Pain control in thoracic oncology

Christine Peeters-Asdourian[1], Gilbert Massard[2], Paragi H. Rana[1], Paul Van Houtte[3], Andrew P. White[4], Bogdan Grigoriu[5], Dominique Lossignol[6], Mohammed Almalki[1], Jean Alexiou[7], Jean-Luc Engelholm[7] and Jean-Paul Sculier[5]

Number 8 in the series "Multidisciplinary questions in thoracic oncology: the team experience" Edited by J-P. Sculier

Affiliations: [1]Dept of Anaesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA. [2]Service de Chirurgie Thoracique, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg (UDS), EA 7293/Federation of Translational Medicine, Strasbourg, France. [3]Service de Radiothérapie, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Bruxelles, Belgium. [4]Dept of Orthopaedic Spine Surgery, Beth Israël Deaconess Medical Center, Harvard Medical School, Boston, MA, USA. [5]Service des soins intensifs et urgences oncologiques & Oncologie thoracique, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Bruxelles, Belgium. [6]Service de Médecine Interne, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Bruxelles, Belgium. [7]Service de Radiologie, Institut Jules Bordet, Université Libre de Bruxelles (ULB), Bruxelles, Belgium.

Correspondence: Christine Peeters-Asdourian, Dept of Anaesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Hospital, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA. E-mail: cpeeters@bidmc.harvard.edu

@ERSpublications
The availability of opioids and analgesic adjuvant medications is of great benefit in the management of cancer pain http://ow.ly/CgIF30e2UkY

Cite this article as: Peeters-Asdourian C, Massard G, Rana PH, *et al*. Pain control in thoracic oncology. *Eur Respir J* 2017; 50: 1700611 [https://doi.org/10.1183/13993003.00611-2017].

ABSTRACT This review of pain management in lung cancer is based on the presentation of four cases of thoracic oncology patients with pain at various stages of their disease. The approach will be multidisciplinary, involving a thoracic oncologist, radiologist, thoracic and orthopaedic spine surgeon, radiation therapist, pain medicine specialist, and palliative care specialist. This multispecialty approach to the management of different painful presentations in thoracic oncology will demonstrate the complexity of each case and the improved patient outcomes which result from the involvement of different disciplines working in concert.

In the USA, Europe and other countries, palliative care specialists often become rapidly involved in the management of these patients, coordinating social care and providing psychological support.

Thoracic and orthopaedic spine subspecialists provide surgical methods to control tumour invasion, and improve quality of life and preservation of function in settings of even diffuse metastatic disease. Similarly, thoracic oncology and radiation therapists utilise both therapeutic and palliative chemotherapeutic and radiation therapy regimens to prolong and improve quality of life.

The pain medicine specialist can, in addition to medication management, offer a variety of interventional approaches including unique drug delivery systems such as epidural analgesia, regional anaesthesia techniques, and intrathecal pumps, as well as neuromodulation techniques and neurolytic or neuroablative procedures.

In the USA, these specialists complete an additional fellowship year in pain medicine following the completion of an anaesthesiology, physical medicine and rehabilitation, neurology or psychiatry residency. These programmes are accredited by the Accreditation Council for Graduate Medical Education, or ACGME (www.acgme.org).

Introduction

Pain continues to be a very prevalent symptom too often undertreated in cancer patients at all stages of their disease. Pain is present in 59% of all patients undergoing cancer treatment, in 64% with advanced disease, and in 33% of patients after curative treatment [1].

A pan-European Survey of 12 countries designed to explore the burden of cancer pain and current pain practices across Europe shows that many patients, up to 25 to 30%, with moderate to severe pain receive no analgesics [2].

Various guidelines for managing pain have been introduced over the past 30 years, starting with the World Health Organization (WHO) "stepladder approach", which was introduced in 1986, updated in 1996, and is now almost universally accepted [3].

This three-tiered approach, based on non-opioid medications such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDS) at the first level and opioids with non-opioid adjuvants at the second and third levels, may be effective for a majority of patients, up to 80%, if used properly. Episodic or breakthrough pain remains problematic for many patients, though a recent study demonstrated an overall improvement in the quality of cancer pain management over the past 20 years [4].

Other methods such as regional anaesthesia, neuromodulation, neuroablative techniques, and alternative drug delivery systems should be considered in cases of recalcitrant pain.

Additional guidelines, including those from the National Comprehensive Cancer Network (NCCN guidelines version 2.2016), as well as recommendations from the European Association for Palliative Care (EAPC) [5] and the European Society for Medical Oncology (ESMO) [6, 7], are available and widely used. These are more detailed than the WHO guidelines, which are easily applicable even in areas with few healthcare resources.

The two primary mechanisms of pain in cancer patients are nociceptive and neuropathic [8].

Somatic nociceptive pain is usually well localised, often described as throbbing or sharp, and can occur after surgery or with bony metastasis. Visceral nociceptive pain is more diffuse, may be referred (*i.e.* pain in the shoulder from diaphragmatic irritation) and is described as aching or cramping. Pleural effusion is one of the most common causes of visceral nociceptive pain in the context of thoracic malignancy.

Neuropathic pain may be described as burning, prickling or shooting, and can often be associated with numbness. It is the result of injuries to the peripheral or central nervous system. In cancer patients, it may be due to tumour infiltration, may occur after radiation therapy, or be the result of chemotherapy-related toxicity. In thoracic oncology, neuropathic pain can be the result of nerve injuries during thoracoscopy or thoracotomy. These can have long-term implications for the patients.

Distinguishing the nature and mechanism of the pain has implications for its treatment (table 1).

Integrating supportive care early after the diagnosis of cancer and involving a multidisciplinary team may be of great benefit to the patients. In France, the *Société Française d'Accompagnement et de soins Palliatifs* (www.sfap.org) offers supportive care, social help and psychological services at the time of diagnosis. This approach may also be advantageous to patients reaching survivorship and to those who develop chronic pain issues [9].

Four common scenarios

1) Post-thoracotomy pain

A 55-year-old man with no significant past medical history presented initially with a lower respiratory tract infection. Chest radiography revealed a lung nodule measuring 26×13 mm. He had a sedentary job

Received: March 23 2017 | Accepted after revision: June 27 2017

Conflict of interest: None declared.

Previous articles in this series: No. 1: Malhotra J, Malvezzi M, Negri E, *et al*. Risk factors for lung cancer worldwide. *Eur Respir J* 2016; 48: 889–902. **No. 2:** McDonald F, De Waele M, Hendriks LEL, *et al*. Management of stage I and II nonsmall cell lung cancer. *Eur Respir J* 2017; 49: 1600764. **No. 3:** Leduc C, Antoni D, Charloux A, *et al*. Comorbidities in the management of patients with lung cancer. *Eur Respir J* 2017; 49: 1601721. **No. 4:** Zugazagoitia J, Molina-Pinelo S, Lopez-Rios F, *et al*. Biological therapies in nonsmall cell lung cancer. *Eur Respir J* 2017; 49: 1601520. **No. 5:** Calvayrac O, Pradines A, Pons E, *et al*. Molecular biomarkers for lung adenocarcinoma. *Eur Respir J* 2017; 49: 1601734. **No. 6:** Meert A-P, Grigoriu B, Licker M, *et al*. Intensive care in thoracic oncology. *Eur Respir J* 2017; 49: 1602189. **No. 7:** Glatzer M, Rittmeyer A, Müller J, *et al*. Treatment of limited disease small cell lung cancer: the multidisciplinary team. *Eur Respir J* 2017; 50: 1700422.

TABLE 1 Classification of pain in lung cancer

Type	Characteristics	Causes
Nociceptive (*via* activation of peripheral nociceptors)		
Somatic	Sharp well localised, arising from bones, muscles, skin May be associated with inflammation and/or infection	Tumour infiltration of muscle, fascia, bones, chest wall pain from rib lesion
Visceral	More diffuse, may result from hollow viscus distention May be referred, *i.e*. shoulder pain from diaphragmatic irritation or tumour infiltration, pleuritic pain causing sharp chest pain	Tumour infiltration of pleura Pleural effusion
Neuropathic (by a lesion of the somato-sensory nervous system)	Burning, tingling, prickling	Tumour infiltration of plexus and peripheral nerves due to chest wall mass, radiculopathy from vertebral lesions and post-surgical chronic pain syndrome following thoracoscopy, VATS or thoracotomy
Treatment-related pain		Painful diagnostic procedures and surgery Post-radiation plexopathies and/or osteonecrosis Long-term consequences of treatment: post thoracotomy, pain, chemotherapy-induced neuropathy Osteonecrosis from corticosteroids (femoral head) and bisphosphonates (mandible, femur)
Breakthrough pain	Episodic, lancinating, unpredictable Time to peak severity median 3 min Duration 30 min Average 4–7 episodes per day	Spontaneous or in response to known or unknown triggers Associated with patient care (mobilisation, physical therapy, incentive spirometry, procedures, dressing changes, positioning for radiation therapy) 55–60% End-of-dose pain

VATS: video-assisted thoracoscopic surgery.

without risk of occupational exposure to carcinogens. He started smoking one pack of cigarettes per day at age 20 years (35 pack-year history of tobacco exposure).

