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1. INTRODUCTION

1.1 Background
1.1.1 Definition of pain (WHO)

“Pain management is a necessity in the work of each physician.”
F. Sauerbruch, 1936

Pain is the most common symptom of any illness; the physician’s therapeutic task is twofold: to discover and treat the cause of pain and to treat the pain itself, whether or not the underlying cause is treatable, to provide relief and reduce the suffering caused by pain.

The International Association for the Study of Pain (IASP) has proposed a 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).

Although we use the term of pain to define all sensations that hurt or are unpleasant, actually two quite different kinds of pain exist. The first is termed nociceptive. This pain is associated with tissue damage or inflammation, so it is also called ‘inflammatory pain’. The second is termed neuropathic and results from a lesion to the peripheral or central nervous systems. Many pains will have a mixed neuropathic and nociceptive aetiology.

From a temporary perspective, pain can be divided in acute and chronic. Acute pain occurs after traumas, operations, or lesions of a nerve, and pain is often recurrent. Chronic pain occurs continuously for at least 3 months. It inhibits feelings, emotions, thinking and reactions. Social interactions and work are restricted to the extent that mobility and physiological functions are inhibited.

Although established analgesic strategies can benefit most patients, undertreatment is common. Inadequate understanding of the principles of cancer pain therapy contributes greatly to undertreatment and efforts to redress this situation are both a therapeutic and an ethical imperative.

1.1.2 Nociception and innervation

Neural mechanisms of nociception
Structure of the peripheral neural apparatus
One of the vital functions of the nervous system is to provide information about the occurrence or threat of injury. The sensation of pain, by its inherent aversive nature, contributes to this function. The peripheral neural apparatus that responds to noxious (injurious or potentially injurious) stimuli provides a signal to alert the organism of potential injury.

This physiological pain is an important and adaptive element of the normal nervous system which, clinically, only needs to be temporarily suppressed or disabled during surgical procedures where damage is deliberately produced. The protective mechanism operates as a result of the presence of a specific set of primary sensory neurones called nociceptors.

Sensory fibers
Highly specialized sensory fibres, alone or in concert with other specialized fibres, provide information to the central nervous system not only about the environment, but also about the state of the organism itself.

Nociceptors
Nociceptors are sub-classified with respect to three criteria:
1. Unmyelinated (C-fibre) versus myelinated (A-fibre) parent nerve fibre
2. Modalities of stimulation that evoke a response
3. Response characteristics.

Chemical sensitivity of nociceptors
Injury results in the local release of numerous chemicals which mediate or facilitate the inflammatory process. These include bradykinin, prostaglandins, leukotrienes, serotonin, histamine, substance P, thromboxanes, platelet activating factor, protons, and free radicals.

Efferent functions of nociceptors
Cutaneous nerves have more than a fourfold higher number of small diameter A- and C-fibres than the larger, myelinated A- fibres (2). Nociceptors, apart from signalling pain, also serve other regulatory and trophic functions (3,4).
Deep pain

Behavioural and clinical studies indicate that there are important differences between cutaneous and deep pain. For example, unlike cutaneous pain, deep pain is diffuse and poorly localized. Deep pain may be associated with strong autonomic responses such as sweating and changes in heart rate, blood pressure and respiration. In addition, deep pain may be produced by stimuli that are not tissue damaging, e.g., distension of bowel and bladder (5,6). Finally, visceral pains may be associated with referred pain as well as cutaneous and deep tissue hyperalgesia.

The role of the dorsal horn

The nociceptors terminate in a high ordered way in the dorsal horn of the spinal cord with the thinly myelinated A-delta ending in laminae I and V and the unmyelinated C-fibres 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 brainstem relay nuclei, to the thalamus and then onto the cortex, where the sensation of pain is generated.

Brain areas involved in nociception and pain

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

- A sensory-discriminative component that refers to the capacity to analyse location, intensity and duration of the nociceptive stimulus
- A motivational component that gives rise to the unpleasant character of painful perception
- A cognitive and evaluative component involved in the phenomena of anticipation, attention, suggestion and past experiences
- A behavioural component that refers to what the patient says and does (or not does) meaning he is suffering.

Modulation of pain

The transmission of pain from peripheral tissues through the spinal cord to the higher centres of the brain is clearly not a passive simple process using exclusive pathways. Rather, circuitry within the spinal cord has the potential to alter, dramatically, the relation between the stimulus and the response to pain in an individual. The sensation of pain is subject not only to modulation during its ascending transmission from the periphery to the cortex but also to segmental modulation and descending control from higher centres. The main neurotransmitters implicated in descending pain control are serotonin, noradrenaline and the endogenous opioids, although others also play a role.

1.1.3 Innervation of the urogenital system

The differences between mechanisms of nociception in the skin and viscera are emphasized by studies on the response properties of visceral afferents from the urinary tract.

Ureter

There have been only a few studies on the properties of primary afferent neurons innervating the ureter (28-30). 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 & Sann (7). 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 (7).

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 (8). The majority of visceral primary afferents from the bladder, urethra, and reproductive and other pelvic organs encode for both noxious and non-noxious stimuli (8-10).

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 (11-14). 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
Free nerve endings derived from A- or C-fibres are abundant throughout the glans penis. The two fibre types associated with these endings appear to be slowly adapting low-threshold stretch receptors and high-threshold mechanoreceptors (15,16).

The sensory innervation of the testes (dog model) show 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) (17). Afferent fibres form a homogeneous group with polymodal receptors in testis and/or epididymis. This applied to both myelinated and unmyelinated afferents. Prostaglandins did not excite but sensitised the afferents to other stimuli (18).

1.1.4 REFERENCES


1.2 Pain evaluation and measurement

1.2.1 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 the pain involves the following:
- Evaluate severity
- Take a detailed history of the pain including an assessment of the pain intensity and character
- Evaluate the psychological state of the patient, including an assessment of mood and coping responses
- Perform a physical examination emphasizing the neurologic examination
- Appropriate diagnostic workup to determine the cause of the pain which may include tumour markers, radiologic studies, scans etc.
- Re-evaluate therapy.

The initial evaluation of pain should include a description of the pain using 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 may have pain from arthritis or cervical spondylitis. Frequently they may have more than one pain problem and each pain will need to be individually assessed and evaluated. Some pains may be due to muscular spasm rather than the cancer itself. A key principle is to constantly re-evaluate pain and the effect and side-effects of analgesic therapy.

Pain in cancer patients may be caused by the cancer itself (e.g., tumour pressure on nerve plexus or tumour infiltration), or may be due to secondary muscular spasm. Additionally pain may be secondary to cancer treatments e.g., radiation induced brachial plexopathy or may 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 and 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 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 nonsteroidal antiinflammatory drugs (NSAIDs) or opioids. Adjuvant analgesics such as anti-depressants and anti-convulsants should be used in the first instance.

1.2.2 Pain measurement
A number of different rating scales have been devised to attempt to methodically measure pain. These have been used in research, audit and in clinical practice. They all rely on a subjective assessment of the pain and therefore make inter-individual comparisons difficult. Additionally, pain is a multidimensional complex phenomenon and is not adequately described by unidimensional scales, however there is value in making some sort of an assessment to aid clinical practice.

- Categorical scales e.g., verbal rating scales: mild, moderate, severe pain
- Visual analogue scale (VAS), e.g., a line is drawn with numbers from 0 (no pain)-10 (severe pain), pain severity is indicated by marking along the line

0 —————————————————————————————————————————— 10

- Complex pain assessment compendiums e.g., Brief Pain Inventory (BPI), McGill Pain Questionnaire. The BPI consists of several visual analogue scales grouped together assessing pain at rest, on movement, and other aspects of the pain including interference with function and effect on work.

Rating pain using a visual analogue scale (VAS) or collection of VAS scales (such as the BPI) is an essential part of pain assessment. It allows some form of comparison to be made and facilitates assessment of the efficacy of treatment.

![Visual analogue scale](image)

Figure 1: Visual analogue scale

1.2.3 REFERENCES
2. CANCER PAIN MANAGEMENT

2.1 Classification of cancer pain (Figure 2)

Urogenital neoplasms frequently metastasize 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 periostial 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. A 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 may occur also 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 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).

2.1.1 REFERENCES


2.2 General management of cancer pain

2.2.1 Principles in 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)

The following structure is intended to offer guidance through the decision-making process and provides a general hierarchy of recommended treatment principles.

1st Individualized treatment for each patient
2nd Causal therapy to be preferred over symptomatic therapy
3rd Local therapy to be preferred over systemic therapy
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 negatively impact the patient’s well-being. Examples can include evisceration to prevent cloaca in cervix carcinoma, or implanting a prosthetic hip due to a pathological fracture originating in metastasized 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:

• 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 analgesic benefit, the immediate risks and 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 emphasized strongly enough. For further discussion of these points see the sections above.

In conclusion, pain management can be highly effective especially when interdisciplinary cooperation occurs.

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**Figure 3: Tumour pain helix**

- **pain**
- **sleeplessness**
- **depression**
- **worries**
- **hopelessness**
- **despair**
- **isolation**

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PAIN CAN BE OVERCOME

2.2.2 Primary analgesic therapies

• **Radiotherapy** has a pivotal role in the treatment of cancer pain and other oncological conditions. In some situations, such as the treatment of bone metastases, the value of radiotherapy is documented by abundant data and a favourable clinical experience (1-3) (level of evidence: la).

• **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 (4) (level of evidence: 1a).

• **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 drain symptomatic ascites (5-7). 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 (8) (level of evidence: 2b).

• **Antibiotics** may be analgesic when the source of the pain involves infection (e.g., pyonephrosis, abscess, and osteitis pubis). In some cases, infection may be occult and confirmed only by the symptomatic relief provided by empiric treatment with these drugs (9) (level of evidence: 2b).

2.2.3 Pharmacotherapy

The success of cancer pain therapy 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 concurrently addressed.

2.2.4 Systemic analgesic pharmacotherapy

**The ‘analgesic ladder’**

Analgesic pharmacotherapy is the mainstay of cancer pain management (10-12). 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:

1. Nonopioid analgesics
2. Opioid analgesics
3. 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 World Health Organization (WHO) has proposed a useful approach to drug selection for cancer pain, which has become known as the ‘analgesic ladder’ (10,12). When combined with appropriate dosing guidelines, this approach is capable of providing adequate relief to 70-90% of patients (13,14). Emphasising 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 ‘analgesic ladder’ according to the World Health Organization.](image-url)
Step 1 Patients with mild to moderate cancer-related pain should be treated with a nonopioid 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 nonopioid analgesic, should be treated with a weak opioid. This treatment is typically accomplished using a combination product containing a nonopioid (e.g., aspirin or acetaminophen) 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 nonopioid analgesic or an adjuvant drug.

2.2.4.1 Nonopioid analgesics

- Nonopioid analgesics = aspirin, acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs)
- May 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 acetaminophen analgesia (15)
- Potential adverse effects (16)

Most common: bleeding diathesis due to inhibition of platelet aggregation, gastro-duodenopathy (including peptic ulcer disease) and renal impairment are the most common. Less common: confusion, precipitation of cardiac failure and exacerbation of hypertension. Particular caution in elderly patients and those with blood-clotting disorders; predisposition to peptic ulceration, impaired renal function and concurrent corticosteroid therapy.

- Nonacetylated 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. Acetaminophen 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 (17).

2.2.4.2 Opioid analgesics

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

Classification

Classification 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 equianalgesic doses

By convention, the relative potency of each of the commonly used opioids is based upon a comparison to 10 mg of parenteral morphine. Equianalgesic dose information provides guidelines for dose selection when the drug or route of administration is changed (18).

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 (18-20). 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 acetaminophen or aspirin plus codeine, oxycodone or propoxyphene. The dose of these combination products can be increased until the maximum dose of the nonopioid coanalgesic is attained (e.g., 4000 mg acetaminophen).

2.2.4.3 Opioid administration

A) Opioid selection

Factors to consider include the following:

- Pain intensity
- Patient age
Prior opioid therapy (response to previous trials of opioid therapy)  
Coexisting disease  
Influence of underlying illness and characteristics of the opioid and concurrent medications.

B) Routes of administration
Classification on the basis of 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 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 (21).

• Transferral routes are not yet very common; fontanel is the only opioid available as a transferral preparation. The fontanel transferral system consists of a drug reservoir that is separated from the skin by a copolymer membrane, which controls the rate of drug delivery to the skin surface such that the drug is released into the skin at a nearly constant amount per unit of time. The system has been demonstrated to be effective in postoperative pain and cancer pain (22). The dosing interval for each system is usually 72 hours, but some patients require a 48-hour schedule. There is some inter individual variability in fentanyl bioavailability by this route, and this phenomenon, combined with large differences in elimination pharmacokinetics, necessitates dose titration in most cases (23). Transdermal patches capable of delivering 25, 50, 75 and 100 mg/h are available. Multiple patches may be used simultaneously for patients who require higher doses. At the present time, the limitations of the transdermal delivery system include its cost and the requirement for an alternative short-acting opioid for breakthrough pain.

• 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 (24).
  
  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 under evaluation. A pilot study in cancer patients suggested that it may be useful to provide rapid relief of breakthrough pain (25).

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 may be administered by the intravenous (iv), intramuscular (im) or subcutaneous (sc) routes, 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 (26).

• 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 (27). 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 (28).
Ambulatory patients can easily use a continuous subcutaneous 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 (29) and clinical experience suggests that dosing may proceed in a manner identical to continuous iv infusion. A range of pumps is available, which 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 (30). Methadone appears to be relatively irritating and is not preferred (31). 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 may 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 equianalgesic dose, the potencies of the iv, sc and im routes are considered equivalent. Perform changes in steps e.g., slowly reducing the parenteral dose and increasing the oral dose over a 2-3 day period (level of evidence: 3).

C) 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 (32,33).

- ‘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.

Adverse effects and their management

- Tolerance
  Patients vary greatly in the opioid dose required to manage pain (400 - 2000 mg of intramuscular morphine per 24 hours) (34). The induction of true analgesic tolerance, which 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 (35). 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:
1. Concern about tolerance should not impede the use of opioids early in the course of the disease and
2. 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, the constipation produced by opioids are 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 coexistent diseases such as dementia, metabolic encephalopathy or brain metastases.

• **Confusion and delirium**

Confusion is a greatly feared effect of the opioid drugs. Mild cognitive impairment is common (36). Similar to sedation, however, pure opioid-induced encephalopathy appears to be transient in most patients, persisting from days to 1-2 weeks. Although persistent confusion attributable to opioid alone occurs, 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 central nervous system, sepsis, vital organ failure and hypoxemia (37). A stepwise approach to management often culminates in a trial of a neuroleptic drug. Haloperidol in low doses (0.5-1.0 mg po or 0.25-0.5 mg iv or im) is most commonly recommended because of its efficacy and low incidence of cardiovascular and anticholinergic effects.

• **Constipation**

Constipation is the most common adverse effect of chronic opioid therapy (38-40). 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 coadministration of a softening agent (docucate) 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 (41). 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 under treatment of pain (42). Patients with chronic cancer pain have a “therapeutic dependence” to 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 (43). Although there are no prospective studies in patients with chronic cancer pain, there is an extensive clinical experience that affirms the extremely low risk of addiction in this population. Healthcare providers, patients and families often require vigorous and repeated reassurance that the risk of addiction is extremely small.

2.2.4.4 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 based on conventional use. The following three groups are distinguished.

A) Multipurpose adjuvant analgesics

- Corticosteroids
  Corticosteroids are among the most widely used adjuvant analgesics (44,45). They have been demonstrated to have analgesic effects; to improve quality of life significantly (46); and to have beneficial effects on appetite, nausea, mood and malaise in the cancer population (47). The mechanism of analgesia produced by these drugs may involve anti-oedema effects, antiinflammatory 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 corticosteroid (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 analgesic effects (48), but this must be balanced by the potential for side-effects, including sedation and confusion. With the important exception of clonazepam, which is widely accepted for the management of neuropathic pain, these drugs are generally used only if another indication exists, such as anxiety or insomnia (level of evidence: 2b).

B) Adjuvants used for neuropathic pain

Neuropathic pains are generally less responsive to opioid therapy than nociceptive pains. The therapeutic outcome of pharmacotherapy may be improved by the addition of an adjuvant medication selected for the particular clinical characteristics of the prevailing neuropathic pain problem.

- Antidepressants
  In the cancer population, antidepressant drugs are commonly used to manage continuous neuropathic pains that have not responded adequately to an opioid (49,50). The evidence for analgesic efficacy is greatest for the tertiary amine tricyclic drugs, such as amitriptyline, doxepin and imipramine. The secondary amine tricyclic antidepressants (such as desipramine and nortriptyline) have fewer side-effects and are preferred when concern about sedation, anticholinergic effects or cardiovascular toxicity is high. The starting dose of a tricyclic antidepressant should be low (e.g., amitriptyline 10 mg in the elderly and 25 mg in younger patients) (level of evidence: 1a).

- Anticonvulsants
  The anticonvulsants Carbamazepine, Phenytoin and Sodium valproate have been used for many years to treat neuropathic pain. Carbamazepine has a license for the treatment of trigeminal neuralgia. Theses drugs are prone to side-effects such as dizziness, drowsiness and Carbamazepine in particular may suppress bone marrow function and therefore requires regular monitoring. A newer anticonvulsant, Gabapentin has shown good efficacy in 2 large placebo-controlled RCT’s. It is generally better tolerated than the older anticonvulsants and it has a licence in the United Kingdom for the treatment of all types of neuropathic pain (level of evidence: 1a).
• **Clonidine**
  Clonidine is an alpha-2 adrenergic agonist that has established analgesic effects (51). In the cancer population, a trial of oral or transdermal clonidine can be considered in the management of continuous neuropathic pain refractory to opioids and other adjuvants (level of evidence: 2b).

**C) Adjuvants used for bone pain**

- **Antinflammatory Drugs**
  Anecdotally, nonsteroidal antiinflammatory drugs appear to be particularly efficacious for malignant bone pain. Corticosteroids are often advocated in difficult cases.

- **Bisphosphonates**
  Bisphosphonates (previously known as diphosphonates) are analogues of inorganic pyrophosphate that inhibit osteoclast activity and consequently reduce bone resorption in a variety of illnesses. This effect presumably underlines the putative analgesic efficacy of these compounds in bone pain. Controlled and uncontrolled trials of zoledronic acid in patients with advanced cancer have demonstrated significant reduction of bone pain. On balance, the data are sufficient to recommend a trial of one of these agents in patients with refractory bone pain; currently the evidence for analgesic effects is best for zoledronic acid. Zoledronic acid is more effective than pamidronate in breast cancer and the only bisphosphonate proven effective for metastatic prostate cancer, lung cancer, renal cell carcinoma and other solid tumours (79). Potential differences in the analgesia produced by various drugs in this class require additional study and neither dose-dependent effects nor long-term risks or benefits in cancer patients are known. The use of any bisphosphonate requires monitoring of serum calcium, phosphate, magnesium and potassium (52,53) (level of evidence: 1a).

- **Radiopharmaceuticals**
  Radiolabelled agents that are absorbed into areas of high bone turnover have been evaluated as potential therapies for metastatic bone disease. Systemically administered phosphorus-32 has long been known to be an effective agent in the management of metastatic bone pain, but its utility is limited by significant bone-marrow depression. More recently, bone-seeking radiopharmaceuticals that link a radioisotope with a bisphosphonate compound have been synthesised. Significant clinical response with acceptable haematological toxicity has been observed with strontium-89, samarium-153-ethylenediaminetetramethylene phosphoric acid, and rhenium-186-hydroxyethylidene diphosphonate. Further studies are needed to identify the risks and benefits of each agent and the durability of the effects produced. It is likely that such agents will become available in the future and represent an important means of treating refractory bone pain from metastatic disease (54-57) (level of evidence: 2b).

2.2.5 **Transcutaneous electrical nerve stimulation (TENS)**
  The mechanisms by which transcutaneous electrical stimulation reduces pain is not well defined; local neural blockade and activation of a central inhibitory systems have been proposed as explanations. Clinical experience suggests that this modality can be a useful adjunct in the management of mild to moderate musculoskeletal or neuropathic pain (61,62) (level of evidence: 4).

2.2.6 **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 (13,14). Anaesthetic and neurosurgical techniques may reduce the requirement for systemically administered opioids to achieve adequate analgesia.

- **Epidural, intrathecal, and intraventricular opioid application**
  The delivery of low opioid doses near the sites of action in the spinal cord may decrease supraspinally-mediated adverse effects. Compared to neuroablative therapies, spinal opioids have the advantage of preserving sensation, strength and sympathetic function. 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 opioid has been demonstrated to increase analgesic effect without increasing toxicity (64,65). The potential morbidity for these procedures indicates the need for a well-trained clinician and long-term monitoring (level of evidence: 3).

- **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. 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. 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 (level of evidence: 4).

- **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. 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 (68).

- **Pituitary ablation** by chemical or surgical hypophysectomy has been reported to relieve diffuse and multifocal pain syndromes that have been refractory to opioid therapy and are unsuitable for any regional neuroablative procedure. Pain relief has been observed from pain due to both hormone-dependent and hormone-independent tumours (69,70) (level of evidence: 4).

- **Calcitonin** There is limited evidence that repeated doses of subcutaneous calcitonin can reduce bone pain. Nonetheless, it is reasonable to consider a trial with this drug (e.g., salmon calcitonin 100-200 IU twice daily subcutaneously for several weeks) in refractory cases (58) (level of evidence: 4).

### 2.2.7 Physical / psychological therapy

#### Physical therapies

Physical techniques can be used to optimise the function of the patient with chronic cancer pain or enhance analgesia through application of modalities such as electrical stimulation, heat or cryotherapy. The treatment of lymphoedema by use of 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).

#### Psychological therapies

Psychological approaches are an integral part of the care of the cancer patient with pain. All patients can benefit from psychological assessment and support (59,61).

- **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 (60).

- **Other approaches** reduce anticipatory anxiety that may lead to avoidant behaviours or lessen the distress associated with the pain.
2.2.9 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 vast majority of patients. Most will require 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 (78).

2.2.9 REFERENCES


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2.3 Pain management in prostate cancer patients

2.3.1 Clinical presentation

Pain can occur in both 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 cancer (77%), related to the cancer treatment (19%) or unrelated to either (3%) (2).

Pain is more common and a real challenge in advanced disease. Therefore pain management has to 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.

2.3.2 Pain due to local impairment

2.3.2.1 Soft-tissue and hollow-viscus invasion

The relief of pain due to hollow-viscus invasion is the domain of surgery and minimally invasive procedures (e.g., catheter, stent, nephrostomy tube).

**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 with 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.

**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. For drainage a nephrostomy tube is superior to a double-J stent, because the endoscopic routine changes of the stent in the following months could be more and more difficult in a continuously growing prostate gland. Another reason is that changing the nephrostomy tube can be performed without any anaesthesia.

**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 are physiatric techniques including use of wraps, pressure stockings or pneumatic pump devices. These can both improve function and relieve pain and heaviness.

**Ileus**

Local obstruction of the rectum occurs commonly 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 has to 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.

### 2.3.3 Pain due to metastases

#### 2.3.3.1 Bone metastases

The following should be recognized:

- 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
- Tumour growth into adjacent nerves
- or 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 which 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. Therapeutic options with fewer side-effects should be administered first. Options are hormone therapy, radiotherapy, isotopes, and systemic analgesic pharmacotherapy (the ‘analgesic ladder’). Other tools in pain management such as nerve blocks are rarely used.

**Hormone therapy**

Huggins & 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, antiandrogen (cyproterone, flutamide), oestrogen-mustine complex (estramustine), progestogens, aminogluthethimide, gonadotrophin-releasing hormones (GnRH) analogues, orchidectomy, adrenalectomy and hypophysectomy. Corticosteroids are also used for the palliation of pain, particularly the kind due to bone deposits.

**Side-effects**

Compared with chemotherapy, hormone therapy is generally much better tolerated. There may also be a ‘flare’ or temporary exacerbation of pain, which is generally a predictor of subsequent response (13). The side-effects have to be considered in GnRH analogues and orchidectomy (loss of body hair, testicular atrophy, gynaecomastia, loss of libido, impotence, relatively low cardiovascular mortality rate, and psychological morbidity), in antiandrogens (gynaecomastia - more often if used alone compared to the combination with GnRH analogues, hepatic impairment, and less sexual dysfunction), in cyproterone acetate (fewer side-effects than oestrogens and lower incidence of cardiovascular complications), in oestrogens (loss of body hair, testicular atrophy, gynaecomastia, loss of libido, impotence, and higher mortality from cardiac and
cerebrovascular disease in the long-term administration), in adrenalectomy (major operative procedure), and in hypophysectomy (small but significant mortality rate and hormone replacement is subsequently required for life).

- **Effects**
  Pain relief in a collected series of protocols has been estimated at between 35% (14) and 70% (15). The differences may be due to selection of patients and problems in pain measurement. Well-differentiated prostatic carcinoma is more likely to respond to hormones than 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.

- **Problem**
  To date most patients with adenocarcinoma of the prostate present in early tumour stages and undergo radical surgery or, less frequently, radiotherapy. In case of 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.

**Radiotherapy**

External radiotherapy for metastatic bone pain is beneficial in the majority of patients. 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% (16).

- The role of radiotherapy in the management of pain due to bone metastases is unquestioned
- 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.
- Standard palliative treatment has been 20 Gy in 5 fractions over 5 days for a small volume, but for larger volumes (such as a hemipelvic field, where there is closely related bowel) 30 Gy in 10 fractions over 12 days has been used (17)
- If the bone to be treated is superficial (e.g., ribs, scapula) then a single field using orthovoltage (300 kV) gives a sufficient tumour dose without irradiating underlying tissues too heavily
- 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.

**Hemibody irradiation (HBI)**

It is common for patients with widespread metastatic disease to present with multiple painful areas, usually due to bony deposits but also because of visceral metastases. The main indications have been for widespread disease such as advanced-stage prostatic carcinoma, using doses of no more than 6 or 8 Gy as a single fraction. Several authors reported prompt pain relief in up to 80% of patients (18-20). However, the acute morbidity and mortality rate is dose-related. Acute radiation sickness (21), radiation pneumonitis (22) and bone marrow suppression are common. If doses as high as 10 Gy to the upper hemibody are given, a 70% mortality from acute radiation pneumonitis at 100 days post irradiation has been reported. When the upper hemibody dose was reduced to 6 Gy, this toxicity was avoided while maintaining a response rate in terms of pain relief as high as 82% (22).

**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 (23,24). 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 (25).

**Radioisotopes**

Widespread axial skeletal involvement in PCa has been successfully treated with systemically administered bone-seeking radioisotopes (see also section 2.4.4). Commonly used radionuclides are Strontium-89 chloride (89Sr), rhenium-186-hydroxethylidene diphosphonate (186Re-HEDP) and Samarium-153-
ethylenediaminetetramethylene phosphonic acid (153Sm-EDTMP).

Comparison of radioisotope vs. hemibody irradiation
Pain control was assessed at 3 months and found to be similar for matched hemibody irradiation and 89Sr patients with 63% and 52% respectively showing benefit. Clinically significant falls in white blood cell and platelet counts were similar in both groups. Strontium had an advantage in its ease of administration and lack of gastrointestinal toxicity, but was more expensive (26,27).

Bisphosphonates
Bisphosphonates are a standard part of supportive care for patients with bone metastases. 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, randomized controlled trials involving more than 3,000 patients (48). Complications of bone metastases include pain, fractures, and spinal cord compression. Although they appear osteoblastic by radiographic imaging, most bone metastases are characterized by excess osteoclast number and activity. In addition, pathologic 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 (49). 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 (50). Zoledronic acid (4 mg intravenously over 15 min. every 3-4 weeks) decreased the frequency of skeletal-related events, delayed the time to a first skeletal-related event, and reduced pain (48). Visual Analogue Scale improvement is positively correlated with decrease of C-telopeptide and bone phosphatase alkaline (p < 0.05) serum levels (51). 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.

Chemotherapy
In about 80 percent of men with metastatic PCa, primary androgen ablation leads to symptomatic improvement and to reduction in serum levels of prostate-specific antigen (PSA), but the disease eventually becomes refractory to hormone treatment. Systemic chemotherapy should be reserved for this patient group. In advanced disease previous clinical trials using single-agent chemotherapy have shown poor results. Newer studies suggest multiagent chemotherapies may be more effective. A randomized trial showed that mitoxantrone plus low-dose prednisone relieved pain and improved the quality of life more frequently than did prednisolone alone (48,49). Multiple other studies confirmed the symptomatic effect of this chemotherapy regimen, but none 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 are:

- Ketoconazole + doxorubicin 55%
- Vinblastine + estramustine 54% - 61%
- Estramustine + etoposide 39% - 58%
- Mitoxantrone + prednisone 33%
- Paclitaxel + estramustine 53%

In 2004 two randomized trials/phase III studies (TAX-327 and SWOG 9916) comparing docetaxel-based chemotherapies with mitoxantrone-based regimes were published (50,51). It could be demonstrated, that docetaxel-based regimens have a very good symptomatic effect; significantly better than the mitoxantrone-based approach. Additionally, for the first time, a significant survival benefit could be shown for the docetaxel group (18.9 versus 16.5 months).
Although most of these regimens have associated side-effects, such as fatigue, mild myelosuppression, and gastro-intestinal irritation, they are generally well tolerated by the majority of patients (28). 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, however it is much more cost intensive than the administration of opioids and the survival advantage is limited.

Systemic analgesic pharmacotherapy (the ‘analgesic ladder’)
In case of insufficient pain management with the treatments described above systemic analgesic pharmacotherapy should be administered (see section 2.4). In most cases the WHO ladder scheme is the treatment of choice.

### 2.3.3.2 Spinal cord compression

Spinal cord compression may be due to collapse of a vertebral body or to pressure from an extradural tumour within the spinal canal and prodromal pain is a feature in 96% of these patients. The overall incidence in PCa patients is less than 10% (29). Thoracic cord compression is the most common area (70%) and the incidence of multiple extradural sites may be as high as 18% (30). 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.

### 2.3.3.3 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 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. Abdominal pain can be improved by hepatic irradiation in over half the patients with little toxicity (31). Doses should not exceed 30 Gy in 15 daily fractions or its equivalent if radiation hepatitis is to be avoided.

### 2.3.4 Pain due to cancer treatment

#### 2.3.4.1 Acute pain associated with hormonal therapy

**Luteinizing 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 (32,33). The flare is presumably caused by an initial stimulation of luteinizing hormone release before suppression is achieved (33,34). The syndrome typically presents as an exacerbation of bone pain or urinary retention; spinal cord compression and sudden death have also been reported (32). Symptom flare is usually observed within the first week of therapy and lasts 1-3 weeks in the absence of androgen antagonist therapy. Coadministration of an androgen antagonist at the start of LHRH agonist therapy can prevent this phenomenon (35).
2.3.4.2 Chronic pain associated with hormonal therapy

Gynaecomastia
Chronic gynaecomastia and breast tenderness are common complications of antiandrogen therapies for PCa. The incidence of this syndrome varies between drugs; it is frequently associated with diethylstilboestrol (36), is less common with flutamide and cyproterone (37-39) and is uncommon among patients receiving LHRH agonist therapy (39). Gynaecomastia in the elderly must be distinguished from primary breast cancer or a secondary cancer in the breast (40).

2.3.5 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. Side-effects caused by the inappropriate use of anti-cancer 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 cooperation. Well-planned clinical trials are required because there is still much to be learned about the indications, dose, frequency and optimal administration of anti-cancer therapies for the relief of pain.

Surgery, radiotherapy, chemotherapy, and hormone therapy are mainly used as anti-tumour 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 (41).

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 emphasized. Education of the patient is crucial. He must be aware of the early signs and symptoms of metastatic disease which do not necessarily involve pain.
### Anticancer treatment

<table>
<thead>
<tr>
<th>GR</th>
<th>LE</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1a</td>
<td>Hormonal therapy (orchiectomy, LHRH analogues, diethylstilboestrol equivalent)</td>
</tr>
<tr>
<td>B</td>
<td>2b</td>
<td>Total androgen blockade: flare prevention, second line</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>Intermittent androgen suppression experimental</td>
</tr>
<tr>
<td>A</td>
<td>1b</td>
<td>To date monotherapy with antiandrogen not recommended</td>
</tr>
<tr>
<td>A</td>
<td>1b</td>
<td>First line treatment controls disease for 12 to 18 months, second line individualized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supportive care</td>
</tr>
<tr>
<td>B</td>
<td>1b</td>
<td>Low-dose glucocorticoids</td>
</tr>
<tr>
<td>B</td>
<td>2b</td>
<td>Mitoxantrone plus prednisolone</td>
</tr>
<tr>
<td>B</td>
<td>2b</td>
<td>Estramustine + vinblastine or etoposide or paclitaxel</td>
</tr>
</tbody>
</table>

### Pain management

<table>
<thead>
<tr>
<th>GR</th>
<th>LE</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>1b</td>
<td>Pain assessment (localization, type, severity, overall distress)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain due to painful or unstable bony metastases (some spots)</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>External beam irradiation</td>
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<tr>
<td></td>
<td></td>
<td>Pain due to painful bony metastases (widespread)</td>
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<tr>
<td>C</td>
<td></td>
<td>Primary hormone therapy, maximum androgen blockade in case of worsening</td>
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<tr>
<td></td>
<td></td>
<td>Hemibody irradiation</td>
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<tr>
<td>B</td>
<td>2b</td>
<td>Radioisotopes (strontium-89 or samarium-153)</td>
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<td></td>
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<tr>
<td>B</td>
<td>2b</td>
<td>Biphosphonates</td>
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<td></td>
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<td>Systemic pain management</td>
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<tr>
<td>B</td>
<td></td>
<td>Around-the-clock dosing, not as ‘required’</td>
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<tr>
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<td></td>
<td>Mild pain</td>
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<tr>
<td>A</td>
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<td>World Health Organization analgesic ladder step 1: NSAID or paracetamol</td>
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<td></td>
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<td>Moderate pain</td>
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<tr>
<td>B</td>
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<td>Codeine, dihydrocodeine or dextropropoxyphene plus acetaminophen or NSAID</td>
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<tr>
<td></td>
<td></td>
<td>Severe pain</td>
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<tr>
<td>B</td>
<td>(C)</td>
<td>Morphine or diamorphine (oral route)</td>
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<td></td>
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<td>Opioid administration</td>
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<tr>
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<td>Dose titration</td>
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<tr>
<td>C</td>
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<td>Access to breakthrough analgesia</td>
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<tr>
<td>B</td>
<td></td>
<td>Prophylactic laxatives</td>
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<tr>
<td>B</td>
<td></td>
<td>Subcutaneous route when parenteral required: transdermal fentanyl equi-effective</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>Tricyclic antidepressant and/or anticonvulsant in case of neuropathic pain</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>High dose dexamethasone in case of severe bone pain, nerve infiltration, spinal cord compression, hepatic capsular pain</td>
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<td></td>
<td></td>
<td>Psychological therapies and psychiatric techniques</td>
</tr>
</tbody>
</table>

### 2.3.6 REFERENCES


42. National Committee on Cancer Care Workgroup on Prostate Cancer. Treatment of Metastatic Prostate Cancer (M1) In: Ministry of Health (Singapore): Prostate cancer 2000, National Guideline Clearinghouse (withdrawn).


2.4. Pain management in transitional cell carcinoma patients

2.4.1 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 the pain no differences can be made between TCC and other histotypes of urothelial malignant tumours. In terms of 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 the cases.

Origin of tumour related pain

- Bladder TCC
  - Obstruction of the upper urinary tract due to growth of bladder tumour close to ureteral orifice.
  - Invasion of the surrounding areas by a locally advanced tumour (pelvic wall, nerve roots, other organs like bowel, rectum)
  - Bone metastases
Soft tissues metastases (seldom painful)

Upper urinary tract TCC

- 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 like bowel, spleen, liver)
- Bone metastases
- Soft tissue metastases (seldom painful)

2.4.2 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 determine 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 appear and 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 - either radical cystectomy or debulking cystectomy - and urinary diversion has 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 the 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 RT 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 tract TCC**

Locally advanced primary tumours (e.g., invasion of the posterior abdominal wall, nerve roots, paraspinous muscles, other organs like 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 upper urinary tract and bladder.

2.4.3 Pain due to metastases

In advanced disease of 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 only. Radiotherapy has a palliative analgesic role in bone metastases. Using ten fractionated doses of 30 - 35 Gy it rapidly reduces if not eliminates pain in 80-90% of cases (10) (level of evidence: 2b). Also hemibody irradiation can be used in diffuse bone metastases (10). No specific studies exist on the radioisotope therapy of bone metastasis in transitional cell carcinoma.

Orthopedic surgery may stabiles pathologic fractures (4). Neurosurgery may have a place in the palliation of pain deriving from compression of the spinal cord.

### REFERENCES


2.5. Pain management in renal cell carcinoma patients

2.5.1 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. 20-30% of the patients present with metastatic disease and 30% of the patients primary presenting with a localised kidney tumour develop metastases during follow-up. That means 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 gland. Patients with metastases have a 2-year survival rate of maximal 20%, which has to be considered in case of palliative treatment.

Origin of tumour related pain:
• Invasion of the surrounding areas by a locally advanced tumour (posterior abdominal wall, nerve roots, paraspinous muscles, other organs like 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).

2.5.2 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 like bowel, spleen, liver) without metastases usually present with pain. Surgical management is the only effective management of this type of
tumour. Sometimes extended operations including 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 case of metastatic disease, palliative nephrectomy is indicated for the control of severe symptoms like 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 to other therapies like angioinfarction of the tumour.

Radiotherapy of soft tissue is without proven benefit concerning pain and tumour control. There is no benefit in survival by standard preoperative (30 Gy) or postoperative radiotherapy and a questionable delay of local progress (1).

In metastatic disease, EORTC study 30947 demonstrated significant increase in survival with palliative nephrectomy plus immunotherapy compared to immunotherapy (interferon-alpha) alone (median survival of 17 compared to 7 months) (2) (level of evidence: 2b). There is no special effect on pain relief by 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 concerning the efficacy of alternative therapies like angioinfarction of the tumour in regard to haemorrhage and pain relief in palliative situations.

Analgesic therapy according to WHO guidelines and/or palliative drainage of the urinary tract should be used if the patient is not fit for major surgery.

2.5.3 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, impending or demonstrated pathologic fracture. In cases of bone metastases with extensive soft tissue involvement and corresponding severe pain sometimes amputation of a leg or arm is required to maintain a certain quality of life. With surgery of bone metastases a significant pain decrease is achieved in 89 - 91 % (4-6) (level of evidence: 2b/3). Additionally, surgery prevents pathologic fractures and spinal compression, and there is a significant impact on survival.

Preoperative embolization of bone metastases or embolization 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 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., Sr-89 therapy, seems to achieve good pain relief in bone metastases from renal cell carcinoma (13) (level of evidence: 3). Large prospective studies in regard to long term pain relief are missing.

Bone metastases show poor response to immunotherapy and there is no proven benefit in pain relief. The results of hormonal or chemotherapy therapy are even less effective and therefore without any importance in pain control.

Therapy of soft tissue metastases is performed analogous to that of locally advanced disease.

Radiotherapy of soft tissue is without proven benefit in terms of pain and tumour control. There is no benefit in survival by standard preoperative (30 Gy) or postoperative radiation therapy and a questionable delay of local progress (1).

Immunotherapy alone achieves an overall response in 15-27% (14). Immunotherapy in combination with chemotherapy (IL-2 + interferon-alpha + 5-fluorouracil) is the most effective immunotherapy with partial tumour response in up to 46% and complete response in maximal 15% of the patients. 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 analogue to the tumour response, but there are no data concerning pain control by immunotherapy.

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

2.5.4 REFERENCES


2.6. Pain management in adrenal carcinoma patients

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

2.6.1 Malignant pheochromocytoma

Pheochromocytomas result from pheochromocytes, 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.

The highest sensitivity in detecting the tumour has CT scan or MRI with 94-100%, 131I-MIBG (131I-metaiodobenzylguanidine) scan is positive in approximately 87% (3).

In case of metastases, chemotherapy with cyclophosphamide, vincristine and dacarbazine has little effect (4) (level of evidence: 2b), but therapeutic doses of 131I-MIBG (33GBq = 900 mCi) may produce some results (5,6) (level of evidence: 2b). The hormone response rate is described at 50%. There is no special literature concerning pain relief with 131I-MIBG in metastatic pheochromocytoma, but at least the same response rate as for the hormone levels should be suspected.

Malignant pheochromocytomas are considered radioresistant. There are some cases where radiation therapy induced partial remission (7) (level of evidence: 3). There is no information about the efficacy of radiation concerning pain relief in case of bone or soft tissue metastases.

<table>
<thead>
<tr>
<th>Treatment of pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue and/or bone pain due to metastases are best treated by therapeutic doses of 131I-MIBG, if the pheochromocytoma takes up this radionuclide (8) (level of evidence: 2b). There is no literature concerning chemotherapy or radiotherapy and pain relief in metastatic pheochromocytoma.</td>
</tr>
<tr>
<td>Symptomatic treatment of the pain with drugs etc. according to Section 2.</td>
</tr>
</tbody>
</table>

2.6.2 Adrenocortical carcinomas

Carcinomas of the adrenal cortex are highly malignant with both local and haematogenous spreading. 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). If there is a prolonged survival by using chemotherapy remains unproven.

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

<table>
<thead>
<tr>
<th>Treatment of the pain depending on its origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal symptoms are typical symptoms when first presenting with the tumour. The treatment is surgical removal of the primary tumour with attempting to remove the entire lesion even if resection of adjacent structures is necessary as well as resection of the local lymph nodes.</td>
</tr>
<tr>
<td>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 and pain relief in metastatic adrenocortical carcinomas.</td>
</tr>
<tr>
<td>Symptomatic treatment of the pain with drugs etc. according to Section 2.</td>
</tr>
</tbody>
</table>

2.6.3 REFERENCES


2.7. Pain management in penile cancer patients

2.7.1 Clinical presentation
Penile cancer is, in Europe, a relatively rare disease; the incidence is less than 2/100,000 men per year; less than 1% of all cancers in men. It is a disease of older men, with an increase in incidence around age 60, peaking around age 80. 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 usually not a presenting complaint (1).

Until now there is no consensus about the therapeutic management of metastatic disease, and there are few controlled studies of statistical significance that study both penile carcinoma and cancer-related pain. Most of the principles about dealing with pain management in prostatic carcinoma are valid here as well; however, the following aspects should also be taken into consideration:
Pain can occur in both early and advanced stages of penile cancer. In early stages, acute pain could be the result of a voiding dysfunction (subvesical obstruction); details are given in chapter 4 on management of bladder outlet obstruction in PCa. 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; inguinal or pelvic lymph nodes are most frequently affected. Positive nodes could be found in about 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 are frequent.

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

2.7.2 Pain due to local impairment

**Soft-tissue and hollow-viscus invasion**
Bladder outlet and ureteric obstruction is managed analogously to that described in section ‘prostatic carcinoma’ (section 2.3.2.1).

**Lymphoedema**
Patients with a huge inguinal tumour mass or in a state of inguinal scarring tissue after lymph node dissection very often show lymphoedema of the lower limbs. This is more frequent in case of involvement of both inguinal and iliac nodes. The treatment of lymphoedema comprise physiatric techniques (use of wraps, pressure stockings or pneumatic pump devices). They 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.

2.7.3 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).

2.7.4 Conclusions
Currently no conclusive or universally applicable recommendations on managing pain related to the treatment of metastatic penile carcinoma can be given. 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 (Section 2).

2.8. Pain management in testicular cancer patients

2.8.1 Clinical presentation
Testicular cancer generally affects younger men in the third or fourth decade of their life. It is mainly diagnosed causally as an intrascrotal mass. Approximately 20% patients are presenting with scrotal or inguinal pain, which disappears after orchiectomy. Only 11% of patients complain of back of flank pain when first presenting. (1). Primary advanced tumour with pain due to bone metastases is very rare, maximal no more than 3% at first presentation (2) and should be treated causally by primary chemotherapy and adjuvant analgesics.

2.8.2 Pain due to local impairment
Local pain due to the scrotal mass is effectively treated by orchiectomy.
2.8.3 Pain due to metastases

- Back or flank pain due to retroperitoneal lymphadenopathy will slowly disappear under chemotherapy with decrease of the mass (level of evidence: 2b) (see guidelines for testicular cancer). Temporary analgesics are advisable (Section 2 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. Therapy of choice is the immediate treatment of the hydronephrosis by ureteral stenting or inserting a percutaneous nephrostomy.
- Bone pain due to bone 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 case 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).

2.8.4 REFERENCES


2.9. Recommendations at a glance

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

<table>
<thead>
<tr>
<th>Origin of pain / Therapeutic options</th>
<th>RCC</th>
<th>TCC</th>
<th>PCA</th>
<th>Penile cancer</th>
<th>Adrenergic cancer</th>
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<td>Bone metastases</td>
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<td>surgery</td>
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<td>immunotherapy</td>
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<td>hormone therapy</td>
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<td>analgetics</td>
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RCC: renal cell carcinoma; TCC: transitional cell carcinoma; PCA: prostate cancer

3. POSTOPERATIVE PAIN MANAGEMENT

3.1. Background

These guidelines are intended to guide urologists in treating postoperative pain.

All dosages refer to an average weight of 70 Kg. These are approximate dose ranges. Actual selected dose depends on individual patient assessment.

3.2. Importance of effective postoperative pain control

Surgery inevitably results in tissue trauma and release of potent mediators of inflammation and pain (1). Substances released from injured tissue evoke stress hormone responses in addition to activation of cytokines, adhesion molecules and coagulation factors (2). Activation of this ‘stress response’ leads to an increase in metabolic rate, water retention and triggering of a ‘fight or flight’ reaction with autonomic features (3). These responses result in pain and surgical morbidity including cardiovascular and respiratory complications which may be particularly pronounced in elderly patients and patients with pre-existing cardio-respiratory disease (level of evidence: 2a).

Poor postoperative pain control

Pain associated with these responses is unpleasant for the patient. Numerous reports have appeared in the
medical literature describing the unacceptability of poorly controlled postoperative pain in hospitals (4,5). One survey found that 77% of adults believed that postoperative pain is to be expected, with almost 60% regarding this as their primary fear before surgery (6). The traditional and common practice of giving “as required” intramuscular opioids has been reported to lead to unrelieved pain in over 50% of patients (7) (level of evidence: 3).

Surgical morbidity
Surgical morbidity associated with poor postoperative pain control is also increasingly recognised. Adverse cardiovascular effects including hypertension, tachycardia and increased cardiac work may result from unrelieved pain. Pain may also lead to shallow breathing and cough suppression increasing the risk of retained pulmonary secretions and chest infection (8) (level of evidence: 2b).

Economic cost
In addition, poor pain control may delay discharge from hospital, and lead to unplanned hospital admission following ambulatory surgery thus increasing medical costs (9) (level of evidence: 3).

Postoperative rehabilitation
Effective pain control is only one aspect of improved postoperative recovery. It is now appreciated that other factors in addition to pain may delay or impair postoperative recovery (10). Such factors include, nausea, immobility, nasogastric tube, drains etc. see diagram below (level of evidence: 2b).

![Figure 6](image)

By addressing these factors using enforced early mobilisation and enteral nutrition, as well as good pain control and reduction of the stress response, improvements in postoperative morbidity following major urological surgery have been reported (11).

3.3. Methods used in treating postoperative pain including drugs, routes of administration, patient controlled analgesia (PCA) and epidurals.

3.3.1 Development of Acute Pain Teams
The importance of effective pain control and recognition of the inadequacy of treatment was appreciated by surgeons and anaesthesiologists in the 1980’s. This led to a number of changes including the development of Acute Pain Teams within hospitals to oversee effective postoperative pain control (12-16) (level of evidence: 3). Many hospitals now unite the different postoperative analgesic techniques such as epidurals and Patient Controlled Analgesia (PCA) under the common management of an Acute Pain Team. These multidisciplinary teams are usually led by an anaesthesiologist and consist of nursing and pharmacy personnel (17). Their aim is to treat pain, introduce systematic pain assessment, introduce new techniques such as PCA and epidurals, and to teach medical and nursing staff. In addition they are responsible for the audit of their services and for research (level of evidence: 3).

Such acute pain services have been shown to improve pain relief and post surgical outcomes (12,13). There is some evidence that ‘low tech,’ low cost approaches such as regular pain assessment, easy access to strong opioid drugs and teaching and education, are just as important as ‘high tech’ approaches such as PCA and epidurals (18). In addition, improved pain control may lead to shorter hospital stays and fewer unscheduled admissions after day-case surgery (19) (level of evidence: 3).
The main aims of effective postoperative pain treatment (12,13);  
• To reduce the incidence and severity of patients’ postoperative pain  
• To educate patients about the need to communicate unrelieved pain so they can receive prompt  
evaluation and effective treatment  
• To enhance patient comfort and satisfaction  
• To contribute to fewer postoperative complications and, in some cases, shorter stays after surgical  
procedures  
• To introduce proper assessment of postoperative pain  
• To introduce planning for effective postoperative pain control  
• To promote nursing and medical staff training and education  
• To provide patient comfort with minimal sedation and impairment of respiratory function  
(level of evidence: 3).

3.3.2 Pain assessment  
The subject of postoperative pain and its control should be part of the surgeon’s initial review of all relevant  
aspects of the planned procedure (20) (level of evidence: 3).

RECOMMENDATIONS  
The surgeon should discuss this with the patient and the family. A more detailed pain history should then be  
obtained by the anesthesiologist to include an assessment of:  
• Preoperative pain,  
• Previously used analgesic methods  
• Patients knowledge of, expectations of, and preferences for pain management methods  

When the preoperative assessment is complete a pain management plan should be developed in cooperation  
with the patient.  

A pain measurement tool should be selected e.g., visual analogue scale or descriptive scale, and the patient  
told how often pain will be assessed.  

Careful assessment of pain should occur initially and then regularly throughout treatment, using self-reporting  
techniques. Pain should be assessed both at rest and during activity and pain relief assessed as to its  
adequacy to allow appropriate function (13).  

A system of postoperative care emphasising staff and patient education, regular pain assessment and  
allowing more frequent doses of strong opioid drugs has been shown to be effective in pain relief and patient  
satisfaction (21) (level of evidence: 2b).

3.3.3 Preoperative cognitive - behavioural interventions  
These aim to reduce pain, anxiety and the amount of drugs needed for pain control. Techniques include  
relaxation, distraction, and imagery. Preparation before surgery may reduce the amount of analgesia required  
postoperatively (22) (level of evidence: 2b).

RECOMMENDATIONS  
Drugs should be administered according to their pharmacokinetic and dynamic attributes.

Analgesic plan as type, dosage and route of administration, should be decided together with the patient and  
be based on the three step ladder of WHO (1986, 1996).

When intravenously administered, analgesics should not be used without a venous line flux control. This is  
particularly stressed when using opioids.
3.3.4 Postoperative analgesic drugs;

- Non steroidal anti-inflammatory drugs (NSAIDs) (23)
  NSAIDs include non-selective cyclo-oxygenase (COX) inhibitors such as aspirin, diclofenac and ibuprofen as well as the newer COX 2 selective inhibitors rofecoxib and celecoxib. These drugs work by inhibiting COX and the subsequent production of prostaglandins. The COX 2 inhibitors have been shown to have fewer gastric side effects such as ulcer formation and gastric bleeding (24). The main advantage of NSAIDs is analgesia without respiratory depression or sedation. However, whilst their analgesic effect has been clearly demonstrated in postoperative pain they are not strong enough to be used alone for severe pain (25,26).
  They can be given orally, intravenously, or intramuscularly. They can be given ‘as needed’ or ‘around-the-clock’ (47) (level of evidence: Ia).

A recent meta-analysis of 3,453 postoperative patients rated NSAIDs highly as effective analgesics (27). Paracetamol and codeine combinations were the next most efficacious group followed by paracetamol alone and tramadol (28). The following recommendations on NSAID use have been based on a summary of recent published information (13);
- NSAIDs are not sufficiently effective as the sole agent after major surgery
- NSAIDs are often effective after minor or moderate surgery
- NSAIDs often decrease opioid requirement

Adverse effects of NSAIDs are potentially serious and it is essential that contraindications are respected (29).
- Gastric irritation, ulcer formation + bleeding
- Renal impairment
- Worsening of asthma
- Platelet inhibition

NSAIDs may be used after major surgical interventions in combination with more powerful analgesics as part of a multimodal or balanced analgesic approach. After minor urological surgery NSAIDs may be sufficiently effective to be the sole agent used (level of evidence: 1b).

Three coxibs — celecoxib, rofecoxib, and valdecoxib — have been approved for use by the Food and Drug Administration (FDA); a fourth, etoricoxib, has been approved by the European regulatory authorities. Etroicoxib and a fifth drug, lumiracoxib, are currently under consideration for FDA approval.

Coxibs have been aggressively marketed directly to consumers and have rapidly dominated the prescription-drug market for NSAIDs. Rofecoxib has now been withdrawn by the Data and Safety Monitoring Board of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study because of a significant increase of serious thromboembolic adverse events in the group receiving 25 mg of rofecoxib per day as compared with the placebo group (48).

There are currently no clear indications for their use in the treatment of postoperative pain, but Coxibs are contraindicated in cardiopatic patients.

**RECOMMENDATIONS**

Typical dosing schedules include the following:
- Diclofenac (Voltarol, Voltaren) 50 mg 3x per day orally (max 200 mg per day), or 100 mg per rectum every 16 hours
- Ibuprofen (Brufen) 400 mg 3x per day orally
- Ketorolac (Toradol) 10-30 mg orally or intravenously every 6 hours
- Rofecoxib (Vioxx) 25 mg orally 1x per day (max 50 mg per day).
THERAPY HAS TO BE STARTED BY ORAL ROUTE

Pain therapy should initially be based on the type of surgery undergone. However, when assessing the level of pain, the patient’s individual evaluation of his/her pain should outweigh this consideration.

- **Metamizole / Dypirone**

  It is prohibited in the USA and the UK because of reported single cases of agranulocytic neutropenia (level of evidence: 3).

  In other countries of Europe and Latin America it is appreciated as an analgesic and antipyretic drug. A single dose of 500 mg has been compared to 400 mg of Ibuprofen (level of evidence: 1b).

  Common side effects are somnolence, gastric discomfort, nausea, light hypotension, allergic reaction.

RECOMMENDATIONS

Metamizole (Novalgin) 500 mg 1-4 x per day orally or 1g 1-4x per day rectally.

Drug has to be used strictly in adherence with the therapeutic index (advised doses have to be respected).

It is indicated in moderate severe postoperative pain.


- **Paracetamol and combinations of paracetamol with codeine and dihydrocodeine**

  Paracetamol (acetaminophen) has been widely used in the treatment of postoperative pain. Its precise mode of action is unclear but it may work by inhibiting centrally produced COX (30).

  Intravenous paracetamol (Perfalgan) was launched in April 2004 for the short-term treatment of moderate pain, especially following surgery, and for the short-term treatment of fever. Perfalgan contains solublised paracetamol (1g in 100 mL).

  Propacetamol is a pro-drug of paracetamol and was available in a parenteral form for many years (Pro-Dafalgan). 2g propacetamol is hydrolysed to 1g paracetamol.

  Perfalgan 1g to be bioequivalent to propacetamol 2g, Perfalgan can be used in the clinical conditions previously treated with propacetamol 2g (49).

  Clinical trials have compared propacetamol 2g with either placebo or other analgesia and concentrated on the morphine-sparing effects of propacetamol, i.e. the reduction in consumption of morphine postoperatively. Patients enrolled in the majority of these trials all had access to an opioid PCA device or could request bolus doses of an opioid.

  Adverse reactions were not significantly reduced in propacetamol-treated patients, compared to those treated with morphine alone or morphine/NSAID in the trials. One trial looked specifically at the incidence of adverse effects but did not conclude that propacetamol reduced morphine-related side effects. Adverse reactions may have been caused by the surgical procedure and/or anaesthetics, not just morphine.

  These drugs are commonly prescribed after minor urological procedures when the patient is able to take oral medications. Alternatively a rectal preparation is available (level of evidence: 3).

  It is effective as an analgesic on its own or in combination with weak opioids such as codeine, dihydrocodeine or dextropropoxyphene (28) and tramadol (31) (level of evidence: 1a).

  Contraindications are relatively few; some patients may be allergic to these preparations or sensitive to the constipating effects of codeine. Overdosing with paracetamol (more then 6g per day) may lead to liver impairment.
Typical dosing schedules include the following:

- Paracetamol 1g orally or rectally every 6 hours
- Co-proxamolb (32.5 mg dextropropoxyphene + 325 mg paracetamol) 2 tablets every 6 hours.

- **Tramadol (Tramal, Zydol)**
  Tramadol is a weak opioid analgesic which is commonly used in postoperative pain control. It can be given orally or intravenously. It is an opioid agonist on the μ receptor and an inhibitor of noradrenaline and serotonin reuptake in descending pain inhibitory pathways (32) level of evidence: 2a).

  Efficacy in post operative pain has been widely reported (28). Tramadol has been reported to be less efficacious than NSAIDs (level of evidence: 2b).

  Combination of Tramadol plus paracetamol shows comparable efficacy to Ibuprofen (level of evidence: 1b).

  Adverse effects include dizziness, sleepiness and nausea.

  Tramadol may be useful in managing pain after minor to intermediate urological surgery (level of evidence: 3).

  Typical dosing schedules:
  - Tramadol 50-100 mg orally or intravenously, every 6 hours or continuously
  - Loading dose 100 mg + 0.2 mg/kg/h as maintainance.

- **Opioids: oral, intravenous, subcutaneous and intramuscular**
  Opioids can be given orally, intravenously, intramuscularly or subcutaneously after surgery. Systemic administration of opioids may be by using the traditional ‘as needed’ schedule or ‘around-the-clock’ dosing. Opioids are first line treatment for severe acute pain. The key principle for safe and effective use is to titrate the dose against the desired effect-pain relief and minimise unwanted effects (33).

  The subcutaneous route is comparable to intravenous (level of evidence: 1a).

  Oral route is the most feasible, easy and efficacious (level of evidence: 1a).

  Side-effects include major problems such as respiratory depression, and more minor problems such as hypotension, sleepiness, nausea and constipation.

**RECOMMENDATIONS**

Close monitoring of patients after administrating opioids is required irrespective of route of administration

Typical dosing schedules:

- Oral morphine (Sevredol, Oramorph) 5-10 mg every 3-4 hours. This is the preferred route of delivery, but requires return of gastric motility.
- Oral Oxycodone (Oxynorm) 10 mg every 4 hours
- Intravenous or subcutaneous morphine infusions (usually managed in a high dependency area) up to 10 mg per hour, but titrated for individual patients to determine both effect and side effects.
- Intermittent intramuscular or subcutaneous injections of morphine 10 mg every 3 hours (level of evidence: 2a)

**Adult daily dosage = (20-70 yrs old) 100 minus patient age**

**Child daily dosage = mg/kg/h 0.01-0.04 mg/kg/h**

Different major and minor opioids are interchangeable (level of evidence: 1a).

Equianalgesic dosing tables helps the conversion of drug and route of administration.
**Patient controlled analgesia (PCA)**

PCA-machines allow the patient to self-medicate opioid by pressing a button which results in the delivery of the drug directly into the bloodstream. The potential advantage is patient control and immediate drug delivery. PCA allows patients to adjust the degree of pain relief to their own desired level of comfort and tolerance of side effects (34). PCA has been shown to provide greater patient satisfaction and improved ventilation compared to conventional routes of administration (35). In addition if the PCA is managed by an acute pain team there is a lower incidence of side effects (36).

Morphine is the usual drug used in PCA machines, but other opioids could be used such as fentanyl or sufentanil (37).

Adverse effects include excessive sedation, respiratory depression and nausea.

Dosing schedule:
- A loading dose may be prescribed e.g., 1-2 mg morphine
- Incremental (bolus) dose: morphine 1 mg, pethidine 10 mg, fentanyl 20 μg
- Lock-out period 5-8 minutes
- Background infusions: may be prescribed - though close monitoring is required
- 1 hour infusion limit: 30 mg of morphine (or equivalent) in 4 hours

Morphine loading dose 0.05-0.2 mg/kg.

<table>
<thead>
<tr>
<th>RECOMMENDATIONS</th>
<th>Dose should be titrated individually.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA III, background infusion and high dosage cancer therapy should be assisted in hospital.</td>
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</tr>
</tbody>
</table>

**Epidurals**

Continuous epidural infusions of local anaesthetic drug (typically bupivacaine/marcaine) and opioid (typically morphine or diamorphine) have been used to effectively relieve postoperative pain (level of evidence: 1a).

Epidurals have been shown to provide superior analgesia compared to PCA and other analgesic techniques such as intermittent intramuscular opioid (38) (level of evidence: 1b).

In addition they result in a significant reduction in the stress response to surgery and to a reduction in surgical morbidity. There is a reduced incidence of postoperative pulmonary complications, cardiac complications and of paralytic ileus (39) (level of evidence: 1a).

Potential adverse effects include:
- Hypotension (can be treated with adrenaline or ephedrine)
- Respiratory depression
- Very low incidence of neurological damage (<1: 20,000) and infection (<1: 10,000).

<table>
<thead>
<tr>
<th>RECOMMENDATIONS</th>
<th>The epidural route could be used in patients after major urological operations such as nephrectomy, radical prostatectomy, where extensive postoperative analgesia is required for 3-4 days.</th>
</tr>
</thead>
</table>

Typical dosing schedule:
- Epidural bupivacaine 0.125% (maximal dosage 175-250 mg/die) + 2 μg of fentanyl/mL or sufentanyl 0.3-1 μg/mL, run at 5-15 mL/h
- Ropivacaine 0.1-0.2 % (maximal dosage 500-700) + 2 μg of fentanyl/mL or Sufentanyl 0.3-1 μg/mL, run at 5-15 mL/h.
• **Intermittent or continuous local neural blockade**

  Local anaesthetic blocks can be used after urological surgical operations to supplement postoperative analgesia (40).

Typical nerve blocks could include the following:

- Wound infiltration with 10-20 mL of 0.25-0.5% bupivacaine
- Iliohypogastric or ilioinguinal nerve infiltration after hernia repair, using 10-20 mL of 0.25-0.5% bupivacaine
- Intercostal nerve infiltration with 5-10 mL of 0.25% bupivacaine
- Intrapleural catheters after intrathoracic surgery, continuous infusion of 10 mL/h of 0.1% bupivacaine.

### 3.3.5 Pain prevention

Recent studies have shown that the central nervous system is capable of being sensitised by persistent noxious stimulus resulting in an exacerbation of pain perception (41). Blocking these noxious stimuli from reaching the central nervous system, by giving analgesic drugs before surgical incision, may result in a reduction of analgesic requirements and reduced postoperative pain (42). However, clinical studies have not yet demonstrated any clear benefit (43,44).

Despite this, it is considered good clinical practice to treat postoperative pain early and aggressively before the pain becomes well established. Such a concept has been called ‘preventative’ analgesia rather than ‘pre-emptive’ (45) (level of evidence: 2b).

### Balanced analgesia

The concept of balanced analgesia is that effective postoperative pain control depends on utilising a number of different analgesics and routes of administration which synergistically act to provide good pain control. For example, using NSAIDs in addition to opioids, or combining local wound infiltration with oral drugs. In general the combined use of different classes of analgesics and analgesic techniques improves the effectiveness of pain relief after surgery, reducing maximal dosage and adverse effects (46) (level of evidence: 2b).

### 3.4 Specific pain treatment after different urological operations

#### 3.4.1 Extracorporeal Shock Wave Lithotripsy (ESWL)

This is minimally invasive treatment. Post-treatment pain is not likely to be severe and the patient is usually able to take oral analgesics.

**Analgesic plan**

**Preoperative assessment**

**Intraoperative:** Opioids such as morphine or fentanyl +/- NSAIDs could be used intravenously by the anesthesiologist.

**Postoperative:** Most patients will be able to tolerate oral analgesics following this procedure. NSAIDs, paracetamol, codeine and paracetamol combination preparations (Co-proxamol, Co-dydramol, Tylex) 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 then oral strong opioid preparations such as morphine could be considered. If the oral route is not available then intramuscular or subcutaneous strong opioid could be prescribed e.g., morphine im 10 mg every 3 hours.

<table>
<thead>
<tr>
<th>Analgesic drug options after ESWL</th>
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<tbody>
<tr>
<td>Diclofenac 50 mg orally/8 h</td>
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<tr>
<td>Diclofenac 100 mg rectally/16 h</td>
</tr>
<tr>
<td>Paracetamol 1 g orally/6 h</td>
</tr>
<tr>
<td>Co-proxamol, co-dydramol, 2 tablets/6 h</td>
</tr>
<tr>
<td>Tramadol 50-100 mg/6 h</td>
</tr>
<tr>
<td>Morphine 10 mg im/3 h</td>
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</table>

The majority of these patients may be day-surgery patients. Upon discharge they should be provided with an analgesic prescription and contingency plan in case the pain worsens. This will reduce the incidence of unplanned hospital re-admissions.
3.4.2 Endoscopic procedures

a) Transurethral procedures

- Transurethral resection of bladder tumour - TURBT
- Transurethral resection of bladder neck - TURNB
- Transurethral incision of prostate - TUIP
- Transurethral resection of prostate - TURP
- Retrograde ureteroscopy (diagnostic and/or operative).

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 postoperative analgesia for 4-6 hours following surgery. After this time oral analgesics could be used.

Analgesic plan

- Preoperative assessment
- Intraoperative: Use of spinal anaesthesia (intrathecal or epidural) will provide intraoperative analgesia and postoperative analgesia for 4-6 hours
- Postoperative: After 4-6 hours, oral mild analgesics such as NSAIDs, paracetamol +/- codeine, or stronger opioids given orally or im could be used.

<table>
<thead>
<tr>
<th>Analgesic drug options after transurethral procedures</th>
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</thead>
<tbody>
<tr>
<td>Diclofenac 50 mg orally/8 h</td>
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<tr>
<td>Diclofenac 100 mg rectally/16 h</td>
</tr>
<tr>
<td>Paracetamol 1g orally/6 h</td>
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<tr>
<td>Co-proxamol, co-dydramol, 2 tablets/6 h</td>
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<td>Tramadol 50-100 mg/6 h</td>
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<tr>
<td>Morphine 10 mg im/3 h</td>
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</tbody>
</table>

b) Percutaneous endoscopic procedures, e.g.:

- Percutaneous nephrolithotomy
- Percutaneous endopyelotomy
- Percutaneous resection of pyelocaliceal tumours
- Antegrade ureteroscopy.

The analgesic plan is the same as for the transurethral procedures with the additional complexity that the skin is breached and that additional analgesia may be required for this. Local anaesthetic could be infiltrated locally into the skin e.g., 10 mL of 0.5% bupivacaine. General anaesthesia is usually required because of the uncomfortable decubitus - prone position on operating table - and the prolonged operating time.

A particular consideration is the development of pain in the shoulder due to diaphragmatic irritation following the pneumoperitoneum.

c) Laparoscopic procedures, e.g.:

- