London Health Sciences Centre
London Regional Cancer Program

Small Cell Lung Cancer

Lung Practice Guideline

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Background

Small Cell Lung Cancer (SCLC) represents approximately 16% of all lung cancers, has been declining in incidence over the last two decades. It has been proposed that the general decline of incidence of SCLC and Squamous Cell Lung Cancer, along with the increase in Adenocarcinoma, may be related to changes in the constituents and filtering of cigarettes, resulting in greater carcinogenic effects in the periphery of the lung, leading to this change in histology. SCLC occurs almost exclusively in smokers.

Diagnostic Investigations

- Chest X-ray
- Bronchoscopy with biopsy
- CT Thorax and upper abdomen
- CT Guided needle biopsy
- MRI/CT Brain
- Bone scan
- ± pulmonary function tests for limited stage disease

Bone marrow aspiration is rarely done now, although involvement may be seen in up to 30%, but is an isolated site of metastatic disease in only 2-6%.

Routine biochemical testing to establish safety of chemotherapy (serum creatinine, GFR, renal function), and rule out paraneoplastic syndromes should include electrolytes and calcium/magnesium (SIADH, hypercalcemia, ectopic ACTH). LDH is often helpful in assessing extent and risk.

Extent of Disease and Staging

Staging of SCLC generally follows a determination of the extent of disease. Intrathoracic disease is felt to be limited stage (SCLC-LS) when the disease is confined to a single hemi-thorax and can be treated with a tolerable radiation plan. Beyond this definition is accepted as extensive disease (SCLC-ES). Thus, disease, which cannot safely be confined to a radiation treatment plan, even if unilateral within the chest, is considered extensive.

The median survival of these two stages from time of diagnosis is:

SCLC-LS	14 to 20 months
SCLC-ES	8 to 13 months

Less than 5% of SCLC-ES survive two years, compared to 20 to 40% for limited stage.

60-70% of SCLC is SCLC-ES at presentation.

Pathology

Three categories of SCLC are as follows:

- Classical SCLC
- Large Cell Neuroendocrine cancer
- Mixed

Typically, poorly differentiated Large Cell Carcinoma with neuroendocrine features and large Neuroendocrine Carcinoma are treated like SCLC.

Almost all SCLCs are immunreactive for keratin and epithelial membrane antigen. Neuroendocrine differentiation manifested by markers can be seen in 75% of SCLC: chromogranin, non-specific enolase and others, but this is not a prerequisite of diagnosis as it is for Large Neuroendocrine Carcinoma.

Genetic markers are not yet widely used.

Treatment Recommendations by Presentation Groups

With the majority of SCLC having extensive disease at presentation, initial treatment is generally with chemotherapy alone, even when anatomical structures are compromised (such as acute cord compression, bronchial obstruction, bleeding).

Patients who progress after initial treatment, with a stable interval of three months or more, are considered to have **relapsed disease**, while patients who relapse within three months have **resistant** disease and those who progress on treatment are considered to have **refractory disease**.

Small Cell Lung Cancer – Limited Stage

LRCP Practice Guideline

Surgery:

The role of surgery is controversial, but survival data for patients presenting with a solitary pulmonary nodule (SPN) following surgery are impressive, some suggesting that five year survival is between 40-50%. Most such patients receive chemotherapy. Surgery following induction therapy, however, has not been found to be beneficial. Given the excellent results in case studies concerning SPN, it is reasonable to consider surgery for T1,T2/N0 (Stage I) and for highly selected stage II disease.

Treatment

Role of combination chemotherapy in the initial management of LS-SCLC:

- An etoposide - cisplatin (EP) combination is the preferred regimen for patients receiving combined - modality therapy for curative intent[1].
- The dose regimen is etoposide 100 mg/m2/cisplatin 25mg/m2 day(s) 1-3 (q21days) x 6 cycles.

