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RADIATION THERAPY FOR SMALL-CELL LUNG CANCER

Expert Panel on Radiation Oncology–Lung: Feng-Ming (Spring) Kong, MD, PhD, MPH[1]; Brian E. Lally, MD[2]; Kenneth E. Rosenzweig, MD[3]; Joe Yujiao Chang, MD, PhD[4]; Indrin J. Chetty, PhD[5]; Roy H. Decker, MD, PhD[6]; Mark E. Ginsburg, MD[7]; Larry L. Kestin, MD[8]; Corey J. Langer, MD[9]; Benjamin Movsas, MD[10]; Gregory M. M. Videtic, MD, CM[11]; Henning Willers, MD.[12]

Summary of Literature Review

Introduction

Small-cell lung cancers (SCLC) make up approximately 15%-20% of all newly diagnosed cases of lung cancer. In 2010, there were an estimated 33,380 new cases and 23,600 deaths [1]. Compared to non-small-cell lung cancer, SCLC can be a more aggressive malignancy secondary to an increased doubling time (faster proliferation). SCLC is considered a systemic disease at presentation. Due to its high rate of metastatic dissemination, the 5-year survival rate is only 5%-6%.

In general, SCLC is classified as either limited stage (LS-SCLC) or extensive stages (ES-SCLC). Only 30% of patients have LS-SCLC, which historically has been defined as disease confined within an ipsilateral hemithorax that can be safely encompassed in a "tolerable" radiation field [2]. The standard of care for LS-SCLC involves the use of chemotherapy and early initiation of thoracic radiotherapy (TRT), followed by prophylactic cranial irradiation (PCI) for patients who have a good treatment response. In highly selected cases, patients will undergo surgical resection followed by chemotherapy with or without radiotherapy (RT). Patients with ES-SCLC have disease beyond the ipsilateral hemothorax, mediastinum, and ipsilateral supraclavicular fossa which may include malignant pleural or pericardial effusions or contralateral lung or extrathoracic metastasis. The standard of care for ES-SCLC involves the use of chemotherapy and PCI for those who achieve a good response. The role of TRT for ES-SCLC is being evaluated in prospective trials and may be used in selected cases.

Treatment of LS-SCLC

Over 30 years ago there was optimism that SCLC would prove to be a curable disease. A unique staging system had been devised, and the effectiveness of several chemotherapeutic agents and RT had been established. The central nervous system was identified as a sanctuary site for metastatic disease [3]. During the last 30 years, landmarks in therapy have been provided by clinical trials of LS-SCLC. However, further research is still needed to improve the outcomes for patients with SCLC.

Surgery Alone

Before chemotherapy was implemented for treatment of SCLC, surgery alone was the standard of care for all lung cancer; long-term treatment outcome was dismal, with 5-year survival rates close to 0%. A randomized trial from the Medical Research Council in the United Kingdom reported medial survival times of 28.5 weeks for surgery and 43 weeks for RT (P=0.04) [4]. Five-year overall survival (OS) rates were 1% for surgery, and 4% for RT. Median OS times were 6 months and 10 months, respectively, and 10-year OS rates were 0% and 4%, respectively [5]. Surgery alone is not a treatment option for patients with SCLC. However, there is new interest in the use of surgery in patients with very early limited-stage disease (such as T1N0) in combination with chemotherapy. Currently patients with clinical stage Ia (T1N0) after standard staging evaluation (including computed tomography [CT] of the chest and upper abdomen, bone scan, brain imaging, and positron emission tomography [PET] imaging) may be considered for surgical resection. Under such circumstance, all patients

[1]Co-author, VA Health Center and University of Michigan, Ann Arbor, Michigan. [2]Co-author, University of Miami, Miami, Florida. [3]Panel Chair, Mount Sinai School of Medicine, New York, New York. [4]Panel Vice-chair, MD Anderson Cancer Center, Houston, Texas. [5]Henry Ford Health System, Detroit, Michigan. [6]Yale University School of Medicine, New Haven, Connecticut. [7]Columbia University, New York, New York, Society of Thoracic Surgeons. [8]21st Century Oncology of Michigan, A Division of Michigan Healthcare Professionals, Farmington Hills, Michigan. [9]Fox Chase Cancer Center, Philadelphia, Pennsylvania, American Society of Clinical Oncology. [10]Henry Ford Health System, Detroit, Michigan. [11]Cleveland Clinic Foundation, Cleveland, Ohio. [12]Massachusetts General Hospital, Boston, Massachusetts.

