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Radiotherapy in Extensive Stage Small Cell Lung Carcinoma – A Review

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Abstract

Small cell lung cancer (SCLC) is an aggressive form of lung cancer and requires multidisciplinary management. Limited-stage patients are those with disease burden limited to one hemi thorax and regional nodes amenable to definitive-intent thoracic radiation therapy (RT) to a reasonable treatment volume, without presence of extra-thoracic disease. Extensive stage (ES-SCLC) encompasses all other SCLC patients. The initial treatment of choice of ES-SCLC is chemotherapy. Although ES-SCLC is highly sensitive to chemotherapy and radiation, nearly all patients eventually relapse, and 2-year overall survival (OS) is poor, at approximately 4-7%. The role of Radiation therapy (RT) had mostly been used in palliation of loco regional and/or metastatic disease. Given the radiosensitive nature of SCLC, radiotherapy has been employed to improve outcome. This includes radiotherapy directed at sites like thorax and brain called Thoracic Radiotherapy (TRT) and Prophylactic Cranial Irradiation (PCI) respectively. In this review article we will discuss the role, indications, evidence, benefits, side effects of radiotherapy in ES-SCLC directed at thorax and brain.

Keywords: Small cell lung carcinoma, Extensive stage, Radiotherapy

Introduction

Lung cancer is the second most common cancer and is the leading cause of cancer related deaths in the world [1]. Small Cell Lung Cancer (SCLC) makes up ~15% of all lung cancer cases [2]. According to GLOBOCON data, it was estimated that in India, a total of 67,795 new lung cancer cases occurred (5.9% of all cancers) in 2018, of which 48,698 (8.5%) occurred in males [1]. These tumors have distinct characteristics which differentiate them from Non-Small Cell Lung Cancer are rapidly progressive nature, higher recurrence rates, poorer outcomes despite being more sensitive to chemotherapy and radiotherapy [3]. Majority of patients present with extensive disease at the time of presentation. It is defined as when the tumor burden cannot be covered by one radiation field. This includes malignant pleural effusion and/or distant metastases as well [4].

Chemotherapy is the cornerstone of treatment for extensive stage disease and four to six cycles of platinum-based chemotherapy without maintenance treatment is the current standard of care [5,6]. More importantly survival for extensive stage small cell lung cancer is poor and has improved little in recent decades despite advancements in both medical and radiation oncology fields. Patients with ES-SCLC have a poor prognosis with a median over all survival of 8–13 months [7-9]. Given the radiosensitive nature of SCLC, radiotherapy has been employed to improve OS, including radiotherapy directed at the thorax (Thoracic Radiotherapy – TRT) and brain (Prophylactic Cranial Irradiation – PCI). The indications, evidence, timing, dose, advantages, and disadvantages of both are important and will be the focus of this review article.

Thoracic Radiotherapy in ES-SCLC

Why is it necessary?

Thoracic disease progression is a major cause of morbidity for patients with ES-SCLC. Patients have high rates of thoracic relapse after systemic chemotherapy alone. Even after chemotherapy, 75-90% of patients have residual intrathoracic disease, and approximately 90% develop intrathoracic progression in the first year [10].

Evidence

There have been numerous phase II and phase III trials which assessed the role of thoracic radiotherapy in ES-SCLC. The two major RCT's were landmark trials regarding use of TRT and are described in this section.

Jeremic et al did a study of 210 patients of ES-SCLC who were treated with three cycles of cisplatin plus etoposide [11]. Out of these 110 patients had partial response in the thorax lesion and complete response (60 patients) was seen in terms of distant metastases. It should be noted that the patient population was carefully selected, with 90% of patients having only 1–2 sites of extra thoracic metastatic disease prior to initial chemotherapy. All patients who had CR or PR received either thoracic RT with concurrent daily carboplatin plus etoposide followed by two cycles of cisplatin plus etoposide or an additional four cycles of cisplatin plus etoposide. All eligible patients also received PCI. The dose of thoracic radiotherapy was 54Gy in 36 fractions over 12 days (thrice daily).

