



Multidisciplinary team care in advanced lung cancer

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Abstract: Lung cancer is the most common cause of cancer mortality globally. A vast majority of lung cancer cases are diagnosed at advanced stages. Management of advanced lung cancer requires several diagnostic and therapeutic procedures provided by various specialists. To optimise the entire diagnostic and therapeutic process, a concept of care provided simultaneously by a multidisciplinary team (MDT) has been developed and implemented in specialised centres worldwide. Observational studies suggest that integrated and coordinated care increases adherence to clinical guidelines, significantly shortens the interval from diagnosis to treatment, and may increase survival and quality of life (QoL). Prospective studies are warranted to assess the real impact of MDT on treatment outcomes and to further refine this approach.

Keywords: Multidisciplinary care; lung cancer; diagnosis; treatment

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Introduction

Lung cancer continues to be the leading cause of cancer mortality globally (1). Advanced lung cancer, not suitable for curative treatment approaches, accounts for 55% to 85% of all newly diagnosed cases (2-4). The development of targeted therapies and immunotherapy has revolutionised the paradigms of lung cancer treatment. However, treatment outcomes in advanced lung cancer remain poor, and virtually all patients succumb to their disease. Apart from increasing survival, the main objective of advanced lung cancer management is maintaining the quality of life (QoL) and prolonging time spent in acceptable health.

Multidisciplinary team (MDT) is a comprehensive group of professionals representing various disciplines who regularly meet to develop joint treatment decisions. MDT based management has been shown to increase survival in various advanced solid malignancies (5-9). The need of MDT care in lung cancer is due to the number of treatments employed: surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and palliative and critical

care. Some of them can be combined or interwoven. Health professionals participating in lung cancer management include pneumonologists, thoracic surgeons, medical oncologists, radiation oncologists, pathologists, molecular pathology specialists, radiologists, nuclear medicine physicians, palliative care physicians, lung cancer nurses, psychologists and cancer care coordinators. Importantly, patients should be involved in decision-making.

Currently, in specialised cancer centres worldwide treatment recommendations in lung cancer are usually made by MDT. MDT meetings have been shown to increase national and international guideline adherence, and significantly shorten the interval from diagnosis to treatment (10). By virtue of MDT consultation, the treatment plan can be more optimised. MDT meetings may substantially reduce the time of patients' consultation, and improve the efficiency of diagnosis and treatment. The need of visiting subsequent departments by patients may be diminished, and treatment decisions are provided more promptly. There are some general rules of lung cancer MDT organisation, but they may differ between particular countries and centres.

Most importantly, MDT management, by timely delivery of best evidence-based practice care, has been shown to improve patient overall survival (OS) and QoL, particularly in stage III and IV lung cancer (9,11-13).

Recently, ongoing expansion of medical literature decision-support tools (artificial intelligence, such as Watson for Oncology) have been invented to help oncologists in providing evidence-based care based on the most recent scientific publications (14). This methodology is also being tested in supporting lung cancer MDT decisions (15).

This article briefly presents the main opportunities and challenges of MDT in advanced lung cancer. However, it should not be considered a comprehensive review of this subject, as no formal evidence-based analysis has been attempted.

Referrals and diagnostic pathways

In advanced lung cancer an MDT meeting convened in the very beginning of the diagnostic process may better encompass the entire patient's diagnostic and therapeutic path, and allow avoiding unnecessary and redundant procedures. The diagnostic work-up and treatment in advanced lung cancer depends on performance status (PS), tumour burden and tumour sites. The referral pathways differ between regions and countries. Typically, patients with suspicion of lung cancer are first seen by general practitioners who perform diagnostic imaging, usually a chest X-ray or CT. Patients may be referred for the MDT meeting after pathological diagnosis and staging have been established, or at early phase of the diagnostic process. The National Comprehensive Cancer Network and National Institute for Health and Care Excellence guidelines recommend that both the diagnostic process and the treatment of lung cancer should be discussed at MDT meetings (16,17), whereas a number of national guidelines recommend an MDT consultation in all patients right after the diagnosis and before commencing treatment (18). Until recently, the diagnosis of lung cancer was frequently based on cytological examination. In the era of personalised medicine, a histopathological diagnosis is necessary to establish tumour phenotype and provide material for molecular testing. An experienced interventional radiologist, pulmonologist or thoracic surgeon is generally able to obtain adequate tumour tissue with minimal risk for the patient, even in the case of hardly accessible lesions (19). MDT care is also instrumental in determining the type and sequence of staging procedures. Many lung cancer patients