A chest computed tomography (CT) scan revealed a non-calcified spiculated nodule with pleural tags (figure 1).

A brain magnetic resonance image (MRI) was negative for metastases. Pulmonary function tests, haematological work-up, and liver function tests were all within normal range.

The lung nodule was positive on positron emission tomography (PET)/CT with a maximum standardized uptake value (SUVmax) of 5.4 at the level of the paratracheal nodes. The mediastinoscopy did not show any additional nodal involvement. The patient was offered a lobectomy *via* a traditional thoracotomy.

The patient requested a consultation to discuss what steps could be taken to minimise the risks of perioperative pain and the incidence of post-thoracotomy pain.

A thoracic surgeon's perspective (G. Massard)

The best that a surgeon can offer in order to reduce postoperative pain is to decrease operative trauma [10]. For this patient with presumably a cT1bN0 lung cancer, according to the American College of Chest Physicians (ACCP) guidelines for treatment of lung cancer, there is an obvious advantage to offering a video-assisted thoracoscopic surgery (VATS) approach with a grade II evidence [11]. The latter allows for an adequate cancer operation combining an anatomical resection (*i.e.* lobectomy) with a formal hilar and mediastinal node dissection, while incisions are reduced to stab wounds and use of a rib retractor is not required.

Several large data studies, including two systematic reviews [12, 13], two database studies from the USA and Europe [14, 15] and two meta-analyses [16, 17], concluded that VATS offers an advantage over thoracotomy in terms of significantly reducing complication rates, shortening hospital stay and enhancing recovery. The authors assume that reduced operative trauma and consequently reduced pain are the

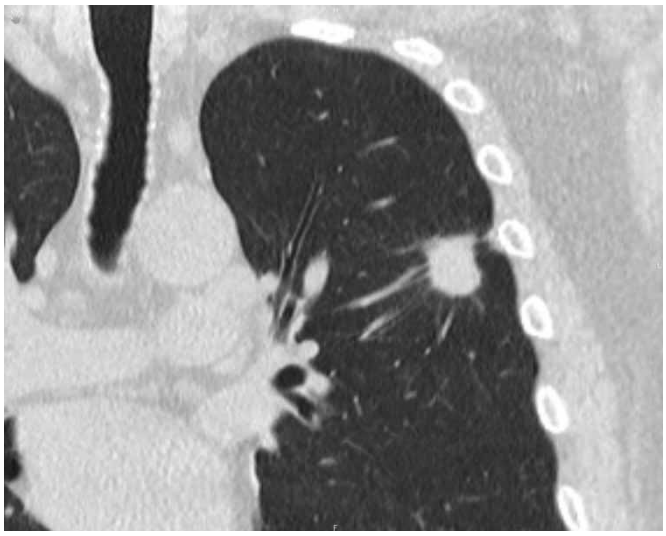

FIGURE 1 Chest computed tomography scan, coronal reconstruction: non-calcified spiculated nodule with pleural tags.

determining factors. A recently published randomised controlled trial by Bendixen *et al.* [18] which enrolled 206 patients confirms this assumption. Pain and self-reported quality of life during the first postoperative year were compared between the two groups, defined either by a four-port VATS approach or an anterolateral thoracotomy. The study demonstrated a statistically significant decrease in pain and an improved self-reported quality of life at different time points for up to 1 year in patients undergoing VATS *versus* anterolateral thoracotomy. The lower complication rate is confirmed in patients with disabled pulmonary function [19].

All these publications converge to the statement that VATS is a better surgical procedure for early-stage disease, and hence it appears unethical to proceed with an open thoracotomy. However, many colleagues remain reluctant to apply minimally invasive techniques; we may estimate from the French database Epithor that only 30% of eligible patients are operated by VATS (unpublished data).

A first series of questions concerns the oncologic value of minimally invasive procedures. These seem to be unfounded, because both anatomical resection and lymph node dissection can be safely and accurately performed [20, 21]. These assumptions have been swept away by two meta-analyses concluding similar overall long-term survival and disease-free survival [22]. In addition, a non-randomised study demonstrated that compliance to adjuvant chemotherapy is significantly improved with a VATS approach [23].

The second reason might be reluctance on the part of experienced consultant surgeons to change working habits and to learn a new technique, which still has the reputation of being complicated and subject to risk of intra-operative complications. However, there is evidence for a relatively short learning curve for experienced surgeons. The author's experience demonstrates that competence (*i.e.* confirmed oncologic quality) is acquired after 30 procedures, and efficacy (*i.e.* decreased operating time, conversion rate and air leak) after 90 procedures [24]. Simulation training may shorten the learning curve [25]. Surgical trainees may be directly oriented towards minimally invasive technique without extensive experience in open surgery [26], and VATS should be taught in any accredited training programme.

Which are the options for future development? There is currently a strong interest, supported by industry, in developing single-incision VATS; however, it remains controversial whether reducing the number of incisions will improve the immediate outcome, or might be deleterious for long-term survival [27]. The effects of market pressure can also be seen as medical centres strive to begin to offer robotically assisted VATS. For the moment, it appears that robot assistance does not improve outcomes, but increases operation time and cost [28]. However, the market is open to competition and the financial conditions may change. With improving technology, perhaps the future might be single-incision robotic surgery?

A pain specialist's perspective (C. Peeters-Asdourian)

Both thoracotomy and video-assisted minimally invasive anatomical resections may be associated with post-thoracotomy pain syndrome, though VATS is associated with less morbidity and a decreased incidence of persistent post-surgical pain syndrome. Overall, when following major surgical procedures, the incidence of persistent pain ranges from 20% to 50% 2 months after surgery [29].

Predictive factors for post-thoracotomy pain include moderate-to-severe perioperative pain, younger age (adults), preoperative anxiety and depression, female sex, radiation therapy to the area, neurotoxic chemotherapy and psychological vulnerability. Genetic predisposition as a result of functional polymorphism of catechol-O-methyltransferase (COMT) may also contribute to chronic pain [30].

The severity of acute postoperative pain may be the most relevant factor contributing to a persistent pain syndrome following surgery [31, 32].

Adequate pain control following thoracotomy and/or VATS includes a multimodal analgesic approach combining thoracic epidural analgesia usually between T4 and T8, provided that there are no pre-existing contraindications such as coagulopathy or sepsis, or paravertebral blocks with NSAIDs and other medications. Regional anaesthesia techniques have been shown to decrease the incidence and severity of post-thoracotomy pain. Paravertebral blocks with or without catheter placement and serratus blocks are an alternative to epidural analgesia and can be performed using ultrasound guidance.

Minimally invasive surgical techniques have also contributed to reducing long-term morbidity, as described above.

Non-opioid analgesics can also play an adjuvant role. These can include NSAIDS, N-methyl-D-aspartate (NMDA)-receptor antagonists, *i.e.* ketamine, alpha-2 agonists such as dexmedetomidine, and the alpha-2-delta subunit ligands of the voltage-gated calcium channels gabapentin and pregabalin. Use of these medications is limited by both patient tolerance and the presence of medical or surgical contraindication [33].

2) Lung apex tumour (Pancoast's syndrome)

A 49-year-old man presented with right shoulder pain.

The patient was initially treated for possible arthritis of the shoulder with physical therapy and NSAIDs. A cervical spine MRI revealed an apical lung tumour associated with a lytic lesion of the first rib. The patient is a smoker: 30 cigarettes per day over 30 years. On physical examination, the patient was found to have right Horner's syndrome with ptosis and myosis.

The chest CT scan revealed a right apical mass invading the pulmonary apex, pleura and surrounding soft tissues, as well as eroding the posterior first and second ribs and the right lateral aspect of the second dorsal vertebra (figure 2).

The PET/CT was intensively positive at the level of the right lung apex mass extending into the T2 vertebra and first rib.

