Guidelines on Pain Management

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European Association of Urology

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1. INTRODUCTION

1.1 The Guideline

The European Association of Urology (EAU) Guidelines Working Group for Pain Management have prepared this guidelines document to assist medical professionals in appraising the evidence-based management of pain in urological practice. These guidelines include general advice on pain assessment, with a focus on treatment strategies relating to common medical conditions and painful procedures. No attempts have been made to exhaustingly cover the topic of pain.

The multidisciplinary panel of experts responsible for this document include three urologists, two radiotherapists and two anaesthesiologists.

*1.1.1 **Methodology***

The recommendations provided in the current guidelines are based on systematic literature search using Medline, the Cochrane Central Register of Controlled Trials, and reference lists in publications and review articles.

It has to be emphasised that the current guidelines contain information for the treatment of an individual patient according to a standardised general approach.

1.2 Publication history

The Pain Management Guidelines were first published in 2003, with a partial update in 2007, followed by a full text update in 2009. In 2010 two new topics were added, Section 5.6 “Peri-operative pain management in children” and Chapter 6 “Non-traumatic acute flank pain”. The quick reference guide was completely reworked. In the 2011 print all chapters were abridged. The current 2012 edition contains partial updates based on the available literature and two new topics were added, Section 3.4 “Denusomab” and Section 3.5 “Palliative care”. A quick reference document presenting the main findings of the General Pain Management guidelines is also available. All texts can be viewed and downloaded for personal use at the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

1.3 Level of evidence and grade of guideline recommendations*

References used in the text have been assessed according to their level of scientific evidence (Table 1) and guideline recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (1). The aim of grading recommendations is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence (LE)*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

**Modified from Sackett et al. (1)*

It should be noted that when recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of randomised controlled trials (RCTs) may not necessarily translate into a grade A recommendation where there are methodological limitations or disparity in published results.

Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence -

although a very important factor - has to be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (2-4).
The EAU Guidelines Office do not perform cost assessments, nor can they address local/national preferences in a systematic fashion. But whenever this data is available, the expert panels will include the information.

Table 2: Grade of recommendation (GR)*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

**Modified from Sackett et al. (1)*

1.4 References

1. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2009). 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. http://www.cebm.net/index.aspx?o=1025 [Access date January 2012]
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2. BACKGROUND

2.1 Definition of pain

Pain is the most common symptom of any illness, and is defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory and emotional experience associated with either actual or potential tissue damage, or described in terms of such damage' (1).

The alerting function of pain evokes protective responses, and is intended to keep tissue damage to a minimum. The capacity to experience pain has a protective role. If tissue damage is unavoidable, a cascade of changes occurs in the peripheral and central nervous system responsible for the perception of pain (2).

Acute pain - usually occurring in response to an identifiable noxious event with stimulation of the nociceptive system - has a time-limited course during which treatment, if necessary, is aimed at correcting the underlying pathological process. In contrast, maladaptive (pathological) pain offers no biological advantage because it is uncoupled from a noxious stimulus or tissue healing, and is usually persistent or recurrent. It may occur in response to damage to the nervous system. It is known as neuropathic pain, and is pain as a disease (3-5).

2.2 What is suffering?

Pain is a complex experience entailing physiological, sensory, affective, cognitive, and behavioural components. An individual's perception of the intensity of pain relates to the interactions of physical, psychological, cultural and spiritual factors (6).

Pain and suffering are closely identified, but are nevertheless distinct. Patients can experience severe pain without suffering (e.g. during childbirth), and suffering can include physical pain, but it is by no means limited to it. Patient distress also results from factors other than pain that add to suffering, such as anxiety, depression, nightmares, change in body perception, and changes in professional and social function.

The differences between pain and suffering are most pronounced in cancer pain patients. Cancer is one of the medical conditions patients fear most, because of the expectation that it will end in death, and that that death will be while in excruciating pain (7,8).

2.3 Nociception and innervation

Structure of the peripheral neural apparatus

Sensory information from the skin is transmitted to the central nervous system (dorsal horn of the spinal cord) via three different types of primary sensory neurones: Aβ-, Aδ-, and C-fibres.

These primary afferent neurones are responsible for transducing mechanical, chemical, and thermal information into electrical activity. Although all three classes can transmit non-nociceptive information, under physiological circumstances only C-fibres (dull pain) and Aδ-fibres (sharp pain) are capable of transmitting nociceptive information from the periphery to the dorsal horn of the spinal cord. Thus, under normal circumstances, Aβ-fibres are responsive only to non-noxious mechanical stimuli, including touch, vibration and pressure (9-12). Nociceptive information for the viscera reaches the central nervous system along the sympathetic chains and pelvic parasympathetic chain. However, the density of visceral afferents is low compared with the skin, which can explain the poor localisation of noxious stimuli in the viscera (responsible for the diffuse nature of visceral pain) (13).

2.4 Neuropathic pain

Definition of neuropathic pain

Neuropathic pain is defined by the IASP as 'pain initiated or caused by a primary lesion or dysfunction of the nervous system' (2). While this definition has been useful in distinguishing some characteristics of neuropathic and nociceptive types of pain, a more precise definition has been developed (14): pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. Where possible, neuropathic pain should be divided into peripheral or central neuropathic pain based on the anatomic location of the lesion or disease.

Both negative and positive sensory symptoms may be present. Positive signs include pain, paraesthesia, dysaesthesia, hyperalgesia, and allodynia. Negative signs involve sensory deficits (hypoaesthesia and hypoalgesia), weakness, and reflex changes. Clinically, patients may complain of spontaneous ongoing pain (stimulus-independent pain) that is burning, with intermittent shooting or electric shock-like (lancinating) sensations, and/or have pain hypersensitivity evoked in response to stimuli (stimulus-evoked pain) such as hyperalgesia and allodynia (15,16).

Mechanisms of neuropathic pain

A change in function, chemistry, and the structure of neurones (neural plasticity) leads to the production of the altered sensitivity characteristics of neuropathic pain. Peripheral sensitisation acts on the nociceptors, and central sensitisation takes place at various levels ranging from the dorsal horn to the brain. In addition, abnormal interactions between the sympathetic and sensory pathways contribute to mechanisms mediating neuropathic pain (17,18).

2.5 Innervation of the urogenital system

The differences between the mechanisms of nociception in the skin and viscera have been emphasised by studies of the response properties of visceral afferents from the urinary tract (19-21). (see also EAU Guidelines "Chronic Pelvic Pain", Chapter 2)

Ureter

The only sensation that can be evoked from the ureter is pain, whereas other organs such as the bladder can give rise to several sensations ranging from mild fullness to pain.

Ureteric afferents are thinly myelinated or unmyelinated, and respond to direct probing of a limited area of tissue. Two populations of afferents have been distinguished by Cervero and Jänig (22). The first responds to contractions of the ureter and is also excited by low levels of distension. The second group does not respond to peristaltic contractions of the ureter, but it is excited by distension with a wide range of thresholds (22).

Activation of muscarinic and adrenergic receptors increases the amplitude of urteral contractions. The sympathetic nerves modulate contraction by α-adrenoceptors and relaxation by α-adrenoceptors. The purinergic system is important in sensory/motor functions. Important non-adrenergic non-cholinergic transmitters are ATP, nitric oxid (NO) and serotonin, as well as the prostataglandins F2, E1 and E2 (23). Understanding ureteral function and physiology is the basis for developing new drugs, for example, in renal colic (23).

Urinary bladder

Two distinct groups of afferent fibres capable of signalling noxious stimuli have been identified in the urinary bladder. Most visceral afferents from the urinary bladder are unmyelinated fibres, although a population of

myelinated A-fibres is also present (18). The majority of visceral primary afferents from the bladder, urethra and reproductive and other pelvic organs encode for both noxious and non-noxious stimuli (19-21).

Graded distension of the healthy urinary bladder in humans initially gives rise to a sensation of fullness and eventually pain as volume increases and intravesical pressure exceeds 25-35 mmHg (19-21). In the inflamed bladder, the sensations during bladder emptying become unpleasant and painful. Nearly all afferents are small, myelinated or unmyelinated, and travel with sympathetic (hypogastric) or parasympathetic (pelvic) nerves.

Male reproductive organs
The sensory innervation of the testes (dog model) shows that more than 95% of the fibres of the superior spermatic nerve are unmyelinated, with the great majority having polymodal properties (i.e., responding to mechanical, chemical and thermal stimuli) (24). Myelinated and unmyelinated afferent fibres form a homogeneous group with polymodal receptors in testes and/or epididymis. Prostaglandins do not excite but sensitise the afferents to other stimuli (25).

2.6 Pain evaluation and measurement

*2.6.1 **Pain evaluation***

Health professionals should ask about pain, and the patient's self-report should be the primary source of assessment. Clinicians should assess pain with easily administered rating scales, and should document the efficacy of pain relief at regular intervals after starting or changing treatment.

Systematic evaluation of pain involves the following steps.

- Evaluate its severity.
- Take a detailed history of the pain, including an assessment of its intensity and character.
- Evaluate the psychological state of the patient, including an assessment of mood and coping responses.
- Perform a physical examination, emphasising the neurological examination.
- Perform an appropriate diagnostic work-up to determine the cause of the pain, which may include tumour markers.
- Perform radiological studies, scans, etc.
- Re-evaluate therapy.

The initial evaluation of pain should include a description of the pain using the PQRST characteristics:

P Palliative or provocative factors: 'What makes it less intense?'
Q Quality: 'What is it like?'
R Radiation: 'Does it spread anywhere else?'
S Severity: 'How severe is it?'
T Temporal factors: 'Is it there all the time, or does it come and go?'

Pain in patients with cancer is a complex phenomenon. Not all pains will be of malignant origin, they will often have more than one pain problem, and each pain must be individually assessed and evaluated. A key principle is constantly to re-evaluate pain and the effect and side-effects of analgesic therapy.

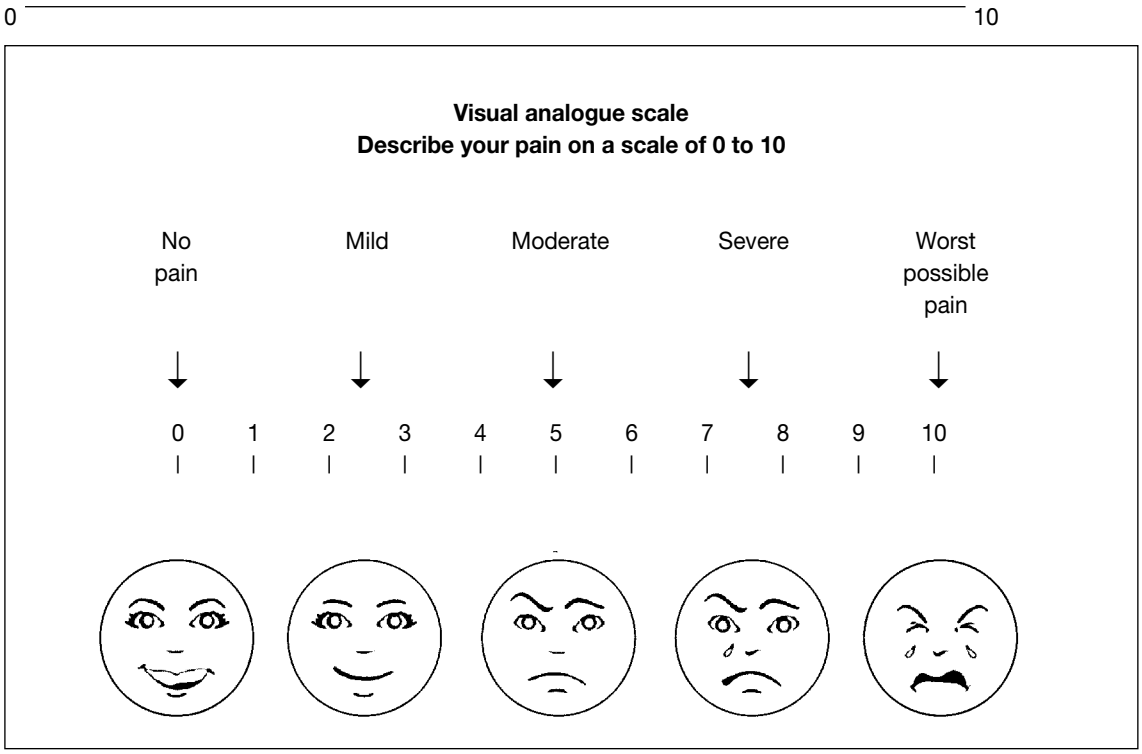
Pain in cancer patients could be caused by the cancer itself, be due to secondary muscular spasm, be secondary to cancer treatments, or have no relation to the cancer, e.g. arthritis.

In general, cancer pain consists of two broad diagnostic types: nociceptive and neuropathic pain. When evaluating pain, it is useful to try to determine whether the pain is one of these types or a mixture of the two. Nociceptive pain includes bone pain and soft tissue pain. Typically it is described as a dull, aching pain. This type of pain will be largely sensitive to non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. Neuropathic pain results from damage to the peripheral or central nervous system. It is usually described as a burning or sharp, shooting pain. Neuropathic pain is usually not particularly responsive to NSAIDs or opioids. Adjuvant analgesics such as anti-depressants and anti-convulsants should be used in the first instance.

*2.6.2 **Assessing pain intensity and quality of life (QoL)***

There are several rating scales available to assess pain. Rating pain using a visual analogue scale (VAS, Figure 1) or collection of VAS scales (such as the brief pain inventory) is an essential part of pain assessment. Its ease of use and analysis has resulted in its widespread adoption. It is, however, limited for the assessment of chronic pain.

Figure 1: Visual analogue scale



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. Several validated questionnaires to assess various QoL dimensions are available, including 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) (26-30).

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3. CANCER PAIN MANAGEMENT (GENERAL)

3.1 Classification of cancer pain

The physical causes of pain are either nociceptive or neuropathic. In cancer patients, nociceptive pain tends to be caused by invasion of the bone, soft tissues or viscera (e.g. bowel, bladder), and neuropathic pain by nerve

compression or infiltration.

Urogenital neoplasms frequently metastasise to bone (e.g. spine, pelvis, skull). Bone metastases are associated with pathological fractures, hypercalcaemia and neurological deficits, leading to substantial impairment of QoL. The release of algogenic substances in the tissue, microfractures and periosteal tension are the main mechanism for pain sensation (1).

Pain caused by bone metastasis is nociceptive, but can become neuropathic if the tumour invades or compresses a nerve, neural plexus or spinal cord. One-third of patients with tumour-related pain are affected by neuropathic pain components (2). Nociceptive pain is well localised. Initially it occurs on physical movement, but later might also occur at rest.

Neuropathic pain frequently has a constant 'burning' character. The efficacy of opioids may be diminished in neuropathic pain, making co-analgesia necessary (3). Patients with severe neuropathic pain are a special challenge. Psychological changes frequently occur, and specific therapeutic intervention may be necessary (4).

The World Health Organization (WHO) recommends a stepwise scheme for the treatment of cancer pain syndromes and neoplastic bone pain. Bisphosphonates and calcitonin are helpful for stabilising bone metabolism. Epidural and intrathecal opioids are sometimes useful in managing metastatic bone pain. Selected patients with neuropathic pain sometimes benefit from nerve destruction by intrathecal or epidural phenol (5).

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3.2 General principles of cancer pain management

The four goals of care are:

- prolonging survival
- optimising comfort
- optimising function
- relieving pain.

Pain leads to a vicious cycle of sleeplessness, worry, despair, isolation, hopelessness, depression, and escalation of pain. The following hierarchy of general treatment principles is useful in guiding the selection of pain management choices.

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 (the WHO ladder).
5. Conformance with palliative guidelines.
6. Both psychological counselling and physical therapy from the very beginning.

The fundamental principle is the individualisation of therapy. Repeated evaluations allow the selection and administration of therapy to be individualised in order to achieve and maintain a favourable balance between pain relief and adverse effects.

The next steps in the hierarchy, especially points 2-4, necessitate a continuing risk-to-benefit assessment between therapeutic outcome versus tolerability and willingness to accept adverse effects.

The more invasive the therapy, the more difficult the decisions become. This is particularly true with palliative medicine, where the prospects of healing are limited and there is the problem of working against time.

If local therapy is not feasible or cannot be well tolerated, then symptomatic measures are appropriate, although local therapy is to be preferred over systemic treatment. In simple cases, measures such as drainage and stenting can make analgesic medication redundant, e.g. gastric probe, ureteral

stent, percutaneous nephrostomy, bladder catheter. Patients with recurrent subileus caused by peritoneal carcinomatosis are immediately relieved of their pain when they are given an artificial anus.

The indication is in direct relation to the severity of the disease and the operation, especially if the aim is palliative, although such cases are sometimes in particular need of invasive measures, not only to relieve pain in the terminal phase, but also to improve the general QoL, despite the potential for surgery to have a negative impact on patients' wellbeing. Examples include evisceration to prevent cloaca in cervical carcinoma, or implanting a prosthetic hip due to a pathological fracture originating in metastasised bladder or kidney cancer.

When dose escalation of a systemically administered opioid proves unsatisfactory, the following gradual strategy can be considered (LE: 4):

- Switch to another opioid.
- Intervene with an appropriate primary therapy or other non-invasive analgesic approach.
- Pursue psychological, rehabilitative and neurostimulatory techniques (e.g. transcutaneous electrical nerve stimulation).
- Use invasive analgesic techniques after careful evaluation of the likelihood and duration of the analgesic benefit, the immediate risks, and the morbidity of the procedure (epidural infusion).
- Use neurodestructive procedures (chemical or surgical neurolysis, coeliac plexus blockade).
- Some patients with advanced cancer where comfort is the overriding goal can elect to be deeply sedated.

The importance of physiotherapy and psychological counselling cannot be emphasised too strongly.

3.3 Non-pharmacological therapies

3.3.1 ***Surgery***

Surgery may have a role in the relief of symptoms caused by specific problems, such as obstruction of a hollow viscus, unstable bony structures and compression of neural tissues or draining of symptomatic ascites (1-3). The potential benefits must be weighed against the risks of surgery, the anticipated length of hospitalisation and convalescence, and the predicted duration of benefit. Radical surgery to excise locally advanced disease in patients with no evidence of metastatic spread may be palliative, and potentially increase the survival of some patients (4) (LE: 2b).

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3.3.2 ***Radionuclides***

3.3.2.1 Clinical background

Bone metastases are the most frequent source of pain during the evolution of cancers (1). Approximately 30% of patients with osseous metastases have pain that requires analgesia, interfering with QoL, causing anxiety, isolation, immobility, depression, and sleeplessness (1).
In single lesions, bone stability and pain reduction can be achieved by external beam radiotherapy (LE: 1b) (GR: A). About 80-90% of patients will experience durable pain relief, but many will develop further multiple painful metastases (1).

3.3.2.2 Radiopharmaceuticals: physical characteristics

- Strontium-89 chloride (^{89}Sr) emits a beta particle with a maximum energy of 1.46 MeV, a mean energy of 0.58 MeV, an average soft-tissue range of 2.4 mm and 0.01% abundant gamma emission with a 0.91 MeV photopeak. The physical half-life is 50.5 days (2,3).
- Samarium-153 lexidronam (^{153}Sm) emits a beta particle with a maximum energy of 0.81 MeV, a mean energy of 0.23 MeV, an average soft-tissue range of 0.6 mm and 28% abundant 0.103 MeV gamma emission with a 0.103 MeV photopeak. The physical half-life is 1.9 days (4).

- Renium-186 etidronate (^{186}Re) emits a beta particle with a maximum energy of 1.07 MeV, a mean energy of 0.349 MeV, an average soft-tissue range of 1.1 mm and a 9% abundant gamma emission with a 0.137 MeV photopeak. The physical half-life is 3.7 days (5).
- Therapy in this context means the intravenous administration of ^{89}Sr or ^{153}Sm (^{153}Sm ethylenediaminetetramethylenephosphonate [EDTMP]).

The most important radiopharmaceuticals are ^{89}Sr, ^{153}Sm and, to a lesser extent, ^{186}Re. There is no clear difference in treatment response between them (2), but, because of the differences in half-life, there is a difference in onset and duration of response, and in toxicity. For ^{153}Sm and ^{186}Re, the onset of response is rapid but duration is shorter (6,7). Note that ^{186}Re is no longer used in many European countries.

3.3.2.3 Indications and contraindications

^{89}Sr and ^{153}Sm are indicated for the treatment of bone pain resulting from skeletal metastases involving more than one site and associated with an osteoblastic response on bone scan but without spinal cord compression (1,8-15) (LE: 2, GR: B).