Reprint requests to: Department of Quality & Safety, American College of Radiology, 1891 Preston White Drive, Reston, VA 20191-4397.

should undergo surgical mediastinoscopy to rule out occult nodal disease. Only those patients with pathologic negative nodes can be treated with radical surgical resection followed by chemotherapy alone. Concurrent chemotherapy and mediastinal radiation therapy is recommended when the nodes are positive on the surgical pathology. (See Variant 1.)

Chemotherapy Alone

Chemotherapy alone is also not a standard option for LS-SCLC, as local tumor progression occurs in up to 80% of such patients and survival is poor [6,7]. As will be discussed shortly, multiple clinical investigations have demonstrated that TRT with chemotherapy results in only a modest improvement in survival. It should be noted that these clinical trials were done in a time when 1) staging was not used extensively, 2) effective, standardized chemotherapy regimens had not been established, 3) the trials utilized moderate RT doses, and 4) the combined therapy was predominantly sequential chemoradiotherapy. It is likely that the benefit from the addition of TRT is greater than the 5.4% reported in the literature.

A breakthrough occurred in the late 1960s with the recognition that SCLC patients were relatively more responsive to available chemotherapeutic agents when compared with an inert compound [8]. While encouraging results were achieved with chemoradiotherapy, the standard of care for LS-SCLC was chemotherapy alone for the better part of two decades [9]. As a result, the 1980s saw a flurry of clinical trials investigating chemoradiotherapy versus chemotherapy alone in LS-SCLC.

Combined-Modality Therapy

The current standard of care for LS-SCLC is combined-modality therapy, including the use of chemotherapy, surgery (in selected cases), TRT, and PCI for those who achieve a good response.

Role of Thoracic Radiation Therapy in LS-SCLC

RT plays an important role in the treatment of patients with LS-SCLC. The addition of TRT has a small but clear survival advantage in this population. Although results from individual randomized trials were often inadequate to definitively determine the standard of care, at least two large meta-analyses have confirmed that TRT decreases thoracic recurrence and improves survival [10,11]. Pignon et al [10] reported that the relative risk of death in the combined-therapy group, as compared with the chemotherapy-alone group, was 0.86, corresponding to a 14% reduction in the mortality rate. The benefit in terms of OS rates at 3 years was 5.4%. A meta-analysis by Warde and Payne [11], based on 11 randomized trials, demonstrated that RT improved 2-year survival rates by 5.4%. In addition, a recent overview of prospective studies in LS-SCLC included 26 randomized clinical trials initiated by cooperative groups in North America between 1972 and 1992, and only five studies showed a statistically significant longer survival in the experimental arm compared with the control arm [12]. All five positive trials studied some aspect of TRT.

The survival benefit associated with the use of TRT outside of clinical trials was also illustrated in a review from the National Cancer Data Base [7]. For patients with LS-SCLC, the 5-year survival rate for the 6,752 patients diagnosed in 2000 was significantly higher in patients treated with TRT plus chemotherapy (13.3% vs 5.7% with chemotherapy alone). Furthermore, data for population databases demonstrate that improvement in outcomes for LS-SCLC has temporal association with the publication of these clinical results [13].

Radiotherapy Doses/Fractionations/Treatment Duration

While a dose-response relationship has been demonstrated for many cancer types, there exists no adequate clinical trial addressing the impact of increasing radiation doses on local tumor control and OS in LS-SCLC. Prospective data indicate that doses of 45-50.4 Gy once daily (QD) are associated with high rates of locoregional failure (ie, ~50% or higher) [14,15]. Radiobiologically, the curve of tumor control probability as a function of radiation dose has its steepest incline at 50%, so that a relatively modest dose increase is expected to have a significant impact on local control rates. If hyperfractionation is not feasible, a dose of at least 60 Gy in 2 Gy daily fractions is recommended [16]. The Cancer and Leukemia Group B (CALGB) has completed studies (CALGB 39808 [17], 30002 [18], and 30202 [14]) of 70 Gy of TRT with different chemotherapy combinations with acceptable toxicity. However, the local tumor control rate associated with this dose level has not yet been established. Retrospective data suggest improved local control with dose levels of 56-60 Gy, (ie, 60%-78% at 3 years) [16,19]. It is important to note that local failure data are difficult to obtain and interpret because of problems associated with scoring local failure after high-dose TRT and competing risks. A Patterns of Care study in 2003 showed that the median RT dose used in the community was 50.4 Gy [15]. The current National Comprehensive Cancer Network

guidelines states that if daily fractionation is used, a dose of at least 66-70 Gy in 2 Gy fractions should be administered [20].