Right bronchial and mediastinal (2R and 4R) nodes were moderately hypermetabolic. The patient underwent an ultrasound-guided endoscopy and biopsy of the 11R nodes, which yielded a diagnosis of squamous cell lung cancer. The tumour was staged as T4N1. The patient was complaining of severe pain largely localised to the posterior aspect of the shoulder and the anterior chest wall in a T1 distribution. He requested consultation to explore medication and interventional options for pain

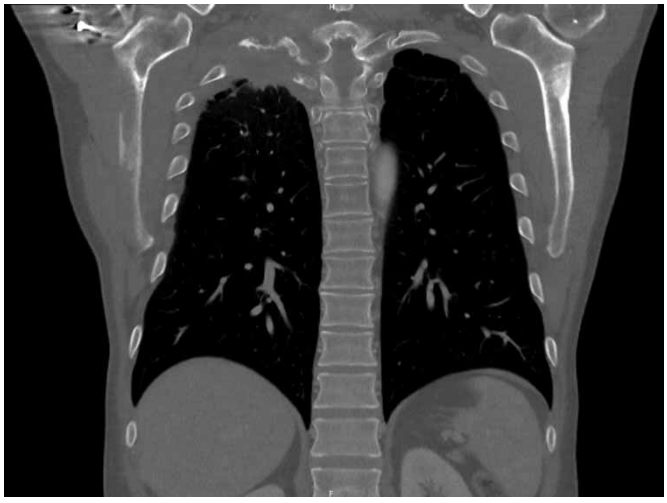

FIGURE 2 Chest computed tomography scan, coronal reconstruction (bone window contrast): right mass invading apex and eroding the posterior first and second ribs and the right lateral part of the second dorsal vertebra.

management, as well as opinions regarding the effectiveness of specific palliative cancer treatments in improving pain control.

A pain specialist's perspective (M. Almalki)

A Pancoast tumour is defined by the ACCP [34] as: "a lung cancer arising in the apex of the lung that involves structures of the apical chest wall. Invasion of apical chest wall structures is required at the level of the first rib or above, but it is not necessary to have Horner syndrome or pain radiating down the arm. These lesions frequently invade the brachial plexus, subclavian vessels, or spine" [35].

Shoulder pain is usually the first and most common presentation owing to extension of the tumour to the extra-thoracic structures. As the tumour proliferates, patients can often develop paraesthesia and weakness along the ulnar nerve distribution. This occurs secondary to tumour invasion of the inferior aspect of the brachial plexus C8-T1 and can, in some cases, extend into the T2 territory (the axilla and medial aspect of the upper arm) as well. These musculoskeletal symptoms may delay the work-up and diagnosis [36]. As the tumour invades the sympathetic chain, a Horner's syndrome may develop in 15–50% of patients [37, 38]. In approximately 5% of patients, spinal cord compression can occur as the tumour spreads into the intervertebral foramina early in the course of disease [39].

The tumour can be seen on chest radiographs as a mass in the apex of the lung or as a pleural thickening. It is important to remember that it can be easily missed on the chest radiograph. A CT scan can confirm the location and the extension of the tumour.

An MRI should be obtained, as well, to better evaluate the extension of the tumour to the surrounding structures, including the brachial plexus, cervical plexus, neural foramen, vertebral body and adjacent vasculature.

Malignant, inflammatory, autoimmune and neuropathic processes of the tumour in the lung, pleura and brachial and cervical plexus can lead to different types of pain. Neuropathic pain is likely the primary aetiology of the pain associated with a Pancoast tumour due to its close proximity to both the cervical and brachial plexus. Neuropathic pain is usually described as burning", "shock-like" or as an "electrical sensation". It may be associated with allodynia (*i.e.* pain induced by non-painful stimuli), hyperalgesia (*i.e.* increased perception of painful stimuli) and other concomitant neurological findings, such as weakness or changes in reflexes, and autonomic dysfunction [40]. The prevalence of neuropathic pain is about 20% to 40% of all cancer pain [41]. Its higher incidence in Pancoast tumour pain is likely due to the reasons detailed above.

Pain control is an important factor in the management of every patient with a Pancoast tumour: through a multidisciplinary approach including radiotherapy, chemotherapy, surgical resection if feasible, pain medications and interventional pain procedures as indicated. The pain is often resistant to opioids alone and will require adjuvant neuropathic pain agents such as antidepressants and gabapentinoids.

Tricyclic antidepressants (amitriptyline, nortriptyline), serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine), and calcium-channel modulators (gabapentin and pregabalin) are the most frequently utilised neuropathic pain medications in the management of neuropathic cancer pain [42]. Topical therapies such as lidocaine patch, diclofenac patch, or compound creams containing a variety of medications ranging from local anaesthetics, neuropathic agents, muscle relaxants, and agents from clonidine to amantadine can also be trialled. Application of a capsaicin patch or ointment which is available in a range of concentrations, typically between 0.025% and 0.075%, can be trialled as well, though it should not be applied to any open skin or wounds [42].

If the pain is resistant to oral medications, an alternative drug delivery route or neuroablative procedure may be necessary. An intrathecal drug delivery system may be considered depending on the patient's life expectancy and prognosis; typically, patients are required to have a 3- to 6-month life expectancy prior to considering implant. A programmable intrathecal pump delivering morphine or hydromorphone as single agents, or in combination with clonidine, bupivacaine and/or ziconotide for their analgesic properties in the management of neuropathic pain, can be used [43].

Less invasive therapies, including stellate ganglion block or neurolysis, intercostal nerve block or neurolysis, and paravertebral blocks, can be considered and tailored to the individual patient depending on the location of pain and extension of the tumour. In cases of brachial plexus involvement, a single-shot ultrasound-guided brachial plexus injection using a combination of local anaesthetic and steroid can serve both a diagnostic and a therapeutic role. Placement of indwelling catheter or neurolysis may provide longer term pain relief [44].

Neuroablative procedures at the level of the dorsal route ganglion may constitute a very effective, well-tolerated and minimally invasive therapy. Such procedures are usually performed under

TABLE 2 Pharmacotherapy of neuropathic pain

Medications	Mechanism of action	Side-effects	Caution
Tricyclic antidepressants: amitriptyline, imipramine, clomipramine	Inhibition of monoamine reuptake, blocking of Na channels, action on β2 receptors	Anticholinergic effects, urinary retention especially with BPH, xerostomia, cardiac conduction anomalies, confusion and sedation	Consider presence of underlying cardiac pathology, QT prolongation Glaucoma
Serotonin–norepinephrine reuptake inhibitor antidepressants: venlafaxine, duloxetine	Serotonin–norepinephrine reuptake inhibition	Nausea and vomiting, xerostomia and weight gain	If used with tramadol or tapentadol, risk of serotoninergic syndrome Caution when used with liver disease and with hypertension
Anticonvulsant calcium channel α-2-δ subunit agonists or gapentinoids: gabapentin, pregabalin	Widely approved, available and utilised for the treatment of neuropathic pain	Sleepiness, negative impact on cognitive function, weight gain, peripheral oedema, especially in the lower extremities	Decrease dose with renal dysfunction
Topiramate	Inhibition of γ-aminobutyric acid (GABA)-mediated neurotransmission NMDA antagonist	Also acts on carbonic anhydrase inhibitor with potential risk of nephrolithiasis and acute angle glaucoma Anorexia and possible weight loss Negative effect on cognition	Decrease dose with renal dysfunction
Topical preparations: lidocaine patches/ointments, capsaicin patches/ointments	Na channel blocker Substance P depletion from nociceptors TRPV1 (transient receptor potential channel vanilloid agonist)	Erythema, pruritus	Do not apply on open sores High strength 8% formulation used in the management of post-herpetic neuralgia; very painful to apply and rarely needed in cancer pain

BPH: benign prostate hypertrophy; NMDA: n-methyl-D-aspartate.

fluoroscopic, CT or MRI guidance using radiofrequency ablative techniques. Cryotherapy can also be helpful (table 2) [45].

A radiation therapist's perspective (P. Van Houtte)

This is an interesting clinical case of superior sulcus tumour with a Pancoast tumour, which is probably not a candidate for a radical trimodality (surgery, radiotherapy, chemotherapy) approach owing to the tumour extent, especially the nodal involvement. N1 involvement would still allow for a reasonable postoperative outcome in a trimodality setting, especially in a low comorbidity context. Extension to the vertebral body or subclavian artery is not an absolute contraindication to a radical R0 resection *per se*.

One key question is how to define the best treatment approach for palliation but also aim for long-term loco-regional control of the disease. Radiation is a very effective treatment regarding pain management owing to bone involvement by tumour, with an early response rate above 60% including pain reduction and even a complete clearance of symptoms. In a series from our service dating back to more than 20 years, pain relief was achieved in 21 out of 28 treated patients [46].

This can be achieved with a short course of radiation (less than 2 weeks) with minimal side effect. It is a purely palliative approach without any aims at controlling the disease and with the risk of recurrence of pain later on, probably within the first year.

To sustain the pain control, which can only be achieved through loco-regional control of the disease, a higher radiation dose is needed to control the tumour while trying to avoid radiation injuries to the brachial plexus and the spinal cord. Currently, for locally advanced lung cancer, including such a superior sulcus tumour, the best approach is certainly to combine chemotherapy and radiotherapy by adding a cisplatin-based chemotherapy with a definitively high radiation dose above 60 Gy. The data clearly show an improved survival, due mainly to a better loco-regional control. This range of dose requires a high and precise radiation technology to cover the tumour, including the vertebral involvement and the positive nodes, without damaging the spinal cord. This may be achieved using an intensity-modulated radiotherapy combined with precise imaging at the linear accelerator to verify the correct positioning of the patient and

delivery of the radiation. Such a treatment is more aggressive and takes 6–7 weeks. It may induce oesophagitis, the main acute side effect. Currently, different reports have demonstrated the feasibility of such an approach for superior sulcus tumour, leading to pain control and even long-term survival [47, 48].

