

# Management of small-cell lung cancer with radiotherapy—a pan-Canadian survey of radiation oncologists

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## ABSTRACT

**Background** The management of small-cell lung cancer (SCLC) with radiotherapy (RT) varies, with many treatment regimens having been described in the literature. We created a survey to assess patterns of practice and clinical decision-making in the management of SCLC by Canadian radiation oncologists (ROs).

**Methods** A 35-item survey was sent by e-mail to Canadian ROs. The questions investigated the role of RT, the dose and timing of RT, target delineation, and use of prophylactic cranial irradiation (PCI) in limited-stage (LS) and extensive-stage (ES) SCLC.

**Results** Responses were received from 52 eligible ROs. For LS-SCLC, staging (98%) and simulation or dosimetric (96%) computed tomography imaging were key determinants of RT suitability. The most common dose and fractionation schedule was 40–45 Gy in 15 once-daily fractions (40%), with elective nodal irradiation performed by 31% of ROs. Preferred management of clinical T1/2a N0 SCLC favoured primary chemoradiotherapy (64%). For ES-SCLC, consolidative thoracic RT was frequently offered (88%), with a preferred dose and fractionation schedule of 30 Gy in 10 once-daily fractions (70%). Extrathoracic consolidative RT would not be offered by 23 ROs (44%). Prophylactic cranial irradiation was generally offered in LS-SCLC (100%) and ES-SCLC (98%) after response to initial treatment. Performance status, baseline cognition, and pre-PCI brain imaging were important patient factors assessed before an offer of PCI.

**Conclusions** Canadian ROs show practice variation in SCLC management. Future clinical trials and national treatment guidelines might reduce variability in the treatment of early-stage disease, optimization of dose and targeting in LS-SCLC, and definition of suitability for PCI or consolidative RT.

**Key Words** Small-cell lung cancer, radiotherapy, radiation, SCLC

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## INTRODUCTION

Radiotherapy (RT) is an important treatment modality in the management of small-cell lung cancer (SCLC). The use of concurrent chemoradiotherapy (CCRT) in limited-stage SCLC (LS-SCLC) is well established, with strong evidence supporting the use of thoracic radiotherapy (TRT) concurrently with platinum-based chemotherapy to achieve improved overall survival (OS)<sup>1–4</sup>.

Although the role of TRT is established in the management of LS-SCLC, the optimal RT dose and fractionation schedule continues to be investigated, with a range of possibilities having been described in the literature<sup>1,2,5</sup>. Additionally, assessments of the suitability of TRT based on classical definitions in LS-SCLC shows variability<sup>6</sup>.

Optimal target delineation and timing of concurrent TRT with chemotherapy can also vary. For those reasons, the clinical management of LS-SCLC can be highly variable and is likely guided by clinician experience and local patterns of practice.

Such variability can extend to the management of extensive-stage (ES) SCLC, in which palliative platinum-based chemotherapy has classically been regarded as standard treatment<sup>1,2</sup>. Consolidative TRT (CTRT) after chemotherapy has the potential to benefit patients with ES-SCLC, and although emerging evidence in the literature supports its use, whether that evidence has translated into consistent practice among radiation oncologists (ROs) is not clear<sup>7–9</sup>.

In addition to TRT, prophylactic cranial irradiation (PCI) is widely used in the management of SCLC and has been

demonstrated to improve OS in patients with both LS and ES disease<sup>10–12</sup>. Currently, PCI is recommended for patients with either LS- or ES-SCLC who have responded to initial chemotherapy<sup>1,2</sup>. However, selecting suitable patients for PCI poses a challenge, because the risk for late radiation effects on the brain might dissuade clinicians from its routine use<sup>5,13</sup>. Other clinical factors such as performance status and age can also affect whether PCI is offered<sup>14</sup>.

We hypothesized that the management of SCLC with RT shows heterogeneity between ROS. Our goal was to construct a national survey to evaluate patterns of practice among Canadian ROS who treat SCLC. Through the survey, we hoped to better understand patient- and treatment-related factors that might influence clinical decision-making in the management of patients with SCLC.

## METHODS

An e-mail message with a link to a 35-item Web-based questionnaire was sent to the 463 physician members of the Canadian Association of Radiation Oncology. The questionnaire targeted ROS who were currently treating lung cancer. Physicians were first asked details about demographics and clinical experience. Questions pertaining to the clinical management of both LS- and ES-SCLC with RT were then presented.

Physicians were instructed to select answers closest to their own clinical practice. The questions chiefly investigated the use and delivery of TRT and PCI in patients with both LS- and ES-SCLC. Factors influencing the use of PCI, the timing and choice of TRT regimens, the role of multidisciplinary case conferencing, and RT planning techniques and delivery were also evaluated. Table 1 provides a complete list of the survey questions.

Responses were collected from April to June 2015. All responses (including partial responses) were deemed eligible for analysis using descriptive statistics.

## RESULTS

### Demographics

The survey response rate was 13% (61 of 463 ROS). Targeted responses from 52 ROS who actively treat lung cancer patients were further analyzed. The level of experience of the respondents varied, with 14 ROS (27%) having treated lung cancer for fewer than 5 years; 18 (35%), for 5–10 years; 5 (10%), for 10–15 years; 9 (17%) for 15–20 years; and 6 (12%) for more than 20 years. Figure 1 shows respondent ages and provinces of practice. The median number of new lung cancer patients seen annually was 100 (range: 12–250), and three quarters of the ROS estimated their proportion of SCLC consultations to be 11%–20%.

### Clinical Assessment of LS-SCLC

The ROS were asked to select the modalities they most often use in assessing patients for intended delivery of TRT for LS-SCLC (Figure 2). Respondents identified staging computed tomography (CT) for some combination of chest, abdomen, and pelvis (96%) and use of CT simulation and dosimetric constraints [that is, lung  $V_{20}$ , mean lung dose (94%)] as the two most important modalities. The rate of multidisciplinary

case-conferencing of patients with LS-SCLC before initiation of CCRT was more prevalent for the more challenging cases than for all cases (58% and 42% respectively).

