incidence of brain metastases and increases OS [30,31]. The effectiveness of PCI in patients with limited stage SCLC has been established by the results from numerous clinical trials. NCCN recommends PCI for all patients with LS-SCLC who have a good response to initial therapy and have good performance status [15].

Higher doses of radiation are associated with better control of brain metastases, although this benefit must be weighed against the risks of toxicity. Indirect evidence supporting the efficacy of higher doses of radiation in reducing brain metastases comes from the initial meta-analysis that established the efficacy of PCI, in which the dose of radiation was broken down into four categories (8 Gy, 24 to 25 Gy, 30 Gy, and 36 to 40 Gy) [30]. A statistically significant trend for improved control of brain metastases was observed with increasing total doses of radiation. The most extensive data on the impact of radiation dose come from a multinational phase III trial (PCI 99-01) in which patients receiving a dose of 36 Gy had a higher mortality and higher neurotoxicity compared to patients treated with 25 Gy [32,33]. The preferred dose for PCI to the whole brain is 25 Gy in 10 daily fractions [15]. Thirty Gy in 2 Gy fractions is

also an acceptable regimen. PCI is not given during chemotherapy to decrease the risk of leukoencephalopathy [34].

Extensive stage disease

The role of thoracic radiotherapy in the extensive stage disease: The majority of patients with SCLC have extensive stage disease, with tumor that includes distant metastases, malignant pericardial or pleural effusions, and/or contralateral supraclavicular or contralateral hilar lymph node involvement. Systemic therapy is the essential element in the treatment of patients with ES-SCLC with good performance status; however thoracic RT may play a role in selected patients. Thoracic RT has typically been used in ES-SCLC primarily for symptom palliation [7]. Based on the results of a randomized trial by Jeremic, et al. [9], the addition of sequential thoracic RT may be considered in select patients with low-bulk metastatic disease who have a complete or near complete response after initial chemotherapy. This study randomized ES-SCLC patients who had received three induction cycles of PE and shown a complete response at distant sites and at least a partial response in the chest to either hyperfractionated thoracic RT (54 Gy in 36 fractions/twice-daily fractions over 18 days) plus daily low-dose chemotherapy or to four additional cycles of PE without RT. PCI was offered to responders in both groups. Thoracic RT significantly increased overall survival compared with chemotherapy (median 17 versus 11 months, five-year survival rate 9% versus 3.7%; $p = 0.041$).

In a European multicenter trial (Dutch Crest Trial), patients with ES-SCLC were initially treated with four to six cycles of platinum-based chemotherapy [10]. Following this, 498 patients with at least some response to chemotherapy were randomly assigned to thoracic RT (30 Gy in 10 fractions) plus PCI or PCI without thoracic RT. The primary endpoint of the trial was overall survival. The authors reported that the addition of sequential thoracic RT did not improve the primary end point of 1-year OS (33% vs. 28%, $p = 0.066$). However, in a secondary analysis, the survival curves diverged after longer follow-up, and subsequent survival was significantly better for those receiving thoracic RT (two-year overall survival rate 13% versus 3%, $p = 0.004$). The findings of Dutch Crest Study [10] and the earlier Jeremic study [9] should encourage clinicians to consider the option of thoracic RT.

Thoracic RT in ES-SCLC is currently the subject of at least two prospective trials in North America. The first trial is Radiation Therapy and Oncology Group (RTOG) 0937. RTOG 0937 is a randomized phase II study in patients with ES-SCLC who have more than three extra-thoracic sites of disease; patients are randomized to receive PCI alone versus PCI and consolidative thoracic RT (45 Gy in 30 fractions/twice-daily), after chemotherapy [35]. The second trial is the Chest Irradiation in Extensive Stage Small Cell Lung Cancer (CREST) trial conducted by Dutch Lung Cancer Study Group. In this trial the patients with ES-SCLC who responded to chemotherapy are randomized to thoracic RT (30 Gy/10 fraction) and PCI versus PCI. The results of these trials will help to clarify the role of thoracic RT in ES-SCLC patients.

