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EAU GUIDELINE

Prostate cancer pain management: EAU guidelines on pain management

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Abstract
Context The first publication of the European Association of Urology (EAU) guidelines on Pain Management in Urology dates back to 2003. Since then, these guidelines have been revised several times with the most recent update achieved in 2010.
Objective Given the scope of the full text guidelines, condensing the entire document was no option in this context. This paper presents a summary of the section of pain management in prostate cancer, a topic considered of direct relevance for the practicing urologist.
Evidence acquisition A multidisciplinary expert panel (urologists, anaesthesiologists, radio-oncologists) compiled this document based on a comprehensive consultation of the literature. Data were identified through a structured search, covering the time frame 2000 through 2010, using Medline and Embase as well as the Cochrane Library of systematic reviews. The scientific papers were weighed by the expert panel and a level of evidence (LE) assigned. Recommendations have been graded as a means to provide transparency between the underlying evidence and the guidance provided.
Evidence summary Pain can occur in each stage of prostate cancer. It could be caused by the cancer itself (77%), be related to the cancer treatment (19%) or be unrelated to either (3%). The incidence of pain rises to 90% as patients enter the terminal phase of their illness. The physician's task is to discover and treat the cause of pain and the pain itself, to determine whether or not the underlying cause is treatable, to provide pain relief and palliative care. These tasks more often than not require a multidisciplinary team. Pain management involves mainly pharmacotherapy, including direct anticancer therapy such as androgen deprivation and chemotherapy, as well as analgetics, for instance non-steroidal anti-inflammatory drugs (NSAIDs) or opioids. In case of local impairment due to the cancer or its metastases, primary treatments like surgery, radiotherapy or radionuclides can provide adequate pain relief. In addition, in palliative care, functional, psychosocial and spiritual support are essential components. The EAU guidelines on Pain Management in Urology are available in a number of different formats through the EAU Central Office and the EAU website (http://www.uroweb.org/guidelines/online-guidelines/).

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Conclusion The mainstay of pain management in prostate cancer is involvement of and collaboration between experts from a number of disciplines to be able to achieve a complete pain evaluation and to offer the full range of treatment options. Prostate cancer–related pain can, in most cases, be managed effectively, but it requires careful monitoring where a balance should be found between pain relief and potential side effects of treatment and quality of life (QoL).

Keywords Prostate cancer · Pain · EAU guidelines · Pharmacotherapy · Radiotherapy · Radionuclides · Surgery · Biphosphonates · Corticosteroids

Introduction

Management of pain related to urological pathologies is an important aspect of urological care. Depending on the site and cause of the pain, a number of options are available to the treating physician. Guiding principle is to balance benefits of treatment against side effects.

This document summarises the findings of the expert panel regarding the management of prostate cancer–related pain. While the urologist will be the main treating physician for most of the patient's clinical course, in many cases—and certainly if treatment extends over a longer period of time—involvement of a number of specialists from other disciplines constitutes a standard approach, irrespective of the healthcare setting.

Evidence acquisition

An international multidisciplinary group of urologists, radio-oncologists and anaesthesiologists have assessed the data based on a structured literature search of MedLine, Embase and the Cochrane Library, covering a time frame of 2000 through 2010. A level of evidence (LE) and grade of recommendation (GR) have been assigned based on a system modified from the Oxford Centre for Evidence-Based Medicine [1].

This article presents a section of the European Association Urology (EAU) Guidelines on General Pain Management which are available in different formats through the EAU Central Office and the association website (http://www.uroweb.org/guidelines/on-line.guidelines/).

Pain evaluation and measurement

Pain can occur in both the early and advanced stages of prostate cancer. It could be caused directly by the cancer (77%), be related to the cancer treatment (19%) or be unrelated to either (3%) [2]. The overall incidence of chronic pain in prostate cancer patients is about 30–50%, but rises to 90% as patients enter the terminal phase of their illness [3]. Pain may be directly attributable to tumour growth in three main areas, i.e. tumour infiltration of bone, nerve or a hollow viscus.

Several rating scales are available to assess pain, including:

- the visual analogue scale (VAS) (unidimensional) (Fig. 1)
- the verbal rating scale (VRS) (unidimensional)
- multiple-item assessments (multidimensional), which measure not only pain intensity but also additional dimensions of the pain experience, such as the emotional, affective, cognitive and social items, e.g. quality-of-life questionnaires, including the McGill Pain questionnaire, the Medical Outcomes Short-Form Health Survey Questionnaire 36 (SF-36) and the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) [4–6].