### RT Planning and Delivery in LS-SCLC

The RT dose and fractionation schedule most commonly used by the responding Canadian ROS was 40–45 Gy in 15 once-daily fractions (40%). Figure 3 shows the other dose and fractionation schedules.

Most of the ROS indicated that they would offer RT concurrently with platinum-based chemotherapy and etoposide (98%), most often initiating the RT during cycle 1 or 2 of chemotherapy (94%) rather than during cycle 3 or 4 (2%), after chemotherapy (2%), or at any point provided that total treatment time was 30 days or fewer (2%).

We asked the ROS to define their clinical target volume (CTV) for a patient undergoing CCRT with T2N2M0 (station 4R) LS-SCLC. Of the responding ROS, 69% would plan their volume as visualized gross disease with an additional microscopic margin. Other responses included CTV extension to next-echelon nodal stations (14%) or to the ipsilateral mediastinum or hilum (10%, Figure 4).

In terms of quality assurance for the LS-SCLC RT plans, most plans were peer-reviewed (73%). Image guidance strategies were variable and are further described in Table 2.

### PCI in LS-SCLC

More than half the responding ROS (52%) would offer PCI in LS-SCLC if *any* radiographic or symptomatic response to CCRT was observed (Table 3). The PCI dose and fractionation schedule was unanimously 25 Gy in 10 daily fractions. Planning for PCI most often consisted of full CT simulation (assuming whole-brain volume delineation) with a thermoplastic mask (73%). Other planning methods included a CT “virtual simulation” (14%) or clinical mark-up (14%). Hippocampal avoidance was not routinely used by any RO. The PCI cases were peer-reviewed in 33% of instances.

### Special Situations in LS-SCLC

If the disease burden had improved by the time of CT simulation, 23% of ROS indicated that they would include the entire pre-chemotherapy disease extent in their CTV. Another 35% would outline only the current visualized disease, and 42% would define the CTV somewhere “in-between” the pre-chemotherapy and the simulation extent.

Of the responding ROS, 64% indicated that primary management of a patient with clinical T1/2aN0 SCLC (assuming medically fitness) should be CCRT (as opposed to primary surgery). If surgery were to be offered first, 36% of ROS would offer some form of adjuvant RT, especially if pathologic N2 disease were to be found (17%) or if a positive margin had been reported (15%).

Of the responding ROS, 35% would not offer CCRT to patients with contralateral supraclavicular lymph node involvement; 65% of the respondents would do so, provided that RT planning was safely achievable.

### RT Planning and Delivery in ES-SCLC

For patients with symptomatic ES-SCLC, 98% of respondents indicated that they would offer palliative RT. After patients had received palliative chemotherapy for ES-SCLC, 50 of

**TABLE I** Survey questions posed to respondents

1. Do you treat lung cancer with radiotherapy (RT)? If "No" then please exit the survey by submitting it on the next page. Thank you. <input type="checkbox"/> Yes <input type="checkbox"/> No
<b>Demographics</b>
2. Please inform us of your approximate age <input type="checkbox"/> 25–39 <input type="checkbox"/> 40–49 <input type="checkbox"/> 50–59 <input type="checkbox"/> 60 or older
3. In which province are you currently working? <input type="checkbox"/> British Columbia <input type="checkbox"/> Alberta <input type="checkbox"/> Saskatchewan <input type="checkbox"/> Manitoba <input type="checkbox"/> Ontario <input type="checkbox"/> Quebec <input type="checkbox"/> New Brunswick <input type="checkbox"/> Nova Scotia/PEI <input type="checkbox"/> Newfoundland and Labrador
4. For how many years have you been treating lung cancer? <input type="checkbox"/> <5 years <input type="checkbox"/> 5–10 years <input type="checkbox"/> 10–15 years <input type="checkbox"/> 15–20 years <input type="checkbox"/> >20 years
5. Approximately how many new lung cancer patients do you see each year? _____
6. What percentage of the above patients have a diagnosis of small cell lung cancer (SCLC)? <input type="checkbox"/> <10% <input type="checkbox"/> 11%–20% <input type="checkbox"/> 21%–30% <input type="checkbox"/> >30%
<b>Management of limited-stage SCLC</b>
7. Limited-stage SCLC (LS-SCLC) is classically defined as disease confined to the ipsilateral hemithorax or mediastinum or supraclavicular lymph nodes that can be encompassed within a tolerable radiation portal. When assessing a patient for "encompassability" (assuming no brain metastases), which modalities do you use? Please select all that apply. <input type="checkbox"/> CT chest/abdomen/pelvis <input type="checkbox"/> PET-CT <input type="checkbox"/> EBUS/mediastinoscopy <input type="checkbox"/> Pleural cytology (if imaging suggests pleural effusion) <input type="checkbox"/> Fluoroscopy <input type="checkbox"/> CT simulation and dosimetric constraints ( $V_{20}$ , mean lung dose) <input type="checkbox"/> Pulmonary function testing (FEV1, DLCO) <input type="checkbox"/> Other: _____
8. How often do you review cases of LS-SCLC in a multidisciplinary case conference setting? <input type="checkbox"/> All cases are reviewed <input type="checkbox"/> Only select/challenging cases are reviewed <input type="checkbox"/> No cases are reviewed
9. Would you offer RT to a patient with contralateral supraclavicular lymph node involvement? Please select the response closest to your own practice. <input type="checkbox"/> No, this is by definition extensive-stage disease based on some RCTs <input type="checkbox"/> Yes, only if safely achievable dosimetrically <input type="checkbox"/> Yes, routinely
10. What would be your initial radiotherapy management for a clinical T1/2a N0 SCLC (assuming a patient was medically fit)? Please select the response closest to your own practice. <input type="checkbox"/> As the primary modality concurrent with chemotherapy (no surgery) <input type="checkbox"/> As adjuvant treatment following surgery regardless of pathologic stage <input type="checkbox"/> As adjuvant treatment following surgery if pathologic N2 disease is discovered <input type="checkbox"/> Following surgery only if positive margins <input type="checkbox"/> As the sole primary modality (stereotactic or otherwise)
11. For most other cases of LS-SCLC, the current standard of care is to offer concurrent chemoradiotherapy (CRT). What is the preferred dose and fractionation of radiation you currently would offer? Please select the response closest to your own practice. <input type="checkbox"/> 40–45 Gy in 15 fractions (once daily) <input type="checkbox"/> 45 Gy in 25 fractions (once daily) <input type="checkbox"/> 45 Gy in 30 fractions (twice daily) <input type="checkbox"/> 50 Gy in 25 fractions (once daily) <input type="checkbox"/> 60–66 Gy in 30–33 fractions (once daily) <input type="checkbox"/> 70 Gy in 35 fractions (once daily) <input type="checkbox"/> Other: _____

