The Optimal Use of Radiotherapy in Small Cell Lung Cancer

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Abstract
Small cell lung cancer is an aggressive malignancy that is highly responsive to radiation therapy (RT), which has an important role in all stages of disease. For locally advanced, limited-stage disease, the standard of care is chemotherapy with concurrent radiation, which should be started early. The optimal radiation dose and field design remain to be determined. Randomized trials are currently being conducted to determine if dose intensification will improve outcomes, whereas consensus on elective nodal irradiation is evolving. Current studies are evaluating the potential benefit of consolidative thoracic RT in the management of patients with extensive-stage disease that has responded favorably to chemotherapy. Finally, prophylactic cranial irradiation improves survival in both limited- and extensive-stage disease that has responded to initial therapy. (JNCCN 2013;11:107–114)

Small cell lung cancer (SCLC) accounts for approximately 15% of all primary lung cancers and is characterized by an aggressive clinical course. Unfortunately, most patients present with metastatic disease. For patients with locally advanced disease, 5-year overall survival (OS) rates remain around 20% despite substantial improvements in chemotherapy and radiation therapy (RT) techniques over the past 3 decades.

RT has an important role in all stages of SCLC as a component of both definitive and palliative therapy. Therefore, radiation oncology input as part of a multidisciplinary evaluation or discussion should be provided for all patients early in the planning of their treatment strategy. Determination of the appropriateness of RT should be made by board certified radiation oncologists who perform lung cancer RT as a prominent component of their practice, especially given the substantial evolution in RT indications and techniques for lung cancer in recent years.

General Principles
To maximize tumor control and minimize treatment toxicity, critical components of modern definitive RT for SCLC include appropriate simulation, accurate target definition, conformal RT planning, and accurate delivery of the planned treatment. A minimum standard is CT-planned 3D conformal RT. Multiple fields (≥4, and ideally more) should be used, with all fields treated each day. When twice-daily fractionation is used, at least a 6-hour interfraction interval should occur to allow for repair of normal tissues. Use of more advanced technologies is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints. These technologies include (but are not limited to) 4D CT and/or PET/CT simulation, intensity-modulated RT (IMRT)/volumetric...
modulated arc therapy, image-guided RT, and respiratory motion management strategies. The higher complexity of advanced technologies increases the risk of errors, and the relatively higher cost of some raises concerns about their value. Thus, centers using these technologies should implement and document modality-specific quality assurance measures. Useful references include the American College of Radiology (ACR)–American Society of Radiation Oncology (ASTRO) Practice Guidelines for Radiation Oncology. Minimum requirements for IMRT are specified in the NCI Advanced Technology Consortium IMRT guidelines, and safety considerations for contemporary RT are detailed in a series of ASTRO-commissioned white papers. The ideal is external credentialing of both planning and delivery, such as is required for participation in RTOG clinical trials using advanced technologies.

**Staging**

A major branch point in the treatment algorithm for SCLC is based on the stage of disease. Although the International Association for the Study of Lung Cancer (IASLC) has proposed using the AJCC Cancer Staging System (TNM) 7th edition for SCLC, treatment approaches are most commonly stratified according to the functional categorizations of limited-stage versus extensive-stage disease. Limited-stage SCLC was originally described in the 1950s by the Veteran’s Administration Lung Study Group as the nonresectable tumor was limited to one hemithorax but may have included [supraclavicular] nodes... and the apparent tumor mass was totally encompassed in every portal for x-ray therapy.

A contemporary definition of limited-stage SCLC adopted by NCCN is “disease confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation field.” This would correspond to AJCC stage Tany,Nany,M0, except T3–4 because of multiple lung nodules that do not fit in a tolerable radiation field. Conversely, extensive-stage SCLC is disease beyond the ipsilateral hemithorax, which may include malignant pleural or pericardial effusion or hematogenous metastases (Tany,Nany,M1a/b; T3–4 because of multiple lung nodules).

**Limited-Stage SCLC**

Approximately one-third of patients present with limited-stage SCLC. Except for the small minority of patients with true stage I SCLC who may be appropriate candidates for surgical resection, most patients who present with limited-stage SCLC will have locally advanced disease and should receive definitive treatment with chemotherapy and concurrent thoracic RT. Chemotherapy most commonly consists of 4 to 6 cycles of cisplatin and etoposide (EP).

