



Treatment of limited disease small cell lung cancer: the multidisciplinary team

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Small cell lung cancer treatment is multifaceted and requires close collaboration within a multidisciplinary team <http://ow.ly/A6FO30c4bts>

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ABSTRACT Small cell lung cancer (SCLC) presents multiple interdisciplinary challenges with several paradigm shifts in its treatment in recent years. SCLC treatment requires multidisciplinary management and timely treatment. The aim of this review is to focus on the team management aspects in the treatment of limited disease SCLC and how this can contribute towards improving outcomes.

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Introduction

Limited disease small cell lung cancer (LD-SCLC) is a potentially curable disease that requires timely coordination of efforts from multiple disciplines. The multidisciplinary team (MDT) meeting is an ideal forum and starting point to discuss each patient in consideration of relevant information from the perspective of all involved specialists.

Role of multidisciplinary teams

MDTs have a long and complex history; they co-developed with educational sessions, regular collaboration among specialists and tumour boards [1, 2]. An MDT meeting is a meeting of a group of people from different healthcare disciplines at a given time to discuss individual patients [3].

Simple organisational versions are based on a unidisciplinary team. These usually consist of the patient, primary treating physician and one or more specialists. Decisions in these teams are often dominated by a single individual. MDTs arise by participation of further specialists and include perspectives from the different disciplines in the decision-making process. Ideally, a transdisciplinary team develops, as described in the continuum model [4]. In a well-working transdisciplinary team cooperation is automatic and barriers between disciplines are removed. Recommendations are based on interdisciplinary insights instead of hierarchical structures. Core team members communicate closely and involve a multitude of other agents, *e.g.* general practitioners, social workers, physiotherapists, administrators, clinical trial specialists and nurses, to achieve the best possible results for the patient [1, 5, 6].

The aim of MDTs is to improve cancer care, although in lung cancer evidence demonstrating a clear survival benefit is controversial [3, 7–9], and evidence is even scarcer for SCLC. Several trials reported outcomes before and after the implementation of MDTs; only three of these included a small number of patients with SCLC [10–12]. A systematic review by COORY *et al.* [3] identified only one randomised trial [13] including SCLC investigating the impact of MDTs. Despite lacking evidence for SCLC, evidence from breast, head-and-neck and rectal cancer has demonstrated that MDTs can reduce rates of positive surgical margins, reduce costs, improve patient satisfaction, improve documentation regarding TNM (tumour, nodes, metastasis) staging or performance status and even decrease the time from diagnosis to treatment [5, 14–17].

The time factor in particular is very important in SCLC where fast-track procedures should be considered [1]. Without treatment, patients with SCLC rarely survive longer than a few weeks to months [5]. Insufficient or late treatments have been associated with poor outcomes [18–20].

Having multiple specialists involved early enables them to anticipate problems or address issues ahead. PRADES *et al.* [9] hit the mark: “the rationale behind the more comprehensive structuring of teamwork in cancer care goes beyond eventual clinical outcomes and embraces the process of care as a whole”. Spatial issues should not be a limiting factor nowadays; depending on the setting, a telecommunication solution might be implemented when physical meetings are difficult [12].

Tumour boards have now developed into multidisciplinary platforms for care teams which, ideally in agreement, recommend further diagnosis and management, take responsibility for these recommendations, and implement them in close partnership with the patient [21]. Tumour boards are established in most hospitals across Europe; however, wide variations of implementation and organisational details exist [6]. These variations, or lack of implementation, are even larger across the world [22]. The European Respiratory Society and the American Thoracic Society have declared tumour boards the standard of care [23].

Although referral practice may vary [24, 25], the basic steps shown in figure 1 are generally followed in the typical management of SCLC.

From symptoms to diagnosis: the multidisciplinary approach

About 30% of patients will present with LD-SCLC at the time of diagnosis [26–28]. Owing to the high proliferation rate of this tumour type, time should not be wasted. Patients often present to physicians with various symptoms, including paraneoplastic syndromes [29]. Potentially, not every clinician will identify all symptoms properly or be able to initiate the correct first steps; however, with proper presentation and the expertise of an MDT, relevant problems can be identified and approached.

