Palliative care in lung cancer: tumour- and treatment-related complications in lung cancer and their management

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Holistic, patient-centred palliative care in lung cancer patients is necessary, with systematic monitoring of patients' symptoms/needs using patient-reported outcomes to improve optimal management of symptoms, quality of life and potentially survival https://bit.ly/3Xa6v5V

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Abstract

Palliative care pertains to the holistic multidimensional concept of "patient-centred" care. It is an interprofessional specialty, primarily aiming to improve quality of care for cancer patients and their families, from the time of diagnosis of malignant disease, over the continuum of cancer care, and extending after the patient's death to the period of bereavement to support the patient's family. There are various complex and frequently unmet needs of lung cancer patients and their families/caregivers, not only physical but also psychological, social, spiritual and cultural. Systematic monitoring of patients' symptoms using validated questionnaires and patient-reported outcomes (PROs), on a regular basis, is highly encouraged and recommended in recent guidelines on the role of PRO measures in the continuum of cancer clinical care. It improves patient–physician communication, physician awareness of symptoms, symptom control, patient satisfaction, health-related quality of life and cost-effectiveness. This implies that all treating physicians should improve their skills in communication with lung cancer patients/relatives and become more familiar with this multidimensional assessment, repeatedly screening patients for palliative care needs. Therefore, they should receive education and training to develop palliative care knowledge, skills and attitudes. This review is dedicated to lung cancer palliative care essentials that should be within the competences of treating physicians, *i.e.* pneumologists/thoracic oncologists.

Educational aims

- To become familiar with the principles of holistic patient-centred aspects of palliative care in lung cancer, as well as the necessary communication skills and use of validated questionnaires and patient-reported outcome measures.
- To improve knowledge and skills for optimal management of disease symptoms and treatment-related side-effects.

Introduction

The generally accepted World Health Organization (WHO) definition of palliative care (PC) is "an approach that improves the quality of life (QoL) of patients and their families who are facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual" [1]. PC has evolved over the past five decades into a well-established holistic multidimensional concept of care based on interprofessional specialty, with a multidisciplinary PC team, to primarily improve QoL and quality of care for cancer patients and their families. The team may include

psychologists, occupational therapists, social workers, physiotherapists, dietitians, pharmacists and other medical specialists, as well as administrative staff, chaplains and volunteers. PC includes the time from the diagnosis of malignant disease, over the continuum of cancer care, and extends after the patient's death to the period of bereavement to support the patient's family (figure 1). Dame Cicely Saunders established the "total pain" concept, encompassing all four causative dimensions (physical, psychological, social and spiritual), with the need for each of these to be adequately assessed and treated [3, 4].

QoL evaluation, defined as the patient's perception of the physical, psychological and social impact of cancer and its treatment, has a central role, together with the classic end-points of efficacy and safety, in assessing the objective value of a treatment and its potential risks and benefits. Patients with lung cancer are heavily burdened by symptoms of the cancer and the treatment, and psychological distress. The widely recognised randomised controlled trial by Temel *et al.* [5] demonstrated that early and prospectively planned PC for metastatic nonsmall cell lung cancer patients led to significant improvements, not only in QoL and mood, with a reduction of depressive symptoms, but also, surprisingly, in prolonged median overall survival, this despite a less aggressive therapy at the end of life, compared to patients treated with standard oncological therapy alone [5–7]. Findings such as these have prompted the development of a range of guidelines on palliative cancer care [3, 6, 7], respecting crucial domains of PC: structure and processes of care, physical aspects of care, psychological and psychiatric, social as well as spiritual/existential, cultural and religious aspects of care, end-of-life care, and important ethical and legal aspects of care. Essential components of PC should include several aspects: building relationships with patients and family caregivers, managing symptoms, functional status and distress, and exploration of understanding and education about illness and prognosis, clarification of treatment goals, assessment and support for coping needs, patients' early involvement in the treatment decision-making, coordination with other care providers, and provision of referrals to other care providers as indicated [3, 5–8]. The treating physician/oncology team should screen a cancer patient repeatedly from initial diagnosis over the course of disease for important domains of PC needs, such as uncontrolled symptoms, particularly cancer pain (the fifth vital sign) or distress (the sixth vital sign), complex psychosocial needs, poor prognostic awareness, and to discuss an advanced "living" will or a patient's request for hastened death [3, 5, 7–9].

Among the pivotal objectives of comprehensive multidimensional assessment are that all PC should be initiated by the primary oncology team, then enhanced by collaboration with PC experts, and importantly that all healthcare professionals should receive education and training to develop PC knowledge, skills and attitudes [3].

Patient-reported outcomes (PROs), as validated assessment tools, have the central role in the holistic patient-centred concept of PC [3, 5, 6, 10]. A number of studies has shown that clinicians miss about half of their patients' symptoms during cancer treatment [8]. The consequences include patient suffering due to poor symptom control, missed treatments, emergency room visits and hospitalisations, and physical deterioration. Systematic monitoring of patients' symptoms using PROs on a regular basis during treatment improves patient–physician communication, physician awareness of symptoms, symptom control, patient satisfaction, health-related QoL and cost-effectiveness. Assessment and integrating PROs into routine care is recommended; moreover, it has shown significant impact on overall survival as well [11, 12]. Validated symptom questionnaires have been developed, and among them the most commonly used is the Edmonton Symptom Assessment System (ESAS) [3, 11, 12]. Based on evidenced benefit, digital symptom monitoring with PROs in routine clinical care during systemic cancer treatment is recommended [12].