The optimal dose fractionation of TRT is not known. Accelerated hyperfractionated RT (45 Gy in 1.5 Gy twice-daily [BID] fractions) is recommended based on the only phase III study on this topic [21]. This dose regimen was studied by Intergroup 0096 [21], which compared QD (45 Gy in 1.8 Gy daily fraction) versus BID RT (45 Gy given in BID 1.5 Gy fractions) in combination with concurrent etoposide and cisplatin (EP) therapy. An improved median survival time and 5-year survival rate was observed in the hyperfractionated arm compared with the QD group, 23 months versus 19 months and 26% versus 16%, respectively (P=.04). One must note that the accelerated hyperfractionated RT was associated with increased toxicities and that a dose of 45 Gy in 1.8 Gy daily fractions is not radiobiologically equivalent to 45 Gy given in BID 1.5 Gy fractions. Daily fractionation regimens such as 50.4-70 Gy in 1.8-2 Gy daily fractions may serve as reasonable alternatives. However, there are no trials that directly compare the efficacy and toxicity of 2 Gy fractions to those of 1.8 Gy fractions. Fractions of 2 Gy may be advantageous due to the associated reduction in overall treatment time (see below) and are commonly used in modern clinical protocols, though there may be concerns about esophageal toxicity due to increased dose intensity. Nevertheless, 45 Gy in 30 fractions over 3 weeks concurrent with EP therapy generated favorable results according to other published reports, and it is the recommended regimen for treating LS-SCLC until results of further phase III trials are available.

Treatment duration is an important factor associated with local control in several cancer types including lung cancer. It is widely accepted that accelerated fractionation (ie, shortening of overall treatment time), has the potential to reduce the negative impact of accelerated repopulation of tumor stem cells during the course of radiation treatment [22]. It is unlikely that the typical delivery of BID fractions in accelerated treatment regimens contributes significantly to improved tumor cell kill, given the generally short repair half-times of rapidly proliferating tumor cells. The concept of treatment acceleration and repopulation can be applied to SCLC. In addition, because of the lack of a so-called shoulder observed for in-vitro radiation survival curves, lowering the dose per fraction in BID regimens is not predicted to spare SCLC cells. In the findings of Intergroup 0096 mentioned earlier [21], 45 Gy given in BID 1.5 Gy fractions with an accelerated with a 3-week treatment duration was associated with improved local tumor control, median survival time, and 5-year OS. In contrast, the North Central Cancer Treatment Group (NCCTG) used a similar regimen of hyperfractionated RT (45 Gy given in BID 1.5 Gy) with a treatment duration of 5.5 weeks (including a treatment break of 2.5 weeks) failed to show a benefit of using hyperfractionated RT as compared to conventional 50.4 Gy at 1.8 Gy QD TRT in 5.5 weeks [23,24]. These findings suggest that the favorable result from 45 Gy given in BID 1.5 Gy is most likely contributed to shortened duration of accelerated TRT rather than hyperfractionation. (See Variant 2.)

Currently, two large-scale phase III randomized trials are underway to attempt to determine the optimum combination of dose, fractionation, and treatment duration. CALGB 30610, a U.S. Intergroup trial, is a three-arm study comparing standard TRT (45 Gy given in BID 1.5 Gy, based on Intergroup 0096) to 70 Gy in 2 Gy daily fractions (CALGB 39808 regimen) and 61.2 Gy concomitant boost TRT (RTOG® 97-12 regimen). After an interim analysis, the experimental arm with the highest rate of acute toxicity will be discontinued. In Europe and Canada, a two-arm trial is comparing standard TRT to 66 Gy QD TRT. In Europe and Canada, a two-arm trial (CONVERT) is comparing 45 Gy given in BID 1.5 Gy to 66 Gy at 2 Gy QD TRT with concurrent EP. Until the results of these trials are available, it is reasonable to consider a regimen of 60-70 Gy at 1.8-2 Gy QD as an alternative if 45 Gy at 1.5 Gy BID is not possible due to logistic considerations.

Timing of TRT Relative to Chemotherapy

TRT in LS-SCLC should be delivered early and concurrently with the chemotherapy rather than sequentially after the completion of chemotherapy. There have been eight randomized trials and three meta-analyses [25-27] that have attempted to address the timing of the delivery of TRT relative to chemotherapy. Studies that used standard cisplatin-based chemotherapy without significant dose reductions convincingly showed that early (with cycle 1 or 2 of chemotherapy) rather than late initiation of TRT is associated with a better outcome.