The goal of diagnostics is to establish the underlying disease and precisely define the tumour stage of SCLC; this is the basis for the subsequent treatment recommendation by the MDT. Statements from the radiation oncologist or surgeon regarding potential local treatments may impact the type of diagnostics being performed and this also applies to information about patient preference or suitability of lesions for potential biopsies. Multiple diagnostic modalities are available, such as multidetector computed tomography (CT), positron emission tomography (PET)/CT, magnetic resonance imaging (MRI), PET/MRI, endobronchial ultrasound (EBUS)-guided fine needle aspiration and bone scanning [30]. Although the

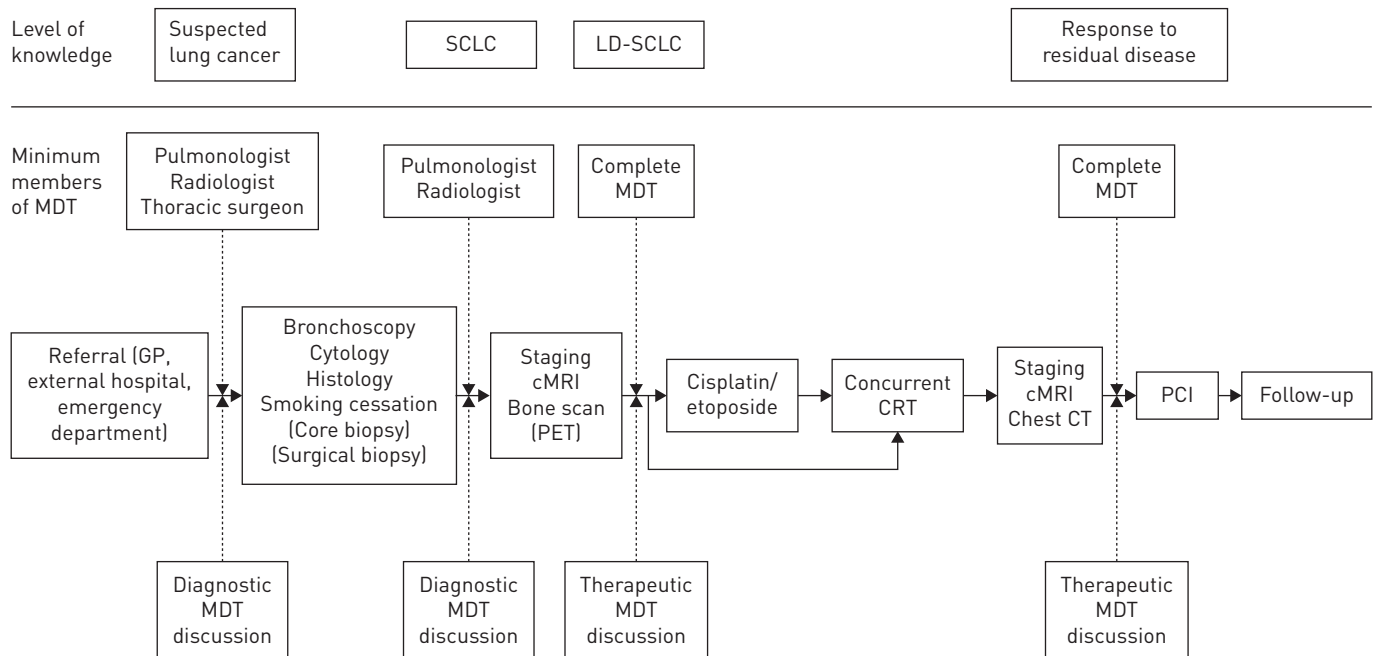


FIGURE 1 Basic steps in the management of small cell lung cancer (SCLC). LD: limited disease; MDT: multidisciplinary team; GP: general practitioner; cMRI: cranial magnetic resonance imaging; PET: positron emission tomography; CRT: chemoradiotherapy; CT: computed tomography; PCI: prophylactic cranial irradiation.

sensitivity and specificity of imaging is improving, histopathological diagnosis is not obsolete. In an MDT it is the task of the radiology and nuclear medicine specialists to show and interpret their results and facilitate their correct interpretation. Conclusions are best drawn by considering all available data, and the team requires information beyond imaging and histology, including patient information (*e.g.* smoking history and geographical background) and/or clinical expertise (*e.g.* considerations on differential diagnoses by the respiratory physician).