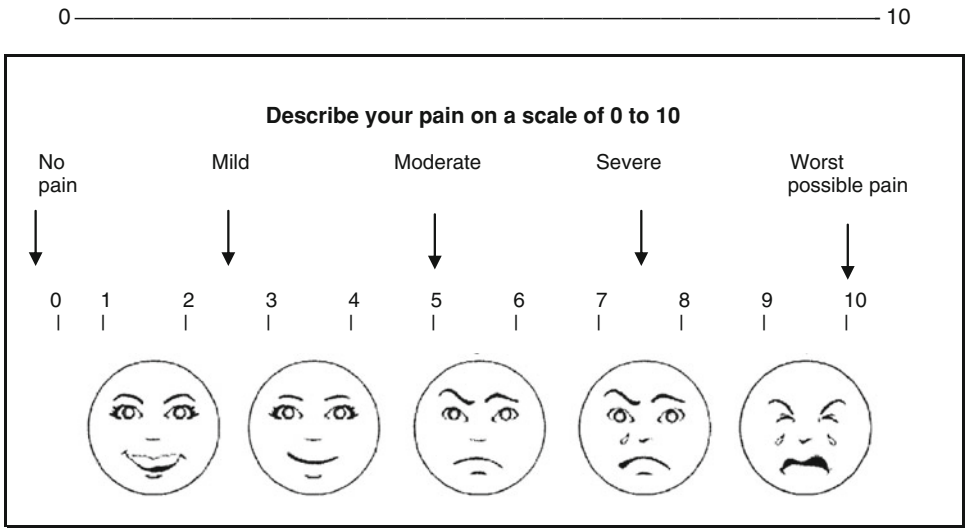

Fig. 1 Visual analogue scale (VAS)

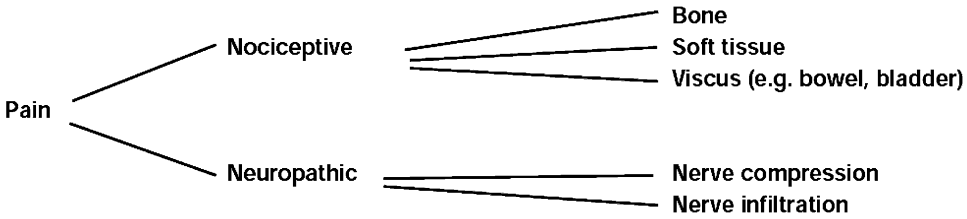

Fig. 2 Classification and origin of cancer pain

Ease of use of the VAS and VRS has resulted in widespread adoption of these scales to measure pain intensity. In chronic pain syndromes, however, both of these measurement scales have shown significant weakness in sensitivity which is attributed to the fact that these are unidimensional tools. Variability between subjects due to, for instance, different emotional, affective and cognitive responses to pain which may also be linked to cultural difference are not measured by the VAS or VRS. To study the effects of both physical and non-physical influences on patient well-being, an instrument must assess more dimensions than the intensity of pain or other physical symptoms. Instruments that assess these aspects during disease or treatment are health-related QoL questionnaires such as the McGill pain questionnaire, the SF36 and the EORTC QLQ-C30 [4–6].

Urogenital neoplasms frequently metastasise to bone. Pathological fractures, hypercalcaemia and neurological deficits lead to the substantial impairment of QoL. The release of algogenic substances in the tissue, microfractures and periosteal tension are the main mechanisms for pain sensation [7].

In patients with cancer pain (Fig. 2), the pathophysiological mechanism is nociceptive in 65–68% of cases, neuropathic in 8–9% or a combination of both nociceptive and neuropathic pain in 23–27% of cases [8, 9]. Neuropathic pain is defined by the International Association for the Study of Pain as 'pain arising as a direct consequence of a lesion affecting the somatosensory system' [10]. It is characterised by positive (allodynia, hyperalgesia) and negative symptoms (muscle weakness, loss of reflexes). Positive symptoms are due to an abnormal excitability of the nervous system, while negative symptoms are due to a loss of sensation resulting from loss of axons or neurons [11].

General principles of cancer pain management

The four main goals of pain management and palliative care are: prolonging survival, optimising comfort, optimising function and relieving pain. Table 1 provides a hierarchy of treatment principles through which these goals can be achieved.

Table 1 Hierarchy of general treatment principles (panel consensus)

1	Individualised treatment for each patient
2	Causal therapy to be preferred over symptomatic therapy
3	Local therapy to be preferred over systemic therapy
4	Systemic therapy with increasing invasiveness (WHO ladder)
5	Conformance with palliative guidelines
6	Supportive therapies, such as psychological counselling and physical therapy, from the very beginning

WHO World Health Organization

Pain due to local impairment

Surgery

While there is a certain reluctance to apply surgical principles in cancer palliation, surgery offers a good chance for symptom improvement when medication therapies are no longer possible. Radical surgery to excise locally advanced disease in patients without evidence of metastatic spread may help prevent painful local problems [12] (LE: 4).

Recurrent bladder outlet obstruction can be extremely disturbing and should be treated endoscopically when hormonal deprivation fails.

Ureteral obstruction can result in pain in prostate cancer patients. Irrespective of QoL issues, percutaneous nephrostomy drainage and retrograde stenting can be acceptable options for untreatable pain. Similarly, unilateral or bilateral ureteral re-implantation can be considered in this setting [13] (LE: 4). Minimally invasive interventions, such as vertebroplasty and kyphoplasty, are options in certain painful vertebral fractures [14].

Table 2 summarises specific pain management in prostate cancer patients suffering from pain due to local impairment [15, 16].

