VIA MEDICA

REVIEW

Fariz Nurwidya, Elisna Syahruddin, Faisal Yunus

Department of Pulmonology and Respiratory Medicine, Universitas Indonesia Faculty of Medicine, Jakarta, Indonesia

Pain management in lung cancer

The authors declare no financial disclosure

Abstract

Lung cancer is the leading cause of cancer-related mortality worldwide. Not only burdened by the limited overall survival, lung cancer patient also suffer from various symptoms, such as pain, that implicated in the quality of life. Cancer pain is a complicated and transiently dynamic symptom that results from multiple mechanisms. This review will describe the pathophysiology of cancer pain and general approach in managing a patient with lung cancer pain. The use of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and adjuvant analgesia, as part of the pharmacology therapy along with interventional strategy, will also be discussed.

Key word: pain, lung cancer, therapeutic strategy

Adv. Respir. Med. 2016; 84: 331–336

Introduction

Pain influenced the total quality of life significantly; unfortunately, pain is under-assessed and undertreated globally. Chronic pain is one of the main problems in cancer survivor population and prevalence varies between 16% and 50% [1]. In meta-analysis report, prevalence of pain was > 50% among six type of cancers; head and neck cancer 70%, gynecological cancer 60%, gastrointestinal cancer 59%, lung cancer 55%, breast cancer 54%, and urogenital cancer 52% [2]. Among patient with advanced metastatic stage including lung cancer, the prevalence even reached about 75–90% [3]. Pain is also among the common symptoms that could bring lung cancer patient to search for medical care [4]. The severity of chronic cancer-related pain is associated with shorter survival in advanced non-small cell lung cancer (NSCLC), independently of known prognostic factors [5].

Definitions

Pain is an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage or described in such terms [6]. There are three main types of pain: somatic (nociceptive) pain, visceral pain, and neuropathic pain. Somatic pain is the most common type of pain in patients with cancer, and is characterized as well localized, intermittent, or constant and described as aching, gnawing, throbbing, or cramping [7]. Visceral pain usually occurs when lung cancer metastases to the intra-abdominal organ [8]. Neuropathic pain is pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory system [9]. Neuropathic pain can affect up to 40% in patients with cancer, which could be related to the tumor, treatment or comorbid diseases [10]. Breakthrough pain (BTP), is defined as transitory, severe flares of pain that occur in opioid-treated patients with chronic background pain [11, 12]. Pain associated with lung cancer is characterized by multiple expressions, due to either the progression of the disease and/or induced by oncological treatment [13]. Refractory pain, or intractable pain, is defined as not responding to standard treatments [14]. Post-thoracotomy pain syndrome (PTPS) is defined as pain that recurs or persists along a thoraco-

Address for correspondence: Fariz Nurwidya, MD, PhD. Department of Pulmonology and Respiratory Medicine, Universitas Indonesia Faculty of Medicine, Persahabatan Hospital, Jalan Persahabatan Raya No.1, Rawamangun Jakarta 13220, Indonesia. Tel.: +62-21-489-3536. Fax: +62-21-489-0744, e-mail: fariz.nurwidya@gmail.com
DOI: 10.5603/ARM.2016.0043
Received: 20.05.2016

ISSN 2451–4934

tomy incision at least two months following the surgical procedure [15, 16]. The most frequently used standardized scales to assess pain are visual analog scales (VAS), a verbal rating scale (VRS) and a numerical rating scale (NRS) [17].

Risk factors

Sociodemographic status, health status, and depression were associated with severity of pain in lung cancer [18]. Moreover, younger age, lower perceived health status and higher levels of other cancer symptoms (fatigue, shortness of breath and difficulty eating) were also significantly associated with a higher likelihood of reporting moderate to severe lung cancer pain [19]. Among lung cancer patients, current smokers reported pain and receiving pain treatment more often than former smokers [20]. The coping style has also been reported to affect pain. In one report, the repressive group showed statistically significant lower mean scores for pain quality and pain catastrophizing compared to the low-anxious group, high-anxious group and defensive high-anxious [21]. Genetic variations study revealed that interleukin (IL)-8-T251A were the most relevant genetic factor for lung cancer pain [22, 23].