The role of prophylactic cranial radiotherapy in the extensive stage disease: PCI decreases the incidence of symptomatic brain metastases in patients with ES-SCLC who have a response to systemic chemotherapy, although its effect on OS is uncertain. In the previously noted meta-analysis by Auperin, et al. [30], it is of interest that 15% of patients who received PCI were noted to have ES-SCLC, and it was found that for this subgroup, the benefit associated with PCI was of same magnitude as the limited disease subgroup [6].

PCI in ES-SCLC has been studied in two randomized multicenter trials: The first trial is a phase III randomized trial conducted by the European Organization for Research and Treatment of Cancer (EORTC), all patients initially received four to six cycles of chemotherapy [8]. At the completion of the initial chemotherapy patients with any degree of response after standard first-line chemotherapy randomized to PCI versus observation. Patients were not routinely imaged for the presence or absence of brain metastases after chemotherapy and prior to PCI. The primary objective of the study was the prevention of symptomatic brain metastases. At 1 year, the PCI patients were found to have a significantly lower rate of symptomatic brain metastases (15% vs. 40%, $p < 0.001$). There were improvements in 1-year (27% vs. 13%) and median (6.7 vs. 5.4 months, $p = 0.003$) survivals. In this study RT doses and schedules ranged from 20 Gy in 5 fractions to 30 Gy in 12 fractions.

Because in the first trial conducted by Slotman, et al. the patients did not have brain imaging prior to PCI, some authors have questioned whether the survival benefits seen with the addition of PCI could have come from an imbalance in the treatment arms such as that those not receiving PCI may have had more "undeclared" subclinical brain metastases which when left untreated would have compromised survival [6]. Therefore the second trial was conducted from Japan. In Japanese trial 224 ES-SCLC patients who had at least some response to their initial chemotherapy were randomly assigned to PCI (25 Gy/10 fractions) or no PCI [36]. Prior to randomization, patients underwent Magnetic Resonance Imaging (MRI) of the brain to rule out occult metastases. The primary endpoint of this trial was OS. Secondary endpoints included the incidence of brain metastases and progression-free survival. Preliminary results were presented at the 2014 American Society of Clinical

Oncology (ASCO) meeting. The trial was stopped prematurely for futility, based upon an analysis after 111 deaths. Although not statistically significant, overall survival was shorter with PCI compared with no PCI (median 10.1 versus 15.1 months, HR 1.38, 95% CI 0.95-2.02). There was a significant decrease in the incidence of brain metastases with PCI (32 versus 58 percent at one year, $p < 0.001$), and fewer patients required RT for symptomatic brain metastases (31 versus 80 percent).

Because of the conflicting results of EORTC and Japanese Studies, Bernhardt, et al. evaluated a cohort of patients with ED-SCLC who had undergone PCI after an initial response to chemotherapy. They assessed to the toxicity and survival outcomes after irradiation after the report of the EORTC trial in 2007 with 9-year experience with PCI for patients with ED SCLC from one of Europe's largest lung cancer centers. Their results suggested that, PCI was associated with improved survival compared with the PCI arm of the EORTC trial, with a nearly doubled median OS period. Also, the median OS was prolonged by 2 months compared with the irradiation arm of the Japanese trial. The authors concluded that PCI should remain the standard of care for all patients with SCLC with a response to initial chemotherapy, at least until fully reported randomized data suggest otherwise [37].

The meta-analysis suggested that the incidence of brain metastases might be reduced with higher PCI doses. Indeed through an indirect comparison of the trials, the estimated reduction in brain metastases with PCI was 24, 48, 68 and 73% with a total dose of 8, 24-25, 30 and 36-40 Gy, respectively [30]. Therefore the PCI Collaborative Group launched a randomized phase III study of 720 SCLC patients who had a complete response to the firs-line chemotherapy. The PCI doses were standard dose with 25 Gy in 10 fractions or high-dose with either 36 Gy in 18 fractions or 24 Gy in 1.5 Gy twice daily fractions [32]. Toxicities an treatment delivery were not different between two arms.

