SMALL CELL LUNG CANCER: LIMITED STAGE

Effective Date: July, 2012

The recommendations contained in this guideline are a consensus of the Alberta Provincial Thoracic Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Lung cancer is the overall leading cause of cancer mortality in Canadian men and women. By the end of 2012, an estimated 25,600 new cases of lung cancer will be diagnosed in Canada.[1] In addition, an estimated 20,100 Canadian men and women will die from their disease; a total higher than the estimated deaths from prostate, breast, and colorectal cancers combined.[1] The economic impact of lung cancer care is equally as staggering: the mean cost associated with the care of each patient diagnosed with lung cancer in Alberta is reported to be $15,350 for non-small cell lung cancer and $18,243 for small cell lung cancer, not including end-of-life care.[2] Smoking remains the largest single risk factor for lung cancer, responsible for 90 percent of lung cancers in men and 80 percent of lung cancers in women in Canada. Exposure to specific industrial and atmospheric pollutants, including second-hand tobacco smoke, also increases an individual's risk of lung cancer.

Lung cancer can be classified into non-small cell lung cancer (NSCLC) or small-cell lung cancer (SCLC). SCLC accounts for 13 to 20 percent of all lung cancers, with incidence rates reportedly declining for men but continuing to increase for women in most countries. [3,4] SCLC is distinguished from NSCLC by its rapid growth rate, early metastasis to regional lymph nodes and/or distant sites, and its initial sensitivity to chemotherapy and radiotherapy. [3-5] SCLC is most commonly staged using a two-tiered system developed by the Veteran's Administration Lung Cancer Study Group. In this system, patients with limited-stage disease have involvement limited to one hemithorax, regional mediastinal lymph nodes, and ipsilateral supraclavicular lymph nodes. Limited disease can be encompassed within a safe radiation treatment plan, and patients with limited disease therefore are treated with curative intent. [3,6] Patients with extensive-stage disease have overt metastatic disease that is identified through imaging or physical examination. [3] The tumour-node-metastasis (TNM) staging system is less frequently used in SCLC because this system relies on surgical confirmation for accuracy and, apart from a very select group of patients with very early limited disease, patients with SCLC seldom present at a stage for which surgery is appropriate. [4] Nevertheless, the Seventh Edition of the Cancer Staging Manual [7] is now applicable to SCLC as well as NSCLC.

GUIDELINE QUESTIONS

- What are the recommended treatment options for patients with limited stage small cell lung cancer?

DEVELOPMENT

This guideline was reviewed and endorsed by the Alberta Provincial Thoracic Tumour Team. Members of the Alberta Provincial Thoracic Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Thoracic Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

This guideline was originally developed in July, 2008.

SEARCH STRATEGY

For this guideline update, a search for new or updated practice guidelines published since September 2009 was conducted by accessing the website of the following organizations: Cancer Care Ontario (CCO), British Columbia Cancer Agency (BCCA), Cancer Care Nova Scotia (CCNS), the National Comprehensive Care Network (NCCN), the Scottish Intercollegiate Guidelines Network (SIGN), the National Institute for Health and Clinical Excellence (NICE), the American College of Chest Physicians (ACCP), Cancer Council Australia, Irish Medical Journal and the European Society of Medical Oncology (ESMO).

Medical journal articles were searched using Medline Ovid, Cochrane Database of Systematic Reviews, and PubMed electronic databases. On PubMed, the search term “limited stage small cell lung cancer” was used and related terms were included in the search. On Medline and Cochrane, “small cell lung cancer” [MeSH term] with subheadings “drug therapy”, “radiotherapy”, “therapy” and “surgery” was used. Limits selected in both searches included: publication in the last five years, “meta-analysis”, “clinical trial”, “randomized controlled trial”(Medline)/”controlled clinical trial”(PubMed), “clinical trial, phase III”, “clinical trial, phase IV” and “comparative study” (PubMed). Results were further excluded if they were not related to treatment, did not report survival outcomes, or were not phase III or phase IV clinical trials. Another search of Medline was done using the term “small cell lung carcinoma” [MeSH term] with “drug therapy” (subheading) combined with “topotecan” to identify literature related to second-line therapy.