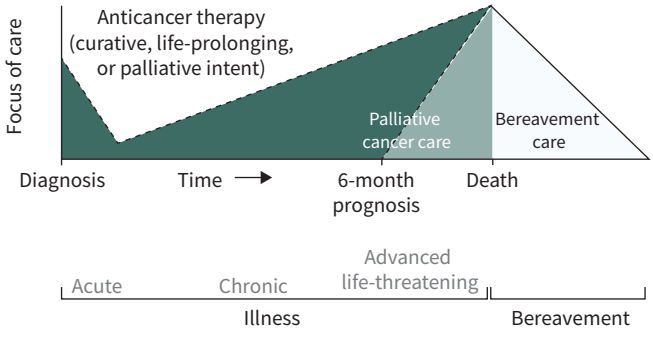

FIGURE 1 Model of palliative cancer care. Reproduced from [2] with permission.

Challenges include unavoidable changes to clinical practice to register patient responses and readily answer any electronic alerts for deteriorating symptoms.

Assessment of coping strategies and spiritual resources is of utmost importance in PC. The evidence shows that most patients want to know the truth and cope better if they are supported through open discussion on their difficult situations, at the same time with respect for ethical principles relevant to PC. The treating physician should be able to understand what matters most to patients/families, to respond to emotions and to discuss the possible outcomes, giving them realistic hope. In order to help patients/families/caregivers to cope with the transition over the disease trajectory, from the early stages to the very end of life, advance care planning should be used. The treating physician should foster prognostic awareness and facilitate advance care planning/end-of-life decision-making with regular review of patients'/families' preferences [3]. "Advanced directives" (an "advanced will") should be openly discussed at different time-points in the continuum of disease, repeatedly, so that patients may express and/or change their preferences about end-of-life care ahead of time. Thus, effective communication, based on empathy, with both patients and relatives, is essential in PC; however, it requires specific skills. For this purpose, stepwise approaches such as the SPIKES protocol have been developed [13] (supplementary table S1).

Given the complexity of various frequently unmet needs of lung cancer patients, not only physical but also psychological, social, spiritual and cultural, it is of utmost importance that treating respiratory physicians improve their skills in communication with lung cancer patients, their relatives and among themselves, become more familiar with this multidimensional assessment, repeatedly screening patients for PC needs, as well receive education and training to develop PC knowledge, skills and attitudes. This review is therefore particularly dedicated to PC essentials in lung cancer patients that should be within the competences of treating physicians, *i.e.* pneumologists and thoracic oncologists. We focus in particular on disease- and treatment-related problems and their management.

Respiratory problems

Dyspnoea

Dyspnoea is one of the most frequent and distressing symptoms in lung cancer. It has major impact on the QoL of the patient, family and caregivers. Its prevalence is up to 74% in advanced stages, increasing in the terminal phase (up to 80–90%) [14]. The differentiation between continuous, episodic, breakthrough or crisis breathlessness, as well as the evaluation of onset, exacerbating and relieving factors, are of utmost importance in order to adjust therapy appropriately, which can involve disease-modifying, causative and symptomatic treatment options. Dyspnoea often leads to severe anxiety but severe anxiety can cause dyspnoea as well; thus, the psychosocial dimension and environmental conditions often play a major role in the clinical condition. This is why routine screening for dyspnoea is very important, and since dyspnoea is completely subjective in perception, the most valid assessment tool is the PRO addressing the multidimensional and multifactorial nature of dyspnoea [14].

The key point is to identify and treat reversible causes according to their pathophysiology mechanisms, if possible, in different situations such as central airway obstruction, pleural/pericardial effusion, superior vena cava syndrome, COPD and anaemia. Grading of dyspnoea severity is essential for decisions on symptomatic treatment.

The multidisciplinary approach to dyspnoea aims to minimise the development, intensity, perception and impact of dyspnoea. Regular, oral, low-dose morphine is the first-line pharmacological therapy for severe chronic dyspnoea. In opioid-naïve patients, a starting daily dose may be 10–30 mg over 24 h, with individual titration depending on the patient's symptoms. In opioid-tolerant patients, an increase in the baseline dose of opioid by 25–50% may be considered. If there are defined triggers leading to significant functional impairment and/or distress despite standard treatment, prophylactic use of opioids prior to the episodes is justified, although only with close monitoring. All patients taking opioids should be offered prophylaxis for constipation with laxatives and, as needed, anti-emetics. Benzodiazepines should not be used for breathlessness as first-line pharmacological therapy because of significant risk of sedation and delirium. They may be used with caution for the relief of breathlessness with associated anxiety if opioids are not effective, and may be considered for palliative sedation in the last days of life. Diverse non-pharmacological procedures may significantly contribute to alleviating dyspnoea [14].

Steroids have proved to be effective in dyspnoea caused by lymphangiosis carcinomatosa, radiation pneumonitis, superior vena cava syndrome or an inflammatory component, and in (cancer-induced) obstruction of the airways. Oxygen therapy is not recommended in patients with resting peripheral oxygen

saturation (S_{pO_2}) ⩾90%, whereas high-flow oxygen may be considered in selected patients, especially if they have hypoxaemic respiratory failure (figure 2) [14].

Pulmonary treatment-related toxicity

Pulmonary treatment-related toxicity with dyspnoea as the key symptom is a very important issue in lung cancer patients. It ranges from asymptomatic mild pneumonitis to a very serious condition with respiratory compromise requiring prompt hospitalisation and urgent therapeutic procedures. Smoking, COPD and pre-existing interstitial pneumonia are important patient risk factors. Different levels of pulmonary toxicity can be seen with different combinations of systemic agents (epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), immunotherapeutic agents and cytotoxic agents), as well as when these are combined with radiation therapy, whereas radiation therapy applied as the only treatment modality induces fibrosis in up to 15% of cases [15–17] (supplementary table S2).

Therefore, particular attention should be paid to some other pre-existing diseases as well as comorbidities, as these often require dose adjustments, for example reduction in the first cycle of chemotherapy and targeted therapy to prevent increased treatment-related toxicity risk, especially pneumonitis. An algorithm for management of immune-related pulmonary toxicity is shown in figure 3.