^{89}Sr and ^{153}Sm have no place in the management of acute or chronic spinal cord compression or in treating pathological fracture (1,8,11) (LE: 2, GR: B).

Some 60-80% of patients presenting with osteoblastic metastases benefit from ^{89}Sr and/or ^{153}Sm (1) (LE: 2). The choice between the two depends solely on practical considerations. ^{89}Sr and/or ^{153}Sm should be administered by a slow (^{89}Sr) or bolus (^{153}Sm) injection using an intravenous (iv) catheter. The recommended doses are 148 MBq (^{89}Sr) (16) and 37 MBq/kg (^{153}Sm) (1,16) (LE: 2).

About 10% of patients experience a temporary increase in bone pain (pain flare) (3,6,7,17), generally 2-4 days after ^{153}Sm, and 1-2 weeks after ^{89}Sr (acute side-effect) (1,4,8,11,12,15,18). Pain flare is associated with a good clinical response (LE: 2) (3,6,7,17), and sometimes requires a transient increase in analgesia. Pain reduction is unlikely to occur within the first week, and can occur as late as 1 month after injection. Analgesics should therefore be continued until bone pain improves (GR: B). Late side-effects include temporary myelosuppression (platelets, white blood cells). Recovery occurs 4-6 weeks later depending on bone marrow reserve. There is generally no significant effect on haemoglobin.

The patient can pose a radiation exposure risk for 2-4 days after ^{153}Sm, and 7-10 days after ^{89}Sr (4,8,11,13-15,18-23) (LE: 2). Information about radioprotection should be provided (GR: B).
If the pain responds to the initial treatment, administration of ^{153}Sm can be repeated at intervals of 8-12 weeks in the presence of recurrent pain (1,2,23) (LE: 2, GR: B). The response rate for second and subsequent treatments may be lower than for the first (1,8,12,23) (LE: 2).

3.3.2.4 Contraindications

Absolute contraindications:

- During or within 4 weeks of myelotoxic chemotherapy (all compounds except cisplatin), or within 12 weeks of hemibody external radiation therapy. The delay between these treatments and metabolic radiotherapy is necessary to avoid severe haematopoietic toxicity. However, treatment can be safely combined with limited local field external beam radiotherapy (LE: 3, GR: C).
- Known hypersensitivity to EDTMP or similar phosphonate compounds for ^{153}Sm (1).
- Glomerular filtration rate (GFR) < 30 mL/min (1,2).
- Pregnancy; continued breastfeeding (2).

Relative contraindications:

- Not recommended for women of child-bearing age (negative pregnancy test and contraception mandatory).
- In acute or chronic severe renal failure (GFR 30-60 mL/min), the dose administered should be adapted: if the GFR is > 60 mL/min, reduce the normal dosage by 25%; if the GFR is 30-60 mL/min, reduce the normal dosage by 50% (LE: 4). GFR should be measured if creatinine is > 20 mg/L.
- With a single painful lesion: external limited field radiotherapy should be performed (16,24) (LE: 1b).

Caution:

Caution must be used in the following circumstances.

- Risk of fracture.
- Nerve or spinal cord compression that requires other treatments in an emergency: external radiotherapy or surgery, or a combination of the two.
- Urinary incontinence: special recommendations including catheterisation before administration of the radionuclide. The catheter should remain in place for 4 days (^{89}Sr), 3 days (^{186}Re), and 24 hours (^{153}Sm), respectively (2) (GR: A).

- Compromised bone marrow reserve.
- White blood cell count of < 2500/µL (LE: 4) (preferably > 3500/µL according to European Association of Nuclear Medicine guidelines) (2).
- Platelets < 80,000/µL (LE: 4) (preferably > 100,000/µL according to the European Association of Nuclear Medicine guidelines) (2).
- Haemoglobin < 90 g/L (2).

3.3.2.5 References

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3.3.3 ***Radiotherapy for metastatic bone pain***

3.3.3.1 Clinical background

Radiotherapy alleviates metastatic bone pain in the majority of patients (1) (LE: 1a). Pain relief is obtained in 50-80% of patients, with complete pain relief at the treated site in up to 30% of patients (1,2) (LE: 1a). The onset of pain relief varies from a few days to 4 weeks (1) (LE: 2b). Re-irradiation should therefore not be considered sooner than 4-6 weeks after the initial radiotherapy. The median duration of pain relief reported by most studies is 3-6 months (1) (LE: 1a).

3.3.3.2 Mechanism of pain relief by radiotherapy

Tumour shrinkage and inhibition of the release of chemical pain mediators are the main mechanisms by which radiotherapy relieves pain. Tumour shrinkage is unlikely to account for early pain relief, which is hypothesised to involve early-reacting and sensitive cells, as well as the molecules that they produce. Obvious candidates are the inflammatory cells present in the bone metastasis microenvironment. Reduction of these cells by ionising radiation inhibits the release of chemical pain mediators, and is probably responsible for the rapid reaction seen in some patients. Another possible mechanism for the analgesic action of ionising irradiation includes its direct effect on osteoclast activity (3) (LE: 3).

3.3.3.3 Imaging

The detection of bone metastases is usually based on 99m technetium bone scintigraphy, which lacks diagnostic specificity (11) (LE: 3), but the addition of single photon emission computed tomography (SPECT) to planar acquisition has been reported to improve its diagnostic accuracy (12-14) (LE: 2b). Regions of increased uptake need further investigation. Plain films have a false-negative rate of 10-17% (LE: 3). At least 50% erosion must be present for a change to be seen on plain films (15) (LE: 3). The combination of bone scintigraphy and plain films results in specificity of 64% and sensitivity of 63% (16) (LE: 3).

Because of the complex anatomy of the vertebrae, computed tomography (CT) is more useful than conventional radiography for evaluating the location of lesions and analysing bone destruction and condensation (17). When combined with myelography, excellent information about the bony anatomy and an accurate view of the compressed neural elements is provided (18-19) (LE: 3). However, CT myelography is invasive and time-intensive, and so, particularly when spinal cord compression is suspected, magnetic resonance imaging (MRI) is currently the gold standard for detection and therapeutic management (20-24) (LE: 2b), with sensitivity of 93% (25) (LE: 3) and specificity of 96% (25) (LE: 3).

3.3.3.4 Radiotherapy scheme

Single-fraction radiotherapy is as effective as multifraction radiotherapy in relieving metastatic bone pain (1, 4-8) (LE: 1a). However, the rates of retreatment and pathological fractures are higher after single-fraction radiotherapy (1,9) (LE: 1a).

Single-fraction radiotherapy is the treatment of choice for alleviating bone pain because of its greater convenience for patients (LE: 1a), as well as faster patient turnover for the radiotherapy unit (10) and lower costs (5,11) (LE: 3). The recommended dose is 8 Gy (LE: 1a) (1,4-8,12,13). Pain relief can be achieved in a significant number of patients with lower doses (LE: 1b), but some studies have indicated that 4 Gy is less effective than 8 Gy (1) (LE: 1b). A dose of 6 Gy gives similar results to 8 Gy but has been insufficiently studied (1) (LE: 1b). A dose of 8 Gy in combination with zoledronic acid is associated with a longer period without skeletal events, compared to 6 Gy with zoledronic acid (14).These lower doses should be borne in mind if a third retreatment is necessary, or if there is concern about radiation tolerance (1) (LE: 2b).

In cases of oligometastases (< 5), a case can be made for aggressive therapy, such as radiosurgery or high-dose radiotherapy to improve survival (LE: 3).

3.3.3.5 Spinal cord compression

Metastatic epidural spinal cord compression (MSCC) is a common, severe complication of malignancy. The most common symptom is back pain (83-95%), and weakness is present in 35-75%. The level of neurological function at the start of treatment determines the functional outcome (15). A delay in treatment, surgery or external radiotherapy is the most common cause of an unfavourable outcome. Magnetic resonance imaging is the best tool for diagnosing MSCC (16).

Corticosteroids reduce oedema and might have an oncolytic effect on certain tumours, such as lymphoma, breast cancer and leukaemia. However, the extent of the benefit obtained from corticosteroids and the optimal dosage are unclear. High-dose corticosteroids carry a significant risk of adverse affects. One randomised controlled trial of patients with carcinomatous MSCC has compared radiotherapy with or without dexamethasone, and showed significantly better functional outcome when dexamethasone was added (17) (LE: 1b).

Radiotherapy is generally the treatment of choice. Surgery is reserved for a selected group of patients who meet the criteria listed below.

To date, there is no standard radiotherapy regimen for MSCC. In general, a multifraction regimen (10 × 3 Gy) is preferable in these patients because it allows for a higher dose and thus greater reduction in tumour size. For patients whose chances of survival are estimated to be poor, a short course of radiotherapy is advised (e.g., 1 × 8 Gy (18) or 2 × 8 Gy (19) (LE: 1b). A small randomised trial, including patients with MSCC and a short life-expectancy (≤ 6 months), has compared a short-course (2 × 8 Gy) with a split-course (5 × 3 Gy followed by 3 × 5 Gy) radiotherapy regimen, and has concluded that there were no significant differences in functional outcome or toxicity (19).

Several uncontrolled surgical trials (20-22) and one meta-analysis (23) have indicated that direct decompressive surgery is superior to radiotherapy alone with regard to regaining ambulatory and sphincter function, and obtaining pain relief (LE: 1a). However, the decision to pursue surgery must be tempered by awareness of the attendant significant morbidity and mortality risks. Careful patient selection is of utmost importance; the criteria are shown in Table 3 (LE: 3).

Table 3: Criteria for selecting patients for primary therapy for spinal cord compression

Absolute criteria	**Surgery**	**Radiotherapy**
Operability	Medically operable	Medically inoperable
Duration of paraplegia	< 48 h	≥ 48 h
Life expectancy	> 3 months	< 3 months
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

A randomised prospective trial has demonstrated that patients treated with a combination of surgery followed by radiotherapy can remain ambulatory longer, and those who are not ambulatory at presentation have a better chance of regaining ambulatory function than those treated with radiotherapy alone (24) (LE: 1b).

3.3.3.6 Pathological fractures

In patients with impending pathological fractures (e.g., femoral lesion with an axial cortical involvement > 30 mm), a prophylactic orthopaedic procedure should be considered (25).

3.3.3.7 Side effects

Side effects are related to the total dose, fractionation size, and the localisation of the metastases. Acute grade 2-4 toxicity is more frequent after multifraction radiotherapy regimens. The incidence of late toxicity is low (9).

The side effects are mostly transient, lasting a few days and include:

1) pain flare (within 24 h and due to oedema). Pain flare is common after palliative radiotherapy for bone metastases, and patients should be counselled accordingly and given breakthrough opioids. Patients receiving single-fraction radiotherapy may be at higher risk than those receiving multifraction radiotherapy (26). A small phase II study has shown that 8 mg dexamethasone is effective for prophylaxis of radiotherapy-induced pain flare after palliative radiotherapy for bone metastases (LE: 3) (27).
2) symptoms depend on the treatment field and location and can include:
   - nausea (especially with larger fields)
   - diarrhoea
   - irritation of the throat and oesophagus.

3.3.3.8 References

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3.3.4 ***Psychological and adjunctive therapy***

3.3.4.1 Psychological therapies

The perception of pain and the suffering it causes derive from a combination of physical, emotional, spiritual, and social constructs. Psychological assessment and support are an integral and beneficial part of treating pain in cancer patients (1,2). There is evidence that highly emotional cancer patients, as detected through their own narratives, experience less pain than their less emotional counterparts (3).

Depression is the most prevalent psychiatric diagnosis in patients with cancer. Although there is no proof that psychotherapy is useful in non-cancer patients with depression, patients with incurable cancer can take advantage of this type of treatment (4). In this setting, structured psychotherapy seems to be more effective than antidepressant medication (5). Interestingly, effective psychological management results in a reduction in depressive complaints, inflammatory markers, pain, and fatigue in cancer patients (6).

Cognitive behavioural therapy (CBT), such as relaxation and distraction, can provide pain relief (7-9). As expected, protocols tailored to individual patient characteristics can result in higher satisfaction in terms of pain relief, mood improvement and general well-being. The possibility of delivering CBT by home visits, telephone, or through the internet seems promising (10-12). Virtual consultation and automated symptom monitoring for cancer patients with depression can exceed all expectations (13). It has also been suggested that CBT is particularly helpful for younger cancer patients (14).

Families can be exposed to poor functioning during palliative care and bereavement. Family-focused grief therapy based on communication, cohesiveness, conflict resolution, and shared grief is effective in protecting family members against the drama of disease and death (15). Other psychological interventions targeted to minimise caregiver emotional distress have not been effective (16).

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3.3.4.2 Adjunctive therapy

A number of therapeutic strategies have been proposed as non-pharmacological adjunctives to medical and surgical procedures. To date, there is no conclusive evidence on the effect of reflexology and massage therapy (1-3). Nevertheless, certain manipulations (e.g., sciatic nerve press) seem to be effective for immediate pain relief in many oncological conditions (4). The notion that acupuncture may be effective for cancer patients is not methodologically supported by the currently available data (5). However, modest although significant improvements in depression and pain scales have been confirmed by well-conducted studies on acupuncture (6). Evidence from robust studies is still lacking on the effect of traditional Chinese medicine and complementary alternative medicine (7,8). Physical exercise (short walks) can positively affect the pain experience of prostate cancer patients (9). Similarly, moderate exercise positively affects cancer-related sleep disturbance (10).

Transcutaneous electrical nerve stimulation might mitigate hyperalgesia in cancer patients. Unfortunately, reliable studies in this field are lacking (11).

Listening to music - an otherwise harmless activity - slightly reduces distress, pain intensity and opioid requirements in cancer patients (12,13).

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3.4 Pharmacotherapy

The successful treatment of cancer pain depends on the clinician's ability to assess the presenting problems, identify and evaluate pain syndromes, and formulate a plan for comprehensive continuing care. This requires familiarity with a range of therapeutic options and responsiveness to the changing needs of the patient. The treatment of pain must be part of the broader therapeutic agenda, in which tumour control, symptom palliation (physical and psychological), and functional rehabilitation are addressed concurrently.

3.4.1 ***Antibiotics***

Antibiotics may be analgesic when the source of the pain involves infection (e.g. pyonephrosis, abscess, osteitis pubis). In some cases, infection may be occult and confirmed only by the symptomatic relief provided by empirical treatment with these drugs (1) (LE: 2b).

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3.4.2 ***Chemotherapy***

A successful effect on pain is generally related to tumour response. There is a strong clinical impression that tumour shrinkage is generally associated with relief of pain, although there are some reports of analgesic value even in the absence of significant tumour shrinkage (1) (LE: 1a).

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3.4.3 ***Bisphosphonates***

Bisphosphonates are pyrophosphate analogues.

3.4.3.1 Mechanisms of action

- Inhibition of bone resorption: beginning 24-48 hours after administration, the target cells are the osteoclasts. There are three different mechanisms of inhibition of bone resorption corresponding to the three generations of bisphosphonates. There are four distinct effects on osteoclasts:
  - reduction of osteoclastic activity;
  - inhibition of osteoclast adhesion;
  - decrease in number of osteoclasts;

- induction of osteoclast apoptosis.
- Inhibition of crystallisation and mineralisation: clinically not relevant.
- Promotion of osteoblastic bone formation and production of osteoclast resorption inhibitor.
- Anti-angiogenic effect and effect on tumour cells.

3.4.3.2 Effects and side-effects

The main effects are:

- decrease of the risk of skeleton-related events, e.g. hormone-refractory prostate cancer with bone metastasis (1) (LE: 1b, GR: A);
- pain response in 60-85% of patients (1-3) (LE: 1b, GR: A).

The main side-effects are:

- flu-like symptoms (20-40%), bone pain, fever, fatigue, arthralgia and myalgia (all < 10%);
- hypocalcaemia (caution: rapid infusion - older patients with vitamin D deficiency);
- acute renal failure (rapid infusion); always check renal function (GFR);
- osteonecrosis of the jaw bones (only after iv therapy);
- gastrointestinal symptoms can occur after oral administration (2-10%).

Some remarks (all grade B recommendations):

- Recognise and treat dehydration before administration of bisphosphonates.
- Reduce the dose in the event of impaired renal function when using zoledronate (4) (LE: 2).
- Avoid simultaneous administration of aminoglycosides (5).
- Perform clinical examination of the patient's mouth and jaws; avoid oral/dental surgery during administration of iv bisphosphonates (6-10) (LE: 2).

3.4.3.3 Denosumab

Histological findings and analysis of bone turnover markers support the view that bone metatases from prostate cancer are characterised by an excess osteoclastic activity inducing bone destruction. This results in an increased risk of skeletal-related events (SREs), such as pathologic fractures, spinal cord compression, pain requiring radiotherapy or surgery, and hypercalcemia. To maintain skeletal integrity and prevent skeletal complications treatment with bisphosphonates are often initiated.

The receptor activator of NF-kB ligand (RANKL), mediates the formation, function, and survival of osteoclasts.

It is hypothesised that through RANKL, tumor cells induce osteoclast activation, which then mediates bone resorption and releases growth factors, resulting in a cycle of bone destruction and tumor proliferation. Denosumab is a fully human monoclonal antibody that specifically binds and neutralises RANKL, inhibiting osteoclastogenesis and decreasing osteoclastmediated bone destruction (11). Improvement in bone metastases free survival (4.2 months) and increased time to first bone metastasis (3.7 months) has been reported with denosumab in a phase III randomised placebo controled trial (12).

Another recently published phase 3 study, randomised men with castration-resistant prostate cancer and no previous exposure to iv bisphosphonate between 120 mg subcutaneous denosumab plus iv placebo, or 4 mg iv zoledronic acid plus subcutaneous placebo, every 4 weeks until the primary analysis cutoff date. Denosumab significantly delayed the time to first onstudy skeletal-related event by 18% compared with zoledronic acid, with a between-group difference of 3-6 months (13). Occurrences of adverse events and serious adverse events were similar between groups. More events of hypocalcaemia occurred in the denosumab group (121 [13%]) than in the zoledronic acid group (55 [6%]; p<0·0001). Osteonecrosis of the jaw was infrequent in both groups. The authors concluded that denosumab was better than zoledronic acid for prevention of skeletal-related events, and potentially represents a novel treatment option in men with bone metastases from castration-resistant prostate cancer (13). However, data on QoL are lacking.

A small randomised phase II trial evaluated the effect of denosumab after iv bispfhosphonates (14). However, actually there are insufficient data to support a routine switch from iv bisphosphonates to denosumab.

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*3.4.4 **Systemic analgesic pharmacotherapy - the analgesic ladder***

Analgesic pharmacotherapy is the mainstay of cancer pain management (1-3). Although concurrent use of other interventions is valuable in many patients, and essential in some, analgesic drugs are needed in almost every case. Based on clinical convention, analgesic drugs can be separated into three groups:

- non-opioid analgesics
- opioid analgesics
- adjuvant analgesics.

Emphasising that pain intensity should be the prime consideration (LE: 1a), the WHO has proposed a three-step approach to analgesic selection for cancer pain (1,3). Known as the analgesic ladder, when combined with appropriate dosing guidelines it can provide adequate relief in 70-90% of patients (4,5).

- **Step 1: non-opioid analgesic** Patients with mild to moderate cancer-related pain should be treated with a non-opioid analgesic.
- **Step 2: non-opioid analgesic + weak opioid** Patients who present with moderate to severe pain or who fail to achieve adequate relief after a trial of a non-opioid analgesia should be treated with a weak opioid (e.g. codeine or tramadol), typically by using a combination product containing a non-opioid (e.g. aspirin or paracetamol) and an opioid (e.g. codeine, tramadol or propoxyphene).
- **Step 3: non-opioid analgesic + strong opioid** Patients who present with severe pain or who fail to achieve adequate relief with step 2 drugs, should receive a strong opioid (e.g. morphine, fentanyl, oxycodone, methadon, buprenorphine, or hydromorphone).

3.4.4.1 Non-opioid analgesics

- Non-opioid analgesics are aspirin, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs).
- Can be useful alone for mild to moderate pain (step 1 of the analgesic ladder).
- May be combined with opioids.
- Have a ceiling effect of analgesic efficacy.
- No tolerance or physical dependence.
- Inhibit the enzyme cyclo-oxygenase and block the synthesis of prostaglandins.
- Involvement of central mechanisms is also likely in paracetamol analgesia (6).
- Potential adverse effects (7): bleeding diathesis due to inhibition of platelet aggregation, gastroduodenopathy (including peptic ulcer disease) and renal impairment are the most common; less common adverse effects include confusion, precipitation of cardiac failure and exacerbation of hypertension. Particular caution must be used in elderly patients and those with blood-clotting disorders, predisposition to peptic ulceration, impaired renal function and concurrent corticosteroid therapy.
- Non-acetylated salicylates (choline magnesium trisalicylate and salsalate) are preferred in patients who have a predilection to bleeding; these drugs have less effect on platelet aggregation and no effect on bleeding time at the usual clinical doses.
- Rarely, paracetamol produces gastrointestinal toxicity, but with no adverse effect on platelet function. Hepatic toxicity is possible, however, and patients with chronic alcoholism and liver disease can develop severe hepatotoxicity at the usual therapeutic doses (8).