The use of RT for the definitive treatment of limited-stage SCLC is supported by 2 meta-analyses. Both concluded that the addition of RT to chemotherapy improved OS with an absolute benefit of 5.4% at 2 to 3 years. Concurrent chemotherapy and RT is preferred over sequential therapy. A randomized trial by the Japan Clinical Oncology Group using EP and accelerated hyperfractionated RT found a trend of improved OS and progression-free survival with concurrent versus sequential chemotherapy and RT, although the difference was not statistically significant (P=.097). Age alone is not a contraindication to concurrent chemotherapy and RT. However, concurrent administration increases hematologic and nonhematologic toxicity, and therefore sequential chemotherapy and RT may be more appropriate for patients with an ECOG performance status greater than 2, large treatment volumes, or significant comorbidities.

**RT Timing:** Several large randomized trials have investigated whether RT should begin early, starting with cycle 1 or 2 of chemotherapy, or late, variably defined as starting with cycle 3 to 6 (mostly 4–6), and the results of these trials were analyzed in a meta-analysis revealing a small but significant improvement in 2-year OS when RT was started early (hazard ratio [HR], 1.17; 95% CI, 1.02–1.35). Early RT improved survival significantly only when it was hyperfractionated and administered with EP. Shorter time from the start of any therapy to the end of RT (SER) may also improve outcomes in SCLC by overcoming the accelerated repopulation of tumor clonogens during RT and chemotherapy. A meta-analysis found that 5-year OS rates were higher when SER was shorter (relative risk, 0.62; 95% CI, 0.49–0.80; P=.0003), and exceeded 20% when the SER was less than 30 days. Each additional week increase in SER was associated with a 1.8% absolute decrease in 5-year OS. Most recently, preliminary data from a

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randomized trial showed equivalent median survival (24.1 vs. 26.8 months, respectively) when RT was initiated with the first versus the third cycle of EP, albeit with a statistically nonsignificant trend toward inferior local control when starting RT with the third cycle. Together, these data indicate that RT should start as early as possible—by cycle 3 of chemotherapy or preferably earlier—and that all therapy should be completed in as short a time frame as possible.

**RT Target Definition and Dose:** RT target volumes should be defined based on a pretreatment PET scan and the CT scan obtained at the time of RT planning. If RT is administered after chemotherapy, randomized and retrospective evidence supports targeting postchemotherapy tumor volumes, but prechemotherapy extent (ie, all initially involved nodal regions). PET/CT should be obtained preferably within 4 weeks and no more than 8 weeks before treatment. Whenever possible, it is best to obtain PET/CT in the treatment position. Definitions of RT treatment volumes are described in International Commission on Radiation Units and Measurements (ICRU) reports 50 and 62.

Consensus on elective nodal irradiation (ENI) is evolving. Over the past 2 decades, in an effort to reduce toxicity while intensifying dose, most major trials gradually reduced the extent of ENI, and some recent trials have eliminated it entirely. Prospective evidence to support this approach is emerging.

Although an initial small phase II trial omitting ENI in the absence of PET staging reported a somewhat high rate (11%) of isolated elective nodal relapse, the same group later performed a second prospective study omitting ENI in patients with PET staging and reported a 3% rate of isolated elective nodal failures. In addition, 2 prospective trials and 2 larger retrospective studies were recently published showing that omission of ENI does not lead to higher rates of failure. Current prospective clinical trials, including CALGB 30610/RTOG 0538 (ClinicalTrials.gov identifier: NCT00632853) and EORTC 08072 (Concurrent Once-Daily Versus Twice-Daily Radiotherapy [CONVERT]; ClinicalTrials.gov identifier: NCT00433563) trials, omit ENI. In fact, the CALGB study initially mandated mediastinal ENI, and then was revisited in 2009 to omit it. Therefore, omission of ENI, while still unresolved, seems reasonable, particularly when PET is incorporated into staging/target definition.

The optimal dose and fractionation of RT for limited-stage SCLC has not been established (Table 1). Although the Intergroup 0096 trial proved the superiority of accelerated hyperfractionation compared with the same dose given daily, the dose used—45 Gy (twice daily) in 3 weeks, despite being the maximum tolerated dose for this fractionation schedule—was associated with a substantial rate of local failure (36%). This suggests that further dose intensification is required to optimize local control. Furthermore, although hyperfractionation reduces late normal tissue damage and counteracts accelerated repopulation, it does so at the cost of patient inconvenience and increased acute toxicity. If once-daily RT is used instead, higher doses of 60 to 70 Gy have been shown to be safe and effective. A concomitant boost approach of 61.2 Gy in 5 weeks has also shown promising local control and is currently being compared with 70 Gy in 7 weeks and the standard arm of 45 Gy (twice daily) in 3 weeks in CALGB 30610/RTOG 0538 (ClinicalTrials.gov identifier: NCT00632853). Similarly, in Europe, the EORTC 08072/CONVERT trial is randomizing patients to either 66 Gy in 33 once-daily fractions or 45 Gy twice daily (ClinicalTrials.gov identifier: NCT00433563).