After the phase III study conducted by Slotman, et al. PCI was extended to patients with ED-SCLC [8]. However, a Japanese phase III study failed to confirm the benefit of PCI for patients with ED-SCLC [36]. All studies have demonstrated the effectiveness of PCI for preventing brain metastasis, this is not in doubt, but PCI seems to have a limited influence on OS. However the results of these trials provide strong evidence that PCI can decrease the incidence of symptomatic brain metastases. The impact of PCI on OS in patients with ES- SCLC who respond to chemotherapy remains uncertain. Thus PCI remains a consideration for ES-SCLC patients demonstrating objective and clinical benefits from their systemic therapies. The preferred dose for PCI to the whole brain is 25 Gy in 10 fractions [15]. Thirty Gy in 15 fractions is also an acceptable regimen. A short course (egg, 20 Gy in 5 fractions) may be appropriate in selected patients with ES-SCLC [15].

Palliative radiotherapy in small cell lung cancer patients

Palliative, or supportive care, is aimed at relieving symptoms and improving a person's quality of life. Patients with metastatic SCLC often benefit from procedures to help with problems caused by the cancer. When delivered with palliative intent, RT can help to alleviate a multitude of symptoms related to advanced cancer. In general, time to symptom relief is measured in weeks to months after the completion of RT.

Brain metastases are very common in SCLC patients. The primary approaches to the treatment of brain metastases include surgery, Stereotactic Radio Surgery (SRS), and Whole Brain Radiation Therapy (WBRT). WBRT should be applied in case of brain metastases in SCLC patients. The most commonly used regimen is a total dose of 30 Gy in 10 daily fractions of 3 Gy. The decision in an individual case depends upon the severity of neurologic symptoms, the extent of systemic disease, and physician preference.

SRS delivers single or very limited number of high doses to a radiographically discrete treatment volume by using multiple convergent beams. This results in a rapid fall-off of dose at the edge of the target volume and a clinically insignificant dose to adjacent normal tissue. High energy x-rays produced by linear accelerators, gamma rays from the Gamma Knife, and less frequently, charged particles such as protons produced by cyclotrons have all been utilized. In controlled studies in patients with tumors up to 3 cm in diameter, SRS produces local control rates of approximately 70 percent at one year following treatment [38]. This rate improves to up to 90 percent when adjunctive WBRT is provided. Although traditionally used to treat a limited number of tumors, prospective nonrandomized data in patients with newly diagnosed brain metastases suggest that up to 10 tumors with a total cumulative volume ≤ 15 mL may be treated in a single session with similar efficacy and no increase in toxicity [39].

In patients with ES-SCLC who did not respond to the chemotherapy may benefit from palliative RT to symptomatic metastatic sites. The most common thoracic symptoms that need palliation are pain, cough, hemoptysis, post-obstructive pneumonia, superior vena cava syndrome. Additionally painful bone metastases may benefit from palliative RT.

Normal tissue toxicity

The risk and severity of radiation toxicity in normal tissue are related to the dose and volume irradiated, as well as the functional organization of the organ at risk. In

serial tissue such as spinal cord, esophagus and trachea and bronchi, injury of one organ subunit may results in total organ dysfunction. Therefore, high dose to small volumes can result in a significant toxicity. On the other hand parallel tissues, such as lung may tolerate high doses to small volumes. Because high dose to small volumes leads dysfunction of the high dose area in that tissue which means a partial organ dysfunction. In parallel tissues, the volume irradiated, even lower dose may lead total organ dysfunction [40].

Emami, et al. defined the partial-volume organ tolerances for normal tissue that served for more than a decade as the standard source for radiation dose limits [41]. In Emami's definition dose limits were defined for specific end points, using a 5% complication rate at 5 years (TD5/5) or 50% complication rate at 5 years (TD50/5). These data were based predominantly on clinical data from 2-dimesional RT planning [40]. A great promise of three dimensional (3D) treatment planning was quantitative correlates of doses/volumes with clinical outcomes. Recently, a multidisciplinary effort was undertaken, the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC), to summarize the available 3-dimesional dose-volume toxicity data in the literature.

The toxicity of the thoracic irradiation

Lung: In patients with lung cancer, clinical pneumonitis occurred in 5 to 20 percent of patients, while radiographic abnormalities were present in 66 percent. It is unclear to what extent the latter were due to irradiation versus tumor. Radiation pneumonitis may occur during fractionated treatment or up to 18 months afterward, with a peak incidence at 2-6 months [40].