The National Cancer Institute of Canada performed a phase III prospective randomized trial to compare the outcomes of early versus late administration of RT [28]. This trial enrolled 308 patients with LS-SCLC, all of whom received cyclophosphamide, doxorubicin, and vincristine alternating with EP chemotherapy for a total of 6 cycles. Patients were randomly assigned to TRT (40 Gy in 15 QD fractions over 3 weeks) delivered during cycle 2 or cycle 6 concurrently with EP. Five-year survival rates showed a significant benefit for early TRT compared to late TRT (22% vs 13%, respectively). Patients were randomized to initiate RT at the second cycle of

chemotherapy (week 3), or during the last cycle of chemotherapy (week 15). The median progression-free survival time was 15.4 months in the early RT group versus 11.8 months in the late RT group (P=.036); the median OS times were 21.2 months and 16 months, respectively (P=.008).

The Lung Cancer Study Group of the Japan Clinical Oncology Group (JCOG) conducted another phase III study in which patients were randomized to sequential chemoradiotherapy or concurrent chemoradiotherapy [29]. A total of 231 patients received 4 cycles of EP and TRT consisting of 45 Gy given BID over 3 weeks. RT was initiated after the fourth cycle of chemotherapy on the sequential arm and on cycle 1 day 2 on the concurrent arm. The median survival time was 19.7 months in the sequential arm versus 27.2 months in the concurrent arm (P=.097). The 5-year survival rate for patients who received sequential chemoradiotherapy was 18.3%, as compared to 23.7% for the patients who received concurrent chemoradiotherapy (P=.097). This study also suggests that chemotherapy and concurrent RT is more effective than the sequential regimen. Thus, early concurrent chemoradiotherapy is the recommended treatment for LS-SCLC.

In a third trial, 107 patients with LS-SCLC were randomly assigned to TRT with carboplatin/etoposide, followed by 4 cycles of EP, or to 2 cycles of EP followed by TRT with carboplatin/etoposide and then two additional cycles of EP [30]. TRT consisted of 54 Gy given in 1.5 Gy fractions BID. Five-year OS rates favored the early treatment arm compared to the late arm (30% vs 15%, respectively). There were no chemotherapy dose reductions in either arm. Of note, there was no difference between the two groups in the rate of distant metastases, but there was a significantly better local control rate for those assigned to the early treatment arm.

Three meta-analyses have examined the optimal timing of TRT. One meta-analysis included seven randomized trials published after 1985 and showed a significant improvement in 2-year OS rates for early TRT versus late TRT [26]. Subset analysis showed that this benefit was more pronounced with the use of hyperfractionated RT and platinum-based chemotherapy. These results are consistent with the opinion that standard treatment for LS-SCLC should include the use of cisplatin-containing regimens and concurrent therapy with TRT delivered early. The Cochrane meta-analysis incorporated data from seven randomized trials and was unable to determine the optimal strategy for integrating chemotherapy and TRT in patients with LS-SCLC, although several of the studies included did not use EP chemotherapy delivered at full doses [27]. An additional meta-analysis from the same group indicated that the most important factor associated with improved 5-year survival was a short interval between the start of any treatment and the completion of TRT (relative risk 0.62) [25]. This observation was attributed to the phenomenon of accelerated repopulation during treatment. The importance of a short interval between the start of treatment and the completion of RT can also be inferred from a report that analyzed outcome for 215 patients treated with concurrent chemotherapy and TRT during cycle 2 or 3 [31]. On multivariate analysis, RT treatment interruptions due to toxicity were the most important adverse prognostic factor for survival.

In all three of the studies that demonstrated a marked survival advantage for early TRT, patients received cisplatin-based chemotherapy, and both the early and late treatment arms had similar and high rates of patients receiving full doses of chemotherapy [28-30]. In contrast, the randomized trials that did not demonstrate an advantage for early TRT either did not use cisplatin-based chemotherapy or had a lower percentage of patients in the early TRT arms who received full-dose chemotherapy compared to those in the late TRT arms [32-36]. These deficits may suffice to explain the lack of an observed benefit for early TRT in those studies. The importance of receiving all planned chemotherapy was further supported in another meta-analysis of eight trials [35].

