Guidelines on
Pain Management

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Association
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1. INTRODUCTION

The European Association of Urology (EAU) Guidelines 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 includes three urologists, two radiotherapists and two anaesthesiologists.

The recommendations provided in the current guidelines are based on a systemic literature search using Medline, the Cochrane Central Register of Controlled Trials, and reference lists in publications and review articles. Where possible a level of evidence (LE) and/or grade of recommendation (GR) have been assigned (1). Recommendations are graded in order to provide transparency between the underlying evidence and the recommendation given (Tables 1 and 2).

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

Publication history information:
The Pain Management Guidelines were first published in 2003, with a partial update in 2007, followed by a full text update in 2009. The current 2010 print includes two new topics, Section 5.6 “Peri-operative pain management in children” and Chapter 6 “Non-traumatic flank pain”. The quick reference guide has been completely reworked.

All texts can be viewed and downloaded for personal use at the society website:
http://www.uroweb.org/professional-resources/guidelines/.

Table 1: Level of evidence

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).

Table 2: Grade of recommendation

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).

1.2 REFERENCE

1. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.
http://www.cebm.net/index.aspx?o=1025 [accessed March 2010].

2. BACKGROUND

2.1 Definition of pain

Pain is the most common symptom of any illness. The physician's therapeutic task is twofold:

- to discover and treat the cause of the pain
- to treat the pain itself, irrespective of whether the underlying cause is treatable, in order to provide relief from it and reduce the suffering caused by it.

The International Association for the Study of Pain (IASP) has proposed the following working definition: pain is '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 (reflex motor withdrawal and behavioural responses), and is intended to keep tissue damage to a minimum. The capacity to experience pain has a protective role. If tissue damage (cellular breakdown with liberation of biochemical substances) is unavoidable, a cascade of changes occurs in the peripheral and central nervous system responsible for the perception of pain (2). A distinction can be made between adaptive and maladaptive pain (3).

Acute pain – usually occurring in response to an identifiable noxious event with stimulation of the nociceptive system (from the periphery through the spinal cord, brain stem, and thalamus to the cerebral cortex where the sensation is perceived) – has a time-limited course during which treatment, if necessary, is aimed at correcting the underlying pathological process. Acute pain is useful or adaptive because it is a vital physiological sensation that alerts a person to something harmful in the environment that should be avoided. Additionally, if tissue injury occurs (following a noxious stimulus), adaptive pain induces a (reversible) state of localised hypersensitivity (stimuli that would normally not cause pain now cause pain) in and around the injured area, resulting in an avoidance of the damaged part. This adaptive, inflammatory pain tries to aid in repair after tissue damage, promoting healing.

In contrast, maladaptive (pathological) pain offers no biological advantage because it is uncoupled from a noxious stimulus or tissue healing. Maladaptive pain is an expression of an inappropriate plasticity or modifiability of the nervous system, and is usually persistent or recurrent. Maladaptive pain may occur in response to damage to the nervous system (peripheral nerve, dorsal root ganglion, dorsal root, central nervous system), and is known as neuropathic pain. Essentially, maladaptive (neuropathic) pain 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). Although the control of pain is central to any effort to relieve suffering, and pain and suffering are closely identified, they are nevertheless distinct.

To define suffering, a psychosocial perspective has been adapted in which suffering is best viewed as a subjective phenomenon that can be influenced by biological, psychological, and social processes. 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: patients and their families are not only convinced that it is the beginning of the end and the patients will certainly die, but they also expect that the patients will die in horrible, excruciating pain (7, 8). Addressing these psychosocial sources as well as the medical sources should be the primary goal of a pain clinic, and can be achieved through a multidisciplinary approach (6).

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).

The role of the dorsal horn

The nociceptors terminate in a highly ordered way in the dorsal horn of the spinal cord, with the thinly myelinated Aδ fibres ending in laminae I and V, and the unmyelinated C-fibres ending in lamina II. These high threshold sensory fibres activate a large number of second order interneurones and projection neurones in the spinal cord. The activity generated by nociceptor input is transferred, after complex active processing in the dorsal horn, directly, or via brain stem relay nuclei, to the thalamus and then on to the cortex, where the sensation of pain is generated. Following integration in the dorsal horn, the pain signal is conducted through ascending pathways to the thalamus which, in interaction with limbic circuits, plays a crucial role in the reception and processing of nociceptive information en route to the cortex (12, 14).

Brain areas involved in nociception and pain

Nociceptive messages become more and more difficult to follow as they travel further along the central nervous system (CNS). Numerous brain areas are involved in the various components of pain, which include:

- a sensory-discriminative component that refers to the capacity to analyse location, intensity and duration of the nociceptive stimulus
- an affective component that gives rise to the unpleasant character of painful perception
- a cognitive and evaluative component, which is involved in the phenomena of anticipation, attention, suggestion and past experiences.

Although several circuits responsible for the sensory-discriminative and affective-cognitive components of pain can be distinguished, the global experience of pain, involves complex interactive neural networks of cerebral structures and multiple thalamocorticolimbic pathways (12, 14, 15).

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). This trauma to neural tissue produces abnormalities of neural function that are perceived by the patient as the symptoms and signs of neuropathic pain.

On examination, 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 (16, 17).

Mechanisms of neuropathic pain

Studies in animal models describe a number of peripheral and central pathophysiological processes after nerve injury that would be the basis of the underlying neuropathic pain mechanism. 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 (14, 18).

Summary of peripheral processes involved in neuropathic pain

The peripheral processes involved in neuropathic pain are:

- nociceptor sensitisation
- alteration in ion channel expression
- neuronal hyperexcitability with ectopic and spontaneous discharge (alteration in the expression of sodium channels and overactive calcium channels)

- sprouting of collateral fibres from intact and damaged sensory axons into denervated areas
- non-synaptic ‘ephatic’ interactions between neurones
- phenotypic switch of Aβ-fibres (substance-P and calcitonin gene-related peptide release)
- sprouting of sympathetic fibres into the primary afferent fibres and the dorsal root ganglia (sympathetic-induced pain).

Summary of central processes involved in neuropathic pain
The central processes involved in neuropathic pain are:
- N-methyl-D-aspartate receptor activation
- wind up: progressive increase in excitability during the course of the stimulus
- translation-dependent central sensitisation:
  - hyperalgesia
  - secondary hyperalgesia
  - allodynia
- activated microglia release proinflammatory cytokines and growth factors that further activate these cells, creating a positive feedback circuit and inducing pathological pain
- transcription-dependent central sensitisation may induce permanent phenotypic/morphological changes
- sprouting of A-fibres in lamina II
- loss of spinal inhibitory control (gamma-aminobutyric acid, glycine)
- cholecystokinin increase dampens μ-opioid inhibitory mechanisms.

2.5 Innervation of the urogenital system

The differences between the mechanisms of nociception in the skin and viscera are emphasised by studies of the response properties of visceral afferents from the urinary tract (19-21).

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 were thinly myelinated or unmyelinated, and responded to direct probing of a limited area of tissue. Two populations of afferents were distinguished by Cervero and Jänig (22). The first responded to contractions of the ureter and could also be excited by low levels of distension (average threshold 8 mmHg). They appeared to encode levels of distension throughout and beyond the physiological range. The second group did not respond to peristaltic contractions of the ureter, but they could be excited by distension with a wide range of thresholds. When ureters were perfused intraluminally, higher pressure thresholds were seen, although some at least still appeared to respond to distension to only 10 mmHg (22).

Systemic administration of morphine, a μ-opiate receptor agonist, produces a dose-dependent decrease of pain caused by ureteric distension (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 (19). 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 about 25-35 mmHg (24-27). 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. Some exhibit a low level of ongoing discharge when the bladder is empty. Distension excited mainly thin myelinated afferents, with pressure thresholds corresponding to the values where humans report the first sensation of fullness. Nearly all units were activated by the intraluminal pressures reached during normal, non-painful micturition. The activation of a numerically significant population of initially unresponsive afferents indicates that peripheral afferent mechanisms encoding pain from pelvic viscera are highly malleable, and are strongly affected by the state of the tissue. These peripheral changes are obviously likely to be important for signalling pain and discomfort in inflammatory conditions.

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) (28). Myelinated and unmyelinated afferents fibres form a homogeneous group with polymodal receptors in testis and/or epididymis. Prostaglandins did not excite but sensitised the afferents to other stimuli (29).

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 consisting of many different aspects. Not all pains will be of malignant origin. For example, cancer patients might have pain from arthritis or cervical spondylosis. They will often have more than one pain problem, and each pain must be individually assessed and evaluated. Some pains may be due to muscular spasm rather than the cancer itself. 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 (e.g. tumour pressure on nerve plexus or tumour infiltration), or could be due to secondary muscular spasm. In addition, pain could be secondary to cancer treatments, e.g. radiation-induced brachial plexopathy, or might 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 is pain as a result of 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

There are several ratings scales available to assess pain. There are single-item ratings of pain intensity and pain relief such as the visual analogue scale (unidimensional) or the verbal rating scale, and multiple-item assessments (multidimensional) that measure not only pain intensity but also additional dimensions of the pain experience, including emotional, affective, cognitive and social items (quality of life questionnaires).

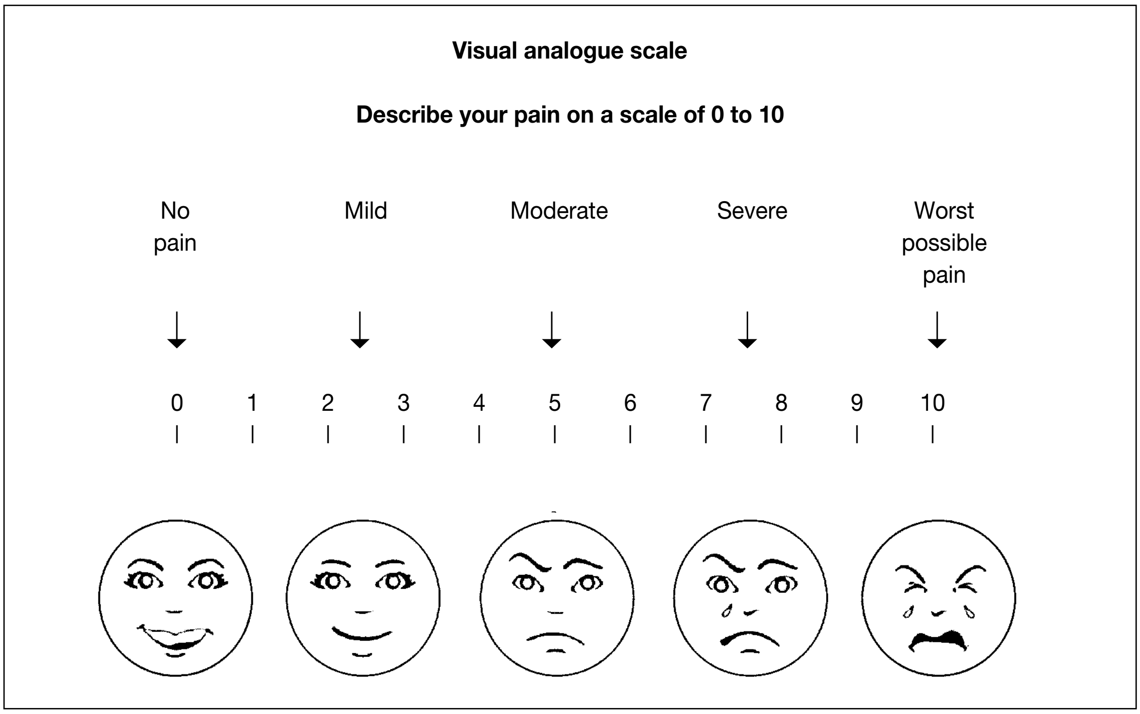
Rating pain using a visual analogue scale (VAS, Figure 1) or collection of VAS scales (such as the brief pain inventory) is an essential part of pain assessment. It allows some form of comparison to be made, and facilitates assessment of the efficacy of treatment. The ease of use (and ease of analysis) of the VAS has resulted in its widespread adoption for the measurement of pain intensity in clinical studies. In addition, the

VAS score for pain intensity has consistently demonstrated sensitivity to changes in pain levels associated with treatment, especially in acute pain states.

Although the VAS appears to be an attractive method to evaluate pain intensity and changes in pain, there are, however, several limitations for this measurement tool for assessing chronic pain. In chronic pain syndromes, the VAS has shown significant weakness in sensitivity owing to large variability between subjects, probably because of emotional, affective, and cognitive responses to pain together with behavioural and cultural biases, items that are not measured by a unidimensional tool. In addition, increased age and a greater amount of opioid consumption have been shown to be associated with a higher failure rate with the VAS score for measurement of pain intensity.

Figure 1: Visual analogue scale

0 ———————————————————————————— 10



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 quality of life 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) (30-34).

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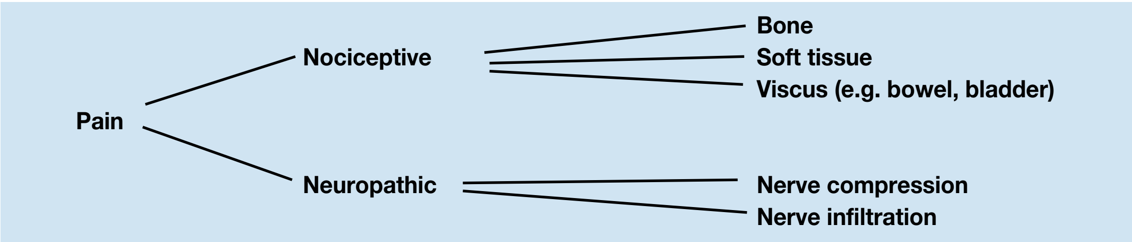
3. CANCER PAIN MANAGEMENT (GENERAL)

3.1 Classification of cancer pain

Figure 2 shows the classification of cancer pain.

Figure 2: Classification of cancer pain



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

Pain caused by bone metastases is nociceptive pain, but can become associated with neuropathic pain 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, and hence additional co-analgesics are necessary (3). Patients with severe neuropathic pain are a special challenge. Psychological changes frequently occur and specific therapeutic intervention may be necessary (4).

The WHO recommends a stepwise scheme for the treatment of cancer pain syndromes and for neoplastic bone pain. Bisphosphonates and calcitonin are helpful for stabilising bone metabolism. Epidural and intrathecal opioids are sometimes useful in managing bone pain from metastases. Nerve destruction by intrathecal or epidural phenol is sometimes useful in selected patients with neuropathic pain (5).

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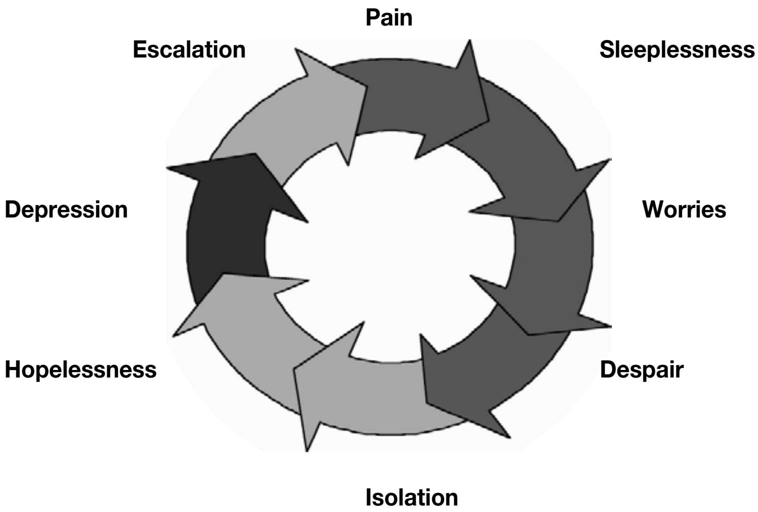
3.2 General Principles of cancer pain management

The therapeutic strategy depends on the four goals of care:
1. Prolonging survival
2. Optimising comfort
3. Optimising function
4. Relieving pain (Figure 3).

Figure 3: Tumour pain helix



The hierarchy of general treatment principles in Table 3 is intended to offer guidance through the decision-making process.

Table 3: Hierarchy of general treatment principles

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 (World Health Organization [WHO] ladder)
5	Conformance with palliative guidelines
6	Both psychological counselling and physical therapy from the very beginning

The guiding principle of care is the individualisation of therapy. Through a process of repeated evaluations, the selection and administration of therapy is individualised so that a favourable balance between pain relief and adverse effects is achieved and maintained.

The next steps in the hierarchy, especially points 2 to 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 of palliative medicine, since here there are limited prospects of healing and there is also 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 given preference over systemic treatment. In simple cases, measures such as drainage and stenting can make analgesic medication redundant. Examples include inserting a gastric probe, a ureteral stent, a percutaneous nephrostomy, or a bladder catheter. To cite another example, patients who receive an artificial anus due to recurrent subileus caused by peritoneal carcinomatosis are relieved of their pain immediately.

The indication stands in direct relation to the severity of the disease and the operation, especially if there are no prospects of healing. Cases such as these, however, are sometimes in particular need of the invasive measures described above. This is not only to relieve pain for the rest of the patient's days, but also to improve the general quality of life, even though invasive operations may also have a negative impact on the patient's well-being. Examples can 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.