need positron emission with computed tomography (PET-CT) and brain magnetic resonance imaging (MRI) for staging assessment. However, in a proportion of advanced lung cancer patients, the high tumour metastatic burden is apparent at primary imaging including chest X-ray or CT and abdominal ultrasonography or CT. In such cases, further diagnostic imaging using PET-CT or MRI may unnecessarily increase costs and delays the start of treatment.

If a patient is referred for an MDT meeting with adequate diagnosis and staging, the decision can be made immediately. If further diagnostic work-up is needed, the institutional algorithm should be employed, and the referrals designed promptly to avoid unnecessary waiting and overloading the meeting. Another MDT meeting should be set only if the available data are insufficient for making an immediate decision.

Patient physical status

MDT treatment recommendations highly depend on patient's physical status. The patient's functional and general health status data presented to the MDT should be based on objective measures or validated assessment tools. The proper assessment of PS according to the Eastern Cooperative Oncology Group or Karnofsky scales is crucial for taking appropriate treatment decisions. Determining PS is necessary to distinguish fit from frail patients, and to predict whether the patient is fit enough to undergo the intended oncological treatment. A significant proportion of advanced lung cancer patients, even in good PS, finally do not receive or are unable to complete MDT designed treatment (20). PS assessed by clinicians may differ in about 20–30% of cases when tested against the patient's perception of general health status, but clinicians' assessment is not biased consistently towards either under- or overestimation (21). Interestingly, only patients' PS assessment was found to correlate with the ability of completing the MDT designed treatment ($P=0.007$), which confirms the importance of patient reported data in final treatment decisions (21).

Another clinical factor which can predict outcomes in advanced lung cancer patients is sarcopenia (muscle mass depletion). This abnormality is present in about half of lung cancer patients and is associated with impaired OS. In the meta-analysis including 13 studies and 1,810 lung cancer patients, sarcopenia was associated with a shorter OS [hazard ratio (HR), 2.23; 95% CI, 1.68–2.94], in both non-small cell

lung cancer (NSCLC) and small cell lung cancer (SCLC) (22). This abnormality was an independent predictor of shorter OS in both stage I–II (HR, 3.23; 95% CI, 1.68–6.23) and stage III–IV NSCLC (HR, 2.19; 95% CI, 1.14–4.24) (22). Additional prognostic information may provide the muscle strength status and physical performance assessed by a short physical performance battery (SPPB) score. Better fitness, with quicker gait speeds, sit-to-stand times or a higher total SPPB score, were found to correlate with the ability to complete more cycles of chemotherapy or the whole planned treatment ($P < 0.05$). A higher SPPB score was also associated with fewer adverse events, less need for hospitalisation and fewer chemotherapy delays ($P = 0.001$). Patients in more advanced stages and with weight loss above 10% were more likely not to complete MDT recommended treatment (23).

Due to populations' aging, particularly in the Western world, a substantial proportion of lung cancer patients are at an older age. Optimising decision-making in this, usually more frail population, is of particular importance. A recent Dutch study showed that only 39% of eligible advanced lung cancer patients aged above 75 years started chemotherapy, compared to 80% of the younger population (24). Treatment modifications were made in 49% and 66% of patients aged below and above 65 years, respectively. The unplanned hospital admissions during chemotherapy were most frequently required for patients aged 65–75 years, indicating that the frailty of this population may be underestimated (24).