Cough

Cough is the most common symptom in lung cancer patients, either dry or productive, but is often undertreated. Validated objective and subjective cough assessment tools to evaluate severity of cough and monitor treatment, such as the Visual Analogue Scale (VAS) and the Manchester Cough in Lung Cancer (MCLC) scale, may be used to treat cough appropriately (supplementary table S3).

Haemoptysis

Although a less common symptom of lung cancer (up to 20%), either at diagnosis or, more often, during the disease course (supplementary table S4a), if massive, haemoptysis is a life-threatening, emergency situation (see the later section of this article on emergency situations) [18].

Tracheo-/broncho-oesophageal fistula

A tracheo-/broncho-oesophageal fistula is a rare complication of lung cancer caused by lung tumour infiltration of the oesophagus wall with subsequent fistula (direct communication between the airway and oesophagus). It may be treatment related, primarily by radiation treatment. It should be suspected in lung cancer patients who develop coughing spells with oral intake (Ono's sign) and have occasional haemoptysis. Treatment is mostly palliative and depends on the location of the fistula, the severity of the symptoms, the associated complications, and the performance status of the patients (supplementary table S4b).

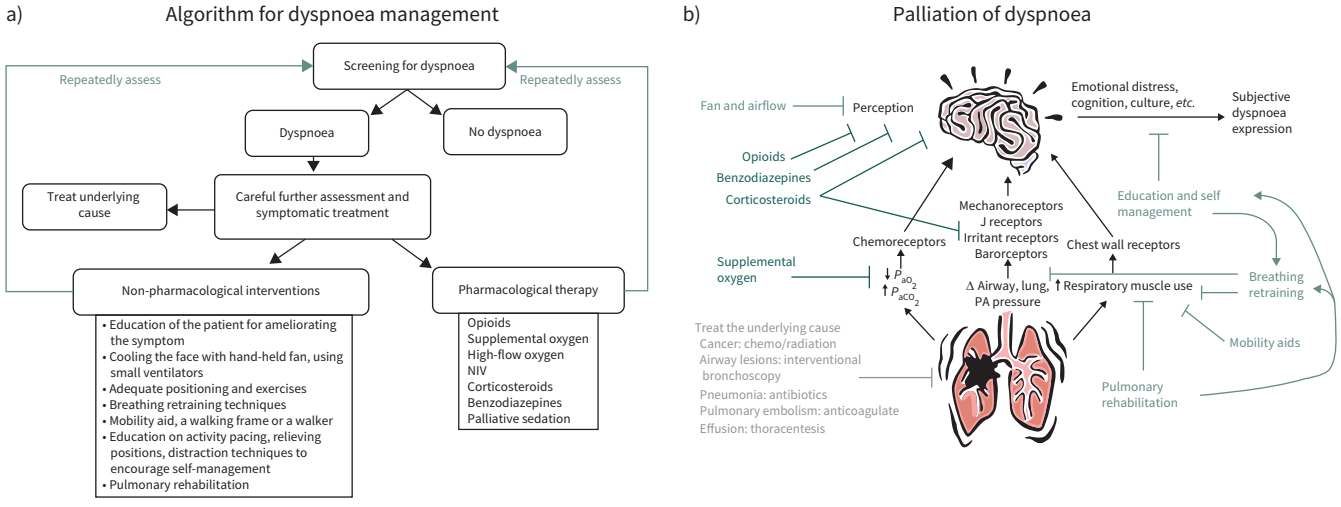

FIGURE 2 a) Algorithm for dyspnoea management. Adapted from [14]. b) Palliation of dyspnoea. Courtesy of David Hui (Department of Palliative Care and Rehabilitation Medicine, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA). NIV: noninvasive ventilation; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; PA: pulmonary artery.

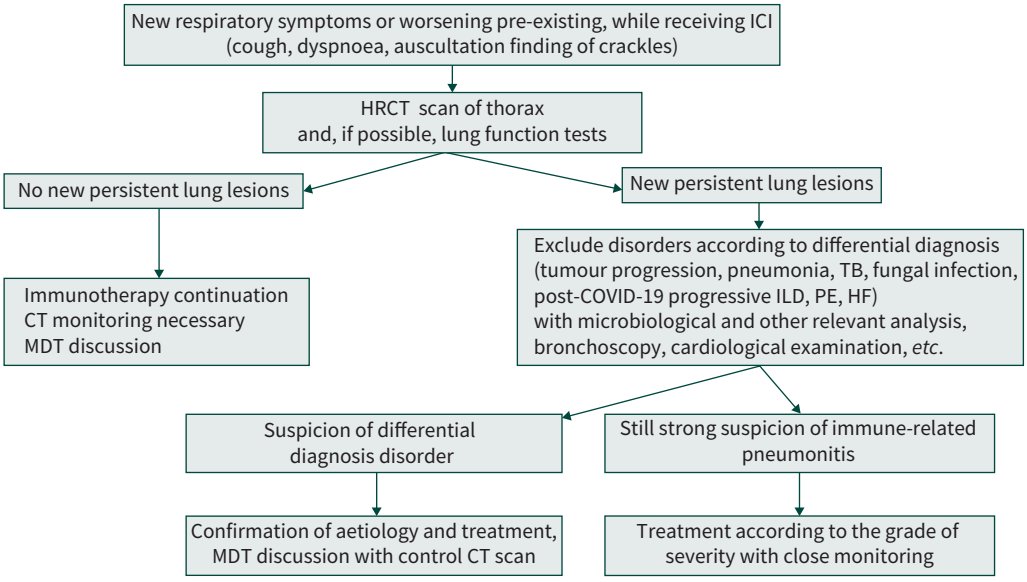

FIGURE 3 Algorithm for management of immune-related pulmonary toxicity. ICI: immune-checkpoint inhibitors; HRCT: high-resolution computed tomography; CT: computed tomography; MDT: multidisciplinary team; TB: tuberculosis; COVID-19: coronavirus disease 2019; ILD: interstitial lung disease; PE: pulmonary embolism; HF: heart failure. Reproduced and modified from [15] with permission.