Pathophysiology

The neurophysiology of cancer pain involves inflammatory, neuropathic, ischemic and compression mechanisms at multiple sites, and knowledge of these mechanisms and the ability to decide whether a pain is nociceptive, neuropathic, and visceral or a combination of all three will lead to best practice in pain management [24]. Many of the same inflammatory factors that promote tumor growth, such as TNFα and NF-kB, are also function as pain modulators [25]. These putative mediators subsequently sensitize and activate primary afferent nociceptors in the cancer microenvironment [26]. Nociceptive pain was the major pathophysiological subtype in lung cancer pain, but neuropathic pain accounted for 30% (range 25–32%) of cases [27]. Cytokines associated with inflammation or tissue damage due to tumor growth and spreads have been thought to contribute to pain hypersensitivity by modifying the activity of nociceptors [28]. Furthermore, tumors growing in the vicinity of peripheral nerves can compromise the integrity of the nerve, inducing a neuropathic condition accompanied by persistent pain, hyperalgesia, or allodynia [29]. Other mediators that have been studied to be involved in the cancer-related pain are nerve growth hormone [30, 31], bradykinin [32–34], endothelin-1 [35, 36], proteases-activated receptor 2 (PAR2) [37, 38], proton and acid-sensing receptor [39, 40]. Carriers of the specific IL-6 (i.e. IL-6-174C/C) genotypes required 4.7 times higher dose of opioids for pain relief compared with other genotypes [41]. Persistent idiopathic facial pain associated with mediastinal involvement in non-small cell lung cancer (NSCLC) may occur at presentation or at relapse [42]. Lung cancers rarely metastasize to the spleen, however if it is the case, the patient could suffer abdominal pain [43, 44]. Patients who undergo thoracotomy for lung cancer also have been reported to experience ipsilateral shoulder pain [45].

General approach in cancer pain management

Medical professionals' practices and knowledge regarding cancer pain management have been said as inadequate, especially due to differences between physicians and nurses in knowledge and practices for cancer pain management [46]. Effective communication is needed for optimal cancer pain management [47]. Open communication and disclosure also played important roles in the appraisal of pain symptoms [48]. Lung cancer patient who continues to smoke should be motivated intensively to quite in order to reduce the level of pain [19]. In general, the following aspect should be taken into consideration: (1) the medication regimen should be kept as simple as possible to avoid further side effect and cost burden; (2) the oral route of administration is preferred, and if is not possible, rectal or transdermal delivery is often feasible; and (3) for parenterally administered medication, the intravenous or subcutaneous routes should be used because intramuscular administration has the disadvantages of increased pain with administration and unpredictable absorption [49].

The mainstay of cancer pain management is systemic pharmacotherapy [50]. The World Health Organization (WHO) has developed a 3-step pain ladder to help the health care professional effectively manage pain, classifying pain intensity according to severity and recommending analgesic agents based on their strength [51]. In step 1, pain can be managed with nonsteroidal anti-inflammatory drugs (NSAIDS) and other non-opioid analgesics [52]. If pain persists or increases, step 2 requires opioids for mild to moderate pain along with NSAIDS and non-opioid analgesics [53]. Step 3 of the ladder is applicable to many can-

cer pain syndromes and includes opioids for moderate to severe pain in conjunction with NSAIDS and non-opioids [54]. Appropriate pain treatments in cancer include opiates, adjuvant medications, nerve blocks, and nondrug interventions [55].