TABLE I Continued

12. Do your patients with LS-SCLC most often receive combination chemotherapy with platinum (cis/carbo) and etoposide (46 cycles) concurrently with RT? If “no”, please select “other” and specify the regimen or regimens that are used.
- ☐ Yes ☐ Other: \_\_\_\_\_
13. During which cycle of chemotherapy would you prefer to begin concurrent CRT in patients with LS-SCLC? Please select the response closest to your own practice.
- ☐ Cycle 1 or 2 ☐ Cycle 3 or 4 ☐ Cycle 5 or 6
- ☐ Radiation is given after chemotherapy (that is, sequentially)
- ☐ It doesn't matter in general
- ☐ It doesn't matter as long as total treatment time is 30 days or less AND chemotherapy is platinum based
14. What is your typical clinical target volume (CTV) when planning a patient for CRT with T2N2M0 (station 4R) LS-SCLC starting cycle 2 of chemotherapy? Please select the response closest to your own practice.
- ☐ Only gross disease as visualized on current CT simulation (no added CTV margin)
- ☐ Gross disease with additional microscopic margin
- ☐ Gross disease plus next echelon lymph node stations (that is, station 2R/7) plus or additional margin
- ☐ Gross disease plus ipsilateral mediastinal plus hilum plus or additional margin
- ☐ Gross disease plus ipsilateral hilum plus entire mediastinum plus or additional margin
- ☐ Other: \_\_\_\_\_
15. If disease burden had improved at time of CT simulation, would you expand your CTV to include the pre-chemotherapy extent of disease? Please select the response closest to your own practice.
- ☐ Yes, I would include the entire pre-chemotherapy volume
- ☐ No, I would only outline my CTV as above
- ☐ I would do something in between
16. Do you perform peer-review on your cases of LS-SCLC treated with thoracic radiotherapy?
- ☐ All cases are peer-reviewed
- ☐ Only select or challenging cases are peer-reviewed
- ☐ No cases are peer-reviewed
17. What image guidance strategy do you use for LS-SCLC thoracic RT?
- ☐ Kilovoltage orthogonal ☐ Megavoltage orthogonal
- ☐ Kilovoltage cone-beam CT ☐ Megavoltage CT/cone-beam CT
- ☐ Other: \_\_\_\_\_
18. What is the frequency of your image guidance?
- ☐ At start of treatment only ☐ Weekly ☐ Daily ☐ Other: \_\_\_\_\_
19. In which scenario would you most commonly offer prophylactic cranial irradiation (PCI) following CRT for LS-SCLC? Please select the response closest to your own practice.
- ☐ I do not offer PCI to any patients
- ☐ Patients with any response (radiographic or symptomatic) to CRT
- ☐ Patients with a partial radiographic response to CRT
- ☐ Patients with a good-complete radiographic response to CRT
20. Are there other factors that would influence your decision to offer PCI in LS-SCLC? Please select all that apply.
- ☐ Not applicable as I do not offer PCI in LS-SCLC
- ☐ No, clinical or radiographic response is what matters most
- ☐ Performance status
- ☐ Bulkiness of intrathoracic disease
- ☐ Significant weight loss (>10%–15%)
- ☐ Toxicity from CRT
- ☐ Baseline cognitive function
- ☐ Repeat brain imaging (CT/MRI) showing no metastases
- ☐ Other: \_\_\_\_\_

**TABLE I** Continued

21. What dose of RT do you offer for PCI in LS-SCLC?

- ☐ 25 Gy in 10 fractions   ☐ 20 Gy in 5 fractions   ☐ 30 Gy in 10 fractions   ☐ 8 Gy in 1 fraction  
☐ Not applicable   ☐ Other: \_\_\_\_\_

22. How do you plan patients for PCI? Please select the response closest to your practice

- ☐ Clinical markup only with or without thermoplastic mask  
☐ Virtual simulation with or without mask  
☐ Full CT simulation with mask  
☐ Full CT simulation with hippocampal avoidance with mask  
☐ Not applicable   ☐ Other: \_\_\_\_\_

23. Do you perform peer-review of your PCI cases?

- ☐ Yes   ☐ No

#### Management of extensive-stage SCLC

24. How often do you review cases of extensive-stage SCLC (ES-SCLC) in a multidisciplinary case conference setting?

- ☐ All cases are reviewed   ☐ Only select/challenging cases are reviewed   ☐ No cases are reviewed

25. Would you offer palliative RT for purposes of alleviating symptoms in patients with symptomatic ES-SCLC?

- ☐ Yes   ☐ No

26. Following palliative chemotherapy for ES-SCLC, do you also believe there is a role for consolidative thoracic RT? Please select the response closest to your own practice.