Radiation-Induced Lung Injury (RILI) which is also named as "radiation pneumonopathy" is a continuous process and regarded as the result of an abnormal healing response. Subclinical early damage in pneumocytes type I progress to an acute interstitial inflammation at 6-12 weeks after the onset of Radio Therapy (RT) and further to lung fibrosis after many months and years. Inflammation is an essential part of the normal wound healing process [42-44]. Clinically radiation-induced lung injury is typically divided into two phases: pneumonitis and fibrosis. The fibrotic phase tends to manifest > 3 months after treatment. Fibrosis is part of the wound-healing process. Therefore radiation fibrosis is a form of chronic lung damage that usually evolves over 4-24 months after irradiation [44].

Symptoms caused by acute radiation pneumonitis usually develop approximately four to twelve weeks following irradiation, whereas symptoms of late or fibrotic radiation pneumonitis develop after six to twelve month. The most common Clinical presentation includes a persistent non-productive cough, dyspnoea, low-grade fever, and fatigue. Patient may experience a chest pain that may be pleuritic or substernal and can represent pleuritis, esophageal pathology, or rib fracture. Malaise and weight loss may be observed [43]. Chest x-ray or Computed Tomography (CT) scan may be normal, or depending on the time course, there may be ground glass opacification (within 2 to 6 months), patchy consolidation 4 to 12 months), or fibrosis (10 months or more); that loosely corresponds to the radiation field [40,45].

Many factors including method of irradiation, volume of irradiated lung, dosage of irradiation, time-dose factor, and the use of concurrent chemotherapy may affect the development of radiation-induced lung disease [45]. Several patient related factors also impact the risk of radiation-induced lung disease. Such as older age, continue to smoke during RT may effect negatively to radiation pneumonitis [40].

QUANTEC data suggests that the risk of radiation pneumonitis is < 20% when the mean lung dose is less than approximately 20 Gy with conventional fractionation [46]. With regard to V_{dose} threshold models, radiation pneumonitis risk is < 20% for V_{20} < 30-35 Gy; or V_5 < 60% with conventional fractionation [40,46].

Esophagus: The esophagus as a central serial organ with radiosensitive mucosa can suffer from side-effects after RT for the treatment of cancers of lungs and bronchi. Acute esophagitis is often the most prominent symptom during fractionated RT for thoracic malignancy, leading to inpatient admissions, dehydration, weight loss, and treatment interruption. On the other hand late esophageal toxicity may include stricture, perforation, or fistula formation [40].

Irradiation-induced cell death affects especially cells with rapid cell turnover. Thus, during an irradiation course the renewal of the surface of the esophageal mucosa is impaired and hence prone to damage and development of esophagitis. Early morphologic radiation induced alterations comprise nuclear hyperchromasia or denudation, focal basal epithelial cell necrosis, epithelial swelling and erosions [47] or edema and petechiae in the lamina propria and in the submucosa. Patients with odynophagia or dysphagia as AET were observed to have discrete ulcers, granular mucosa and a narrowed lumen of the gullet. Additionally, the damaged mucosa is vulnerable for superinfection or growth of candida. The described radiation induced morphological changes can lead to abnormal peristalsis, typically beginning in the cranial irradiated aspects of the organ, passing down to the lower sphincter [47,48]. Abnormal motility has been seen for up to more than a decade after treatment [48-50].

Dysphagia is the main clinical symptom of radiation induced esophagitis and can be associated with severe pain [50]. Grade 3 or garter acute esophagitis occurs in

15-25% of patients during or shortly after irradiation and may lead hospitalization and unwanted treatment breaks [40].

Esophageal toxicity is related to both dose and volume of irradiation. Accelerated fractionation, older patient age, the use of concurrent chemotherapy may also increase the risk of acute esophagitis [40]. For conventional thoracic RT the volume of the esophagus receiving 40 or 50 Gy (V40, V50) is commonly accepted as a guidance level to estimate the risk of esophagitis [50]. However the relationship between esophageal side effects and treatment outcome for patients with esophageal cancer needs better understanding.