Although outdated, SCLC is still commonly staged using the Veterans Administration Lung Study Group system [31]. LD-SCLC means that the cancer is confined to one hemi-thorax, all of which can be encompassed in a safe radiotherapy field. The seventh edition of the Union for International Cancer Control TNM Classification of Malignant Tumours (2009) as well as the updated eighth edition (2016) recommend the use of the TNM classification for staging SCLC, which also has a demonstrated prognostic value [32, 33]. LD-SCLC now corresponds to T1–4 N0–3 M0 tumours, whereas metastatic tumours encompass former extensive disease (ED-SCLC).

Histological confirmation should always be sought in a timely fashion [34, 35]. The rate of pathological tissue confirmation is higher among patients discussed at an MDT [24]; however, obtaining tissue samples can be challenging and may require multiple specialities [36]. The team should ensure that the most conveniently accessible site with the highest chance of obtaining tissue is targeted first, minimising the risk of repetitive procedures [37]. Potential side-effects should be considered individually for each patient (*e.g.* the risk of pneumothorax based on lung imaging). CT and PET/CT images can provide a valuable basis for determining the best strategy, which may include various combinations of imaging and external biopsies and/or transbronchial or surgical approaches, making interdisciplinary exchange essential [26, 38, 39].

Once tissue samples have been retrieved, histological evaluation can be challenging due to differential diagnoses [26, 40–43]. Information on a history of inflammation or the presence of other malignancies such as lymphoma is crucial to the pathologist and is essential information that must be communicated. SCLC can present as an extensively necrotic neoplasm, making histological diagnosis difficult. Biopsies should take details of imaging into account and provide a good opportunity to include a broad team in the process. Depending on local practice, the pathologists may be actively involved in obtaining biopsies. Pathologists can be pivotal in differentiating recurrence from a new primary or a metastasis from a different neoplasm, with a major impact on treatment decisions.

Mediastinal staging is recommended before curative treatment [44]. EBUS bronchoscopy is preferred for the staging of mediastinal lymph nodes. Mediastinoscopy can be used to sample mediastinal lymph nodes

not accessible with EBUS or with inconclusive results [45]. The pulmonologist, thoracic surgeon and imaging specialist should all be involved in mediastinal staging.

Since in most institutions MDT meetings will occur once a week, potential delays in the management of SCLC need to be weighed against the advantages of such meetings. The MDT should be involved throughout the patient pathway, before and after the meeting, especially when treatment is initiated in an acute setting. Relevant information needs to be available for the MDT and the questions to the board should always be specific [1]; this might seem obvious, but all of the current co-authors have experienced otherwise. The results should be well documented and communicated [20, 46].

On average, the time from the first abnormal radiological finding to the first day of treatment in all lung cancer patients is ~2.5 months [47, 48], which may be deleterious in this fast-growing tumour. After therapy is proposed, initiation of radical treatment in lung cancer involving radiotherapy or surgery usually requires 2–3 weeks [24]. In SCLC, in particular, there are some scenarios demanding rapid introduction of therapy, such as vena cava superior syndrome or syndrome of inappropriate antidiuretic hormone. The most intense teamwork is required in the first days when diagnosis and staging are performed and the first treatment initiated. Treatment start within 1–2 weeks after suspected SCLC should be pursued. This is even more important for symptomatic patients.

Breaking bad news

Receiving a diagnosis of lung cancer can be devastating, and many patients are left with feelings of hopelessness and uncertainty about the future. Accurate and sensitively delivered information is crucial and, next to physicians, lung cancer specialist nurses are a valuable resource in this regard. Nurses act as key workers, offering practical and emotional support, and providing a consistent presence at clinic appointments. This support is critical not at a single time-point, but throughout the process of diagnosis and beyond [49]. Their role throughout the multidisciplinary process should not be underestimated. Psycho-oncologists should also be integrated very early in the disease course, especially for teaching in self-coping strategies, one of the key factors that enable the patient to adapt to distress, leading to a better quality of life [50].

Coordinating treatment

Radiochemotherapy

Once the diagnosis of LD-SCLC is established the standard treatment for fit patients will be concurrent radiochemotherapy [39], but chemotherapy is often initiated first to rapidly counter the fast-growing tumour [35]. Chemotherapy should commence without delay after the tumour board decision. SCLC is a chemo-sensitive tumour and a rapid response is often observed. Even in urgent situations with vena cava superior syndrome [51] rapid initiation of chemotherapy is preferred over interventional radiological treatment [52], yet both should be evaluated. In the meantime, preparation for radiotherapy should be initiated [26, 39].