Androgen deprivation

A variety of additive or ablative hormone manipulations have been used (Table 3), including oestrogen, anti-androgen (bicalutamide, flutamide, cyproterone), oestrogen-mustine complex (estramustine) and gonadotropin-releasing hormone (GnRH) analogues. Hormone therapy can cause a

Table 2 Specific pain management in case of local impairment

Local impairment	Symptoms	Pain management
Invasion or compression of a hollow viscus	Various (e.g. flank pain, fever)	Surgery and minimal-invasive procedures (e.g. ureteral stent, nephrostomy)
Bladder outlet obstruction	Lower urinary tract symptoms	(Suprapubic) catheter and hormonal therapy, palliative TURP after ≥6 weeks of hormonal therapy
Ureteric obstruction, typically asymmetric	Hydronephrosis and subsequent renal failure	Nephrostomy or double-J stent
Lymphoedema of the legs due to a huge prostate mass and/or lymph node metastases in the pelvis	Heaviness of the legs	Physiatric techniques, e.g. wraps, pressure stockings or pneumatic pump devices
Ileus	Mechanical obstruction	Surgery: colostomy/ileostomy
	Paralytic ileus due to tumour infiltration of a nerve plexus or secondary to analgesics	Laxatives to improve motility and reduce pain

Table 3 Hormone therapy

Hormone therapy	Side effects
GnRH analogues and orchidectomy	Loss of body hair
	Testicular atrophy
	Gynaecomastia
	Loss of libido
	Impotence
	Psychological morbidity
Anti-androgens	Gynaecomastia
	Hepatic impairment
	Sexual dysfunction
Cyproterone acetate	Fewer side effects than oestrogens
Oestrogens	Loss of body hair
	Testicular atrophy
	Gynaecomastia
	Loss of libido
	Impotence
	Higher mortality from cardiac and cerebrovascular disease

GnRH gonadotropin-releasing hormone analogues

'flare' or temporary exacerbation of pain, which is generally a predictor of subsequent response.

Cyproterone acetate provides fewer side effects than oestrogens and has a lower incidence of cardiovascular complications [17] (LE: 1a).

Pain due to metastases

Bone metastases are the commonest cause of chronic pain in prostate cancer, and multifocal pain is frequent. More than 25% of patients with bone metastases are pain-free. Patients with multiple bone metastases typically report pain in only a few sites. Treatment options are hormone therapy (*see* Table 3), radiotherapy, radionuclides, orthopaedic surgery, bisphosphonates, corticosteroids, chemotherapy and systemic analgesic pharmacotherapy ('analgesic ladder').

Radiotherapy

The role of radiotherapy in the palliation of symptomatic bone metastases is well established [18], with complete or partial pain relief obtained in 20–50% and in 50–80% of patients, respectively. The onset of pain relief varies from a few days to 4 weeks. Single-fraction radiotherapy, with a recommended dose of 8 Gy, is as effective as multifraction radiotherapy in relieving metastatic bone pain [19, 20] (LE: 1a).

Metastatic epidural spinal cord compression is a severe complication that affects almost 5–10% of patients with cancer (there are no data exclusively on prostate cancer). Functional outcome is determined by neurological function. A delay in treatment is the most common cause of an unfavourable outcome. High-dose corticosteroids—although 'a must' in every guidance approaching cord compression—carries a significant risk of serious adverse effect [21]. Direct decompressive surgery is superior to radiotherapy alone, with regard to regaining ambulatory function, pain relief and recovering sphincter function [22] (LE: 1a). Radiotherapy is recommended as the primary treatment for patients who do not fulfil the recommendations for surgery listed in Table 4. In general, multifraction radiotherapy is preferable [21].

Ambulatory function is superior in patients treated with surgery followed by radiotherapy, compared to radiotherapy alone. For impending pathological fractures, a prophylactic orthopaedic procedure should be considered.

Radionuclides

The most important radiopharmaceuticals are strontium-89 chloride and samarium-153 lexidronam. Both radiopharmaceuticals emit predominantly beta particles, which are

Table 4 Criteria for selecting patients for primary therapy for spinal cord compression

	Surgery	Radiotherapy
Absolute criteria		
Operability	Medically operable	Medically inoperable
Duration of paraplegia (h)	<48	≥48
Life expectancy (months)	≥3	<3
Radiosensitivity		Highly sensitive
Relative criteria		
Diagnosis of primary tumour	Unknown	Known
Bone fragments with compression	Present	Absent
Number of foci of compression	1 focus	>1 foci

responsible for the therapeutic response in 60–80% of patients [23].

Radiopharmaceuticals are indicated for treating bone pain, resulting from skeletal metastases involving >1 site and associated with an osteoblastic response on bone scan, but without spinal cord compression [24] (LE: 2, GR: B). Pain reduction occurs after the first week. Analgesics should be continued until pain improves.

There is a risk of temporary pain flare in 10% of the patients [25, 26]. The most important late side effect is temporary myelosuppression [23, 24] (LE: 2). Radiation exposure to the public is possible [4] (LE: 2).

Radiopharmaceuticals should not be administered if the glomerular filtration rate is <30 mL/min [27]. Because of the myelosuppression, white blood cell count >3,500/μL and platelets >100,000/μL are desirable [23, 26].