Patients who received thoracic RT had significantly better survival rates than those who received only chemotherapy (median OS 17 months versus 11 months; 5-year survival 9.1% versus 3.7%, respectively; P = 0.041). Acute high-grade toxicity was higher in the RT group. Although nearly 1 in four patients (27%) experienced acute grade 3 esophagitis with consolidative TRT, no treatment interruptions were reported, and CTRT was generally well tolerated [11]. In the CREST trial, 495 patients with extensive-stage SCLC who were responders to initial chemotherapy were randomized to receive either PCI alone or PCI with thoracic RT [12]. The dose of thoracic RT was 30 Gy/10-15 fractions. No significant improvement in 1-year OS was seen (33% versus 28% for thoracic RT versus no thoracic RT). Secondary analysis showed 2-year OS was 13% versus 3% favoring thoracic RT (P = 0.004).

Patients receiving consolidative TRT had a near 50% reduction in intrathoracic progression (43.7 vs. 79.8%; p < 0.0001) with no significant toxic effects reported. There was significant difference in the 6-month progression free survival as well. Patients with residual intrathoracic disease, the OS was significantly longer in the thoracic RT group. No significant differences in toxicity were seen between the treatment arms. Only 4 of 247 patients receiving consolidative TRT experienced grade 3 or greater esophagitis, and the only grade 4 toxicity reported was fatigue in a patient enrolled in the control arm. Despite the CREST study not meeting its primary endpoint, the authors concluded that consolidative TRT may improve long-term survival and should be considered for ES-SCLC patients who have had any response to initial chemotherapy. Subgroup analyses of the CREST trial suggest that patients with residual intrathoracic disease (a stratification factor at the time of randomization) benefited the most from consolidative TRT [12]. In a separate secondary analysis of a subset of CREST patients (89% of whom had intrathoracic residual disease), patients with 2 or fewer metastases had improved OS and progression-free survival (PFS), and the presence of liver and/or bone metastases was a negative prognostic factor for OS. Updated analyses suggest that the presence of intrathoracic residual disease, in addition to overall metastatic disease burden, are important factors to consider when identifying ES patients that are most likely to benefit from consolidative TRT [13].

A meta-analysis of the two randomised trials concluded that TRT improves overall survival and progression-free survival in patients with extensive stage SCLC. Although oesophageal toxicity was increased with the use of TRT, grade ≥3 oesophageal toxicity was uncommon (6.6%). When the dose of TRT was 30 Gy in 10 fractions the incidence of grade 3 oesophageal toxicity was low (2%) [14]. There were few phase II trials done which as well are worth mentioning. In a study done by Yee et al, 32 patients of ES-SCLC who attained an objective response to chemotherapy were treated with PCI (25Gy/10#) and TRT (40Gy/15#) simultaneously after chemotherapy completion. Thoracic target volume was the post-chemotherapy residual chest disease plus margin. There were 4 complete responses and 28 partial responses to chemotherapy. Maximal acute RT toxicity was grade 2 esophagitis (18 patients). There were no RT-related deaths. Median time to disease progression and overall survival were 4.2 and 8.3 months, respectively (median follow-up=21.8 months). They concluded that post-chemotherapy consolidation chest RT for ES-SCLC patients on this trial was well tolerated and associated with symptomatic chest recurrences in only 5/32 treated patients [15].

Another study of 119 patients with ES-SCLC retrospectively compared patients receiving platinum-based chemotherapy + TRT (n=60) vs. patients receiving platinum-based chemotherapy alone (n=59). TRT doses ranged from 40 to 60 Gy. On multivariable analysis, the use of TRT was associated with improved OS, at the expense of higher rates of pneumonitis (8% grade 2-5, with one death), esophagitis (22% grade 2-3), and leukopenia [16].