Lung cancer pain management

Opioids

The second step of the WHO analgesic ladder comprises opioid analgesics such as tramadol, codeine, dihydrocodeine, and dextropropoxyphene [56]. Morphine activates the μ-opioid receptors, resulting in not only analgesia and sedation, but also euphoria, respiratory depression, constipation, and pruritus [57]. An opioid receptor is significantly implicated in anti-nociceptive processes and is found to be represented in the regions involved in nociception and pain [58]. All opioids are effective in controlling cancer pain and there is no proof that one opioid is better than another one [59]. However in poorly responsive patients, it is possible to do rotation from one drug to another [60]. Opioid rotation is a therapeutic maneuver aiming in improving analgesic response and/or reducing adverse effects, including a change to different medication using the same administration route, maintaining the current medication but altering administration route, or both [61]. Opioids could be administered through oral, transdermal, intravenous, subcutaneous, rectal, or intraspinal [62]. Opioids are normally administrated at relatively low dose initially, and the dose is increased only if the pain is unchanged or increased during next pain level assessment [63]. In acute exacerbation of pain (i.e. BTP), fentanyl buccal tablet (FBT) provides a rapid onset of analgesia (10–15 minutes) by enhancing fentanyl absorption across the buccal mucosa [64]. For continuous chronic pain, opioids should be administered around-the-clock and several long-acting formulations are available that require administration only once or twice daily [65]. For example, transdermal fentanyl, common controlled-release transdermal formulations, combines a strong opioid with a 72-hour release profile and the benefits of a parenteral route, avoiding the first-pass metabolism [66].

Cancer patients received a significantly higher cumulative opioid dose compared with dementia and chronic obstructive pulmonary disease patients [67]. Various clinical studies demonstrated tramadol analgesia and acceptable toxicity in patients with cancer pain [68]. Lung cancer patients enrolled in the European Pharmacogenetic Opioid Study (EPOS) received opioids varied from 10 to 5072 mg (mean 414, median 175) however only minority of patients achieved complete pain relief [69].

The use of opioid in lung cancer pain is not without problems. Preclinical studies have demonstrated that opioid receptor agonists increase the rate of non-small cell lung cancer (NSCLC) growth and metastasis [70]. Opioid receptor expression was increased significantly in cancer samples from patients with lung cancer compared with adjacent control tissue [71]. From *in vitro* study, opioid receptor regulates growth factor receptor signaling and epithelial-mesenchymal transition (EMT) in human NSCLC cells that is required for cells proliferation and migration [72]. Intraoperative opioid use is associated with decreased overall survival (OS) in stage I but not stage II-III NSCLC patients [73]. There has been an association between increased doses of opioids during the initial 96 hours postoperative period with a higher recurrence rate of NSCLC within 5 years which could be related to suppression of natural killer cells by opioid analgesics [74]. However, a study from single institution recently revealed that opioids were found to have no negative influence on survival time [75]. Moreover, morphine showed a beneficial effect on dyspnea in terminally ill lung cancer patients [76].

Non-opioid drugs

Anti-inflammatory drugs such as acetaminophen/paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) could be used for mild cancer pain, and although adding a NSAID to an opioid for stronger cancer pain is efficacious, but the risk of long-term adverse effects has not been quantified [77]. One finding showed there is insufficient data to support the addition of NSAIDs to WHO Step III opioids to improve analgesia or to reduce opioid dose requirement [53].

Adjuvant analgesics

Adjuvant analgesics are defined as drugs with a primary indication other than pain that have analgesic properties in some painful conditions [78]. These type of drug were classified as: (a) multipurpose adjuvant analgesics such as antidepressants, corticosteroids, α2-adrenergic agonists, neuroleptics, (b) neuropathic pain such as anticonvulsants, local anesthetics, N-methyl-D-aspartate receptor antagonists, (c) bone pain (calcitonin, bisphosphonates, radiopharmaceuticals), (d) musculoskeletal pain (muscle relaxants), or pain from bowel obstruction (octreotide, anticholinergics) [78]. For the first line of neuropathic

pain, the National Institute for Health and Care Excellence (NICE) recommends amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain [79].