A gradual strategy (level of evidence: 4) can be considered when dose escalation of a systemically administered opioid fails to yield a satisfactory result. The steps to follow are as follows.

- 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. This approach should be based on a 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)
- Finally, some patients with advanced cancer who have comfort as the overriding goal of care, can elect to be deeply sedated.

As is widely discussed in pain-management literature, the importance of physiotherapy and psychological counselling cannot be emphasised too strongly. For further discussion of these points see the sections above.

In conclusion, pain management can be highly effective, especially when interdisciplinary co-operation occurs: pain can be overcome.

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) (level of evidence: 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 such a degree of pain that analgesics are required and day-to-day activities are disturbed (1): the pain interferes with patients' quality of life, causing anxiety, isolation, immobility, depression and sleeplessness.

In single lesions, bone stability and pain reduction can be achieved by external beam radiotherapy (level of evidence: Ib; grade of recommendation: A). About 80-90% of these patients will experience durable pain relief, but many will further develop multiple painful metastases (1)

3.3.2.2 Radiopharmaceuticals: physical characteristics

The main physical characteristics of radiopharmaceuticals are as follows.

- ^{89}Sr (strontium-89 chloride) 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).
- ^{153}Sm (samarium-153 lexidronam) 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 photo peak. The physical half-life is 1.9 days (4).
- ^{186}Re (renium-186 etidronate) 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 chloride or ^{153}Sm lexidronam (^{153}Sm ethylenediaminetetramethylenephosphonate [EDTMP]).

The most important radiopharmaceuticals are ^{89}Sr (strontium-89 chloride), ^{153}Sm (samarium-153 lexidronam) and, to a lesser extent, ^{186}Re (renium-186 etidronate).

There is no clear difference in treatment response between ^{89}Sr, ^{153}Sm and ^{186}Re (2). However, in view of the half-life of the different isotopes, there is a difference in onset of response, duration of response and toxixity. 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 lexidronam 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) (level of evidence: 2, grade of recommendation: B).

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

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

There is a risk of temporary increase in bone pain (pain flare) in about 10% of the patients (3,6,7,17). This "flare phenomenon" generally occurs 2-4 days after ^{153}Sm lexidronam and 1-2 weeks after ^{89}Sr (acute side-effect) (1,4,8,11,12,15,18) and is associated with good clinical response (level of evidence: 2) (3,6,7,17). A transient increase in analgesia is sometimes necessary. Pain reduction is unlikely to occur within the first week, and can occur as late as one month after injection. Analgesics should therefore continue to be prescribed to patients until bone pain improves (grade of recommendation: B).

Late side-effects include temporary myelosuppression (platelets, white blood cells). Recovery occurs 4-6 weeks later depending on bone marrow reserve. In general, there is no significant effect on haemoglobin.

Radiation exposure to family members and the public can be present for 2-4 days after ^{153}Sm lexidronam, and 7-10 days after ^{89}Sr (4,8,11,13-15,18,19,20-23) (level of evidence: 2). Information concerning radioprotection should be provided (grade of recommendation: B).

If the pain responds to the initial treatment, administration of ^{153}Sm lexidronam can be repeated at intervals of 8-12 weeks in the presence of recurrent pain (1,2,23) (level of evidence: 2, grade of recommendation: B). The response rate for second and subsequent treatments may be lower than on the first occasion (1,8,12,23) (level of evidence: 2).

3.3.2.4 Contraindications

Absolute contraindications

- During or shortly after (less than 4 weeks) myelotoxic chemotherapy (all compounds except cisplatin) or hemibody external radiation therapy (less than 12 weeks). The delay between the end of these treatments and the start of metabolic radiotherapy is necessary in order to avoid severe haematopoietic toxicity. However, treatment can be safely combined with limited local field external beam radiotherapy (level of evidence: 3, grade of recommendation: C).
- Known hypersensitivity to EDTMP or similar phosphonate compounds for 153Sm lexidronam (1).
- Glomerular filtration rate (GFR) < 30 mL/min (1, 2).
- Pregnancy; continued breast-feeding (2).

Relative contraindications

- Radiopharmaceuticals are not recommended for women of child-bearing age (negative pregnancy test and contraception absolutely required).
- Acute or chronic severe renal failure (GFR of 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 between 30 mL/min and 60 mL/min, reduce the normal dosage by 50%) (expert opinion: level 4). Measurement of GFR is performed in the presence of elevated creatinine > 20 mg/L.
- Solitary painful lesion: external limited field radiotherapy should be performed (16, 24) (level of evidence Ib).

Caution

Caution must be used in the following circumstances:

- risk of fracture
- nervous 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 catheterization 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) (grade of recommendation: A).
- compromised bone marrow reserve
- white blood cell count of < 2500/µL (expert opinion, level 4) (preferably > 3500/µL according to European Association of Nuclear Medicine guidelines) (2).
- platelets < 80,000/µL (expert opinion, level 4) (preferably > 100,000/µL according to European Association of Nuclear Medicine guidelines) (2).
- Haemoglobin <90 g/l (2).

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3.3.3 Radiotherapy for metastatic bone pain

3.3.3.1 Clinical background

The role of radiotherapy in the palliation of symptomatic bone metastases is well established. Radiation therapy alleviates metastatic bone pain efficiently in the majority of patients and is particularly useful in treating metastatic bone pain (1-5) (level of evidence: 1A). According to controlled studies, complete pain relief is obtained in 20-50% of patients, with partial relief in 50-80% (level of evidence: 1A). The onset of pain relief varies from a few days to 4 weeks. Re-irradiation should therefore not be considered sooner than 4-6 weeks after the first radiotherapy (6) (level of evidence: 2B). Pain relief can be obtained for 3-6 months (3, 4, 7) (level of evidence: 1A).

3.3.3.2 Mechanism of pain relief by radiotherapy

The main mechanisms by which pain relief is obtained after radiotherapy are tumour shrinkage (level of evidence: 3) and inhibition of the release of chemical pain mediators (level of evidence: 3). However, tumour shrinkage is unlikely to account for the early period of pain relief. One hypothesis is that early reacting and very sensitive cells, plus the molecules they produce, are involved in the rapid onset of pain relief. Obvious candidate cells are the inflammatory cells that are largely present in the bone metastasis microenvironment. Reduction by ionising radiation of the inflammatory cells inhibits the release of chemical pain mediators and is probably responsible for the rapid reaction seen in some patients (8-10) (level of evidence: 3).

3.3.3.3 Imaging

The detection of bone metastases is usually based on technetium-99m bone scintigraphy, which lacks diagnostic specificity (11) (level of evidence: 3). The addition of single photon emission computed tomography (SPECT) to planar acquisition has been reported to improve the diagnostic accuracy of bone scintigraphy (12-14) (level of evidence: 2B). Regions of increased uptake must be further investigated. Plain films have a false-negative rate of 10-17% (level of evidence: 3). At least 50% erosion must be present for a change to be seen on plain films (15) (level of evidence: 3). The combination of bone scintigraphy and plain films results in specificity of 64% and sensitivity of 63% (16) (level of evidence: 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) (level of evidence: 3). However, CT myelography is invasive and time-intensive, and so, particularly when spinal cord compression is suspected, MRI is currently the gold standard for detection and therapeutic management (20-24) (level of evidence: 2B), with sensitivity of 93% (25) (level of evidence: 3) and specificity of 96% (25) (level of evidence: 3).

3.3.3.4 Radiotherapy scheme

Single-fraction radiotherapy is as effective as multifraction radiotherapy in relieving metastatic bone pain (4-5) (level of evidence: 1A). However, the rates of retreatment and pathological fractures are higher after single-fraction radiotherapy (4-5) (level of evidence: 1A).

A single fraction is the treatment of choice for alleviating bone pain because of its greater convenience for the patient (4-5) (level of evidence: 1A), as well as its faster patient turn-over for the radiotherapy unit and lower cost (26) (level of evidence: 3). The recommended dose is 8 Gy (level of evidence: 1A) (4-6, 26-28, 30). With lower doses, pain relief can be achieved in a significant number of patients (level of evidence: 1B). However, studies have indicated that 4 Gy is less effective than 8 Gy (31-32) (level of evidence: 1B). A dose of 6 Gy gives similar results to those obtained with 8 Gy, but has been insufficiently studied (32) (level of evidence: 1B). These lower doses should be borne in mind in case there is a need for a third retreatment, or if there is concern about radiation tolerance (31-32) (level of evidence: 2B).

In cases of oligometastases (≤ 5 metastases), a case can be made for aggressive therapy, such as radiosurgery or high-dose radiotherapy, in order to improve survival (33-35) (level of evidence: 3).

3.3.3.5 Spinal cord compression

Metastatic epidural spinal cord compression is a common and severe complication of malignancy that affects almost 5-10% of patients with cancer (36). The most common symptom is back pain, present in 83-95% of patients. Weakness is present in 35-75% of patients (37).

The level of neurological function at the start of treatment determines the functional outcome. A delay in treatment, surgery or external radiotherapy, is the most common cause of an unfavourable outcome (24, 38) (level of evidence: 3).

Corticosteroids reduce oedema and might have an oncolytic effect on certain tumours, e.g. lymphoma, breast cancer, leukaemia. However, both the extent of the benefit obtained from corticosteroids, and what the optimal dosage is, are unclear. High dose corticosteroids carry a significant risk of adverse affects. One randomised controlled trial of patients with carcinomatous metastatic spinal cord compression compared radiotherapy with or without dexamethasone, and showed significantly better functional outcome when dexamethasone was added (39) (level of evidence: 1B).

Radiotherapy is recommended as the primary treatment for patients who do not fulfil the recommendations for surgery listed below. For patients whose chances of survival are estimated to be poor, a short course of radiotherapy is advised (e.g. 1 x 8 Gy (40) or 2 x 8 Gy [41]) (level of evidence: 3).

There have not been any trials comparing radiotherapy doses in patients with a good prognosis, so no conclusions can be drawn about the optimal dose of radiotherapy for those patients. However, in general, a multifraction regimen (10 x 3 Gy) is preferable in these patients as it allows for a higher dose and thus greater reduction in tumour size (42-43) (level of evidence: 2A).

Until the mid-1980s, posterior **decompressive laminectomy** was viewed as the only surgical option for patients with spinal cord compression. However, several studies have shown that decompressive laminectomy offers no additional benefit over conventional radiotherapy in terms of maintaining and recovering neurological function and pain control (44) (level of evidence: 2B). In addition, laminectomies are associated with important complications, most significantly wound infections, and new or worsened pre-existing spinal instability (44-45) (level of evidence: 2B).

Several uncontrolled surgical trials (46-48) and one meta-analysis (49-51) have indicated that **direct decompressive surgery** is superior to radiotherapy alone with regard to regaining ambulatory function, pain relief and recovering sphincter function (level of evidence: 1A). However, the decision to pursue surgery must be tempered by awareness of the significant morbidity and mortality risks that accompany it. Careful patient selection is of utmost importance. The criteria for the selection of candidates for primary therapy for spinal cord compression are shown in Table 4 (42-43, 52) (level of evidence: 3).

Table 4: 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 (52) (level of evidence: 1B).

3.3.3.6 Pathological fractures

In patients with impending pathological fracture, a prophylactic orthopaedic procedure should be considered. Several publications advise post-operative radiotherapy after (prophylactic) orthopaedic procedures for bone metastases (53) (level of evidence: 3). Some authors argue that if bone cement is used for fixation, post-operative radiotherapy is not needed (53-55) (level of evidence: 3).

3.3.3.7 Side-effects

Side-effects are related to the total dose, fractionation size and the localisation of the metastases (56) (level of evidence: 3) and include:

- pain flare-up (within 24 h and due to oedema)
- symptoms depend on the treatment field and location and can include:
  - nausea (especially with larger fields)
  - diarrhoea
  - irritation of the throat and oesophagus.

These side-effects are mostly transient within a few days (56).

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3.3.4 Physical/psychological therapy

3.3.4.1 Physical therapies

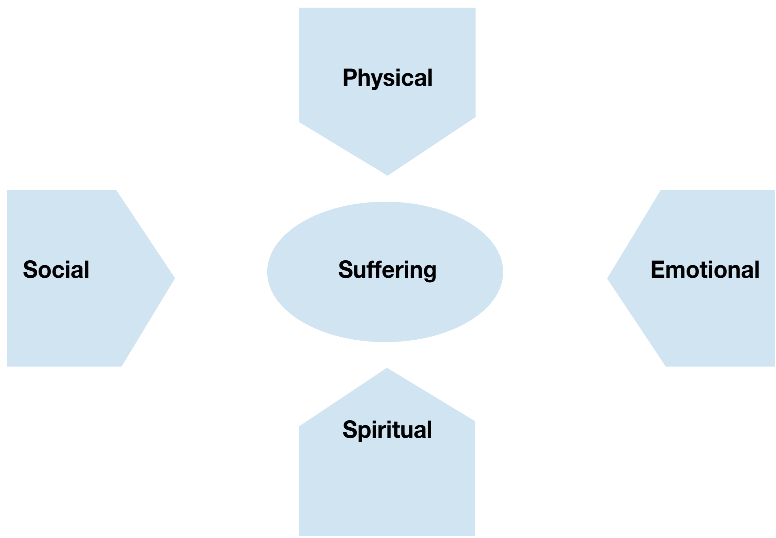
Physical techniques can be used to optimise function in patients with chronic cancer pain or enhance analgesia through the application of modalities such as electrical stimulation, heat or cryotherapy. The treatment of lymphoedema with wraps, pressure stockings or pneumatic pump devices can both improve function and relieve pain and a feeling of heaviness. The use of orthotic devices can immobilise and support painful or weakened structures, and assistive devices can be of great value to patients with pain precipitated by weight-bearing or ambulation (level of evidence: 4).

3.3.4.2 Psychological therapies

Psychological approaches are an integral part of the care of cancer patients with pain. All patients can benefit from psychological assessment and support (1, 2). Therapies include the following.

- Cognitive-behavioural interventions can help some patients decrease the perception of distress engendered by the pain through the development of new coping skills, and the modification of thoughts, feeling and behaviours.
- Relaxation methods may be able to reduce muscular tension and emotional arousal, or enhance pain tolerance (3).
- Other approaches reduce anticipatory anxiety, which can lead to avoidant behaviours, or lessen the distress associated with the pain.

Figure 4: Pain factors



3.4 Pharmacotherapy

The success of therapy for cancer pain depends on the ability of the clinician 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 an approach to long-term care that is responsive to the changing needs of the patient. This approach emphasises the need to incorporate pain treatment within a 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 (4) (level of evidence: 2b).

3.4.2 Chemotherapy

The likelihood of a successful effect on pain is generally related to the likelihood of 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 (5) (level of evidence: 1a).

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3.4.4 BISPHOSPHONATES

Bisphosphonates are pyrophosphate analogues.

3.4.4.1 Mechanisms of action

There are four mechanisms of action.

- Inhibition of bone resorption. This commences 24-48 hours after administration. The target cells are the osteoclasts. The inhibition of bone resorption is performed by three different mechanisms corresponding to the three generations of bisphosphonates. There are four distinct effects on osteoclasts:

1. reduction of osteoclastic activity
2. inhibition of osteoclast adhesion
3. decrease in number of osteoclasts
4. 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.

3.4.4.2 Effects and side-effects

The main effects are:

- decrease of the risk of skeleton-related events (for example hormone refractory prostate cancer with bone metastasis [1]) (level of evidence Ib) (grade of recommendation: A).
- pain response in 60-85% of the patients (1-3) (level of evidence Ib) (grade of recommendation: A).

Side-effects

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 (glomerular filtration rate)
- osteonecrosis of the jaw bones (only after iv therapy)
- gastrointestinal symptoms can occur after oral administration (2-10%).

Points for attention

The main points to note are (all grade B recommendations):

- recognise and treat dehydration before administration of bisphosphonates
- a reduction in the dose is necessary in the event of impaired renal function while using zoledronate (4) (level of evidence 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) (level of evidence 2).

3.4.4.3 References

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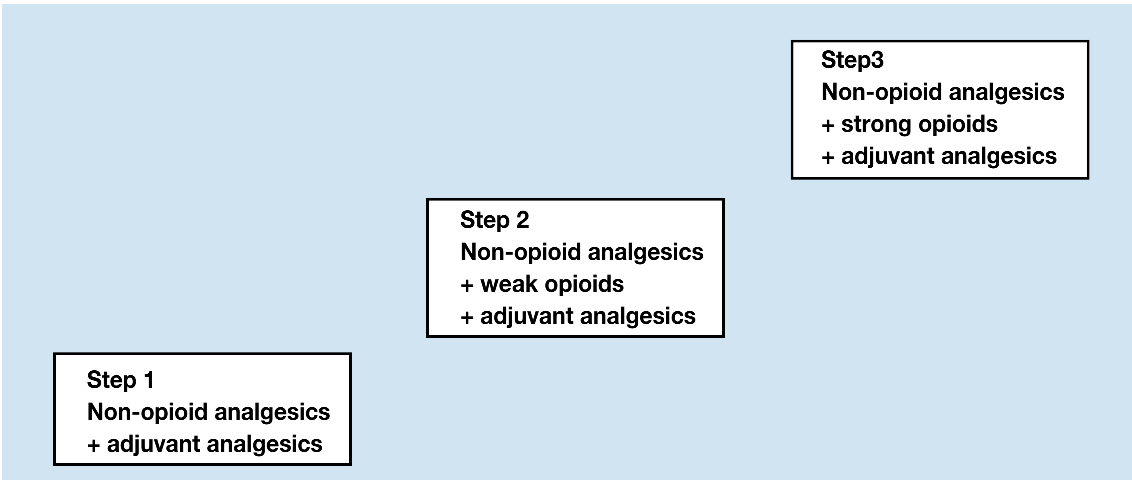
3.4.5 Systemic analgesic pharmacotherapy - the 'analgesic ladder'

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, which are drugs with other primary indications that can be effective analgesics in specific circumstances.