Opposite to chemotherapy, elderly patients may have substantial benefit from immunotherapy (25). Hitherto, these patients have been under-represented in phase III randomised clinical trials investigating immune checkpoint inhibitors. However, the pooled data from four studies comparing inhibitors of programmed death 1 receptor (PD-1) or its ligand 1 (PD-L1) *vs.* docetaxel in the second line treatment of advanced NSCLC, confirmed the efficacy of immunotherapy irrespective of patient age, with lower treatment-related and severe adverse events rates in older patients (26). Notably, immune checkpoint inhibitor studies in advanced NSCLC included mostly PS 0–1 patients, therefore a potential benefit of these compounds in patients with poor PS remains not well recognised. A small retrospective study including poor PS lung cancer patients suggests no advantage of nivolumab compared to best supportive care (27).

Early introduction of pneumonological and palliative care intervention may improve the condition of patients

and increase their treatment adherence (28). Since advanced lung cancer patients frequently present with multiple smoking-related comorbidities, many of them necessitate pneumonological intervention. This is particularly important in patients with accompanying chronic obstructive pulmonary disease. This entity strongly influences patient fitness, and its proper management may facilitate the institution of planned treatment (28,29). Particularly debilitating symptoms affecting advanced lung cancer patients are central airway obstruction (CAO) and malignant pleural effusion (MPE). Minimally invasive bronchoscopic interventions, such as stent implementation or intraluminal brachytherapy for CAO, and thoracentesis with or without pleurodesis for MPE, may substantially improve patients' condition and make them suitable for further diagnostic and therapeutic procedures (30).

Early palliative care

As advanced lung cancer is generally incurable, with estimated median OS of less than 1 year (31), anticancer therapy should be supplemented by early palliative care. Patients should be aware of the limited treatment efficacy, and increased risk of early toxicity, including lethal events (32). The benefits and risks of planned treatment should be carefully evaluated at the MDT meeting. The majority of lung cancer patients suffer from various symptoms, including dyspnoea, chest pain, anorexia, fatigue and cough, therefore a palliative care specialist should be a part of MDT. Palliative care, including for example adequate analgesics, nutrition intervention or anabolics, provides an opportunity to relieve troublesome symptoms, and to improve QoL and PS (33,34). Addition of early palliative care to standard management in advanced NSCLC was also shown to prolong OS (35). The beneficial effect of early palliative care implementation in advanced lung cancer on both QoL and OS was confirmed in a pivotal phase III study (36). A recent Cochrane meta-analysis of five studies in various advanced malignancies, including one in NSCLC, demonstrated increased overall health-related QoL improvement and decreased symptom intensity, but no OS impact from early palliative care (37). However, the lack of an average OS benefit was most probably due to the large outcomes' heterogeneity of particular studies, related to specific features of the studied malignancies and the variability of palliative care interventions (37). Indeed, of the four studies assessing the OS impact of early palliative care, three showed its benefit (36,38,39), and one

demonstrated an adverse effect (40). However, the only negative study included mostly patients with recurrent cancers, whereas the above-mentioned phase III lung cancer trial (36) introduced palliative care within eight weeks from first cancer diagnosis, corresponding to the real definition of early intervention.

The European Society for Medical Oncology, The American Society of Clinical Oncology and many other international and national oncological societies recommend close cooperation between oncologists and palliative care physicians to earlier relieve disease symptoms, improve QoL, increase patients' and caregivers' satisfaction, optimise hospice referral, and reduce pointless emergency and intensive care (41-43).

Patients with early palliative support are more likely to receive systemic anticancer therapies and more lines of treatment ($P=0.001$). Early introduction of palliative care also allows for less hospitalisations in the last three months of life (38), and less chemotherapy administered near the end of life (in the last 14 or 30 days), without affecting OS (36,43). Finally, patients with early palliative care are also more likely to participate in clinical trials ($P=0.014$) (44).