**Normal Tissue Dose Constraints:** The organs at risk for radiation toxicity depend on tumor location and extent. For similar RT prescription doses, the normal tissue constraints used for non–small cell lung cancer (NSCLC) are appropriate and are summarized in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC (to view the most recent version of these guidelines, visit NCCN.org). When administering lower total RT doses (eg, 45 Gy), more conservative constraints are achievable using conformal techniques and should be used to reduce toxicity. When using accelerated schedules (eg, 3–5 weeks), the spinal cord constraints from the CALGB 30610/RTOG 0538 protocol should be used as a guide; in other words, the maximum spinal cord dose should be limited to 41 Gy or less (including scatter radiation) for 45 Gy twice daily, and to 50.5 Gy or less for more protracted schedules.

**Extensive-Stage SCLC**

The primary treatment for extensive-stage SCLC is chemotherapy. RT has an important role in palliation of symptomatic metastatic sites. However, in patients who have an initial response to treatment,
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Table 1  Selected Cooperative Group Studies of Dose and Fractionation Schedules for Limited-Stage Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Trial</th>
<th>Dose and Fractions</th>
<th>Chemotherapy</th>
<th>Acute Toxicity</th>
<th>PCI</th>
<th>Survival (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turrisi et al, 1999</td>
<td>Phase III</td>
<td>45 Gy/25 fx QD vs. 45 Gy/30 fx BID</td>
<td>EP, RT started with first cycle</td>
<td>Esophagitis Grade 3: 11% (QD) vs. 27% (BID) Grade 4: 5% both groups</td>
<td>Mandatory MS, 1.6 (QD RT) vs. 1.9 (BID RT) (P=.04)</td>
<td></td>
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<tr>
<td>Bogart et al, 2004</td>
<td>Phase II</td>
<td>70 Gy/35 fx QD</td>
<td>2 cycles induction paclitaxel and topotecan followed by 2 cycles then carboplatin + etoposide with concurrent RT</td>
<td>Dysphagia Grade 3: 16% Grade 4: 5%</td>
<td>Optional MS, 1.9</td>
<td></td>
</tr>
<tr>
<td>Choi et al, 1998</td>
<td>Phase I</td>
<td>Dose escalation trial, MTD found to be ≥70 Gy/35 fx QD and 45 Gy/30 fx BID</td>
<td>3 cycles induction EP + cyclophosphamide followed by EP with concurrent RT</td>
<td>Grade 4 esophagitis at MTD: 33% (QD) and 29% (BID)</td>
<td>Mandatory MS, 2.2 for QD, 1.9 for BID (P=.589)</td>
<td></td>
</tr>
<tr>
<td>Komaki et al, 2012</td>
<td>Phase II</td>
<td>61.2 Gy/34 fx QD→BID using concomitant boost</td>
<td>EP, RT started with first cycle</td>
<td>Esophagitis Grade 3: 16% Grade 4: 1%</td>
<td>Optional MS, 1.6</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice daily; EP, etoposide and cisplatin; fx, fraction; MS, median survival; MTD, maximum tolerated dose; QD, once daily; PCI, prophylactic cranial irradiation; RT, radiotherapy.

aGrade 3 is defined as an inability to swallow solids, requiring narcotic analgesics or the use of a feeding tube; grade 4 is defined as hospitalization of the patient or perforation of the esophagus.

bGrade 3 is defined as dysphagia requiring intravenous hydration; grade 4 is defined as complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support; perforation; or fistula.

cGrade 4 is defined as severe esophagitis that may require intravenous hydration, nasogastric tube feeding, or total parenteral nutrition.

Locoregional and central nervous system (CNS) relapses are the most common types of failure, suggesting a role for RT in prolonging survival given the predictable and morbid nature of these anatomically confined patterns of relapse.