An expert committee convened by the Cancer Unit of the WHO has proposed a useful approach to drug selection for cancer pain, which has become known as the 'analgesic ladder' (1, 3). When combined with appropriate dosing guidelines, this approach is capable of providing adequate relief to 70-90% of patients (4, 5). Emphasizing that pain intensity should be the prime consideration in analgesic selection, the approach advocates three basic steps (Figure 4) (level of evidence: 1a).

Figure 4: The World Health Organization's 'analgesic ladder'



Step 1

Patients with mild to moderate cancer-related pain should be treated with a non-opioid analgesic, which should be combined with an adjuvant analgesic if a specific indication for one exists.

Step 2

Patients who present with moderate to severe pain, or who fail to achieve adequate relief after a trial of a non-opioid analgesics, should be treated with a weak opioid (codeine, tramadol). This treatment is typically accomplished using a combination product containing a non-opioid (e.g. aspirin or paracetamol) and an opioid (such as codeine, oxycodone or propoxyphene). This drug can also be co-administered with an adjuvant analgesic.

Step 3

Patients who present with severe pain, or who fail to achieve adequate relief following appropriate administration of drugs on the second rung of the 'analgesic ladder', should receive a strong opioid, such as morphine or hydromorphone. This drug may also be combined with a non-opioid analgesic or an adjuvant drug.

3.4.5.1 Non-opioid analgesics

The main points to note are:

- non-opioid analgesics = aspirin, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)
- can be useful alone for mild to moderate pain (step 1 of the analgesic ladder)

- provide analgesia when 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 are 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
- paracetamol also rarely produces gastrointestinal toxicity and there are no adverse effects 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).

3.4.5.2 Opioid analgesics

Cancer pain of moderate or severe intensity should generally be treated with a systemically administered opioid analgesic (9).

Classification

Classification is based on their interactions 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.

Relative potency and equi-analgesic doses

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).

Selecting patients for opioid therapy

A trial of systemic opioid therapy should be administered to all cancer patients with moderate or severe pain. This is true regardless of the pain mechanism (10-13). Patients who present with severe pain should be treated with a 'strong' opioid from the start. Patients with moderate pain are commonly treated with a combination drug containing paracetamol or aspirin plus codeine, oxycodone or propoxyphene. The dose of these combination products can be increased until the maximum dose of the non-opioid co-analgesic is attained (e.g. 4000 mg paracetamol).

3.4.5.2.1 Opioid administration

Opioid selection

Factors to consider include the following:
- pain intensity
- patient age
- prior opioid therapy (response to previous trials of opioid therapy)
- co-existing disease
- influence of underlying illness and characteristics of the opioid and concurrent medications.

Routes of administration

Classification is on the basis of the degree of invasiveness. Opioids should be administered by the least invasive and safest route capable of providing 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 or gastrointestinal dysfunction, those who require a very rapid onset of analgesia, and those who are unable to utilise or tolerate the oral route.
- **Rectal** suppositories containing oxycodone, hydromorphone, oxycodone and morphine in

combination have been formulated, and controlled-release morphine tablets can also be administered per rectum. The potency of opioids administered rectally is believed to approximate to oral dosing (14).

- **Transdermal** routes: fentanyl and buprenorphine are the opioids for transdermal administration. The system has been demonstrated to be effective in post-operative pain and cancer pain (15). In addition, the fentanyl transdermal therapeutic system dosing interval is usually 72 hours, but some patients require a 48-hour schedule. There is some interindividual variability in fentanyl bioavailability by this route, and this phenomenon, combined with large differences in elimination pharmacokinetics, necessitates dose titration in most cases (16). The efficacy of fentanyl administered transdermally is equal to morphine. The incidence of side-effects such as sedation and constipation are lower compared with morphine (17, 18) (level of evidence: 1b).
  Transdermal patches capable of delivering 12, 25, 50, 75 and 100 mg/h are available. Multiple patches can be used simultaneously for patients who require higher doses. Currently, the limitations of the transdermal delivery system include its cost and the requirement for an alternative short-acting opioid for breakthrough pain.
  Recently, buprenorphine has become available for transdermal administration. Buprenorphine, a high-affinity partial μ-opioid agonist, 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, at higher doses, buprenorphine's physiological and subjective effects, including respiratory depression and euphoria, reach a plateau. This ceiling may limit the abuse potential, and might result in a wider safety margin (21). Additionally, dose adaptations are not necessary in patients with renal and/or hepatic impairment. Pre-clinical and clinical trials demonstrate the effectiveness of buprenorphine in the treatment of neuropathic pain. In a human model, administration of buprenorphine led to the alleviation of hyperalgesia (comparable with S(+)-ketamine). These studies provide promising evidence for the use of buprenorphine in neuropathic pain conditions.
- Sublingual absorption of any opioid could potentially yield clinical benefits, but bioavailability is very poor with drugs that are not highly lipophilic and the likelihood of an adequate response is consequently low (22). Sublingual buprenorphine, a relatively lipophilic partial agonist, can provide adequate relief of mild to moderate cancer pain. Overall, however, the sublingual 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, which incorporates the drug into a sugar base, is useful for providing rapid relief of breakthrough pain (23, 24). Additionally, this opioid delivery system using fentanyl is more effective in terms of pain relief than oral morphine (level of evidence: 2).

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

GR = grade of recommendation

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 by intravenously (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). Repetitive im injections are a common practice, but they are painful and offer no pharmacokinetic advantage; 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, if necessary, until adequate relief is achieved.
- **Continuous parenteral infusions** are useful for many patients who cannot be maintained on oral opioids. Long-term infusions may be administered iv or sc. In practice, the major indication for continuous infusion occurs in patients who are unable to swallow or absorb opioids. Continuous

infusion is also used in some patients whose high opioid requirement renders oral treatment impractical (27).

Ambulatory patients can easily use a continuous sc infusion using a 27-gauge 'butterfly' needle. The butterfly can be left under the skin for up to a week. A recent study demonstrated that the bioavailability of hydromorphone is 78% by this route (28), and clinical experience suggests that dosing may proceed in a manner identical to that for continuous iv infusion. A range of pumps is available that vary in complexity, cost and ability to provide patient-controlled 'rescue doses' as an adjunct to a continuous basal infusion.

Opioids suitable for continuous sc infusion must be soluble, well absorbed and non-irritant. Extensive experience has been reported with diamorphine, 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 routes of administration

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

Dosing

Around-the-clock' (ATC) dosing

Patients with continuous or frequent pain generally benefit from scheduled 'around-the-clock' dosing, which can provide the patient with continuous relief by preventing the pain from recurring. Clinical vigilance is required, however, when this approach is used in patients with no previous opioid exposure. Patients should also be provided with a so-called 'rescue dose', which is a supplemental dose offered on an 'as needed' basis to treat pain that breaks through the regular schedule. The integration of 'around-the-clock' dosing with 'rescue doses' provides a gradual method for safe and rational dose escalation, which is applicable to all routes of opioid administration.

Controlled-release drug formulations

Controlled release preparations of oral opioids can lessen the inconvenience associated with the use 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 when rapid dose escalation is needed or therapy is begun with a long half-life opioid such as 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 accomplished via the subcutaneous route using an ambulatory infusion device. In most cases, PCA is added to a basal infusion rate and acts essentially as a rescue dose.

3.4.5.2.2 Adverse effects and their management

Tolerance

Patients vary greatly in the opioid dose required to manage pain (400-2000 mg of intramuscular 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 an escalation in dose to manage increasing pain have demonstrable progression of disease (34). These observations suggest that true pharmacological tolerance to the analgesic effects of opioids is not a common clinical problem. This conclusion has two important implications:

- concern about tolerance should not impede the use of opioids early in the course of the disease
- worsening pain in a patient receiving a stable dose of opioids should not be attributed to tolerance, but should be assessed as presumptive evidence of disease progression or, less commonly, increasing psychological distress.

Adverse drug interactions
The potential for additive side-effects and serious toxicity from drug combinations must be recognised. The sedative effect of an opioid may add to that produced by numerous other centrally acting drugs, such as anxiolytics, neuroleptics and antidepressants. Likewise, constipation produced by opioids is probably worsened by anticholinergic drugs.

Respiratory depression
Respiratory depression is potentially the most serious adverse effect of opioid therapy. All phases of respiratory activity (rate, minute volume and tidal exchange) may be impaired by these drugs. Clinically significant respiratory depression is always accompanied by other signs of central nervous system depression, including sedation and mental clouding. With repeated opioid administration, tolerance appears to develop rapidly to the respiratory depressant effects of the opioid drugs. As a result, opioid analgesics can be used in the management of chronic cancer pain without significant risk of respiratory depression. When respiratory depression occurs in patients on chronic opioid therapy, administration of the specific opioid antagonist naloxone usually improves ventilation.

Sedation
Sedation usually persists until tolerance to this effect develops, usually within a period of days to weeks. It is useful to forewarn patients of this potential, and thereby reduce anxiety and encourage avoidance of activities such as driving that may be dangerous if sedation occurs. Some patients have a persistent problem with sedation, particularly in combination with other sedating drugs or co-existent diseases 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, the aetiology of persistent delirium is usually related to the combined effect of the opioid and other contributing 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. Alternatively, opioidrotation may be an option.

Constipation
Constipation is the most common adverse effect of chronic opioid therapy (37-39). Laxative medications should be prescribed prophylactically. There are no controlled comparisons of the various laxatives for opioid-induced constipation, and published recommendations are based entirely on anecdotal experience. Combination therapy is frequently used, particularly co-administration of a softening agent (docusate) and a cathartic (e.g. senna, bisocodyl or phenolphthalein). The doses of these drugs should be increased as necessary, and an osmotic laxative (e.g. milk of magnesia) should be added if needed. Chronic lactulose therapy is an alternative that some patients prefer, and occasional patients are managed with intermittent colonic lavage using an oral bowel preparation.

Nausea and vomiting
Opioids may produce nausea and vomiting through both central and peripheral mechanisms. These drugs stimulate the medullary chemoreceptor trigger zone, increase vestibular sensitivity, and have effects on the gastrointestinal tract (including increased gastric antral tone, diminished motility and delayed gastric emptying). In ambulatory patients, the incidence of nausea and vomiting has been estimated to be 10-40% and 15-40%, respectively (40). The likelihood of these effects is greatest at the start of opioid therapy.

Metoclopramide is the most reasonable initial treatment. Tolerance typically develops within weeks. Routine prophylactic administration of an antiemetic is not necessary. The serotonin antagonists (e.g. ondansetron) are not likely to be effective with opioid-induced symptoms since they do not eliminate apomorphine-induced vomiting and motion sickness, which appear to be appropriate models for opioid effects. Clinical trials of the latter agents are needed to confirm this conclusion.

Addiction and dependence
Confusion about physical dependence and addiction augment the fear of opioid drugs and contribute substantially to the undertreatment of pain (41). Patients with chronic cancer pain have a 'therapeutic dependence' on their analgesic pharmacotherapy. This relationship may or may not be associated with the development of physical dependence, but is virtually never associated with addiction. The medical use of opioids is very rarely associated with the development of addiction (42). Although there are no prospective studies in patients with chronic cancer pain, there is extensive clinical experience that affirms the extremely low risk of addiction in this population (level of evidence: 3). Healthcare providers, patients and families often require vigorous and repeated reassurance that the risk of addiction is extremely small.

3.4.5.2.3 Adjuvant analgesics
An 'adjuvant analgesic' is 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 in any of the three steps of the 'analgesic ladder' to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side-effects. In the management of cancer pain, adjuvant analgesics can be broadly classified on the basis of conventional use. The following three groups are distinguished.

- **Corticosteroids** These are among the most widely used adjuvant analgesics (43, 44). They have been demonstrated to have analgesic effects, to improve quality of life significantly (45), and to have beneficial effects on appetite, nausea, mood and malaise in the cancer population (46). The mechanism of analgesia produced by these drugs may involve anti-oedemic effects, anti-inflammatory effects, and a direct influence on the electrical activity in damaged nerves. 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) (level of evidence: 2a).
- **Neuroleptics** The role of neuroleptic drugs in the management of cancer pain is limited. Methotrimeprazine is a proven analgesic that has been very useful in bedridden patients with advanced cancer who experience pain associated with anxiety, restlessness or nausea. In this setting, the sedative, anxiolytic and antiemetic effects of this drug can be highly favourable, and side-effects, such as orthostatic hypotension, are less of an issue. A prudent dosing schedule begins with 5-10 mg every 6 hours, which is gradually increased as needed (level of evidence: 1a).
- **Benzodiazepines** Benzodiazepines have an analgesic effect (47), but this must be balanced by the potential for side-effects, including sedation and confusion. These drugs are generally used only if another indication exists, such as anxiety or insomnia (level of evidence: 2b).

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3.4.5.3 Treatment of neuropathic pain

Numerous treatment options are available for relieving neuropathic pain, including opioids, with which patients experience significant pain reduction with greater satisfaction than with antidepressants (1, 2). Although opioids are clearly efficacious in the treatment of neuropathic pain, the prospect of commencing an analgesic whose use may be complicated by analgesic tolerance, withdrawal reactions after discontinuation, and always a (slight) possibility of addiction is not satisfactory (3).

Beside opioids, the available therapies shown to be effective in 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).

3.4.5.3.1 Antidepressants

There is clear evidence for the effectiveness of antidepressants in the treatment of neuropathic pain (5). The primary mode of action is an interaction with pathways running through the spinal cord from serotoninergic and noradrenergic structures in the brain stem and mid-brain. Tricyclic antidepressants (TCA) including amitriptyline, nortriptyline (metabolite of amitriptyline), imipramine, and desipramine (metabolite of imipramine), are often the first drugs selected to alleviate neuropathic pain (level of evidence: 1a) (6, 7).

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 Ca^{2+} or Na^{+}), and interaction with adenosine and NMDA receptors. However, treatment with these analgesics may be compromised (and outweighed) by their side-effects. TCA must be used cautiously in patients with a history of cardiovascular disorders, glaucoma, and urine retention. In addition, combination therapy with monoamino-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 at 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) (level of evidence: 1b).

Selective serotonin reuptake inhibitors (SSRI: sertraline, paroxetine, fluoxetine and citalopram) selectively inhibit the reuptake of serotonin. These antidepressants have a more favourable side-effect profile than TCA, but their effectiveness in managing neuropathic pain is disputed due to conflicting reports in the available literature (second-line pharmacological treatment).

Recommendation	**GR**
• Amitriptyline and nortriptyline are the first line treatment for neuropathic pain; nortriptyline has fewer side-effects	A
• TCA 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	GPP

GGP = good clinical practice; GR = grade of recommendation

3.4.5.3.2 Anticonvulsant medication

The rationale for the use of antiepileptic 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 Ca^{2+} or Na^{+}), effects on neurotransmitters (enhancement of GABA, inhibition of glutamate release), and/or neuromodulation systems (blocking the NMDA receptor) (9, 10). Initially, carbamazepine and phenytoin were used for the treatment of trigeminus neuralgia. Although both drugs reduce neuropathic pain, their attendant side-effects and complicated pharmacokinetic profile limit their use in treating neuropathic pain. Despite the introduction of these newer anticonvulsants with a more favourable side-effect profile, carbamazepine remains the drug of choice in treatment of trigeminus neuralgia (level of evidence: 1a) (11). However, oxcarbazepine (10-keto analogue of carbamazepine), a new anticonvulsant with similar mechanism of action to that of carbamazepine but with a better side-effect profile, may replace carbamazepine for treating trigeminus neuralgia (12).

Gabapentin and pregabalin (level of evidence: 1a) are emerging as first-line treatments for neuropathic pain (reducing elements of central sensitisation), especially in post-zoster neuralgia and diabetic polyneuropathy (13-15). More recently, 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 showed greater analgesic activity in rodent models of neuropathic pain than 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 TCA are contraindicated	A

GR = grade of recommendation

3.4.5.3.3 Topical analgesics

Neuropathic pain syndromes are typically associated with touch-evoked allodynia and hyperalgesia that impair patients' quality of life. Besides treatment with anticonvulsants and antidepressants, the application of a topical drug on to the painful area of skin 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; level of evidence: 1b). The 5% lidocaine patch (up to three patches, once daily for 12 hours) is applied to the painful skin, covering as much of the affected area as possible.

Capsaicin causes pain due to a release of substance P (initiating nociceptive firing) from the nociceptive terminals. Subsequently, 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), and it is applied in a 0.075% concentration (22) (level of evidence: 3).

Recommendations	**GR**
• Lidocaine 5% should be used as an adjuvant in patients suffering from post-herpetic neuralgia	A
• Capsaicin may be used as an adjuvant in patients with neuropathic pain	C

GR = grade of recommendation

3.4.5.3.4 NMDA receptor antagonists

Within the dorsal horn, ionotropic glutamate receptors (NMDA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate [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) (level of evidence: 2b). Unfortunately, administration of ketamine may result in unwanted changes in mood, conscious perception, and intellectual performance. Additionally, psychomimetic side-effects (including visual and auditory hallucinations, dissociation, and nightmares) are prominent with ketamine, limiting its usefulness and widespread use in treating neuropathic pain (25).

Thus, although ketamine has analgesic properties in patients with chronic neuropathic pain, because of its side-effects, ketamine has to be reserved as a third-line option for when other standard analgesic treatments are exhausted (26, 27).

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

GR = grade of recommendation

3.4.5.3.5 Other drug treatments

Baclofen, a muscle relaxant, exerts its analgesic effect via an agonistic effect on the inhibitory GABAB-receptors. Baclofen has demonstrated efficacy in patients with trigeminal neuralgia, but not in patients with other neuropathic pain conditions (28). 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 (level of evidence: 3).

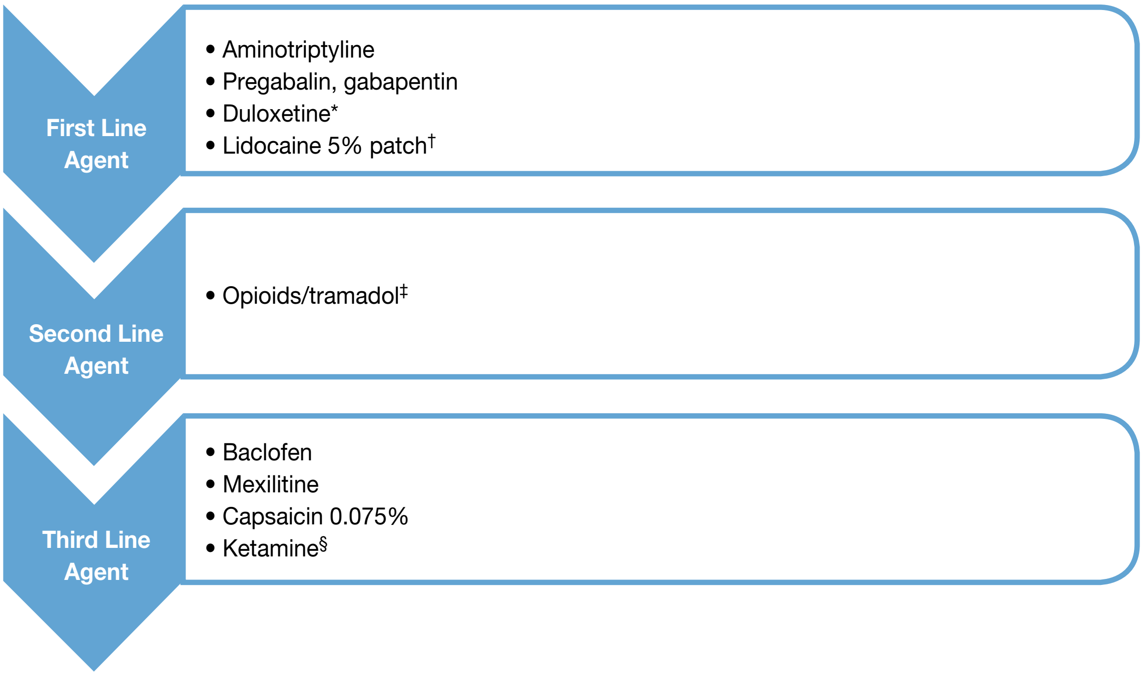
Mexilitine, an oral analogue of lidocaine, is effective in a number of chronic neuropathic pain conditions (29). After a successful trial with iv lidocaine, treatment with mexilitine seems to be justified (second-line pharmacological treatment). However, their role in the management of neuropathic pain is limited due to adverse gastrointestinal (33% of patients), central nervous system, and cardiac effects (level of evidence: 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. Its use in neuropathic pain treatment, however, is focused on intrathecal or epidural administration, in combination with an opioid and/or local anaesthetics. Clonidine has been shown to improve pain control in combination with intrathecal opioids and/or local anaesthetics because of a possible supra-additive effect during neuropathic pain treatment (30) (level of evidence: 2b).

3.4.5.3.6 Summary: treatment of neuropathic pain

Figure 5 gives a summary of the treatment of neuropathic pain.

Figure 5: The treatment of neuropathic pain



* = first-line treatment in diabetic polyneuropathy only
† = first-line treatment in post-herpetic neuralgia only

‡ = first-line treatment in patients with neuropathic cancer pain only
§ = ketamine is an anaesthetic.

3.4.5.4 Invasive analgesic techniques
The results of the WHO 'analgesic ladder' validation 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 (31, 32). Anaesthetic and neurosurgical techniques may reduce the need for systemically administered opioids for the achievement of adequate analgesia.

3.4.5.4.1 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 the following is recommended (33,34).

Recommendation	**GR**
Reversible regional anaesthetic techniques must be considered for the management of neuropathic pain	GPP

GR = grade of recommendation; GPP = good clinical practice

3.4.5.4.2 Neurolytic blocks to control visceral cancer pain
Visceral cancer pain is primarily treated with NSAIDs and opioids. However, different neurolytic blockades have been described to optimise palliative treatment for cancer in the viscera. Continuation of the pharmacological therapy can, however, be necessary because these patients experience frequently co-existing somatic and neuropathic pain not relieved by neurolytic blockades. Different approaches to achieving neurolysis, including the coeliac plexus block and the superior hypogastric plexus block, have been described (35, 36).

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) (37) (level of evidence: 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 more conservative (i.e. pharmacological) treatment (level of evidence: 3) (38- 40).

3.4.5.4.3 Epidural and intrathecal opioid application
The delivery of low opioid doses 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 (41, 42). 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. In some patients, the addition of a low concentration of a local anaesthetic, such as 0.125-0.25% bupivacaine, to an epidural/intrathecal opioid has been demonstrated to increase analgesic effect without increasing toxicity (43, 44). The potential morbidity for these procedures indicates the need for a well-trained clinician and long-term monitoring (level of evidence: 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

GR = grade of recommendation

3.4.5.4.4 Chemical rhizotomy
Chemical rhizotomy, produced by the instillation of a neurolytic solution into either the epidural or intrathecal space, can be an effective method of pain control for patients with otherwise refractory localised pain syndromes (45, 46). The technique is most commonly used in the management of 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-existent urinary diversion. Adverse effects can be related to the injection technique (spinal headache, mechanical neural damage, infection and arachnoiditis) or to the destruction of non-nociceptive nerve fibres (47) (level of evidence: 4).

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

GR = grade of recommendation

3.4.5.4.5 Cordotomy

During cordotomy, the anterolateral spinothalamic tract is sectioned to produce contralateral loss of pain and temperature sensibility. 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 (48). Of surviving patients, 50% have recurrent pain after 1 year. Repeat cordotomy can sometimes be effective. The neurological complications of cordotomy include paresis, ataxia and bladder dysfunction (49) (level of evidence: 3).

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3.5 Quality of life

Issues that affect quality of life include the following:

- **Anxiety** Anxiety is a common symptom associated with patients near the end of life. Currently there is insufficient evidence about the role of drugs in the treatment of anxiety associated with terminal illness, and it is therefore not possible to draw any conclusions about the effectiveness of pharmacotherapy in anxiety in terminally ill patients (1).
- **Cancer-related fatigue** Fatigue associated with cancer is a significant problem. It can occur because of the side-effects of treatment or because of the disease itself. It can have a significant impact on a person's ability to function. The causes of fatigue are not fully understood and so it is very difficult to treat it appropriately. Trials of erythropoietin and darbopoeitin (for anaemic patients on chemotherapy) and psychostimulants provide evidence for improvement in cancer-related fatigue at a clinically meaningful level. There are no data to support the use of paroxetine or progestational steroids for the treatment of cancer-related fatigue. The obvious candidate drug for use in a large-scale cancer-related fatigue study is methylphenidate (2).
- **Sexual dysfunction** The proportion of people living with and surviving cancer is growing. This has led to an increased awareness of the importance of quality of life, including sexual function, in people with cancer. Sexual dysfunction is a potential long-term complication of cancer treatments. There is some evidence that, following treatment for prostate cancer, transurethral alprostadil and vacuum constriction devices reduce sexual dysfunction, although negative effects were fairly common, and that vaginal lubricating creams reduce sexual dysfunction. PDE5 inhibitors are an effective treatment for sexual dysfunction secondary to treatments for prostate cancer (3).
- **Selenium** Selenium is a mineral necessary for human health. Selenium acts against cell damage in the body and might help to alleviate treatment side-effects such as nausea, diarrhoea or lymph retention in the limbs in cancer patients. Selenium supplements are frequently used by cancer patients. To date there is insufficient evidence that selenium supplementation alleviates the side-effects of tumour-specific chemotherapy or radiotherapy treatments, or that it improves the after-effects of surgery or quality of life in cancer patients, or that it reduces secondary lymphoedema (4).

3.5.1 Conclusions

The goal of analgesic therapy in cancer patients is to optimise analgesia with the minimum of side-effects. Currently available 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 can occur in both the early and advanced stages of prostate cancer (PCa). In early cases it may be a presenting symptom, have clinical usefulness and therefore be tolerated by (and at least partly acceptable to) the patient. In advanced disease, it no longer has a specific diagnostic meaning but only serves to underline the patient's illness (1). Pain could be caused directly by the cancer (77%), be related to the cancer treatment (19%), or be unrelated to either (3%) (2).

Pain is more common, and a real challenge, in advanced disease, and pain management must therefore focus on the symptomatic patient with metastases.

The overall incidence of chronic pain in PCa patients is about 30-50%, but as patients enter the terminal phase of their illness this figure rises to 90% (3). Pain may be directly attributable to tumour growth in three main areas, which include tumour infiltration of 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

The relief of pain caused by invasion of a hollow viscus is the domain of surgery and minimally invasive procedures (e.g. catheter, stent, 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. In these cases of acute pain, prompt relief is necessary. The best method is inserting a suprapubic catheter and starting hormonal treatment in case of advanced disease. If after 3 months the outlet obstruction persists, a transurethral palliative resection (TURP) could be performed for palliative reasons.

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 typically asymmetric.

Untreated progressive ureteric obstruction results in bilateral hydronephrosis and subsequent renal failure. In terminal cancer patients, the decision to drain the kidneys can be difficult. It is good practice to drain symptomatic hydronephrosis at once, and to drain only one kidney (the one with the better function) in asymptomatic patients. A nephrostomy tube is superior to a double-J stent for drainage because the routine endoscopic changes of the stent in the following months could be increasingly difficult in a continuously growing prostate gland. Another reason is that the 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 very often show lymphoedema of the legs. The treatment of lymphoedema includes physiatric techniques such as wraps, pressure stockings or pneumatic pump devices. These can both improve function and relieve pain and heaviness.

4.1.2.5 Ileus

Local obstruction of the rectum is a common occurrence in advanced cancer of the prostate and can lead to abdominal pain caused by ileus. Peritoneal involvement, which is rare, can also result in ileus. Surgery must be performed in case of 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

The following points should be noted.

- Bone metastases are the most common cause of chronic pain in the prostate cancer population (8, 9).
- Widespread bony metastases causing multifocal pain are frequent.
- More than 25% of patients with bony metastases are pain-free (10).

- Patients with multiple bony metastases typically report pain in only a few sites.
- The factors that convert a painless lesion to a painful one are unknown.
- Bone metastases could potentially cause pain by:
  - endosteal or periosteal nociceptor activation (by mechanical distortion or release of chemical mediators)
  - tumour growth into adjacent soft tissues or nerves
  - other complex mechanisms (9).

The choice of treatment will depend on the tumour site, histology, stage and the patient's physical and emotional condition. Although therapies are being developed that will target tumour cells specifically, the most commonly used techniques will continue to result in a degree of damage to normal tissues with consequent side-effects. In each case, the benefits and side-effects should be considered. The therapeutic options with fewer side-effects should be 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.

4.1.3.1.1 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, gonadotropin-releasing hormone (GnRH) analogues, orchidectomy, adrenalectomy and hypophysectomy. Corticosteroids are also used for the palliation of pain, particularly the kind due to bone deposits.

4.1.3.1.2 Side-effects

Hormone therapy is generally much better tolerated than chemotherapy. There can also be a 'flare' or temporary exacerbation of pain with it, which is generally a predictor of subsequent response (13).

The side-effects that must be considered are:

- GnRH analogues and orchidectomy:
  - loss of body hair
  - testicular atrophy
  - gynaecomastia
  - loss of libido
  - impotence
  - relatively low cardiovascular mortality rate
  - psychological morbidity.
- Anti-androgens:
  - gynaecomastia (more often if used alone than when used in combination with GnRH analogues)
  - hepatic impairment
  - less sexual dysfunction.
- Cyproterone acetate:
  - fewer side-effects than oestrogens
  - lower incidence of cardiovascular complications.
- Oestrogens:
  - loss of body hair
  - testicular atrophy
  - gynaecomastia
  - loss of libido

- impotence
- higher mortality from cardiac and cerebrovascular disease in long-term administration.

- Adrenalectomy:
  - major operative procedure.
- Hypophysectomy:
  - small but significant mortality rate
  - hormone replacement is subsequently required for life.

4.1.3.1.3 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.

4.1.3.1.4 Problems

To date, most patients with adenocarcinoma of the prostate present in early tumour stages and undergo radical surgery or radiotherapy. In cases of prostate-specific antigen (PSA) recurrence and/or symptoms, hormone therapy is indicated and patients can be asymptomatic for years. Pain is associated with a hormone-resistant tumour in progression, which necessitates alternative management options for the treatment of pain.

4.1.3.1.5 Radiotherapy

In the management of metastatic adenocarcinoma of the prostate, radiotherapy is associated with palliation of pain from osseous metastases and improving quality of life. Radiation therapy is well known to be effective in treating painful sites, and might also be effective in reducing the propensity for adjuvantly treated disease to become symptomatic in the majority of 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).

The main points to note are:

- 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
- field size is a compromise
- avoid treating larger volumes than necessary in order to minimise morbidity
- bear in mind that radiological evidence of a deposit may considerably underestimate the extent of disease.

4.1.3.1.6 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 to avoid pathological fractures. 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).

4.1.3.1.7 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-ethylenediamine-tetramethylene phosphonic acid (^{153}Sm-EDTMP). The addition of ^{89}Sr (single injection of 10.8 mCi [399.6 MBq]) is an effective adjuvant therapy to local field radiotherapy, reducing disease progression, as evidenced by new sites of pain, the requirement for further radiotherapy, and analgesic support (16), and improving quality of life.

There is some evidence to indicate that radioisotopes could give complete reduction in pain over one to six months, with no increase in analgesic use, although adverse effects, specifically leucocytopenia and thrombocytopenia, have also been experienced (21).

4.1.3.1.8 Bisphosphonates

Complications of bone metastases include pain, fractures, and spinal cord compression. Bisphosphonates are a standard part of supportive care for patients with bone metastases, and there is evidence to support their effectiveness in providing some pain relief. Bisphosphonates act by inhibiting osteoclast activities and are a potential therapeutic option for metastatic prostate cancer. In recent studies, there was no statistically significant difference between the bisphosphonate groups and the control groups in terms of prostate cancer death, disease progression, radiological response and PSA response. However, bisphosphonates should be considered for patients with metastatic prostate cancer for the treatment of refractory bone pain and prevention of skeletal events (22).

Zoledronic acid, a nitrogen-containing third-generation bisphosphonate, is effective in the treatment of complications of metastatic bone disease. Its efficacy and safety has been established in three pivotal prospective, randomised controlled 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. In addition, 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 in this setting (24).

Zoledronic acid administration for 1 year to patients with hormone-sensitive PCa and bone metastases who were receiving androgen-deprivation therapy was safe and prevented bone loss, as demonstrated 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 a first skeleton-related event, 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). Additional studies are needed to determine the optimal timing, schedule, and duration of treatment in men with bone metastases, as well as the potential role of bisphosphonates in other settings, including the prevention of bone metastases (see also section 3.4.4).

4.1.3.1.9 Calcitonin

The limited evidence currently available does not support the use of calcitonin to control pain arising from bone metastases (27).

4.1.3.1.10 Chemotherapy

In about 80% of men with metastatic PCa, primary androgen ablation leads to symptomatic improvement and to a reduction in the serum levels of PSA, but the disease eventually becomes refractory to hormone treatment. Systemic chemotherapy should be reserved for this patient group. Recent data from randomised studies, particularly those using docetaxel, have provided encouraging improvements in overall survival, palliation of symptoms, and improvements in quality of life (28).

In advanced disease, previous clinical trials using single-agent chemotherapy have shown poor results. Newer studies suggest multiagent chemotherapies may be more effective. A randomised trial showed that mitoxantrone plus low-dose prednisone relieved pain and improved the quality of life more frequently than did prednisolone alone. Many other studies have confirmed the symptomatic effect of this chemotherapy regimen, but none has found that this approach improved survival as well.