Interventional options

Although the use of oral analgesics for the control of cancer pain has been demonstrated to be successful in most patients, some patients will fail to respond to pharmacological therapy or will suffer unacceptable adverse effects [80]. Several intervention strategies have been studied with various efficacies, such as neuraxial infusion, paravertebral blocks, and cordotomy [81]. Indications for neuraxial infusion include pain refractory to systemic opioids after trials of dose escalation and/or opioid rotation and the occurrence of unacceptable side effects [82]. Paravertebral blocks usually performed for post-thoracic surgery analgesia [83]. For lung cancer located in the apex, known as the Pancoast tumor, it can cause pain due to compression of the brachial plexus. The addition of paravertebral cervical nerve block could relieve the lung cancer (Pancoast tumor) patient from pain [84]. The target of computed tomography (CT)-guided percutaneous cordotomy is the lateral spinothalamic tract located in the anterolateral region of the spinal cord at the C1-C2 level [85, 86]. CT-guided percutaneous cordotomy has been shown to provide sufficient pain relieve among lung cancer patient, including Pancoast tumor, and mesothelioma [87–90]. Lastly, there are insufficient data to say whether acupuncture is effective in treating cancer pain in adults [91].

Role of radiotherapy in reducing pain in lung cancer

Radiation was indicated in the palliation of hemoptysis, chest pain, dysphagia, and dyspnea in a patient with lung cancer [92]. A randomized trial showed palliative radiotherapy of 17 Gy mid-point dose in two fractions 1 week apart does relieve chest pain in lung cancer pain [93]. Generally, a significant number of patients achieved complete resolution of symptoms and palliation of chest pain with the fractionated regimen of radiotherapy [94]. However, radiotherapy was found to be ineffective for reducing morphine dose in patients with bone metastasis from lung cancer [95].

Conclusion

Pain affects the majority of lung cancer patient and, if it's left under-treated, it will implicate in the significant reduction of quality of life. Lung cancer pain could be a nociceptive pain, visceral pain, or neuropathic pain. General approach in managing lung cancer pain follows the WHO pain ladder strategy. Despite its disadvantage in the increased incidence of recurrence, opioid remain the mainstay of lung cancer treatment. Interventional options serves as the alternative strategy if the optimal dose of opioid failed to relieve the patient from pain.

Conflict of interest

The authors declare no conflict of interest.

References:

1. Kurita GP, Sjogren P. Pain management in cancer survivorship. Acta Oncol 2015; 54: 629–634.
2. van den Beuken-van Everdingen MH, 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.
3. Wu J, Wei Y, Shi J et al. The potential therapeutic targets to bone pain induced by cancer metastasis. J Cancer Res Ther 2013; 9 Suppl: S135–141.
4. Walter FM, Rubin G, Bankhead C et al. Symptoms and other factors associated with time to diagnosis and stage of lung cancer: a prospective cohort study. Br J Cancer 2015; 112 Suppl 1: S6–13.
5. Zylla D, Kuskowski MA, Gupta K, Gupta P. Association of opioid requirement and cancer pain with survival in advanced non-small cell lung cancer. Br J Anaesth 2014; pii: aeu351.
6. GF G. Scientific Issues of Pain and Distress. In National Research Council (US) Committee on Regulatory Issues in Animal Care and Use. Definition of Pain and Distress and Reporting Requirements for Laboratory Animals: Proceedings of the Workshop Held June 22, 2000. Washington (DC): National Academies Press (US) 2000.
7. Carver AC, Foley KM. Types of pain. In: Kufe DW, Pollock RE, Weichselbaum RR (eds): Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker 2003.
8. Davis MP. Drug management of visceral pain: concepts from basic research. Pain Res Treat 2012; 2012: 265605.
9. Jensen TS, Baron R, Haanpaa M et al. A new definition of neuropathic pain. Pain 2011; 152: 2204–2205.
10. Boland EG, Mulvey MR, Bennett MI. Classification of neuropathic pain in cancer patients. Curr Opin Support Palliat Care 2015; 9: 112–115.
11. Messina J, Darwish M, Fine PG. Fentanyl buccal tablet. Drugs Today (Barc) 2008; 44: 41–54.
12. Gatti A, Gentili M, Iorno V et al. Beyond the traditional definition of breakthrough pain: an observational study. Adv Ther 2013; 30: 298–305.
13. Mercadante S, Vitrano V. Pain in patients with lung cancer: pathophysiology and treatment. Lung Cancer 2010; 68: 10–15.
14. Bentley JN, Viswanathan A, Rosenberg WS, Patil PG. Treatment of medically refractory cancer pain with a combination of intrathecal neuromodulation and neurosurgical ablation: case series and literature review. Pain Med 2014; 15: 1488–1495.
15. Gerner P. Postthoracotomy pain management problems. Anesthesiol Clin 2008; 26: 355–367, vii.
16. Hopkins KG, Hoffman LA, Dabbs Ade V et al. Postthoracotomy Pain Syndrome Following Surgery for Lung Cancer: Symptoms and Impact on Quality of Life. J Adv Pract Oncol 2015; 6: 121–132.
17. Ripamonti CI, Bandieri E, Roila F. Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol 2011; 22 Suppl 6: vi69–77.
18. Martinez KA, Snyder CF, Malin JL, Dy SM. Is race/ethnicity related to the presence or severity of pain in colorectal and lung cancer? J Pain Symptom Manage 2014; 48: 1050–1059.