- ☐ No  
☐ I would only use consolidative thoracic RT in the context of a clinical trial  
☐ Yes, only if there is a complete radiographic response to chemotherapy OUTSIDE the chest and a complete or partial response INSIDE the chest  
☐ Yes, if there is any response to chemotherapy, BUT the chest disease is the largest burden  
☐ Yes, if there is any response to chemotherapy, REGARDLESS of burden of disease  
☐ Other: \_\_\_\_\_

27. If you were to offer consolidative thoracic RT to patients with ES-SCLC, what dose/fractionation would you use? Please select the response closest to your own practice.

- ☐ 20 Gy in 5 fractions (once daily)  
☐ 30 Gy in 10 fractions (once daily)  
☐ 40–45 Gy in 15 fractions (once daily)  
☐ 45–50 Gy in 25 fractions (once daily)  
☐ 45 Gy in 30 fractions (twice daily)  
☐ 54 Gy in 36 fractions (twice daily)  
☐ 60–70 Gy in 30–35 fractions (once daily)  
☐ Not applicable   ☐ Other: \_\_\_\_\_

28. Would you request concurrent chemosensitization with consolidative RT?

- ☐ Yes   ☐ No   ☐ Not applicable

29. What would be your CTV when treating ES-SCLC with consolidative thoracic RT? Please select the response closest to your own practice.

- ☐ Only residual disease visualized on CT simulation  
☐ Residual disease plus pre-chemotherapy involved parenchymal disease and nodal stations  
☐ Residual disease plus entire mediastinum  
☐ Not applicable   ☐ Other: \_\_\_\_\_

30. Do you perform peer review of your cases of ES-SCLC treated with consolidative thoracic RT?

- ☐ All cases are peer-reviewed   ☐ Only select/challenging cases are peer-reviewed  
☐ No cases are peer-reviewed   ☐ Not applicable

**TABLE I** Continued

<p>31. Would you offer consolidative RT outside of the thorax in patients with ES-SCLC? Please select the response closest to your own practice.</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Only in the context of a clinical trial</p> <p><input type="checkbox"/> Only if the disease was encompassable and was limited (oligometastatic) before AND after chemotherapy</p> <p><input type="checkbox"/> Only if the disease was encompassable and was limited (oligometastatic) after chemotherapy, REGARDLESS of burden prior to chemotherapy</p>
<p>32. In which scenario would you most commonly offer prophylactic cranial irradiation (PCI) following palliative chemotherapy for ES-SCLC? Please select the response closest to your own practice.</p> <p><input type="checkbox"/> I do not offer PCI to any patients</p> <p><input type="checkbox"/> Patients with any response (radiographic or symptomatic) to chemotherapy</p> <p><input type="checkbox"/> Patients with a partial radiographic response to chemotherapy</p> <p><input type="checkbox"/> Patients with a good-to-complete radiographic response to chemotherapy</p>
<p>33. Are there other factors that would influence your decision to offer PCI in ES-SCLC? Please select all that apply.</p> <p><input type="checkbox"/> Not applicable as I do not offer PCI in ES-SCLC</p> <p><input type="checkbox"/> No, clinical/radiographic response is what matters most</p> <p><input type="checkbox"/> Performance status</p> <p><input type="checkbox"/> Bulkiness of intrathoracic disease relative to distant disease</p> <p><input type="checkbox"/> Use of consolidative RT for intrathoracic disease</p> <p><input type="checkbox"/> Use of extrathoracic consolidative RT</p> <p><input type="checkbox"/> Significant weight loss (&gt;10%–15%)</p> <p><input type="checkbox"/> Toxicity from chemotherapy</p> <p><input type="checkbox"/> Baseline cognitive function</p> <p><input type="checkbox"/> Repeat brain imaging (CT/MRI) showing no metastases</p> <p><input type="checkbox"/> Other: _____</p>
<p>34. What dose of RT do you offer for PCI in patients with ES-SCLC?</p> <p><input type="checkbox"/> 25 Gy in 10 fractions    <input type="checkbox"/> 20 Gy in 5 fractions    <input type="checkbox"/> 30 Gy in 10 fractions    <input type="checkbox"/> 8 Gy in 1 fraction</p> <p><input type="checkbox"/> Not applicable    <input type="checkbox"/> Other: _____</p>
<p>35. How do you plan patients for PCI in ES-SCLC?</p> <p><input type="checkbox"/> Same as for LS-SCLC</p> <p><input type="checkbox"/> Clinical markup only with or without thermoplastic mask</p> <p><input type="checkbox"/> Virtual simulation with or without mask</p> <p><input type="checkbox"/> Full CT simulation with mask</p> <p><input type="checkbox"/> Full CT simulation with hippocampal avoidance with mask</p> <p><input type="checkbox"/> Not applicable    <input type="checkbox"/> Other: _____</p>

the 52 analyzed ROS would be willing to offer CRT in some capacity, depending on various disease-related factors (Table IV). If CRT were to be offered, most respondents (70%) would use a dose of 30 Gy in 10 once-daily fractions (Table IV). Almost all ROS (98%) would not recommend CCRT. With respect to multidisciplinary case-conferencing, 75% of responding ROS indicated that only select or challenging ES-SCLC cases are reviewed; 17% reviewed all cases, and 8% reviewed no cases.

The CTV for CRT was defined by 48% of ROS as encompassing residual disease after chemotherapy. Other CTVs extended to the pre-chemotherapy involved parenchymal

