Lung cancer crash course

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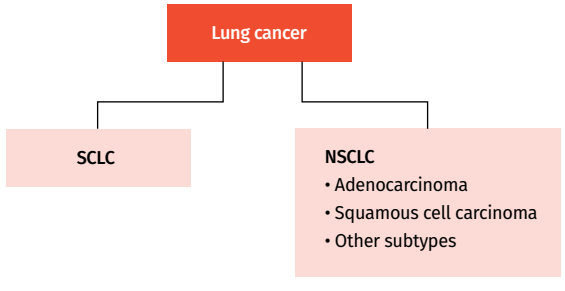
Lung cancer has the highest mortality rate of any cancer in Canada, causing 25.5% of all cancer deaths, with a 5-year survival rate of only 19%.[1] More than half of lung cancers are metastatic at diagnosis, with common sites of metastases in the brain, bone, liver, and adrenal glands. Lung cancer is a heterogeneous group of cancers broadly separated into small cell lung cancer (SCLC)—approximately 15% of all lung cancer cases—and non–small cell lung cancer (NSCLC), which is further divided into predominantly adenocarcinoma and squamous cell carcinoma subtypes (**Figure 1**). More than 80% of lung cancer cases are related to smoking, meaning smoking cessation remains the cornerstone of lung cancer prevention.[2] Low-dose computed tomography is a valuable screening tool for lung cancer that can identify lung cancers at an earlier stage and reduce lung cancer–specific mortality and all-cause mortality.[3] Although lung cancer screening is recommended by the Canadian Task Force on Preventive Health Care, it is currently available in only a few Canadian provinces.[4]

Definitions and staging

Small cell lung cancer is divided into *limited* and *extensive* disease, dating back to initial efforts to cure this cancer where *limited* disease (equivalent of stage I to III cancer) was confined to the ipsilateral thorax and could fit within 1 radiation field, whereas *extensive* disease did not.[5] On the other hand, NSCLC is classified from stage I to IV and is based on the widely used TNM (tumour, node, metastasis) system. Clinical, pathologic, and radiologic investigations are used in the staging process, with positron emission tomography scans being used only if definitive treatment is being considered. Cancer stage ultimately dictates therapeutic options as well as prognosticates risk of recurrence and mortality.[6] The treatment of both SCLC and NSCLC is rapidly evolving.

Figure 1. Lung cancer subtypes



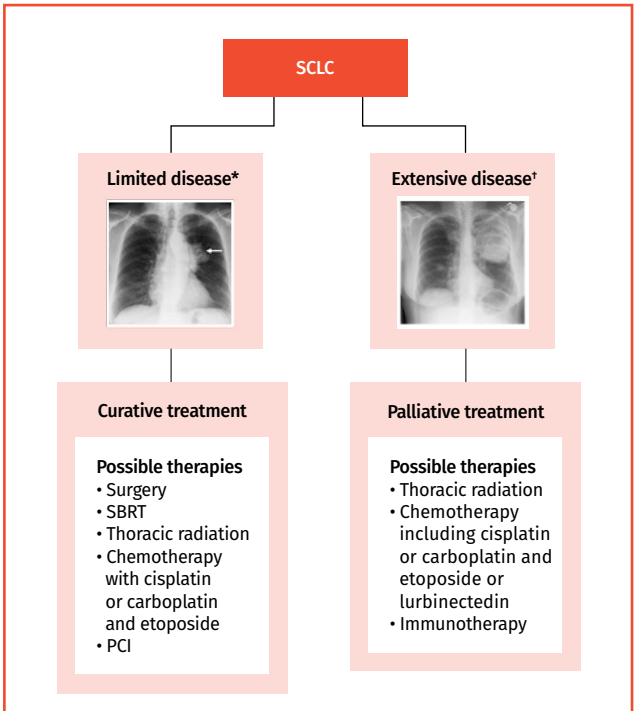
NSCLC—non–small cell lung cancer, SCLC—small cell lung cancer.