19. Daniel M, Keefe FJ, Lyna P et al. Persistent smoking after a diagnosis of lung cancer is associated with higher reported pain levels. J Pain 2009; 10: 323–328.
20. Gonzalez A, Japuntich S, Keating NL et al. Pain experiences among a population-based cohort of current, former, and never regular smokers with lung and colorectal cancer. Cancer 2014; 120: 3554–3561.
21. Prasertsri N, Holden J, Keefe FJ, Wilkie DJ. Repressive coping style: relationships with depression, pain, and pain coping strategies in lung cancer outpatients. Lung Cancer 2011; 71: 235–240.
22. Reyes-Gibby CC, Wang J, Spitz M et al. Genetic variations in interleukin-8 and interleukin-10 are associated with pain, depressed mood, and fatigue in lung cancer patients. J Pain Symptom Manage 2013; 46: 161–172.
23. Reyes-Gibby CC, Spitz M, Wu X et al. Cytokine genes and pain severity in lung cancer: exploring the influence of TNF-alpha-308 G/A IL6-174G/C and IL8-251T/A. Cancer Epidemiol Biomarkers Prev 2007; 16: 2745–2751.
24. Ahmedzai SH, Barrie J, Bennet M et al. Cancer pain management. London: The British Pain Society 2010.
25. Reyes-Gibby CC, Spitz MR, Yennurajalingam S et al. Role of inflammation gene polymorphisms on pain severity in lung cancer patients. Cancer Epidemiol Biomarkers Prev 2009; 18: 2636–2642.
26. Schmidt BL. The neurobiology of cancer pain. Neuroscientist 2014; 20: 546–562.
27. Potter J, Higginson IJ. Pain experienced by lung cancer patients: a review of prevalence, causes and pathophysiology. Lung Cancer 2004; 43: 247–257.
28. Reyes-Gibby CC, Swartz MD, Yu X et al. Symptom clusters of pain, depressed mood, and fatigue in lung cancer: assessing the role of cytokine genes. Support Care Cancer 2013; 21: 3117–3125.
29. Schmidt BL, Hamamoto DT, Simone DA, Wilcox GL. Mechanism of cancer pain. Mol Interv 2010; 10: 164–178.
30. Ye Y, Dang D, Zhang J et al. Nerve growth factor links oral cancer progression, pain, and cachexia. Mol Cancer Ther 2011; 10: 1667–1676.
31. Zhu Z, Friess H, diMola FF et al. Nerve growth factor expression correlates with perineural invasion and pain in human pancreatic cancer. J Clin Oncol 1999; 17: 2419–2428.
32. Heitsch H. Bradykinin B2 receptor as a potential therapeutic target. Drug News Perspect 2000; 13: 213–225.
33. Golias C, Charalabopoulos A, Stagikas D et al. The kinin system-bradykinin: biological effects and clinical implications. Multiple role of the kinin system-bradykinin. Hippokratia 2007; 11: 124–128.
34. da Costa PL, Sirois P, Tannock IF, Chammas R. The role of kinin receptors in cancer and therapeutic opportunities. Cancer Lett 2014; 345: 27–38.
35. Tang Y, Peng H, Liao Q et al. Study of breakthrough cancer pain in an animal model induced by endothelin-1. Neurosci Lett 2016; 617: 108–115.
36. Yan XB, Peng TC, Huang D. Correlations between plasma endothelin-1 levels and breakthrough pain in patients with cancer. Onco Targets Ther 2015; 8: 3703–3706.
37. Lam DK, Schmidt BL. Serine proteases and protease-activated receptor 2-dependent allodynia: a novel cancer pain pathway. Pain 2010; 149: 263–272.
38. Lam DK, Dang D, Zhang J et al. Novel animal models of acute and chronic cancer pain: a pivotal role for PAR2. J Neurosci 2012; 32: 14178–14183.
39. Justus CR, Dong L, Yang LV. Acidic tumor microenvironment and pH-sensing G protein-coupled receptors. Front Physiol 2013; 4: 354.
40. Yoneda T, Hata K, Nakanishi M et al. Involvement of acidic microenvironment in the pathophysiology of cancer-associated bone pain. Bone 2011; 48: 100–105.
41. Reyes-Gibby CC, El Osta B, Spitz MR et al. The influence of tumor necrosis factor-alpha -308 G/A and IL-6 -174 G/C on pain and analgesia response in lung cancer patients receiving supportive care. Cancer Epidemiol Biomarkers Prev 2008; 17: 3262–3267.