3.4.4.2 Opioid analgesics

Cancer pain of moderate or severe intensity should generally be treated with a systemically administered opioid analgesic (9). Classification is based on interaction with the various receptor subtypes:

- Agonist: most commonly used in clinical pain management, no ceiling effect.
- Agonist-antagonist (pentazocine, nalbuphine and butorphanol): ceiling effect for analgesia.

By convention, the relative potency of each of the commonly used opioids is based on a comparison with 10 mg of parenteral morphine. Equi-analgesic dose information provides guidelines for dose selection when the drug or route of administration is changed (10).

A trial of systemic opioid therapy should be administered to all cancer patients with moderate or severe pain (10-13). Patients who present with severe pain should be treated with a strong opioid from the outset. Patients with moderate pain are commonly treated with a combination drug containing paracetamol or aspirin plus codeine, tramadol, or propoxyphene, the dose of which can be increased until the maximum dose of the non-opioid co-analgesia is attained (e.g. 4000 mg paracetamol).

Factors to consider when selecting an opioid include:

- pain intensity
- patient age
- response to previous trials of opioid therapy
- co-existing disease
- influence of underlying illness, characteristics of the opioid and concurrent medications.

Routes of administration

Opioids should be administered by the least invasive and safest route that can provide adequate analgesia. In a survey of patients with advanced cancer, more than half required two or more routes of administration prior to death, and almost a quarter required three or more.

Non-invasive routes

- **Oral** routes are the preferred approach in routine practice. Alternative routes are necessary for patients who have impaired swallowing, gastrointestinal dysfunction, require a very rapid onset of analgesia, or cannot tolerate the oral route.
- **Rectal** suppositories containing oxycodone, hydromorphone, oxycodone and morphine in combination are available, and controlled-release morphine tablets can also be administered per rectum. The potency of rectally administered opioids is believed to approximate to oral dosing (14).
- **Transdermal** routes: fentanyl and buprenorphine have been demonstrated to be effective in postoperative and cancer pain (15). The fentanyl transdermal therapeutic system dosing interval is usually 72 h, but some patients require a 48 h schedule. There is some interindividual variability in fentanyl bioavailability by this route, which, combined with large differences in elimination pharmacokinetics, necessitates dose titration in most cases (16). The efficacy of transdermal fentanyl

is equal to morphine. The incidence of side-effects such as sedation and constipation are lower than for morphine (17,18) (LE: 1b).

- Transdermal patches able to deliver 12,25,50,75 and 100 mg/h are available. Multiple patches can be used simultaneously for patients who require higher doses. Current limitations of the transdermal delivery system include costs, and the need for an alternative short-acting opioid for breakthrough pain.
- Recently, buprenorphine has become available for transdermal administration. A high affinity partial μ-opioid agonist, it is in clinical use for the treatment of acute and chronic pain (19). Its analgesic effect is comparable with that of other opioids, and it shows no relevant analgesic ceiling effect throughout the therapeutic dose range (20). Unlike full μ-opioid agonists, buprenorphine's physiological and subjective effects, including respiratory depression and euphoria, reach a plateau at higher doses. This ceiling may limit the abuse potential, and might result in a wider safety margin (21).

- **Sublingual** absorption of any opioid is potentially clinically beneficial, but bioavailability is very poor with drugs that are not highly lipophilic, so the chances of an adequate response are low (22). Sublingual buprenorphine, a relatively lipophilic partial agonist, can provide adequate relief for mild to moderate cancer pain. Overall, this route has limited value due to the lack of formulations, poor absorption of most drugs, and the inability to deliver high doses or prevent swallowing of the dose. An oral transmucosal formulation of fentanyl (incorporated into a sugar base) is useful for the rapid relief of breakthrough pain (23,24). Fentanyl delivered by this means is more effective than oral morphine at relieving pain (LE: 2).

Recommendation	GR
Oral transmucosal administration of fentanyl should be used to provide rapid relief of breakthrough pain. The starting dose is 400 μg, or 200 μg in the elderly and those with a history of opioid sensitivity or underlying pulmonary disease.	B

Invasive routes

For patients undergoing a trial of systemic drug administration, a parenteral route must be considered when the oral route is not available. Repeated parenteral bolus injections, which can be administered iv, intramuscularly (im) or subcutaneously (sc), may be useful in some patients, but are often compromised by the occurrence of prominent bolus effects (toxicity at peak concentration and/or pain breakthrough at the trough). Repeated im injections are common, but are painful and offer no pharmacokinetic benefit; their use is not recommended (25).

- **Intravenous bolus** administration provides the most rapid onset and shortest duration of action. Time to peak effect correlates with the lipid solubility of the opioid, and ranges from 2-5 minutes for methadone, to 10-15 minutes for morphine (26). This approach is appropriate in two settings:
  - To provide parenteral opioids, usually transiently, to patients who already have venous access and are unable to tolerate oral opioids.
  - To treat very severe pain, for which iv doses can be repeated at an interval as brief as that determined by the time to peak effect until adequate relief is achieved.
- **Continuous parenteral infusions** is mainly used in patients who are unable to swallow, absorb opioids or otherwise tolerate the oral route, but is also employed in patients whose high opioid requirement renders oral treatment impractical (27). Long-term infusions can be administered iv or sc.
  - Ambulatory patients can easily receive a continuous sc infusion using a 27-gauge butterfly needle, which can be left in place for up to a week. A recent study demonstrated that the bioavailability of hydromorphone by this route is 78% (28), and clinical experience suggests that dosing can be identical to that for continuous iv infusion. A range of pumps is available to provide patient-controlled rescue doses (supplemental doses offered on an as-needed basis to treat pain that breaks through the regular schedule) as an adjunct to continuous basal infusion.
  - Opioids suitable for continuous sc infusion must be soluble, well absorbed and non-irritant. Extensive experience has been reported with hydromorphone, oxycodone and morphine (29). Methadone appears to be relatively irritating and is not preferred (30). To maintain the comfort of an infusion site, the sc infusion rate should not exceed 5 cc/h.
  - The infraclavicular and anterior chest sites provide the greatest freedom of movement for patients, but other sites can be used. A single infusion site can usually be maintained for 5-7 days.

Changing the route of administration

Switching between oral and parenteral routes should be guided by a knowledge of relative potency to avoid subsequent over- or underdosing. In calculating the equi-analgesic dose, the potencies of the iv, sc and im routes are considered equivalent. Perform changes slowly in steps, e.g. gradually reducing the parenteral dose and increasing the oral dose over a 2-3 day period (LE: 3).

Dosing

- **Around-the-clock dosing** Patients with continuous or frequent pain generally benefit from scheduled around-the-clock dosing, which provides continuous relief by preventing recurrence of the pain. This approach should be used only in patients with no previous opioid exposure. Patients should also be provided with a rescue dose. This combination offers gradual, safe and rational dose escalation that is applicable to all routes of opioid administration.
- **Controlled-release drug formulations** These preparations of oral opioids can lessen the inconvenience of around-the-clock administration of drugs with a short duration of action. Numerous studies have demonstrated the safety and efficacy of these preparations in cancer patients with pain (31,32).
- **As-needed (prn) dosing** This strategy is beneficial if rapid dose escalation is necessary or when beginning therapy with opioids with a long half-life (e.g. methadone or levorphanol). As-needed dosing may also be appropriate for patients who have rapidly decreasing analgesic requirements, or intermittent pains separated by pain-free intervals.
- **Patient-controlled analgesia (PCA)** This is a technique of parenteral drug administration in which the patient controls an infusion device that delivers a bolus of analgesic drug on demand according to parameters set by the physician. Long-term PCA in cancer patients is most commonly sc using an ambulatory infusion device. PCA is usually added to a basal infusion rate and acts, in effect, as a rescue dose.

Adverse effects and their management

- **Tolerance** There is great variation in the opioid dose required to manage pain (400-2000 mg of im morphine per 24 hours) (33). The induction of true analgesic tolerance that could compromise the utility of treatment can only be said to occur if a patient manifests the need for increasing opioid doses in the absence of other factors (e.g. progressive disease) that would be capable of explaining the increase in pain. Extensive clinical experience suggests that most patients who require dose escalation to manage increasing pain do have demonstrable disease progression (34). This suggests that true pharmacological tolerance to the analgesic effects of opioids is not a common clinical problem, and has two important implications:
  - Concern about tolerance should not impede the use of opioids early in the course of the disease.
  - Worsening pain in patients receiving a stable dose of opioids should not be attributed to tolerance, but be assessed as evidence of disease progression or, less commonly, increasing psychological distress.
- **Adverse drug interactions** There is potential for cumulative side-effects and serious toxicity to arise from combinations of drugs. The sedative effect of an opioid may add to that of other centrally acting drugs, such as anxiolytics, neuroleptics and antidepressants. Likewise, constipation produced by opioids is probably worsened by anticholinergic drugs.
- **Respiratory depression** This is the most serious adverse effect of opioid therapy, which can impair all phases of respiratory activity (rate, minute volume and tidal exchange). Clinically significant respiratory depression is always accompanied by other signs of central nervous system depression, including sedation and mental clouding. Repeated administration of opioid drugs appears to produce a rapid tolerance to their respiratory depressant effects, however, so these drugs can be used in the management of chronic cancer pain without significant risk of respiratory depression. When this does occur in patients on chronic opioid therapy, administration of the specific opioid antagonist naloxone usually improves ventilation.
- **Sedation** Tolerance to this effect usually develops within a period of days to weeks. Patients should be warned about it, to reduce anxiety and discourage activities that could be dangerous if sedation occurs (e.g. driving). Some patients have a persistent problem with sedation, particularly if other sedating drugs are also being taken or if there is co-morbidity such as dementia, metabolic encephalopathy or brain metastases.
- **Confusion and delirium** Confusion is a greatly feared effect of opioid drugs, and mild cognitive impairment is common (35). However, similar to sedation, pure opioid-induced encephalopathy appears to be transient in most patients, persisting from days to 1-2 weeks. Although persistent

confusion attributable to opioids alone does occur, it is usually related to the combined effect of the opioid and other factors, including electrolyte disorders, neoplastic involvement of the central nervous system, sepsis, vital organ failure and hypoxaemia (36). A stepwise approach to management often culminates in a trial of a neuroleptic drug. Haloperidol in low doses (0.5-1.0 mg orally or 0.25-0.5 mg iv or im) is most commonly recommended because of its efficacy and low incidence of cardiovascular and anticholinergic effects.

- **Constipation** This is the most common adverse effect of chronic opioid therapy (37-39), and laxative medication should be prescribed prophylactically. There are no controlled comparisons of the performance of the various laxatives in opioid-induced constipation. Combination therapy is frequently used, particularly co-administration of a softening agent (e.g. docusate) and a cathartic (e.g. senna, bisocodyl or phenolphthalein). The doses should be increased as necessary, and an osmotic laxative (e.g. magnesium sulphate) should be added if required. Chronic lactulose therapy is an alternative that some patients prefer, and the occasional patient is managed with intermittent colonic lavage using an oral bowel preparation.
- **Nausea and vomiting** Opioids may produce nausea and vomiting via both central and peripheral mechanisms. These drugs stimulate the medullary chemoreceptor trigger zone, increase vestibular sensitivity, and affect the gastrointestinal tract (increased gastric antral tone, diminished motility, delayed gastric emptying). The incidence of nausea and vomiting in ambulatory patients is estimated to be 10-40%, and 15-40%, respectively (40), with the effects greatest at the start of therapy. Metoclopramide is the most reasonable initial treatment. Tolerance typically develops within weeks. Routine prophylactic administration of an anti-emetic is not necessary. Serotonin antagonists (e.g. ondansetron) are not likely to be effective with opioid-induced symptoms as they do not eliminate apomorphine-induced vomiting and motion sickness, which appear to be appropriate models for opioid effects. Clinical trials are needed to confirm this.
- **Addiction and dependence** Confusion about physical dependence and addiction augments the fear of opioids and contributes substantially to the undertreatment of pain (41). Patients with chronic cancer pain have a so-called therapeutic dependence on their analgesic pharmacotherapy, which may or may not be associated with the development of physical dependence, but is seldom associated with addiction. The medical use of opioids is rarely associated with the development of addiction (42). There are no prospective studies in patients with chronic cancer pain, but extensive clinical experience affirms the low risk of addiction in this population (LE: 3). Healthcare providers, patients and families often require vigorous and repeated reassurance that the risk of addiction is small.

Adjuvant analgesics

Defined as a drug that has a primary indication other than pain but is analgesic in some conditions, these drugs may be combined with primary analgesics on 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, adjuvant analgesics are conventionally categorised as follows.

- **Corticosteroids** Widely used as adjuvant analgesics (43,44), this group has been demonstrated to have analgesic effects, to improve QoL significantly (45), and to have beneficial effects on appetite, nausea, mood and malaise in patients with cancer (46). The mechanism of analgesia may involve anti-oedemic and anti-inflammatory effects, plus a direct influence on the electrical activity in damaged nerves. (i.e. reduction of neuropathic pain). 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) (LE: 2a).
- **Benzodiazepines** These drugs have a small analgesic effect (47), and must be balanced by the potential for side-effects, including sedation and confusion. Benzodiazepines are generally used only if another indication exists, such as anxiety or insomnia (LE: 2b).

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3.4.5 ***Treatment of neuropathic pain***

Numerous options are available for relieving neuropathic pain, including opioids, which give patients significant pain reduction with greater satisfaction than antidepressants (1,2). However, the potential complications of opioids mean that they are not always a satisfactory option (3). Beside opioids, effective therapies for managing neuropathic pain include antidepressants, anticonvulsants, topical treatments (lidocaine patch, capsaicin), N-methyl-D-aspartate (NMDA) receptor antagonists, baclofen, local anaesthetics, and clonidine (4,5).

3.4.5.1 Antidepressants

There is clear evidence for the effectiveness of antidepressants in the treatment of neuropathic pain (5), which work primarily via interaction with pathways running through the spinal cord from serotoninergic and noradrenergic structures in the brain stem and mid-brain.

Tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline (metabolite of amitriptyline), imipramine, and desipramine (metabolite of imipramine) are often the first drugs selected to alleviate neuropathic pain (6,7) (LE: 1a). The mechanism of action is predominantly by blocking the reuptake of norepinephrine and serotonin (dual acting), together with a blockade of neuronal membrane ion channels (reducing neuronal influx of Ca2+ or Na+), and interaction with adenosine and NMDA receptors. However, treatment with these analgesics may be compromised (and outweighed) by their side-effects. TCAs must be used cautiously in patients with a history of cardiovascular disorders, glaucoma, and urine retention. In addition, combination therapy with monoamine-oxidase inhibitors could result in the development of serotonin syndrome.

Duloxetine enhances both serotonin and norepinephrine function in descending modulatory pathways. It has weak affinity for the dopamine transporter and insignificant affinity for several neurotransmitters, including muscarinic, histamine, glutamate, and gamma-aminobutyric acid (GABA) receptors. Duloxetine has demonstrated a significant pain-relieving effect with a generally favourable side-effect profile in painful diabetic neuropathy (7) (LE: 1b).

Selective serotonin reuptake inhibitors (SSRIs) - sertraline, paroxetine, fluoxetine and citalopram - selectively inhibit the reuptake of serotonin. These antidepressants have a more favourable side-effect profile than TCAs, but their effectiveness in neuropathic pain is disputed in the literature (second-line pharmacological treatment).

Recommendations	GR
Amitriptyline and nortriptyline are the first line treatment for neuropathic pain; nortriptyline has fewer side-effects.	A
TCAs must be used cautiously in patients with a history of cardiovascular disorders, glaucoma, and urine retention.	
Duloxetine is the first-line treatment for neuropathic pain due to diabetic polyneuropathy.	A
Duloxetine may be tried as an analgesic in other neuropathic pain syndromes.	GCP

GCP = good clinical practice.

3.4.5.2 Anticonvulsant medication

The rationale for the use of anti-epileptic drugs in treating neuropathic pain is the reduction of neuronal hyperexcitability, one of the key processes in the development and maintenance of neuropathic pain (8). Different anticonvulsants have demonstrated pain relief by a blockade of neuronal membrane ion channels (reducing neuronal influx of Ca2+ or Na+), and effects on neurotransmitters (enhancement of GABA, inhibition of glutamate release) and/or neuromodulation systems (blocking the NMDA receptor) (9,10). Carbamazepine and phenytoin were initially used for the treatment of trigeminus neuralgia. Although both drugs reduce neuropathic pain, their attendant side-effects and complicated pharmacokinetic profile limit their use.

Despite the introduction of newer anticonvulsants with better side-effect profiles, carbamazepine remains the drug of choice for treating trigeminus neuralgia (11) (LE: 1a). However, oxcarbazepine (10-keto analogue of carbamazepine), a new anticonvulsant with a similar mechanism of action to that of carbamazepine but with a better side-effect profile, may replace carbamazepine for this (12).

Gabapentin and pregabalin are first-line treatments for neuropathic pain (reducing elements of central sensitisation), especially in post-zoster neuralgia and diabetic polyneuropathy (13-15) (LE: 1a). The combination of gabapentin with opioids seems to display synergistic effects in relieving neuropathic pain (16,17). Gabapentin has a favourable safety profile with minimal concern for drug interactions and no interference with hepatic enzymes. However, renal failure results in higher gabapentin concentrations and a longer elimination half-life, making dose adjustments necessary. Pregabalin (3-isobutyl GABA) is a structural analogue of gabapentin, but shows greater analgesic activity in rodent models of neuropathic pain than did gabapentin (18). Recent studies confirm the effectiveness of pregabalin in peripheral (including post-herpetic neuralgia and diabetic polyneuropathy) and central neuropathic pain (19).

Recommendation	GR
Gabapentin and pregabalin are first line treatments for neuropathic pain, especially if tricyclic antidepressants are contraindicated.	A

3.4.5.3 Topical analgesics

Neuropathic pain syndromes are typically associated with touch-evoked allodynia and hyperalgesia that impair patients' QoL. As well as treatment with anticonvulsants and antidepressants, a topical drug can be effective in treating ongoing pain and allodynia, supporting the idea that peripheral actions are of key importance in the initiation and maintenance of neuropathic pain.

Topical treatments for neuropathic pain include the 5% lidocaine patch, and capsaicin. The 5% lidocaine patch, a targeted peripheral analgesic, is effective in the treatment of post-herpetic neuralgia and a variety of other focal peripheral neuropathies (20,21) (first-line pharmacological treatment; LE: 1b). Once a day, up to three patches are applied to the painful skin, covering as much of the affected area as possible.

Capsaicin causes pain due to release of substance P from the nociceptive terminals, initiating nociceptive firing. An analgesic response follows because prolonged exposure to capsaicin desensitises the nociceptive terminals and elevates the pain threshold. Capsaicin (third-line pharmacological treatment) reduces pain in a variety of neuropathic pain conditions (including post-herpetic neuralgia, diabetic neuropathy and painful polyneuropathy). It is applied in a 0.075% concentration (22) (LE: 3).

Recommendations	GR
Topical lidocaine 5% should be used as an adjuvant in patients suffering from post-herpetic neuralgia.	A
Transdermal capsaicin may be used as an adjuvant in patients with neuropathic pain.	C

3.4.5.4 NMDA receptor antagonists

Within the dorsal horn, ionotropic glutamate receptors (NMDA, ⟨-amino-3-hydroxyl-5-methyl-4-

isoxazolepropionate [AMPA], kainate) and metabotropic glutamate receptors are all involved in neuropathic pain (23). However, the actions of excitatory amino acids (glutamate) on the NMDA receptor is considered a pivotal event in the phenomenon of wind-up and neuronal hyperexcitability (enhancement and prolongation of sensory transmission) that eventually leads to allodynia, and primary and secondary hyperalgesia.