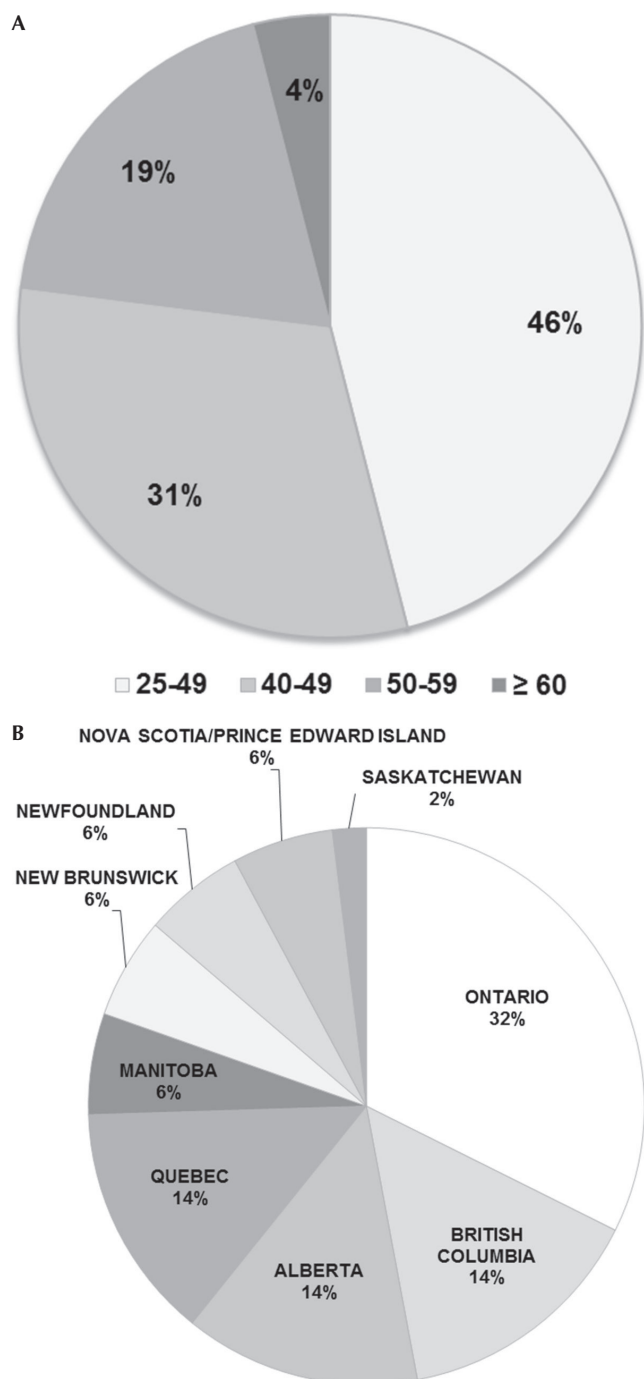
disease and nodal stations (32%) or to the entire mediastinum (4%), or were based on personal preference (6%).

### **PCI in ES-SCLC**

More than half the responding ROS would offer PCI to patients with ES-SCLC if *any* radiographic or symptomatic response to chemotherapy was observed (Table III). The most common dose and fractionation schedule in that scenario was 25 Gy in 10 fractions (71%).

Planning ES-SCLC patients for PCI most often used full CT simulation and mask (67%); virtual simulation or clinical mark-up were less often used (18% and 16% respectively).





**FIGURE 1** Proportions of respondents (A) by age range and (B) by province.

Hippocampal avoidance was not routinely used by any responding ro.

### Special Situations in ES-SCLC

Of the responding ROS, 44% would not offer extrathoracic consolidative RT. However, 33% would offer it in the context of a clinical trial, and 21% would offer it if the disease was oligometastatic before chemotherapy; only 2% would offer

it if the disease was oligometastatic, regardless of burden before chemotherapy.

## DISCUSSION

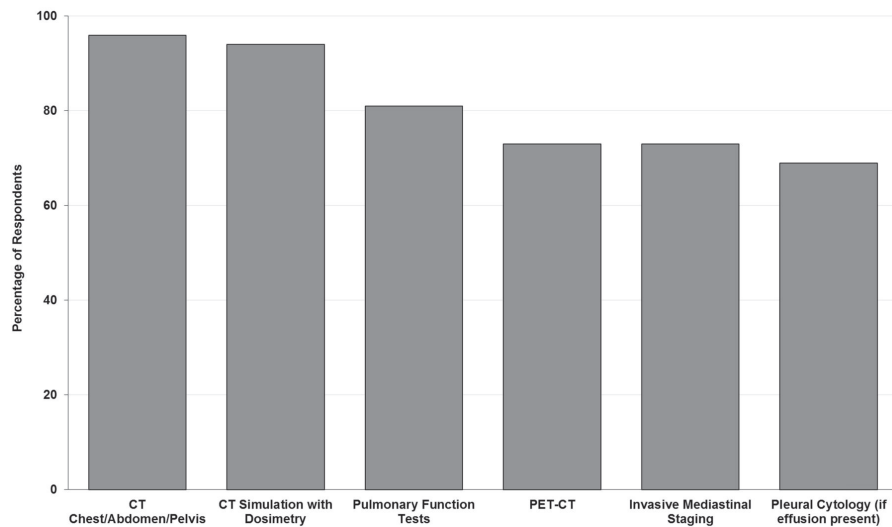
Results of this pan-Canadian survey of ROS indicate that variation and alignment of practice both occur in the treatment of SCLC. With respect to defining LS-SCLC, we observed a general consensus that the original Veterans Administration Lung Study Group definitions are insufficient<sup>15,16</sup>. With advances in the technology of combined positron-emission tomography (PET) and CT staging<sup>1,17</sup>, increased use of invasive mediastinal evaluation, and almost universal implementation of CT-based planning (with adherence to lung constraints such as  $V_{20}$  and mean lung dose), ROS rely on several tools to make an informed decision about TRT suitability. The use of those tools also extends to offering RT for contralateral supraclavicular disease, in which most of our respondents would still offer RT, even though such patients had been excluded from previous randomized controlled trials (RCTs)<sup>18</sup>.

The most commonly used dose and fractionation schedule for LS-SCLC in Canada was 40–45 Gy in 15 daily fractions (more common in Quebec), followed by 45 Gy in 30 twice-daily fractions. The choice of the former schedule might be influenced by a Canadian RCT (Murray *et al.*<sup>19</sup>) of early compared with late TRT using 40 Gy in 15 once-daily fractions in LS-SCLC. Accelerated hyperfractionated RT, as demonstrated in the Intergroup trial by Turrise *et al.*<sup>18</sup> showed an os benefit for 45 Gy in 30 twice-daily fractions compared with 45 Gy in 25 once-daily fractions, but at the expense of increased grade 3 esophagitis (both compared with a potentially less-aggressive standard RT arm).