NRG Oncology RTOG 0937 was a randomized phase II trial which evaluated 1-year OS with PCI or PCI plus consolidative radiation therapy (PCI+cRT) to intrathoracic disease and extra cranial metastases for extensive-disease SCLC. In this study patients with one to four extra cranial metastases were eligible after a complete response or partial response to chemotherapy. Patients were stratified in terms of response to chemotherapy, number of metastases and age as well. PCI consisted of 25 Gy in 10 fractions. cRT consisted of 45 Gy in 15 fractions. In the study 42 patients received PCI and 44 received PCI+cRT. At planned interim analysis, the study crossed the futility boundary for OS and was closed before meeting the accrual target. Median follow-up was 9 months. The 1-year OS was not different between the groups: 60.1% for PCI and 50.8% for PCI+cRT. The 3- and 12-month rates of progression were 53.3% and 79.6% for PCI and 14.5% and 75% for PCI+cRT, respectively. Time to progression favoured PCI+cRT. One patient in each arm had grade 4 therapy-related toxicity and one had grade 5 therapy-related pneumonitis with PCI+cRT. RTOG 0937 did demonstrate that consolidative RT to residual sites of disease reduced the risk of intrathoracic progression from 83 to 26% [17].

Take home message

Consolidative thoracic radiotherapy after chemotherapy is beneficial for patients with complete response or good response to initial chemotherapy, in those patients who have residual

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intrathoracic disease or low bulk extrathoracic metastatic disease.

Dose

The optimal dose of TRT is uncertain. Higher doses of TRT appear to be associated with a high risk of esophagitis [16], and this is in keeping with a previous meta-analysis indicating that in non-small cell lung cancer, high-dose metrics (such as the volume of oesophagus receiving 60 Gy) are the best predictors of esophagitis risk [18]. Considering that intrathoracic progression in the CREST study was 44% (with 30 Gy in 10 fractions), one interpretation is that higher radiation doses (such as the preferred dose of 45 Gy in 15 fractions used in RTOG 0937) may achieve better local control rates, which may influence survival outcomes. In fact, retrospective series have demonstrated that consolidative TRT doses with a BED (with α/β= 10 (BED10) > 50 Gy10 are associated with improved intrathoracic control and OS [19,20].

Generally, radiotherapy (30 Gy in 10 fractions based on CREST trial) after induction chemotherapy is used if the patient is fit and there is presence of limited extra-thoracic tumour burden and initial bulky disease with either a complete extra-thoracic response or partial thoracic response [21]. As per American Society of Clinical Oncology, the dose of 30 Gy/10 fractions is a conditional recommendation, and they support the consideration of a higher dose (45-54 Gy) if the patient is expected to have prolonged survival. More prospective studies are required to inform patient selection for those who would benefit most from a higher dose.

Prophylactic Cranial Irradiation in ES-SCLC

Brain metastases are present in nearly 20% of patients of small cell lung carcinoma at the time of presentation. It is also one of the common sites of failure after treatment whether it is for extensive stage or limited stage disease. There is a high chance of development of occult brain metastases even in patients who do not have neurologic symptoms and those who have had a good response to initial chemotherapy [22,23]. Although more than 50% of patients with SCLC will eventually develop intracranial metastases, the role of PCI in ES-SCLC is often debated, especially in the present era of MRI imaging [24]. Goal of PCI: To eradicate undetectable micro metastases before they clinically manifest, to improve overall survival as well as quality of life.

Evidence

A meta-analysis of 987 patients among seven randomized trials was done by Aupérin et al. In this patient with complete response to initial therapy were randomized to either PCI or observation alone. Dose regimen varied from 8Gy to 40Gy. Patients in PCI group were found to have a reduced incidence of brain metastases at the end of three years and improved OS. Even in those patients in which PCI was given at an early stage showed improved results. In this meta-analysis 85% of the patients were in limited stage [25].

In EORTC trial, 286 patients of ES-SCLC were randomized to either PCI or observation alone after any response to upfront chemotherapy. The timing of PCI was within 4-6 weeks of completion of systemic treatment [26]. No brain imaging was done in this study. Various fractionation regimens were used in this trial (20 Gy in 5–8; 24 Gy in 12; 25 Gy in 10; or 30 Gy in 10–12 fractions). This study also showed a 1 year decreased incidence of brain metastases in the PCI arm (15% vs. 40%) along with improvement in OS (27% vs 13%). Importantly the Biologically Effective Dose (BED) ranged from 25Gy to 39Gy. The risk of extra cranial progression did not differ significantly between the two groups (89 versus 93 percent at one year). In terms of tolerability, there was no statistically significant difference between global health status between each arm (p = 0.10). Nevertheless, PCI was associated with significantly more fatigue and hair loss, with exploratory analyses demonstrating higher rates of decreased appetite, nausea/vomiting, and leg weakness in those who underwent PCI. A major critique of the EORTC study, however, was that the absence of pre-treatment imaging may have resulted in the treatment of subclinical intracranial metastases with PCI, leading to the modest improvement in median OS observed. An additional criticism is the use of several different PCI dose/fractionation regimens, which limits the ability to make conclusions regarding optimal radiation delivery [26].

