Recent advances in cancer pain management
James Wilson¹*, Catherine Stack² and Joan Hester²

Addresses: ¹Department of Anaesthetics, St George’s Hospital, Blackshaw Road, Tooting, London SW17 0QT, UK; ²Department of Anaesthetics, King’s College Hospital, Denmark Hill, London SE5 9RS, UK

* Corresponding author: James Wilson (jamesfwilson@doctors.org.uk)

F1000Prime Reports 2014, 6:10 (doi:10.12703/P6-10)

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial License (http://f1000.com/prime/reports/m/6/10), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. You may not use this work for commercial purposes.

The electronic version of this article is the complete one and can be found at: http://f1000.com/prime/reports/m/6/10

Abstract

Pain is the most feared symptom of cancer. New oncological cancer treatments are improving survival, but advanced cancer presents challenges that have not been seen before, often with pain that is very difficult to manage because of a recurrent tumour that is invading the central nervous system. In some of the older interventional techniques of destroying nerve pathways, expertise has diminished or has been deemed unnecessary with the development of specialist palliative care. Not all pain is managed adequately with the analgesic ladder. Knowledge of pain mechanisms, careful assessment and selection of the right technique at the right time will enhance cancer pain management. New techniques include intrathecal drug therapy, vertebroplasty, cordotomy, ultra-sound guided nerve blocks, neuromodulation and advances in drug therapies.

Introduction

Unrelieved pain is the most feared symptom of cancer and occurs in over 75% of people with advanced disease [1]. Pain relief in palliative care was founded on the oral administration of morphine regularly “by the clock”, initiated by the late Dame Cicely Saunders in the 1950s in London, and promoted by the WHO in 1986 as the third step of the analgesic ladder [2] for pain relief in cancer in developing countries around the world. The analgesic ladder approach has been outstandingly successful in alleviating pain and suffering when it is applied and used correctly, leading to a decline in the use of other interventions, such as nerve blocks. However, in the past decade, advances in the use of chemotherapy, radiotherapy and other cancer treatments have improved survival, sometimes at the expense of more complex pain from cancer that may spread to involve nerve plexuses, the spinal canal and the brain. Studies have shown that at least 20-40% of cancer pain is not adequately relieved by application of the analgesic ladder [3,4]. It is time to move on. Patients rightly want to maintain a good quality of life without the burdensome effect of sedating drugs. The long-term adverse effects of opioids on cognitive function, and on the immune and endocrine systems [5] have been largely ignored in palliative care but are significant in cancer survivors [6].

Pain mechanisms are important in the understanding of cancer pain, as is the interaction of emotions, memory, life experiences, mood, expectations, and the roller coaster of the cancer patient’s journey on the pain experience. Every experience is a different one. There is always much to learn.

Advances in cancer pain management are evolving but the aim now is to manage complex and difficult pain while minimising the adverse effects of sedating drugs.

This article discusses several advances in this area:

(a) the mechanisms of cancer pain, and how knowledge of these mechanisms may lead to the development of novel analgesic agents;

(b) advances in drug therapy;

(c) intrathecal drug therapy;
(d) vertebroplasty and kyphoplasty;

(e) useful interventional therapies, such as cordotomy, coeliac plexus block, intrathecal neurolysis, and ultrasound guided techniques;

(f) the pain relieving role of chemotherapy and radiotherapy;

(g) neuromodulation;

(h) and other techniques.

**Mechanisms of cancer pain**

Cancer causes pain by many different routes, including direct tissue invasion, inflammation, obstruction (viscera, nerves and cerebrospinal fluid [CSF]) and can also result from cancer treatment (surgery, radiotherapy and chemotherapy). As a consequence, it has nociceptive, neuropathic and ischaemic elements. Debate is ongoing about whether cancer pain is distinct from other forms of pain or merely a composite of these separate mechanisms. Animal models have provided a greater understanding of the distinct central and peripheral mechanisms of cancer pain.

**Peripheral mechanisms**

Recent studies have provided more information about the molecular interactions within the cancer microenvironment [7]. These are often dependent on the tumour type. Nociceptive mediators present at high concentrations include protons [8,9], endothelin-1 [10-14], bradykinin [15,16], cytokines such as tumor necrosis factor (TNF)-α [17], nerve growth factor (NGF) and proteases such as trypsin [18]. These stimulate primary afferent sensory neuron receptors resulting in nociception, as well as peripheral and central sensitisation. As such, they are potential targets for novel selective cancer pain analgesics.