Subanaesthetic doses of ketamine, and its active enantiomer S(+)-ketamine, given parenterally, neuraxially, nasally, transdermally or orally, alleviate pain post-operatively and in a variety of neuropathic pain syndromes, including central pain (24) (LE: 2b). However, ketamine may result in unwanted changes in mood, conscious perception, and intellectual performance, as well as psychomimetic side-effects (including visual and auditory hallucinations, dissociation and nightmares), limiting its use for neuropathic pain (25). It must therefore be reserved as a third-line option for when other standard analgesic treatments are exhausted (26,27).

Low dose systemic ketamine's primary role (bolus 0,25 mg/kg followed by a continuous administration between 0.1 - 0.4 mg/kg/h) is as an anti-hyperalgesic, anti-allodynic, or tolerance-protective compound in patients with severe acute pain, chronic or neuropathic pain, opioid tolerance, or those at risk for developing chronic post surgical pain (following laparotomy, thoractomy, breast surgery, and nephrectomy) (28,29).

In the acute setting ketamine is effective as a rescue analgesic (0.25 mg/kg, iv) for acute pain that is not, or poorly, responsive to opioids (30).

Despite improved and prolonged analgesia following caudal administration of ketamine in paediatric anaesthesia, there remains a controversy in the preclinical (animal) and clinical literature as to the safety and justifiability of this compound for neuraxial administration. In a case report as well as in an animal study, severe histological abnormalities indicating neurotoxicity were observed following neuraxial administration of ketamine (31,32).

Recommendation	**GR**
Ketamine is effective as an analgesic in neuropathic pain, but may be responsible for severe life-threatening side-effects and should be reserved for specialised pain clinics and as a last resort (third-line treatment).	B

3.4.5.5 Other drug treatments

Baclofen, a muscle relaxant, is analgesic due to its agonistic effect on the inhibitory GABAB receptors. Baclofen is efficacious in patients with trigeminal neuralgia, but not in those with other neuropathic pain conditions (33). However, this analgesic also has antispasticity properties and may induce analgesia by relieving muscle spasms, a frequent accompaniment of acute neuropathic pain. Baclofen can be considered a second-line agent for trigeminus neuralgia, or a third-line agent in neuropathic pain syndromes (LE: 3).

Clonidine, an α2-adrenoreceptor agonist, is available as a patch for transdermal administration and has been used in neuropathic pain states. When used topically, it seems to enhance the release of endogenous encephalin-like substances, but its use in the treatment of neuropathic pain is focused on intrathecal or epidural administration in combination with opioids and/or local anaesthetics. This delivery improves pain control because of a possible supra-additive effect during neuropathic pain treatment (34) (LE: 2b).

Summary: treatment of neuropathic pain

- **First-line agent:**
  - nortirptylinepregabalin, gabapentin;
  - duloxetine (first-line treatment in diabetic polyneuropathy only);
  - lidocaine 5% patch (first-line treatment in post-herpetic neuralgia only).
- **Second-line agent:**
  - opioids/tramadol (first-line treatment in patients with neuropathic cancer pain only).
- **Third-line agent:**
  - baclofen;
  - transdermal capsaicin 0.075%;
  - ketamine (an anaesthetic).

3.4.5.6 Invasive analgesic techniques

Studies suggest that 10-30% of patients with cancer pain do not achieve a satisfactory balance between relief and side-effects using systemic pharmacotherapy alone without unacceptable drug toxicity (35,36). Anaesthetic and neurosurgical techniques may reduce the need for systemically administered opioids, while achieving relief.

Peripheral nerve catheterisation in the management of cancer pain

Tumour infiltration or compression of a peripheral nerve or plexus can result in severe neuropathic pain resistant to pharmacological treatment. In these patients invasive analgesic techniques may be emphasised (37,38).

Recommendation	GR
Reversible regional anaesthetic techniques must be considered for the management of neuropathic pain.	GCP

GCP = good clinical practice.

Neurolytic blocks to control visceral cancer pain

Visceral cancer pain is mainly treated with NSAIDs and opioids, but neurolytic blockade can be used to optimise palliative treatment for cancer in the viscera.

Different neurolytic blockades have been described (39,40). A coeliac plexus block is indicated to treat pain secondary to malignancies of the retroperitoneum or upper abdomen (distal part of the stomach, pancreas, liver, gall bladder) (41) (LE: 1b). A superior hypogastric plexus block has proven utility for pelvic pain (rectum, vaginal fundus, bladder, prostate, testes, seminal vesicles, uterus and ovaries) due to a neoplasm that is refractory to pharmacological treatment (LE: 3) (42-44).

Neuraxial administration of opioids

The delivery of low-dose opioids near the sites of action in the spinal cord may decrease supraspinally mediated adverse effects. Compared with neuroablative therapies, spinal opioids have the advantage of preserving sensation, strength and sympathetic function (45,46). Contraindications include bleeding diathesis, profound leucopenia and sepsis. A temporary trial of spinal opioid therapy should be performed to assess the potential benefits of this approach before implantation of a permanent catheter.

The addition of a low concentration of a local anaesthetic, such as 0.125-0.25% (levo)bupivacaine, to an epidural/intrathecal opioid increases the analgesic effect without increasing toxicity (47,48). The potential morbidity of these procedures requires well-trained clinicians and long-term monitoring (LE: 2).

Recommendation	GR
Continuous intrathecal or epidural administration of morphine may be considered in patients with inadequate pain relief despite escalating doses with sequential strong opioids, or the development of side-effects (nausea, vomiting, constipation, drowsiness, sedation) limiting further dose increase.	B

Chemical rhizotomy

Chemical rhizotomy, produced by the instillation of a neurolytic solution into the epidural or intrathecal space, can be an effective method of pain control for patients with otherwise refractory localised pain syndromes (49,50). The technique is most commonly used in chest-wall pain due to tumour invasion of somatic and neural structures. Other indications include refractory upper limb, lower limb, pelvic or perineal pain (lower end block).

Because of the significant risk of increased disability through weakness, sphincter incompetence and loss of positional sense, chemical rhizotomy of lumbosacral nerve roots is best reserved for patients with limited function and pre-existing urinary diversion. Adverse effects can be related to the injection technique (spinal headache, mechanical neural damage, infection and arachnoiditis) or to the destruction of nonnociceptive nerve fibres (51) (LE: 4).

Recommendation	GR
Lower end block may be considered in patients with intractable perineal pain (bladder, rectum) that has responded insufficiently to more conservative therapy. This technique may only be performed in patients with loss of sphincter function (rectum and/or bladder).	C

Cordotomy

During cordotomy, the anterolateral spinothalamic tract is sectioned to produce contralateral loss of pain and temperature sensitivity. The patient with severe unilateral pain arising in the torso or lower extremity is most likely to benefit from this procedure. The percutaneous technique is generally preferred. Significant pain relief is achieved in more than 90% of patients during the period immediately following cordotomy (52). Of surviving patients, 50% have recurrent pain after 1 year. Repeated cordotomy can sometimes be effective. The neurological complications of cordotomy include paresis, ataxia and bladder dysfunction (53) (LE: 3).

3.4.5.7 References

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3.5 Quality of life

It seems beyond question that systematic assessment and objective pain evaluation can be of help for pain control in cancer patients (1-3). There is also proof of the strong relationship between pain, anxiety and depression, and health-related QoL in cancer patients (4,5). Anxiety is a common symptom in patients near the end of life. There is currently insufficient evidence on the role of drugs for treatment of anxiety associated with terminal illness, and it is therefore not possible to draw any conclusions about the effectiveness of

pharmacotherapy in this setting (6).

Cancer-related fatigue (CRF) is a significant problem. It can occur because of the side effects of treatment or the disease itself, and can have a significant impact on a person's ability to function. The causes of fatigue are not fully understood and so it is difficult to treat it appropriately. Trials of erythropoietin and darbopoetin (for anaemic patients on chemotherapy) and psychostimulants (amphetamines) provide evidence for improvement in CRF at a clinically meaningful level. There are no data to support the use of paroxetine or progestational steroids for the treatment of CRF. Methylphenidate is an obvious candidate for a large CRF study (7).

The proportion of people surviving and living with cancer is growing, which has led to increased awareness of the importance of QoL, including sexual function, to people with cancer. Sexual dysfunction is a potential long-term complication of cancer treatment. Following treatment for prostate cancer, there is evidence that transurethral alprostadil and vacuum constriction devices reduce sexual dysfunction, although negative effects are common. Vaginal lubricating creams are also effective, as are PDE5 inhibitors for sexual dysfunction secondary to prostate cancer treatment (8). Psychological **interventions** focused on **sexual dysfunction following cancer** can be considered as moderately effective (9).

Chronic constipation can be a serious problem for cancer patients taking opioids. In this setting, lactulose seems more effective than polyethylene glycol (10).

Palliative care / physical-psychological support / quality of life
Palliative care includes pain management as well as functional, psychosocial and spiritual support. Medical, psychological, physical, social, hospicial, and pastoral interdisciplinary services could be helpful at the end of life (11). Patients facing advance stages of prostate cancer frequently experience 'total pain', a mix of physical, psychological, spiritual and social suffering (12). Information about the illness and the process of care has been proved to reduce distress (13,14). Treatment should include both psychological and somatic symptoms (12). Moderate exercise seems to provide a certain benefit in the treatment of fatigue (15,16). Family caregivers and support groups are crucial components of the patient support system (11). Members of prostate cancer self-help groups provide each other with various types of help, usually nonprofessional and nonmaterial, for a particular shared, usually burdensome, characteristic (14). 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 aimed the improvement of the QoL (14).

3.6 Conclusions

The goal of analgesic therapy in cancer patients is to optimise analgesia with the minimum of side-effects. Current techniques can provide adequate relief for the large majority of patients. Most will need ongoing analgesic therapy, and requirements often change as the disease progresses. Patients with refractory pain should have access to specialists in pain management or palliative medicine who can provide an integrated multidisciplinary approach.

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4. PAIN MANAGEMENT IN UROLOGICAL CANCERS

4.1 Pain management in prostate cancer patients

*4.1.1 **Clinical presentation***

Pain in both early and advanced prostate cancer (PCa) can be caused directly by the cancer (77%), be related to the treatment (19%), or be unrelated to either (3%) (1). Management must focus on symptomatic patients with locally advanced disease or metastases.

The overall incidence of chronic pain in PCa patients is about 30-50%, but as patients enter the terminal phase this rises to 90% (2). Pain may be directly attributable to tumour infiltration of and growth in three main areas: bone, nerve or a hollow viscus.

*4.1.2 **Pain due to local impairment***

4.1.2.1 Invasion of soft tissue or a hollow viscus

Pain caused by invasion of a hollow viscus is treated with surgery or minimally invasive procedures (e.g. catheter, stent or nephrostomy tube).

4.1.2.2 Bladder outlet obstruction

Continuous growth of the prostate can lead to an outlet obstruction. Lower urinary tract symptoms (LUTS) can occur, especially stranguria and an inability to void. Acute pain requires prompt relief. The best method is to insert a suprapubic catheter and treat the tumour according to the stage (3). If the outlet obstruction persists

transurethral palliative resection (TURP) is an option if no curative therapy can be offered.

4.1.2.3 Ureteric obstruction

Ureteric obstruction is most frequently caused by tumour compression or infiltration within the true pelvis (4-7). Less commonly, obstruction can be more proximal, associated with retroperitoneal metastases. In most cases, obstruction is primarily asymmetrical. Untreated progressive ureteric obstruction results in bilateral hydronephrosis and subsequent renal failure. It is good practice to drain symptomatic hydronephrosis at once, and to drain only one kidney (the less dilated and better appearing kidney or the one with the better function if known) in asymptomatic patients. A nephrostomy tube is superior to a double-J stent for drainage because the subsequent routine endoscopic replacement of the stent could be increasingly difficult in a continuously growing prostate gland, and a nephrostomy tube can be changed without anaesthesia.

4.1.2.4 Lymphoedema

Patients with a huge prostate mass and/or lymph node metastases in the pelvis frequently get lymphoedema of the legs. Physiatric techniques such as wraps, pressure stockings and pneumatic pumps can improve function and relieve pain and heaviness.

4.1.2.5 Ileus

Local obstruction of the rectum is a common occurrence in advanced PCa, and can lead to abdominal pain caused by obstructive ileus. Rarely, peritoneal involvement can also result in ileus. Surgery and/or rectal stenting must be performed for mechanical obstruction. Paralytic ileus due to tumour infiltration of a nerve plexus or secondary to analgesics may require laxatives for opioid-induced constipation to improve motility and reduce pain.

4.1.3 ***Pain due to metastases***

4.1.3.1 Bone metastases

- Bone metastases are the most common cause of chronic pain in patients with PCa (8,9) as a result of:
  - endosteal or periosteal nociceptor activation (mechanical distortion or release of chemical mediators)
  - tumour growth into adjacent soft tissues or nerves and
  - other complex mechanisms (9).
- Widespread bony metastases frequently cause multifocal pain. Patients with multiple bony metastases typically report pain in only a few sites.
- More than 25% of patients with bony metastases are pain-free (10).
- The factors that convert a painless lesion into a painful one are unknown.

The choice of treatment will depend on the site, histology and stage of the tumour, and on the patient's physical and emotional condition. Although tumour-cell specific therapies are being developed, most commonly used techniques damage normal tissues, with consequent side-effects. The pros and cons of the therapeutic options should be considered in each case, those with fewest side-effects being administered first. The options are:

- hormone therapy;
- radiotherapy;
- orthopaedic surgery;
- radioisotopes;
- bisphosphonates;
- calcitonin;
- chemotherapy;
- systemic analgesic pharmacotherapy (the analgesic ladder).

Other pain management tools such as nerve blocks are rarely used.

Hormone therapy

Huggins and Hodges (11) first noted the effect of exogenous oestrogen administration on prostatic carcinoma. Hormone changes may cause complex endocrine effects, such as pituitary inhibition of luteinising hormone (LH), follicle-stimulating hormone (FSH) and prolactin, as well as changes in endogenous corticosteroid hormone production (12). A variety of additive or ablative hormone manipulations have been employed, including oestrogen, anti-androgen (cyproterone, flutamide), oestrogen-mustine complex (estramustine), progestogens, aminoglutethimide, gonadotrophin-releasing hormone (GnRH) analogues, orchidectomy, adrenalectomy and hypophysectomy. Corticosteroids are also used for the palliation of pain, particularly that due to bone deposits.

Side-effects

Hormone therapy is generally much better tolerated than chemotherapy. It can cause a temporary exacerbation of pain (pain flare), which is generally predictive of a subsequent response (13). The side-effects are:

- GnRH analogues and orchidectomy:
  - loss of body hair
  - testicular atrophy
  - gynaecomastia
  - loss of libido
  - impotence
  - increased cardiovascular mortality rate in long term administration
  - psychological morbidity.
- anti-androgens:
  - gynaecomastia (more often if used alone than when used in combination with GnRH analogues)
  - hepatic impairment
  - less sexual dysfunction than with GnRH analogues.
- cyproterone acetate:
  - fewer side-effects than oestrogens
  - lower incidence of cardiovascular complications than with oestrogens.
- oestrogens:
  - loss of body hair
  - testicular atrophy
  - gynaecomastia
  - loss of libido
  - impotence.
- Long-term administration results in higher mortality from cardiac and cerebrovascular disease as compared to GnRH analogues.
- adrenalectomy:
  - major operative procedure.
- hypophysectomy:
  - small but significant mortality rate
  - hormone replacement is subsequently required for life.

Efficacy

In a collected series of protocols, pain relief has been estimated at between 35% (14) and 70% (15). The differences may be due to the selection of patients and problems in pain measurement. Well-differentiated prostatic carcinoma is more likely to respond to hormones than are poorly differentiated tumours. Manipulations that include replacement corticosteroid therapy or have additional corticoid effects seem to give higher response rates. Corticosteroids are also used for the palliation of pain, particularly in bone metastases.

Problems

To date, most patients with adenocarcinoma of the prostate present in early tumour stages and undergo radical surgery or radiotherapy. In cases of disease progression and symptoms, hormone therapy can be indicated with patients remaining asymptomatic for years. Pain is associated with a hormone-resistant tumour in progression, which necessitates alternative therapeutical options.

Radiotherapy

- The role of radiotherapy in the management of pain due to bone metastases is unquestionable.
- Radiotherapy techniques vary widely, from a large dose given as a single treatment to as many as 20 smaller treatments given over 4 weeks.
- Dose-time factors: the biological effect of the radiation depends not only on the total dose delivered, but also on the number of separate treatments and the total time over which the irradiation therapy is administered.
- Palliative doses are smaller than maximum tolerance doses.
- Bear in mind that radiological evidence of a deposit may considerably underestimate the extent of disease.

In metastatic adenocarcinoma of the prostate, radiotherapy is associated with palliation of pain from bony metastases and improved QoL. Radiation therapy is effective at treating painful sites, and might also be effective at reducing the propensity for adjuvantly treated disease to become symptomatic in most patients

(16). This effect does not appear to be significantly influenced by dose-time relationships or histology. The proportion of patients achieving complete pain relief approaches 80% (17) (see also Section 3.3.3).

Orthopaedic surgery
If more than 50% of the thickness of the cortex of a long bone is eroded by metastasis, prophylactic fixation rather than radiotherapy alone should be considered. Internal fixation should be followed by postoperative radiotherapy because there is a real danger of continued tumour growth and further structural weakness (18,19). Radiotherapy should not be withheld for fear of inhibiting bone healing and regrowth. There is good evidence that palliative doses of radiotherapy are associated with recalcification (20).

Radioisotopes
Widespread axial skeletal involvement in PCa has been successfully treated with systemically administered bone-seeking radioisotopes (see also Section 3.3.2). Commonly used radionuclides are strontium-89 chloride (^{89}Sr) and samarium-153-ethylenediaminetetramethylene phosphonic acid (^{153}Sm-EDTMP). The addition of ^{89}Sr as a single injection of 10.8 mCi (399.6 MBq) is an effective adjuvant therapy to local field radiotherapy, reducing disease progression, the requirement for further radiotherapy and analgesic support (16), and improving QoL. Some evidence suggests that radioisotopes could give complete relief from pain over 1-6 months, with no increase in analgesia, although adverse effects, specifically leucocytopenia and thrombocytopenia, have been experienced (21).

Bisphosphonates
Bisphosphonates are routine supportive care for patients with bone metastases, and in a meta-analysis of 8 randomised studies some improvement in pain control due to bone metastases could be demonstrated (22). Bisphosphonates act by inhibiting osteoclast activities. Recent studies showed no statistically significant difference between the bisphosphonate and control groups in terms of PCa death, disease progression, and radiological and PSA response, but they should be considered for treating refractory bone pain and preventing skeletal events in those with metastatic PCa (22).

Zoledronic acid is effective for treating the complications of bone metastasis. Its efficacy and safety have been established in three pivotal trials involving more than 3000 patients (23). Although they appear osteoblastic on radiographic imaging, most bone metastases are characterised by excess osteoclast volume and activity. Pathological osteoclast activation is associated with increased risk of skeletal complications. Zoledronic acid, a potent inhibitor of osteoclast activity, differentiation and survival, decreases the risk of skeletal complications in men with androgen-independent PCa and bone metastases. Other bisphosphonates, including pamidronate and clodronate, seem to be less effective (24).

Zoledronic acid administration for one year to patients with hormone-sensitive PCa and bone metastases who were on androgen-deprivation therapy was safe and prevented bone loss, as shown by significant increases in bone mineral density and sustained suppression of biochemical markers of bone turnover (25). Zoledronic acid (4 mg intravenously over 15 minutes every 3-4 weeks) decreased the frequency of skeleton-related events, delayed the time to the first occurance, and reduced pain (23). Visual analogue scale improvement is positively correlated with a decrease of C-telopeptide and bone phosphatase alkaline ($p < 0.05$) serum levels (26). Studies are needed to determine the optimal timing, schedule and duration of treatment in men with bone metastases, as well as other potential roles for bisphosphonates, e.g. prevention of bone metastases (see Section 3.4.3).

Calcitonin
Current evidence does not support the use of calcitonin to control pain arising from bone metastases (27).

Chemotherapy
In about 80% of men with metastatic PCa, primary androgen ablation leads to symptomatic improvement and a reduction in the serum levels of PSA. The disease eventually becomes refractory to hormone treatment, and systemic chemotherapy should be reserved for this patient group. Recent data have shown encouraging signs in overall survival, palliation of symptoms and improvements in QoL (28), particularly with docetaxel.

Trials using single-agent chemotherapy in advanced disease have shown poor results, but newer studies suggest multiagent chemotherapies may be more effective. A randomised trial showed that mitoxantrone plus low-dose prednisone relieved pain and improved QoL more frequently than did prednisolone alone.
Other studies have confirmed the symptomatic effect of this regimen, but none found improved survival.