Heart: The majority of the radiation-induced cardiovascular disease has been reported in patients who previously treated with thoracic RT for Hodgkin's disease and breast cancer. Estimated relative risk of fatal cardiovascular events after RT for Hodgkin's disease and left-sided breast cancer range between 2.2 and 7.2 and 1.0 to 2.2, respectively, compared to healthy controls. Risk is life long and absolute risk appears to increase with length of time since exposure. Radiation-associated cardiovascular toxicity may in fact be progressive [51]. Reported toxicities include acute pericarditis, which can progress to chronic pericardial fibrosis, effusion, or rarely constrictive pericarditis. Valvular abnormalities were also reported [40,51].

Numerous studies of radiation-induced toxicity show that endothelial cell injury is the key point in most tissues even though the endothelial cells compromise only a minor fraction of cardiac cells [52]. The sequence of endothelial injury, cell detachment, thrombosis and fibrosis result in significant tissue injury that often limits radiation oncologist in attempting to deliver curative doses to a nearby tumor. Steward and Fajardo have demonstrated that damage to the myocardium develops through three phases of injury [53]. The acute inflammation phase occurs about 6 hours after RT and a neutrophilic infiltrate develops involving all layers of heart. The second phase also known as latent phase in which a slight progressive fibrosis begins about 2 days after exposure. However electron microscopy of the myocardial capillary endothelial cells demonstrates progressive damage leading to obstruction of the lumen and thrombi of fibrin and platelets. Though healthy endothelial cell replication in the vicinity occurred, it is generally inadequate and an inevitable ischemia leads to progressive fibrosis. Animals begin to die at approximately 70^{th} day due to extensive fibrosis. The hallmark of this late stage is extensive fibrosis.

Both the treatment related factors including the dose, the volume of heart irradiated; and the patient related factors including hypertension, diabetes, obesity and genetic predisposition may affect the risk of radiation-induced cardiac toxicity. The risk of pericardial toxicity has been correlated with treatment of > 50% of the heart contour in 2-dimensional planning and to the volume of ≥ 30 Gy in 3-dimensional planning. The risk of pericarditis can be minimized by keeping the mean pericardial dose < 26 Gy or the pericardial V_{30} < 46% [40].

Brachial plexus: Radiation brachial plexopathy is a rare condition which is therefore poorly described. There are case reports of an early transient plexopathy that occurs during or within weeks to months of radiation. On the other hand late radiation plexopathy manifests years after radiation to the supraclavicular area with hypoesthesia, paresthesia, and weakness of the affected arm or shoulder. It may progress to total paralysis of the affected arm with severe pain Late plexopathy is rare in patients who have received ≤ 60 Gy [40].

The toxicity of the brain irradiation: Even if there are strong evidence suggesting that PCI reduces the incidence of brain metastases and increases overall survival in SCLC patients, its indications should be considered in the light of its potential neurotoxicity. Acute toxicities associated with PCI include fatigue, alopecia, scalp erythema, and to a lesser extent, headaches and low-grade nausea, all of which are usually self-limited. These reactions are usually treated symptomatically by anti-edema therapy with corticosteroids or Glyceol Fatigue and alopecia are the most prevalent short-term toxicities [54,55]. Long-term toxicity is of concern, as sequela including memory loss, intellectual impairment or even dementia, ataxia, or seizures have been reported in retrospective studies attributed to PCI. However most of these are retrospectively designed studies conducted on limited number of patients. Therefore it is difficult to conclude whether PCI alone is responsible for the observed neurological sequela [54].

The frequency and severity of chronic toxicities associated with PCI are still unclear. Since the patients undergoing PCI have an improvement in overall survival, they are more likely to develop chronic neurotoxicity. Tai, et al. designed a retrospective study in order to investigate the therapeutic usefulness and cost-effectiveness of PCI in patients with LS-SCLC) who had achieved a complete remission [55]. Their results suggested that the patients who received PCI a significant improvement in mean quality time without symptoms and toxicity. In a similar analysis, qualitatively life expectancy adjusted quality adjusted life expectancy was evaluated. PCI offers a benefit over no-PCI [56]. The results of these analyses suggested benefit of PCI despite chronic toxicity. However, it is necessary to design clinical trials with the specific aim to adequately answer the question of benefit vs. neurotoxicity and quality of life in patients receiving PCI [1].