In another trial which was conducted in Japan, 224 patients of ES-SCLC who had some response to their initial chemotherapy were randomly assigned to PCI or no PCI. Prior to the start of the trial, patients underwent MRI brain to rule out occult brain metastases. The patients were randomized to PCI or MRI surveillance (every 3 months in year 1, and then every 6 months until 24 months). The dose of PCI was 25Gy in 10 fractions. There was a statistically significant decrease in the incidence of brain metastases with PCI (33 versus 59 percent at one year) however there was no difference in overall survival [27]. Only a minority of the patients in the landmark Auperin meta-analysis had ES disease (140 vs. 847 LS patients), subgroup analysis demonstrated a persistent benefit of PCI regardless of the initial extent of disease in patients with a CR to initial chemotherapy with or without TRT [25].

Dose

Higher doses of radiation are associated with better control of brain metastases, although this benefit must be weighed against the risks of toxicity. Similar to radiation dose used in thoracic radiotherapy in ES-SCLC, there have been quite a varied dose regimens used while using PCI. To address this issue. A multi-institutional intergroup trail was done to compare standard dose PCI and high dose PCI [28]. All patients were given PCI treatment after initial response to treatment. In standard regimen the dose fractionation schedule used was 25 Gy in 10 fractions. In high dose PCI 36 Gy was given in 18 fractions or 24 twice daily fractions. At the end of 2 years the incidence of brain metastases was not

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statistically different in both the groups (29% vs. 23%). The OS was poor for high dose PCI arm (36% vs. 42%) (28). Wolfson et al reported neuropsychological difference between the two groups. There was increased chronic neurotoxicity at 12 months in the high dose PCI arm [29].

Generally, an individualized patient approach is recommended, whereby a discussion regarding the potential benefits (e.g., reduced risk for the development of brain metastases) and detriments of PCI (e.g., increased risk of neurocognitive toxicity) should be done [21]. Higher PCI doses, concurrent chemotherapy, treatment of elderly patients and/or those with poor performance status should be avoided given the potential for increased toxicity. MRI surveillance can be done in these patients, but they do have a poorer outcome according to the outline provided by Takahashi et al. [27].

Take home message

Dose regimen of 25 Gy in 10 fractions is recommended as standard protocol for PCI.

Timing

PCI is not given during chemotherapy to decrease the risk of leukoencephalopathy. PCI is given after completion of systemic chemotherapy in cases of ES-SCLC in those who have had response to it. PCI and TRT can be give side by side together.

Toxicity

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. Fatigue and alopecia are the most prevalent short-term toxicities.

Chronic long-term toxicity includes neurocognitive impairment. In certain old studies neurologic and intellectual disabilities were seen with earlier treatment techniques that used concurrent chemotherapy, large fraction sizes (3.0 to 4.0 Gy), and/or a high total dose, all of which have been shown to be associated with severe late neurotoxicity. In RTOG 0212 trial, chronic neurotoxicity was significantly less frequent in patients treated with 25 Gy compared with 36 Gy (60 vs. 85%) [29]. Research efforts to minimize the neurotoxicity of PCI include 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.

Whats New?