TARGET POPULATION

The recommendations in this guideline apply to adult patients over the age of 18 years.

RECOMMENDATIONS

1. Whenever possible, patients should be considered for eligibility in ongoing clinical trials.
2. Patients with limited stage SCLC should receive treatment with curative intent, combining thoracic irradiation with chemotherapy.
    - Four cycles of etoposide/cisplatin is recommended for good performance status patients with good renal function with limited-stage SCLC.
    - Patients undergoing consolidation thoracic irradiation should receive a dose in the range of 40 Gy in 15 fractions over 3 weeks to 50 Gy in 25 fractions over 5 weeks.
3. Patients with limited stage SCLC who have achieved at least stable disease after primary treatment should be offered prophylactic cranial irradiation.
    - A dose of 25 Gy in 10 fractions over two weeks is recommended.
4. If progressive disease occurs after more than three months of response to first line chemotherapy, second line chemotherapy is recommended. Cisplatin-etoposide is the preferred option, followed by topotecan or cyclophosphamide, doxorubicin and vincristine (CAV). For those patients with progressive disease less than 3 months from the completion of first line chemotherapy, the cancer should be considered chemo-resistant. Second-line therapy is ineffective. Clinical trials, if available, should be considered.
5. In general, routine surgery for limited-stage SCLC is not recommended.

DISCUSSION

Chemoradiotherapy

Etoposide combined with cisplatin has been demonstrated in clinical trials as being effective and superior to other chemotherapy regimens in treating limited stage SCLC. [8-11] A recent meta-analysis by Rossi et al. (2012) compared the outcomes of patients who received carboplatin-based versus cisplatin-based chemotherapy. Median overall survival and progression free survival was comparable between groups (Carboplatin OS= 9.4 months, PFS=5.3 months versus Cisplatin OS=9.6 months, PFS=5.5 months).[12] However, the toxicity profiles were significantly different in each arm, with hematologic toxicity higher with carboplatin and nonhematologic toxicity higher with cisplatin.[12]

There is evidence that the addition of thoracic radiotherapy to this combination improves both local control and overall survival when compared with chemotherapy alone.[13-15] For this reason, patients with limited stage SCLC should receive treatment with curative intent, combining thoracic irradiation and with chemotherapy (recommendation #2). This recommendation is consistent with ACCP, BCCA and CCO guidelines on the treatment of limited-stage SCLC.[3,16,17]

At present, it is unclear whether the timing of thoracic RT is important for survival. In a meta-analysis of seven randomized controlled trials, the authors reported that there was no statistically significant difference in overall survival whether chest radiotherapy was delivered within 30 days after the start of chemotherapy or later.[18] However, a subgroup analysis involving only the trials that used platinum chemotherapy concurrent with thoracic RT showed that five-year survival was significantly better for patients who received thoracic RT delivered in an overall treatment time of less than 30 days compared with a longer treatment time (RR 0.90, p= .006). [18] A study by Spiro et al. (2006) also showed no evidence of a difference in survival between patients who received early or late RT.[19] Park et al. reported in abstract form during the American Society of Clinical Oncology Meeting 2012 a phase III trial comparing concurrent chemoradiotherapy starting cycle 1 versus cycle 3 of cisplatin and etoposide. After a median follow-up of 4.9 years, the median survival (24.1 months versus 26.8 months, p=0.6) and median progression-free survival (12.2 months versus 12.1 months, p=0.94) were similar between the 2 arms. A similar proportion of patients underwent PCI in both arms (49.5% versus 55.6%, p=0.37). However, there was a significantly higher risk for febrile neutropenia in the early arm (21.6% versus 10.2%, p=0.02).[20]