Cancer pain

Pain in a lung cancer patient is multifactorial (as described in the "total pain" concept), and its different characteristics may suggest its mechanism and aetiology; however, it is often untreated [19–21]. While the nociceptive type of pain is predominant, encompassing somatic pain (sudden onset; well localised and sharp; throbbing or pressure) and visceral pain (difficult to localise; starts slowly in organs or viscera; often described as cramping, gnawing or burning), neuropathic pain, which is caused by nerve damage (burning, stabbing, tingling or prickling), is observed in 30–40% of lung cancer patients with pain. However, mixed pain is the most frequent (supplementary table S5a and b) [19–23].

The neuropathic component of cancer pain is not always fully known, only in 40–50% of cases. "Standard" cancer neuropathic pain is related to direct nerve invasion/damage and to paraneoplastic neuropathies, whereas the "new" type of cancer neuropathic pain is related to post-chemotherapy pain (axon degeneration or demyelination) and bone metastasis pain, which has both inflammatory and neuropathic components.

Initial evaluation pertains to comprehensive assessment of causes of pain, the onset, description of the pain quality, type, site and spreading, its duration, intensity, relief and temporal patterns of the pain, number of breakthrough pains (temporary worsening of pain that occurs spontaneously or in connection with some trigger, predictable or not, in a patient who has relatively stable and adequately controlled basic pain), pain syndrome, pain at rest and/or while moving, presence of trigger or relieving factors, psychosocial factors, detailed medical history and precise data on use of analgesics and their efficacy and tolerability [19, 20]. The intensity of cancer pain is assessed with validated scales [19].

Treatment

Patient education and active participation in the management process are important aspects in the treatment approach for cancer pain, and patients/family/caregivers should be informed about possible side-effects. The basic principles of drug administration for cancer pain are "by the mouth" (the oral route is preferred whenever possible), "by the clock" (at regular intervals, preventive, not only if necessary), "by the WHO pain ladder" (three steps for treatment of cancer pain by its intensity (mild, moderate and severe/persistent pain)) and "by the individual" (individual approach, paying attention to details).

Analgesic treatment should be initiated according to the severity of pain, assessed by the patient using validated scales for cancer pain, but taking into account the patient's performance status and known

comorbidities as well as the pharmacokinetics of the drugs. Adequate and effective analgesia is crucial for the patient's QoL, as well as that of the family/caregivers, and reduces hospitalisations and possible opioid misuse/abuse. Therapy should be accompanied by psychosocial support, skills training, performing cognitive, physical or interventional modalities, and spiritual support [19, 22–24].

Non-opioid analgesics are recommended for mild pain. Nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol (also known as acetaminophen) and dipyrone may be prescribed while monitoring possible toxicity carefully. Paracetamol-related liver toxicity is increased when used with opioids, whereas patients using NSAIDs should be monitored carefully for gastrointestinal, haematological or renal toxicities. Cardiovascular side-effects may be increased when used together with chemotherapy. In cases of contraindication of non-opioid pain-relieving drugs, or if complications develop during treatment, low-dose opioids may be alternative analgesics (moving one step up the "analgesic ladder") (figure 4).

For mild to moderate pain (step 2), weak μ-opioid receptor agonist opioids (hydrocodone, codeine and tramadol) are widely preferred analgesics, starting with the lowest oral dose that controls the pain [19, 22–24]. Provided that liver and renal functions are normal, the starting dose of tramadol may be 100 mg, and further increased up to a maximum daily dose of 400 mg. In elderly patients (age ⩾75 years), lower treatment doses are necessary, with a starting dose of 50 mg. Headaches, constipation, feeling dizzy and risk of serotoninergic syndrome are the most common side-effects. Low-dose strong opioids can be an alternative [19, 23] (figure 4).