Small cell lung cancer

This type of cancer is extremely aggressive. Patients with extensive SCLC who do not receive treatment often survive for only weeks.[7] Owing to its tendency to spread early, patients frequently present with symptoms of metastatic disease, including weight loss, bone pain, and neurologic symptoms. The rapidity of growth and resultant tumour bulk can also cause patients to present with local complications, such as cough, dyspnea, postobstructive pneumonia, or superior vena cava obstruction. Hyponatremia is common due to the syndrome of inappropriate secretion of antidiuretic hormone, which can be seen with SCLC and with other paraneoplastic syndromes.[8]

Limited SCLC can be treated with curative intent while extensive SCLC is treated with palliative intent (**Figure 2**).[9,10] In the very rare case that tumours are less than 5 cm with no nodal involvement, curative-intent treatment may involve surgical resection or stereotactic ablative radiotherapy in patients with comorbidities that preclude surgery. Adjuvant

Figure 2. Overview of limited and extensive disease SCLC



PCI—prophylactic cranial irradiation, SBRT—stereotactic ablative radiotherapy, SCLC—small cell lung cancer.

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chemotherapy (cisplatin or carboplatin and etoposide) is given after definitive treatment to reduce risk of recurrence. More commonly, patients will have larger tumours (>5 cm) or nodal metastases, in which case curative-intent treatment is composed of concurrent chemotherapy and thoracic radiation.[5] Patients with a good response to curative therapy are considered for prophylactic cranial irradiation (25 Gy in 10 fractions), which improves overall survival by 5% at 5 years and decreases the incidence of brain metastases by 50% within 3 years, but comes with the risk of developing chronic neurotoxicity.[11]

Patients with extensive SCLC and even poor performance status are often treated urgently with palliative chemotherapy for symptom control and survival benefit, as SCLC is extremely chemosensitive, responding to chemotherapy in up to 80% of cases.[5] Patients are generally treated with 4 cycles of cisplatin or carboplatin and etoposide in conjunction with immunotherapy agent durvalumab.[5,12] The rapid breakdown of the tumour in response to chemotherapy creates a risk of tumour lysis syndrome, so allopurinol is prescribed prophylactically for patients with bulky tumours.[13] After initial treatment with palliative chemotherapy, individuals may be free of disease progression for months; however, they will ultimately relapse. Lurbinectedin is a novel chemotherapy agent that can be used as second-line treatment; however, median survival time remains measured in months.[14]

Curative-intent treatment of NSCLC

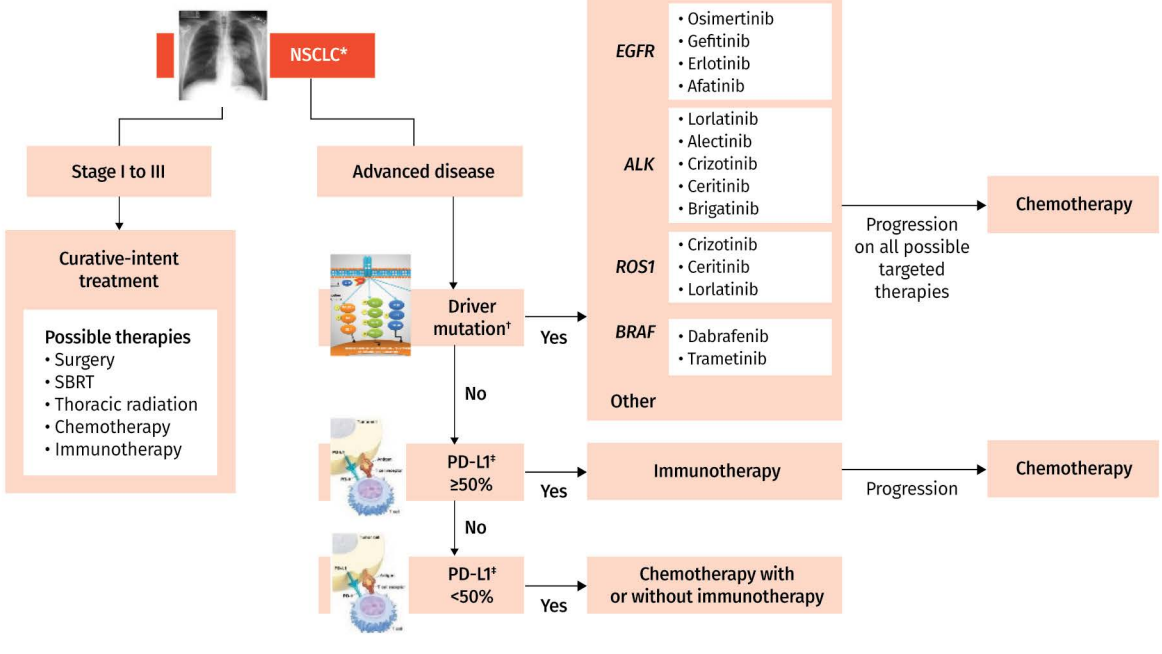
Stage I and II NSCLC are generally treated with curative intent (**Figure 3**),[15-18] with surgery or stereotactic ablative radiotherapy if surgery is not possible.[2] Risk of recurrence begins to mount as tumour sizes grow larger than 4 cm or if there is nodal disease. In this case, 4 cycles of adjuvant platinum doublet chemotherapy consisting of cisplatin paired with an additional drug such as vinorelbine or pemetrexed can be given.[6]