**Central mechanisms**

Spinal and supra-spinal mechanisms may affect the perception and perpetuation of cancer pain. In animal models of bone cancer pain, increases in descending facilitation from the rostroventral medulla mediated by serotonin (5HT3) lead to enhanced nociception from innocuous stimulation [19]. Ondansetron is an antagonist of 5HT3 though not, as yet, of known clinical benefit.

N-methyl-D-aspartate (NMDA) receptor activation in the cord can result in long term potentiation and central sensitisation. Increase in the ratio of wide dynamic range to nociceptive only neurones in the dorsal horn can lead to nociceptive only neurones.

Ketamine and dextromethorphan have been used as NMDA antagonists and, although evidence for effectiveness in cancer pain as an adjunct to opioids is weak [20], they have a role in opioid-induced hyperalgesia, caused by high dose opioid use, and can “reset” opioid receptors to regain responsiveness.

Specific combinations of spinal cord changes are seen in animal models of cancer pain [21]. Increased glial fibrillary acidic protein (GFAP) is seen in the spinal cord in bone cancer models. This is associated with astrocyte activation. Activation of glia, which is also seen in other pain states, can perpetuate pain by secreting inflammatory cytokines such as interleukin (IL)-1 & 6, TNF-α and prostaglandins, leading to a positive feedback loop. Glial inhibitors, such as anti-TNF-α drugs, are a potential target for analgesics. Increased dynorphin levels are also seen, which at high concentration leads to NMDA receptor activation and pro-nociception. Again, this may be reversed by ketamine.

**Advances in drug therapy**

**New preparations of fentanyl**

Buccal, sublingual and intranasal preparations of fentanyl (a highly potent opioid analgesic with a short duration of action) for breakthrough pain, are used widely in palliative care. Analgesia is of rapid onset. Within 15 minutes, the drug is absorbed through the oral mucosa, is usually well tolerated and is effective in about 75% of patients for breakthrough cancer pain. These preparations can be difficult to withdraw in cancer survivors and should not be used outside their licensed indication.

**Agents for neuropathic pain**

Tricyclic antidepressants and gabapentinoids are often used as adjuncts to opioids for neuropathic pain. In neuropathic cancer pain they are rarely used alone, prior to opioids: a recent study showed that all antineuropathic agents are effective and there is a morphine-sparing effect of pregabalin [22]. Combinations are more effective than one drug alone, and only 15-30% of patients attain the gold standard of 50% pain relief. Preliminary studies show that duloxetine, a serotonin and noradrenaline re-uptake inhibitor originally developed as an antidepressant, reduces chemotherapy-induced peripheral neuropathic pain in some patients [23].

**Tapentadol**

Tapentadol is a novel centrally acting analgesic that is both a noradrenaline uptake inhibitor and a mu agonist (acts on opioid receptors). A study by Mercadante et al. concluded that it is effective for cancer pain [24]. This 50 patient 4-week open label prospective study of opioid naïve patients with moderate to severe cancer pain demonstrated that tapentadol was effective in reducing pain and improving functional status compared to placebo.

N-methyl-D-aspartate (NMDA) receptor activation in the cord can result in long term potentiation and central sensitisation. Increase in the ratio of wide dynamic range to nociceptive only neurones in the dorsal horn can lead to nociceptive only neurones.
pain showed significantly improved pain scores and quality of life.

**Capsaicin**
Capsaicin, the active ingredient of the hot red chilli pepper, activates the transient receptor potential vanilloid 1 (TRPV) receptor expressed in nociceptive sensory nerves and defunctionalizes nociceptor activity. A recent Cochrane review suggests that low dose topical capsaicin is no better than placebo cream for peripheral neuropathic pain but high concentrations can be effective [25]. It is available as an 8% skin patch (Qutenza), which is applied to a hypersensitive area after local anaesthetic as a "one off" treatment. If effective it can be repeated after 3 months. Qutenza is not licensed for cancer- or chemotherapy-related neuropathic pain and its role in cancer treatment has not yet been evaluated.