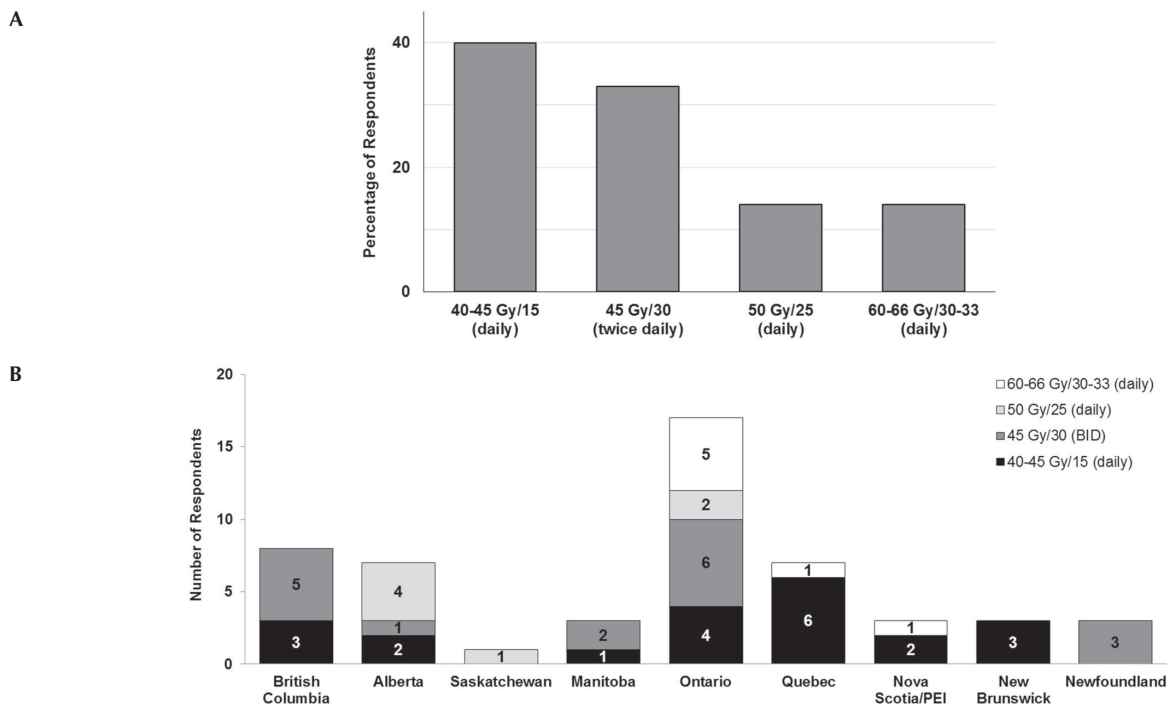
Increasing interest in dose escalation was also demonstrated (14% of respondents would offer 60–66 Gy in 30–33 once-daily fractions), a technique that has been evaluated in prospective trials<sup>20,21</sup>. Fortunately, a large multicentre RCT of CCRT (CONVERT)<sup>22</sup> comparing 45 Gy in 30 twice-daily fractions with 66 Gy in 33 once-daily fractions has been completed; hopefully, the results of that study will better define the optimal RT dose in LS-SCLC. Although our survey did not ask the specific reasons for the choice of dose and fractionation schedule, we recognize that variability can exist for several reasons, and until a specific regimen is clearly shown to be more effective, practice will continue to vary.

Timing of TRT was fairly unanimous across Canada, with CCRT starting early, at cycle 1 or 2, for 98% of respondents. That finding is again supported by the Murray *et al.* trial<sup>19</sup>, despite a similar RCT conducted in the United Kingdom, which suggested no os benefit for early compared with late CCRT<sup>23</sup>. A meta-analysis by De Ruyscher *et al.*<sup>24</sup> of trials evaluating the timing of CCRT showed a trend toward improved os with early CCRT, particularly if the chemotherapy was platinum-based. The CONVERT trial also mandated early CCRT, and because many Canadian centres were involved in that trial, their involvement likely influenced our findings.

Of the responding ROS, 69% would define the ctrv for LS-SCLC by encompassing visualized gross disease only (Figure 4). Respondents were less likely to pursue elective



**FIGURE 2** Clinical modalities most frequently used to define tolerability for thoracic radiotherapy. CT = computed tomography; PET = positron-emission tomography.

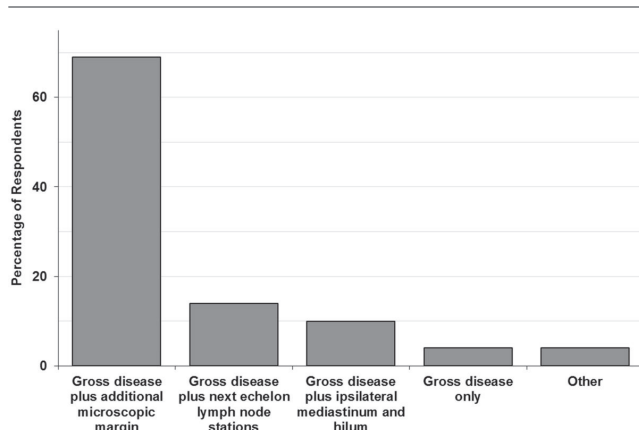


**FIGURE 3** (A) Dose and fractionation schedules commonly used for thoracic radiotherapy in limited-stage small-cell lung cancer. (B) Dose and fractionation used for thoracic radiotherapy in limited-stage small-cell lung cancer by province.