42. Pembroke CA, Byrne A, Lester JF, Button M. Persistent unilateral facial pain in lung cancer patients with mediastinal nodal involvement. Lung Cancer 2013; 82: 173–175.
43. Eisa N, Alhafez B, Alraiyes AH, Alraies MC. Abdominal pain as initial presentation of lung cancer. BMJ Case Rep 2014; 2014.
44. Schmidt BJ, Smith SL. Isolated splenic metastasis from primary lung adenocarcinoma. South Med J 2004; 97: 298–300.
45. Imai Y, Imai K, Kimura T et al. Evaluation of postoperative pregabalin for attenuation of postoperative shoulder pain after thoracotomy in patients with lung cancer, a preliminary result. Gen Thorac Cardiovasc Surg 2015; 63: 99–104.
46. Jho HJ, Kim Y, Kong KA et al. Knowledge, practices, and perceived barriers regarding cancer pain management among physicians and nurses in Korea: a nationwide multicenter survey. PLoS One 2014; 9: e105900.
47. Canivet D, Delvaux N, Gibon AS et al. Improving communication in cancer pain management nursing: a randomized controlled study assessing the efficacy of a communication skills training program. Support Care Cancer 2014; 22: 3311–3320.
48. Miller LM, Lyons KS, Bennett JA. Incongruent perceptions of pain and physical function among families living with lung cancer. Support Care Cancer 2015; 23: 2755–2762.
49. Ferrell B, Koczywas M, Grannis F, Harrington A. Palliative care in lung cancer. Surg Clin North Am 2011; 91: 403–417, ix.
50. Schug SA, Chandrasena C. Pain management of the cancer patient. Expert Opin Pharmacother 2015; 16: 5–15.
51. Prommer EE. Pharmacological Management of Cancer-Related Pain. Cancer Control 2015; 22: 412–425.
52. Brant JM. The global experience of cancer pain. Asian Pac J Cancer Prev 2010; 11 Suppl 1: 7–12.
53. Nabal M, Librada S, Redondo MJ et al. The role of paracetamol and nonsteroidal anti-inflammatory drugs in addition to WHO Step III opioids in the control of pain in advanced cancer. A systematic review of the literature. Palliat Med 2012; 26: 305–312.
54. Sollami A, Marino L, Fontechiari S et al. Strategies for pain management: a review. Acta Biomed 2015; 86 Suppl 2: 150–157.
55. Smith TJ, Saiki CB. Cancer Pain Management. Mayo Clin Proc 2015; 90: 1428–1439.
56. Leppert W, Luczak J. The role of tramadol in cancer pain treatment — a review. Support Care Cancer 2005; 13: 5–17.
57. Plante GE, VanItallie TB. Opioids for cancer pain: the challenge of optimizing treatment. Metabolism 2010; 59 Suppl 1: S47–52.
58. Przewlocki R, Przewlocka B. Opioids in chronic pain. Eur J Pharmacol 2001; 429: 79–91.
59. Mercadante S. The use of opioids for treatment of cancer pain. Expert Opin Pharmacother 2015; 16: 389–394.
60. Portenoy RK, Ahmed E. Principles of opioid use in cancer pain. J Clin Oncol 2014; 32: 1662–1670.
61. Vadalouca A, Moka E, Argyra E et al. Opioid rotation in patients with cancer: a review of the current literature. J Opioid Manag 2008; 4: 213–250.
62. Cherny NJ, Chang V, Frager G et al. Opioid pharmacotherapy in the management of cancer pain: a survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. Cancer 1995; 76: 1283–1293.
63. Huang Z, Liang L, Li L et al. Opioid doses required for pain management in lung cancer patients with different cholesterol levels: negative correlation between opioid doses and cholesterol levels. Lipids Health Dis 2016; 15: 47.
64. Simpson DM, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. Clin Ther 2007; 29: 588–601.
65. Nicholson B. Responsible prescribing of opioids for the management of chronic pain. Drugs 2003; 63: 17–32.
66. Vallerand AH. The use of long-acting opioids in chronic pain management. Nurs Clin North Am 2003; 38: 435–445.
67. Romem A, Tom SE, Beauchene M et al. Pain management at the end of life: A comparative study of cancer, dementia, and chronic obstructive pulmonary disease patients. Palliat Med 2015; 29: 464–469.