Consolidative thoracic RT was shown in a randomized trial to benefit selected patients with extensive-stage SCLC, excluding CNS metastases, and good performance status. Patients who achieved complete response (CR) at distant sites and intrathoracic (local) CR/partial response (PR) after 3 cycles of EP were randomized to either 4 additional cycles of EP or hyperfractionated thoracic RT (54 Gy in 1.5-Gy fractions twice daily, including elective nodal regions) with concurrent carboplatin/etoposide, followed by 2 additional cycles of EP. Both groups were also treated with prophylactic cranial irradiation (PCI). The 5-year survival rate was significantly improved with thoracic RT compared with chemotherapy alone (9.1% vs 3.7%, respectively). More recently, a small prospective trial and a larger retrospective study have shown similarly promising results with consolidative thoracic RT.

Based on these results, thoracic RT could be considered for selected patients with extensive-stage SCLC with good performance status who have experienced a CR at their sites of distant disease and at least a PR at their locoregional thoracic site in response to chemotherapy. Variations on this approach are being further evaluated in prospective clinical trials (RTOG 0937 [ClinicalTrials.gov identifier: NCT01055197] and Dutch Lung Cancer Study Group Chest Radiotherapy in Extensive-Stage SCLC [CREST] trial).
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PCI

Up to 18% of patients with SCLC have brain metastases at diagnosis, and approximately 50% eventually develop them after experiencing an initial CR to therapy. PCI reduces the incidence of brain metastases and improves OS in patients with both limited- and extensive-stage SCLC.

A meta-analysis by Auperin et al supports the use of PCI in patients who experienced a CR to initial therapy; 85% of patients included in this analysis had limited-stage disease. PCI resulted in significant decreases in both the relative risk of brain metastases and the risk of death (HR, 0.46 and 0.84, respectively). The 3-year OS rate was significantly improved in the PCI arm (20.7% vs. 15.3%).

A randomized trial conducted by the EORTC showed that patients with extensive-stage SCLC who experienced a response to chemotherapy also benefitted significantly from PCI. CT or MRI scan of the brain was not required before randomization, which occurred 5 weeks after 4 to 6 cycles of chemotherapy. Most patients receiving PCI were treated with 20 Gy in 5 fractions. PCI reduced the cumulative incidence at 1 year of brain metastases (14.6% vs. 40.4%) and was associated with a 14% improvement in OS (27.1% vs. 13.3%). Notably, these levels of OS improvement from PCI in both limited- and extensive-stage SCLC are comparable in absolute magnitude to the impact of any other therapeutic intervention, including chemotherapy and thoracic RT, used with definitive intent.

The optimal dose of PCI in limited-stage SCLC was recently addressed by an international Inter-group trial that randomized patients with limited-stage SCLC in CR after initial therapy to 25 Gy in 10 fractions (considered a standard dose), or 36 Gy using either conventional fractionation (2 Gy once daily) or accelerated hyperfractionation (1.5 Gy twice daily). Brain imaging was required before randomization. A nonsignificant trend was seen toward a lower incidence of brain metastases in patients treated with the higher dose, but a significantly worse 2-year survival rate (42% vs. 37%) was associated with a higher rate of chest relapse. Side effects were mild and not significantly different between the groups. Thus, 25 Gy in 10 fractions remains the standard PCI dose for limited-stage SCLC, whereas shorter fractionation schemes, 20 Gy in 5 fractions, are also considered appropriate for extensive-stage SCLC.

With respect to the timing of PCI, the trials described earlier were designed for patients who experienced response to their initial therapy, but none specifically studied the optimal interval before beginning a course of PCI. The meta-analysis by Auperin et al showed a significant (P=.01) decrease in the risk of brain metastasis with earlier administration of PCI after initiation of induction chemotherapy, but no difference in OS.

Because a realistic goal of PCI is to increase survival, chronic neurotoxicity from PCI is an important consideration. Neurotoxicity from PCI for SCLC is potentiated by dose and patient age, and possibly concurrent chemotherapy. Acute effects include nausea, headache, hair loss, and fatigue, but are generally self-limited. Several earlier prospective trials using neurocognitive function (NCF) testing failed to show a significant increase in chronic neurotoxicity as a result of PCI. Interestingly, almost half of the patients in one study had significant cognitive impairment before PCI despite the absence of metastases on brain imaging, and transient further declines in NCF after PCI, some of which were not significant when controlling for non-CNS disease progression, suggesting possible cognitive effects of chemotherapy and paraneoplastic factors. In contrast, a more recent randomized trial of PCI (RTOG 0214), albeit in the setting of NSCLC, found a significant decline in NCF that persisted at least 1 year when using the Hopkins Verbal Learning Test, highlighting the importance of sensitive assessments. Similarly, a dose-response was found in RTOG 0212, in which patients with limited-stage SCLC had a greater incidence of chronic neurotoxicity 1 year after 36 Gy compared with 25 Gy of PCI.