3) Bone pain and epidural metastases

A 55-year-old woman with no prior history of smoking was referred for treatment of lung adenocarcinoma at the level of the left inferior lobe, with brain and bone metastases including involvement of the L1 and L2 vertebrae. There was no active genetic alteration. Cerebral and lumbar spine radiotherapy was performed and chemotherapy with cisplatin and vinorelbine was delivered with some improvement. 1 year later, a relapse occurred and docetaxel was administered for six cycles, in addition to cerebral stereotaxic irradiation. 1 year later again, the patient complained of low back pain. Paracetamol was not effective. A chest CT scan showed progression of disease in the lung.

A spine MRI demonstrated, on a T1 and STIR (short tau inversion recovery) sequence without intravenous contrast injection, two metastatic lesions at L1 and L4 levels with vertebral compression of the L1 vertebral body and discrete anterior epidural tumour infiltration (figure 3a and b).

The pain management plan for this patient was to initiate opioid therapy and consider invasive management of the vertebral lesions after consultation with the pain and orthopaedic spine services, respectively.

A pain specialist's perspective (C. Peeters-Asdourian)

Bony metastases occur frequently in lung cancer, accounting for a large number of vertebral lesions. These vertebral metastases are associated with pain and morbidity. They have a significant impact on the patient's quality of life and can cause severe breakthrough pain with physical activity. Additionally, pathologic fractures can result in spinal cord compression.

Bone-targeted agents (BTAs) are an important part of the management of bony metastases. These include inhibitors of osteoclastogenesis and osteoclast activation and receptor activator factor kappa-B ligand (RANKL) inhibitors such as bisphosphonates and denosumab respectively. ESMO, NCCN and the American Society of Clinical Oncology support the use of BTAs in patients with breast cancer, prostate cancer and multiple myeloma to prevent and delay skeletal complications and pain. In lung cancer patients, the data shows some benefit in reducing skeletal-related events and bone pain, but further studies are needed to explore the impact of these agents on survival. Both bisphosphonates and denosumab are associated with complications including jaw osteonecrosis, hypocalcaemia and infections, which are more frequent with denosumab [49].

In addition to offering opioids and adjuvant medications such as NSAIDS, and gabapentin or pregabalin as tolerated, the pain specialist may offer less invasive treatment options than spine surgery.

Radiofrequency spinal tumour ablation (RFA) can be considered as it is safe and effective for well-selected patients. RFA can be performed with and without cement [50].

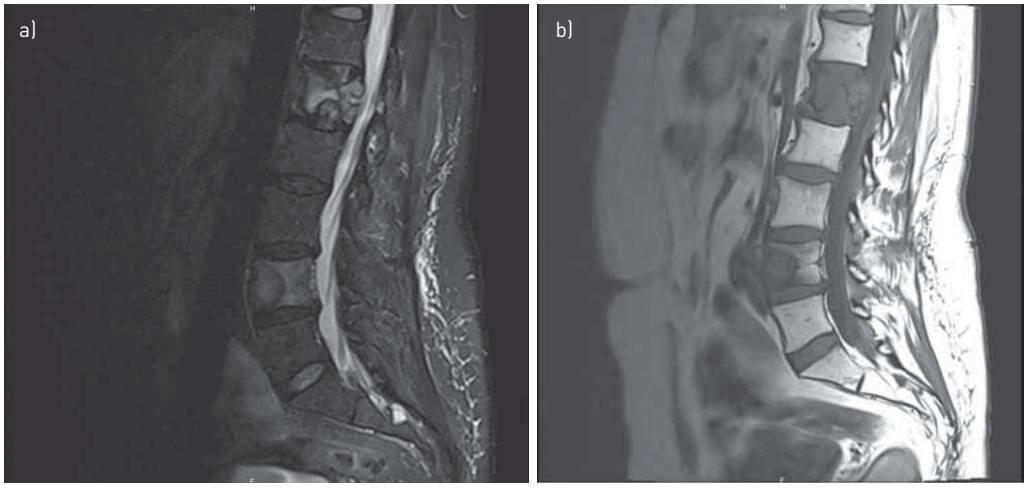

FIGURE 3 a) Sagittal STIR (short tau inversion recovery) sequence, and b) sagittal spin-echo T1 sequence: two metastatic lesions at L1 and L4 levels with vertebral compression of the vertebral body of L1 and discrete anterior epidural tumoural infiltration.

Cryoablation techniques have been used as well and may be safer in terms of risks for spinal complications.

Vertebral augmentation procedures, vertebroplasty and kyphoplasty, can certainly be considered. All of these techniques require imaging guidance, fluoroscopy or computed tomography (CT scans). These procedures are minimally invasive and are performed under conscious sedation or monitored anaesthesia care, but in some cases, may require a general anaesthethic.

Exclusion for these approaches includes posterior extension of the tumour into the spinal canal, bone fragment extension into the spinal canal or retropulsion, and spinal instability [51]. Various specialists can perform these procedures: interventional radiologists, spine surgeons or interventional pain specialists, depending on the country.

Pulsed radiofrequency of the dorsal root ganglion (DRG) can be used successfully for intractable vertebral metastatic pain. Radiofrequency has been effective in the management of neuropathic pain syndromes and will help in cases where a radiculopathy is a part of the pain presentation.

Contraindications are the same as for all the minimally invasive techniques and include coagulopathy and sepsis [45].

A spine surgeon's perspective (A.P. White)

This 55-year-old woman with lung adenocarcinoma had previously undergone chemo- and radiotherapies to address (in part) L1 and L2 vertebral lesions. 1 year later, back pain prompted imaging re-evaluation. Marrow-replacing lesions were found within the vertebral bodies of L1 and L4. The L1 lesion encroached upon the epidural space.

Patients with metastatic epidural spine lesions can benefit from surgical management when certain aspects of the spine anatomy become compromised [52]. When there is significant axial pain related to spine instability, and when the integrity of the neurological elements has been compromised (or may become compromised), surgery can be considered. Surgical decompression and stabilisation has been shown to reduce pain, to prolong the ability to walk, and to preserve bowel and bladder continence for patients with epidural metastasis.

The benefit of surgery is not applicable to all patients. One of the most relevant considerations is the overall prognosis of the patient [53]. If the patient were expected to survive for less than 6 months, many surgeons would not consider the short-term morbidity of the surgery (including short-term postoperative pain) to be worth the proposed benefit of longer-term pain relief and neurological preservation. For this reason, patients with longer-term survival expectations should be considered to be better candidates for surgery.

In this particular case, if the patient were expected to survive for 6 months or more, surgery would be considered to be helpful. The images indicate that there is significant compromise of the integrity of the L1 vertebrae. There is epidural involvement with stenosis. The risk of vertebral collapse will increase over time. The consequence of that may be significant, including lower extremity paraplegia with bowel and bladder incontinence. Surgery can effectively reduce that risk, and can also reduce pain associated with the instability, particularly in the long term.

Surgical decompression and stabilisation can be accomplished by a variety of approaches, each with its own risks and benefits [54, 55]. In patients with metastatic disease, the spinal reconstruction should be immediately robust. Overall, this patient population has a high risk of non-union following spinal fusion; the implanted hardware comprising the spinal reconstruction should be expected to remain intact and robust for the duration of the patient's life. One cannot rely on bone fusion or healing to provide additional stability. For these reasons, in part, spinal reconstructions for many patients (including this one) may involve combined anterior and posterior surgery.

Independent of the benefits of pain reduction, preservation of mobility, and preservation of continence, spine surgery should not be expected to prolong the life of the patient with metastatic disease. It can, however, be expected to improve comfort, maintain independence and preserve dignity for patients while they navigate the other aspects of this difficult disease.