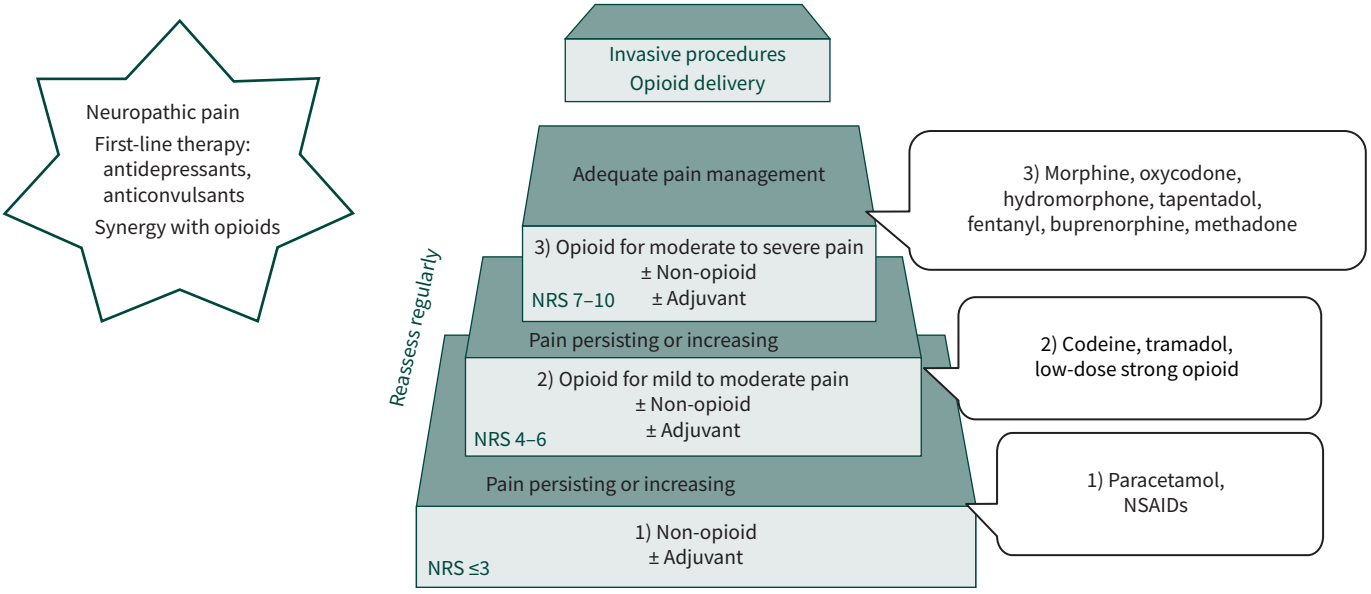

FIGURE 4 Management of cancer pain, based on the World Health Organization pain ladder, with pain scores indicated by the Numerical Rating Scale (NRS). NSAIDs: nonsteroidal anti-inflammatory drug. When it is necessary to switch treatment up to step 3 in a patient in follow-up, this should be started with short-acting oral morphine. The titration of short-acting oral morphine dose is necessary; it should be administered at short intervals, commonly 4–6 times a day (every 4 h, usually 10 mg per interval with total daily dose of 60 mg), increasing the interval dose gradually until pain is under control with only up to 3–4 times per day breakthrough pain. Once this titration process completed, a long-acting drug should be introduced instead in the equianalgesic dose. Immediate or modified/slow-release drugs such as hydromorphone or oxymorphone are preferable alternatives to morphine. Transdermal fentanyl and buprenorphine are widely used alternatives using a noninvasive route, for patients with renal dysfunction or those unable to take drugs orally. In case of severe pain, the parenteral route may be preferred, to relieve pain quickly. Reassessment of pain and treatment is needed on regular basis, pain most commonly by NRS. Additional interventions may be needed, as follows: 1) different adjuvant medications related to specific situations, such as bisphosphonates or denosumab (in bone metastases), corticosteroids (mandatory in some situations such as brain metastasis oedema), antidepressants or anticonvulsants (as the first-line therapy for neuropathic pain, exhibiting synergy with opioids); 2) supportive interventions, such as psychosocial counselling or physical therapy (rehabilitation, relaxation, spiritual support, hypnosis or nutrition); 3) interventional procedures, such as radiotherapy, neurolytic block or neuraxial drug delivery, surgery, cementoplasty or stoma placement; and 4) symptom control (as appropriate). In cases of persisting moderate/strong pain despite opioid rotation and all (non)pharmacological therapy, invasive interventions should be considered. Information from [23].

For severe and persistent pain, therapy comprises strong opioids such as morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone and oxymorphone, according to the availability in the country [19, 25] (supplementary table S6).

In patients unable to receive opioids by oral or transdermal routes, the subcutaneous route is simple and effective, but intravenous infusion should be considered when subcutaneous administration is contraindicated; intravenous infusion is also an option for opioid titration when rapid pain control is needed. In patients with chronic kidney disease (estimated glomerular filtration rate $\leqslant 30\ mL \cdot min^{-1}$), fentanyl and buprenorphine *via* the transdermal route or intravenously are the safest opioids of choice. Analgesics and adjuvants can be applied in combination if necessary. For breakthrough pain, rescue medication can be given up to 20% of the total daily opioid dose. Immediate-release opioids like oral/subcutaneous morphine or transmucosal fentanyl formulations can be prescribed [19, 23] (figure 4 and supplementary figure S1).

Adverse effects

Adverse effects from opioid therapy are numerous and include bowel dysfunction (*e.g.* constipation, bloating, incomplete evacuation and increased gastric reflux), nausea, vomiting, pruritus, respiratory depression and central nervous system toxicities (drowsiness, cognitive impairment, confusion, hallucinations, myoclonic jerks and, rarely, opioid-induced hyperalgesia). Adverse effects should be carefully assessed and adequate approaches made. Reducing the opioid dose or opioid rotation may diminish the incidence and/or severity of adverse effects.

In cases of unacceptable/persistent adverse events, toxicity, or insufficient analgesic effect, opioid rotation is the solution: switching one opioid to another. When switching one opioid to another, or in cases of changes in administration route (*e.g.* oral to parenteral), an equivalent dose scheme must be used according to guidelines [26].

Neuropathic pain

Neuropathic pain is a result of damage to the central or peripheral nervous system due to tumour- or treatment-related factors (chemotherapy, targeted or immunotherapy, radiotherapy or surgery) [21, 26]. Peripheral-type neuropathy is more common, and it may present as radiculopathy, plexopathy, mono-neuropathy or peripheral neuropathy. Radiculopathy is caused by compression of a vertebral metastasis to the nerve root. Superior sulcus tumours and radiotherapy-related secondary nerve damage are well-known causes of malignant brachial plexopathy [21, 22]. Paraneoplastic peripheral neuropathy is a different type of neuropathic pain, considered to be due to autoimmune inflammatory mechanisms or toxic metabolic substances damaging the dorsal root ganglion, and most commonly associated with small cell lung cancer [26]. The main symptoms are usually burning, tingling, paraesthesia and glove-and-stocking-type sensory loss in advanced cases.

Patients with neuropathic pain should be given either a tricyclic antidepressant or an anticonvulsant, and be monitored for side-effects. Gabapentin, pregabalin, duloxetine and tricyclic antidepressant (doses $\leqslant 75\ mg \cdot day^{-1}$) are strongly recommended as single agents for first-line treatment of neuropathic pain [19, 22, 24, 25]. Opioids may be combined with pregabalin or with gabapentin because of their additive or synergistic effects. Dexamethasone is recommended, but starting dose varies by clinical situation (*i.v.* or *p.o.*), standard dose being $4–16\ mg \cdot day^{-1}$. Interventional procedures should be restricted to patients with neuropathic pain syndromes that cannot be managed with pharmacological therapy only [19, 24].

Chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (axon degeneration or demyelination) has a particular significance for QoL, especially for survivors. In lung cancer it is most frequently induced by cisplatin (grade 3–4 toxicity in 2% of patients), is dose dependent, and in the majority of cases has more severe symptoms when induced by cisplatin than when induced by taxanes and vinca alcaloids. It occurs after cumulative dosage of $\geqslant 300\ mg \cdot m^{-2}$, and when doses reach $500–600\ mg \cdot m^{-2}$ almost every patient faces neuropathy symptoms. Grading of peripheral neuropathy is necessary for decision making [19, 24]. There is only symptomatic treatment and the recovery is partial. First-line treatment is administration of one of the co-analgesic drugs for (peripheral) neuropathic pain, often combined with opioids for their synergistic or additive effects [19, 24].

Bone metastasis

Bone metastasis has great impact on QoL, as it leads to many skeletal-related complications, not only pain, particularly when of lytic type. Clinicians should be aware of oncological emergencies such as fracture of

weight-bearing bones, compression fracture of the vertebral corpus and spinal cord compression, which cause significant morbidity, loss of autonomy and reduced QoL in lung cancer patients [3, 7, 20, 27]. Bone metastasis pain has two components, neuropathic and inflammatory [27].

As well as appropriate analgesic therapy prescribed according to the intensity of pain, bone-modifying agents (bisphosphonates or denosumab), radiotherapy (external beam radiotherapy single-shot 8-Gy or stereotactic body radiotherapy) or a surgical approach, if necessary, should be considered. Bone-modifying agents are given in addition to offering opioids and adjuvant medications such as NSAIDs and gabapentin or pregabalin, as tolerated [19, 22].

Haematological disorders/toxicity

Chronic anaemia, low haemoglobin and/or low serum iron levels are frequent in lung cancer, but most cases of haematological disorders of different grades are chemotherapy-induced (supplementary table S7). Chemotherapy adverse effects are most commonly haematological. With cisplatin-based chemotherapy, typically up to 30% of patients experience grade 3–4 toxicity, with the most frequent type being haematological (in 14%), requiring a modification or delay of therapy.

Chemotherapy-induced anaemia and iron deficiency

The major aim of management of anaemia (haemoglobin <12 $g \cdot dL^{-1}$) is improvement of the symptoms, especially fatigue, and of QoL. Baseline assessments of haemoglobin, iron status (measuring transferrin saturation and serum ferritin) and C-reactive protein are necessary prior to any chemotherapy cycle (supplementary table S8a).

Neutropenia

Neutropenia is caused by radiation and chemotherapy, and can lead to severe bacterial, fungal and viral infections (including sepsis and septic shock) (supplementary table S8b).

Thrombocytopenia

Thrombocytopenia, a potentially life-threatening situation if there is major bleeding, is most commonly caused by chemotherapy. Supportive transfusion therapies using platelet concentrates, fresh frozen plasma and plasma-derived or recombinant concentrates may be applied in cases of severe thrombocytopenia with bleeding episodes, if acute and as prevention (supplementary table S8c).

Gastrointestinal problems

Anorexia and cachexia

Cancer-related cachexia is characterised by physical wasting with loss of muscle mass and adipose tissue, and it is closely related to anorexia. Possible causes and contributing factors in lung cancer patients may include anorexia, disease progression, increased treatment toxicity, delayed start of treatment, early treatment termination and psychosocial distress. The treatment of cancer cachexia needs a comprehensive approach (supplementary table S9).

Oesophagitis

Oesophagitis, if acute and caused by thoracic radiotherapy, is treated symptomatically. Occasionally, stopping radiotherapy may be required due to severe symptoms, but this should be avoided as much as possible as it may reduce therapeutic efficacy. Management includes topical anaesthetics (viscous lidocaine-based formulations), analgesics (anti-inflammatory agents, paracetamol or narcotics), coating agents (sucralfate), antisecretory proton pump inhibitors or histamine type 2 receptor blockers, and dietary adjustments (more frequent meals, avoiding alcohol, tobacco, caffeine, extremely hot or cold foods, spicy or acidic, or indigestible foods).

Nausea and vomiting

Nausea and vomiting are most frequently treatment related, induced by chemotherapy and radiation. Three distinct types of chemotherapy-induced nausea and vomiting (CINV) have been defined: acute, delayed and anticipatory emesis. Chemotherapy agents are categorised into four classes based on their emetogenicity [28, 29]. Management of CINV and radiotherapy-induced emesis should follow the 2023 Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO) guideline update [29] (supplementary tables S10 and S11). For anticipatory emesis, the primary approach is the prevention of CINV beginning with the initial cycles, and behavioural therapy and/or just benzodiazepines are suggested [28, 29]. For breakthrough emesis, olanzapine 10 mg is effective and tolerable as a rescue anti-emetic in patients who did not receive it as part of the primary anti-emetic prophylaxis [28, 29].

Diarrhoea

Diarrhoea is a common adverse event in numerous cancer systemic treatments, caused by complex interacting mechanisms, but it can also be a side-effect of the cancer itself. Major pathogenetic mechanisms in cancer drug-induced diarrhoea may be secretory, osmotic, related to altered motility, inflammatory, or multimodal [30].

Agents causing diarrhoea are cytostatic drugs such as taxanes and cisplatin, targeted therapies such as EGFR TKIs, multi-TKIs, anti-VEGFR (vascular endothelial growth factor receptor) and ALK (anaplastic lymphoma kinase) inhibitors, and the immune checkpoint inhibitors anti-CTLA4 (cytotoxic T-lymphocyte associated protein 4) and anti-PD-L1/anti-PD-1 (programmed cell death ligand/protein 1). Around 50–80% of patients on systemic treatment may experience diarrhoea. The frequency, severity and causes of diarrhoea are different according to the agent used, and even when of mild intensity, it can have a long duration. Combination of treatments can worsen diarrhoea. Diarrhoea may cause dehydration, kidney failure, electrolyte imbalance, metabolic acidosis, malnutrition, fatigue or sleep disorders, and, although rarely, can even be life-threatening. Moreover, it leads to changes in treatment schedules, often dose reduction and treatment discontinuation [30] (supplementary table S12).