The current standard chemotherapy regime for ED- and LD-SCLC in the Western world consists of four to six cycles of platinum and etoposide [26]. Combination therapies have been shown to be superior to single-agent treatment [53, 54].

Historically, twice-daily and once-daily radiotherapy regimes have evolved for SCLC side-by-side [55–61]. SCLC can be treated with daily radiotherapy (to 66 Gy) or with twice-daily treatment (to 45 Gy), both with a relatively favourable 3-year survival rate of ~40% and similar toxicity rates [62]. Patient preference should be accommodated when choosing among these regimes; the decision may be influenced by factors such as availability of transportation.

Two meta-analyses demonstrated that concurrent radiochemotherapy improved survival [39, 63, 64]. In addition to an absolute gain of 5% in overall survival at 5 years (23.7% *versus* 18.3%) with concomitant radiochemotherapy [65], it is important to evaluate the general condition of the patient. The expected survival benefit needs to be weighed against potential increased toxicity [59, 65]. The decision for either should be met by an MDT considering the overall performance status, age and comorbidities of the patient. Typically, multiple disciplines are involved during radiochemotherapy; side-effects such as neutropenic fever, pneumonia or oesophagitis require rapid and precise communication to initiate timely counter-measures and potentially adapt treatments, avoiding unnecessary treatment breaks. It should be noted that age alone should not be considered a prohibiting factor to concurrent treatment [66].

Despite controversial findings in the literature [67–69], most data and guidelines support early thoracic radiotherapy beginning with the first or second cycle when cisplatin-based chemotherapy is used [26, 39, 68, 70–72], as the majority of studies indicate a benefit with early radiotherapy [73].

In some cases radiotherapy may be considered too toxic due to the extent of the disease and pre-treatment assessment [38, 74]. Transdisciplinary teamwork is important between radiologists and radiation oncologists to ensure correct volume definition. If the treatment volume remains too extensive then delaying radiotherapy after an initial shrinking of the tumour may be a viable option.

Various factors influence treatments, including insurance status, availability of technology, professional and patient preference, or even rural or urban location [75]. A review in the Commonwealth of Kentucky in the USA demonstrated utilisation of radiochemotherapy in approximately two-thirds of LD-SCLC patients [76], which corresponds to other reported utilisation rates [77, 78], despite a relatively high proportion of rural settings. Although clear evidence is difficult to obtain, the improvements in outcome in LD-SCLC in recent decades are being attributed to higher utilisation rates of active or multimodal treatment [76, 79], which is at least partially facilitated by MDTs [80, 81].

Prophylactic cranial irradiation

The risk of brain metastases can be nearly halved in LD-SCLC with the use of prophylactic cranial irradiation (PCI) [82–85]. PCI is favourable for patients with at least stable disease after radiochemotherapy, demonstrating a significant improvement in overall survival [86]. Response evaluation should be interdisciplinary, including the treating clinicians and imaging specialists. Close communication is required to avoid confusing radiation-induced changes with progressive disease. Cranial MRI before PCI should be considered as it identifies patients who might require therapeutic whole-brain radiotherapy (with a higher dose) for brain metastases [87]. Before initiating PCI, prognostic factors such as performance status, age, life expectancy and comorbidities need to be considered and presented in the MDT meetings by the treating clinicians. Advanced age only should not rule out PCI [88].

The risk for neurocognitive decline after PCI has been reported as 30–60% after 1 year [85, 89–91], depending on the measure of neurocognitive impairment. Patients at higher risk for neurocognitive deterioration (e.g. with diabetes or pre-existing cerebrovascular problems) [92–94] should be critically evaluated, involving neurologists for neurocognitive assessments. An important region for neurocognitive function is located in the hippocampus and current research includes investigating hippocampal-sparing cranial irradiation to reduce neurocognitive dysfunction [95, 96].

In addition to neurocognitive dysfunction, hair loss is another detrimental side-effect. Patients have to be prepared for hair loss, potentially with the help of psycho-oncologists, to minimise the impact on quality of life. When PCI is not implemented, close follow-up with cranial MRI should be performed if therapeutic radiotherapy would be an option [97].