Practically, since treatment can often be initiated faster with chemotherapy than with TRT, delivery of TRT is often integrated early at the second cycle of chemotherapy. For patients with a good performance status and nonbulky disease, intensive therapy with RT early in the course of treatment is appropriate. However, delayed RT does have the advantage of avoiding the significant myelosuppression seen with full-dose chemotherapy and large-volume RT. Therefore, for patients with either a poor performance status or very bulky disease, delaying the initiation of RT until the third cycle of chemotherapy might be prudent. As the elderly comprise increasing portions of patients with SCLC, determining which patients will benefit from intensive therapy and which will benefit from delayed RT becomes critical. Available evidence does suggest that abbreviated therapy may still be of benefit to elderly and infirm patients [37].

Radiation Treatment Volume

Several reports [23,24] have demonstrated that the use of postchemotherapy volumes, with an associated smaller radiation field size does not increase the local recurrence rate after TRT. However, these fields still, in general, encompassed the primary tumor, ipsilateral hilum, mediastinum, and sometimes the supraclavicular region. While

the use of elective nodal irradiation has not been adequately studied, the Intergroup 0096 trial [21] limited elective radiation by not allowing treatment with radiation to the contralateral hilum or to supraclavicular nodes, unless there was bulky superior mediastinal adenopathy. The use of even larger fields otherwise may increase the toxicity with a therapeutic benefit. Bulky SCLC tumors often require large radiation field size that can be reduced after effective chemotherapy shrinks the tumor, potentially reducing toxicity to the lungs and esophagus. The role of elective nodal irradiation has been summarized by a report from International Atomic Energy Agency (IAEA) on this issue [38].

PET may have a role in designing radiation treatment volumes. In a prospective evaluation, the principal value of PET in LS-SCLC was the detection of additional sites of disease within the thorax. PET identified unsuspected regional nodal metastasis in six (25%) of 24 patients, and the RT plan was significantly altered to include the PET-positive/CT-negative nodes within the high-dose region in each of these patients [39]. Selective nodal irradiation on the basis of FDG-PET scans in LS-SCLC was also examined by a prospective study [40]. PET-based involved nodal radiation resulted in a low rate of isolated nodal failures (3%), with a low percentage of acute esophagitis, while CT-based selective nodal irradiation resulted in an unexpectedly high percentage of isolated nodal failures (11%).

Prophylactic Cranial Radiation Therapy in LS-SCLC

Many clinical trials have been conducted to assess the role of PCI in SCLC treatment. Arriagada et al [41] reported a prospective randomized study to evaluate the effects of PCI on SCLC. The rate of brain metastasis was significantly reduced by PCI, with a 2-year rate of brain metastasis decreasing from 67% to 40% with the use of PCI ($P<10^{-13}$). The 2-year cumulative rate of brain metastasis as an isolated first site of relapse was 45% in the control group and 19% in the treatment group ($P<10^{-6}$). The 2-year rate of OS was 29% in the PCI group and 21.5% in the control group (P=0.14). There were no significant differences between the two groups in terms of neuropsychological function or abnormalities indicated by CT brain scans. A multicenter randomized study reported by Gregor et al [42] showed similar results, with a significant decrease in brain metastasis. In 1999, Auperin et al [43] performed a meta-analysis on 987 patients with SCLC (847 patients with limited disease and 140 patients with extensive disease) who were in complete remission from seven trials that compared the use of PCI versus no PCI. PCI was associated with an absolute decrease of 25.3% in the cumulative incidence of brain metastasis at 3 years — from 58.6% in the control group to 33.3% in the PCI group. The relative risk of death in the treatment group as compared with the control group was 0.84 (95% confidence interval, 0.73-0.97; P=0.01), which corresponded to an absolute increase in OS of 5.4% at 3 years — from 15.3% in the control group to 20.7% in the treatment group (P=0.01). As a result of this meta-analysis, PCI has become standard practice for patients with SCLC who have complete remission after chemoradiotherapy of the primary thoracic tumor.