Oligometastatic disease

Particular consideration should be given to patients with low oligometastatic disease. These patients account for 15–55% of all metastatic patients from different primaries (45–48). These patients represent a considerable proportion of all patients subjected to MDT decisions. Lung cancer patients with low metastatic burdens represent a highly specific population, and some of them may be amenable for locoregional, potentially curative therapies (49,50). For example, in the Galata *et al.* study (45) MDT recommended local therapy in 64.5% of oligometastatic lung cancer patients. However, owing to the lack of oligometastatic disease definition, selection of patients amenable to local approaches is still subjective. Recently, the European clinicians defined the oligometastatic lung cancer as a maximum of five lesions in up to three organs (51). The same criteria have been proposed by the pan-European Multidisciplinary Consensus Group (52). This consensus does not consider mediastinal lymph node as a metastatic site, and recommends the staging including obligatory fludeoxyglucose F 18 positron emission tomography-computed tomography and brain imaging. The Group also recommends biopsy of a solitary metastatic location unless the MDT is of the opinion that the risks outweigh the benefits.

The clinical evidence regarding the management of these patients is limited. The first phase II randomised trial comparing local ablative treatment *vs.* standard care after front-line systemic therapy in oligometastatic NSCLC showed a significantly longer median progression-free survival in the intervention group (53). In a recent retrospective study oligometastatic disease defined as up to three synchronous metastases, was identified in 74% of all stage IV NSCLC patients, 62% of whom received local consolidative therapy to all metastatic sites (54). Local therapy was independently associated with improved OS, particularly among patients without thoracic nodal disease or bone metastases, and with more than one metastatic site (54). In another retrospective study, OS benefit from the addition of local therapy was confined to T1–2, N0–1 squamous cell carcinoma patients with one metastasis (HR, 0.68; 95% CI, 0.57–0.80; $P<0.001$), whereas those with adenocarcinoma, T3–T4, N2–N3 and two or more metastases showed inferior OS compared to systemic therapy alone (55).

Brain metastases

MDT treatment recommendations may be of particular relevance in patients with brain metastases. Brain involvement at diagnosis is present in about 25% of advanced NSCLC patients and is the most common oligometastatic site (56). This tumour location carries a particularly poor prognosis and necessitates specific management. Solitary brain metastases are usually approached by neurosurgery or radiosurgery. New radiotherapy techniques (stereotactic radiotherapy, radiosurgery) allow for the treatment of inoperable oligometastatic lesions and increase local control after resection (57). Adequate local management of solitary brain metastases significantly improves OS and QoL. In oncogene driven NSCLCs, particularly *ALK*-rearranged or *EGFR*-mutant cancers, new potent CNS penetrating tyrosine kinase inhibitors may constitute the primary treatment (58). This strategy is recommended in asymptomatic patients with disseminated lesions, as it allows deferring whole-brain radiation-therapy with its detrimental side-effects.

Molecular testing

Proper diagnostic pathway recommended by MDT may increase treatment efficacy by virtue of its tailoring to individual patient. Targeted therapy is the treatment

of choice for tumours harbouring actionable molecular alterations. Consequently, tumour genetic testing is currently considered a mandatory procedure at the diagnosis of advanced NSCLC (59). Molecular assessment is recommended in all non-squamous NSCLCs, particularly in adenocarcinomas, as well as in patients at a young age, with no or light smoking history (60). The optimal sequence of molecular tests depends on various clinical factors and the time needed for obtaining the results (61). Use of next generation sequencing platforms enables simultaneous detection of multiple targets and alteration types, but its cost-effectiveness remains an issue (62).

The quick diagnostic work-up is of particular importance in subpopulations of patients prone to rapid deterioration. For example, clinical presentation with pericardial or pleural effusion and brain metastases is frequent in patients with *ALK*-rearranged lung cancer (63). Specific clinical and imaging features of these patients help in their selection for molecular testing (64). Patients with rare driver mutations may be subjected to numerous clinical trials investigating new molecules. The participation in a clinical trial should be considered at early phases of the diagnostic process, to avoid discouraging patients due to treatment delay. An attractive option of molecular profiling is a liquid biopsy. This procedure is particularly useful in patients with scarce tumour tissue and in those with contraindications for invasive diagnostics (65).