Renal problems

Chemotherapy agents, with cisplatin as one of the most nephrotoxic, are the most common cause of renal disorders, with a range of symptoms and signs, from an asymptomatic increase of serum creatinine and electrolyte imbalance to acute kidney damage that necessitates dialysis. With cisplatin-based chemotherapy, 1% of patients experience grade 3–4 renal toxicity.

Patients with pre-existing renal disease and those who have kidney damage need to be closely monitored during lung cancer treatment and have doses adjusted for some chemotherapy agents. Hydration is vital for any patient in order to avoid cisplatin-induced nephrotoxicity. Patients with a serum creatinine >1.5 $mg \cdot dL^{-1}$ (>133 $\mu mol \cdot L^{-1}$) or an estimated glomerular filtration rate <50 $mL \cdot min^{-1}$ per 1.73 m^2 are not recommended to take cisplatin [31].

Neurological complications

Brain metastasis

Brain metastasis is common in lung cancer, occurring in up to 40% of cases and leading to increased intracranial pressure with headaches, whereas generally symptoms depend on the tumour's location. Prompt recognition, diagnosis and treatment are crucial in preventing neurological deterioration. Diagnostic magnetic resonance imaging is preferred over computed tomography scanning.

Initial treatment of increased intracranial pressure focuses on symptomatic relief in the short-term, followed by definitive local treatment. Corticosteroids are routinely used to reduce cerebral oedema: dexamethasone is preferred, with an initial dose of 8–16 mg once or twice daily. Mannitol and hypertonic saline for osmotic diuresis are recommended over 3–4 days [32, 33].

The combination of radiation therapy and surgical resection is the preferred treatment of solitary metastasis. Surgery is also recommended for patients with large tumours with mass effect. Cases of multiple brain metastases and/or uncontrolled systemic disease are less likely to benefit from surgery unless the remaining disease is controllable *via* other measures, when radiation and systemic options are considered [33, 34]. For patients who will receive both radiation therapy and surgery, no recommendation regarding the specific sequence of therapy can be made [33] (supplementary table S13).

Spinal cord compression

Spinal cord compression is a medical emergency, caused by tumour spread to the vertebral column, with subsequent epidural extension, resulting in extrinsic compression. Direct leptomeningeal extension is less frequent. Pathological vertebral body fractures can directly compress the spinal cord, which may result in rapid loss of neurological function. The main treatment options include surgery, conventional or stereotactic radiotherapy and supportive measures [32, 35] (supplementary table S14).

Leptomeningeal metastasis

Leptomeningeal metastasis is one of the underdiagnosed complications of lung cancer associated with poor prognosis. It has been increasingly recognised in patients with otherwise well-controlled systemic disease, such as mutated EGFR- or ALK-rearranged nonsmall cell lung cancer controlled with EGFR/ALK inhibitors. Current treatment options for leptomeningeal metastasis are restricted to palliative whole-brain

radiotherapy, systemic therapy or symptomatic therapy only. High-dose oral osimertinib and afatinib in EGFR-positive nonsmall cell lung cancer may be efficient [32, 36, 37] (supplementary table S14).

Emergency situations in lung cancer

Oncological emergencies comprise a wide spectrum of profound disorders that can result from the tumour and its paraneoplastic syndromes (which are occasionally the initial manifestation of a previously undiagnosed malignancy) or from tumour progression; however, they can also be treatment related. Given these are life-threatening conditions, prompt recognition and an appropriate treatment approach are crucial, often affecting the outcomes and long-term prognosis.

Central airway obstruction

Central airway obstruction, either tracheal or bronchial, presents with symptoms that range from mild dyspnoea to emergency situations with stridor and severe respiratory compromise. Various bronchoscopic interventional procedures are used. The decision about systemic and radiation therapy should be discussed by a multidisciplinary team [38]. The intervention that is preferred/appropriate primarily depends on the type of major airway obstruction (tracheal or bronchial). Options may include stenting, laser therapy, cryotherapy, balloon bronchoplasty and mechanical debulking. Intubation, cricothyroidotomy or tracheotomy may occasionally be required to establish an emergency airway. Post-obstructive pneumonia requires broad-spectrum antibiotics.

Massive haemoptysis

Massive haemoptysis (blood loss >200 $mL \cdot day^{-1}$) requires an initial management focus on airway and haemodynamic stabilisation, as well as maintenance of oxygenation. Placing the patient in the lateral decubitus position with the affected lung down can prevent aspiration of blood into the unaffected lung. Bronchoscopy is an essential intervention for the management of life-threatening haemoptysis [18, 38, 39]. Bronchoscopic methods include topical and endobronchial therapies. Topical therapies that may be used are cold saline irrigation, epinephrine, vasopressin, thrombin-fibrinogen complex, tranexamic acid, and oxidised regenerated cellulose. Endobronchial treatment procedure options are diverse, *e.g.* Fogarty balloon tamponade, endobronchial blocker, silicone spigots, thermal ablative techniques (laser, argon plasma coagulation, cryotherapy) or double lumen endotracheal intubation.

Cardiac tamponade

Cardiac tamponade is a potentially fatal condition when pericardial effusion pressure compromises ventricular filling, resulting in the diastolic collapse of ventricles and reduced cardiac output. Despite interventions, the median survival time is, in the majority of cases, ⩽3 months. As it is a poor prognostic factor, therapy focuses primarily on relieving symptoms. Pericardiocentesis is usually the first step in the treatment. Once the patient is stabilised, further diagnostic and therapeutic management can be planned [40], for example including pericardiectomy with or without pericardial window, in selected cases with cytostatic instillation.