A PSA-response rate and a reduction of pain were also reported with other combined chemotherapies (Table 4). Individualised therapy was necessary as side-effects were common and no regimen showed a survival benefit.

A major proportion of the morbidity and mortality related can be traced to the burden of bone metastases (29). Any effective hormone therapy or chemotherapy is generally suited to relieve metastatic pain, or to limit, at least. Over the last decade, several new agents for mCRPC targeting different mechanisms of progression have been applied successfully: docetaxel, cabazitaxel, sipuleucel-T, denosumab, and abiraterone acetate (30). Docetaxel is the standard first-line chemotherapeutic agent (31). Despite a survival benefit the prognosis remains limited. Second-line therapeutic options are limited. Results from recently completed trials show a statistically and clinically significant improvement in pain relief and overall survival with cabazitaxel compared with mitoxantrone. Cabazitaxel has been shown to be well tolerated and has been approved as second-line chemotherapy for mCRPC (31,32). In 2010 two further randomized trials were published which demonstrate a survival benefit in the second-line setting: sipuleucel-T (immunotherapy) and abiraterone acetate versus placebo (20). The identification of intracellular androgen synthesis by prostate cancer cells has led to the development of third generation drugs for the therapy of mCRPC. Inhibitors of androgen synthesis and more potent androgen receptor antagonists will relief pain and improve palliation. A significant reduction of tumor-associated pain and a survival advantage of 4.6 months compared to placebo following docetaxel-based chemotherapy has already been shown for abiraterone (phase III study) (32) (LE: 1b, GR: A).

Table 4: PSA-response rates to selected combined chemotherapy regimens

Chemotherapy agent	Plus	Response rate (%)
Ketoconazole	+ doxorubicin	55
Vinblastine	+ estramustine	54-61
Estramustine	+ etoposide	39-58
Mitoxantrone	+ prednisone	33
Paclitaxel	+ estramustine	53

In 2005, two studies demonstrated that docetaxel-based regimens have a very good symptomatic effect that is significantly better than that of the mitoxantrone-based approach (Table 5) (25,26). Additionally, for the first time, a significant survival benefit was shown for the docetaxel group (18.9 versus 16.5 months).

Table 5: Docetaxel-based chemotherapy versus mitoxantrone-based regimens

Chemotherapy	Plus	Frequency	Response rate (29)	
agent			Pain (%)	Quality of life (%)
Docetaxel	+ prednisone	Every 3 weeks	35	22
Docetaxel	+ prednisone	Weekly	31	23
Mitoxantrone	+ prednisone	Every 3 weeks	22	13

Although most of these regimens are associated with side-effects such as fatigue, mild myelosuppression and gastrointestinal irritation, they are generally well tolerated by most patients (33). The docetaxel-based regimens are now the standard of care for patients with advanced hormone-refractory PCa. Soft-tissue lesions could be influenced to a greater extent than bony metastases. Pain management by chemotherapy could be effective, although it is much more cost-intensive than the administration of opioids, and the survival advantage is limited.

4.1.4 Systemic analgesic pharmacotherapy (the analgesic ladder)

If the treatments described above provide insufficient pain relief, systemic analgesic pharmacotherapy should be administered (see Section 3.4.4). In most cases, the drug selection scheme proposed by the World Health Organization (WHO), the analgesic ladder, is recommended.

Short-term studies have shown that NSAIDs alone are effective in managing cancer pain, with side-effects similar to those with placebo. In about 50% of studies, increasing the dose of NSAIDs increased efficacy but not the incidence of side-effects. No large clinical difference has been demonstrated between combining an NSAID with an opioid versus either medication alone (34).

Tramadol extended-release tablets and dihydrocodeine extended-release tablets were effective for the management of chronic tumour pain associated with PCa with bone metastasis on step 2 of the WHO ladder, with the tramadol giving slightly better pain management and fewer side-effects, particularly constipation (35). The treatment of constipation in palliative care is based on experimental evidence, and uncertainty persists about its optimum management in this group of patients (36).

Oral morphine is an effective analgesic for cancer pain, with qualitative evidence showing that it compares well with other opioids. Morphine is the gold standard for moderate to severe cancer-related pain. Alternatives such as hydromorphone are now available, but no clinically significant difference has been shown compared to and other strong opioids such as morphine (37). Patients with inadequate pain control and intolerable opioid related toxicity/adverse effects may have to switch to an alternative opioid for symptomatic relief, although the evidence to support opioid switching is largely anecdotal, observational or from uncontrolled studies (38).

Breakthrough pain is a common and debilitating problem for patients with cancer. Evidence suggests that oral transmucosal fentanyl citrate is effective for breakthrough pain (39), giving more rapid relief than morphine (40).

4.1.5 ***Spinal cord compression***

Spinal cord compression can occur due to the collapse of a vertebral body or to pressure from an extradural tumour within the spinal canal. Prodromal pain is a feature in 96% of these patients. The overall incidence in PCa patients is less than 10% (42). Thoracic cord compression is the most common area (70%), and the incidence of multiple extradural sites can be as high as 18% (43). Definitive treatment with surgery (anterior decompression with spinal stabilisation) or radiotherapy should be considered. The symptom of local back pain sometimes disappears, despite an increase in motor deficits, because of the evolving sensory component of the paraplegia.

Corticosteroids (typically dexamethasone 16 mg daily) are of only temporary use in cord oedema. There is evidence that decompressive surgery benefits ambulant patients with poor prognostic factors for radiotherapy, and non-ambulant patients with a single area of compression, paraplegia of < 48 hours' duration, nonradiosensitive tumours and predicted survival of > 3 months. There is a significant risk of serious adverse effects from high-dose corticosteroids (44).

4.1.6 ***Hepatic invasion***

Hepatic invasion by secondary tumour is a common cause of severe hypochondrial pain, often radiating to the back and shoulder blade. The mechanism may be the stretching of nerve endings in the liver capsule, diaphragmatic irritation, or haemorrhage into a necrotic area of tumour. Liver pain can often be controlled by conventional titration of appropriate analgesics or with corticosteroids.
Whole-liver palliative radiotherapy can also be useful in carefully selected patients with refractory pain, giving far fewer side-effects than the alternatives of intra-arterial chemotherapy or hepatic artery embolisation. Hepatic irradiation can improve abdominal pain with little toxicity in more than half of patients (45). Doses should not exceed 30 Gy in 15 daily fractions or its equivalent if radiation hepatitis is to be avoided.

4.1.7 ***Pain due to cancer treatment***

4.1.7.1 Acute pain associated with hormonal therapy

Luteinising hormone-releasing hormone (LHRH) tumour flare in PCa

Initiation of LHRH therapy for PCa produces a transient symptom flare in 5-25% of patients (46,47), presumably caused by an initial stimulation of LH release before suppression is achieved (47,48). The syndrome typically presents as an exacerbation of bone pain or urinary retention. Spinal cord compression and sudden death have also been reported (46). Symptom flare is usually observed within the first week of therapy, and lasts 1-3 weeks. Co-administration of an androgen antagonist at the start of LHRH agonist therapy can prevent this (49).

4.1.7.2 Chronic pain associated with hormonal therapy

Gynaecomastia

Chronic gynaecomastia and breast tenderness are common complications of anti-androgen therapies for PCa, the incidence varying between drugs. Frequently associated with diethylstilboestrol (50), it is less common with flutamide and cyproterone (51-53), and uncommon in patients receiving LHRH agonist therapy (54). In elderly patients, it must be distinguished from primary breast cancer or secondary cancer in the breast (54).

4.1.8 ***Conclusions***

Radio-, chemo- and hormone therapy are all valuable options for relieving cancer pain. The side-effects of

inappropriate anticancer treatments can be very distressing, and so the disadvantages of treatments must be balanced against the palliative benefits. In many patients, the best approach to pain relief is through interdisciplinary co-operation.

Surgery, radio-, chemo- and hormone therapy are mainly used as antitumour treatment in the relief of pain. The rational use of any of these treatments demands knowledge not only of tumour biology, but also of the mechanisms of action of these specific oncological techniques. The therapeutic aim should be clearly understood prior to starting treatment.

Radical treatment should be given if the disease is potentially curable, but the intent should be symptomatic or palliative if the tumour is advanced or widely disseminated (55). The importance of early intervention needs to be emphasised, and education is crucial: patients must be aware of the early signs and symptoms of metastatic disease, which does not necessarily involve pain.

*4.1.9 **Recommendations at a glance (stage M1) (56-61)***

ANTICANCER TREATMENT		
Recommendation	**LE**	**GR**
Hormonal therapy (orchiectomy, LHRH analogues, diethylstilboestrol equivalent)	1a	A
Total androgen blockade: flare prevention, second-line	2b	B
Intermittent androgen suppression experimental	3	B
Monotherapy with anti-androgen is an option	2	B
First-line treatment controls disease for 12-18 months, second-line individualised	1b	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		
Recommendation	**LE**	**GR**
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 (^{89}Sr or ^{153}Sm-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

*4.1.10 **References***

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4.2 Pain management in transitional cell carcinoma patients

*4.2.1 **Clinical presentation***

In more developed countries, urothelial cancer is the 5th most common cancer in men and the 13th in women (1). Transitional cell carcinoma (TCC) is the most frequent cancer of the bladder and upper urinary tract. It arises much more frequently in the bladder than in the collecting system (calices, renal pelvis and ureter).

From the perspective of pain, there are no differences between TCC and other histotypes of urothelial malignant tumour. In bladder carcinoma, pain can be present at an early stage as a burning pain (dysuria),

together with irritative symptoms (urgency and frequency), or late in advanced disease due to obstruction of the upper urinary tract, or local invasion of neighbouring tissues causing pelvic or metastatic organ invasion.

TCC of the renal collecting system represents 5-10% of all kidney tumours and 5% of all TCC of the urinary tract (2). TCC of the ureter accounts for only 3% of all TCC (3). In upper urinary tract TCC, pain is an initial symptom in 18-30% of cases (4,5).

*4.2.2 **Origin of tumour-related pain***

4.2.2.1 Bladder TCC

The main causes of tumour-related pain in bladder TCC are:

- obstruction of the upper urinary tract due to growth of bladder tumour close to the ureteral orifices.
- invasion of the surrounding areas by a locally advanced tumour (pelvic wall, nerve roots, other organs such as bowel, or rectum)
- bone metastases
- soft tissue metastases (seldom painful)

4.2.2.2 Upper urinary tract TCC

The main causes of tumour-related pain in the upper urinary tract TCC are:

- obstruction of the upper urinary tract (presenting symptom in around 30% of cases)
- acute obstruction due to blood clots
- invasion of the surrounding areas by a locally advanced tumour (posterior abdominal wall, nerve roots, paraspinous muscles, other organs such as bowel, spleen, or liver)
- bone metastases
- soft tissue metastases (seldom painful)

*4.2.3 **Pain due to local impairment***

4.2.3.1 Bladder TCC

Obstruction of the ureteral orifices by tumour infiltration may lead to hydronephrosis and consecutive flank pain due to ureteral distension (visceral pain). Transurethral resection of the tumour may be effective in eliminating ureteral obstruction, but in palliative situations, hydronephrosis is mainly treated by temporary or permanent ureteral stenting or percutaneous/open nephrostomy, similar to the treatment of obstruction caused by prostate cancer (6).

In locally advanced disease, symptoms are comparable with those caused by T4 prostate cancer. Infiltration of the contiguous soft tissue and neighbouring organs can cause acute burning pain by infiltration of the pelvic nerves (neuropathic pain), sometimes associated with paraesthesia irradiating to the lower limb, or motor deficit. If the tumour invades adjacent organs (small bowel or rectum), there can be obstruction, and visceral pain due to distension of hollow organs. Growing bladder tumour can cause complete bladder outlet obstruction, with hypogastric abdominal pain from bladder distension. Obstruction of the lymphatic vessels by lymphadenopathy can cause lymphoedema of the lower limbs with pain due to distension of muscle fascia (somatic pain) (6).

In infiltrating and advanced bladder cancer, radical or debulking cystectomy and urinary diversion have a positive impact on pain, by removing the neoplastic mass invading the surrounding tissues (see EAU Guidelines on Muscle Invasive Bladder Cancer, Chapter 8.1). Extended operations, including excision of involved bowel, are sometimes indicated. Palliative surgery may be necessary in occlusive intestinal syndromes (7). In a small retrospective study of patients with tumour infiltration of the rectum by locally recurrent prostate cancer, total exenteration resulted in significant pain reduction in all patients, and 79% were completely pain free (8). In a mixed group of cancer patients (colorectal, urinary or gynaecological) with different symptoms such as bleeding, fistula, or pelvic pain or obstruction, palliative pelvic exenteration improved QoL in 88% (9).

First-line chemotherapy strategies that are mainly based on platinum-containing regimens have some effect in 12-75% of patients with advanced disease (see EAU Guidelines on Muscle Invasive Bladder Cancer Guidelines, Chapter 12). It probably relieves pain by decreasing the neoplastic mass in respondent patients (10-14) (LE: 1a), but pain control was one of the study end points in only one small study (15).

In a phase III trial vinflunine, as new second line chemotherapy agent, proved to be very effective in disease control with 76%, but pain control was not an end point. Quality of life stayed unchanged during chemotherapy despite drug toxicity (16).

Radiotherapy can be effective in controlling pelvic pain and other symptoms such as frequency and haematuria due to local disease progression. In a large randomised study with 500 participants, two radiotherapy schedules (35 Gy in 10 fractions and 21 Gy in 3 fractions) were compared for symptomatic improvement of bladder-related symptoms. 68% of the participants achieved symptomatic improvement, 71% with 35 Gy radiotherapy and 64% with 21Gy. Acute bowel toxicity was noticed in one third of the patients. There was no significant difference between the 2 study arms (17) (LE 1a). Some smaller studies have shown comparable results with respect to improvement of QoL by local radiotherapy (18).
The effect of radiotherapy in controlling local symptoms of advanced bladder cancer needs to be balanced against the risk of inducing proctitis.

4.2.3.2 Upper urinary tract TCC

Transitional cell carcinoma (TCC) of the upper urinary tract often presents with microscopic or gross haematuria (70-80%), but flank pain also occurs in 20-40% of patients due to obstruction or lumbar mass (see EAU Guidelines on Upper Urinary Tract Urothelial Cell Carcinomas, Chapter 3.4). A multi-institutional study with 654 patients has shown that local symptoms do not confer worse prognosis compared with patients with incidentally detected upper urinary tract TCC (19). Locally advanced primary tumours are usually managed by radical nephroureterectomy. Extended operations including excision of involved bowel, spleen or abdominal wall muscle are sometimes indicated.

With regard to chemotherapy, the same considerations are valid for upper urinary tract TCC as for bladder TCC (compare with EAU Guidelines on Upper Urinary Tract Urothelial Cell Carcinomas, Chapter 3.7.2). The standard chemotherapy regimens that provide moderately prolonged survival are MVAC (methotrexate, vinblastin, adriamycin, cisplatin) and gemcitabine/cisplatin as first-line drugs, as in bladder cancer (20). In a phase II study of 151 patients with locally advanced or metastatic urothelial cancer, 45 patients (29%) with upper urinary tract carcinoma were included, and vinflunine as second-line chemotherapy demonstrated moderate activity in these patients (21)

*4.2.4 **Pain due to metastases***

Haematogenous metastases to the bone are often found in advanced bladder or upper urinary tract TCC. No data are available in the literature concerning the specific effect of chemotherapy on bone metastases alone.

Radiotherapy has a palliative analgesic role in bone metastases (see Chapter 3.3.3) and pain reduction > 50% can be achieved in 50% of patients (22) (LE: 1b). All the data concerning radiotherapy or radionuclide therapy of bone metastases have been taken from series including different carcinomas such as prostate, breast or kidney cancer. There are no specific trials studying the effect of radiotherapy on painful bone metastases in bladder cancer. Single-fraction radiotherapy is as effective as multifraction radiotherapy in relieving metastatic bone pain (23,24) (LE: 1a). However, the rates of retreatment and pathological fractures are higher after single-fraction radiotherapy (23,24) (LE: 1a).

Radioisotope treatment (see Chapter 3.3.2) or hemi-body irradiation can be used in patients with multiple bone metastases (22). There are no specific studies of radioisotope therapy for bone metastasis in TCC.

Orthopaedic surgery can stabilise pathological fractures, as for those from prostate cancer (see Chapter 3.3.3.6).

*4.2.5 **Conclusion for symptomatic locally advanced or metastatic urothelial cancer***

- In locally advanced bladder cancer, palliative cystectomy or exenteration might be an option for symptom relief (LE 3; GR B)
- Chemotherapy in urothelial cell carcinoma is effective in terms of disease control (LE 1b, GR A)
- The effect on pain control and quality of life seems to be analogue (LE 2a)
- Radiotherapy reduces pain and symptoms of locally advanced bladder cancer (LE 1a, GR B), but this needs to be balanced against the risk of inducing proctitis
- Radiotherapy is effective in reducing pain due to bone metastases (LE 1b; GR A)

*4.2.6 **References***

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4.3. Pain management in renal cell carcinoma patients

*4.3.1 **Clinical presentation***

Renal cell carcinoma (RCC) is mainly diagnosed incidentally. There is no pain unless tumour invades adjacent areas or obstructs urine outflow due to haemorrhage and blood clot formation. Some 20-30% of patients present with metastases, and 30% of patients primarily presenting with a localised kidney tumour develop them during follow-up. RCC metastasises mainly to lung, bone, brain, liver and ipsilateral or contralateral adrenergic glands. Such patients have a maximal 2-year survival rate of 20%. Overall 50-60% of patients may need treatment for the symptoms of metastatic disease, mainly pain.

The main origins of tumour-related pain are:

- invasion of the surrounding areas by a locally advanced tumour (posterior abdominal wall, nerve roots, paraspinous muscles, other organs such as bowel, spleen, liver)
- obstruction of the upper urinary tract due to haemorrhage and subsequent formation of blood clots
- bone metastases
- soft tissue metastases (seldom painful).

*4.3.2 **Pain due to local impairment***

Patients with invasion of surrounding areas (e.g. the posterior abdominal wall, nerve roots, paraspinous muscles, other organs such as bowel, spleen, liver) by a locally advanced primary tumour without metastases usually present with pain. Surgical management is the only effective option for this type of tumour. Extended operations that include excision of involved bowel, spleen or abdominal wall muscle are sometimes indicated.

Adjuvant immunotherapy or radiotherapy is without proven benefit with regard to recurrence. Even in cases of metastatic disease, palliative nephrectomy is indicated for the control of severe symptoms such as haemorrhage, pain or paraneoplastic syndromes (GCP). The frequency with which each of these symptoms is controlled, however, is unclear and there are no data in the literature comparing efficacy of nephrectomy in palliative situations with other therapies such as angioinfarction of the tumour.

Standard pre-operative (30 Gy) or post-operative radiotherapy offers no survival benefit, and its role in delaying local progression is questionable (1). Radiotherapy of soft tissue has no proven benefit for pain and tumour control.

In metastatic disease, the European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group study 30947 demonstrated a significant increase in survival with palliative nephrectomy plus immunotherapy compared with immunotherapy (interferon-alpha) alone (median survival of 17 compared with 7 months) (2) (LE: 2b). There is no special effect on pain relief from immunotherapy.

Obstruction of the upper urinary tract due to haemorrhage and subsequent formation of blood clots is effectively treated by radical nephrectomy in non-metastatic tumour (GCP). If the patient is physically fit for surgery, this should be done to increase the QoL, e.g. palliative nephrectomy in cases of metastatic tumour (GCP).

There are no data in the literature about the efficacy of other therapies such as angioinfarction of the tumour with regard to haemorrhage and pain relief in palliative situations. WHO guidelines recommend analgesic therapy and/or palliative drainage of the urinary tract if patients are not fit for major surgery.

*4.3.3 **Pain due to metastases***

Patients with bone metastases have a significantly better life expectancy (30 months) than those with visceral metastases (11.6 months) (3).

Surgery is indicated for solitary bone metastases that can be resected completely, intractable bone pain, and impending or demonstrable pathological fracture. In bone metastases with extensive soft tissue involvement and severe pain, amputation of a limb is sometimes required to maintain quality of life. Surgery for bone metastases achieves a significant decrease in pain in 89-91% of patients (4-6) (LE: 2b/3). Additionally, surgery prevents pathological fractures and spinal compression, and there is a significant impact on survival.

Pre-operative embolisation of bone metastases or embolisation alone achieves good pain relief in hypervascular bone metastases (7,8) (LE: 3).