Dose Fractionations for PCI

There have been multiple dose-fractionation schemes for PCI for LS-SCLC. A common one has been 25 Gy in 2.5 Gy daily fractions over 12-14 days [21,44]. A review including 42 PCI trials with 4,749 patients revealed the optimal total RT dose to be 30-35 Gy given in 2 Gy fractions [45]. In a multinational phase III trial, 720 patients with LS-SCLC who had a complete response to their initial treatment were randomly assigned to PCI at a dose of either 25 Gy in 10 fractions or a dose of 36 Gy administered either as 18 fractions of 2 Gy each or 24 fractions given in BID 1.5 Gy fractions) [46]. Among the patients randomized to the 36 Gy treatment arm, 78% received QD therapy. The 2-year incidence rates of brain metastases were 23% with the higher radiation dose and 29% with the lower dose. This difference was not statistically significant (hazard ratio [HR] 0.80, 95% confidence interval [CI], 0.57-1.11). However, the higher dose was associated with a significantly lower 2-year survival rate (37% vs 42%, HR 1.20, 95% CI, 1.00-1.44). There was no obvious explanation for the increased mortality in the group treated with higher doses of PCI. Therefore, the standard dose of PCI should be 25 Gy in 10 fractions within 2 weeks. A dose of 30 Gy over 3 weeks may be an acceptable alternative, though it has not been directly compared to the 25 Gy dose.

Treatment of ES- SCLC

With improvements in staging through the use of CT, magnetic resonance imaging (MRI), and PET with fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG-PET) tracer, more patients who previously were considered to have limited-stage disease are found to have ES-SCLC. The ratio of LS-SCLC to ES-SCLC was formerly 1:1 and is now 1:3. For ES-SCLC, the treatment of choice is chemotherapy with PCI, with or without TRT. Although many attempts have been made to develop newer therapies, cisplatin-based combination chemotherapy remains the mainstay of treatment [47]. RT may also be used as a palliative therapy in some situations such as superior vena

cava obstruction, brain metastasis, or bone metastasis. Concurrent chemotherapy in this setting is not recommended.

Chemotherapy for ES-SCLC

Several therapeutic agents and strategies have been tested during the last three decades in ES-SCLC. Response rates of 70%-85%, with complete response rates of 20%-30%, are encouraging, but virtually every patient relapses. The standard of care in the U.S. has been to use the EP combination since the 1980s [48]. Carboplatin may be substituted for cisplatin without an apparent loss of effect and is preferred in older patients or those with renal insufficiency [49].

Newer agents do not appear to be more active than older agents. For example, epirubicin, ifosfamide, vinorelbine, carboplatin, gemcitabine, the taxanes, and the topoisomerase I inhibitors tested in the 1990s and 2000s are not more active than doxorubicin, cyclophosphamide, vincristine, cisplatin, and the topoisomerase II inhibitors tested in the 1970s and 1980s. Still, some promising results have been reported. Noda et al [50] demonstrated the superiority of cisplatin plus irinotecan compared with cisplatin plus etoposide in a JCOG trial. Hanna et al [51] performed a comparative trial in the U.S. and did not demonstrate superiority with the use of irinotecan. In general, two-agent regimens have been demonstrated to be more effective than single-agent regimens, even in elderly patients with a poor performance status [52-54]. The addition of a third agent has produced higher response rates but at the cost of greater toxicity, without an improvement in survival [55-58]. Treatment beyond 4 to 6 cycles of any chemotherapy regimen is not beneficial. After 4 cycles of a standard EP regimen, treatment with either maintenance therapy or 4 cycles of topotecan failed to improve survival [59,60]. A large challenge in the treatment of ES-SCLC remains the rapid development of drug resistance and the failure of second-line therapy to produce meaningful response rates and longer survival times. (See Variant 3.)

Thoracic Radiotherapy for ES-SCLC

The role of TRT in ES-SCLC is unclear, and it is typically not considered part of the standard of care. There is some preliminary evidence that adding TRT to chemotherapy improves the survival of patients with ES-SCLC. In one trial, patients who had a complete response outside the thorax to an initial 3 cycles of EP chemotherapy and an at least partial response in the thorax benefitted from subsequent concurrent chemotherapy and radiation [61]. Median survival time (17 months vs 11 months, P=0.041), 5-year survival rate (9.1% vs 3.7%, P=0.041), and median time to local recurrence (30 vs 22 months, P=0.062) were all improved in the RT group. RTOG® 0937 is investigating the role of extracranial RT in addition to PCI following platinum-based chemotherapy in patients with extensive-disease small-cell lung cancer (ED-SCLC). A similar trial is being performed within the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group Study (EORTC).