Role of thoracic radiotherapy (TR) in limited stage small cell lung cancer:

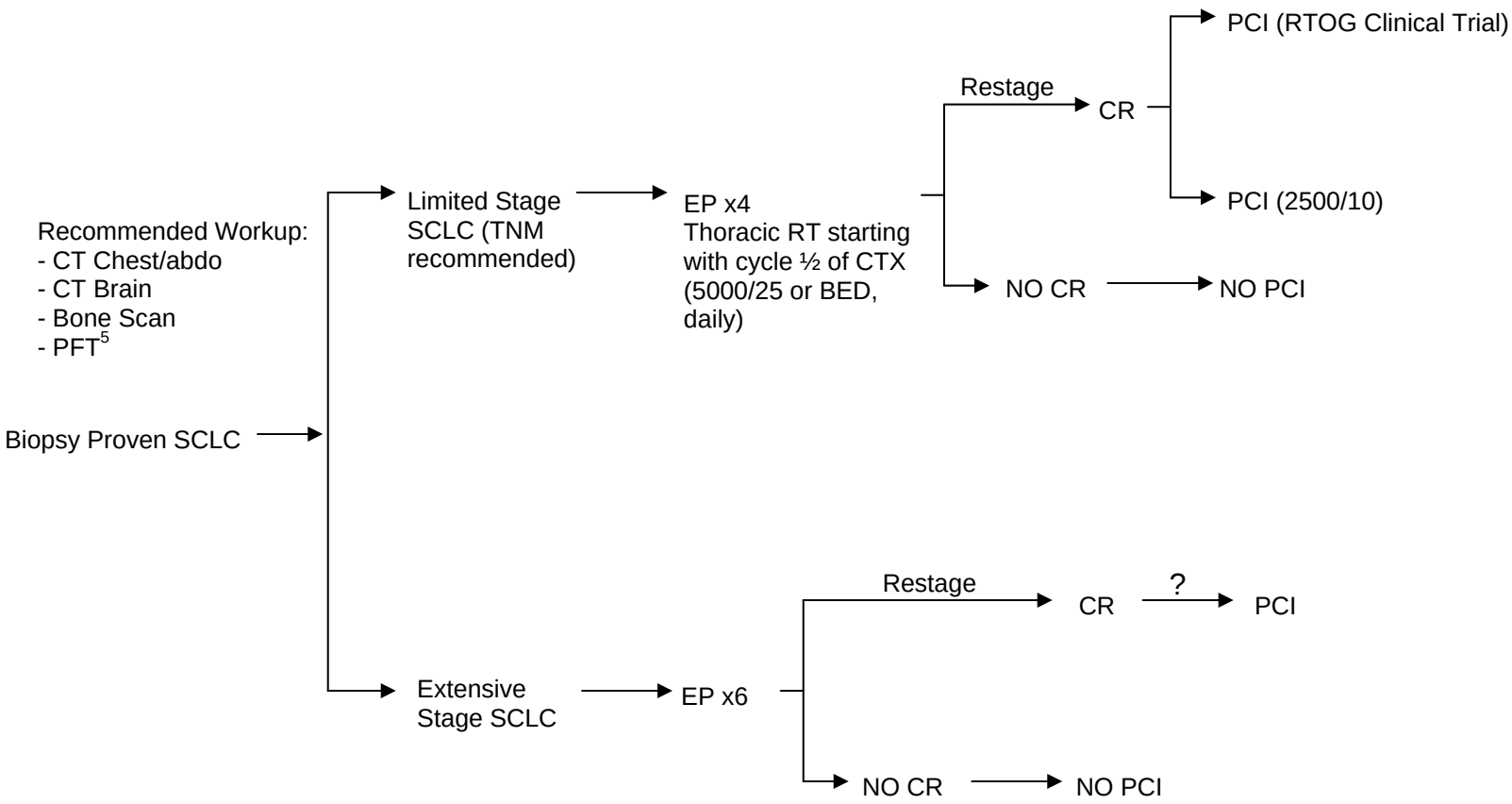
- TR should be offered to patients with LS-SCLC in combination with standard EP chemotherapy is possible. The addition of TR improves local control and overall survival[2].
- Radiotherapy should be offered concurrently with chemotherapy. However, the timing (early vs. late) of TR is not well established. At LRCP, attempt is made to start TR with cycle 2 EP[3].
- Total dose recommendations of TR is a minimum of 5000 cGy in 25 daily fractions. Biologic equivalent once-daily dosing may also be considered (4500 cGy in 15 fractions; 4000 cGy in 15 fractions). Patients may also be considered for twice-daily (BID) fractionation (4500 cGy in 30 fractions, twice daily). [4]