Bisphosphonates

Bisphosphonates are pyrophosphate analogues that act through five mechanisms:

- Inhibition of bone resorption (24–48 h after administration) due to reduction of osteoclastic activity;
- Inhibition of osteoclast adhesion;
- Decrease in number of osteoclasts and induction of osteoclast apoptosis;
- Inhibition of crystallisation and mineralisation;
- Promotion of osteoblastic bone formation and production of osteoclast resorption inhibitor.

Anti-angiogenic effect and effect on tumour cells

The main effects of bisphosphonates are a decrease in the risk of skeleton-related events and adequate pain alleviation in 60–85% [28] (LE: 1a). Their side effects are 'flu-like' symptoms (20–40%), bone pain, fever, fatigue, arthralgia and myalgia (all <10%), hypocalcaemia, acute renal failure and osteonecrosis of the jaw bones. Dental status has to be evaluated prior to administration. Zoledronic acid, a nitrogen-containing third-generation bisphosphonate, is the most effective bisphosphonate in the treatment of metastatic bone disease [29] (GR: A). Other bisphosphonates, including pamidronate and clodronate, seem to be less effective in this setting [30].

Corticosteroids

Corticosteroids are also used for the palliation of pain, particularly due to bone deposits. Patients with advanced cancer who experience pain and other symptoms may respond favourably to a relatively small dose of corticosteroids (e.g. dexamethasone 1–2 mg twice daily) [31] (LE: 1b).

Chemotherapy

The possibility of successful pain relief is usually related to the likelihood of tumour response. There is a strong clinical impression that tumour shrinkage is generally associated with pain relief, though there are some reports of analgesia, even in the absence of significant tumour shrinkage. Chemotherapy is much more cost-intensive than the administration of opioids and has a limited survival advantage. However, recent data from randomised studies in patients with metastatic prostate cancer after chemotherapy, particularly those using docetaxel, have provided encouraging improvements in overall survival, palliation of symptoms and improvements in QoL. Docetaxel compared to mitoxantrone provided a better response to pain and improvement in QoL (31–35% vs. 22%) [32] (LE:1a).

Systemic analgesic pharmacotherapy

Analgesic drugs used in prostate cancer pain management are separated into three groups:

- non-opioid analgesics
- opioid analgesics
- adjuvant analgesics—drugs with other primary indications that can be effective analgesics in specific circumstances.

The Cancer Unit of the WHO proposed a useful approach to drug selection for cancer pain, which has become known as the 'analgesic ladder' (Fig. 3) [33]. With appropriate dosing, this approach provides adequate relief in 70–90% of patients [34].

In incurable oncologic patients with quick progression of the disease and reduced life expectancy, recent data, however, suggest a direct move from step 1 to step 3 (excluding step 2) resulting in superior pain relief and increased patient satisfaction [35].

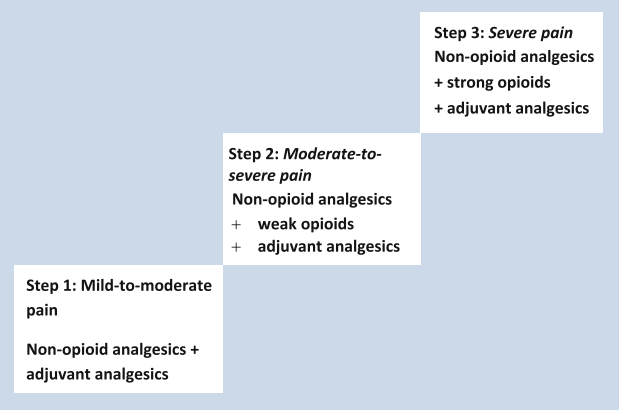

Fig. 3 The World Health Organization's 'analgesic ladder'

The introduction of a fourth step in the WHO analgesic ladder (including interventional treatment such as intrathecal administration of analgesics, peripheral nerve catheterisation and neurolytic blockades) has been proposed in patients with intractable cancer pain who failed to response adequately to pharmacological treatment [36, 37].

Non-opioid analgesics

Non-opioid analgesics can be useful alone for mild-to-moderate pain (Step 1 of the analgesic ladder), or combined with opioids (Steps 2 and 3). The use of NSAIDs has not been established for cancer pain treatment, even though there is some evidence that ibuprofen is effective for cancer pain [38].

The adverse effects of NSAIDs are gastric irritation, ulcer formation, bleeding, renal impairment, bronchospasm, asthma deterioration, platelet dysfunction and inhibition of osteogenesis.

The use of cyclo-oxygenase 2 (COX-2) selective inhibitors is not established for cancer pain, even though their use is associated with fewer gastrointestinal complications and minimal platelet inhibition compared with non-selective COX inhibitors. This is because their long-term use has been associated with cardiovascular problems [39].