A PSA-response rate and a reduction of pain were also reported with other combined chemotherapies. Individual concepts had to be developed for the patient, as these chemotherapy regimens were associated with side-effects and none showed a survival benefit.

PSA response rates to selected combined chemotherapy regimens are shown in Table 5.

Table 5: 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 2004, two randomised trials/phase III studies (TAX-327 and SWOG 9916) comparing docetaxel-based chemotherapies with mitoxantrone-based regimes were published (25, 26). It was demonstrated that docetaxel-based regimens have a very good symptomatic effect, one that is significantly better than the mitoxantrone-based approach (Table 6). Additionally, for the first time, a significant survival benefit was shown for the docetaxel group (18.9 versus 16.5 months).

Table 6: Docetaxel-based chemotherapy versus mitoxantrone-based regimens

Chemotherapy agent	Plus	Frequency	Response rate (29) 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 have associated side-effects, such as fatigue, mild myelosuppression, and gastrointestinal irritation, they are generally well tolerated by the majority of patients (30). 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')

In cases of insufficient pain management with the treatments described above, systemic analgesic pharmacotherapy should be administered (*see section 3.4*). In most cases, the World Health organization (WHO) ladder scheme is the treatment of choice. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used, often in combination with an opioid, for the treatment of cancer pain. Short-term studies have shown that NSAIDs alone are effective in managing cancer pain, with side-effects similar to placebo, and that in about 50% of studies, increasing the dose of NSAID can increase efficacy without increasing the incidence of side-effects.

Studies have not demonstrated a large clinical difference when combining an opioid with an NSAID versus either medication alone (31). Tramadol extended-release tablets and dihydrocodeine extended-release tablets were effective for the management of chronic tumour pain associated with prostate cancer with bone metastasis at the WHO Step II. Tramadol extended-release tablets provided slightly better pain management and a lower incidence of side-effects, particularly with regard to constipation (32). The treatment of constipation in palliative care is based on inadequate experimental evidence. There persists an uncertainty about the 'best' management of constipation in this group of patients (33).

Oral morphine is an effective analgesic for cancer pain. There is qualitative evidence for the effectiveness of oral morphine that compares well with other available opioids. There is limited evidence to suggest that transmucosal fentanyl provides more rapid pain relief for breakthrough pain than morphine (34).

Morphine is the gold standard for the management of moderate to severe cancer-related pain. Alternatives to morphine are now available, including hydromorphone. The limited evidence available does not demonstrate any clinically significant difference between hydromorphone and other strong opioids such as morphine (35). For patients with inadequate pain relief and intolerable opioid-related toxicity/adverse effects, a switch to an alternative opioid may be the only option for symptomatic relief. However, the evidence to support the practice of opioid switching is largely anecdotal or based on observational and uncontrolled studies (36).

Breakthrough pain is a common and debilitating component of pain in patients with cancer. There is evidence that oral transmucosal fentanyl citrate is an effective treatment in the management of breakthrough pain (37).

4.1.5 Spinal cord compression

Spinal cord compression can be 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% (38).

Thoracic cord compression is the most common area (70%), and the incidence of multiple extradural sites can be as high as 18% (39). Definitive treatment with surgery (anterior decompression with spinal stabilisation) or radiotherapy should be considered. Sometimes the symptom of local back pain disappears despite increasing motor deficits. This is due to the evolving sensory component of the paraplegia. The use of corticosteroids (typically dexamethasone 16 mg daily) to treat oedema of the cord is temporary.

There is some evidence of benefit from decompressive surgery in ambulant patients with poor prognostic factors for radiotherapy, and in non-ambulant patients with a single area of compression, paraplegia < 48 hours' duration, non-radiosensitive tumours and a predicted survival of more than three months. High-dose corticosteroids carry a significant risk of serious adverse effects (40).

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 against the pain or with corticosteroids.

Whole liver palliative radiotherapy can also be useful in carefully selected patients with refractory pain, with 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 (41). 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 prostate cancer

Initiation of LHRH therapy for PCa produces a transient symptom flare in 5-25% of patients (42, 43). The flare is presumably caused by an initial stimulation of LH release before suppression is achieved (43, 44). The syndrome typically presents as an exacerbation of bone pain or urinary retention. Spinal cord compression and sudden death have also been reported (42). Symptom flare is usually observed within the first week of therapy, and lasts 1-3 weeks in the absence of androgen antagonist therapy. Co-administration of an androgen receptor antagonist at the start of LHRH agonist therapy can prevent this phenomenon (45).

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 of this syndrome varies between drugs. It is frequently associated with diethylstilboestrol (46), is less common with flutamide and cyproterone (47-49), and is uncommon among patients receiving LHRH agonist therapy (49).

In the elderly, gynaecomastia must be distinguished from primary breast cancer or a secondary cancer in the breast (50).

4.1.8 Conclusions

Radiotherapy, chemotherapy and hormone therapy are all valuable techniques for the relief of cancer pain, and those concerned with the care of cancer patients must have some knowledge of the potential of all these therapies. The side-effects caused by the inappropriate use of anticancer treatments can be very distressing, and in all cases the disadvantages of a treatment must be balanced against the palliative benefit. In many patients, the best approach to pain relief will be through interdisciplinary co-operation.

Well-planned clinical trials are required because there is still much to be learned about the indications, dose, frequency and optimal administration of anticancer therapies for the relief of pain. Surgery, radiotherapy, chemotherapy and hormone therapy are mainly used as antitumour treatment in the relief of pain. The rational use of any of these types of treatment demands knowledge both of tumour biology and 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 (29).

The various regimens employed to treat pain in PCa patients have been described above, and the scientific bases for their use have been explained. However, the importance of early intervention needs to be emphasised. Education of patients is crucial. They 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) (51-56)

The levels of evidence (LE) (1a, 1b, 2a, 2b, 3, 4), grades of recommendation (GR) (A, B, C) are shown below.

Recommendation	**LE**	**GR**
ANTICANCER TREATMENT		
Hormonal therapy (orchiectomy, LHRH analogues, diethylstilboestrol equivalent)	1a	A
Total androgen blockade: flare prevention, second line	2b	B
Intermittent androgen suppression experimental	3	B
To date monotherapy with anti-androgen not recommended	1b	A
First line treatment controls disease for 12 to 18 months, second line individualized	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		
Pain assessment (localization, 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)		
Primary hormonal therapy	1a	A
Radioisotopes (strontium-89 or samarium-153)	2	B
Pain due to painful metastases (many spots)		
Bisphosphonates	1b	A
Systemic pain management		
World Health Organization 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

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4.2 Pain management in transitional cell carcinoma patients

4.2.1 Clinical presentation

Urothelial cancer is the fourth most common cancer in men and the ninth 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 tumours. In bladder carcinoma, pain can be present during the natural history of the disease (early as a burning pain together with irritative symptoms, or late in the advanced disease due to local invasion of neighbouring tissues 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 TCC of the upper urinary tract, pain is an initial symptom in around 30% of cases.

4.2.2 Origin of tumour-related pain

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 orifice
- invasion of the surrounding areas by a locally advanced tumour (pelvic wall, nerve roots, other organs such as bowel, rectum)
- bone metastases
- soft tissues metastases (seldom painful).

Upper urinary tract TCC

The main causes of tumour-related pain in 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, liver)
- bone metastases
- soft tissue metastases (seldom painful).

4.2.3 Pain due to local impairment

Bladder TCC

Obstruction of the ureteral orifice by tumour infiltration may lead to hydronephrosis and consecutive flank pain due to ureteral distension (visceral pain). Transurethral resection of the tumour is often effective in eliminating ureteral obstruction. Otherwise hydronephrosis is treated by temporary or permanent percutaneous nephrostomy.

In locally advanced disease, infiltration of the contiguous soft tissue and neighbouring organs can cause acute burning pain by infiltration of the pelvic nerves (neuropathic pain). This pain is sometimes associated with paraesthesia irradiating to the lower limb or with motor deficit. If the tumour invades adjacent organs – small bowel, rectum – obstruction of these organs could occur, along with visceral pain due to distension of hollow organs. Additionally, growing bladder tumour can cause complete bladder outlet obstruction with hypogastric abdominal pain due to 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).

In infiltrating and advanced bladder cancer, cystectomy (whether radical or debulking cystectomy) and urinary diversion have a positive impact on pain, removing the neoplastic mass invading the surrounding tissues. Sometimes extended operations including excision of involved bowel are indicated. Palliative surgery may be necessary in occlusive intestinal syndromes (4).

Chemotherapy has some effect in 40-75% of patients with advanced disease (see guidelines on bladder cancer). Chemotherapy is able to relieve pain by decreasing the neoplastic mass in responder patients (5-9) (level of evidence: 1a).

Radiotherapy can be effective in controlling pelvic pain due to local disease progression. Using 40-45 Gy on target volume, radiotherapy can reduce the local painful symptoms, but it can also worsen the irritative bladder symptoms and can induce proctitis (10) (level of evidence: 2b).

Upper urinary tract TCC

Locally advanced primary tumours (e.g. invasion of the posterior abdominal wall, nerve roots, paraspinous muscles, other organs such as bowel, spleen, liver) are usually managed by surgery. Sometimes extended operations including excision of involved bowel, spleen or abdominal wall muscle are indicated. In terms of the value of chemotherapy, the same considerations are valid for TCC of the upper urinary tract as for TCC of the bladder.

4.2.4 Pain due to metastases

In advanced bladder or upper urinary tract TCC, haematogenous metastases to the bone are often found. 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. Using 10 fractionated doses of 30-35 Gy, it rapidly reduces, if not eliminates, pain in 80-90% of cases (10) (level of evidence: 2b).

Hemibody irradiation can also be used in diffuse bone metastases (10). No specific studies exist on the radioisotope therapy of bone metastasis in TCC.

Orthopaedic surgery can stabilise pathological fractures (4). Neurosurgery may have a place in the palliation of pain derived from compression of the spinal cord.

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4.3. Pain management in renal cell carcinoma patients

4.3.1 Clinical presentation

Renal cell carcinoma is mainly diagnosed incidentally. Pain cannot be expected unless a tumour invades surrounding areas or obstructs the outflow of urine owing to haemorrhage and subsequent formation of blood clots. Between 20% and 30% of patients present with metastatic disease, and 30% of patients who primarily presented with a localised kidney tumour develop metastases during follow-up. Thus 50-60% of all patients with renal cell carcinoma develop metastases during their life and may have to be treated because of symptoms, mainly pain.

Renal cell carcinoma spreads mainly to lung, bone, brain, liver and ipsilateral or contralateral adrenergic glands. Patients with metastases have a maximal 2-year survival rate of 20%, which has to be considered in cases of palliative treatment.

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

There is no benefit in survival from standard pre-operative (30 Gy) or post-operative radiation therapy, and a questionable delay in local progress (1).

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) (level of evidence: 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 (GPP). If the patient is physically fit for surgery, this should be done to increase the quality of life, for example palliative nephrectomy in cases of metastatic tumour (GPP).

There are no data in the literature about the efficacy of alternative therapies such as angioinfarction of the tumour with regard to haemorrhage and pain relief in palliative situations.

According to the WHO guidelines, analgesic therapy and/or palliative drainage of the urinary tract should be used if the patient is 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).

Indications for surgery for bone metastases are solitary metastases that can be resected completely, intractable bone pain, and impending or demonstrable pathological fracture. In cases of bone metastases with extensive soft tissue involvement and corresponding severe pain, amputation of a leg or arm is sometimes required to maintain a certain quality of life. With surgery for bone metastases, a significant pain decrease is achieved in 89-91% of patients (4-6) (level of evidence: 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) (level of evidence: 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) (level of evidence: 3), and in 67% for bone metastases in general (12) (level of evidence: 2b). There is no impact on survival.

In small studies, radionuclide therapy, e.g. strontium-89 (^{89}Sr) therapy, seems to achieve good pain relief in bone metastases from renal cell carcinoma (13) (level of evidence: 3). There have been no large prospective studies with regard to long-term pain relief.

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 are therefore without any importance in pain control.

Therapy for soft tissue metastases is performed in a similar manner to that for locally advanced disease. Radiotherapy for soft tissue metastases is without proven benefit in terms of pain and tumour control. There is no benefit in survival by standard pre-operative (30 Gy) or post-operative radiation therapy, and a questionable delay of local progress (1).

Immunotherapy alone achieves 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%. However, these response rates are observed nearly exclusively for lung and lymph node metastases (15).

Pain due to soft tissue metastases probably behaves in a manner analogous to the tumour response, but there are no data concerning pain control utilising immunotherapy.

Hormonal therapy has no proven benefit concerning survival or pain relief.

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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 quantities 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 ^{131}J-MIBG (^{131}J-metaiodobenzylguanidine) scan is positive in approximately 87% of cases (3).

In cases of metastases, chemotherapy with cyclophosphamide, vincristine and dacarbazine has little effect (4) (level of evidence: 2b), but therapeutic doses of ^{131}J-MIBG (33 GBq = 900 mCi) may produce some results (5, 6) (level of evidence: 2b). The hormone response rate is described as 50%. There is no special literature concerning pain relief with ^{131}J-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 radio-resistant, although there are some cases in which radiation therapy induced partial remission (7) (level of evidence: 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*

The main points to note are as follows.

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

4.4.2.1 *Adrenocortical carcinomas*

Carcinomas of the adrenal cortex are highly malignant, with both local and haematogenous metastasis. Five-year survival rates are 25-43% in patients treated by all modalities. Patients with distant metastases have a mean survival of only 4 months (9). An autopsy study showed metastases to lung (60%), liver (50%), lymph nodes (48%), bone (24%) and pleura/heart (10%) (10). In addition, these tumours often extend directly into adjacent structures, especially the kidney.

Chemotherapy is of low efficacy. The most effective drug is mitotane, an adrenolytic drug. The tumour response rate is 25-35% (9, 11) (level of evidence: 2a). It remains to be proven whether chemotherapy prolongs survival.

Radiation therapy has not been useful except for palliation and pain management (12) (level of evidence: 2b).

4.4.2.2 *Treatment of the pain depending on its origin*

The main points to note are as follows.

- Abdominal symptoms are typical symptoms when first presenting with 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 the local lymph nodes.
- Soft tissue and/or bone metastases causing local symptoms can be treated by radiation therapy (8, 12). There is no literature concerning chemotherapy or radiotherapy as tools for pain relief in metastatic adrenocortical carcinomas.
- Treat the pain symptomatically with drugs etc. following the recommendations given in Section 3.4.

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4.5. Pain management in penile cancer patients

4.5.1 Clinical presentation

In Europe, penile cancer is a relatively rare disease; the incidence is less than 2/100,000 men per year, accounting for less than 1% of all cancers in men. It is a disease of older men, with an increase in incidence around age 60 years, peaking around the age of 80 years. The penile lesion itself usually alerts the patient to the presence of a penile cancer, which in most cases occurs on the glans (48%) and prepuce (21%). Patients with cancer of the penis seem to delay seeking medical attention (embarrassment, guilt, fear, ignorance and neglect). This level of denial is substantial, given that the penis is observed and handled every day. Pain does not develop in proportion to the extent of the local tumour, and is not usually a presenting complaint (1).

To date there has been no consensus on the therapeutic management of metastatic disease, and there are few controlled studies of statistical significance that look at both penile carcinoma and cancer-related pain. Most of the principles for dealing with pain management in prostatic carcinoma are also valid here, but the following aspects should also be taken into consideration.

Pain can occur in both the early and advanced stages of penile cancer. In the early stages, acute pain could be the result of a voiding dysfunction (subvesical obstruction). Chapter 4 gives details about the management of bladder outlet obstruction in prostate cancer.

In advanced stages of the disease, pain is usually caused by metastases or lymph node involvement. Inguinal lymph node involvement plays an important role. Positive lymph nodes are relatively common in penile cancer, with inguinal or pelvic lymph nodes being the most frequently affected. Positive nodes may be present in over 50% of cases, and systematic lymphadenectomy is curative in about 50% of these patients.

Among all the possible complications after inguinal and ilioinguinal lymphadenectomy, permanent and disabling lymphoedema of the scrotum and lower limbs is frequent.

Pain can result from:
- local pressure from the tumour mass or infiltration of hollow viscus organs
- lymphoedema of the scrotum and lower limbs.

4.5.2 Pain due to local impairment

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 left with scarred inguinal tissue after lymph node dissection, very often show lymphoedema of the lower limbs. This is more frequent in cases of involvement of both inguinal and iliac nodes. The treatment of lymphoedema comprises physiatric techniques (use of wraps, pressure stockings or pneumatic pump devices), which can both improve function, and relieve pain and heaviness. The use of orthotic devices can immobilise and support painful or weakened structures, and assistive devices can be of great value to patients with pain precipitated by weight-bearing or ambulation.

4.5.4 Pain due to metastases

Anti-cancer management for pain relief

The first phase of pain management entails anti-tumour treatment: usually surgery (partial or total penectomy or emasculation and lymphadenectomy), radiotherapy (not as effective, but for palliation), and chemotherapy. If this is unsuccessful or not feasible, the second phase requires systemic analgesic pharmacotherapy (WHO ladder). Experience with combined therapeutic management using chemotherapy plus surgery or radiotherapy is very limited due to the relative rarity of penile carcinomas (1) (see also guidelines for penile cancer).