68. Leppert W. Tramadol as an analgesic for mild to moderate cancer pain. Pharmacol Rep 2009; 61: 978–992.
69. Salminen EK, Silvoniemi M, Syrjanen K et al. Opioids in pain management of mesothelioma and lung cancer patients. Acta Oncol 2013; 52: 30–37.
70. Lennon FE, Moss J, Singleton PA. The mu-opioid receptor in cancer progression: is there a direct effect? Anesthesiology 2012; 116: 940–945.
71. Singleton PA, Mirzapoiazova T, Hasina R et al. Increased mu -opioid receptor expression in metastatic lung cancer. Br J Anaesth 2014; 113 Suppl 1: i103–108.
72. Lennon FE, Mirzapoiazova T, Mambetsariev B et al. The Mu opioid receptor promotes opioid and growth factor-induced proliferation, migration and Epithelial Mesenchymal Transition (EMT) in human lung cancer. PLoS One 2014; 9: e91577.
73. Cata JP, Keerty V, Keerty D et al. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non -small cell lung cancer resection. Cancer Med 2014; 3: 900–908.
74. Maher DP, Wong W, White PF et al. Association of increased postoperative opioid administration with non-small-cell lung cancer recurrence: a retrospective analysis. Br J Anaesth 2014; 113 Suppl 1: i88–94.
75. Minami S, Fujimoto K, Ogata Y et al. Opioids have no negative effect on the survival time of patients with advanced lung cancer in an acute care hospital. Support Care Cancer 2015; 23: 2245–2254.
76. Gamborg H, Riis J, Christrup L, Krantz T. Effect of intraoral and subcutaneous morphine on dyspnea at rest in terminal patients with primary lung cancer or lung metastases. J Opioid Manag 2013; 9: 269–274.
77. Vardy J, Agar M. Nonopioid drugs in the treatment of cancer pain. J Clin Oncol 2014; 32: 1677–1690.
78. Lussier D, Huskey AG, Portenoy RK. Adjuvant analgesics in cancer pain management. Oncologist 2004; 9: 571–591.
79. Longson D, Bhojani I, Brandner B et al. Neuropathic pain — Pharmacological management. In The pharmacological management of neuropathic pain in adults in non-specialist settings. Manchester: National Institute for Health and Care Excellence 2013.
80. Mercadante S, Villari P, Ferrera P. Dialogues on complex analgesic strategies for difficult pain syndromes. Support Care Cancer 2004; 12: 599–603.
81. Vayne-Bossert P, Afsharimani B, Good P et al. Interventional options for the management of refractory cancer pain-what is the evidence? Support Care Cancer 2016; 24: 1429–1438.
82. Yennurajalingam S, Dev R, Walker PW et al. Challenges associated with spinal opioid therapy for pain in patients with advanced cancer: a report of three cases. J Pain Symptom Manage 2010; 39: 930–935.
83. Chen J, Zhang Y, Huang C et al. Effects of thoracic paravertebral block on postoperative analgesia and serum level of tumor marker in lung cancer patients undergoing video-assisted thoracoscopic surgery. Zhongguo Fei Ai Za Zhi 2015; 18: 104–109.
84. Pelaez R, Pascual G, Aguilar JL, Atanassoff PG. Paravertebral cervical nerve block in a patient suffering from a Pancoast tumor. Pain Med 2010; 11: 1799–1802.
85. Kanpolat Y, Ugur HC, Ayten M, Elhan AH. Computed tomography-guided percutaneous cordotomy for intractable pain in malignancy. Neurosurgery 2009; 64: ons187–193; discussion ons193–184.
86. Oran NT. Percutaneous chordotomy for managing cancer pain. Aorn j 2001; 74: 363–369, 371-362; quiz 373–368.
87. Kanpolat Y, Ozdemir M, Al-Beyati E. CT-guided percutaneous cordotomy for intractable pain in what is more than a disease: lung malignancies. Turk Neurosurg 2013; 23: 81–87.
88. Kanpolat Y, Savas A, Ucar T, Torun F. CT-guided percutaneous selective cordotomy for treatment of intractable pain in patients with malignant pleural mesothelioma. Acta Neurochir (Wien) 2002; 144: 595–599; discussion 599.
89. Bekar A, Kocaeli H, Abas F, Bozkurt M. Bilateral high-level percutaneous cervical cordotomy in cancer pain due to lung cancer: a case report. Surg Neurol 2007; 67: 504–507.
90. Kanpolat Y, Caglar S, Akyar S, Temiz C. CT-guided pain procedures for intractable pain in malignancy. Acta Neurochir Suppl 1995; 64: 88–91.
91. Paley CA, Johnson MI, Tashani OA, Bagnall AM. Acupuncture for cancer pain in adults. Cochrane Database Syst Rev 2015; 10: Cd007753.
92. Brundage MD, Bezjak A, Dixon P et al. The role of palliative thoracic radiotherapy in non-small cell lung cancer. Can J Oncol 1996; 6 Suppl 1: 25–32.
93. Rees GJ, Devrell CE, Barley VL, Newman HF. Palliative radiotherapy for lung cancer: two versus five fractions. Clin Oncol (R Coll Radiol) 1997; 9: 90–95.
94. Erridge SC, Gaze MN, Price A et al. Symptom control and quality of life in people with lung cancer: a randomised trial of two palliative radiotherapy fractionation schedules. Clin Oncol (R Coll Radiol) 2005; 17: 61–67.
95. Ishiyama H, Shibata A, Niino K, Hosoya T. Relationship between morphine and radiotherapy for management of symptomatic bone metastases from lung cancer. Support Care Cancer 2004; 12: 743–745.