Paracetamol (acetaminophen) is used for mild-to-moderate cancer pain. In cases of moderate-to-severe post-operative pain, the co-administration of paracetamol with strong opioids appears to reduce opioid consumption [40] (LE: 1a). The exact mode of action of paracetamol is unclear, but probably involves the central inhibition of COX production. The dose (500 mg to 1 g 3–4 times daily (orally or rectally) should be reduced in patients with hepatic impairment or chronic alcoholism as exceeding the dose can cause acute hepatic failure. A dose greater than 6 g in 24 h can cause acute renal failure.

Table 5 Opioids: drugs, dosage and administration

Drug	Dosage per day	Route of administration
Strong opioids[a]		
Morphine	5 mg × 6–8	Orally controlled release
	10–100 mg × 2	
	15–30 mg × 6	Rectally
Oxycodone	5–10 mg × 4–6	Orally
		Rectally
Hydromorphone	1–3 × 6	Orally
	4 mg × 2	Orally controlled release
Fentanyl	25–200 µg/h	Transdermally
	200–800 µg × 4	Sublingually
Buprenorphine	5–70 µg/h	Transdermally
	200–400 µg × 3–4	Sublingually
Weak opioids		
Tramadol	50–100 mg × 4–6	Orally
Codeine	30–60 mg × 4	Orally

[a] Strong opioids have no real upper limit in dosage (except buprenorphine). The dose must be titrated against pain relief and taking into account the individual strength of unwanted effects, such as respiratory depression

Opioids

Opioids are the choice for moderate-to-severe cancer pain (Table 5). The key principle for their safe and effective use is to titrate the dose against pain relief and to minimise unwanted effects. Factors to consider for opioid selection are: age, pain intensity, prior opioid therapy and co-existing disease. Opioids should be given by the least invasive and safest route that is capable of providing adequate analgesia. Their main adverse effects are respiratory depression, apnoea, sedation, confusion, delirium, nausea, vomiting, pruritus, constipation, hypotension, addiction, dependence and tolerance.

Weak opioids, such as codeine and tramadol, along with tricyclic antidepressants (TCAs) and NSAIDs produce a variable response in different population groups, due to genetic polymorphism of cytochrome P450 enzymes, and careful dose titration is therefore necessary [41]. Oral administration is the preferred route in routine practice. The potency of opioids administered rectally is believed to approximate oral dosing [42]. The transdermal system for fentanyl and buprenorphine administration has been demonstrated to be effective in cancer pain [43]. The incidence of side effects, such as sedation and constipation, is lower compared with morphine [43, 44].

An oral transmucosal (sublingual) formulation of fentanyl, which incorporates the drug into a sugar base, is useful for providing rapid relief of breakthrough pain and appears to be more effective than oral morphine [45]. There are

many different opioids combinations with paracetamol for oral or rectal administration.

Opioids in patients with continuous or frequent pain can be administered using an 'around-the-clock' dosing schedule, with a so-called 'rescue dose' as needed. The 'as needed' dosing scheme may be appropriate for patients, who have rapidly decreasing analgesic requirements or intermittent pain separated by pain-free intervals. They can also be administered as controlled release preparations.

Patient-controlled analgesia (PCA) is a technique that can be used in postoperative patients and may also be used to manage acute pain in end-stage cancer patients. It consists of parenteral (intravenous or epidural) drug administration, in which the patient controls an infusion device that delivers a bolus of analgesic drug 'on demand'. In most cases, PCA is added to a basal infusion rate and acts essentially as a rescue dose. Opioids are also provided in controlled release preparations, which can lessen the inconvenience associated with the short duration of action.

Adjuvant analgesics

Adjuvant analgesics may be combined with primary analgesics in any of the three steps of the 'analgesic ladder' to improve the outcome for patients, who cannot otherwise attain an acceptable balance between relief and side effects. In the management of cancer pain, the following groups are distinguished:

- corticosteroids (*see above*)
- antidepressants
- benzodiazepines
- anticonvulsants.
- S(+)-ketamine.

Antidepressants tricyclic antidepressants (TCAs) are often the first drugs selected and have a particular role in the treatment of neuropathic pain [46]. They act by blocking the reuptake of norepinephrine and serotonin. Tricyclic antidepressants must be used cautiously in patients with a history of cardiovascular disorders, glaucoma and urine retention. Although TCAs are first-line treatment in patients with neuropathic (non-cancer) pain, there are few data evaluating its analgesic effect in patients with neuropathic cancer pain. Based on the available literature (in non-cancer neuropathic pain), it is assumed that these analgesics also have an analgesic effect in patients with neuropathic pain due to cancer (LE: 4, GR: C).

Selective serotonin reuptake inhibitors (SSRIs), such as sertraline, paroxetine, fluoxetine and citalopram, selectively inhibit the reuptake of serotonin and have a more favourable side effect profile than TCAs. However, their analgesic effect is questionable in neuropathic (cancer) pain [46].

Benzodiazepines these drugs are known to relieve patients' anxiety, insomnia and phobia. Their analgesic effect is associated with conditions of high anxiety, muscle spasm and deafferentation [47].

Anticonvulsants lamotrigine, carbamazepine, diphantoine, pregabaline and gabapentine are effective in the treatment of neuropathic pain. However, studies are only available for gabapentine in neuropathic cancer pain, and gabapentine is therefore recommended as first-line treatment in the management of neuropathic cancer pain ([48] (LE: 2, GR: A).