**Lidocaine**
Topical lidocaine 5% medicated plasters are licensed for post herpetic neuralgia but are recommended in a recent review as first-line treatment for localized neuropathic pain from a variety of causes [26]. The plasters are cooling, liked by patients, and are remarkably safe. There are no studies of their use in cancer pain.

**Intrathecal drug therapy**
Neuraxial (epidural and intrathecal) infusions of local anaesthetic with or without opioid make a most important contribution to the management of severe cancer pain. Indeed, it has been suggested that intrathecal morphine should be the top rung of the analgesic ladder and that intraspinal therapy should be used when the usual pharmacological therapies have failed [27]. Sadly, the provision of intrathecal drug therapy is all too rare in the UK, although the expertise is available [28].

Epidural infusions of local anaesthetic with opioid, targeting the appropriate nerve roots, are effective but require large infusion volumes (2-10 mls/hour) delivered by an external pump. This can be achieved in a hospice or hospital setting but is not practicable for use at home. Intrathecal infusions (into cerebrospinal fluid) are of low volume and can be delivered via a fully implanted pump, which allows the patient complete independence in between pump reservoir refills, at intervals between 3 weeks and 3 months.

The main indications for use of intrathecal drug delivery are:

(a) uncontrolled pain despite high doses of opioids and adjunct drugs;
(b) unacceptable side effects from analgesics;
(c) cancer involving a nerve plexus, most commonly the lumbosacral plexus;
(d) and widespread bony metastases.

Battery powered fully programmable pumps (e.g. those made by Medtronic Ltd; Fig 1) contain a drug reservoir of 20 or 40 ml. The intrathecal catheter and pump are inserted under general anaesthesia by a surgeon and are programmed via a computer and telemetric head held over the abdominal skin where the pump is sited. Drugs that can be used are: preservative-free morphine, hydromorphone, clonidine, baclofen, bupivacaine and ziconotide. Doses can be altered as often as necessary and the patient can deliver pre-set boluses via a hand held device called a PTM (Personal Therapy Manager; Fig 2).

A randomised controlled trial showed improved quality of life, sustained pain control and significantly less drug-related toxicity with intrathecal drug delivery (ITDD) compared to comprehensive medical management [29]. Survival was significantly longer in the ITDD arm of the trial. There have been other case series and a recent review article supportive of the technique [30-32].

**Figure 1. Intrathecal pump (Medtronic Ltd.)**
Personal experience consisting of a case series of 24 patients with pain from advanced cancer (where other therapies have failed to provide pain relief) supports the findings of sustained pain control, lack of sedation, no serious complications and improved quality of life. Here is a recent quote from the widow of a patient: “…without the benefit of the pump I cannot imagine how much additional medication he would have needed and what effect that would have had on the quality of his life”.

**Vertebroplasty and kyphoplasty**

Metastatic spread of cancer to the vertebral bodies in the spine occurs in one third of patients with carcinoma and half of those with distant metastases [33], most commonly in the thoracic spine. Pain is a common symptom, presenting as back pain if the metastasis is isolated to the body of the vertebra, or with radiating pain in the distribution of compressed nerve roots if the tumour starts to invade the spinal canal. Vertebroplasty is a technique of injecting acrylic cement percutaneously into the affected vertebral body or bodies under fluoroscopic imaging. Kyphoplasty is a newer modification of vertebroplasty where a specialised balloon is inflated in the vertebral body prior to injection of cement. This minimises leakage of cement and reduces kyphotic deformity. A systematic review of safety and efficacy of percutaneous vertebroplasty in malignancy in 987 cases indicated pain reduction ranging between 47 and 87%, but a 2% risk of serious complications including 5 deaths, 4 cement pulmonary emboli, and frequent cement leaks, 12 of which caused neuropathy requiring emergency decompression [34]. The authors comment on a lack of robust data. The same authors published a more optimistic prospective study of percutaneous vertebroplasty in 125 patients with myeloma and spinal metastases and reported reduction in pain and improvement in mobility without serious complications [35].

**Useful interventional techniques**

Since the palliative care movement gathered pace in the 1970s and 1980s, requests for “permanent” nerve blocks have become fewer, partly because of perceived lack of effectiveness or harm from the blocks and partly because anaesthetists (who perform the blocks) became more remote and less experienced. There are a few interventional techniques that still have an important role in complex cancer pain management.