4.5.5 Conclusions

Currently no conclusive or universally applicable recommendations can be given on managing pain related to the treatment of metastatic penile carcinoma. To date, treatment has been experimental in nature; findings from other cancer treatment regimes must be adapted for want of a better-documented strategy. As is the case elsewhere, attention is paid to the guidelines that are appropriate for treating metastases and the involved organs (See also EAU guidelines on Penile Cancer).

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4.6 Pain management in testicular cancer patients

4.6.1 Clinical presentation

Testicular cancer generally affects younger 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 of flank pain when first presenting (1). Points to note are:
- primary advanced tumour with pain due to bone metastases is very rare, maximally no more than 3% at first presentation
- 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 the scrotal mass.

4.6.3 Pain due to metastases

The main points to note are as follows.
- Back or flank pain due to retroperitoneal lymphadenopathy will slowly disappear under chemotherapy as the mass decreases (level of evidence: 2b) (see guidelines for testicular cancer). Temporary analgesics are advisable (see Section 3.4.5 of these guidelines).
- 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 mainly occurs in patients with primary advanced disease and relapse after chemotherapy (2, 3). Treatment may be possible by chemotherapy or second line chemotherapy (see guidelines for testicular cancer). There is no literature considering

radiotherapy in cases of relapse and limitation for further chemotherapy.

- Back pain and neurological symptoms due to spinal cord compression by vertebral metastases may require urgent surgery (4) (level of evidence: 3).

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4.7. Recommendations at a glance

Table 7 shows the efficacy of the therapeutic options in pain relief (expert opinion).

Table 7: 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. POST-OPERATIVE PAIN MANAGEMENT

5.1 Background

Post-operative pain is defined as an expected, inevitable symptom in a surgical patient associated with surgical tissue damage, the presence of drains and tubes, post-operative complications or a combination of the above (1, 2).

Post-operative pain is usually underestimated and undertreated (1, 3). Approximately 70% of surgical patients experience a certain degree (moderate, severe or extreme) of post-operative pain (3, 4) (level of evidence: 1a).

The results of post-operative pain undertreatment include increased morbidity and mortality, mostly due to respiratory and thromboembolic complications, increased hospital stay, impaired quality of life, and development of chronic pain (1, 3, 5-7) (level of evidence: 1a).

The aim of the post-operative pain guidelines is to establish safer and more effective pain management, to introduce proper assessment of pain and planning of pain control techniques, and to promote training of medical and nursing staff in this area (1, 3).

5.2 The importance of effective post-operative pain management

The physiological consequences of post-operative pain are shown in Table 8, all of which could delay or impair post-operative recovery and increase the economic cost of surgery as a result of the longer period of hospitalisation (13, 14) (level of evidence: 3). Inadequate post-operative pain control may also lead to the development of chronic pain after surgery (15, 16) (level of evidence: 2b).

Table 8: Physiological consequences of post-operative 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, which may lead to: - myocardial ischaemia - angina - infarction • These are the most common cardiovascular complications after urological surgery	10	2b
Thromboembolic complications	• Reduced mobility due to inadequate pain management can lead to thromboembolic episodes	11	2a
Gastrointestinal complications	• Gastric stasis • Paralytic ileus • These occur often, mostly after open urological operations	12	2b
Musculoskeletal complications	• Prolonged confinement to bed due to inadequate pain management leads to: - reduced mobility - muscle atrophy	13	3

Psychological complications	• Peri-operative pain may provoke fear and anxiety, which can lead to: - anger - resentment - hostility to medical and nursing personnel • These symptoms are often accompanied by insomnia	13, 14	3

LE = level of evidence

5.2.1 The aims of effective post-operative pain management

The aims of effective post-operative pain management are:

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

Recommendation	GR
• Post-operative pain should be treated adequately, to avoid post-operative complications and the development of chronic pain	B

GR = grade of recommendation

5.3 Pre- and post-operative pain management methods

5.3.1 Pre-operative patient preparation:

- patient evaluation
- adjustment or continuation of medication in order to avoid abstinence syndrome
- pre-medication as part of multi-modal analgesia
- behavioural-cognitive interventions for the patient and family with the aim of alleviating anxiety and fear of post-operative pain. This in turn leads to a reduction in the amount of analgesia required post-operatively and better and more efficient pain management (1) (level of evidence: 1a).

During this phase, patients should be informed about the different options and methods of post-operative analgesia and their benefits and adverse effects. This will enable them to make an informed decision together with their clinicians (1).

Recommendation	GR
• Pre-operative assessment and preparation of the patient allow more effective pain management	A

GR = grade of recommendation

5.3.2 Pain assessment

Careful pain assessment by the surgeon or the acute pain team can lead to more efficient pain control, adequate doses of the correct drugs, and diminished morbidity and mortality (1, 4) (level of evidence: 2a). Pain should be assessed before and after treatment.

In the post-anaesthesia care unit (PACU), pain should be evaluated, treated and re-evaluated initially every 15 minutes and then every 1-2 hours. After discharge from the PACU to the surgical ward, pain should be assessed every 4-8 hours before and after treatment (17, 18).

Various rating scales have been described to measure post-operative pain, but their major disadvantage is that they are all subjective, making their results difficult to evaluate, especially in patients with communication difficulties (18). Table 9 gives examples of such scales.

Table 9: Post-operative pain rating scales*

Type of scale	Description
• Verbal rating scale (VRS)	This is a five-point scale that describes pain as absent, mild, moderate, severe, very severe
• Visual analogue scale (VAS)	This is a straight line, 100 mm in length, with one end representing absence of pain and the other the most severe pain. The patient marks the line at the point that reflects the level of pain being experienced

• Numerical rating scale (NRS)	Pain is rated numerically from 0 (absence of pain) to 10 (severe pain)
• Facial expression	This is a scale of six faces showing expressions ranging from smiling to tearful. It is usually used with children or patients who have difficulty with communication
• Complex pain assessment indices	An example is the McGill Pain Questionnaire. This consists of 20 groups of words to describe the pain, from which the patient selects following a specific protocol

** From Jensen et al. (1992) (17) and Herr et al. (2002) (18).*

Recommendation	GR
• Adequate post-operative pain assessment can lead to more effective pain control and fewer post-operative complications	B

GR = grade of recommendation

5.3.3 Pre-emptive analgesia

Pre-emptive or preventive analgesia is defined as the administration of analgesia before surgical incision to prevent establishment of central sensitisation from incision or inflammatory injury in order to achieve optimal post-operative pain control (19). A variety of pharmacological agents and techniques have been used for this purpose. The results of clinical trials on the efficacy of pre-emptive analgesia are controversial (19, 20) (level of evidence: 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 produce analgesia without respiratory depression or sedation, and they seem to decrease the need for opioids (21). However, their analgesic effect is not sufficiently strong for the management of severe post-operative pain (22). Table 10 gives dosage and administration details for NSAIDs.

Table 10: NSAIDS: drugs, dosage and administration

Drug	Dosage per day	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

NSAID = non-steroidal anti-inflammatory drug; iv = intravenous.

Intravenous 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 post-operative pain control is generally avoided because of the variability of serum drug concentrations and the pain caused by the injection (23).

Adverse effects

The main adverse effects are (22):

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

COX-2 selective inhibitors are associated with fewer gastrointestinal complications and better bone healing and 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, such as myocardial infarction, angina pectoris, hypertension and atherosclerosis. This is because rofecoxib (which has already been withdrawn) caused a significant increase in thromboembolic events compared with placebo (25). The use of COX-2 inhibitors is approved for short-term post-operative pain therapy.

Recommendations	GR
• NSAIDs are not sufficient as the sole analgesic agent after major surgery	B
• 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

GR = grade of recommendation

5.3.4.2 Paracetamol

Paracetamol (acetaminophen) is a relatively safe and effective antipyretic and analgesic for mild to moderate post-operative pain. In cases of severe post-operative pain, the co-administration of paracetamol with strong opioids seems to reduce the consumption of opioids (26) (level of evidence: 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
- Intravenous 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 post-operative pain. Caution should be used when administering it to patients with chronic alcoholism or hepatic failure. A dose > 6 g/24 h can cause acute renal failure.

Combinations of paracetamol with opioids

Paracetamol in combination with an opioid (Table 11) provides adequate post-operative analgesia for mild to moderate pain without the adverse effects of strong opioids. The paracetamol/opioid combinations are given four times daily.

Table 11: Dosage and administration of paracetamol/opioid combinations

Paracetamol	Opioid	Times per day	Route of administration
• Paracetamol 1 g	Codeine 60 mg	x 4	Orally or rectally
• Paracetamol 600-650 mg	Codeine 60 mg	x 4	Orally or rectally
• Paracetamol 500 mg	Codeine 30 mg	x 4	Orally or rectally
• Paracetamol 300 mg	Codeine 30 mg	x 4	Orally or rectally
• Paracetamol 650 mg	Dextropropoxyphene 65 mg	x 4	Orally
• Paracetamol 600-650 mg	Tramadol 75-100 mg	x 4	Orally
• Paracetamol 325 mg	Oxycodone 5 mg	x 4	Orally

Recommendations	GR
• Paracetamol can be very useful for post-operative pain management as it reduces the consumption of opioids	B
• Paracetamol can alleviate mild post-operative pain as a single therapy without major adverse effects	B

GR = grade of recommendation

5.3.4.3 Metamizole (dipyrone)

Metamizole is an effective antipyretic and analgesic drug used for mild to moderate post-operative pain and renal colic. Its use is prohibited in the USA and some European countries because of single reported cases of neutropenia and agranulocytosis. In other countries, it is considered to be a useful analgesic and antipyretic drug for use in moderate pain. Even though data are controversial, long-term use of metamizole is best avoided (28, 29) (level of evidence: 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, light hypotension and allergic reactions. Allergic reactions and the rare complication of agranulocytosis have been described only after direct iv administration, and so iv metamizole should therefore 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 post-operative pain (Table 12). The key principle for their safe and effective use is to titrate the dose against pain relief and to minimise unwanted effects (30).

Table 12: Opioids: drugs, dosage and administration

Drug	Dosage per day	Route of administration
Strong opioids		
• Morphine*	5-10 mg six to eight times	Orally
• Morphine*	10-15 mg six to 12 times	sc or im
• Pethidine (meperidine)	50-100 mg six to eight times	iv, sc or im
• Oxycodone	5-10 mg four to six times	orally, iv or sc
Weak opioids		
• Tramadol	50-100 mg four to six times	orally, iv or im
• Codeine	30-60 mg (combined with paracetamol) four times	orally or rectally

**A simple way of calculating the daily dosage of morphine for adults (20-75 years) is: 100 – patient's age = morphine per day in mg.*
sc = subcutaneous; im = intramuscularly; iv = intravenously.

Routes of administration
Opioids can be administered orally, intravenously, subcutaneously, transdermally, epidurally, intrathecally and intramuscularly. However, intramuscular administration is less common because of erratic absorption and the unnecessary pain of injection (2).

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 patient-controlled analgesia (PCA) (31, 32) (level of evidence: 1a). Typical PCA dosing schedules are shown in Table 13.

Table 13: 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 PCA provides superior post-operative analgesia, improving patient satisfaction and decreasing the risk of respiratory complications	A

GR = grade of recommendation

5.3.4.6 Fentanyl
Fentanyl has been administered transdermally for post-operative pain management, but its use by this route has been limited by the difficulty of titrating the drug levels (33). The fentanyl HCl iontophoretic transdermal system (fentanyl ITS) is a needle-free patient-controlled system that releases a pre-programmed dose of fentanyl on demand. It is very effective in the management of severe post-operative pain (34) (level of evidence: 1a).

Adverse effects
The main adverse effects are:

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

5.3.4.7 Opioid equi-analgesic doses
The commonest parenteral and oral equi-analgesic doses of opioids are shown in Table 14.

Table 14: Common equi-analgesic dosages 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 1/100th, and the epidural dose 1/10th, of the dose required systemically.*

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. Ropivacaine has the longest duration of action.

5.3.5.2 Epidural analgesia
Epidural analgesia provides excellent post-operative pain relief for extended periods after major surgical operations, reducing post-operative complications and the consumption of opioids (1, 2) (level of evidence: 1a). Typical epidural dosing schemes are shown in Table 15.

Table 15: 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)
Patient-controlled epidural analgesia has become very common because it allows individualisation of analgesic requirements, a decrease in the use of drugs, greater patient satisfaction and superior analgesia. In addition, PCEA seems to provide better analgesia compared with intravenous PCA (35, 36) (level of evidence: 1a). Typical PCEA dosing schemes are shown in Table 16.

Table 16: 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. It is therefore preferable to systemic techniques (2)	A

GR = grade of recommendation

5.3.5.4 Neural blocks

Local anaesthetic blocks (intermittent and continuous) can be used after urological surgical operations to supplement post-operative analgesia (37) (level of evidence: 2a). Examples of such blocks are shown in Table 17. Note that lidocaine is not usually used because of its short duration of action.

Table 17: 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

Intra-operative wound infiltration with local anaesthetic (usually 10-20 mL of ropivacaine or bupivacaine 0.25-0.5%) can provide some post-operative analgesia and may reduce the requirement for systematic analgesia (38) (level of evidence: 2b).

5.3.5.6 Continuous wound instillation

Continuous post-operative wound instillation of a local anaesthetic via a multi-hole catheter placed intra-operatively by the surgeon has been proven to provide satisfactory analgesia for moderate to severe post-operative pain, reducing the consumption of systemic analgesics (39-41) (level of evidence: 2b).

5.3.6 Multi-modal analgesia

The concept of multi-modal ('balanced') analgesia is that effective post-operative pain control depends on the use of several different analgesics and routes of administration, which then act in synergy. The combined use of different classes of analgesics and analgesic techniques improves the effectiveness of pain relief after surgery and reduces the maximal dosage and adverse effects (42) (level of evidence: 2b).

Multi-modal analgesia seems to be more effective when different drugs are administered via different routes than when different drugs are administered via a single route (1) (level of evidence: 2b).

Recommendation	GR
• Multi-modal pain management should be employed whenever possible since it helps to increase efficacy while minimising adverse effects	B

GR = grade of recommendation

5.3.7 Special populations

5.3.7.1 Ambulatory surgical patients

The main aim of analgesia in these patients is to achieve adequate pain relief so that patients can be discharged from hospital. It also avoids the use of opioids, the side-effects of which can prolong hospital stay (43,44) (level of evidence: 2a).

A multi-modal analgesic plan uses a combination of NSAIDs or paracetamol plus local anaesthetics used as peripheral nerve blocks, tissue infiltration, or wound instillation. In this way, ambulatory patients can be given pain relief that does not use opioids (45) (level of evidence: 2b).

Recommendations	GR
• For post-operative pain control in out-patients, multi-modal analgesia with a combination of NSAIDs or paracetamol plus local anaesthetics should be used	B
• If possible, avoid opioids	B

GR = grade of recommendation

5.3.7.2 Geriatric patients

The perception of pain appears to be reduced in geriatric patients, and the requirement for analgesia generally decreases with increasing age (46, 47). Geriatric patients can also suffer from emotional and cognitive impairments, such as depression and dementia, which could affect adequate pain management (48).

Post-operative delirium in the elderly is a fairly common complication and is often multi-factorial. It may be associated with the administration of pethidine (49).

Multi-modal post-operative analgesia may be the pain management technique of choice in elderly patients, as the dosages of medication required are lower. However, it is important to be vigilant for adverse reactions, as they tend to increase in number in the geriatric population (50) (level of evidence: 2b).

Epidural analgesia might diminish the risk of post-operative delirium and respiratory complications in elderly patients (51) (level of evidence: 2b).

Recommendation	GR
• Multi-modal and epidural analgesia are preferable for post-operative pain management in elderly patients because these techniques are associated with fewer complications	B

GR = grade of recommendation

5.3.7.3 Obese patients

Obese patients appear to be at higher risk for certain post-operative complications, including respiratory (hypoxia, atelectasis, arrest), cardiovascular (ischaemia, arrhythmias, infarction), thromboembolic episodes, and wound infections (52, 53). Because the administration of opioids to obese patients is associated with sudden respiratory arrest, a combination of NSAIDs or paracetamol with a local anaesthetic epidural might be the safest analgesic solution (54, 55) (level of evidence: 2b).

If absolutely necessary, opioids should be used with caution and under careful titration to avoid depression of the respiratory drive (55). Oxygen therapy should also be applied post-operatively to increase oxygen saturation (56).

Recommendations	GR
• The post-operative use of opioids should be avoided in obese patients unless absolutely necessary	B
• An epidural of local anaesthetic in combination with NSAIDs or paracetamol is preferable	B

GR = grade of recommendation

5.3.7.4 Other groups

Critically ill or cognitively impaired patients present special difficulties in pain management. Regional or multi-modal analgesia might be more effective in such patients because drug dosages are reduced and behavioural interventions and patient-controlled methods are unsuitable (1) (level of evidence: 3).