Lifestyle modification

Lifestyle modification can also improve outcomes. SCLC represented 17% of lung cancer cases in the USA in 1986 and declined to 13% in 2002, likely attributed to changes in smoking behaviour [98]. Outcomes are improved even when smoking is stopped after diagnosis [99, 100]. Multidisciplinary lung cancer treatment programmes offer an ideal environment to optimally deliver effective smoking cessation services. Smoking cessation should be offered utilising the services of dedicated smoking cessation programmes and tailoring cessation interventions to the patient's cancer treatment plan [101].

Individual treatment approaches

Surgery

Surgery can be considered for several indications in SCLC patients: in localised disease, for mixed histological tumour types, for salvage resection for persistent local disease after radiochemotherapy and for early locally relapsed (potentially chemo-resistant) tumours [102]. Recent analyses of the SEER (Surveillance, Epidemiology and End Results) database (seer.cancer.gov) also, with limitations, suggest that surgery may be appropriate for some patients with localised disease [82, 83].

Despite these uncertainties, surgery is an option for T1–2 N0 SCLC in current guidelines after appropriate staging [26, 103]. It is important that surgical resection and its potential extent are discussed in an MDT, bringing this option to attention.

Before radical treatment, interdisciplinary cardiopulmonary function testing of the patient should be performed [74], including pulmonologists and nuclear medicine specialists for evaluation of lung function, surgeons estimating the extent of surgery, and anaesthesiologists evaluating operability.

Lobectomy is favoured over segmental or wedge resections; obviously, an R0 (complete excision) needs to be achieved [39].

Evidence for the use of PCI after complete resection of SCLC is limited. However, PCI should be discussed by the MDT [104].

Adjuvant treatment

After resection, further therapy has to be discussed with all involved specialists, including pathologists, radiologists, oncologist, surgeons and radiation oncologists. With a high risk of loco-regional recurrence, surgery alone is not sufficient [105]. Adjuvant chemotherapy is recommended even in patients with pN0 lymph node status [106, 107]. In the case of positive nodes, post-operative radiation therapy should also be discussed [108, 109].

The decision should be made considering performance status, age, lung function, comorbidities and extent of disease, and with close collaboration between pulmonologists, surgeons and pathologists. In case of an inadequate resection margin (R1), the involved surgeon and the pathologist support the radiation oncologist in defining the target if radiotherapy is indicated.

Novel treatment approaches

Whether immunotherapy improves outcomes in LD-SCLC is currently under investigation. The MDT provides a good platform to present ongoing trials to colleagues of other disciplines and to select patients for whom trial participation can be proposed. Patients who are seen by MDT members have a higher enrolment rate in clinical trials [110]. The support of a study nurse cannot be underestimated, to the patient as well as the treating physicians.

Follow-up

High recurrence rates justify follow-up. Follow-up includes contrast-enhanced CT [26, 39, 111]. The aim of close follow-up is early detection of recurrence in a stage where patients still have a good performance status and localised disease. Next to imaging, smoking cessation should be actively discussed. Although plasma progastrin-releasing peptide with or without neuron-specific enolase measurements may be a useful diagnostic marker to detect early recurrence [112–115], prospective trials evaluating the benefit are lacking and therefore routine tumour marker assessment is not recommended in this setting.

Any form of suspected recurrence should be discussed in an interdisciplinary setting; post-radiotherapy changes in the lung might need interpretation. Histological verification may exclude a second primary tumour which could be treated in a potentially curative manner. Second-line treatments are at least as multidisciplinary as the primary treatment. Referral to palliative care services among patients who were discussed at tumour boards is higher, suggesting that symptom control and quality of life can be better addressed in an MDT setting [7].

Follow-up also serves to detect and treat treatment-related side-effects. Depending on the setting, follow-up is often performed by a single specialist. Feedback to the MDT and cooperation is crucial for correct interpretation and treatment.

Summary

SCLC is a rapidly growing tumour with poor prognosis, even in LD-SCLC. Optimal treatment involves timely concurrent radiochemotherapy and prophylactic brain irradiation in most patients. For this to be delivered optimally, diagnosis and staging need to be well coordinated, timely and accurate. Well-organised interdisciplinary collaboration is essential to facilitate adequate treatment considering all aspects of care, including patient preference.

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