S(+)-ketamine oral or intravenous administration of S(+)-ketamine may be effective in patients with severe neuropathic cancer pain, despite treatment with anticonvulsants and/or antidepressants (LE: 4, GR: C). It can have severe side effects (including hallucinations, dissociation and nightmares), which limit its usefulness and widespread use in neuropathic cancer pain. For this reason, S(+)-ketamine should only be considered as a third-line option, for use when standard analgesic treatments are exhausted [49].

Invasive analgesic techniques

In patients with cancer pain that fails to respond to systemic analgesics, interventional procedures can be considered.

Effective relief of neuropathic pain due to malignant infiltration of the lumbar plexus has been achieved with local anaesthetic agents administered through a psoas sheet catheter. A continuous sacral root nerve block has been used to treat severe neuropathic cancer pain due to infiltration of a sacral nerve [50, 51].

For progressive tumour invasion (involvement of the whole sacral plexus), it may be more appropriate to control pain using intrathecal morphine, given alone or in combination with local anaesthetic agents. The aim is to induce pain relief by placing a small dose of an opioid close to opioid receptors located at the dorsal horn of the spinal cord. This also means that the total dose of opioids administered can be reduced, leading to less opioid-induced side effects. It may be beneficial to add a low dose of a local anaesthetic agent (usually bupivacaine), particularly in patients with neuropathic pain. Intrathecally administered local anaesthetic agents can result in sensory and motor impairment. The potential for other complications, such as meningitis, should also be taken into account [52, 53].

Finally, the sympathetic nervous system has been implicated in the maintenance of cancer pain syndromes. In patients with intractable pelvic pain due to genitourinary neoplastic disease, a superior hypogastric block may result in pain control [54].

Table 6 Recommendations for pain control in metastasised prostate cancer

Recommendation	LE	GR
Anticancer treatment		
Hormonal therapy (orchiectomy, LHRH analogues, diethylstilboestrol equivalent) in hormone naïve PCA	1a	A
Supportive care		
Low-dose glucocorticoids	1b	A
Chemotherapy		
Mitoxantrone plus prednisolone	1b	B
Estramustine + vinblastine or etoposide or paclitaxel	2b	B
Docetaxel	1b	A
Pain management		
Pain assessment (localisation, type, severity, overall distress)		B
Pain due to painful or unstable bony metastases (single lesions)		
External beam irradiation	1b	A
Pain due to painful bony metastases (widespread)		
Radioisotopes (89Sr or 153Sm-EDTMP)	2	B
Pain due to painful metastases (many spots)		
Bisphosphonates	1b	A
Systemic pain management		
WHO analgesic ladder step 1: NSAID or paracetamol	1a	A
Opioid administration		
Dose titration	2	B
Access to breakthrough analgesia	1b	A
Tricyclic antidepressant and/or anticonvulsant in case of neuropathic pain	1a	A

Table 6 presents recommendations for pain control in metastasised prostate cancer.

Palliative care/physical-psychological support/ quality of life

Palliative care is defined by the WHO as an approach that improves the QoL of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. It includes pain management, as well as functional, psychosocial and spiritual support [14]. Palliative care may take place at any stage of the disease, alone, or in combination with active curative treatment.

Medical, psychological, physical, social, hospice and pastoral interdisciplinary services can be helpful at the end of a patient's life [15]. Patients in an advanced stage of prostate cancer often experience 'total pain', which is a mixture of physical, psychological, spiritual and social suffering [55]. Information about the illness and the process of care has been proven to reduce distress [56, 57] and treatment should include both psychological and somatic symptoms [55].

Moderate exercise seems to provide a certain benefit in the treatment of fatigue [58, 59] (LE: 1a). Family caregivers and support groups are crucial components of the patient's support system [15]. Members of prostate cancer self-help groups provide each other with various types of help, usually non-professional and non-material, for a particular, shared, usually burdensome, feature [57]. The help may take the form of providing and evaluating relevant information, relating personal experiences, listening to and accepting others' experiences, providing sympathetic understanding and establishing social networks. A supporting self-help group may also work to inform the public or engage in advocacy. All efforts are aimed at improving a patient's QoL [56].

Summary

This text presents a summary of only one section of the EAU Guidelines on Pain Management. More detailed information on this topic, as well as additional information on the management of pain in urological practice, can be found in the full text version. These guidelines are available on the EAU Web site (http://www.uroweb.org/guidelines/online-guidelines/).

Conflict of interest The authors declare that they have no conflict of interest in relation to the content of the manuscript. They have all contributed equally to the writing of this document.

References

1. Oxford Centre for Evidence-Based Medicine Levels of Evidence (2001) Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick, March 2009. Centre for Evidence Based Medicine Web site. http://www.cebm.net/index.aspx?o=5653. Accessed Apr 2011.
2. Foley KM (1979) Pain syndromes in patients with cancer. In: Bonica JJ, Ventafridda V (eds) Advances in pain research and therapy 2. Raven Press, New York, pp 59–75
3. Twycross RG, Lack SA (1983) Symptom control in far advanced cancer: pain relief. Pitman, London, p 6
4. Jensen MP (2003) The validity and reliability of pain measures in adults with cancer. J Pain 4(1):2–21
5. Rosier EM, Iadarola MJ, Coghill RC (2002) Reproducibility of pain measurement and pain perception. Pain 98(1–2):205–216
6. Melzack R (1975) The McGill pain questionnaire: major properties and scoring methods. Pain 1:277–299
7. Mercadante S (1997) Malignant bone pain: pathophysiology and treatment. Pain 69(1–2):1–18
8. Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA (1995) Validation of the world health organization guidelines for cancer pain relief: a 10-year prospective study. Pain 63:65–76
9. Caraceni A, Portenoy RK (1999) An international survey of cancer pain, characteristics and syndromes. Pain 82:263–274
10. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J (2008) Neuropathic pian. Redefinition and a grading system for clinical and research purposes. Neurology 70:1630–1635
11. Rasmussen PV, Sindrup SH, Jensen TS, Bach FW (2004) Symptoms and signs in patients with suspected neuropathic pain. Pain 110:461–469
12. Kamat AM, Huang SF, Bermejo CE, Rosser CJ, Pettaway CA, Pisters PW, Guitreau DP, Pisters LL (2003) Total pelvic exenteration: effective palliation of perineal pain in patients with locally recurrent prostate cancer. J Urol 170(5):1868–1871
13. Wilson JR, Urwin GH, Stower MJ (2005) The role of percutaneous nephrostomy in malignant ureteric obstruction. Ann R Coll Surg Engl 87(1):21–24
14. Thompson JC, Wood J, Feuer D (2007) Prostate cancer: palliative care and pain relief. Br Med Bull 83:341–354
15. Ok JH, Meyers FJ, Evans CP (2005) Medical and surgical palliative care of patients with urological malignancies. J Urol 174:1177–1182
16. Russo P (2000) Urologic emergencies in the cancer patient. Semin Oncol 27(3):284–298
17. Schröder FH, Whelan P, de Reijke TM, Kurth KH, Pavone-Macaluso M, Mattelaer J, van Velthoven RF, Debois M (2004) Members of the EORTC Genito-Urinary Group Metastatic prostate cancer treated by flutamide versus cyproterone acetate. Final analysis of the "European Organization for Research and Treatment of Cancer" (EORTC) Protocol 30892. Eur Urol 45(4):457–464
18. McQuay HJ, Collins SL, Carroll D (2000) Radiotherapy for the palliation of painful bone metastases. Cochrane Database Sys Rev 2:CD001793
19. Wu J, Wong R, Johnston M et al (2003) Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. Int J Radiot Oncol Biol Physiol 55:594–605
20. Sze WM, Shelley M, Held I et al (2004) Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy. Cochrane Database Syst Rev 2:CD004721
21. George R, Jeba J, Ramkumar G et al (2008) Interventions for the treatment of metastatic extradural spinal cord compression in adults. Cochrane Database Syst Rev 8(4):CD006716
22. Klimo P, Thompson CJ, Kestle JRW et al (2005) A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. Neuro Oncol 7:64–76
23. Paes FM, Serafini AN (2010) Systemic metabolic radiopharmaceutical therapy in the treatment of metastatic bone pain. Semin Nucl Med 40:89–104
24. Krishnamurthy GT, Krishnamurthy S (2000) Radionuclides for metastatic bone pain palliation: a need for rational re-evaluation in the new millennium. J Nucl Med 41(4):688–691
25. Finlay IG, Mason MD, Shelley M (2005) Radioisotopes for the palliation of metastatic bone cancer: a systematic review. Lancet Oncol 6:392–400
26. Resche I, Chatal JF, Pecking A, Ell P, Duchesne G, Rubens R, Fogelman I, Houston S, Fauser A, Fischer M, Wilkins D (1997) A dose-controlled study of 153Sm- ethylenediaminetetramethylene-phosphonate (EDTMP) in the treatment of patients with painful bone metastases. Eur J Cancer 33:1583–1591
27. Bodei L, Lam M, Chiesa C, Flux G, Brans B, Chiti A (2008) Giammarile. European Association of Nuclear medicine (EANM): EANM procedure guidelines for treatment of refractory metastatic bone pain. Eur J Nucl Med Mol Imaging 35(10):1934–1940
28. Saad H, Higano C, Sartor O, Colombel M, Murray R, Mason MD, Tubaro A, Schulman C (2006) The role of bisphosphonates in the treatment of prostate cancer: recommendations from an expert panel. Clin Genitourin Cancer 4(4):257–262
29. Smith MR (2005) Zoledronic acid to prevent skeletal complications in cancer: corroborating the evidence. Cancer Treat Rev 31(Suppl.3):19–25
30. Michaelson MD, Smith MR (2005) Bisphosphonates for treatment and prevention of bone metastases. J Clin Oncol 23(32):8219–8224
31. Shih A, Jackson KC, II (2007) Role of corticosteroids in palliative care. J Pain Palliat Care Pharmacother 21(4):69–76
32. Berthold DR, Pond GR, Roessner M, de Wit R, Eisenberger M (2008) TAX-327 investigators. Treatment of hormone-refractory prostate cancer with docetaxel or mitoxantrone: relationships between prostate-specific antigen, pain, and quality of life response and survival in the TAX-327 study. Clin Cancer Res 14(9):2763–2767
33. World Health Organization (1990) Cancer pain relief and palliative Care. Report of a WHO expert committee. World Health Organization Technical Report Series, 804. Geneva, Switzerland: World Health Organization
34. Grond S, Zech D, Schug SA, Lynch J, Lehman KA (1991) Validation of the world health organization guidelines for cancer pain relief during the last days and hours of life. J Pain Symptom Manage 6(7):411–422
35. Maltoni M, Scarpi E, Modonesi C et al (2005) A validation study of the WHO analgesic ladder: a two-step vs three-step strategy. Supp Care Cancer 13:888–894
36. Miguel R (2000) Interventional treatment of cancer pain: the fourth step in the World Health Organization analgesic ladder? Cancer Control 7:149–156
37. Vranken JH (2003) The palliative treatment with catheter techniques of intractable cancer pain: fourth step in the World Health Organization analgesic ladder. In: Recent Research development in Anesthesia & Analgesia. Transworld Research Network, Kerala, pp 59–71
38. Drew J, Stambaugh JE Jr (1988) The combination of ibuprofen and oxycodone/acetaminophen in the management of chronic cancer pain. Clin Pharmacol Ther 44(6):665–669