Recommendation	GR
• There are no sufficient data to support a specific post-operative pain management plan for critically ill or cognitively impaired patients	C

GR = grade of recommendation

5.3.8 Post-operative pain management teams

The importance of efficient post-operative pain management has led to the development of acute post-operative pain management teams. These are multi-disciplinary teams, which generally consist of nursing and pharmacy personnel led by an anaesthesiologist. Their aims are post-operative pain assessment and treatment using various methods, including PCAs or PCEAs, and education of medical and nursing staff. Such services have been shown to improve pain relief, decrease analgesic medication-related side-effects (e.g. nausea, vomiting, pruritus, sedation and respiratory depression), improve patient satisfaction, and decrease overall costs and morbidity rates (57-9) (level of evidence: 2b). In addition, improved pain control can lead to a shorter period of hospitalisation and fewer unscheduled re-admissions after day-case surgery (60) (level of evidence: 3).

However, these teams do not exist in every country. In some countries, surgeons manage mild to moderate post-operative pain, and anaesthesiologists are involved in epidurals or PCAs.

5.4 Specific pain treatment after different urological operations

5.4.1 Extracorporeal shock wave lithotripsy (ESWL)

This is a minimally invasive treatment, during and after which between 33% and 59% of patients do not need any analgesia (61, 62, 63) (evidence level 2b). In those patients who do need pain relief, post-treatment pain is unlikely to be severe and oral analgesics are usually sufficient.

Analgesic plan

- Pre-operative assessment: see section 5.3.2.
- Intra-operatively: the most experience exists for alfentanil (0.5-1.0 mg/70 kg iv), given on demand during ESWL, either by the urologist or the anaesthesiologist. Non-steroidal anti-inflammatory drugs (NSAIDs) or midazolam as pre-medication 30-45 min before treatment reduces the need for opioids during the procedure (evidence level 2b). With a pre-medication of diclofenac (100 mg rectally), only 18% of patients needed pethidine during the lithotripsy (64). After a pre-medication with midazolam (5 mg orally), 70% of patients were completely free of pain during the treatment, and if buprenorphine was added this proportion rose to 87% (65). After pre-medication with midazolam (2 mg iv, 5 min before the treatment), diclofenac or tramadol proved to be safe and effective analgesics with fewer side-effects than fentanyl (66) (evidence level 1b). Other effective regimes for intra-operative pain treatment are fentanyl (1 µg/kg iv [67]) or sufentanil or remifentanil. These drugs are usually given by the anaesthesiologist because of the risk of respiratory depression. The incidence of respiratory depression after the procedure was significantly lower (20% vs 53%) if remifentanil was used instead of sufentanil (68, 69) (evidence level 1b). There is not enough evidence to prove an advantage for any of the combinations used.
- Post-operative: most patients will be able to tolerate oral analgesics following this procedure. NSAIDs, metamizole, paracetamol, codeine and paracetamol combination preparations or tramadol could all be used. These drugs could be prescribed on an ‘as needed’ or a time-contingent basis. If pain is more severe or persistent, patients usually need to be examined to exclude hydronephrosis or haematoma of the kidney.

Table 18 gives drug options for after ESWL.

Table 18: Analgesic drug options after ESWL

Drug	Dosage (mg)	Method of administration	Frequency (max.)
Diclofenac	50	Orally	Three times daily
	100	Rectally	Every 16 h
Metamizole	500-1000	Orally	Four times daily
Paracetamol	500-1000	Orally	Four times daily
Tramadol	50-100	Orally	Four times daily

The majority of patients for this procedure will be outpatients who have come in just for the day. Upon discharge, they should be provided with a prescription for analgesics and a contingency plan in case the pain worsens. This will reduce the incidence of unplanned hospital readmissions.

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

GR = grade of recommendation

5.4.2 Endoscopic procedures

5.4.2.1 Transurethral procedures

The main procedures include:

- transurethral resection of bladder tumour (TURB)
- transurethral resection of bladder neck
- transurethral incision of prostate
- transurethral resection of prostate (TURP)
- retrograde ureteroscopy (diagnostic and/or for stone treatment).

These operations are usually performed under spinal anaesthesia (epidural or subarachnoid block) with the patient awake or mildly sedated. These regional anaesthetic techniques will usually provide post-operative analgesia for 4-6 h following surgery.

Much of the post-operative pain is generally caused by the indwelling catheter or the double-J (ureteral stent following ureterorenoscopy), which mimics overactive bladder syndrome. For this reason, drugs with an antimuscarinic effect have been proven to be useful in addition to the opioids (70) (evidence level 1b).

For post-operative pain control, oral or iv analgesia is preferable.

Analgesic plan

- Pre-operative assessment: see section 5.3.2.
- Intra-operative: spinal (intrathecal or epidural) anaesthesia will provide intra-operative analgesia and last for 4-6 h post-operatively.
- Post-operative: after 4-6 h, mild oral analgesics such as NSAIDs or paracetamol +/- codeine, or stronger opioids, also orally, could be used. In the case of bladder discomfort (overactive bladder syndrome) resulting from the indwelling catheter, metamizole (orally or iv), pethidine (iv) or piritramid (iv) would also be effective. In addition, antimuscarinic drugs such as oxybutynin (5 mg orally three times daily) are useful and reduce the need for opioids (70) (evidence level 1b).

Table 19 lists the analgesic drug options after transurethral procedures.

Table 19: Analgesic drug options after transurethral procedures

Drug	Dosage (mg)	Method of administration	Frequency (max.)
Diclofenac	50	Orally	Three times daily
	100	Rectally	Every 16 h
Metamizole	500-1000	Orally or iv	Four times daily
Paracetamol	500-1000	Orally or iv	Four times daily
Tramadol	50-100	Orally, im, sc or iv	Four times daily
Piritramid	15	iv or sc	Four times daily
Pethidine	25-100	Orally, im, sc or iv	Four to six times daily
Morphine	10	im	Eight times daily

Recommendations	GR
• Postoperative analgesics with a 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

GR = grade of recommendation

5.4.2.2 Percutaneous endoscopic procedures

These include:

- percutaneous nephrolithotomy
- percutaneous endopyelotomy
- percutaneous resection of pyelocaliceal tumours
- antegrade ureteroscopy.

The analgesic plan is the same as that for transurethral procedures, but with the additional complexity caused by the skin having been breached, which could mean that additional analgesia is required. Local anaesthetic could be infiltrated locally into the skin, e.g. 10 mL of 0.5% bupivacaine.

General anaesthesia is usually 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 include:

- laparoscopic lymph node dissection
- diagnostic laparoscopy
- laparoscopic removal of organ or tumour.

These procedures are usually performed under general anaesthesia, and so patients cannot take oral medication for at least 4-6 h post-operatively. It is therefore necessary to use iv analgesia (or im or sc as second choice options) during this period.

After this time, analgesia can be given orally or systemically, depending on bowel motility.

Most data concerning post-operative pain exist for laparoscopic cholecystectomy. A particular consideration after this procedure is the development of pain in the shoulder as a result of diaphragmatic irritation following the pneumoperitoneum. This problem seems to be dependent on the intra-abdominal pressure used during the procedure, as reduced carbon dioxide insufflation reduces post-operative shoulder pain (71, 72, 73) (level of evidence 1b).

Analgesic plan

- Pre-operative assessment: see section 5.3.2.
- Intra-operative: iv opioids +/- NSAIDs or metamizole administered by the anaesthesiologist. The infiltration of local anaesthetic into the port incisions reduces pain after laparoscopy (74).
- Post-operative: the administration of a systemic opioid iv (im or sc), either 'as needed' or on a time-contingent basis, is very effective in the immediate post-operative period, but the prophylactic use of opioids after laparoscopic procedures is not recommended in order to hasten recover. NSAIDs (e.g. paracetamol and/or metamizole) and incisional local anaesthetics (multimodal concept) can be given to reduce the need for opioids (74, 75).

Table 20 lists the drug options after laparoscopic surgery.

Table 20: Analgesic drug options after laparoscopic surgery

Drug	Dosage (mg)	Method of administration	Frequency (max.)
Metamizole	500-1000	Orally or iv	Four times daily
Paracetamol	500-1000	Orally or iv	Four times daily
Tramadol	50-100	Orally, im, sc or iv	Four times daily
Piritramid	15	iv or sc	Four times daily
Morphine	10	Intermittent im	Eight times daily
	1 mg bolus	iv	PCA, 5 min lockout
Diclofenac	50	Orally	Three times daily
	100	Rectally	Every 16 h

PCA = patient-controlled analgesia

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

GR = grade of recommendation

5.4.3 Open surgery

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

These two types of surgical operations are relatively minor and nearly all patients will be able to take oral analgesia following the operation. The operation is often performed as an ambulatory procedure under local anaesthesia or with the aid of an ilioinguinal or iliohypogastric nerve block.

The analgesic options after surgery are outlined in Table 21.

Table 21: Analgesic drug options after minor surgery of the scrotum, penis, and inguinal region

Drug	Dosage (mg)	Method of administration	Frequency (max.)
Diclofenac	50	Orally	Three times daily
	100	Rectally	Every 16 h
Paracetamol	1000	Orally	Four times daily
Metamizole	500-1000	Orally	Four times daily
Tramadol	50-100	Orally	Four times daily

Recommendations	GR
• For post-operative 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

GR = grade of recommendation

5.4.3.2 Transvaginal surgery

These procedures would include:

- pelvic floor surgery
- stress incontinence surgery.

Local or regional anaesthesia can be used for these operations.

After surgery, the analgesic options listed in Table 22 are possible.

Table 22: Analgesic drug options after transvaginal urological surgery

Drug	Dosage (mg)	Method of administration	Frequency (max.)
Diclofenac	50	Orally	Three times daily
	100	Rectally	Every 16 h
Paracetamol	1000	Orally	Four times daily
Metamizole	500-1000	Orally or iv	Four times daily
Tramadol	50-100	Orally	Four times daily
Piritramid	15	iv or sc	Four times daily
Pethidine	25-100	Orally, im, sc or iv	Four to six times daily
Morphine	10	im	Eight times daily

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

GR = grade of recommendation

5.4.3.3 Perineal open surgery

These procedures include:

- perineal radical prostatectomy (PRPE)
- posterior urethroplasty.

Analgesic plan

- Pre-operative assessment: see section 5.3.2.
- Intra-operative: general anaesthesia is usually used, particularly for PRPE, because of the uncomfortable exaggerated lithotomy position on the operating table. Sometimes an intrathecal catheter (epidural) can be sited for intra-operative and post-operative pain control.
- Post-operative: continuous epidural infusion of a combination of opioids and local anaesthetic or PCA is usually used. When systemic opioids are used, it is advisable to use them in combination with

NSAIDs so as to reduce their dose and consequently their side-effects. When the patient is able to take oral analgesics, usually after 1-3 days, oral metamizole or paracetamol +/- codeine could be used. There are no data in the literature to recommend specific post-operative pain management or to show which is superior.

The analgesic options that are possible after surgery are shown in Table 23.

Table 23: Analgesic options after major perineal open surgery

Drug	Dosage	Method of administration	Frequency (max.)
Bupivacaine 0.25% + fentanyl 2 μg/mL	5-15 mL/h	Continuous epidural infusion	n.a.
Morphine	1 mg bolus	iv	PCA, 5 min lockout
Metamizole	500-1000 mg	Orally or iv	Four times daily
Paracetamol	500-1000 mg	Orally or iv	Four times daily
Tramadol	50-100 mg	Orally, im, sc or iv	Four times daily
Piritramid	15 mg	iv or sc	Four times daily
Diclofenac	50 mg	Orally	Three times daily
	100 mg	Rectally	Every 16 h

PCA = patient-controlled analgesia.

5.4.3.4 Transperitoneal laparotomy

These include:

- retroperitoneal lymph node dissection (RLND)
- radical nephrectomy -/+ caval thrombectomy
- cystectomy + urinary diversion.

Post-operatively, patients are usually managed in an intermediate or intensive care unit. A combined general anaesthetic and regional technique is usually used.

Analgesic plan

- Pre-operative assessment: see section 5.3.2.
- Intra-operative: general anaesthetic and regional technique; sometimes an intrapleural catheter can be sited.
- Post-operative: continuous epidural infusion of a combination of opioids and local anaesthetic. Once the patient is able to take oral analgesics (dependent on bowel motility), which is usually 3-4 days after surgery, metamizole, paracetamol +/- codeine or tramadol could 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 (76).

Table 24 lists the analgesic options after the transperitoneal approach.

Table 24: Analgesic options after transperitoneal laparotomy

Drug	Dosage	Method of administration	Frequency (max.)
Bupivacaine 0.25% + fentanyl 2 μg/mL	5-15 mL/h	Continuous epidural infusion	n.a.
Morphine	1 mg bolus	iv	PCA, 5 min lockout
Metamizole	500-1000 mg	Orally or iv	Four times daily
Paracetamol	500-1000 mg	Orally or iv	Four times daily
Tramadol	50-100 mg	Orally, im, sc or iv	Four times daily
Piritramid	15 mg	iv or sc	Four times daily
Diclofenac	50 mg	Orally	Three times daily
	100 mg	Rectally	Every 16 h

PCA = patient-controlled analgesia.

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 patient-controlled epidural analgesia (PCEA), provides superior post-operative analgesia, reducing complications and improving patient satisfaction. It is therefore preferable to systemic techniques (see sections 5.3.5.2 and 5.3.5.3).	A

GR = grade of recommendation

5.4.3.5 Suprapubic/retropubic extraperitoneal laparotomy

These procedures include:

- open prostatectomy
- radical retropubic prostatectomy.

Post-operatively, patients are usually managed in an intermediate or intensive care unit. A combined general anaesthetic and regional technique is usually used. It will be possible to use the oral route for analgesia sooner than after a transperitoneal procedure. Oral opioids, metamizole and/or paracetamol +/- NSAIDs could be used.

Analgesic plan

- Pre-operative assessment: see section 5.3.2.
- Intra-operative: general anaesthetic and regional technique.
- Post-operative: continuous epidural infusion of a combination of opioids and local anaesthetic. Once the patient is able to take oral analgesics, usually 1-3 days after surgery, metamizole, paracetamol +/- codeine, +/- NSAIDs could be used.

Table 25 lists the post-operative analgesic options.

Table 25: Analgesic options after suprapubic/retropubic extraperitoneal laparotomy

Drug	Dosage	Method of administration	Frequency (max.)
Bupivacaine 0.25% + fentanyl 2 µg/mL	5-15 mL/h	Continuous epidural infusion	n.a.
Morphine	1 mg bolus	iv	PCA, 5 min lockout
Metamizole	500-1000 mg	Orally or iv	Four times daily
Paracetamol	500-1000 mg	Orally or iv	Four times daily
Tramadol	50-100 mg	Orally, im, sc or iv	Four times daily
Piritramid	15 mg	iv or sc	Four times daily
Diclofenac	50 mg	Orally	Three times daily
	100 mg	Rectally	Every 16 h

PCA = patient-controlled analgesia.

5.4.3.6 Retroperitoneal approach – flank incision – thoracoabdominal approach

These procedures include:

- nephrectomy
- pyeloplasty
- pyelonephrolithotomy.

Post-operatively, patients are usually managed in an intermediate or intensive care unit. A combined general anaesthetic and regional technique is usually used.

Analgesic plan

- Pre-operative assessment: see section 5.3.2.
- Intra-operative: general anaesthetic and regional technique; sometimes an intrapleural catheter can be sited.
- Post-operative: continuous epidural infusion of a combination of opioids and local anaesthetic. Several meta-analyses have shown significantly better pain control with this technique compared with iv analgesics (77, 78). If epidural analgesia is not possible or is refused by the patient, PCA should be provided. Once the patient is able to take oral analgesics, usually 1-3 days after surgery (depending on bowel motility), paracetamol +/- codeine or metamizole could be used in addition (to reduce the need for opioids) or alone.

Table 26 lists the analgesic options.

Table 26: Analgesic options after retroperitoneal approach – flank incision

Drug	Dosage	Method of administration	Frequency (max.)
Bupivacaine 0.25% + fentanyl 2 μg/mL	5-15 mL/h	Continuous epidural infusion	n.a.
Morphine	1 mg bolus	iv	PCA, 5 min lockout
Metamizole	500-1000 mg	Orally or iv	Four times daily
Paracetamol	500-1000 mg	Orally or iv	Four times daily
Tramadol	50-100 mg	Orally, im, sc or iv	Four times daily
Piritramid	15 mg	iv or sc	Four times daily
Diclofenac	50 mg	Orally	Three times daily
	100 mg	Rectally	Every 16 h

PCA, patient-controlled analgesia.

Recommendation	GR
• Epidural analgesia, especially PCEA, provides superior post-operative analgesia, reducing complications and improving patient satisfaction. It is therefore preferable to systemic techniques (see sections 5.3.5.2 and 5.3.5.3).	A

GR = grade of recommendation

5.5 Dosage and method of delivery of some important analgesics

5.5.1 NSAIDs

Table 27 gives details of the most important drugs in this category.

Table 27: Dosage and delivery of NSAIDs

Drug	Method of administration	Single dosage (mg)	Maximal dosage (mg) per 24 h
Diclofenac	Orally	50-75	150
	Rectally	100	150
Ibuprofen	Orally	200-800	2400

5.5.2 NSAIDs with antipyretic effect

Table 28 gives details of the most important drugs in this category.