High dose radiation therapy for palliation of painful bony metastases has been shown to be effective in 50-75% of all renal cancer patients (9-11) (LE: 3), and in 67% with general bone metastases (12) (LE: 2b). There is no impact on survival. Small studies of radionuclide therapy (e.g. with 89Sr) have shown good pain relief in bony metastases from RCC (13) (LE: 3).

Standard pre-operative (30 Gy) or post-operative radiotherapy offers no survival benefit; its role in delaying local progression is questionable (1); there is no proven benefit for pain and tumour control for soft tissue metastases.

Bone metastases show poor response to immunotherapy, and there is no proven benefit in pain relief. Hormonal therapy and chemotherapy are even less effective, and have no room in pain control.

Immunotherapy alone achieved an overall response in 15-27% of patients (14). Immunotherapy in combination with chemotherapy (interleukin-2 + interferon-alpha + 5-fluorouracil) is the most effective therapy, achieving partial tumour response in up to 46% of patients and complete response in a maximal 15%, although these rates are mainly for lung/lymph node metastases (15).

Pain due to soft tissue metastases probably behaves analogous to tumour response, but there are no data on immunotherapy for pain control. Hormonal therapy has no proven benefit for survival or pain relief.

First-line chemotherapy (docetaxel), second line chemotherapy (microtubule inhibitor cabazitaxel), and third generation anti-androgen therapy (abiraterone acetate)

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4.4 Pain management in patients with adrenal carcinoma

Adrenal carcinoma is a rare disease and has a poor prognosis. Non-functional adrenal lesions of more than 5 cm in diameter should be removed because there is a high probability of malignancy (1).

*4.4.1 **Malignant phaeochromocytoma***

Phaeochromocytomas result from phaeochromocytes, which are the predominant cells of the adrenal medulla and are also found in the paraganglia near the aorta and in lesser numbers in the ganglia of the sympathetic nervous system (2). When correctly diagnosed and treated, the disease is curable, unless there are metastases.

Computed tomography (CT) and magnetic resonance imaging (MRI) have the highest sensitivity in detecting the tumour, achieving 94-100%. A 131J-metaiodobenzylguanidine (131J-MIBG) scan is positive in approximately 87% of cases (3).

Chemotherapy with cyclophosphamide, vincristine and dacarbazine has little effect on metastases (4) (LE: 2b), but therapeutic doses of 131J-MIBG (33 GBq = 900 mCi) may produce some results (5, 6) (LE: 2b). The hormone response rate is 50%. There are no data on pain relief with 131J-MIBG in metastatic phaeochromocytoma, but a response rate that is at least the same as for hormone levels should be expected.

Malignant phaeochromocytomas are considered radioresistant, although there are some cases in which radiation therapy induced partial remission (7) (LE: 3). There is no information about the efficacy of radiation concerning pain relief in cases of bone or soft tissue metastases.

*4.4.2 **Treatment of pain***

- Soft tissue and/or bone pain due to metastases are best treated by therapeutic doses of 131J-MIBG, if the phaeochromocytoma takes up this radionuclide (8) (LE: 2b). There is no literature concerning chemotherapy or radiotherapy and pain relief in metastatic phaeochromocytoma.
- Treat the pain symptomatically following the recommendations made in Section 3.4.

4.4.2.1 Adrenocortical carcinomas

Carcinoma of the adrenal cortex is highly malignant, with local and haematogenous metastasis, and 5-year

survival rates of 25-43% for all treatments. Patients with distant metastases have a mean survival of only 4 months (9). An autopsy study showed metastasis to lung (60%), liver (50%), lymph nodes (48%), bone (24%) and pleura/heart (10%) (10). These tumours often extend directly into adjacent structures, especially the kidney.

Chemotherapy is of low efficacy. The most effective drug is mitotane, an adrenolytic. The tumour-response rate is 25-35% (9,11) (LE: 2a). It remains to be proven whether chemotherapy prolongs survival. Radiation therapy has not been useful except for palliation and pain management (12) (LE: 2b).

4.4.2.2 Treatment of the pain depending on its origin

- Abdominal symptoms are typical on first presentation of the tumour. The treatment is surgical removal of the primary tumour, with attempts to remove the entire lesion even if resection of adjacent structures is necessary, as well as resection of local lymph nodes.
- Soft tissue and/or bone metastases causing local symptoms can be treated by radiotherapy (8,12). There are no data on chemotherapy or radiotherapy for pain relief in metastatic adrenocortical carcinomas.
- Treat the pain symptomatically following the recommendations given in Section 3.4.

4.4.3 ***References***

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4.5 Pain management in penile cancer patients

4.5.1 ***Clinical presentation***

Penile cancer is rare in Europe, with an annual incidence of 0.3-1.0 new cases per 100,000 men (1). It mostly affects men between the ages of 50 and 70 years, with only 19% of cases in those aged < 40 years and 7% in those < 30 years (2). The penile lesion itself usually alerts the patient to the presence of a penile cancer

but there is often a delay in seeking medical attention. Lymph node involvement is a critical component of treatment planning and prognosis. Up to 60% of the patients at the time of presentation have palpable inguinal lymphadenopathy, and up to 85% of them will be found to have metastatic disease (3). Pain can occur in both early and advanced penile cancer. In the early stages, acute pain is expressed mainly by voiding dysfunction (infravesical obstruction) due to invasion of the corpus spongiosum. In advanced disease, pain is also caused by enlarged inguinal or pelvic node metastases and lymphoedema of the scrotum and lower limbs. Azotemia can develop secondary to nodal obstruction of the ureters. Hypercalcemia was reported in 17-21% of patients in two series (4). This was attributed to the parathyroid-hormone-like substances secreted by bulky metastases that stimulate osteoclastic bone resorption.

4.5.2. ***Pain due to local impairment***

4.5.2.1 Soft tissue and hollow-viscus invasion

Bladder outlet and ureteric obstruction is managed in the same manner as that described in Section 4.1.2.2.

4.5.3 ***Lymphoedema***

Patients with a huge inguinal tumour mass, or scarred inguinal tissue after lymph node dissection, often show lymphoedema of the lower limbs. This is more frequent in cases involving both inguinal and iliac nodes.

Lymphoedema is treated with physiatric techniques (wraps, pressure stockings or pneumatic pumps), which can both improve function, and relieve pain and heaviness. Orthotics can immobilise and support painful or weakened structures, and assistive devices can benefit patients with pain on weight-bearing or ambulation.

4.5.4 ***Pain due to metastases***

Pain management begins with antitumour treatment; usually surgery that includes partial/total penectomy, and inguinal and pelvic lymphadenectomy, depending on the clinical stage of the disease. Advanced penile cancer has a poor prognosis and must be approached with a multimodal treatment regimen that includes neoadjuvant chemotherapy, radiotherapy, followed by surgical resection (6). The chemotherapy regimen that is so far most effective and well tolerated is paclitaxel, ifosfamide and cisplatin (TIP), although large randomised trials are lacking (5). The role of radiotherapy is mainly palliative because its use after chemotherapy might decrease the pain from fixed inguinal nodes, bone metastases, spinal cord compression and paraplegia (7). Treatment of hypercalcemia consists of administration of iv saline for volume expansion, furosemide to promote diuresis and bisphosphonates to prevent osteoclastic bone resorption. When tumour erosion into femoral vessels is suspected, emergency intervention with endoluminal vascular stents or transobturator bypass graft should be undertaken (8,9).

4.5.5 ***Conclusions***

Pain management related to advanced penile carcinoma should include a multimodality regimen that consists of cisplatin-based chemotherapy, radiotherapy and surgical resection. The goals of palliative care should be: alleviation of pain using systemic analgesic pharmacotherapy (WHO Ladder) if multimodality therapy is unsuccessful, wound care, treatment of hypercalcemia and tumor erosion of the large groin vessels.

4.5.6 ***References***

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4.6 Pain management in testicular cancer patients

*4.6.1 **Clinical presentation***

Testicular cancer generally affects men in the third or fourth decade of life. It is mainly diagnosed causally as an intrascrotal mass. Approximately 20% of patients present with scrotal or inguinal pain, which disappears after orchiectomy. Only 11% of patients complain of back or flank pain at first presentation (1). Primary advanced tumour with pain due to bone metastases is very rare, maximally 3% at first presentation. It should be treated causally by primary chemotherapy and adjuvant analgesics.

*4.6.2 **Pain due to local impairment***

Orchiectomy is an effective treatment for local pain due to scrotal masses.

*4.6.3 **Pain due to metastases***

- Back or flank pain due to retroperitoneal lymphadenopathy slowly disappears as chemotherapy causes the mass to decrease (LE: 2b) (see EAU Guidelines on Testicular Cancer). Temporary analgesia is advisable (see Section 3.4.4).
- Retroperitoneal lymph node metastases can also cause obstruction of the ureter, leading to a symptomatic hydronephrosis with back or flank pain and perhaps additional fever. The therapy of choice is the immediate treatment of the hydronephrosis by ureteral stenting or the insertion of a percutaneous nephrostomy.
- Bone pain due to bony metastases is very rare and occurs mainly in patients with primary advanced disease and relapse after chemotherapy (2,3). Treatment with chemotherapy or second-line chemotherapy may be possible (see EAU Guidelines on Testicular Cancer). There is no literature on radiotherapy in cases of relapse and limitation of further chemotherapy.
- Back pain and neurological symptoms due to spinal cord compression by vertebral metastases may require urgent surgery (4) (LE: 3).

*4.6.4 **References***

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4.7 Recommendations at a glance

Table 6: Efficacy of the therapeutic options in pain relief (expert opinion)

Origin of pain/therapeutic options	RCC	TCC	PCa	Penile cancer	Adrenergic cancer	Testicular cancer
Bone metastases						
Surgery	+++	?	+	?	?	+
Radiation	++	++	+++	?	+	?
Radionuclide	+	?	+++	?	++	-
Chemotherapy	-	?	+	?	-	
Immunotherapy	-	-	-	?	?	?
Hormone therapy	-	-	++	-	-	-
Analgesics	+++	+++	+++	+++	+++	+++
Soft tissue infiltration						
Surgery	+++	+++	-	?	?	+
Radiation	-	+	++	?	+	?
Chemotherapy	+	++	+	?	++	+++
Immunotherapy	+	-	-	?	?	?
Hormone therapy	-	-	++	-	-	-
Analgesics	+++	+++	+++	+++	+++	+++
Nerve compression/nerve infiltration						
Surgery	+++	+++	++	?	?	++
Radiation	+	+	++	?	+	?
Chemotherapy	+	++	+	?	?	+++
Immunotherapy	+	-	-	?	?	?
Hormone therapy	-	-	++	-	-	-
Analgesics	+++	+++	+++	+++	+++	+++

RCC = renal cell carcinoma; TCC = transitional cell carcinoma; PCa = prostate cancer;
? = no conclusive data on pain control; - = no pain control; + = low pain control;
++ = moderate pain control; +++ = good pain control.

5. POSTOPERATIVE PAIN MANAGEMENT

Key Words: Postoperative analgesia, postoperative pain, opioids, NSAIDs, coxibs, paracetamol, urological procedures, epidural, PCA, PCEA, ketamine, clonidine, local anaesthetics

5.1 Background

Postoperative pain is inevitable in surgical patients, and is associated with tissue damage, the presence of drains and tubes, or postoperative complications, or a combination of these (1,2).

Approximately 70% of surgical patients experience a certain degree (moderate, severe or extreme) of postoperative pain (3,4) (LE: 1a). This is usually underestimated and undertreated (1,3), leading to increased morbidity and mortality, mostly due to respiratory and thromboembolic complications, increased hospital stay, impaired QoL, and development of chronic pain (1,3,5-7) (LE: 1a).

5.2 Importance of effective postoperative pain management

The physiological consequences of postoperative pain are shown in Table 7. All of these can delay or impair postoperative recovery and increase the economic cost of surgery (longer hospitalisation) (13,14) (LE: 3). Inadequate postoperative pain control may also lead to development of chronic pain (15,16) (LE: 2b).

Table 7: Physiological consequences of postoperative pain

Condition	Consequences	Ref.	LE
Stress response to surgery	Tissue trauma results in release of mediators of inflammation and stress hormones Activation of this stress response leads to: - retention of water and sodium - increase in metabolic rate	8	2a
Respiratory complications	Shallow breathing Cough suppression Lobular collapse Retention of pulmonary secretions Infections	9	2b
Cardiovascular complications	Hypertension Tachycardia Increased myocardial work, - myocardial ischaemia - angina - infarction	10	2b
Thromboembolic complications	Reduced mobility due to inadequate pain management can lead to thromboembolic episodes	11	2a
Gastrointestinal complications	Gastric stasis Paralytic ileus mostly after open urological operations	12	2b
Musculoskeletal complications	Prolonged confinement to bed: - reduced mobility - muscle atrophy	13	3
Psychological complications	Perioperative pain may provoke fear and anxiety, which can lead to: - anger - resentment - hostility to medical and nursing personnel - insomnia	13, 14	3

5.2.1 ***Aims of effective postoperative pain management:***

- to improve patient comfort and satisfaction;
- to facilitate recovery and functional ability;
- to reduce morbidity;
- to promote rapid discharge from hospital (1-3) (LE: 1a).

Recommendation	GR
Postoperative pain should be treated adequately, to avoid complications and development of chronic pain.	B

5.3 Pre- and postoperative pain management methods

5.3.1 ***Preoperative patient preparation:***

- patient evaluation;
- adjustment or continuation of medication to avoid abstinence syndrome;
- premedication as part of multimodal analgesia;
- behavioural-cognitive interventions for patients and families to alleviate anxiety and fear of postoperative pain reduce post-opeative analgesic requirements and result in better pain management (1) (LE: 1a).

Recommendation	GR
Preoperative assessment and preparation of patients allow more effective pain management.	A

*5.3.2 **Pain assessment***

Careful pain assessment by the surgeon or the acute pain team before and after treatment can lead to more efficient pain control, and diminished morbidity and mortality (1,4) (LE: 2a). In the post-anaesthesia care unit, pain should be evaluated, treated and re-evaluated initially every 15 min and then every 1-2 h. After discharge to the surgical ward, pain should be assessed every 4-8 h before and after treatment (17,18).

Various rating scales have been described to measure postoperative pain, but their major disadvantage is that they are all subjective, making their results difficult to evaluate, especially in patients with communication difficulties (18).

Recommendation	GR
Adequate postoperative pain assessment can lead to more effective pain control and fewer complications.	B

*5.3.3 **Pre-emptive analgesia***

Pre-emptive or preventive analgesia is defined as the administration of analgesia before surgical incision to prevent central sensitisation from incision or inflammatory injury, to achieve optimal postoperative pain control (19). The results of clinical trials on its efficacy are controversial (19,20) (LE: 2b).

*5.3.4 **Systemic analgesic techniques***

5.3.4.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

These drugs act by inhibiting cyclo-oxygenase (COX) and the subsequent production of prostaglandins . The main advantages of NSAIDs are that they do not produce respiratory depression or sedation, and seem to decrease the need for opioids (21). However, their analgesic effect is not strong enough for the management of severe postoperative pain (22). For NSAID dosage and administration, see Table 12.

Intravenous (iv) administration of NSAIDs should start 30-60 min before the estimated end of surgery, and oral administration should start as soon as possible. Intramuscular administration of analgesic drugs for postoperative pain control is generally avoided because of variability of serum drug concentrations (23).

Their main adverse effects are (22):

- gastric irritation, ulcer formation, bleeding;
- renal impairment;
- bronchospasm, deterioration of asthma;
- platelet dysfunction, inhibition of thromboxane A2;
- perioperative bleeding;
- inhibition of bone healing and osteogenesis.

COX-2 selective inhibitors are associated with fewer gastrointestinal complications and better bone healing. In addition, they cause minimal platelet inhibition compared with non-selective COX inhibitors (24). However, COX-2 inhibitors are contraindicated for long-term use in patients with cardiovascular problems (25). The use of COX-2 inhibitors is approved only for short-term postoperative pain therapy.

Recommendations	GR
NSAIDs are often effective after minor or moderate surgery.	B
NSAIDs often decrease the need for opioids.	B
Avoid long-term use of COX inhibitors in patients with atherosclerotic cardiovascular disease.	B

5.3.4.2 Paracetamol

Paracetamol (acetaminophen) is a relatively safe and effective antipyretic and analgesic for mild to moderate postoperative pain. In cases of severe postoperative pain, co-administration of paracetamol with strong opioids seems to reduce the consumption of opioids (26) (LE: 2). Its exact mode of action is unclear, although it may act by centrally inhibiting COX production (27).

Dosage and routes of administration

- 1 g four times daily (orally, iv or rectally). Dose should be reduced to 1 g three times daily in patients with hepatic impairment.
- iv administration of paracetamol should start 30 min before the end of surgery, and oral administration as soon as possible.

Adverse effects

No significant adverse effects have been observed in patients receiving paracetamol for acute postoperative pain. Caution should be taken when it is administered to patients with chronic alcoholism or hepatic failure. A dose > 6 g/day can cause acute renal failure.

Combinations of paracetamol with opioids

Paracetamol in combination with an opioid provides adequate postoperative analgesia for mild to moderate pain without the adverse effects of strong opioids. For dosage and administration of paracetamol/opioid combinations, see Table 13.

Recommendations	GR
Paracetamol can be very useful for postoperative pain management because it reduces consumption of opioids.	B
Paracetamol can alleviate mild postoperative pain as a single therapy without major adverse effects.	B

5.3.4.3 Metamizole (dipyrone)

Metamizole is an effective antipyretic and analgesic drug used for mild to moderate postoperative pain and renal colic. Its use is prohibited in the USA and some European countries because of single reported cases of neutropenia and agranulocytosis. Elsewhere, it is considered to be a useful analgesic and antipyretic drug for moderate pain. Long-term use of metamizole is best avoided (28,29) (LE: 2b).

Dosage and route of administration

The dose is 500-1000 mg qds (orally, iv or rectally).

Adverse effects

Apart from single sporadic cases of neutropenia and agranulocytosis, metamizole can cause minor side effects such as nausea, mild hypotension, and allergic reactions. Allergic reactions and the rare complication of agranulocytosis have been described only after direct iv administration, therefore, iv metamizole should be administered as a drip (1 g in 100 mL normal saline).

5.3.4.4 Opioids

Opioids are the first-line treatment for severe acute postoperative pain. Correct dose titration can minimise their unwanted effects (30). Opioid dosage and administration can be found in Table 14 and 15.

5.3.4.5 Patient-controlled analgesia (PCA)

Systemic administration of opioids may follow the “as needed” schedule or “around-the-clock” dosing. The most effective mode is PCA (31,32) (LE: 1a) (Table 8).

Table 8: Typical PCA dosing schedule

Drug (concentration)	Bolus size	Lockout interval (min)	Continuous infusion
Morphine (1 mg/mL)	0.5-2.5 mg	5-10	0.01-0.03 mg/kg/h
Fentanyl (0.01 mg/mL)	10-20 µg	5-10	0.5-0.1 µg/kg/h
Pethidine (10 mg/mL)	5-25 mg	5-10	-

Recommendation	GR
Intravenous patient controlled analgesia provides superior postoperative analgesia, improving patient satisfaction and decreasing risk of respiratory complications.	A

Opioids adverse effects are:

- respiratory depression, apnoea;
- sedation;
- nausea, vomiting;
- pruritus;
- constipation;
- hypotension.

5.3.4.6 Adjuncts to postoperative analgesia

Adjuncts to postoperative analgesia in low doses, such as ketamine, α2 agonists (clonidine, dexmedetomidine) gabapentinoids (gabapentin or pregabalin) in appropriate doses and monitored care are beneficial in improving analgesic efficacy and reducing opioid-related side effects, with good safety and tolerability (33,34) (LE:1a, GR: A).

Low-dose ketamine is defined as a bolus dose < 2 mg/kg when given intramuscularly or less than 1 mg/kg when administered via the intravenous or epidural route. For continuous i.v. administration, low-dose ketamine is defined as a rate of ≤ 20 g/kg/min (35). Its use is contraindicated in patients with coronary disease, uncontrolled hypertension, congestive heart failure and arterial aneurysms. There are insufficient data to confirm the neurotoxicity of ketamine, even though some animal studies have shown some degree of neurodegeneration after continuous use (36) (LE:2b).

Clonidine when given preoperatively, or epidurally postoperatively (1mcg/kg) can reduce opioid requirements (37) (LE:1a, GR: A).

More clinical evidence on dexmedetomidine is necessary to confirm its definite role in acute postoperative pain control (38).