nodal irradiation (ENI). The clinical rationale for ENI is to attempt to lower the rate of isolated nodal failures (INFs) by prophylactically irradiating radiographically uninvolved locoregional micrometastatic disease<sup>18,25–27</sup>. The use of ENI raises a clinical dilemma, however, because larger treatment volumes can result in greater RT-related toxicity, and omission of ENI can potentially increase the risk of INFs outside the treated volume. A trial by De Ruyscher *et al.*<sup>28</sup> omitted ENI in LS-SCLC patients treated with CCRT (45 Gy in 30 fractions). That study demonstrated a higher-than-expected

number of INFs (11%)—all confined to the nonirradiated ipsilateral supraclavicular fossa—without a reduction in RT-related toxicities compared with historical data<sup>28</sup>. However, the fact that pre-treatment CT imaging was used for clinical disease staging could represent a limitation to the study. The use of <sup>18</sup>F-fluorodeoxyglucose PET imaging might improve the accuracy of the initial clinical staging and potentially “upstage” patients by identifying involved nodal areas unidentified on traditional CT-based imaging<sup>1,29</sup>. In fact, in a follow-up study in which pre-treatment





**FIGURE 4** Clinical target volume for patients with T2N2M0 (nodal station 4R) limited-stage small-cell lung cancer undergoing chemoradiotherapy.

**TABLE II** Image guidance strategies in thoracic radiotherapy for limited-stage small-cell lung cancer

Variable	Responses [ <i>n</i> (%)]
<b>Image guidance strategy</b>	
Kilovolt cone-beam CT	56 (29)
Kilovolt orthogonal	23 (12)
Megavolt CT/cone-beam CT	12 (6)
Other	10 (5)
<b>Frequency of image guidance</b>	
Daily	58 (29)
Weekly	27 (14)
Treatment start only	8 (4)
Other	8 (5)

PET-based imaging was used for clinical staging, a low rate of INFS was found (3%), coupled with acceptable toxicity<sup>30</sup>. However, Colaco *et al.*<sup>31</sup> also evaluated the omission of ENI based on CT imaging in a subset of 31 patients enrolled on the CONVERT trial. That report demonstrated no INFS and lower rates of acute grade 3 esophagitis and pneumonitis compared with historical data<sup>25–27</sup>. Given the conflicting findings, further investigation with large prospective RCTs to address the issue of omitting ENI is important.

Nonetheless, our results indicate that Canadian ROS are willing to forego ENI in patients with LS-SCLC treated with CCRT, despite recommendations that such omission occur only in the context of a clinical trial<sup>32</sup>. That observation is probably influenced by a desire to limit RT-related toxicity; by the finding that, when PET-based staging is used, the rate of INFS remains low<sup>30</sup>; and by established practice in the management of non-small-cell lung cancer<sup>33</sup>. The trend toward a smaller treatment volume was also apparent when only 23% of the responding ROS indicated that, if the disease burden had improved at the time of CT simulation, their CTV would include the entire pre-chemotherapy volume.

Historical trials have established CCRT as the mainstay of treatment for LS-SCLC<sup>1–3,34,35</sup>. However, several

**TABLE III** Indications and influencing factors for offering prophylactic cranial irradiation (PCI) in patients with limited- and extensive-stage small-cell lung cancer

Variable	Responses by stage [ <i>n</i> (%)]	
	Limited	Extensive
<b>Clinical indication</b>		
Any radiographic or symptomatic response	52 (27)	54 (28)
Good or complete radiographic response	27 (14)	25 (13)
At least a partial radiographic response	21 (11)	19 (10)
No indication for PCI	0	2 (1)
<b>Influencing factor</b>		
Performance status	83 (43)	88 (45)
Baseline cognition	65 (34)	68 (35)
No metastasis on repeat brain imaging	46 (24)	47 (24)
Toxicity from chemoradiation or chemotherapy	33 (17)	43 (22)
Weight loss exceeding 10%–15% of body weight	17 (9)	25 (13)
Bulkiness of intrathoracic disease	8 (4)	16 (8)
Use of consolidative thoracic radiotherapy	—	16 (8)
Use of extrathoracic consolidative radiotherapy	—	10 (5)
Age	6 (3)	8 (4)
Patient preference	6 (3)	8 (4)
No factor other than clinical or radiographic response	8 (4)	6 (3)

retrospective analyses suggest improved OS with surgery in T1/2aN0 disease<sup>36–38</sup>. Guidelines recommend that surgical resection of clinical stage I SCLC remain reserved for medically fit patients, only after confirmation with invasive mediastinal staging and extrathoracic imaging<sup>1,2,39</sup>. Our survey shows that 64% of responding ROS would instead prefer to manage such patients with primary CCRT. A limitation to that finding is that, if surgical resection were not to be performed before RO assessment, full tumour and lymph node evaluation would not be available to guide RT management. Respondents were most willing to offer post-operative RT if pathologic N2 disease was discovered after surgical resection (17%). That finding is likely influenced by large retrospective cohort studies that have suggested improved OS with postoperative RT for N2 disease in SCLC as well as in non-small-cell lung cancer<sup>36,40</sup>.

With respect to ES-SCLC, nearly all the responding ROS (98%) agreed that RT was suitable for symptom management, and yet a large proportion (88%) would also routinely use CCRT after palliative chemotherapy (with 8% willing to offer it only in the context of a clinical trial). Our survey was conducted shortly after results of the CREST trial were published<sup>9</sup>. Although CREST did not meet its primary endpoint