Effectiveness of MDT

Most national and international guidelines recommend MDT based management of lung cancer, and this approach is currently widely implemented. However, the evidence of its efficacy in advanced lung cancer is scarce. In the majority of published lung cancer series, the number of patients with advanced disease and poor PS presented to MDT has been relatively low. No randomised studies have been performed to investigate the impact of MDT care on OS and QoL, and the results of retrospective series are inconsistent. In the Boxer et al.'s study (66) including 70% stage III and IV lung cancers, MDT care allowed for the delivery of more treatment but did not improve OS. In turn, other studies showed improved OS in NSCLC patients managed with MDT care (67-69). For example, in a retrospective study from Texas including 70% of advanced lung cancer cases, MDT decisions increased the median OS and progression-free survival by 8 and 5 months, respectively (69). In another retrospective series including various lung

cancer stages, 5-year OS rates were higher among patients managed by MDT in the entire study group ($P<0.001$), in stage III (19.3% *vs.* 9%, $P<0.001$) and stage IV (7.1% *vs.* 3.1%, $P<0.001$) (11). In the Taiwanese study OS in stage III and IV patients managed with MDT was significantly longer compared to non-MDT managed patients (adjusted HR 0.87, 95% CI, 0.84–0.90) (11). In the Australian single-institution retrospective study, MDT management resulted in improved 1-, 2- and 5-year OS rates among advanced lung cancer patients (13).

Even though OS was not improved in some studies, MDT meetings resulted in better uptake of the intended treatment (66), and in better scoring of stage and PS (10,13,66).

Quality of MDT

MDT care requires strict guidelines including frequency of meetings, staff requirements, data collection, documentation and description of care coordination, and communication between healthcare professionals and patients. The quality of MDT necessitates regular assessment. All MDT decisions should be collected and their accuracy monitored. The diagnostic and treatment plan developed by MDT should be circulated to team members and presented to the patient. The reasons for not following MDT decisions should be recognised. Some patients do not follow these decisions due to insurance and social issues. Other reasons can be deterioration of patient general health, comorbidities and treatment toxicity. These situations should be captured and subjected to analysis. Assessment should also include time to final diagnosis and staging, time to MDT presentation, and time to starting treatment. Quality of data presented at the MDT meeting should be assessed, areas for improvement identified and corrective measures implemented. Quality of MDT decision-making is dependent on the quality of diagnostic radiology and pathology, accurate data collection, documentation of consensus and the decision-making process, and effective communication between patients and healthcare providers (70).

A good indicator of the care efficacy are failure rates to achieve prompt MDT treatment decisions. In a Swedish study including various malignancies, the main causes of delayed MDT treatment decisions were the need for further investigations and insufficient pathology (71). In retrospective studies up to 16% of patients failed the MDT treatment recommendations, mainly due to deterioration of PS or the patient's decision (72,73).

Conclusions

The majority of lung cancers are diagnosed in advanced, incurable stages, resulting in generally poor treatment outcomes. New treatment modalities and novel agents have increased survival in selected lung cancer populations, but there is still a sore need for further improvements. MDT care allows for better and prompter designing of the patient's diagnostic and therapeutic path. Owing to the complexity of the diagnostic process and the high prevalence of patients with poor PS, comorbidities and disease-related symptoms, MDT care should be implemented early to allow for the introduction of adequate diagnostic and staging procedures, molecular tests and specialist care. Coordinated diagnostics avoids unnecessary and redundant procedures, thus decreasing its costs. Proper assessment of PS and the early implementation of coordinated management including palliative care may increase adherence to MDT recommendations. The quality of MDT has to be monitored to achieve further improvement.

The value of MDT care in advanced lung cancer and its clinical effectiveness are generally based on observational studies. The assessment of the real impact of MDT care on treatment outcomes is difficult due to parallel implementation of new effective therapies, such as tyrosine-kinase inhibitors or immune checkpoint inhibitors. Future prospective studies are warranted to elucidate these questions and to optimise MDT care in this particularly demanding population of patients.

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