4) Painful terminal situation

A 68-year-old man presents with primary complaint of right shoulder pain. A chest CT scan revealed multiple pleural nodules in the right lobe which were found to be hypermetabolic on PET/CT scans. A pleuroscopy followed by pleurodesis with talc yielded the diagnosis of malignant mesothelioma. Chemotherapy with cisplatin and pemetrexed was started with a good response and resolution of the pain. Eighteen months later, the disease relapsed. The patient experienced a transient regression of symptoms and disease burden with administration of the same chemotherapy regimen. After several months, metastases

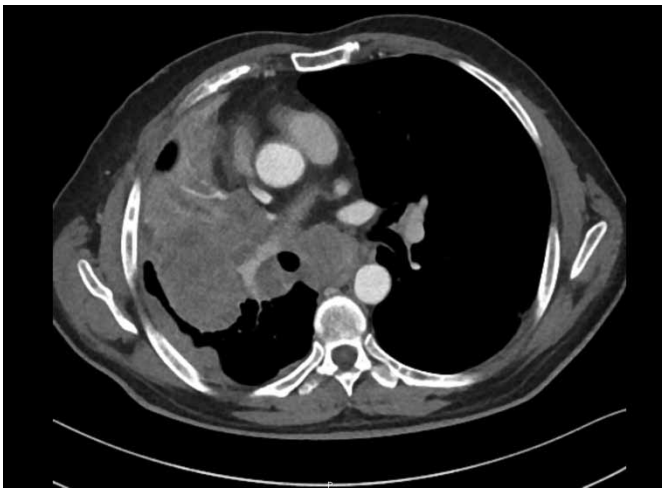

FIGURE 4 Contrast-enhanced chest computed tomography scan: supracentimetric mediastinal and right hilar lymphadenopathies, right parahilar lung mass and right pleural nodular thickening.

developed in the bone, liver and muscles in addition to a massive progression of the thoracic tumour burden. The patient had severe thoracic pain in addition to cough and anorexia. A CT scan showed supracentimetric mediastinal and right hilar lymphadenopathies, right perihilar lung mass and right pleural nodular thickening (figure 4). The palliative care service was consulted for symptom management.

A pain medicine specialist's perspective (C. Peeters-Asdourian and P.H. Rana)

This case illustrates the need for collaboration with the palliative care team for optimal analgesic management, with the thoracic oncologist for possible optional palliative chemotherapy and radiation therapy, and with the pain medicine specialist for consideration of the spinal route of opioid administration or other advanced interventional therapies. These interventions may be needed in 5%–15% of cancer patients who are in advanced or terminal stages of their disease [56]. Aetiology of pain in complex cancer patients is multifactorial, and the presence of pleural nodular thickening may contribute to the development of pleural effusion and visceral pain, which can be particularly challenging to manage.

The oral route (*p.o.*) is the preferred route in most cancer patients. However, a recent study shows, as expected, with our improved knowledge of pharmacokinetics, pharmacodynamics and pharmacogenetics, that patients may have varying responses to different medications, impacting their effectiveness as a treatment modality.

The CYP2D6 isoenzyme of the cytochrome P450-system is highly polymorphic.

Because of variations in the alleles of CYP2D6, about 10% of the Caucasian population is categorised as poor metabolisers and about 4–5% as ultra-rapid responders. These differences may account for the lack of effect in some patients and adverse drug reactions in others.

Poor metabolisers may not respond to codeine and not fully to tramadol [57].

Hepatic and renal function may have an impact on the drug efficacy, side-effects and toxicity. The addition of adjuvant drugs may create drug interactions that will modify the response to treatment as well (table 3).

One recent study demonstrated that terminal cancer patients may not be receiving strong opioids in a timely manner. The intravenous route should be considered, and in many cases preferred, when swift titration is required. The peak effect occurs more rapidly after approximately 15 min, as compared with a *p.o.* or subcutaneous route, which may take up to 30 min and is less reliable. Intravenous administration needs to be considered when absorption of the medication is suboptima, for example, in a patient with persistent pain receiving *p.o.* morphine sulphate immediate-release (MSIR) and with a short gut. Allowing the patient to self-titrate with a patient-controlled analgesia device can also be very helpful.

Intrathecal administration of opioids, local anaesthetics, clonidine (alpha-2 agonist) and ziconotide (N-type calcium channel blocker) as needed for neuropathic pain can be realised using an intrathecal catheter and an internalised pump which is both programmable and refillable. This approach requires a team with the appropriate expertise and a support team which, after implant, will be able to follow the patient, to adjust the regimen, refill the pump and programme it [55]. Contraindications include failed trial of intrathecal administration of analgesic, and systemic infection, while relative contraindications are

TABLE 3 Opioid medications

	s.c./i.v. dose	Oral dose	Side-effects and relevant facts
Codeine (step 2 WHO)	15–30 mg	120–240 mg per day	Usually associated with an NSAID or paracetamol CYP2D6 metabolism Constipation and drowsiness
Dihydrocodeine (step 2 WHO)	30–60 mg per day	60–120 mg per day Extended release formulation available	Dihydrocodeine analgesia is not dependent on CYP2D6 activity Demonstrates affinity for mu, kappa and delta receptors
Tramadol (step 2 WHO)	50 mg (max 200 mg per day)	50–100 mg every 6–8 h as needed; 400 mg per day maximum Formulation in combination 37.5 mg tramadol and 325 mg paracetamol	Centrally acting mu opioid agonist and inhibition of serotonin and norepinephrine reuptake CYP3A4 and CYP2D6 mediated M1 active metabolite and some N-methyl-D-aspartate antagonistic properties are therefore useful for neuropathic pain Seizures with high doses (maximum 400 mg *p.o.* with normal kidney function and 200 mg *i.v.*), headache, nausea, less constipating than codeine
Tapentadol[#] (step 2 WHO)	Not available	50 mg *p.o.* Maximum daily dose 500 mg Extended-release formulation available as 50, 100, 150, 200 and 250 mg (preferred) Conversion ratio with oral morphine 1:3.3	Dual mechanism of action similar to tramadol with higher selectivity for blocking norepinephrine reuptake
Morphine (step 3 WHO); most frequently used and universally available	10 mg doses PCA variable doses	Morphine immediate release (MSIR) 5, 10 and 30 mg every 3–4 h Morphine extended release (ER) 15, 30, 45, 60, 100 and 200 mg every 12 h	Metabolised to morphine-3 glucuronide and to morphine-6 glucuronide, which are active metabolites Constipation, drowsiness, respiratory depression rare in cancer patients, may need to decrease dose with renal impairment Titrate to effect or side effect with immediate release formulation or *i.v.* with PCA
Hydromorphone immediate release[#] (step 3 WHO)	2.0 mg Can be titrated *via* PCA	2, 4, 8 and 16 mg every 3–4 h[¶]	Very similar to morphine, glucuronidation to hydromorphone-3-glucuronide and hydromorphone-6-glucuronide
Hydromorphone extended release[#] (step 3 WHO)		8, 12, 16 and 32 mg every 12 h[¶]	Accumulation of active metabolites with renal failure with resulting increased toxicity; thus, need to decrease dose with renal impairment
Oxycodone (step 3 WHO)	Not available	5–10–15–20–30 mg every 4 h; Immediate release[¶] Available as 1 mg·mL^{-1} oral solution 10, 20, 40, 80 mg Extended release formulation[¶]	Can be associated with paracetamol, NSAIDS or aspirin Metabolised by CYP3A4 and CYP2D6 Clearance of the drug affected by liver disease and renal impairment High potential for abuse and misuse
Fentanyl	Variable doses *i.v.*	Transdermal formulations 12.5, 25, 50, 75 and 100 µg per h[¶]	Very potent opioid Do not start therapy with transdermal fentanyl in opioid-naïve patients Metabolised in the liver to non-toxic, inactive metabolites by CYP3A4 Fentanyl not easily dialysable
Fentanyl transmucosal		200, 400, 600 and 800 µg[¶]	For breakthrough pain Not indicated for opioid-naïve patients
Fentanyl nasal spray		100, 200 and 400 µg[¶]	
Fentanyl effervescent gingival tablets		100, 200 and 400 µg[¶]	

Continued

TABLE 3 Continued

	s.c./i.v. dose	Oral dose	Side-effects and relevant facts
Buprenorphine (step 3 WHO)	Sublingual 2 and 8 mg tablets[¶] Primarily utilised for detox combined with naloxone	Transdermal 7.5, 10, 15 and 20 μg per h patches can be worn for 7 consecutive days[¶] 35, 52.5 and 70 μg per h patches can be worn for 3 consecutive days and are indicated for moderate to severe cancer pain[¶]	Long-acting partial μ agonist with ceiling effect Metabolised in the liver to mostly inactive norbuprenorphine Most of the drug is eliminated in the faeces; thus, not affected by renal impairment
Methadone (step 3 WHO)	5–10 mg *i.v.* every 6–12 h	100–200 mg maximum per day recommended Careful titration	Long and unpredictable half-life (24–72 h) Duration of analgesic effect 6–8 h Respiratory depression with quick dose escalation Do not use for breakthrough pain Can cause QT prolongation and Torsade de pointes

[#]: not available in some countries; [¶]: different formulations are available in various countries. *s.c.*: subcutaneous; *i.v.*: intravenous; WHO: World Health Organization; NSAID: non-steroidal anti-inflammatory drug; PCA: patient-controlled analgesia.

coagulopathy, immunosuppression, poor support, and life expectancy. The EAPC has published evidence-based recommendations [7].

Pain due to chest wall invasion or rib metastases can be treated by intercostal neurolysis or DRG radiofrequency ablation or neurolysis [45]. Once again, specialised providers and support staff will be needed, as well as equipment, fluoroscopy or a CT scan for needle guidance, and an RFA machine, for the provision of these therapeutic modalities. In the USA and throughout the world, as restrictions on its use and decriminalisation take hold, many patients and caregivers enquire about the use of *Cannabis sativa*, more commonly known as marijuana, for the management of a multitude of cancer-related symptoms including pain, particularly at end of life.