Massive pleural effusion

In cases of massive malignant pleural effusion (MPE), urgent thoracentesis with pleural fluid aspiration can be an appropriate first therapeutic procedure for effective symptom relief. It may be followed by serial thoracentesis to control MPE (at the cost of adhesion formation and loculations) for patients with limited survival expectancy (<1 month), and for patients with poor performance status who would not tolerate other drainage procedures. For most patients with longer life expectancy and good performance status whose symptomatic/massive MPE re-accumulates rapidly, current treatment options remain palliative, including chest tube and talc slurry, talc poudrage at thoracoscopy and indwelling pleural catheter with or without talc slurry [41].

Superior vena cava syndrome

Superior vena cava syndrome arises from partial or complete obstruction of the superior vena cava. The most common symptoms and signs of partial obstruction are face or neck swelling, upper extremity swelling, dyspnoea, cough, distended chest and neck veins, arm oedema, and aggravation by bending forward, whereas complete obstruction (which is less common) presents with plethora, severe dyspnoea, orthopnoea, cough, hoarseness, cyanosis, headache, vision changes, mental confusion, seizures, and even syncope. A grading system for severity of superior vena cava syndrome symptoms is used to determine the urgency of intervention, and appropriate imaging diagnostics lead to decisions on interventional procedures and/or diverse treatment options [42] (supplementary table S15).

Management of superior vena cava syndrome should include measures such as elevating the head to minimise venous congestion, minimising use of diuretics, use of *i.v.* corticosteroids to decrease extrinsic pressure on the superior vena cava, and administration of anticoagulants in cases with suspected thrombosis. Endovascular stenting is often the first step before further diagnostic procedures. Other treatment options include radiation therapy, systemic therapy (such as chemotherapy) and open surgery. Urgent thrombolysis, thrombectomy or placement of a venous stent may alleviate stridor, altered mental status and haemodynamic compromise, although vascular intervention risks luminal perforation. Fibrinolytic therapy can reduce the risk of thromboembolism. Urgent medical and radiation oncology consultation is mandatory to initiate appropriate systemic therapy in order to reduce tumour bulk.

Spinal cord compression

Spinal cord compression as a medical emergency should be suspected if there is acute sensory deficit, loss of bladder and/or bowel sphincter tone (constipation), perineal numbness or sudden inability to walk. These may suggest irreversible vascular injury and spinal cord infarction [32, 35]. Comprehensive neurological examination followed by total spine magnetic resonance imaging is the gold standard. For management, opiate pain control and dexamethasone 10 mg *i.v.* loading dose followed by 4 mg every 6 h are initiated, along with urgent neurosurgical and radiation oncology consultation. If surgery is not indicated, palliative stereotactic body radiotherapy of 16–24 Gy in one fraction or 24–30 Gy in three fractions is administered.

Syndrome of inappropriate antidiuretic hormone secretion

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is diagnosed if urine osmolarity is >100 mOsm and coincident with euvolaemic hypotonic hyponatraemia. Acute hyponatraemia is associated with headaches and neurocognitive slowing. Severe hyponatraemia can be associated with seizures and death. It must be distinguished from hypovolaemic hyponatraemia due to excessive gastrointestinal losses when urine osmolarity is >300 mOsm, but urine sodium <20 $mEq \cdot L^{-1}$ [43]. In the emergency department, management of symptomatic hyponatraemia requires 100 mL 3% normal saline bolus to acutely raise serum sodium by 2–3 $mEq \cdot L^{-1}$. The total increase of serum sodium should not exceed 4–6 $mEq \cdot L^{-1}$ in 24 h, to avoid central pontine myelinolysis. Free water restriction and sodium chloride tablets are preferred for correcting chronic hyponatraemia. Correction of hyponatraemia is usually necessary prior to initiating systemic therapy.

Ectopic adrenocorticotropic hormone syndrome

Ectopic adrenocorticotropic hormone (ACTH) syndrome may present as a hypertensive urgency/emergency. Additional key features are hypokalaemia and associated muscle weakness, with generalised oedema [43]. Acute management is needed for electrolyte disturbances and hypertensive crisis. Ketoconazole and metyrapone, which are agents that inhibit steroidogenesis, are often used.

Carcinoid syndrome

Carcinoid syndrome features sudden episodes of acute watery diarrhoea, flushing, bronchospasm, and hypotension from excess serotonin secretion. Findings include elevated urinary hydroxyindoleacetic acid, right heart valvular disease, niacin deficiency and hypoproteinaemia from preferential tryptophan diversion towards serotonin production [43]. Definitive therapy requires complete surgical resection of the tumour, if possible. When curative-intent surgery is not possible, systemic therapy may include long-acting somatostatin receptor inhibitors and systemic therapy (chemotherapy and biological agents). Antidiarrhoeals, bronchodilators and vasoconstrictors can provide acute symptomatic relief.

Self-evaluation questions

1. What is a starting daily dose of oral morphine in opioid-naïve patients suffering from severe dyspnoea in advanced stage lung cancer?
    a) 10–30 mg over 24 h, with individual titration depending on the patient's symptoms.
    b) 30–60 mg over 24 h, with individual titration depending on the patient's symptoms.
2. What is the first-line treatment of neuropathic pain in lung cancer patients?
    a) A tricyclic antidepressant (TCA) or a slow-releasing morphine drug, with monitoring for side-effects. Hydromorphone and TCA are strongly recommended as agents for first-line treatment of neuropathic pain.
    b) A TCA or an anticonvulsant, with monitoring for side-effects. Gabapentin, pregabalin, duloxetine and TCA are strongly recommended as single agents for first-line treatment of neuropathic pain.
    c) A TCA with a non-opioid, with monitoring for side-effects. Pregabalin or duloxetine and paracetamol are strongly recommended as agents for first-line treatment of neuropathic pain.

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Suggested answers

1. a.
2. b.