In 17 studies up to 2007, patients received a single preoperative dose of 300-1200 mg gabapentin, 30 min-2 h before surgery in the remaining studies, the drug was administered at a dose of 1200-1800 mg/day at 1-24 h before the procedure and continued for 10 days. Gabapentin, used before, as well as before and after surgery, decreases pain severity and the need for analgesic supplementation (39) (LE:1a, GR:A).

Perioperative pregabalin (300 mg/day) reduces opioid consumption and opioid-related adverse effects after surgery, however postoperative pain intensity is not reduced by pregabalin (40).

Single-injection caudal blocks with clonidine or ketamine are beneficial in paediatric patients (41).

5.3.5 ***Regional analgesic techniques***

5.3.5.1 Local anaesthetic agents

The most commonly used local anaesthetics are:

- bupivacaine
- l-bupivacaine
- ropivacaine.

Bupivacaine is considered to be cardiotoxic in high doses. l-Bupivacaine and ropivacaine appear to be safer, but the degree of motor blockage they provide is not as good as that of bupivacaine. Ropivacaine has the longest duration of action.

5.3.5.2 Epidural analgesia

Epidural analgesia provides excellent postoperative pain relief for extended periods after major surgery, and reduces postoperative complications and consumption of opioids (1,2) (LE: 1a) (Table 9).

Table 9: Typical epidural dosing schemes*

Drug	Single dose	Continuous infusion
Morphine	1-5 mg	0.1-1 mg/h
Fentanyl	50-100 µg	25-100 µg/h
Sufentanil	10-50 µg	10-20 µg/h
Pethidine	10-30 mg	10-60 mg/h

Bupivacaine 0.125% or ropivacaine 0.2% + fentanyl 2 µg/mL	10-15 mL	2-6 mL/h

**l-bupivacaine doses are equivalent to those of bupivacaine.*

5.3.5.3 Patient-controlled epidural analgesia (PCEA)

PCEA has become very common because it allows individualisation of dosage, decreased drug use, and greater patient satisfaction. It also seems to provide better analgesia than intravenous PCA (42,43) (LE: 1a) (Table 10).

Table 10: Typical PCEA dosing schemes

Drug	Demand dose	Lockout interval (min)	Continuous rate
Morphine	100-200 µg	10-15	300-600 µg/h
Fentanyl	10-15 µg	6	80-120 µg/h
Pethidine	30 mg	30	-
Bupivacaine 0.125% + fentanyl 4 µg/mL	2 mL	10	4 mL/h
Ropivacaine 0.2% + fentanyl 5 µg/mL	2 mL	20	5 mL/h

Recommendation	GR
Epidural analgesia, especially PCEA, provides superior post-operative analgesia, reducing complications and improving patient satisfaction, and is therefore preferable to systemic techniques (2).	A

5.3.5.4 Neural blocks

Local anaesthetic blocks (intermittent and continuous) can be used after urological surgical operations to supplement postoperative analgesia (44) (LE: 2a) (Table 11).

Table 11: Examples of neural blocks

Procedure	Drug/dosage
Iliohypogastric or ilioinguinal nerve infiltration after hernia repair	10-20 mL bupivacaine or ropivacaine 0.25-0.5%
Intercostal nerve infiltration	5-10 mL bupivacaine or ropivacaine 0.25-0.5%
Continuous intrapleural infusion	10 mL/h bupivacaine or ropivacaine 0.1-0.2%

5.3.5.5 Wound infiltration

Intraoperative wound infiltration with local anaesthetic (usually 10-20 mL ropivacaine or 0.25-0.5% bupivacaine) can provide some postoperative analgesia and may reduce the requirement for systemic analgesia (45) (LE: 2b).

5.3.5.6 Continuous wound instillation

Continuous postoperative wound instillation of a local anaesthetic via a multi-hole catheter placed intraoperatively by the surgeon has been shown to provide satisfactory analgesia for moderate to severe postoperative pain, reducing consumption of systemic analgesics (46-48) (LE: 2b).

5.3.6 ***Multimodal analgesia***

The concept of multimodal (balanced) analgesia is that combining different doses and routes of administration of analgesics improves the effectiveness of pain relief after surgery and reduces the maximal dosage and adverse effects (49) (LE: 2b). It seems to be more effective when different drugs are administered via different routes than when different drugs are administered via a single route (1) (LE: 2b).

Recommendations	GR
Multimodal pain management should be used whenever possible because it helps to increase efficacy while minimising adverse effects.	B

*5.3.7 **Special populations***

5.3.7.1 Ambulatory surgical patients

A multimodal analgesic plan uses a combination of NSAIDs or paracetamol plus local anaesthetics used as peripheral nerve blocks, tissue infiltration, or wound instillation so as to avoid the use of opioids, which can prolong hospital stay (50,51, LE: 2a; 52, LE: 2b).

Recommendations	GR
For postoperative pain control in outpatients, multimodal analgesia with a combination of NSAIDs or paracetamol plus local anaesthetics should be used.	B
If possible, avoid opioids.	B

5.3.7.2 Geriatric patients

Pain perception appears to be reduced in geriatric patients, and requirement for analgesia generally decreases with increasing age (53,54). Geriatric patients can also suffer from emotional and cognitive impairment such as depression and dementia, which could affect adequate pain management (55). Postoperative delirium in elderly patients is a common complication and is often multifactorial. It may be associated with administration of pethidine (56). Multimodal postoperative analgesia may be the pain management technique of choice in elderly patients, as the drug doses required are lower. However, it is important to be vigilant for adverse reactions, because they tend to increase in number in the geriatric population (57) (LE: 2b). Epidural analgesia might diminish the risk of postoperative delirium and respiratory complications in elderly patients (58) (LE: 2b).

Recommendations	GR
Multimodal and epidural analgesia are preferable for postoperative pain management in elderly patients because these techniques are associated with fewer complications.	B

5.3.7.3 Obese patients

Obese patients appear to be at higher risk for certain postoperative complications, including respiratory, cardiovascular and thromboembolic episodes, and wound infections (59,60). Administration of opioids to obese patients is associated with sudden respiratory arrest, therefore, a combination of NSAIDs or paracetamol with an epidural local anaesthetic might be the safest analgesic solution (61,62) (LE: 2b).

If absolutely necessary, opioids should be used with caution under careful titration to avoid depression of the respiratory drive (62). Oxygen therapy should also be applied postoperatively to increase oxygen saturation (63).

Recommendations	GR
Postoperative use of opioids should be avoided in obese patients unless absolutely necessary.	B
An epidural local anaesthetic in combination with NSAIDs or paracetamol is preferable.	B

5.3.7.4 Drug- or alcohol-dependent patients

It has been proved that regional anaesthesia and analgesia are preferable to opioids in drug addicts. Moreover, clonidine is beneficial in those with withdrawal syndrome due to opioid or alcohol abstinence and postoperative delirium tremens (64) (LE:1a).

5.3.7.5 Other groups

Critically ill or cognitively impaired patients present special difficulties. Regional or multimodal analgesia might be more effective in such patients because drug doses are reduced and behavioural interventions and patient-controlled methods are unsuitable (LE: 3).

Recommendations	GR
There are no sufficient data to support a specific postoperative pain management plan for critically ill or cognitively impaired patients.	B

*5.3.8 **Postoperative pain management teams***

The importance of efficient postoperative pain management has led to the development of acute postoperative pain management teams, which generally consist of nursing and pharmacy personnel led by an anaesthesiologist. They have been shown to improve pain relief, decrease analgesic side effects, improve patient satisfaction, and decrease overall costs and morbidity rates (65-67) (LE: 2b). Improved pain control can lead to shorter hospitalisation and fewer unscheduled readmissions after day surgery (68) (LE: 3).

5.4 Specific pain treatment after different urological operations

*5.4.1 **Extracorporeal shock wave lithotripsy (ESWL)***

ESWL is a minimally invasive treatment, during and after which 33-59% of patients do not need any analgesia (69-71) (LE: 2b). Post-treatment pain is unlikely to be severe and oral analgesics are usually sufficient.

Analgesic plan

- Preoperative assessment (see Section 5.3.2)
- Intraoperatively: experience exists for alfentanil (0.5-1.0 mg/70 kg iv), given on demand during ESWL.

NSAIDs or midazolam given 30-45 min before treatment reduces the need for opioids during the procedure (LE: 2b). With diclofenac premedication (100 mg rectally), only 18% of patients needed pethidine during lithotripsy (72). After premedication with 5 mg midazolam orally, 70% of patients were completely free of pain during treatment, and if buprenorphine was added, this proportion rose to 87% (73). After premedication with midazolam (2 mg iv, 5 min before treatment), diclofenac or tramadol was safe and effective, with fewer side effects than fentanyl (74) (LE: 1b). Other effective regimes for intraoperative pain treatment are fentanyl (1 µg/kg iv [75]), sufentanil or remifentanil. These drugs are usually given by the anaesthesiologist because of the risk of respiratory depression, which was significantly lower (20% vs 53%) after the procedure if remifentanil was used instead of sufentanil (76,77) (LE: 1b).

- Postoperative: NSAIDs, metamizole, paracetamol, codeine and paracetamol combination or tramadol can all be used on an as needed or time-contingent basis. If pain is more severe or persistent, examination is generally necessary to exclude hydronephrosis or renal haematoma.

Recommendations	GR
Analgesics should be given on demand during and after ESWL because not all patients need pain relief.	B
Premedication with NSAIDs or midazolam often decreases the need for opioids during the procedure.	B
iv opioids and sedation can be used in combination during ESWL; dosage is limited by respiratory depression.	C

Post-ESWL, analgesics with a spasmolytic effect are preferable (C).

*5.4.2 **Endoscopic procedures***

5.4.2.1 Transurethral procedures

Transurethral operations are usually performed under spinal anaesthesia (epidural or subarachnoid block) with the patient awake or mildly sedated, and usually with analgesia for 4-6 h after surgery. Pain is generally caused by the indwelling catheter or the double-J (ureteral stent following ureterorenoscopy), which mimics overactive bladder syndrome. Drugs with an antimuscarinic effect have been proven to be useful in addition to the opioids (78) (LE: 1b).

Analgesic plan

- Preoperative assessment: see Section 5.3.2.
- Intraoperative: spinal (intrathecal or epidural) anaesthesia provides intraoperative analgesia and last for 4-6 h postoperatively.
- Postoperative: after 4-6 h, mild oral analgesics such as NSAIDs or paracetamol ± codeine, or stronger opioids; also orally. In the case of bladder discomfort from the indwelling catheter, metamizole (orally or iv), pethidine (iv) or piritramide (iv) is also effective. Antimuscarinic drugs such as oxybutynin (5 mg

orally three times daily) are useful and reduce the need for opioids (78) (LE: 1b).

Recommendations	GR
Postoperative analgesics with spasmolytic effect or mild opioids are preferable.	C
Antimuscarinic drugs could be helpful in reducing discomfort resulting from the indwelling catheter.	B
Antimuscarinic drugs may reduce the need for opioids.	B

5.4.2.2 Percutaneous endoscopic procedures

The analgesic plan is nearly the same as that for transurethral procedures. Local anaesthetic (e.g., 10 mL 0.5% bupivacaine) can be infiltrated locally into the skin incision. General anaesthesia is required for the procedure because of the uncomfortable decubitus (prone position) and the prolonged duration of the operation.

5.4.2.3 Laparoscopic procedures

These procedures are performed under general anaesthesia, therefore, patients cannot take oral medication for at least 4-6 h postoperatively, so parenteral analgesia should be used. Then, oral or systemic analgesia can be given, depending on bowel motility.

A particular problem after laparoscopic cholecystectomy is the development of shoulder pain as a result of diaphragmatic irritation following pneumoperitoneum. This seems to be dependent on the intra-abdominal pressure used during the procedure, because reduced CO2 insufflation reduces postoperative shoulder pain (79-81) (LE: 1b). The same could apply for some transabdominal urological laparoscopic interventions.

Analgesic plan

Preoperative assessment: see Section 5.3.2.

Intraoperative: iv opioids ± NSAIDs, paracetamol or metamizole administered by an anaesthesiologist. The infiltration of local anaesthetic into the port incisions reduces pain after laparoscopy (82).

Postoperative: administration of systemic opioids iv (im or sc), is very effective in the immediate postoperative period. NSAIDs (e.g., paracetamol and/or metamizole) and incisional local anaesthetics (multimodal concept) can be given to reduce the need for opioids (82,83).

Recommendations	GR
Low intra-abdominal pressure and good desufflation at the end of the procedure reduces postoperative pain.	A
NSAIDS are often sufficient for postoperative pain control.	B
NSAIDs decrease the need for opioids.	B

5.4.3 ***Open surgery***

5.4.3.1 Minor operations of the scrotum/penis and the inguinal approach

These two types of operations are relatively minor and nearly all patients can take oral analgesics afterwards. The operation is often performed as an ambulatory procedure under local anaesthesia, or with the aid of an ilioinguinal or iliohypogastric nerve block.

Recommendations	GR
For postoperative pain control, multimodal analgesia with a combination of NSAIDs or paracetamol plus local anaesthetics should be used.	B
If possible, avoid opioids for outpatients.	C

5.4.3.2 Transvaginal surgery

General, local or regional anaesthesia can be used for these operations.

Recommendations	GR
NSAIDS are often sufficiently effective after minor or moderate surgery.	B
NSAIDs decrease the need for opioids.	B

5.4.3.3 Perineal open surgery

Analgesic plan

- Preoperative assessment: see Section 5.3.2.
- Intraoperative: general anaesthesia is usually used, particularly for perineal radical prostatectomy, because of the uncomfortable exaggerated lithotomy position. Sometimes an intrathecal catheter (epidural) can be sited for intra- and postoperative pain control.
- Postoperative: continuous epidural infusion of a combination of opioids and local anaesthetic or PCA is usually used. When systemic opioids are required, it is advisable to use them in combination with NSAIDs so as to reduce their dose and side effects. When the patient is able to take oral analgesics, metamizole or paracetamol ± codeine can be used.

5.4.3.4 Transperitoneal laparotomy

Analgesic plan

- Preoperative assessment: see Section 5.3.2.
- Intraoperative: general anaesthetic and regional technique; sometimes an intrapleural catheter can be sited.
- Postoperative: continuous epidural infusion of a combination of opioids and local anaesthetic. Once the patient is able to take oral analgesics (depending on bowel motility) metamizole, paracetamol ± codeine or tramadol can be used. Multimodal concepts (combining NSAIDs with opioids, fast-track strategies, keeping abdominal and urinary drainage as short as possible) are useful in reducing the need for analgesia (84).

Recommendations	**GR**
The most effective method for systemic administration of opioids is PCA (see Section 5.3.4.5), which improves patient satisfaction and decreases the risk of respiratory complications.	A
Epidural analgesia, especially PCEA, provides superior postoperative analgesia, reducing complications and improving patient satisfaction, and is preferable to systemic techniques (see Sections 5.3.5.2 and 5.3.5.3).	A

5.4.3.5 Suprapubic/retropubic extraperitoneal laparotomy

Postoperatively, it is possible to use the oral route for analgesia earlier than after a transperitoneal procedure. Oral opioids, metamizole and/or paracetamol ± NSAIDs can be used.

Analgesic plan

- Preoperative assessment: see Section 5.3.2.
- Intraoperative: general anaesthetic and regional technique.
- Postoperative: continuous epidural infusion of a combination of opioids and local anaesthetic. Once the patient is able to take oral analgesics metamizole, paracetamol ± codeine, ± NSAIDs can be used.

5.4.3.6 Retroperitoneal approach - flank incision - thoracoabdominal approach

Analgesic plan

- Preoperative assessment: see Section 5.3.2.
- Intraoperative: general anaesthetic and regional technique; sometimes an intrapleural catheter can be inserted.
- Postoperative: continuous epidural infusion of a combination of opioids and local anaesthetic gives significantly better pain control compared with iv analgesics (85,86) . If epidural analgesia is not possible or refused, PCA should be provided. Once the patient is able to take oral analgesics (depending on bowel motility) paracetamol ± codeine or metamizole can be associated (to reduce the need for opioids) or used alone.

Recommendations	**GR**
Epidural analgesia, especially PCEA, provides superior postoperative analgesia, reducing complications and improving patient satisfaction and is therefore preferable to systemic techniques (see Sections 5.3.5.2 and 5.3.5.3.	A

5.5 Dosage and method of delivery of some important analgesics

5.5.1 ***NSAIDs***

Table 12: Dosage and delivery of NSAIDs

Drug	Daily dose	Route of administration
Conventional NSAIDs (non-selective COX inhibitors)		
Ketorolac	10-30 mg four times daily	Orally or iv
Ibuprofen	400 mg three times daily	Orally
Ketoprofen	50 mg four times daily	Orally or iv
Diclofenac	75 mg twice daily	Orally or iv
	50 mg three times daily	Orally or iv
	100 mg twice daily	Rectally
COX-2 selective inhibitors		
Meloxicam	15 mg once per day	Orally
Lornoxicam	4-8 mg twice daily	Orally or iv
Celecoxib	200 mg once per day	Orally
Parecoxib	40 mg once or twice daily	iv form only
Etoricoxib	90-120 mg once daily	Orally

Table 13: Dosage and delivery of paracetamol, metamizole and its combinations with opioids

Drug	Method of administration	Single dose (mg)	Maximal dose (mg/day)
Paracetamol	Orally	500-1000	4000 (50 mg/kg)
Paracetamol	iv	1000	4000 (50 mg/kg)
Metamizole	Orally	500-1000	4000
Metamizole	iv	1000-2500	5000

Paracetamol	Opioid	Times per day	Route of administration
Paracetamol 1 g	Codeine 60 mg	Four	Orally or rectally
Paracetamol 600-650 mg	Codeine 60 mg	Four	Orally or rectally
Paracetamol 500 mg	Codeine 30 mg	Four	Orally or rectally
Paracetamol 300 mg	Codeine 30 mg	Four	
Orally or rectally			
Paracetamol 650 mg	Dextropropoxyphene 65 mg	Four	Orally
Paracetamol 600-650 mg	Tramadol 75-100 mg	Four	Orally
Paracetamol 325 mg	Oxycodone 5 mg	Four	Orally

5.5.2 ***Opioids***

Table 14: Dose and delivery of opioids

Drug	Method of administration	Common single dose (mg)	Maximal dose (mg)
Tramadol	Orally	50	400-600
Tramadol	iv	50-100	400-600
Dihydrocodeine	Orally	60-120	240
Piritramid	sc/im	15-30	120

Pethidine	Orally	25-150	500
Pethidine	Rectally	100	500
Pethidine	sc/im	25-150	500
Pethidine	iv	25-100	500
Morphine*	Orally	Starting with 10	No maximal dose
Morphine*	Rectally	Starting with 10	No maximal dose
Morphine*	sc/im	Starting with 5	No maximal dose
Morphine*	iv	Starting with 2	No maximal dose
Morphine*	iv (PCA)	0.5-2.5 mg bolus 10-15 min lockout	No maximal dose

**Strong opioids have no real upper dose limit (except buprenorphine). The dose must be titrated in correlation with pain relief and depending on the individual strength of unwanted effects such as respiratory depression (see Section 5.3.4.4).*
**A simple way of calculating the daily dose of morphine for adults (20-75 years) is: 100 - patient's age = morphine per day in mg.*

Table 15: Common equi-analgesic doses for parenteral and oral administration of opioids*

Drug	Parenteral (mg)	Oral (mg)
Morphine	10	30
Fentanyl	0.1	-
Pethidine	75	300
Oxycodone	15	20-30
Dextropropoxyphene	-	50
Tramadol	37.5	150
Codeine	130	200

**All listed opioid doses are equivalent to parenteral morphine 10 mg. The intrathecal opioid dose is 1/100, and the epidural dose 1/10 of the dose required systemically.*

5.6 Perioperative pain management in children

*5.6.1 **Perioperative problems***

The main preoperative problems in children are fear of surgery, anxiety about separation from their parents, and the pain of procedures such as venipuncture. Contrary to the popular belief, the presence of parents during anaesthesia induction does not alleviate children's anxiety (87) (LE: 1a). The preoperative use of oral morphine sulphate, 0.1 mg/kg, can help to prevent crying in children and thereby reduce oxygen consumption and pulmonary vasoconstriction (Table 16). The prior application of EMLA (2.5% lidocaine and 2.5% prilocaine) cream helps to reduce the pain of venipuncture (88) (LE: 1a). Atropine, 0.01-0.02 mg/kg iv, im, orally or rectally, prevents bradycardia during anaesthesia induction.