Mounting evidence suggests that radiation-induced damage to the hippocampus plays a role in neurocognitive decline for patients receiving WBRT; therefore novel strategies regarding to improve radiation-induced neurocognitive function are warranted. Hippocampal Avoidance Whole-Brain Radiotherapy (HA-WBRT) has been proposed to reduce the putative neurocognitive deficits by limiting the dose to the hippocampus. Two recent clinical trials, phase III RTOG 0614 and phase II RTOG 0933, showed some effectiveness of Memantine and IMRT planning for hippocampus sparing, among patients receiving WBRT [57,58]. The precise mechanisms by which WBRT leads to cognitive decline are largely unknown. Ablation of hippocampal neurogenesis and radiation-induced vascular damage in the brain [59] have been proposed as potential mechanisms that may play roles in the development of late delayed radiation-induced brain injury. Radiation Therapy Oncology Group (RTOG) 0614 was a phase III trial [57] that considered the role of Memantine, an N-Methyl D-Aspartate (NMDA) antagonist, which is traditionally used for dementia, including vascular dementia, while RTOG 0933 was a phase II single arm trial that considered the role of avoiding the hippocampus on cognitive decline [58]. The majority of surveyed radiation oncologists in the US do not use Memantine, or IMRT planning for hippocampus sparing in patients receiving WBRT. Further validation of the hippocampus sparing concept in a phase III trial was supported, before adopting it in routine clinical practice [59]. There are ongoing studies including NCT01797159 about the role of hippocampal prophylactic cranial Irradiation for small cell lung cancer.

As treatment for SCLC becomes more successful, the potential for long-term neurotoxicity due to PCI will be more relevant. Research efforts to minimize the neurotoxicity of PCI have included twice daily fractionation (1.5 Gy twice-daily to 30 to 36 Gy), hippocampal-sparing whole brain radiotherapy, and the use of alternative systemic agents [34,60-62].

Conclusion

RT has and important role in the management of SCLC patients. In LS-SCLC both thoracic RT and PCI improves local control as well as overall survival. In ES-SCLC patients thoracic RT becoming more and more important, since growing evidence suggests that the use of consolidation thoracic RT after first-line chemotherapy in the selected patients also improve both local control and overall survival. The use of PCI in ES-SCLC patients who have any degree of response to systemic therapy decreases the incidence of symptomatic brain metastases. Ongoing trials seek to better define the dose and fractionation of thoracic RT in both ES-SCLC and LS-SCLC, and the role of consolidation thoracic RT in ES-SCLC patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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References

1. Alvarado-Luna G, Morales-Espinosa D (2016) Treatment for small cell lung cancer, where are we now ? -a review. Transl Lung Cancer Res 5: 26-38.
2. Govindan R, Page N, Morgensztern D, et al. (2006) Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 24: 4539-4544.
3. Elias AD (1997) Small cell lung cancer: state-of-the-art therapy in 1996. Chest 112: 251S-258S.
4. Zelen M (1973) Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 3 4: 31-42.
5. Micke P, Faldum A, Metz T, et al. (2002) Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer-what limits limited disease? Lung Cancer 37: 271-276.
6. Videtic GM (2015) The role of radiotherapy in small cell lung cancer: a revisit. Curr Oncol Rep 17: 37.
7. Videtic GM (2013) The role of radiation therapy in small cell lung cancer. Curr Oncol Rep 15: 405-410.
8. Slotman B, Faivre-Finn C, Kramer G, et al. (2007) Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 357: 664-672.
9. Jeremic B, Shibamoto Y, Nikolic N, et al. (1999) Role of radiation therapy in the combined-modality treatment of patients with extensive stage small-cell lung cancer: A randomized study. J Clin Oncol 17: 2092-2099.
10. Slotman BJ, van Tinteren H, Praag JO, et al. (2015) Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 385: 36-42.
11. Yu JB, Decker RH, Detterbeck FC, et al. (2010) Surveillance epidemiology and end results evaluation of the role of surgery for stage I small cell lung cancer. J Thorac Oncol 5: 215-219.
12. Kalemkerian GP, Akerley W, Bogner P, et al. (2013) Small cell lung cancer. J Natl Compr Canc Netw 11: 78-98.
13. Simon GR, Turissi A, American College of Chest Physicians (2007) Management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 132: 324S-339S.
14. Schneider BJ, Saxena A, Downey RJ (2011) Surgery for early stage small cell lung cancer. J Natl Compr Canc Netw 9: 1132-1139.
15. (2016) Small Cell Lung Cancer. NCCN Guidelines Version 1.
16. Murray N (2000) Small cell lung cancer at the millennium: radiotherapy innovations improve survival while new che-

motherapy treatments remain unproven. Clin Lung Cancer 1: 181-190.