Brain Metastases

Brain metastases in SCLC should be treated with whole-brain RT (WBRT) alone or in combination with surgery or stereotactic radiosurgery (SRS). SRS or surgery alone is not recommended because of the high likelihood of multiple disease foci beyond gross disease. On the other hand, for limited intracranial recurrences, SRS is a reasonable treatment modality, whereas for extensive intracranial failures after PCI or WBRT, repeat WBRT has been reported to be safe in carefully selected patients.
Conclusions

RT plays a prominent role in the care of patients with SCLC at all stages. Current clinical trials are seeking to identify the most effective dose and fractionation schedule for the treatment of limited-stage SCLC and the role of thoracic radiation in treating extensive-stage SCLC (Table 2). Looking forward, the optimal use of radiation in the treatment of SCLC will likely be impacted by improvements in systemic therapy. Better control of micrometastatic disease will increase the need for better long-term local control that can be achieved with RT, and longer survival may highlight the impact of chronic neurotoxicity from PCI and the need for strategies to optimize it.

Table 2 Currently Enrolling Randomized Cooperative Group Trials of RT in SCLC

<table>
<thead>
<tr>
<th>Name</th>
<th>Eligibility</th>
<th>Randomization</th>
<th>Primary Outcome</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 30610/RTOG 0538 (ClinicalTrials.gov identifier: NCT00632853)</td>
<td>Limited-stage SCLC without contralateral hilar or supraclavicular lymph nodes</td>
<td>45 Gy/30 fx BID vs. 70 Gy/35 fx QD vs. 61.2 Gy/34 fx QD→BID using concomitant boost, all 3 arms starting with first or second of 4 cycles EP*</td>
<td>MS and 2-y OS</td>
<td>Toxicity, response rates, FFS, LF, DM, brain metastases, patterns of IMRT use</td>
</tr>
<tr>
<td>EORTC 08072 (CONVERT; ClinicalTrials.gov identifier: NCT00433563)</td>
<td>Limited-stage SCLC defined as disease that can be encompassed within a radical radiation portal</td>
<td>45 Gy/30 fx BID vs. 66 Gy/33 fx QD, both arms starting with second of 4-6 cycles EP</td>
<td>OS</td>
<td>LPFS, MFS, toxicity, RR, cytotoxic dose intensity, RT dose intensity</td>
</tr>
<tr>
<td>RTOG 0937 (ClinicalTrials.gov identifier: NCT01055197)</td>
<td>Extensive-stage SCLC, excluding CNS metastases or &gt;4 extracranial sites of disease; PR or CR to platinum-based chemotherapy in a minimum of one site of disease, no PD any site</td>
<td>PCI (25 Gy/10 fx +/- consolidative RT to locoregional and residual metastatic disease (45 Gy/15 fx or 30–40 Gy/10 fx)</td>
<td>1-y OS</td>
<td>Toxicity, patterns of failure, time to first failure, % of planned RT dose given to each site</td>
</tr>
<tr>
<td>Dutch CREST trial (NTR1527)a</td>
<td>Extensive-stage SCLC, excluding CNS metastases, with PR or CR to chemotherapy</td>
<td>PCI (20 Gy/5 fx or 30 Gy/10 fx) +/- thoracic RT (30 Gy/10 fx)</td>
<td>1-y OS</td>
<td>Toxicity, local control, patterns of failure</td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice daily; CNS, central nervous system; CONVERT, Concurrent Once-Daily Versus Twice-Daily Radiotherapy; CR, complete response; CREST, Chest Radiotherapy in Extensive-Stage SCLC trial; DM, distant metastasis; EP, etoposide and cisplatin; FFS, failure-free survival; fx, fraction; IMRT, intensity-modulated radiation therapy; LF, local failure; LPFS, local progression-free survival; MFS, metastasis-free survival; MS, median survival; OS, overall survival; PCI, prophylactic cranial irradiation; PD, progressive disease; PR, partial response; QD, once daily; RR, response rate; RT, radiotherapy; SCLC, small cell lung cancer.

*Protocol amended to allow radiation to begin during cycle 2 instead of cycle 1 to increase enrollment rate.

References


5. Advanced Technology Consortium. ATC Guidelines for the Use of IMRT. Available at: http://atc.wustl.edu/home/NCI/NCI_IMRT_...
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