Table 16: Premedication drugs in children

Drug	Dosing	Route of administration	Category
Ketamine	6 mg/kg	Oral, intranasal, im	NMDA antagonist
Midazolam	0.5 mg/kg	Oral, intranasal, rectally	Benzodiazepine
Dexmedetomidine	4 µg/kg	Oral, intranasal	α2-receptor agonist
Clonidine	4 µg/kg	Oral	α2-receptor agonist
Pentobarbital	4-6 mg/kg	im	Barbiturate
Chloral hydrate	50-100 mg/kg	Oral	Barbiturate
Methohexital	25-30 mg/kg	Rectally	Barbiturate

Recommendations	GR
EMLA local application alleviates significantly venipuncture pain in children.	A

*5.6.2 **Postoperative analgesia***

Postoperatively, paracetamol, NSAIDs, opioids and their combinations are used according to the severity of the surgical procedure (Table 17).

Table 17: Dosage of analgesics in children for postoperative analgesia

Drug	Dose	Route of administration	Severity of surgical procedure
Paracetamol	10-15 mg/kg every 4 h 20-30 mg/kg every 6 h	Oral Rectally	Minor Minor
Ibuprofen	10-15 mg/kg every 6 h	Oral, iv, rectally	Minor, medium
Naproxen	6-8 mg/kg every 8-12 h	Oral, iv, rectally	Minor, medium
Codeine	0.5-1 mg/kg every 3-4 h	Oral	Minor, medium
Morphine	0.1 mg/kg every 2-4 h Infusion: 0.03 mg/kg/h 0.3 mg/kg every 3-4 h	iv, sc Oral	Medium, major
Oxycodone	0.1-0.2 mg/kg every 3-4 h	Oral	Medium
Hydromorphone	0.04-0.08 mg/kg every 3-4 h	Oral	Medium
Tramadol	1 mg/kg every 4-6 h	iv	Medium, major
Pethidine	2-3 mg/kg every 3-4 h	iv	Medium, major

The postoperative use of COX-2 inhibitors in children is still controversial. PCA can be used safely in children older than 6 years. Nurse-controlled analgesia is effective in infants and children unable to use PCA (89).

Locoregional techniques such as wound infiltration, nerve blocks, and caudal and epidural analgesia are also successful (90,91). The most commonly drugs used are bupivacaine and ropivacaine (Table 18). Higher volumes of lower drug concentrations appear to be more effective than lower volumes of higher concentrations (92) (LE: 1a). The addition of opioids, ketamine or clonidine increases the duration of pain relief and reduces the need for rescue analgesia, thus providing more effective pain relief than local anaesthesia alone in caudal analgesia (93-95) (LE: 1a).

Table 18: Epidural dose of local anaesthesia

Drug	Bolus 0-12 months	Bolus > 1 year	Infusion for 0-12 months	Infusion > 1year
Bupivacaine	2 mg/kg	2.5 mg/kg	0.2 mg/kg/h	0.4 mg/kg/h
Ropivacaine	2.5 mg/kg	3.5 mg/kg	0.3 mg/kg/h	0.6 mg/kg/h

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6. NON-TRAUMATIC ACUTE FLANK PAIN

6.1 Background

Acute flank pain is a frequently occuring and complex medical problem. Ureterolithiasis is the most common non-traumatic cause. However, half of all renal colics are not caused by urolithiasis (1-3) (Table 32).

Table 32: Main urological and non-urological causes of flank pain

Urological causes	Non-urological causes
Renal or ureteral stones	Aortic aneurysm
Urinary tract infection (pyelonephritis, pyonephrosis, renal abscess)	Gallbladder disorder
Uretero-pelvic junction obstruction	Gastrointestinal disorders
Renal vascular disorders (renal infarction, renal vein thrombosis)	Pancreatic disease
Papillary necrosis	Gynaecological disorders
Intra- or peri-renal bleeding	Musculoskeletal disease
Testicular cord torsion.	

6.2 Initial diagnostic approach

*6.2.1 **Symptomatology***

History and physical examination, including body temperature, can be very helpful in the differential diagnosis of acute flank pain (4).

- **Acute renal colic** is indicated by pain of short duration (< 12 hours), nausea, vomiting, loin tenderness and haematuria (erythrocytes > 10,000/mm3) (4).
- Because the signs and symptoms can be very similar, **acute uncomplicated pyelonephritis** should be immediately differentiated from complicated renal colic:
  - concomitant fever (> 38°C) makes imaging obligatory (5). A radiological evaluation of the upper urinary tract should be offered to every patient presenting with flank pain and fever to rule out urinary tract obstruction irrespective of the accompanying symptoms, duration of the episode and urine macroscopic or microscopic findings.
  - imaging is also imperative in patients with acute flank pain and a solitary kidney (LE: 4).
- **Acute flank pain in patients with an increased risk for thromboembolic events should raise the** suspicion of **renal infarction** (6).
- Careful abdominal examination can reveal an abdominal **aortic aneurysm** (misdiagnosed in 30% of patients).
- **Renal vein thrombosis** (RVT) may often present with symptoms of acute flank pain, proteinuria, haematuria, hypotension and renal insufficiency.
- **Obstruction of the UPJ** can result in acute flank or abdominal pain after a high fluid volume intake, especially in paediatric patients.
- **Renal papillary necrosis** is not uncommon in the course of systemic diseases such as diabetes mellitus or analgesic nephropathy; the passage of sloughed papillae down the ureter may cause flank pain and haematuria.
- **Testicular torsion** should always be excluded in children with acute abdominal/flank pain.
- **Torsion of the appendix testis** can also result in abdominal pain or radiate to the flank.
- **Spontaneous bleeding** either within the kidney or to the retroperitoneum can be caused by kidney tumours (including angiomyolipomas), bleeding disorders or anticoagulation; acute flank pain is sometimes the presenting symptom.

Recommendation	GR
Febrile patients (> 38°C) with acute flank pain and/or with a solitary kidney need urgent imaging.	B

*6.2.2 **Laboratory evaluation***

All patients with acute flank pain require a urine test (red and white cells, bacteria or urine nitrite), blood cell count, and serum creatinine measurement. In addition, febrile patients with flank pain require C-reactive protein and urine culture. Pyelonephritis ± obstructive uropathy should be suspected when the white blood count exceeds 15,000/mm^3.

*6.2.3 **Diagnostic imaging***

6.2.3.1 Ultrasonography

Unenhanced helical computed tomography has high sensitivity and specificity for the evaluation of acute flank pain (7,8) (LE: 1a). Unenhanced helical computed tomography is superior because it detects ureteral stones with a sensitivity and specificity of 94-100%, regardless of stone size, location and chemical composition, and identifies extraurinary causes of flank pain in about one-third of all patients presenting with it. In addition, it does not need contrast agent, and is a time-saving technique (8,9) (LE: 1a).

6.2.3.2 Intravenous urography (IVU)

The use of US in the management of acute flank pain has been increasing. If the findings of pelvic and/or ureteral dilatation, stone visualisation and the absence of ureteral ejaculation are combined, sensitivity to ureteral dilatation can be 96% (7,10,11) (LE: 2a). Together with a plain abdominal radiograph, US can be accepted when computed tomography (CT) is not available (7,12-16) (LE: 1b).The disadvantages of US include inability to differentiate dilatation from true obstruction and the need for highly specialised personnel (12). Sensitivity varies from 58-96% in untrained staff in emergency rooms (15), but evidence suggests that, with even short training, non-specialists can be highly effective at excluding disorders such as abdominal aortic aneurysm, free abdominal fluids, gallstones and obstructive uropathy (15) (LE: 2b). US is the diagnostic imaging modality of choice during pregnancy.

6.2.3.3 Unenhanced helical CT (UHCT)

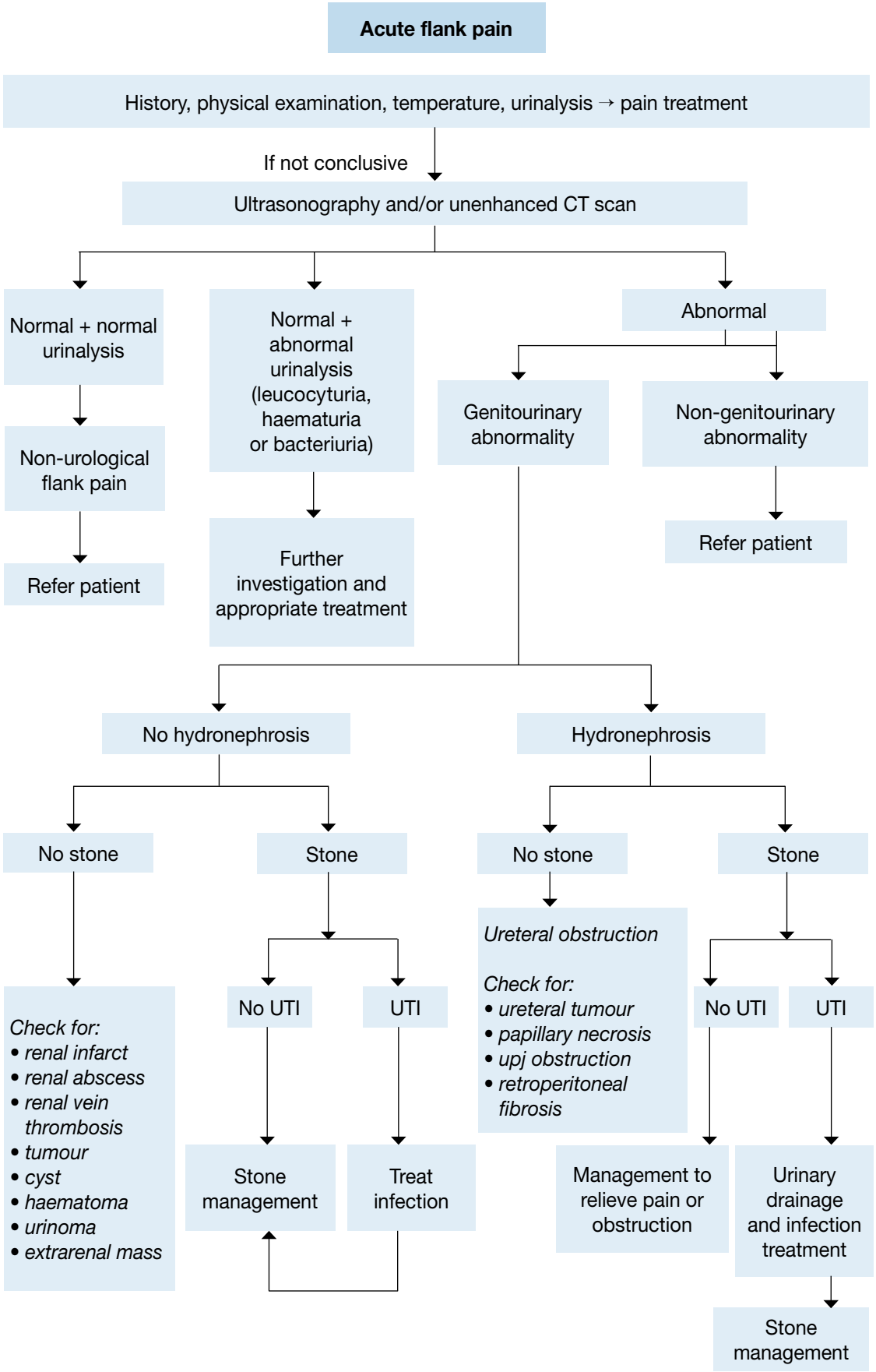
IVU reliably provides information on the anatomy of the urinary collecting system (ureteral and renal pelvic dilatation) in 80-90% of cases and can indentify ureteral calculi in 40-60% of cases.

Direct identification of ureteral calculi can be achieved in 40-60% of cases, whereas indirect signs (e.g. ureteral and renal pelvic dilatation) allows detection in 80-90% of cases. Drawback is that IVU results can be hampered by poor quality related to suboptimal bowel preparation, toxicity of contrast agents, allergic and anaphylactic reactions, and by significant radiation exposure. In emergency cases, IVU should be avoided due to the risk of fornix rupture.

UHCT or IVU should be considered in patients initially evaluated by other means who are still febrile after 72 h of treatment to rule out further complicating factors (renal, perinephric or prostatic abscesses) (8,9).

Table 33 shows comparative results of UHCT US and IVU in assessing acute flank pain and suspicion of ureterolithiasis (17-19). Figure 2 summarises the diagnostic approach to non-traumatic acute flank pain.

Figure 2: Diagnostic approach to non-traumatic acute flank pain



CT = computed tomography; UTI = urinary tract infection.

Recommendations	GR
Unenhanced helical computed tomography is the diagnostic imaging modality with the highest sensitivity and specificity for evaluation of non-traumatic acute flank pain.	A
Ultrasound can be an alternative to unenhanced helical computed tomography in the initial approach to non-traumatic acute flank pain.	A

Table 33: Comparative results of UHCT, US and IVU in assessment of acute flank pain and suspected ureterolithiasis (12)

Imaging modality	Performance	Ref. no.
UHCT	Sensitivity 100%, specificity 96%, accuracy 98%	17
Abdominal radiograph + US versus UHCT	UHCT: sensitivity and specificity of 100% US: sensitivity 100%, specificity 90%	18
Low-dose UHCT versus IVU	UHCT: sensitivity 97%, specificity 96% Low-dose UHCT is superior to IVU	19

6.3 Initial emergency treatment

*6.3.1 **Systemic analgesia***

Pain relief is usually the first, most urgent, therapeutic step (20,21):

- Intravenous (iv) non-steroidal anti-inflammatory drugs (nsaids) are very effective in most cases, e.g. a bolus of diclofenac sodium, 75 mg (le: 1a) (21); a slow iv injection of ketorolac, 30 mg, 4 times daily, is equivalent to diclofenac in the treatment of renal colic (22).
- Tests have shown a single dose of dipyrone to be less effective than diclofenac, 75 mg (23) (le: 1a), but a slow iv infusion of dipyrone, 1 g or 2 g, is just as effective as diclofenac (24).
- In cases of unresponsiveness to diclofenac (25) (le: 1b), or contraindication of NSAIDs (24) (le: 1b), iv papaverine hydrochloride (120 mg) is a safe and effective alternative.
- Large-scale studies have shown that NSAIDs and opioids are both effective analgesics, but vomiting is more prevalent with opioids (particularly pethidine) (21).
- The combination of iv morphine + ketorolac seems superior to either drug alone, and appears to be associated with a decrease in the need for rescue doses of analgesia (26).
- Antimuscarinics are often used in acute renal colic; there is no evidence that hyoscine butylbromide reduces opioid requirements in this condition (26) (LE: 1b).

The origin of the pain should be immediately clarified in febrile patients and those with a solitary kidney.

Recommendation	GR
In patiens presenting with acute flank pain NSAIDs such as diclofenac (75 mg bolus) and dipyrone (1-2 g slow iv injection) are the drugs of first choice.	A

*6.3.2 **Local analgesia***

A number of manipulations have been tested in the field of acute renal colic.

- Local warming of the abdomen and lower back region seems to decrease pain in patients with acute renal colic (27) (LE: 1a).
- Trigger-point injection of lidocaine can provide effective pain relief in 50% of patients with renal colic (28); it is significantly better than iv butylscopolamine bromide + sulpyrine (28) (LE: 1a). There are no comparative studies with NSAIDs.

*6.3.3 **Supportive therapy***

Patients with acute flank pain often present with moderate to severe dehydration. Fever, vomiting and anorexia produce serious discomfort and should be treated from the outset. If possible, iv fluids should be generous (60 mL/h normal saline and 60 mL/h 5% glucose solution), but maintenance iv fluids (20 mL/h normal saline) can be as effective as forced hydration with regard to pain perception and analgesic use (29) (LE: 1b). No clear evidence supports using diuretics to treat acute ureteral colic (30). Metoclopramide chloride (0.5 mg/kg/24 h in three divided doses) can be effective in controlling nausea and vomiting irrespective of aetiology (infectious, obstructive, oncological).

*6.3.4 **Upper urinary tract decompression***

If pain relief cannot be achieved using medical therapy and there are signs of infection and impaired renal

function, upper urinary tract drainage should be undertaken. The main indications for stenting for urgent relief of obstruction include (31):

- urine infection with urinary tract obstruction
- urosepsis
- intractable pain and/or vomiting
- obstruction of a solitary or transplanted kidney
- bilateral obstructing stones
- ureteral calculus obstruction in pregnancy.

6.4 Aetiological treatment

*6.4.1 **Urolithiasis***

General concepts for treating urolithiasis have been defined in the EAU Guidelines on Urolithiasis (32).

*6.4.2 **Infectious conditions***

Infectious uncomplicated conditions (i.e. acute pyelonephritis in otherwise healthy individuals) should be treated with appropriate antibiotics and analgesics according to the EAU Guidelines on Urological Infections (33).

The first-line treatment of mild cases should be an oral fluoroquinolone (twice daily for 7 days) in areas with low rates of fluoroquinolone-resistant Escherichia coli. In areas with raised resistance rates, or in pregnancy, lactation or adolescence, a second- or third-generation oral cephalosporin is recommended. Pain can usually be controlled with oral NSAIDs (diclofenac 75 mg, three times daily, or dipyrone 500 mg three times daily) except in pregnant or lactating women.

*6.4.3 **Other conditions***

6.4.3.1 Uretero-pelvic junction obstruction

Uretero-pelvic junction obstruction obstruction can result in intermittent flank or abdominal pain. Symptoms may worsen during brisk diuresis (after consumption of caffeine or alcohol). Dismembered or non-dismembered pyeloplasty is standard. A ureteral stent can help to relieve pain in very symptomatic patients prior to definitive surgery. Outcomes are excellent, with resolution of the obstruction in 90-95% of cases, including newborns (34).

6.4.3.2 Papillary necrosis

Papillary necrosis commonly presents as painless macroscopic haematuria, but can be complicated by ureteral obstruction. As well as symptomatic treatment, treatment should be given for the underlying cause of papillary necrosis, such as interstitial nephritis, acute pyelonephritis, diabetes mellitus, analgesic abuse or sickle cell disease. Ureteral obstruction due to sloughed papillae can be successfully treated with ureteroscopy or temporary ureteral stenting (35).

6.4.3.3 Renal infarction

There is no specific treatment for acute renal infarction, but the underlying disease (atrial fibrillation, left ventricular thrombus or a hypercoagulable state) may require anticoagulation with iv heparin followed by warfarin to prevent future events (36).

6.4.3.4 RVT

RVT is often clinically silent, but can present with acute flank pain. Systemic anticoagulation with heparin to prevent further propagation of thrombus or other thromboembolic phenomena (37) is standard, but the successful use of fibrinolytic agents in selected patients without clinical contraindications has been reported (38). Thrombectomy or nephrectomy is reserved for cases refractory to medical therapy.

6.4.3.5 Intra- or peri-renal bleeding

Acute spontaneous intra- or peri-renal bleeding often results in acute flank pain. Spontaneous renal haemorrhage (Wunderlich's syndrome), is an unusual and life-threatening cause of acute abdomen. Nephrectomy is usually the only therapeutic alternative (39,40).

6.4.3.6 Testicular cord torsion

Testicular cord torsion can produce lower abdomen and flank pain; it should be treated surgically at once.

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7. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
ATC	around-the-clock
CNS	central nervous system
COX	cyclo-oxygenase
CT	computed tomography
EDTMP	ethylenediaminetetramethylenephosphonate
EORTC	European Organisation for Research and Treatment of Cancer
ESWL	extracorporeal shock wave lithotripsy
GABA	gamma-aminobutyric acid
GFR	glomerular filtration rate
GCP	good clinical practice
IASP	International Association for the Study of Pain
Im	intramuscular
iv	intravenous
IVU	intravenous urography
^{131}J-MIBG	131J-metaiodobenzylguanidine
MRI	magnetic resonance imaging
NMDA	N-methyl-D-aspartate
NRS	numerical rating scale
NSAIDs	non-steroidal anti-inflammatory drugs
PACU	post-anaesthesia care unit
PCa	prostate cancer
PCA	patient-controlled analgesia
PCEA	patient-controlled epidural analgesia
prn	as needed
PRPE	perineal radical prostatectomy
RCC	renal cell carcinoma
RLND	retroperitoneal lymph node dissection
sc	subcutaneous
^{153}Sm	samarium-153
^{89}Sr	strontium-89
SRI	selective serotonin reuptake inhibitors
SPECT	single photon emission computed tomography
TCA	tricyclic antidepressants
TCC	transitional cell carcinoma
TURB	transurethral resection of bladder tumour
TURP	transurethral resection of prostate
UHCT	unenhanced helical CT
VAS	visual analogue scale
VRS	verbal rating scale
WHO	World Health Organization

Conflict of interest

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