PCI for ES-SCLC

Although routine use of TRT to treat ES-SCLC should not yet be integrated into the standard care of patients, there is more convincing evidence for offering PCI to patients with ES-SCLC. In 2007, the EORTC published a landmark trial examining the role of PCI in ES-SCLC [62]. It demonstrated that, in patients with ES-SCLC who responded to chemotherapy, PCI reduced the risk of brain metastases at 1 year by 26% (40% brain metastases in the control group vs 15% in the PCI group). Moreover, the 1-year survival rate was 27% in the irradiation group and was 13% in the control group. However, this gain may be associated with a negative impact on quality of life. In a correlative study for this trial [63] the mean global health status score was 8 points higher in the PCI group, a difference that is below the cut off of a 10-point difference for clinical significance. The most significant side effects of PCI were fatigue and hair loss, whereas the impact on other health related quality-of-life aspects, such as cognitive and emotional functioning, was limited. However, it is reasonable to offer PCI to all patients with ES-SCLC who respond to first-line chemotherapy.

A caveat of the EORTC trial is that brain imaging was not mandatory prior to PCI. Only 29% of patients had brain imaging studies done at diagnosis. As the incidence of asymptomatic brain metastases in SCLC is as high as ~15%, it is likely that a sizeable fraction of these patients had clinically silent brain metastases for which PCI was therapeutic rather than prophylactic. Notably, in the observation arm, symptomatic brain metastases began to be diagnosed within only 1-2 months, which is consistent with the emergence of pre-existing disease that would have been picked up had a brain scan been performed. Therefore, the magnitude of the benefit of PCI in a clinical setting where all patients undergo brain imaging prior to PCI is not defined.

A balanced discussion between the patient and physician is necessary before making a decision to administer PCI. PCI is recommended for patients with either limited or extensive disease who obtain a complete or partial

response. PCI is not recommended for patients with poor performance status (3-4) or impaired mental function. The recommended dose for PCI is 25 Gy in 10 fractions. PCI should not be given concurrently with systemic chemotherapy because of the increased risk of neurotoxicity, but should be initiated within 3-6 weeks after the last chemotherapy cycle.

Summary

The treatment of patients with SCLC remains a clinical challenge. The Expert Panel on Radiation Oncology–Lung recommends:

- For patients with clinical stage T1N0, pathologic stage T1-T2N0 limited-stage disease after lobectomy and nodal dissection or nodal sampling, the treatment should be chemotherapy followed by PCI. TRT is not considered unless there is a concern of mediastinum nodal disease or surgical margins are suspicious or positive.
- For nodal positive LS-SCLC (cT-1-4pN1-3M0), the consensus standard of care is chemotherapy with concurrent TRT. PCI should be recommended for patients with good treatment response to chemoradiation.
- For patients with ES-SCLC, TRT may be recommended in patients after 4-6 cycles of chemotherapy, particularly when PCI is planned, and local thoracic disease is remarkable, or causing local symptoms.
- TRT should start concurrently during the 1st or 2nd cycle of chemotherapy in LS- SCLC, sequentially after completion of 4th or 6th cycle of chemotherapy in ES-SCLC.
- For TRT in LS-SCLC, 45 Gy given in BID 1.5 Gy fractions is the preferred regimen. When BID radiation is not possible due to logistical reasons, 60-70 Gy in 2 Gy daily fractions is an acceptable alternative. Radiation should cover involved primary tumor and nodal diseases with elective radiation of the 1st echelon nodal regions.
- When TRT is recommended for ES-SCLC, conventionally fractionated 30-54 Gy in 2-3 Gy daily is the preferred regimen. BID radiation is not recommended. Radiation can cover post-chemotherapy volumes of involved primary tumor and nodal diseases without elective nodal radiation.
- PCI is to start after completion of TRT and systemic therapy, and restaging workup showing a good treatment response.
- For PCI, 25 Gy in 2.5 Gy daily fractions for 10 treatments is the consensus recommendation. For younger patients with excellent performance status, 30 Gy in 10 daily fractions is an acceptable alternative.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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Clinical Condition: **Radiation Therapy for Small-Cell Lung Cancer**

Variant 1: **68-year-old man with a good performance status with pT1pN0M0 limited-stage small-cell right lung cancer, status post lobectomy with negative margins, with 0/15 nodal involvement.**