**TABLE IV** Responses related to consolidative radiotherapy in extensive-stage small-cell lung cancer

Question	Responses [n (%)]
After palliative chemotherapy for patients with extensive-stage small-cell lung cancer, do you believe that there is a role for consolidative thoracic radiotherapy?	
Yes, if there is any response to chemotherapy and if the chest disease is the largest burden	37 (19)
Yes, if there is a complete response to chemotherapy outside the chest and a complete or partial response inside the chest	23 (12)
Yes, if there is any response to chemotherapy, regardless of disease burden	23 (12)
Yes, only if chemoradiotherapy was offered in the context of a clinical trial	8 (4)
Yes, on a case-by-case basis according to personal preference	6 (3)
TOTAL “yes”	96 (50)
TOTAL “no”	4 (2)
If chemoradiotherapy were to be offered, what dose and fractionation would you use? (if responded “yes” to the preceding question)	
30 Gy in 10 fractions (daily)	70 (35)
40–45 Gy in 15 fractions (daily)	14 (7)
20 Gy in 5 fractions (daily)	8 (4)
45–50 Gy in 25 fractions (daily)	2 (1)
45 Gy in 30 fractions (twice daily)	2 (1)
Other	4 (2)

of an improvement in 1-year os, it did show, on secondary analysis, an improvement in 2-year os to 13% from 3% (with CTRT vs. without CTRT respectively). Although CREST might have influenced our survey results (including the choice of 30 Gy in 10 once-daily fractions as the preferred dose and fractionation schedule), the concept of CTRT is not novel. A study conducted by Jeremic *et al.*<sup>41</sup> demonstrated an os benefit with hyperfractionated high-dose CTRT, albeit only if patients demonstrated extrathoracic complete response. In Canada, CTRT (using 40 Gy in 15 once-daily fractions, the second most common CTRT regimen in the survey) was investigated in a phase II trial that showed a median survival duration of 8.3 months—higher than was seen in historical controls<sup>8</sup>.

The issue of CTRT has recently been significantly debated<sup>42,43</sup>, and it is clear that offering it might not be an “all-or-none” phenomenon. Further complicating matters, the Radiation Therapy Oncology Group 0937 trial, which randomized patients to CTRT (including extrathoracic oligometastatic disease) or to no CTRT, was recently closed because it had crossed the futility boundary for survival and had demonstrated excessive grades 4 and 5 toxicity in the CTRT arm. Those findings likely influenced the reluctance of Canadian ros to routinely offer extrathoracic consolidative RT. Factors apart from disease burden and not specifically cited in our survey (including age, weight loss, performance status, intrathoracic residual disease, advanced imaging and RT planning techniques, use of updated staging systems, and increased multidisciplinary input) might therefore be important for pragmatic decision-making for CTRT.

The use of PCI in LS-SCLC, and especially in ES-SCLC, has also been debated. Although the results of a PCI meta-analysis demonstrated an os benefit in LS-SCLC, that benefit came in the context of a complete response to treatment<sup>11</sup>. However, it is clear from the results of our survey that most

ros (73% in LS- and ES-SCLC) would offer PCI with even a partial or minimal response to initial therapy, as an extension of the results from the European Organisation for Research and Treatment of Cancer trial in ES-SCLC<sup>12</sup>. That trial was recently debated because routine pre-PCI brain imaging was not performed, several PCI doses were used, and concerns about long-term neurocognitive dysfunction arose<sup>44</sup>. A recently presented Japanese Clinical Oncology Group trial did not demonstrate an os benefit from PCI compared with no PCI when brain magnetic resonance imaging was performed pre-randomization and in follow-up<sup>45</sup>. Nonetheless, those results have not dissuaded Canadian ros from offering PCI, and only approximately half the ros will routinely offer pre-PCI brain imaging. However, it is clear that the ros regard baseline neurocognition, performance status, and tolerability of prior treatment to be important contributing factors. Understanding the factors that might predict the risk for brain metastases (and hence benefit from PCI) are therefore of utmost importance to Canadian ros.

Although not specifically addressed in our survey, the use of novel neuroprotectants such as the *N*-methyl-D-aspartate receptor antagonist memantine might also have a role in preserving neurocognition in patients undergoing PCI. In a phase III study of adult patients with brain metastases, the addition of memantine to whole-brain RT was associated with a delay in the decline of cognitive function<sup>46</sup>. The use of novel neuroprotectants in conjunction with whole-brain RT remains an active area of investigation, and to our knowledge, no such trials have investigated the use of such agents in SCLC patients undergoing PCI. To summarize, improving Canadian standards with respect to PCI dose and fractionation (as in the case of LS-SCLC) and introducing trials involving hippocampal-sparing PCI<sup>47</sup>—akin to the Dutch HA-PCI trial (<https://clinicaltrials.gov/ct2/show/NCT01780675>)—with or

without the use of neuroprotective agents such as memantine, could further influence the future management of Canadian patients receiving PCI.

A potential limitation of our study is that respondents might have modified their survey responses knowing that their behaviours were being observed and recorded. Additionally, our low overall response rate (13%) is unfavourable; however, given that our survey targeted ros managing lung cancer, it is likely that our eligible cohort of 52 respondents represented a large proportion of ros actively treating lung cancer across Canada.

## CONCLUSIONS

The present survey demonstrates that the management of SCLC by Canadian ros is generally evidence-based and in line with established practice guidelines<sup>1,2</sup>. Although alignment in practice was observed in many domains (such as initiating RT early with platinum-based chemotherapy in the management of LS-SCLC), divergence remains in other areas (such as choosing the optimal dose and fractionation of CCRT and defining optimal target volumes when planning RT). In ES-SCLC, almost all Canadian ros (98%) would offer RT for palliation or consolidation (88%) after palliative chemotherapy. The selection of suitable patients for CCRT varied depending on response to palliative chemotherapy. Most respondents (70%) believed that 30 Gy in 10 once-daily fractions was an appropriate regimen for CCRT. The use of PCI was favoured in both LS- and ES-SCLC; however, suitability for PCI varied according to treatment response and clinical factors (such as baseline cognition and performance status). We suspect that discrepancies in the management of SCLC by Canadian ros could be explained by local patterns of practice, physician preference and experience, logistics and resource constraints, the influence of Canadian RCTs, and an emerging and evolving evidence base. We hope that the results of ongoing and future clinical trials will allow ros to better standardize patterns of care for future patients diagnosed with SCLC—particularly in areas such as managing early-stage disease, optimizing radiation dose and targeting in LS-SCLC, and defining patient suitability for PCI and CCRT.

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## CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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