17. Slotman BJ, Senan S (2011) Radiotherapy in small-cell lung cancer: lessons learned and future directions. Int J Radiat Oncol Biol Phys 79: 998-1003.
18. Pignon JP, Arriagada R, Ihde DC, et al. (1992) A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 327: 1618-1624.
19. Warde P, Payne D (1992) Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol 10: 890-895.
20. Gaspar LE, Gay EG, Crawford J, et al. (2005) Limited-stage small-cell lung cancer (stages I-III): observations from the National Cancer Data Base. Clin Lung Cancer 6: 355-360.
21. Turrisi AT 3rd, Kim K, Blum R, et al. (1999) Twice-daily compared with one-daily thoracic radiotherapy in limited stage small cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 340: 265-271.
22. (2014) Convert: concurrent once daily versus twice daily: radiotherapy: a 2-arm randomized controlled trial of concurrent chemoradiotherapy comparing twice-daily and once-daily radiotherapy schedules in apteints with limited stage small cell lung cancer (SCLC) and good performance status. The Christie NHS.
23. (2013) Phase III comparison of thoracic radiotherapy regimens in patients with limited small cell lung cancer also receiving cisplatin and etoposide.
24. Johnson DH, Turrisi AT, Chang AY, et al. (1993) Alternating chemotherapy and twice-daily thoracic radiotherapy in limited-stage small-cell lung cancer: a pilot study of the Eastern Cooperative Oncology Group. J Clin Oncol 11: 879-884.
25. Mornex F, Trillet V, Chauvin F, et al. (1990) Hyperfractionated radiotherapy alternating with multidrug chemotherapy in the treatment of limited small cell lung cancer (SCLC). Groupe Lyonnais d'Oncologie Thoracique. Int J Radiat Oncol Biol Phys 19: 23-30.
26. Kies MS, Mira JG, Crowley JJ, et al. (1987) Multimodal therapy for limited small-cell lung cancer: a randomized study of induction combination chemotherapy with or without thoracic radiation in complete responders; and with wide-field versus reduced-field radiation in partial responders: a Southwest Oncology Group Study. J Clin Oncol 5: 592-600.
27. Pijls-Johannesma MC, De Ruysscher D, Lambin P, et al. (2005) Early versus late chest radiotherapy for limited stage small cell lung cancer. Cochrane Database Syst Rev CD004700.
28. De Ruysscher D, Pijls-Johannesma M, Bentzen SM, et al. (2002) Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. J Clin Oncol 24: 1057-1063.
29. Fried DB, Morris DE, Poole C, et al. (2004) Systemic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol 22: 4837-4845.
30. Aupérin A, Arriagada R, Pignon JP, et al. (1999) Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 341: 476-484.
31. Arrigada R, Le Chevalier T, Riviere A, et al. (2002) Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: analysis of 505 randomized patients. Ann Oncol 13: 748-754.
32. Le Péchoux C, Dunant A, Senan S, et al. (2009) Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. Lancet Oncol 10: 467-474.
33. Wolfson AH, Bae K, Komaki R, et al. (2011) Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. Int J Radiat Oncol Biol Phys 81: 77-84.
34. Slotman BJ, Mauer ME, Bottomley A, et al. (2009) Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol 27: 78-84.
35. (2014) 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).
36. Seto T, Takahashi T, Yamanaka T, et al. (2014) Prophylactic cranial irradiation (PCI) has a detrimental effect on the overall survival (OS) of patients (pts) with extensive disease small cell lung cancer (ED-SCLC): Results of a Japanese randomized phase III trial. J Clin Oncol 32: 5S.
37. Bernhardt D, Adeberg S, Bozorgmehr F, et al. (2016) Nine year Experience: Prophylactic Cranial Irradiation in Extensive Disease Small-cell Lung Cancer. Clin Lung Cancer S1525-S7304.
38. Kocher M, Soffietti R, Abacioglu U, et al. (2011) Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 29: 134-141.
39. Andrews DW, Scott CB, Sperduto PW, et al (2004) Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 363: 1665-1672.
40. Rengan R, Chetty IJ, Decker R, et al. (2013) Lung Cancer in Principles and Practice of Radiation Oncology. (6th edn), Wolters Kluwer, Lippincott Williams & Wilkins, Philadelphia.
41. Emami B, Lyman J, Brown A, et al. (1991) Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21: 109-122.
42. Graves PR, Siddiqui F, Anscher MS, et al. (2010) Radiation pulmonary toxicity: from mechanisms to management. Semin Radiat Oncol 20: 201-207.
43. Kocak Z, Evans ES, Zhou SM, et al. (2005) Challenges in defining radiation pneumonitis in patients with lung cancer. Int J Radiat Oncol Biol Phys 62: 635-638.
44. Trott KR, Herrmann T, Kasper M (2004) Target cells in radiation pneumopathy. Int J Radiat Oncol Biol Phys 58: 463-469.