Role of prophylactic cranial irradiation in SCLC:

- Adult patients with either limited or extensive stage SCLC who achieve a good response (*) after induction therapy with chemotherapy +/- thoracic radiation should be offered PCI. (*No measurable disease on restaging with CT chest/upper abdomen/brain, bone scan) [5].

- PCI should not be offered concurrently with systemic therapy but as soon as possible after completion of chemotherapy.
- Although a definitive PCI dose recommendation is difficult to make, the current LRCP (and Canadian) standard is 2500 cgy in 10 fractions over 2 weeks to whole brain[6].

SCLC Treatment Guidelines (January 2007)



Small Cell Lung Cancer – Extensive Stage

LRCP Practice Guideline

Chemotherapy Naïve

Multiple chemotherapy regimes have activity in small cell, with agents including platinum, podophyllotoxins, camptothecins, alkylating agents, anthracyclines, taxanes and vincristine, but platinum based regimes provide the best results[7-9], of which cisplatinum plus etoposide is commonly used, and requires no alterations during radiotherapy. Carboplatin is often substituted for Cisplatinum because of renal toxicity or neurotoxicity.

1. Cisplatinum 25 mg/M^2 IV daily x 3 + Etoposide 100 mg/M^2 IV daily x 3 q 3 weeks [OPIS: EP]
2. Carboplatin AUC 5 IV daily x 1 + Etoposide 100 mg/M^2 IV d1, then etoposide 200 mg/M^2 po d2, 3 q 3 weeks [OPIS: ECARBAUC5-CARB-FIRST]
3. Carboplatin AUC 2 IV dailyx3 + Etoposide 100 mg/M^2 IV daily x 3 q 3 weeks [OPIS: EC-AUC-CARB-FIRST]
4. Cyclophosphamide 1000 mg/M^2 IV, Adriamicin 50 mg/M^2 IV and Vincristine 2 mg/M^2 IV day 1, every 3 weeks for patients who cannot tolerate cisplatinum or Carboplatin. [OPIS: CAV]

Complete Remissions

Patients entering complete remissions could be considered for Prophylactic Cranial Radiation, in order to reduce CNS relapse.

Relapsed Disease

For relapsed disease, even if the remission is as short as two to three months, it is reasonable to try Platinum based chemotherapy again. Often, a change to Carboplatin will be required to avoid further neurotoxicity, especially when total cumulative doses of Cisplatinum reach 400 mg/M^2 IV. Drugs such as Topotecan (oral or IV) may be preferable, but are not available/funded for this indication in Ontario.

Resistant or Refractory Disease

At present, there is no indication for active treatment in patients with resistant or refractory disease, outside of best supportive care, palliative radiation.

Duration of Treatment

Most oncologists give four to six cycles of chemotherapy, as maintenance therapy has not been associated with statistically significant improvement in overall survival.

Benefit of Treatment

Analyses of 21 trials suggest a 2 month statistically significant improvement in survival[10]. Clinical experience strongly suggests an improved quality of life for many of these patients.

Follow-up Recommendations

Because on the speed with which this disease recurs, such patients when off treatment, should be followed closely, perhaps every three months at a minimum, unless their disease appears to be stable over a longer period of time.

Genetic Counselling

No genetic markers or counselling is advised at present.

References

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This guideline is a statement of consensus of the Thoracic Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgement of the physician in the context of individual clinical circumstances to determine any patient's care or treatment.