Cannabinoid binds as agonists, antagonists or inverse agonists at the classical G protein-coupled CB1 and CB2 receptors, as well as at a multitude of non-cannabinoid receptors such as transient receptor potential vanilloid (TRPV). Cannabidiol (CBD), first isolated in 1963, has in animal models been shown to have an anti-emetic, analgesic and anti-inflammatory effect without displaying overt psychomimetic properties, making it attractive as a therapeutic agent [58, 59]. Whiting *et al.* [60] published a large systematic review involving 79 randomised trials and 6462 patients, a minority of whom were cancer patients; overall, the average number of patients who reported at least 30% improvement in pain was greater with cannabinoids than with placebo. Two recent trials involving the use of nabiximol, an oromucosal spray containing 2.7 mg of tetrahydrocannabinol (THC) and 2.5 mg CBD per 100 mL, in cancer patients with poorly controlled pain had mixed results. Johnson *et al.* (2010) noted a statistically significant improvement in NRS (Numerical Rating Scale) pain score in favour of CBD/THC *versus* placebo (improvement −1.37 *versus* −0.69) [61]. In a more recent study published in 2012, a continuous responder analysis demonstrated that the number of patients reporting analgesia was greater in the CBD group than in the placebo group ($p=0.35$); however, it failed to reach the primary outcome of 30% reduction in pain severity [62]. Overall, there is thought to be moderate evidence to support the use of cannabinoids as an adjuvant agent in the management of opioid refractory active cancer pain, though its use remains contentious and further investigation is required (table 4).

A chest physician's perspective (B. Grigoriu)

Pain, fatigue, cough and dyspnoea are the main symptoms experienced by patients with advanced intrathoracic tumours [63]. Mesothelioma patients are more prone to experiencing difficult-to-manage pain and dyspnoea owing to the local progression of the disease. In addition, this particular patient had bone metastases. Progressive tissue invasion generates pain that may be difficult to control with analgesics alone. A systematic review of chemotherapy trials showed that a minority of trials report symptom control, but in those that do, it has been shown that pain and dyspnoea may be improved by chemotherapy despite low response rates and variable effect on survival [64]. Modern treatments involving a new generation of antifolate and a platinum derivative significantly improve survival over platinum alone, but surprisingly, published data show no difference in any component of quality of life (which includes pain) [65]. However, old and less effective regimens such as MVP (methotrexate, vincristine, cisplatin) [66] or vinorelbine

TABLE 4 Interventional procedures in pain management

Procedure	Indication	Caution/miscellaneous
Intrathecal delivery system, *i.e.* implantable pump or external catheter	Recalcitrant cancer pain	A variety of medications can be infused, including opioids, bupivacaine, clonidine and ziconotide Contraindication: coagulopathy, sepsis 100 mg morphine *i.v.* equivalent to 10 mg epidural and 1 mg intrathecal
Radiofrequency ablation	Treatment of vertebral metastasis, painful radicular pain (dorsal root ganglion ablation) and peripheral nerves	Usually well tolerated Caution in coagulopathic patients
Vertebral augmentation: vertebroplasty and balloon kyphoplasty	Vertebral metastasis	Not indicated in cases of spinal instability or if there is spinal canal involvement
Neuromodulation	Chronic well-localised neuropathic pain syndromes Consider in cancer survivors with chronic neuropathic pain	Caution in coagulopathic or immunosuppressed patients
Neurolysis, *i.e.* intercostal alcohol or phenol block for well-localised dermatomal pain	Well-localised severe pain in patients with short life expectancy	Caution in coagulopathic patients

monotherapy [67] may improve symptoms in more than half of the patients. A feasibility study of active symptom control (ASC) alone or associated with chemotherapy (MVP regimen or vinorelbine alone) showed that this approach may be used for palliation of pain and possibly dyspnoea, leading to a doubling of the percentage of patients experiencing improvement compared to ASC alone [68]. A retrospective English cohort showed that two-thirds of patients experienced symptom improvement during chemotherapy [69]. However, a clinical improvement was noted in only one-third of patients receiving cisplatin, doxorubicin and mitomycin in an older Italian Phase II trial [70]. A three-arm randomised trial comparing ASC either alone or with MVP or vinorelbine showed no significant difference in symptom control (global physical functioning, pain, dyspnoea and global quality of life) in patients receiving chemotherapy despite the fact that in the first 3 months chemotherapy seems to generate a decrease in moderate and severe chest pain [71].

Dyspnoea is almost invariably present in mesothelioma and may be related to both tumour development and pleural fluid accumulation. Indwelling pleural catheters (IPCs) offer an option as they allow for convenient pleural fluid removal [72]. A randomised trial showed that IPCs offer the same level of improvement as pleurodesis, but the trial is not specific to mesothelioma [73, 74]. The diffuse nature of mesothelioma infiltration renders lung expansion difficult, so direct pleurodesis is rarely possible in advanced cases. Thus, the use of IPCs is a convenient option for dyspnoea management.

A palliative care specialist's perspective (D. Lossignol)

Pain is a major problem in cancer as it occurs in 30–50% patients in earlier stages and in 70–90% of these patients with advanced disease and is often associated with other symptoms (dyspnoea, gastrointestinal tract disorders, neurological syndromes, *etc.*) [75].

The three-step framework for cancer-related pain management was published for the first time in 1986. Step I recommends non-opioid analgesics (NSAIDs, paracetamol) for mild pain. Step II specifies the use of weak opioids for moderate pain (codeine, tramadol). Step III comprises the use of strong opioids for severe pain (morphine, methadone, fentanyl, hydromorphone).

To achieve better pain relief, an appropriate application of adjuvant analgesics (*i.e.* for neuropathic pain), supportive drugs (for the prevention and treatment of opioid adverse effects), and non-pharmacological measures such as radiotherapy and invasive procedures (nerve blockades and neurolytic blocks) should be considered and applied [76].

There is a growing recognition of the importance of the psychological impact of pain on cancer patients, regardless of the type of cancer, especially as the number of cancer survivors increases. Psychological factors can exert an important influence across a range of pain-related behaviour, treatment outcomes, and social and familial activities [77–80].

Dyspnoea due to pleural effusion, lymphangitis or bronchial obstruction remains a challenge at the end of life, especially because the patient will not benefit from intensive care and invasive procedures.

Non-invasive ventilation offers an option but remains unusual in palliative care because it remains difficult to identify patients who will benefit from this technique, and this option remains controversial in patients who have elected specific limits to life support [81, 82]. Thoracocentesis, chemical or talc pleurodesis, and minimally invasive palliative treatment options such as chronic IPCs may all be helpful in cases of pleural effusion. Steroids are proposed in cases of pulmonary lymphangitis. The effect on dyspnoea is short in duration because of progressive disease. Intercostal muscle atrophy is of concern, especially in debilitated or cachectic patients. Nebulised or parenteral morphine may be helpful, but its effectiveness is controversial [83].

Continuous sedation is a therapeutic option that makes it possible to relieve a patient from unbearable suffering related to refractory symptoms [84–86].

A symptom is considered refractory when the clinician believes that interventions, invasive or not, will no longer provide adequate relief, that their use will produce intolerable or excessive morbidity, or that it is not possible to hope for relief in an acceptable period of time. The suffering that occurs is considered to be intolerable by the patient. These terms obviously have subjective value and must be interpreted within a closely monitored medical context. The decision to put a patient into a state of irreversible unconsciousness is not without ethical consequence, and it is essential to have a clearer view of the practice of sedation [87]. The essential role of the palliative care specialist is to alleviate the burden of suffering and to do more good than harm in respect of the patient's expectations.

Conclusions

The WHO stepladder and other guidelines use morphine as the cornerstone of their recommendations, however, the availability of a multitude of other formulations of opioids which can be given transmucusoally, transdermally, intravenously and orally, as well as, the availability of analgesic adjuvant medications has greatly expanded the armamentarium available to clinicians in the management of cancer pain.

Overall, a polypharmacologic approach using the recommendations of the WHO can provide benefit to approximately 80–85% of patients with cancer pain. As can be seen in the cases presented above a multi-disciplinary approach will be needed to provide optimal care often involving an oncologist, radiation therapist, surgeons, pain medicine specialists, and palliative or supportive care practitioners [88].

As advancements are made in the treatment of various cancers the number of cancer survivors will increase.

According to the Centers for Disease Control (CDC), a report by the National Cancer Institute and EUROCARE-5 data population based study, there has been a steady rise in the 5-year overall survival rate from cancer both in the USA and in Europe. In the USA, there were about 3 million cancer survivors in 1971. This number is up to 15 million as of January 2016 and is expected to grow to 19 million by 2024 [89].