To date, no published trial has established an optimal dose for thoracic RT in any schedule. Data from several randomized trials suggest that higher doses of thoracic RT may produce better local control and progression-free survival.[21,22] In a retrospective review of 54 patients, Roof et al. (2003) reported that overall survival, local control and disease-free survival rates were thoracic RT doses of 50 Gy or more.[21] In a phase III trial of 471 patients, Turrisi et al. randomized participants to either 45 Gy in 5 weeks (1.8 Gy daily, 25 fractions) or 45 Gy in 3 weeks (1.5 Gy twice daily, 30 fractions).[22] The authors reported a statistically significant five-year overall survival benefit with twice daily therapy (26% versus 16%, p=0.04). However, there was a significant increase in toxicity in the twice-daily treatment arm, specifically grade 3 esophagitis. [22] Similar findings resulted from the phase III trial conducted by Bonner et al. (1999). All patients in this trial initially received three cycles of etoposide (130mg/m^2 x 3) and cisplatin (30mg/m^2 x 3), and then were randomized to twice-daily thoracic irradiation versus once-daily, given concomitantly with two additional cycles of cisplatin and etoposide. No difference was found between the two treatments with respect to local-only progression rates, overall progression rates, or overall survival. [23]

Regarding the effects of radiotherapy treatment interruptions, the secondary data analysis of the CALGB trial 9235[24] undertaken by Bogart et al.(2008) found there was no association between the presence of RT interruptions and overall survival. Also, the duration of RT interruptions (e.g. 0-3 days vs. 4-10 days vs. >10 days) was not found to predict for survival or local relapse free survival.[25] An exploratory analysis further indicated that when patients were stratified based on their response to induction chemotherapy, a significant impact of RT interruptions on local relapse free survival and overall survival was not observed.[25]

Prophylactic Cranial Irradiation

Metastasis to the brain is a frequent problem in patients with SCLC. There is increasing evidence that prophylactic cranial irradiation (PCI) substantially reduces the risk of brain metastases from SCLC and prolongs disease-free and overall survival.[26,27]

Patients with limited stage SCLC who have achieved at least stable disease after primary treatment should be offered prophylactic cranial irradiation (recommendation #3). In a recently completed trial of 720 patients with limited stage SCLC, participants were randomized to either a standard PCI dose (25 Gy/10 fractions) or to a higher PCI dose (36 Gy/18 fractions or 36 Gy/24 twice-daily fractions).[28] The investigators reported no significant difference in the two-year incidence of brain metastases among the two comparison groups. However, they did report a statistically significant difference in the two-year overall survival rates: patients in the standard dose group had a 42% two-year survival rate compared to 37% in the higher dose group (HR=0.80; 95% CI 1.00-1.44, p=0.05). The meta-analysis conducted by the Prophylactic Cranial Irradiation Overview Collaborative Group found that increasing doses of irradiation decreased the risk of brain metastases when the four dosing groups included (8 Gy, 24-25 Gy, 30 Gy, 36-40 Gy) were analyzed (trend test, p=0.02), but the effect on survival did not differ significantly according to dose. However, when the delivery of PCI was initiated over 60 days after induction treatment began, higher doses were necessary to achieve the same effects and there was a trend towards decreased brain metastases among those who received the treatment earlier. The authors conclude that further clinical trials are needed to confirm the noted greater benefit on brain metastases rate suggested when cranial irradiation is given earlier or at higher doses.[26]

Second Line Therapy

If progressive disease occurs after more than three months of response to first line chemotherapy, second line chemotherapy is recommended. Cisplatin-etoposide is the preferred option, followed by topotecan or cyclophosphamide, doxorubicin and vincristine (CAV) (recommendation #4). Although small cell lung cancer is initially chemosensitive, relapse is common.[29] Despite high initial response, the majority of SCLC patients require salvage therapy for disease progression within several months after front line therapy.[30] Median survival is 2-3 months for patients who do not received second-line therapy.[31] Owonikoko et al. (2012) and Cheng et al. (2007) both recommend that patients with sensitive disease and relapse should be re-treated with a platinum/etoposide regimen.[30,31] However, for those patients with progressive disease less than 3 months from the completion of first line chemotherapy, the cancer should be considered chemo-resistant. Second-line therapy is ineffective. Clinical trials, if available, should be considered.