One-quarter of patients present with stage III disease (with either larger tumours or mediastinal nodal involvement). If these tumours are not resectable, thoracic radiation therapy is indicated with concurrent chemotherapy for synergy, followed by adjuvant immunotherapy for 1 year.[19] A recent trial showed improved event-free survival when resectable stage II and III NSCLC were treated with 3 cycles of neoadjuvant chemotherapy and immunotherapy before surgery, a practice that will likely become common in the future.[20]

Advanced NSCLC

Pathologic analysis of NSCLC includes not only histologic examination, but also driver mutations and programmed cell death 1 ligand 1 (PD-L1) status.

Figure 3. Treatment of NSCLC



NSCLC—non–small cell lung cancer, PD-L1—programmed cell death 1 ligand 1, SBRT—stereotactic ablative radiotherapy.

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Programmed cell death 1 ligand 1 is found on cancer cells and works to inhibit the immune system; levels of expression of this biomarker can help predict immunotherapy response. While PD-L1 is an imperfect marker for predicting tumour response, higher levels of expression generally predict a higher chance of response to immunotherapy.[21] Patients with stage III NSCLC who are not candidates for curative-intent treatment and those with stage IV disease will have personalized therapy based on detailed tumour pathology.

Driver mutations are genetic alterations in cellular signaling systems causing uncontrolled cellular replication and tumour growth. These are most commonly found in adenocarcinomas and are typically seen in younger patients, those of East Asian descent, and in those who have never smoked, or in those with a minimal remote smoking history. Mutations *KRAS* and *EGFR* are the most common, but there are many other driver mutations, including the *BRAF* V600E mutation, *ROS1* mutation, *ALK* rearrangements, *NTRK* gene fusions, and *MET* mutations, to name a few.[22,23] Targeted therapies have been specifically developed for many of the known driver mutations and typically increase progression-free survival compared with chemotherapy, sometimes up to 4 to 6 years in the case of *ALK* rearrangements. Chemotherapy should be used in these patients only once there is resistance to all possible targeted therapies. Most patients with driver mutations, with the exception of *KRAS*, do not respond well to immunotherapy.[19] The role of targeted therapies in the curative treatment of lung cancers continues to evolve, and these agents may soon be part of the adjuvant therapy for resected cancers found to have driver mutations.[24]

In the absence of a driver mutation, PD-L1 status is used to determine the likelihood of a patient benefiting from immunotherapy. Patients with a PD-L1 status of greater than or equal to 50% are offered immunotherapy alone, sparing patients the potential toxicity of chemotherapy, whereas those with PD-L1 less than 50% are offered chemotherapy, potentially in combination with immunotherapy. Long-term survival with immunotherapy has been observed, with up to 40% of patients still alive at 3 years in 1 trial[21] and a sustained response in 20% of patients at 4 years.[25] Patients who progress on immunotherapy are treated with chemotherapy as second-line treatment.

Conclusion

Lung cancer is a collection of various cancers with differing genetic and histologic subtypes. Family physicians are in an ideal position to prevent lung cancer by promoting smoking cessation and referring to screening programs where available, and to expedite diagnosis through the recognition of presenting clinical signs and symptoms. This article should provide family physicians with more knowledge on the range of therapies and outcomes possible in the treatment of lung cancer.

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Competing interests
None declared

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