**Percutaneous cervical cordotomy**

This is a radiofrequency lesion to the spinothalamic tract at C1-2 level in the cervical spinal cord for pain on the opposite side of the body, usually from mesothelioma or breast carcinoma causing severe unilateral pain. It is performed at four centres only in the UK. Case series show effectiveness in 85-90% cases, and a reduction in drug-related toxicity, with minimal adverse effects [36].
Coeliac plexus block
This is a neurolytic block of the coeliac ganglia, situated anterior to the body of L1 vertebra, which innervate the organs of the upper abdomen through the sympathetic nervous system. It is a technique that was widely performed via a posterior approach until the mid 1990s when a retrospective postal survey showed an incidence of paraplegia following the block of 0.15% [37]. However, evidence points to effective pain relief and reduction in opioid use following a successful block [38-40]. There are many approaches to the coeliac ganglia described in the literature: none is better than another, but use of CT scanning, ultrasonography-guided blocks via the anterior route, or the video-thorascopic approach adopted in recent years may improve safety [41].

Intrathecal neurolysis
This is the injection of phenol or alcohol onto the dorsal roots of selected nerves via a spinal needle sited within the dural sac. Safety depends on correct positioning of the patient and skill of the operator. The technique is performed in a few centres only in the UK but selective dorsal thoracic root blocks are helpful for chest wall pain and saddle blocks for pelvi-sacral pain [42].

Ultrasound guided nerve blocks
Improvements in ultrasound technology have greatly improved accuracy of placement of needles and catheters adjacent to nerves, and there is increasing use by anaesthetists for regional anaesthesia. A literature review by Tran et al. concluded that for axillary blocks the use of ultrasound increases the likelihood of the block being successful [43]. Portable machines make bedside use in hospices and other settings a realistic goal. Brachial plexus, lumbar plexus, femoral, intercostal, sciatric and other nerve blocks are now readily achievable and may become more commonplace again.

The pain-relieving role of radiotherapy and chemotherapy
Palliative radiotherapy is used to relieve pain from brain and bony metastases. A Cochrane review shows a complete response in 25% at one month, with a further 40% of patients with painful bony metastases getting 50% pain relief [44-46]. The radionuclides strontium-89 and radium-223 have been used successfully to treat pain from prostate cancer bone secondaries [47].

Palliative chemotherapy is most successful in lymphoma, germ cell tumours, small cell lung tumours and breast carcinoma. Chemotherapy can also induce pain, especially neuropathic pain.

Coeliac plexus block
This is a neurolytic block of the coeliac ganglia, situated anterior to the body of L1 vertebra, which innervate the organs of the upper abdomen through the sympathetic nervous system. It is a technique that was widely performed via a posterior approach until the mid 1990s when a retrospective postal survey showed an incidence of paraplegia following the block of 0.15% [37]. However, evidence points to effective pain relief and reduction in opioid use following a successful block [38-40]. There are many approaches to the coeliac ganglia described in the literature: none is better than another, but use of CT scanning, ultrasonography-guided blocks via the anterior route, or the video-thorascopic approach adopted in recent years may improve safety [41].

Intrathecal neurolysis
This is the injection of phenol or alcohol onto the dorsal roots of selected nerves via a spinal needle sited within the dural sac. Safety depends on correct positioning of the patient and skill of the operator. The technique is performed in a few centres only in the UK but selective dorsal thoracic root blocks are helpful for chest wall pain and saddle blocks for pelvi-sacral pain [42].

Ultrasound guided nerve blocks
Improvements in ultrasound technology have greatly improved accuracy of placement of needles and catheters adjacent to nerves, and there is increasing use by anaesthetists for regional anaesthesia. A literature review by Tran et al. concluded that for axillary blocks the use of ultrasound increases the likelihood of the block being successful [43]. Portable machines make bedside use in hospices and other settings a realistic goal. Brachial plexus, lumbar plexus, femoral, intercostal, sciatric and other nerve blocks are now readily achievable and may become more commonplace again.