The meta-analysis by Owonikoko et al. (2012) of second-line chemotherapy in sensitive and resistant/refractory SCLC demonstrated an overall response rate of 17.9%; 27% in patients with sensitive disease (progression after > 90 days) and 14.8% for resistant/refractory patients (progression after > 90 days). Furthermore, overall median survival following second-line treatment was 6.7 months; 7.73 months weighted average for sensitive SCLC and 5.45 months for resistant/refractory disease.[30] In the systematic

review by Cheng et al. (2007), none of the trials examining different second-line chemotherapy regimens detected a statistically significant difference in tumour response or survival between treatment arms.[31]

Topotecan and best supportive care has been demonstrated as superior to best supportive care alone in a phase III trial.[32] Patients in this study had relapsed SCLC and were randomized to either best supportive care (n=70) or oral topotecan and best supportive care (n=71). The intent-to-treat analysis found that median overall survival was significantly longer in the topotecan group (25.9 weeks versus 13.9 weeks).[32] Patients within this study were considered unsuitable for IV-delivered topotecan. However, another phase III study suggests that oral topotecan demonstrates activity and tolerability similar to IV topotecan.[33] The response rate for those who received oral topotecan was 18.3% (95% CI 12.2%-24.4%) and 21.9% (95% CI 15.3%-28.5%) for those who received IV topotecan. Median survival was 33 weeks in the oral group and 35 weeks among patients who received IV.[33] A phase II trial also found similar efficacy between IV and oral topotecan.[34]

Von Pawel et al. (1999) conducted a phase III trial comparing CAV with IV topotecan in SCLC patients with progression after 60 or more days.[35] Response rates were 18.3% in the CAV arm versus 24.3% in the topotecan group (p=0.285). Median overall survival was 24.7 months in the CAV arm and 25.0 months with topotecan, and was also not statistically significant (p=0.795).[35] Nevertheless, patients in the CAV arm had lower rates of grade 3-4 thrombocytopenia (15% versus 58%) and anemia (20 % versus 42%).[35]