The data from the Surveillance, Epidemiology, and End Results study showed that approximately 46% of these survivors will be 70 years of age or older [90].

These patients may have long term pain issues related to their cancer treatment such as chronic pain syndromes following surgical procedures, as well as, chemotherapy or radiation therapy toxicities. Chronic pain may be present in 5 to 56% of the survivors. It is one of the most prevalent symptoms together with fatigue and mood disorders in this patient population [91, 92].

Some cancer survivors may need long term opioid management. Careful patient selection and monitoring is indicated to avoid drug misuse and/or abuse. These patients may resemble chronic non-cancer pain patients and may require the application of general opioid prescribing guidelines as detailed by the CDC including opioid contracts, prescription monitoring and routine urine toxicology. The side effects of long term opioid therapy need to be taken into consideration and treated symptomatically as indicated including constipation, hypogonadism, and immunosuppression.

Recurrence of disease needs to be considered with any unexplained increase in pain [93].

These cancer survivors will require access to the same multidisciplinary teams as the patients with active disease, in addition to multidisciplinary pain clinics for continued complex care.

References

1 van den Beuken-van Everdingen MHJ, Hochstenbach LMJ, Joosten EAJ, *et al.* Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. *J Pain Symptom Manage* 2016; 51: 1070–1090.e9.
2 Breivik H, Cherny N, Collett B, *et al.* Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. *Ann Oncol* 2009; 20: 1420–1433.
3 World Health Organization. Cancer Pain Relief. 2nd Edn. Geneva, World Health Organization, 1996.

4 Greco MT, Roberto A, Corli O, *et al.* Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. *J Clin Oncol* 2014; 32: 4149–4154.
5 Caraceni A, Hanks G, Kaasa S, *et al.* Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol* 2012; 13: e58–e68.
6 Ripamonti CI, Santini D, Maranzano E, *et al.* ESMO Guidelines Working Group. Management of cancer pain: ESMO Clinical Practice Guidelines. *Ann Oncol* 2012; 23: Suppl. 7, vii139–vii154.
7 Kurita GP, Kaasa S, Sjøgren P. European Palliative Care Research Collaborative (EPCRC). Spinal opioids in adult patients with cancer pain: a systematic review: a European Palliative Care Research Collaborative (EPCRC) opioid guidelines project. *Palliat Med* 2011; 25: 560–577.
8 Caraceni A, Weinstein SM. Classification of cancer pain syndromes. *Oncology (Williston Park)* 2001; 15: 1627–1640.
9 Kapo JM, Akgün KM. Integrating palliative care into the care of patients with advanced lung cancer. *Cancer J* 2015; 21: 434–439.
10 Yan TD, Cao C, D'Amico TA, *et al.* Video-assisted thoracoscopic surgery lobectomy at 20 years: a consensus statement. *Eur J Cardiothorac Surg* 2014; 45: 633–639.
11 Howington JA, Blum MG, Chang AC, *et al.* Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd edn: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143: Suppl. 5, e278S–e313S.
12 Whitson BA, Andrade RS, Boettcher A, *et al.* Video-assisted thoracoscopic surgery is more favorable than thoracotomy for resection of clinical stage I non-small cell lung cancer. *Ann Thorac Surg* 2007; 83: 1965–1970.
13 Yan TD, Black D, Bannon PG, *et al.* Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. *J Clin Oncol* 2009; 27: 2553–2562.
14 Paul S, Altorki NK, Sheng S, *et al.* Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. *J Thorac Cardiovasc Surg* 2010; 139: 366–378.
15 Falcoz P-E, Puyraveau M, Thomas P-A, *et al.* Video-assisted thoracoscopic surgery *versus* open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. *Eur J Cardiothorac Surg* 2016; 49: 602–609.
16 Cao C, Manganas C, Ang SC, *et al.* Video-assisted thoracic surgery *versus* open thoracotomy for non-small cell lung cancer: a meta-analysis of propensity score-matched patients. *Interact Cardiovasc Thorac Surg* 2013; 16: 244–249.
17 Chen FF, Zhang D, Wang YL, *et al.* Video-assisted thoracoscopic surgery lobectomy *versus* open lobectomy in patients with clinical stage I non-small cell lung cancer: a meta-analysis. *Eur J Surg Oncol* 2013; 39: 957–963.
18 Bendixen M, Jørgensen OD, Kronborg C, *et al.* Postoperative pain and quality of life after lobectomy *via* video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. *Lancet Oncol* 2016; 17: 836–844.
19 Berry MF, D'Amico TA, Onaitis MW, *et al.* Thoracoscopic approach to lobectomy for lung cancer does not compromise oncologic efficacy. *Ann Thorac Surg* 2014; 98: 197–202.
20 Licht PB, Jørgensen OD, Ladegaard L, *et al.* A national study of nodal upstaging after thoracoscopic *versus* open lobectomy for clinical stage I lung cancer. *Ann Thorac Surg* 2013; 96: 943–949.
21 Taioli E, Lee D-S, Lesser M, *et al.* Long-term survival in video-assisted thoracoscopic lobectomy *vs* open lobectomy in lung-cancer patients: a meta-analysis. *Eur J Cardiothorac Surg* 2013; 44: 591–597.
22 Lee JG, Cho BC, Bae MK, *et al.* Thoracoscopic lobectomy is associated with superior compliance with adjuvant chemotherapy in lung cancer. *Ann Thorac Surg* 2011; 91: 344–348.
23 Mazzella A, Olland A, Falcoz PE, *et al.* Video-assisted thoracoscopic lobectomy: which is the learning curve of an experienced consultant? *J Thorac Dis* 2016; 8: 2444–2453.
24 Jensen K, Ringsted C, Hansen HJ, *et al.* Simulation-based training for thoracoscopic lobectomy: a randomized controlled trial: virtual-reality *versus* black-box simulation. *Surg Endosc* 2014; 28: 1821–1829.
25 Mu J-W, Gao S-G, Xue Q, *et al.* A propensity matched comparison of effects between video assisted thoracoscopic single-port, two-port and three-port pulmonary resection on lung cancer. *J Thorac Dis* 2016; 8: 1469–1476.
26 Perna V, Carvajal AF, Torrecilla JA, *et al.* Uniportal video-assisted thoracoscopic lobectomy *versus* other video-assisted thoracoscopic lobectomy techniques: a randomized study. *Eur J Cardiothorac Surg* 2016; 50: 411–415.
27 Borro JM, Regueiro F, Pértega S, *et al.* Statistically worse long-term survival after single port lung cancer lobectomy. Comparative study of different videothoracoscopic approaches. *Arch Bronconeumol* 2017; 53: 199–205.
28 Swanson SJ, Miller DL, McKenna RJ, *et al.* Comparing robot-assisted thoracic surgical lobectomy and wedge resection: results from a multihospital database. *J Thorac Cardiovasc Surg* 2014; 147: 929–937.
29 Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; 367: 1618–1625.
30 Diatchenko L, Slade GD, Nackley AG, *et al.* Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* 2005; 14: 135–143.
31 Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg* 2008; 248: 189–198.
32 Buvanendran A, Kroin JS, Della Valle CJ, *et al.* Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg* 2010; 110: 199–207.
33 Chou R, Gordon DB, de Leon-Casasola OA, *et al.* Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain* 2016; 17: 131–157.
34 Kozower BD, Larner JM, Detterbeck FC, *et al.* Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd edn: American College of Chest Physicians' evidence-based clinical practice guidelines. *Chest* 2013; 143: Suppl. 5, e369S–e399S.
35 Foroulis CN, Zarogoulidis P, Darwiche K, *et al.* Superior sulcus (Pancoast) tumors: current evidence on diagnosis and radical treatment. *J Thorac Dis* 2013; 5: Suppl. 4, S342–S358.