Chemotherapy combined with immunotherapy has become the new systemic standard of care treatment following the results of randomized phase III trials investigating anti-PD-L1 in addition to chemotherapy in ES-SCLC [30,31]. The use of immunotherapy may enhance efficacy of thoracic RT in ES-SCLC. While there are no randomized data evaluating the combination of immunotherapy and thoracic radiotherapy in ES-SCLC, the safety data and efficacy of the combination in the locally advanced non-small cell lung cancer (NSCLC) setting provides a foundation to build on. The PACIFIC trial evaluated patients with unresectable locally advanced NSCLC who completed definitive concurrent chemo radiotherapy and were then randomized to the PD-L1 inhibitor durvalumab vs. placebo [32]. The immunotherapy arm had significantly prolonged progression-free survival (median 17.2 vs. 5.6 months) and improved 2-year OS (66.3% vs. 55.6%). Additionally, immunotherapy following definitive radiotherapy doses was well-tolerated, with only a modest increase in any grade pneumonitis (34% for durvalumab vs. 25% for placebo), and a similar rate of grade 3–4 pneumonitis (3.4% vs. 2.6%, respectively) [33].

Additionally, the use of thoracic RT may enhance the effect of immunotherapy. Radiotherapy itself influences the immune system and its interactions with cancer cells and tumours, producing cytokines that recruit anti-tumour immune cells, increasing the exposure of tumour antigens, and improving cross-presentation of these antigens to the adaptive immune system [34-36]. Preclinical data show evidence of a synergistic effect between radiotherapy and immunotherapy, leading to improved tumour control with a combination of RT and immunotherapy than with either therapy alone [37,38]. Additionally, cases of tumour regression outside of the radiation treatment field after radiotherapy is added to immunotherapy have been reported, termed the abscopal effect. Although rare, the concurrent use of immunotherapy appears to improve the chances of an abscopal response [39].

Increased utilization of immunotherapy for ES-SCLC may further erode the potential use of PCI in this population however there is no direct evidence in small cell lung cancer. There is evidence from the PACIFIC trial in NSCLC in which the addition of immunotherapy reduced the incidence of brain metastases in NSCLC (6.3% vs. 11.8%). There is also evidence of CNS activity with immunotherapy in a study of ipilimumab/nivolumab in melanoma metastatic to the brain [40]. Here in lies a potential for the future. If the inclusion of immunotherapy does reduce the incidence (or pace) of brain metastases presentation in ES-SCLC, then the rationale for upfront, routine PCI usage would be further decreased. At present, PCI holds an important position in the management of ES-SCLC on chemotherapy having any response.

Role of Thoracic Radiotherapy in Polymetastatic Disease

We have discussed about the role of thoracic radiotherapy in cases of oligometastatic disease after initial response to chemotherapy. We now look at the role of the same in case of polymetastatic disease. In a study done by Li-Xu Ming et al, 270 ES-SCLC cases were retrospectively studied. Out of these, 78 patients (28.9%) had oligometastases and 192 (71.1%) had polymetastases. Among these 51 oligometastatic patients

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(65.4%) and 93 polymetastatic patients (51.6%) received TRT. The 2-year OS, progression free survival (PFS) and local control (LC) in oligometastatic and polymetastatic patients were 22.8% and 4.5% ($p < 0.001$), 12.0% and 3.8% ($p < 0.001$), and 36.7% and 6.1% ($p < 0.001$), respectively. The 2-year OS in oligometastatic patients with the chemotherapy + radiotherapy and chemotherapy alone were 25.2% and 12.7% ($p = 0.002$), in contrast to 10.0% and 6.8% ($p = 0.030$) in polymetastatic patients. The estimated hazard ratios for survival were 2.9 and 1.7 for both oligometastatic and polymetastatic patients with radiotherapy. TRT improved OS of patients with oligometastases and polymetastases. They concluded that aggressive TRT might be a suitable addition to chemotherapy when treating ES-SCLC patients with oligometastases and polymetastases [41]. This study not only proves that there is a beneficial role of thoracic radiotherapy in oligometastatic disease but in polymetastatic disease as well.

Conclusion

Thoracic Radiotherapy and Prophylactic Cranial Irradiation are important components of treatment in ES-SCLC. Its timing, dose and integration into chemotherapy treatment can play a crucial role in improvement of disease progression. Randomized prospective trials need to be done for evaluation of dose regimen for thoracic radiotherapy and its integration with immunotherapy.

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