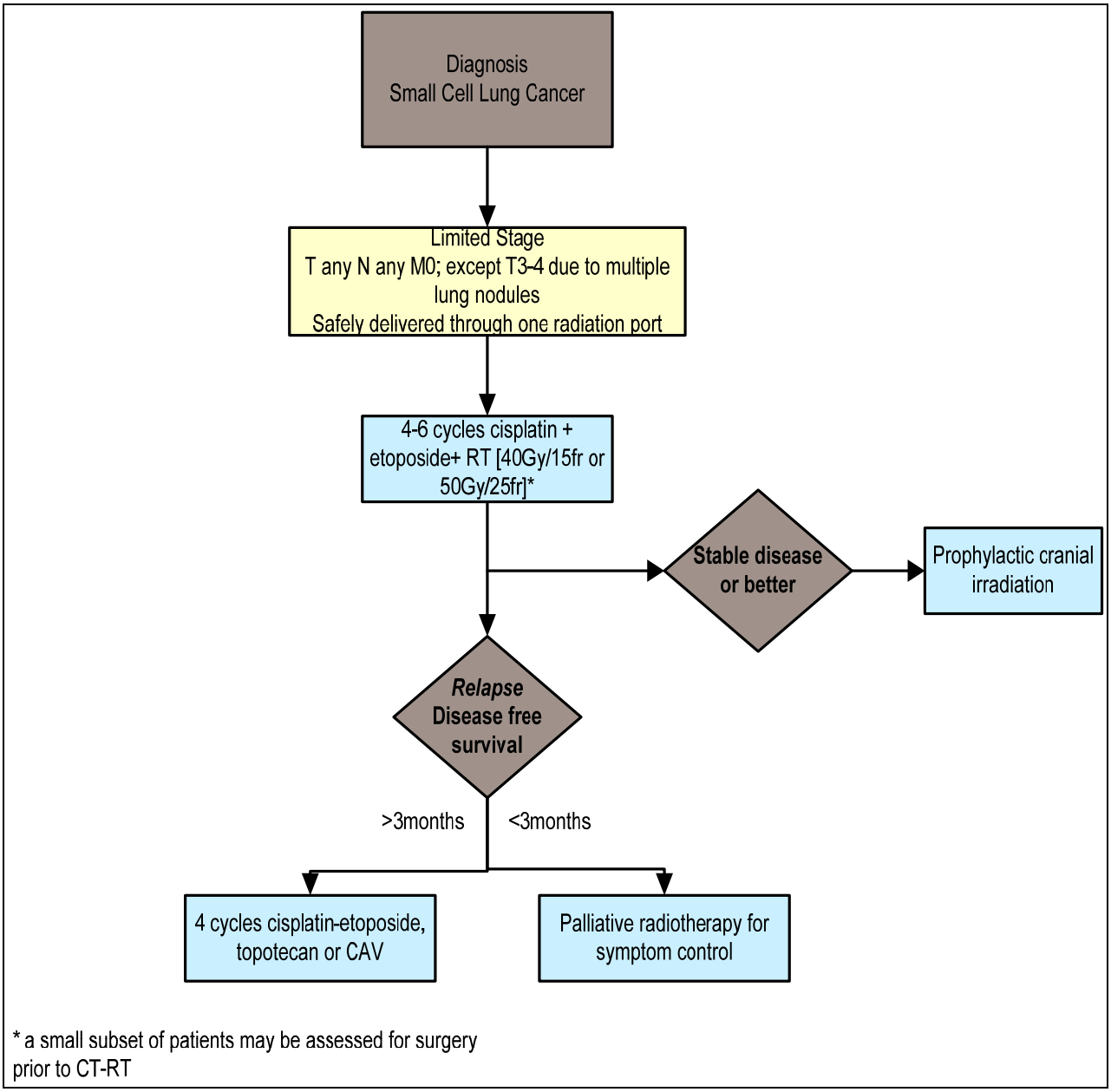
Surgery

Surgery may be an option for select patients with early stage disease.[36,37] However, there is a lack of published data from randomized trials and its value remains uncertain.[27,36] Nevertheless, in the past two years, there has been increased interest in the potential of surgery for reducing local recurrence in limited-stage SCLC.

Varlotto et al.(2011) retrospectively analyzed the incidence, treatment patterns and outcomes of 2214 patients with limited-stage small cell lung cancer identified from the SEER database from 1988-2005. The authors discovered that those patients treated with lobectomy or greater resections without RT had longer median survival (50 months) than those treated with sublobar resections without RT (30 months, p=.006) or those treated with RT alone (20 months, p<.0001).[38] Another study by Yu et al. (2010) analyzed the SEER database from 1988-2004 and achieved similar results. [39] However, since the SEER database does not contain chemotherapy details, it cannot be determined if patients were given CT in addition to resection or RT. It also contains no information about surgical margins.[38]

Regardless, both of these retrospective analyses suggest there may be a role for surgery in the management of limited stage SCLC. Since the population of patients for whom surgery is appropriate is small, it is unlikely that clinical trials on this question will be done.[39]

Figure 1. Algorithm for the management of limited-stage small cell lung cancer



GLOSSARY OF ABBREVIATIONS

Acronym	Description
ACCP	American College of Chest Physicians
BCCA	British Columbia Cancer Agency
CCO	Cancer Care Ontario
CI	Confidence interval
HR	Hazard ration
NSCLC	Non-small cell lung cancer
PCI	Prophylactic cranial irradiation
RR	Risk ratio
RT	Radiotherapy
SCLC	Small-cell lung cancer

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of Alberta Health Services, Cancer Care.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Thoracic Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. Alberta Health Services – Cancer Care recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Thoracic Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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