36 Panagopoulos N, Leivaditis V, Koletsis E, *et al.* Pancoast tumors: characteristics and preoperative assessment. *J Thorac Dis* 2014; 6: Suppl. 1, S108–S115.
37 Detterbeck FC. Changes in the treatment of Pancoast tumors. *Ann Thorac Surg* 2003; 75: 1990–1997.
38 Marulli G, Battistella L, Mammana M, *et al.* Superior sulcus tumors (Pancoast tumors). *Ann Transl Med* 2016; 4: 239.
39 Rusch VW. Management of Pancoast tumours. *Lancet Oncol* 2006; 7: 997–1005.
40 Esin E, Yalcin S. Neuropathic cancer pain: What we are dealing with? How to manage it? *Onco Targets Ther* 2014; 7: 599–618.
41 Bennett MI, Rayment C, Hjermstad M, *et al.* Prevalence and aetiology of neuropathic pain in cancer patients: a systematic review. *Pain* 2012; 153: 359–365.
42 Finnerup NB, Attal N, Haroutounian S, *et al.* Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015; 14: 162–173.
43 Deer TR, Prager J, Levy R, *et al.* Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation. *Neuromodulation* 2012; 15: 436–464.
44 Vranken JH, Zuurmond WW, de Lange JJ. Continuous brachial plexus block as treatment for the Pancoast syndrome. *Clin J Pain* 2000; 16: 327–333.
45 Gulati A, Shah R, Puttanniah V, *et al.* A retrospective review and treatment paradigm of interventional therapies for patients suffering from intractable thoracic chest wall pain in the oncologic population. *Pain Med* 2015; 16: 802–810.
46 Van Houtte P, MacLennan I, Poulter C, *et al.* External radiation in the management of superior sulcus tumor. *Cancer* 1984; 54: 223–227.
47 De Bari B, Lestrade L, Souquet P-J, *et al.* Analyse rétrospective monocentrique française du contrôle local des cancers bronchiques non à petites cellules de l'apex après radiothérapie de haute dose avec ou sans chimiothérapie. [Single French centre retrospective analysis of local control after high dose radiotherapy with or without chemotherapy and local control for Pancoast tumours.] *Cancer/Radiothérapie* 2012; 16: 107–114.
48 Kappers I, Klomp HM, Koolen MGJ, *et al.* Concurrent high-dose radiotherapy with low-dose chemotherapy in patients with non-small cell lung cancer of the superior sulcus. *Radiother Oncol* 2011; 101: 278–283.
49 LaVasseur N, Clemons M, Hutton B, *et al.* Bone-targeted therapy use in patients with bone metastases from lung cancer: A systematic review of randomized control trials. *Cancer Treat Rev* 2016; 50: 183–193.
50 Arai Y-CP, Nishihara M, Yamamoto Y, *et al.* Dorsal root ganglion pulsed radiofrequency for the management of intractable vertebral metastatic pain: a case series. *Pain Med* 2015; 16: 1007–1012.
51 Berenson J, Pflugmacher R, Jarzem P, *et al.* Balloon kyphoplasty *versus* non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. *Lancet Oncol* 2011; 12: 225–235.
52 White AP, Kwon BK, Lindskog DM, *et al.* Metastatic disease of the spine. *J Am Acad Orthop Surg* 2006; 14: 587–598.
53 Tokuhashi Y, Matsuzaki H, Toriyama S, *et al.* Scoring system for the preoperative evaluation of metastatic spine tumor prognosis. *Spine* 1990; 15: 1110–1113.
54 Patchell RA, Tibbs PA, Regine WF, *et al.* Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet* 2005; 366: 643–648.
55 Sundaresan N, Rothman A, Manhart K, *et al.* Surgery for solitary metastases of the spine: rationale and results of treatment. *Spine* 2002; 27: 1802–1806.
56 Staats PS. Neuraxial infusion for pain control: when, why, and what to do after the implant. *Oncology (Williston Park)* 1999; 13: 5 Suppl. 2, 58–62.
57 Mercadante S. Opioid metabolism and clinical aspects. *Eur J Pharm* 2015; 769: 71–78.
58 Davis M. Cannabinoids for symptom management and cancer therapy: the evidence. *J Natl Compr Canc Netw* 2016; 14: 7.
59 Birdsall SM, Birdsall TC, Tims LA. The use of medical marijuana in cancer. *Curr Oncol Rep* 2016; 18: 40.
60 Whiting PF, Wolff RF, Deshpande S, *et al.* Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015; 313: 2456–2473.
61 Johnson JR, Burnell-Nugent M, Lossignol D, *et al.* Multicenter, double-blind, randomized, placebo-controlled, parallel group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer related pain. *J Pain Symptom Manage* 2010; 39: 167–179.
62 Potternoy RK, Ganae-Moran ED, Allende S, *et al.* Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded dose trial. *J Pain* 2012; 13: 438–449.
63 Ziegler L, Mulvey M, Blenkinsopp A, *et al.* Opioid prescribing for patients with cancer in the last year of life: a longitudinal population cohort study. *Pain* 2016; 157: 2445–2451.
64 Mak KS, van Bommel ACM, Stowell C, *et al.* Defining a standard set of patient-centred outcomes for lung cancer. *Eur Respir J* 2016; 48: 852–860.
65 Scherpereel A, Astoul P, Baas P, *et al.* Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. *Eur Respir J* 2010; 35: 479–495.
66 van Meerbeeck JP, Gaafar R, Manegold C, *et al.* Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005; 23: 6881–6889.
67 Middleton GW, Smith IE, O'Brien ME, *et al.* Good symptom relief with palliative MVP (mitomycin-C, vinblastine and cisplatin) chemotherapy in malignant mesothelioma. *Ann Oncol* 1998; 9: 269–273.
68 Steele JP, Shamash J, Evans MT, *et al.* Phase II study of vinorelbine in patients with malignant pleural mesothelioma. *J Clin Oncol* 2000; 18: 3912–3917.
69 Muers MF, Rudd RM, O'Brien MER, *et al.* BTS randomised feasibility study of active symptom control with or without chemotherapy in malignant pleural mesothelioma: ISRCTN 54469112. *Thorax* 2004; 59: 144–148.
70 Andreopoulou E, Ross PJ, O'Brien MER, *et al.* The palliative benefits of MVP (mitomycin C, vinblastine and cisplatin) chemotherapy in patients with malignant mesothelioma. *Ann Oncol Off J Eur Soc Med Oncol* 2004; 15: 1406–1412.

71 Pennucci MC, Ardizzoni A, Pronzato P, *et al.* Combined cisplatin, doxorubicin, and mitomycin for the treatment of advanced pleural mesothelioma: a phase II FONICAP trial. *Cancer* 1997; 79: 1897–1902.
72 Muers MF, Stephens RJ, Fisher P, *et al.* Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. *Lancet* 2008; 371: 1685–1694.
73 Van Meter MEM, McKee KY, Kohlwes RJ. Efficacy and safety of tunneled pleural catheters in adults with malignant pleural effusions: a systematic review. *J Gen Intern Med* 2011; 26: 70–76.
74 Davies HE, Mishra EK, Kahan BC, *et al.* Effect of an indwelling pleural catheter *vs* chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA* 2012; 307: 2383–2389.
75 Meuser T, Pietruck C, Radbruch L, *et al.* Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain* 2001; 93: 247–257.
76 van den Beuken-van Everdingen MHJ, de Rijke JM, Kessels AG, *et al.* Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007; 18: 1437–1449.
77 Zaza C, Baine N. Cancer pain and psychosocial factors: a critical review of the literature. *J Pain Symptom Manage* 2002; 24: 526–542.
78 Lossignol DAF. Psychological interventions to reduce pain in patients with cancer. *Curr Opin Oncol* 2013; 25: 368–372.
79 Sheinfeld Gorin S, Krebs P, Badr H, *et al.* Meta-analysis of psychosocial interventions to reduce pain in patients with cancer. *J Clin Oncol* 2012; 30: 539–547.
80 Folkman S, Lazarus RS, Gruen RJ, *et al.* Appraisal, coping, health status, and psychological symptoms. *J Pers Soc Psychol* 1986; 50: 571–579.
81 Gifford AH. Noninvasive ventilation as a palliative measure. *Curr Opin Support Palliat Care* 2014; 8: 218–224.
82 Kacmarek RM. Should noninvasive ventilation be used with the do-not-intubate patient? *Respir Care* 2009; 54: 223–229.
83 Barnes H, McDonald J, Smallwood N, *et al.* Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database Syst Rev* 2016; 3: CD011008.
84 de Graeff A, Dean M. Palliative sedation therapy in the last weeks of life: a literature review and recommendations for standards. *J Palliat Med* 2007; 10: 67–85.
85 Morita T, Tsuneto S, Shima Y. Definition of sedation for symptom relief: a systematic literature review and a proposal of operational criteria. *J Pain Symptom Manage* 2002; 24: 447–453.
86 Lossignol D. End-of-life sedation: is there an alternative? *Curr Opin Oncol* 2015; 27: 358–364.
87 Simonds AK. Ethics and decision making in end stage lung disease. *Thorax* 2003; 58: 272–277.
88 Carlson CL. Effectiveness of the World Health Organization cancer pain relief guidelines: an integrative review. *J Pain Res* 2016; 9: 515–534.
89 DeSantis CE, Lin CC, Mariotto AB, *et al.* Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin* 2014; 64: 252–271.
90 Glare PA, Davies PS, Finlay E, *et al.* Pain in cancer survivors. *J Clin Oncol* 2014; 32: 1739–1747.
91 van den Beuken-van Everdingen M. Chronic pain in cancer survivors: a growing issue. *J Pain Palliat Care Pharmacother* 2012; 26: 385–387.
92 Carmona-Bayonas A, Jiménez-Fonseca P, Castañón E, *et al.* Chronic opioid therapy in long-term cancer survivors. *Clin Transl Oncol* 2017; 19: 236–250.
93 Chou R, Turner JA, Devine EB, *et al.* The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med* 2015; 162: 276–286.