Treatment	Rating	Comments
Treatment Options		
Chemotherapy alone	9	
Sequential chemotherapy then thoracic radiotherapy	2	
Concurrent chemotherapy and thoracic radiotherapy	2	
Prophylactic cranial irradiation	7	
Postoperative Thoracic Radiotherapy Doses		
45 Gy/3 weeks (1.5 Gy BID)	2	
45-54 Gy/5-6 weeks	2	
60-70 Gy/6-7 weeks	2	
Thoracic Radiotherapy Volume		
No thoracic radiotherapy	9	
Selective elective nodal irradiation to high risk nodal regions (first echelon N1 and N2)	1	
Elective nodal irradiation to all N1, N2 and contralateral mediastinum N3	1	
Extensive elective nodal irradiation to all nodal levels with inclusion of contralateral hilar and supraclavicular N3	1	
Prophylactic Cranial Irradiation Doses (if recommended)		
25 Gy/2 weeks	9	
30 Gy/3 weeks	5	
36 Gy/3-4 weeks	3	
Timing of Thoracic Radiotherapy		
Early during chemotherapy (cycle 1 or 2)	1	
Late during chemotherapy (cycle 3 or 4)	1	

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

Clinical Condition: **Radiation Therapy for Small-Cell Lung Cancer**

Variant 2: **74-year-old man with a good performance status presents with a limited-stage cT2pN2M0 small-cell lung cancer of left lower lobe.**

Treatment	Rating	Comments
Treatment Options		
Thoracic radiotherapy alone	1	
Chemotherapy alone	2	
Sequential chemotherapy then thoracic radiotherapy	4	Should only be considered in patients whom the treating radiation oncologist thinks cannot tolerate concurrent treatment.
Concurrent chemotherapy and thoracic radiotherapy	9	
Consideration of surgical resection	1	
Prophylactic cranial irradiation	9	
Thoracic Radiotherapy Doses		
45 Gy/3 weeks (1.5 Gy BID)	9	
50.4-54 Gy/5-6 weeks (1.8 Gy QD)	4	Assuming severe dosimetric limitations.
55.8-61.2 Gy/6-7 weeks (1.8 Gy QD)	7	
60-70 Gy/6-7 weeks (2 Gy QD)	8	
Thoracic Radiotherapy Volume		
Involved sites (primary and nodes)	7	If using biologic imaging. Depends on the treatment plan.
Involved sites + first echelon nodal regions (can be N1, N2, or N3 nodal regions)	8	
Involved sites + elective nodal irradiation to all N1, N2 and mediastinal N3	5	
Involved sites + comprehensive elective nodal irradiation covering all N1, N2, and N3 with inclusion of contralateral hilar and supraclavicular N3 regions	3	
Prophylactic Cranial Irradiation Doses (if recommended)		
25 Gy/2 weeks	9	
30 Gy/3 weeks	5	
36 Gy/3-4 weeks	3	
Timing of Thoracic Radiotherapy		
Cycle #1, day #1	9	
During cycle 1 (ie, after day #1)	8	
Cycle #2, day #1	7	
Early during chemotherapy (cycle 1 or 2)	7	
Late during chemotherapy (cycle 3 or 4)	5	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Radiation Therapy for Small-Cell Lung Cancer**

Variant 3: **58-year-old man with a good performance status presents with extensive-stage small-cell left lower lobe lung cancer with multiple liver and bone metastases.**

Treatment	Rating	Comments
Treatment Options		
Thoracic radiotherapy alone	1	
Chemotherapy alone	9	
Sequential chemotherapy then thoracic radiotherapy	5	
Concurrent chemotherapy and thoracic radiotherapy	2	
Prophylactic cranial irradiation	8	
Thoracic Radiotherapy Doses (if recommended)		
45 Gy/3 weeks (3 Gy QD)	5	
45-54 Gy/5-6 weeks (1.8-2.0 Gy QD)	5	
30-35 Gy /2-3 weeks (2.5-3 Gy QD)	7	
45 Gy/3 weeks (1.5 Gy BID)	3	
60-70 Gy/6-7 weeks	2	
Thoracic Radiotherapy Volume (if recommended)		
Involved sites (primary and nodes)	8	
Involved sites + high risk nodal regions (1st echelon N1 and N2)	5	
Involved sites + elective nodal irradiation to all N1, N2 and contralateral mediastinal N3	3	
Involved sites + comprehensive elective nodal irradiation covering all N1N2 N3 with inclusion of contralateral hilar and supraclavicular N3 regions	1	
Prophylactic Cranial Irradiation Doses (if recommended)		
25 Gy/2 weeks	9	
30 Gy/3 weeks	5	
36 Gy/3-4 weeks	3	
Timing of Thoracic Radiotherapy		
Early during chemotherapy (cycle 1 or 2)	2	
Late during chemotherapy (cycle 3 or 4)	3	
At time of symptoms	8	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**