45. Merrill WW (2017) Radiation-induced lung injury. Up to date.

46. Marks LB, Yorke ED, Jackson, et al. (2010) Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 76: S10-S19.

47. Coia LR, Myerson RJ, Tepper JE (1995) Late effects of radiation therapy on the gastrointestinal tract. Int J Radiat Oncol Biol Phys 31: 1213-1236.

48. Seeman H, Gates JA, Traube M (1992) Esophageal motor dysfunction years after radiation therapy. Dig Dis Sci 37: 303-306.

49. Kaplinsky C, Kornreich L, Tiomny E, et al. (1991) Esophageal obstruction 14 years after treatment for Hodgkin's disease. Cancer 68: 903-905.

50. Adebahr S, Schimek-Jasch T, Nestle U, et al. (2016) Oesophagus side effects related to the treatment of oesophageal cancer or radiotherapy of other thoracic malignancies. Best Pract Res Clin Gastroenterol 30: 565-580.

51. Adams MJ, Hardenbergh PH, Constine LS, et al. (2003) Radiation-associated cardiovascular disease. Crit Rev Oncol Hematol 45: 55-75.

52. Rubin DB (1998) The radiation biology of the vascular endothelium. (1st edn), CRC Press.

53. Stewart JR, Fajardo LF, Gillette SM, et al. (1995) Radiation injury to the heart. Int J Radiat Oncol Biol Phys 31: 1205-1211.

54. Blanchard P, Le Pechoux C (2010) Prophylactic cranial irradiation in lung cancer. Curr Opin Oncol 22: 94-101.

55. Tai TH, Yu E, Dickof P, et al. (2002) Prophylactic cranial irradiation revisited: cost-effectiveness and quality of life in small-cell lung cancer. Int J Radiat Oncol Biol Phys 52: 68-74.

56. Lee JJ, Bekele BN, Zhou X, et al. (2006) Decision analysis for prophylactic cranial irradiation for patients with small-cell lung cancer. J Clin Oncol 24: 3597-3603.

57. Brown PD, Pugh S, Laack NN, et al. (2013) Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol 15: 1429-1437.

58. Gondi V, Pugh SL, Tome WA, et al. (2014) Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. J Clin Oncol 32: 3810-3816.

59. Slade AN, Stanic S (2016) The impact of RTOG 0614 and RTOG 0933 trials in routine clinical practice: The US Survey of Utilization of Memantine and IMRT planning for hippocampus sparing in patients receiving whole brain radiotherapy for brain metastases. Contemp Clin Trials 47: 74-77.

60. Wolfson AH, Bains Y, Lu J, et al. (2001) Twice-daily prophylactic cranial irradiation for patients with limited disease small-cell lung cancer with complete response to chemotherapy and consolidative radiotherapy: report of a single institutional phase II trial. Am J Clin Oncol 24: 290-295.

61. Khuntia D, Brown P, Li J, et al. (2006) Whole-brain radiotherapy in the management of brain metastasis. J Clin Oncol 24: 1295-1304.

62. Mehta MP (2006) Models support prophylactic cranial irradiation. J Clin Oncol 24: 3524-3526.