Table 28: Dosage and delivery of antipyretics

Drug	Method of administration	Single dosage (mg)	Maximal dosage (mg/24 h)
Paracetamol	Orally	500-1000	4000 (50 mg/kg)
	iv	1000	4000 (50 mg/kg)
Metamizole	Orally	500-1000	4000
	iv	1000-2500	5000

5.5.3 Selective COX-2 inhibitor

Table 29 gives details of the most important drugs in this category.

Table 29: Dosage and delivery of selective COX-2 inhibitors

Drug	Method of administration	Single dosage (mg)	Maximal dosage (mg/24 h)
Celecoxib	Orally	100-200	400

5.5.4. Opioids

Table 30 gives details of the most important drugs in this category.

Table 30: Dosage and delivery of opioids

Drug	Method of administration	Common single dosage (mg)	Maximal dosage (mg)
Tramadol	Orally	50	400-600
	iv	50-100	400-600
Dihydrocodeine	Orally	60-120	240
Piritramid	iv	7.5-22.5	≈90
	iv (PCA)	1-2	≈300
	sc/im	15-30	≈120
Pethidine	Orally	25-150	500
	Rectally	100	500
	sc/im	25-150	500
	iv	25-100	500
Morphine*	Orally	Starting with 10	No maximal dose
	Rectally	Starting with 10	No maximal dose
	sc/im	Starting with 5	No maximal dose
	iv	Starting with 2	No maximal dose
	iv (PCA)	0.5-2.5 mg bolus 10-15 min lockout	No maximal dose
Fentanyl†	iv	0.05-0.1 mg (1 µg/kg)	Limited by respiratory depression

PCA = patient-controlled analgesia.
**A simple way of calculating the daily dosage of morphine for adults (aged 20-75 years) is: 100 – patient's age = morphine per day in mg.*
†Strong opioids have no real upper limit in dosage (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).

5.6 Peri-operative pain management in children

5.6.1 Pre-operative problems

The main pre-operative problems concerning children are fear of surgery, anxiety of separation from their parents, and pain caused by interventional procedures, mostly venepuncture. Contrary to popular belief, the presence of parents during anaesthesia induction does not alleviate children's anxiety before surgery (80) (level of evidence: 1a). The pre-operative use of morphine sulfate, 0.1 mg/kg, can help to prevent crying in children and thereby reduce oxygen consumption and pulmonary vasoconstriction. Table 31 lists the drugs given most often for pre-operative sedation and separation anxiety in children. The prior application of EMLA (lidocaine 2.5%, prilocaine 2.5%) cream helps to reduce the pain of venepuncture pain (81) (level of evidence: 1a). Atropine, 0.01-0.02 mg/kg iv, im, orally or rectally, prevents bradycardia during anaesthesia induction.

Table 31. Premedication drugs in children

Drug	Dosing	Route of administration	Category
• Ketamine	6 mg/kg	Oral, intranasal, intramuscular	NMDA antagonist
• Midazolam	0.5 mg/kg	Oral, intranasal, rectally	Benzodiazepine
• Dexmedetomidine	4 µg/kg	Oral, intranasal	α_2- receptor agonist
• Clonidine	4 µg/kg	Oral	α_2- receptor agonist
• Pentobarbital	4-6 mg/kg	Intramuscular	Barbiturate
• Chloral hydrate	50-100 mg/kg	Oral	Barbiturate
• Methohexital	25-30 mg/kg	Rectally	Barbiturate

Recommendation	GR
• EMLA local application alleviates significantly venepuncture pain in children	A

5.6.2 Post-operative analgesia

For post-operative analgesia in children, paracetamol, NSAIDs, opioids and their combinations are used according to the severity of the surgical procedure's severity. The dosage of each analgesic agent is calculated according to body weight. Most common drugs and the dosages used for paediatric analgesia are listed in Table 32.

Table 32: Dosage of analgesics in children for post-operative analgesia

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

The use of COX-2 inhibitors in children post-operatively is still controversial. Patient-controlled analgesia (PCA) can be used safely in children older more than 6 years old. In infants and children unable to use PCA, nurse-controlled analgesia is effective (82). Locoregional techniques such as wound infiltration, nerve blocks, caudal and epidural analgesia are also used successfully (83,84). The most common drugs used are bupivacaine and ropivacaine (Table 33). Higher volumes of lower drug concentrations appear to be more effective than lower volumes of higher concentrations (85) (level of evidence: 1a). The addition of opioids, ketamine or clonidine increases the duration of pain relief and reduces the need for rescue analgesia, so providing more effective pain relief than local anaesthesia alone in caudal analgesia (86-88) (level of evidence: 1a).

Table 33: Epidural dosage 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/hour	0.4 mg/kg/hour
• Ropivacaine	2.5 mg/kg	3.5 mg/kg	0.3 mg/kg/hour	0.6 mg/kg/hour

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6. NON-TRAUMATIC ACUTE FLANK PAIN

6.1 Background

Acute flank pain is a common 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 34).

Table 34: Main urological and non-urological causes of flank pain.

Urological causes
• Renal or ureteral stones
• Urinary tract infection (pyelonephritis, pyonephrosis, renal abscess)
• Uretero-pelvic junction obstruction
• Renal vascular disorders (renal infarction, renal vein thrombosis)
• Papillary necrosis
• Intra- or peri-renal bleeding
• Testicular cord torsion.

Non-urological causes
• Aortic aneurysm • Gallbladder disorder • Gastrointestinal disorders • Pancreatic disease • Gynaecological disorders • Musculoskeletal disease

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/mm^3).
- Because the signs and symptoms can be very similar, *acute uncomplicated pyelonephritis* should be immediately differentiated from complicated renal colic.
  - o Concomitant fever (≥ 38°C) makes imaging obligatory (5).
  - o 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.
  - o Imaging is also imperative in patients with acute flank pain and a solitary kidney (level of evidence: 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.
- *Uretero-pelvic junction* (UPJ) *obstruction* 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 (CRP) 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

The use of ultrasonography (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, the sensitivity to detect ureteral dilatation can be as high as 96% (7-9) (level of evidence: 2a). Together with a plain abdominal radiograph, US provides an acceptable imaging procedure if computed tomography (CT) is not available (7,10-14) (level of evidence: 1b).

Disadvantages of US include an inability to differentiate dilatation from true obstruction and the need for highly specialised personnel (10). Sensitivity varies from 58-96% in non-trained personnel in emergency rooms (13). Nevertheless, there is convincing evidence to suggest that non-specialised professionals, who have only be given a short training, can be highly effective in excluding potentially life-threatening disorders such as abdominal aortic aneurysm, free abdominal fluids, gallstones and obstructive uropathy (13) (level of evidence: 2b). For obvious reasons, US is the diagnostic imaging modality of choice during pregnancy.

6.2.3.2 Intravenous urography (IVU)

Intravenous urography has been the imaging modality of choice for evaluating acute flank pain for decades. Direct identification of ureteral calculi can be achieved in 40-60% of cases, whereas using indirect signs (e.g. ureteral and renal pelvic dilatation) makes detection possible in 80-90% of all cases. However, IVU results may 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.

6.2.3.3 Unenhanced helical CT (UHCT)

Recently, UHCT has been introduced as an imaging modality with a high sensitivity and specificity for the evaluation of acute flank pain (7,15) (level of evidence: 1a). Unenhanced helical CT 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 extra-urinary causes of flank pain in about one-third of all patients presenting with acute flank pain. Additionally, it does not need contrast agent, and is a time-saving technique (15,16) (level of evidence: 1a).
Unenhanced helical CT or IVU should be considered in patients initially evaluated with other imaging modalities and who are still febrile after 72 hours of treatment to rule out further complicating factors (renal, perinephric or prostatic abscesses) (15,16).

Table 35 shows comparative results of US, IVU and UHCT in assessing acute flank pain and suspicion of ureterolithiasis (17-19). Figure 6 summarises the diagnostic approach to non-traumatic acute flank pain.

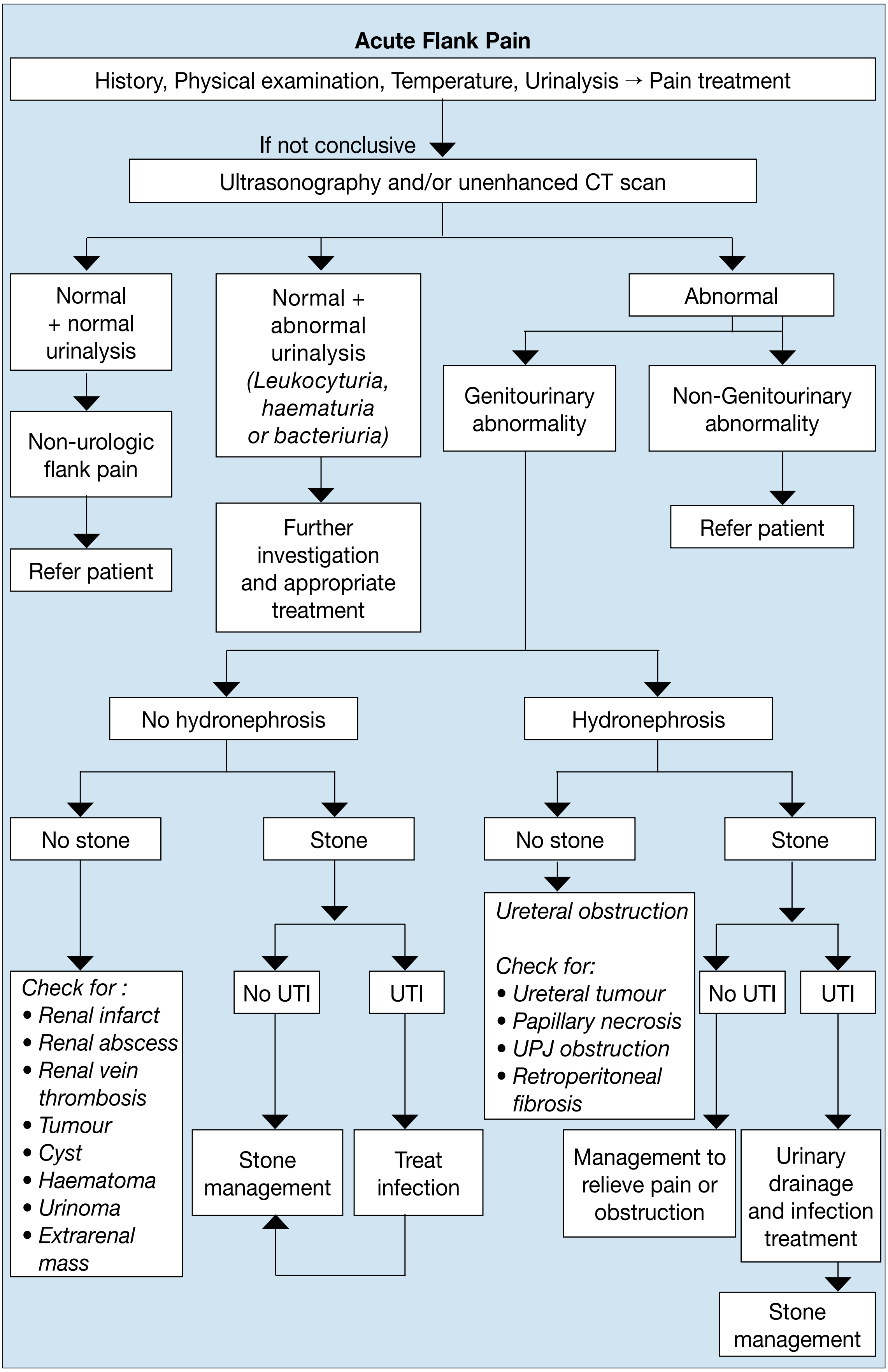
Recommendation	GR
• Unenhanced helical CT (UHCT) is the imaging diagnostic modality with the highest sensitivity and specificity for evaluation of non-traumatic acute flank pain	A
• Ultrasound can be an alternative to UHCT in the initial approach to non-traumatic acute flank pain	A

Table 35: Comparative results of ultrasound (US), intravenous urography (IVU) and unenhanced helical CT (UHCT) in assessment of acute flank pain and suspected ureterolithiasis*.

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

* From the ACR Appropriateness Criteria® guideline, *Acute onset flank pain–suspicion of stone disease*, reviewed 2007 (10).

Figure 6. Diagnostic approach to non-traumatic acute flank pain



CT = computed tomography; UTI = urinary tract infection

6.3 Initial emergency treatment

6.3.1 Systemic analgesia

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

- Intravenous non-steroidal anti-inflammatory drugs (NSAIDs) are very effective in most cases, e.g. a bolus of diclofenac sodium, 75 mg (level of evidence: 1a) (21). A slow intravenous injection of ketorolac, 30 mg, 4 times daily, is equivalent to diclofenac in the treatment of renal colic (22).
- A single dose of dipyrone has been rigorously tested and seems to be less effective than diclofenac, 75 mg (23) (level of evidence: 1a). However, a slow intravenous infusion of dipyrone, 1 g or 2 g, is just as effective as diclofenac (24).
- Intravenous papaverine hydrochloride (120 mg) can be an alternative to diclofenac in patients with contraindications to NSAIDs (24) (level of evidence: 1b).
- Large-scale studies proved that both NSAIDs and opioids can be effective in providing analgesia, but vomiting is more prevalent among patients treated with opioids (particularly, pethidine) (21).
- Intravenous papaverine can effectively and safely relieve patients not responding to conventional agents (diclofenac) (25) (level of evidence: 1b).
- The combination of intravenous morphine + ketorolac seems superior to either drug alone and appears to be associated with a decrease in rescue analgesia (26).
- Antimuscarinics are often used in patients with a clinical diagnosis of acute renal colic. Nevertheless, there is no evidence that hyoscine butylbromide reduces opioid requirements in acute renal colic (26) (level of evidence: 1b).

Meanwhile, pain origin should be clarified in febrile patients and in patients with a solitary kidney.

Recommendation	**GR**
• NSAIDs such as diclofenac (75 mg, bolus), and dipyrone (1-2 g, slow intravenous injection) are both very effective for acute flank pain	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) (level of evidence: 1a);
- Trigger-point injection of lidocaine can provide effective pain management in half of patients suffering renal colic (28). It is significantly superior to the combination of intravenous administration of butylscopolamine bromide + sulpyrine (28) (level of evidence: 1a).

There are no comparative studies with NSAIDs.

6.3.3 Supportive therapy

Many patients with acute flank pain present with moderate-to-severe dehydration. Fever, vomiting and anorexia produce serious discomfort and should be treated from the beginning. When possible, intravenous fluids should be administered generously (60 mL/hour of normal saline and 60 mL/hour of a 5% glucose solution). Nevertheless, it has been proven that maintenance intravenous fluids (20 mL/hour of normal saline) can be as effective as forced hydration (2 L of normal saline over 2 hours) with regard to the pain perception and analgesic use of the patient (29) (level of evidence: 1b). Similarly, there is no clear-cut evidence for the use of diuretics in the treatment of acute ureteral colic (30). Irrespective of the aetiology (infectious, obstructive, oncological) metoclopramide chloride, 0.5 mg/kg/24 hours in three different doses, can be effective in controlling nausea and vomiting.

6.3.4 Upper urinary tract decompression

If pain relief cannot be achieved using medical therapy and there are signs of infection and of impaired renal function, upper urinary tract drainage should be carried out (*see Treatment of patients with renal colic*). Indications for stenting to relieve obstruction urgently have been defined elsewhere (31) (Table 36). Ureteral stenting and percutaneous nephrostomy can be equally effective.

Table 36: Indications for stenting for urgent relief of obstruction

- 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 (33).

Briefly, 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*. A second- or third-generation oral cephalosporin is recommended in those areas with raised resistance rates to *E. coli*, or in pregnancy, lactating women, or adolescence. 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 (UPJ) obstruction can result in intermittent flank or abdominal pain. Symptoms may worsen during brisk diuresis (after consumption of caffeine or alcohol). The standard surgical procedure is dismembered or non dismembered pyeloplasty. Insertion of a ureteral stent can help to relieve pain in very symptomatic patients prior to definitive surgical treatment. 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 has been successfully treated with ureteroscopy or temporary ureteral stenting (35).

6.4.3.3 Renal infarction

There is no specific treatment for acute renal infarction. However, anticoagulation with intravenous heparin followed by warfarin may be warranted by the underlying disease (atrial fibrillation, left ventricular thrombus, or a hypercoagulable state). The aim of anticoagulation is to prevent future events (36).

6.4.3.4 Renal vein thrombosis

Renal vein thrombosis (RVT) is often clinically silent; however, acute flank pain can be the presenting symptom. Standard treatment for RVT has been systemic anticoagulation with heparin to prevent further propagation of thrombus or other thromboembolic phenomena (37). There have been case reports of the successful use of fibrinolytic agents in selected patients without clinical contraindications (38). Surgical therapy with thrombectomy or nephrectomy is reserved for cases refractory to medical therapy.

6.4.3.5 Intra- or peri-renal bleeding

Acute spontaneous intra- or perirenal bleeding often results in acute flank pain. Spontaneous renal haemorrhage, or Wunderlich's syndrome, is an unusual and life-threatening cause of acute abdomen. Surgical approach (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 surgically treated immediately.

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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
GPP	good practice points
IASP	International Association for the Study of Pain
im	intramuscular
iv	intravenous
IVU	intravenous urography
131J-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
153Sm	samarium-153
89Sr	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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