39. Fitzgerald GA (2002) Cardiovascular pharmacology of nonselective nonsteroidal anti-inflammatory drugs and coxibs: clinical considerations. Am J Cardiol 89(6A):26D–32D
40. Schug SA, Sidebotham DA, Mc Guinnety M, Thomas J, Fox L (1998) Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain. Anesth Analg 87(2):368–372
41. Stamer UM, Stüber F (2007) Genetic factors in pain and its treatment. Curr Opin Anaesthesiol 20(5):478–484
42. Hanning CD (1990) The rectal absorption of opioids. In: Benedetti C, Chapman C R, Giron G (eds) Opioid analgesia. Advances in pain research and therapy, vol 14. Raven Press, New York, pp 259–269
43. Clark AJ, Ahmedzai SH, Allan LG, Camacho F, Horbay GL, Richarz U, Simpson K (2004) Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. Curr Med Res Opin 20(9):1419–1428
44. Ahmedzai S, Brooks D (1997) Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. J Pain Symptom Manage 13(5):254–261
45. Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, Chavez J, Ashley J, Lebo D, McCracken M, Portenoy RK (2001) Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). Pain 91(1–2):123–130
46. Saarto T, Wiffen PJ (2007) Antidepressants for neuropathic pain. Cochrane Database Syst Rev 4:CD005454
47. Greenberg DB (1991) Strategic use of benzodiazepines in cancer patients. Oncology (Williston Park). 5(4):83–88; discussion 88, 90, 95.
48. Caraceni A, Zecca E, Bonezzi C et al (2004) Gabapentin for neuropathic cancer pain: a randomized controlled trial from the gabapentin cancer pain study group. J Clin Oncol 22:2909–2917
49. Bell R, Eccleston C, Kalso E (2003) Ketamine as an adjuvant to opioids for cancer pain. Cochrane Database Syst Rev 1:CD003351
50. Douglas I, Bush D (1999) The use of patient-controlled boluses of local anaesthetic via a psoas sheath catheter in the management of malignant pain. Pain 82:105–107
51. Vranken JH, van der Vegt MH, Ubags LH, Pijl AJ, Dzoljic M (2002) Continuous sacral nerve root block in the management of neuropathic cancer pain. Anesth Analg 95:1724–1725
52. van Dongen RT, Crul BJ, de Bock M (1993) Long-term intrathecal infusion of morphine/bupivacaine mixtures in the treatment of cancer pain: a retrospective analysis of 51 cases. Pain 55:119–123
53. van Dongen RTM, van Ee R, Crul BJP (1997) Neurologic impairment during long-term intrathecal infusion of bupivacaine in cancer patients; a sign of spinal cord compression. Pain 69:205–209
54. Plancarte R, de Leon Casasola OA, El Helaly M, Allende S, Lema MJ (1997) Neurolythic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Reg Anesth 22(6):562–568
55. Saunders C (1987) The philosophy of terminal cancer care. Ann Acad Med Singapore 16(1):151–154
56. Nanton V, Docherty A, Meystre C, Dale J (2009) Finding a pathway: information and uncertainty along the prostate cancer patient journey. Br J Health Psychol 14:437–458
57. Thaxton L, Emshoff JG, Guessous O (2005) Prostate cancer support groups: a literature review. J Psychosoc Oncol 23(1):25–40
58. Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, Wittink HM (2010) The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of randomised controlled trials. Clin Oncol (R Coll Radiol) 22(3):208–221
59. Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott SG, Venner PM, Quinney HA, Jones LW, Slovinec D'Angelo ME, Wellset GA (2003) Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. J Clin Oncol 21:1653–1659