The pain-relieving role of radiotherapy and chemotherapy
Palliative radiotherapy is used to relieve pain from brain and bony metastases. A Cochrane review shows a complete response in 25% at one month, with a further 40% of patients with painful bony metastases getting 50% pain relief [44-46]. The radionuclides strontium-89 and radium-223 have been used successfully to treat pain from prostate cancer bone secondaries [47].

Palliative chemotherapy is most successful in lymphoma, germ cell tumours, small cell lung tumours and breast carcinoma. Chemotherapy can also induce pain, especially neuropathic pain.
blinding. Further, higher quality studies are needed to confirm the efficacy of these treatments.

**Educational interventions**

Although opioids are effective drugs at reducing cancer pain, there are significant psychological barriers that prevent physicians from prescribing them and patients from accepting them. These are illustrated in the recent National Institute for Health and Clinical Excellence (NICE) guidelines on opioids in palliative care [61]. Several interview-based studies have highlighted patients’ concerns about opioids [62-64]. They include concerns over addiction, tolerance, side effects and issues such as acceptance of palliation rather than treatment, and the feeling that starting opioids is a landmark for end-of-life care.

Educational interventions aim to reduce these barriers by providing information, thus increasing patient satisfaction and adherence to medication, leading to improved pain control. There have been many studies on the efficacy of educational interventions. The meta-analysis performed by Bennett et al. in 2009 demonstrated that educational interventions, compared to usual care, led to improvements in patients knowledge and attitudes and an improvement in average pain score of around 1 point out of 10 [65]. Interestingly, they did not find any improvement in the consequence of pain on patient function or adherence to medication. A systematic review by Ling et al. in 2012 again found a significant improvement in pain control with educational interventions but no improvement in quality of life [66].

**In summary**

Cancer pain is complex and multifactorial in origin, which makes management of pain difficult in at least a quarter of patients. Careful assessment of the types and sources of pain must be made and then treated holistically, adapting treatment to the needs of the individual. Recent advances in drug therapies, interventional techniques and the multiplicity of approaches that may be necessary are outlined in this short article; there are few rigorous trials in cancer patients and there remain many unknowns. The specialties of oncology, palliative care and pain medicine must work together to achieve the best possible pain management for patients.

**Abbreviations**

ITDD, intrathecal drug delivery; NMDA, N-methyl-D-aspartate; PTM, personal therapy manager; TNF, tumor necrosis factor.

**Disclosures**

The authors declare that they have no disclosures.

**Acknowledgments**

The authors would like to thank Dr Mark Linch, Consultant Medical Oncologist, Sarcoma Unit, Royal Marsden Hospital, Fulham Road, London SW3 6JJ for advice about the pain relieving role of radiotherapy and chemotherapy.

**References**

1. Bonica J VV, Twycross RG: Cancer pain. In The Management of Pain. 2nd edition. Philadelphia: Lea and Febiger; 1990, 400-401.
2. WHO: Cancer Pain Relief. In Geneva; 1986.
3. Twycross R, Harcourt J, Bergl S: A survey of pain in patients with advanced cancer. J Pain Symptom Manage 1996, 12:273-82.
4. Weiss SC, Emanuel LL, Fairclough DL, Emanuel EJ: Understanding the experience of pain in terminally ill patients. Lancet 2001, 357:1311-5.
5. Seyfried O, Hester J: Opioids and Endocrine Dysfunction. British Journal of Pain 2012, 6(1):17-24.
6. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, Kaur G, Bruea E: Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. Cancer 2004, 100:851-8.
7. Schmidt BL, Hamamoto DT, Simone DA, Wilcox GL: Mechanism of cancer pain. Mol Interv 2010, 10:164-78.
8. Ghilardi JR, Röhrich H, Lindsay TH, Sevcik MA, Schwe Mj, Kubota K, Halvorsen KG, Poblete J, Chaplan SR, Dubin AE, Carruthers NI, Swanson D, Kuskowski M, Flores CM, Julius D, Mantyh PW: Selective blockade of the capsaicin receptor TRPV1 attenuates bone cancer pain. J Neurosci 2005, 25:3126-31.
9. Nage M, Hiraga T, Yoneda T: Acidic microenvironment created by osteoclasts causes bone pain associated with tumor colonization. J Bone Miner Metab 2007, 25:99-104.
10. Nelson J, Bagnato A, Battistini B, Nisen P: The endothelin axis: emerging role in cancer. Nat Rev Cancer 2003, 3:110-6.
11. Cain DM, Wacnik PW, Turner M, Wendelschafer-Crabb G, Kennedy WR, Wilcox GL, Simone DA: Functional interactions between tumor and peripheral nerve: changes in excitability and morphology of primary afferent fibers in a murine model of cancer pain. J Neurosci 2001, 21:9367-76.
12. Wacnik PW, Eikmeier LJ, Ruggles TR, Ramnaraine ML, Walcheck BK, Beitz AJ, Wilcox GL: Functional interactions between tumor and peripheral nerve: morphology, algogen identification, and behavioral characterization of a new murine model of cancer pain. J Neurosci 2001, 21:9355-66.
13. Quang PN, Schmidt BL: Peripheral endothelin B receptor agonist-induced antinociception involves endogenous opioids in mice. Pain 2010, 149:254-62.
14. Quang P, Schmidt B: Endothelin receptor-mediated attenuation of carcinoma-induced nociception is opioid-dependent in mice. The Journal of Pain 2009, 10(4 suppl):322.
15. Sevcik MA, Ghilardi JR, Halvorsen KG, Lindsay TH, Kubota K, Mantyh PW: Analgesic efficacy of bradykinin B1 antagonists in a murine bone cancer pain model. J Pain 2005, 6:771-5.
16. Fujita M, Andoh T, Ohashi K, Akira A, Saiki I, Kuraishi Y: Roles of kinin B1 and B2 receptors in skin cancer pain produced by
orthotopic melanoma inoculation in mice. *Eur J Pain* 2010, 14:588-94.

17. Constantin CE, Mair N, Sailer CA, Andratsch M, Xu Z, Blumer MJF, Scherbakov N, Davis JB, Bluetmann H, Ji R, Kress M: Endogenous tumor necrosis factor alpha (TNFalpha) requires TNF receptor type 2 to generate heat hyperalgesia in a mouse cancer model. *J Neurosci* 2008, 28:5072-81.

18. Lam DK, Schmidt BL: Serine proteases and protease-activated receptor 2-dependent allodynia: a novel cancer pain pathway. *Pain* 2010, 149:263-72.

19. Gordon-Williams RM, Dickenson AH: Central neuronal mechanisms in cancer-induced bone pain. *Curr Opin Support Palliat Care* 2007, 1(6-10).

20. Bell RF, Eccleston C, Kalso EA: Ketamine as an adjuvant to opioids for cancer pain. *Cochrane Database Syst Rev* 2012, 11:CD003351.

21. Currie GL, Delaney A, Bennett MI, Dickenson AH, Egan KJ, Vesterinen HM, Sena ES, Macleod MR, Calvisi LA, Fallon MT: Animal models of bone cancer pain: systematic review and meta-analyses. *Pain* 2013, 154:917-26.

22. Mishra S, Bhatnagar S, Goyal GN, Rana SPS, Upadhyaya SP: A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. *Am J Hosp Palliat Care* 2012, 29:177-82.

23. Smith EML, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Falud CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL: Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA* 2013, 309(13):1359-67.

24. Mercadante S, Porzio G, Ferrera P, Aielli F, Adile C, Ficorella C, Giarratano A, Casuccio A: Tapentadol in cancer pain management: a prospective open-label study. *Curr Med Res Opin* 2012, 28:1775-9.

25. Derry S, Lloyd R, Moore RA, McQuay HJ: Topical capsaicin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev* 2009, CD007393.

26. Mick G, Correa-Illanes G: Topical pain management with the 5% lidocaine medicated plaster—a review. *Curr Med Res Opin* 2012, 28:937-51.

27. de Leon-Casasola OA, Medicis ED: My patient with rectal cancer does not have pain control despite high doses of opioids and optimal doses of gabapentin and desipramine. Now what?—Advanced strategies for cancer pain management. *Techniques in Regional Anaesthesia and Pain Management* 2000, 4:167-173.

28. Williams JE, Grady K: *Pain News: Intrathecal drug delivery for the management of pain and spasticity in adults; a national audit*. BPS National Intrathecal Drug Audit group 2008, [http://www.britishpainsociety.org/bps_nl_winter_2008.pdf](http://www.britishpainsociety.org/bps_nl_winter_2008.pdf).

29. Smith TJ, Staats PS, Deer T, Stearns LJ, Rauck RL, Boorutz-Maxx RL, Buchzer E, Català E, Bryce DA, Coyne PJ, Pool GE: Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol* 2002, 20:4040-9.

30. Burton AW, Rajagopal A, Shah HN, Mendoza T, Cleveland C, Hassenbusch SJ, Arens JF: Epidural and intrathecal analgesia is effective in treating refractory cancer pain. *Pain Med* 2004, 5:239-47.

31. Deer TR, Smith HS, Burton AW, Pope JE, Doleys DM, Levy RM, Staats PS, Wallace MS, Webster LR, Rauck RL, Cousins M: Comprehensive consensus based guidelines on intrathecal drug delivery systems in the treatment of pain caused by cancer pain. *Pain Physician* 2011, 14:E283-312.

32. Upadhyaya SP, Mallick PN: Intrathecal drug delivery system (IDDS) for cancer pain management: a review and updates. *Am J Hosp Palliat Care* 2012, 29:388-98.

33. DRURY AB, PALMER PH, HIGHMAN WJ: *Carcinomatous metastasis to the vertebral bodies*. *J Clin Pathol* 1964, 17:448-57.

34. Chew C, Craig L, Edwards R, Moss J, O’Dwyer PJ: Safety and efficacy of percutaneous vertebroplasty in malignancy: a systematic review. *Clin Radiol* 2011, 66:63-72.

35. Chew C, Ritchie M, O’Dwyer PJ, Edwards R: A prospective study of percutaneous vertebroplasty in patients with myeloma and spinal metastases. *Clin Radiol* 2011, 66:1193-6.

36. Jackson MB, Pounder D, Price C, Matthews AW, Neville E: Percutaneous cervical cordotomy for the control of pain in patients with pleural mesothelioma. *Thorax* 1999, 54:238-41.

37. Davies DD: Incidence of major complications of neurolytic coeliac plexus block. *J R Soc Med* 1993, 86:264-6.

38. Wong GY, Schroeder DR, Carns PE, Wilson JL, Martin DP, Kinney MO, Mantilla CB, Werner DO: Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. *JAMA* 2004, 291:1092-9.

39. Polati E, Finco G, Gotin L, Bassi C, Pedezzoli P, Ischia S: Prospective randomized double-blind trial of neurolytic celiac plexus block in patients with pancreatic cancer. *Br J Surg* 1998, 85:199-201.

40. Arcidiacono PG, Calori G, Carrara S, McNicol ED, Testoni PA: Celiac plexus block for pancreatic cancer pain in adults. *Cochrane Database Syst Rev* 2011, CD007519.

41. Stefaniak T, Basinski A, Vingerhoets A, Makarewicz W, Connor S, Kaska L, Stanek A, Kwiecinska B, Lachinski AJ, Sledzinski Z: A comparison of two invasive techniques in the management of intractable pain due to inoperable pancreatic cancer: neurolytic celiac plexus block and videothoracoscopically assisted splanchnectommy. *Eur J Surg Oncol* 2005, 31:768-73.

42. Slatkin NE, Rhiner M: Phenol saddle blocks for intractable pain at end of life: report of four cases and literature review. *Am J Hosp Palliat Care* 2003, 20:62-6.
43. Tran DQH, Clemente A, Tran DQ, Finlayson Rj: A comparison between ultrasound-guided infraclavicular block using the "double bubble" sign and neurostimulation-guided axillary block. Anesth Analg 2008, 107:1075-8.

44. McQuay HJ, Collins SL, Carroll D, Moore RA: Radiotherapy for the palliation of painful bone metastases. Cochrane Database Syst Rev 2000: CD001793.

45. Chow E, Harris K, Fan G, Tiao M, Sze WM: Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007, 25:1423-36.

46. Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, Howell D, Konski A, Kashnic L, Lo S, Sahgal A, Silverman L, Gunten C von, Mendel E, Vassil A, Bruner DW, Hartsell WV: Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys 2011, 79:965-76.

47. Nilsson S, Franzen L, Parker C, Tyrrell C, Blom R, Tennvall J, Lennermans B, Petersson U, Johannessen DC, Sokal M, Pigott K, O'Bryan-Tear CG, Thuresson M, Bolstad B, Bruoland OS: Two-year survival follow-up of the randomized, double-blind, placebo-controlled phase II study of radium-223 chloride in patients with castration-resistant prostate cancer and bone metastases. Clin Genitourin Cancer 2013, 11:20-6.

48. Coleman RE, Guise TA, Lipston A, Roodman GD, Berenson JR, Body J, Boyce BF, Calvi LM, Hadji P, McCluskey EV, Saad F, Smith MR, Suva LJ, Taichman RS, Vessella RL, Weilbaecher KN: Advancing treatment for metastatic bone cancer: consensus recommendations from the Second Cambridge Conference. Clin Cancer Res 2008, 14:6387-95.

49. Wong R, Wiffen PJ: Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database Syst Rev 2002: CD002068.

50. Linch M: Cancer treatments for Pain Relief. In. Royal Marsden Hospital, 2013.

51. van Buyten J, Al-Kaisy A, Smet I, Palmisani S, Smith T: High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter European clinical study. NeuroModulation 2013, 16:59-65 discussion 65-6.

52. Lihaa P, Su M, Zajun Z, Ke W, Bennett MI: Spinal cord stimulation for cancer-related pain in adults. Cochrane Database Syst Rev 2013, 2:CD009389.

53. Shimizu K, Hokari T, Kano T, Tomita M, Kimura R, Watanabe S, Endoh H, Fukuda S, Fujiwara N, Aida S: Management of intractable pain with percutaneous epidural spinal cord stimulation: differences in pain-relieving effects among diseases and sites of pain. Anesth Analg 1993, 77:110-6.

54. Yakovlev AE, Resch BE, Kasarov SA: Treatment of cancer-related chest wall pain using spinal cord stimulation. Am J Hosp Palliat Care 2010, 27:552-6.

55. Yakovlev AE, Resch BE: Spinal cord stimulation for cancer-related low back pain. Am J Hosp Palliat Care 2012, 29:93-7.

56. Pasta JP, Cordura JV, Burton AW, Hasemansbusch SJ, Weng H, Dougherty PM: Spinal cord stimulation relieves chemotherapy-induced pain; a clinical case report. J Pain Symptom Manage 2004, 27:72-8.

57. Tsubota S, Higaki N, Nagaro T: [A case of neuropathic cancer pain in the lower extremities successfully treated with spinal cord stimulation]. Masui 2009, 58:1460-1.

58. Yakovlev AE, Ellias Y: Spinal cord stimulation as a treatment option for intractable neuropathic cancer pain. Clin Med Res 2008, 6:103-6.

59. Nouri KH, Brish E: Spinal cord stimulation for testicular pain. Pain Med 2011, 12:1435-8.

60. Bardia A, Barton DL, Prokop LJ, Bauer BA, Moynihan TJ: Efficacy of complementary and alternative medicine therapies in relieving cancer pain: a systematic review. J Clin Oncol 2006, 24:3457-64.

61. NICE clinical guideline 140: Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care in adults. National Institute for Health and Clinical Excellence 2012, [http://www.nice.org.uk/nicemedia/live/13745/59285/59285.pdf]

62. Blanchard H, Batten B: Designing and producing a patient leaflet on morphine. Eur J Pall Care 1996, 3:106-8.

63. Bender JL, Hohendel J, Wong J, Katz J, Ferris LE, Shobblebrook C, Warr D, Jaday AP: What patients with cancer want to know about pain: a qualitative study. J Pain Symptom Manage 2008, 35:177-87.

64. Reid CM, Gooberman-Hill R, Hanks GW: Opioid analogics for cancer pain: symptom control for the living or comfort for the dying? A qualitative study to investigate the factors influencing the decision to accept morphine for pain caused by cancer. Ann Oncol 2008, 19:44-8.

65. Bennett MI, Bagnall A, José Closs S: How effective are patient-based educational interventions in the management of cancer pain? Systematic review and meta-analysis. Pain 2009, 143:192-9.

66. Ling C, Lui LYY, So WKW: Do educational interventions improve cancer patients’ quality of life and reduce pain intensity? Quantitative systematic review. J Adv Nurs 2012, 68:511-20.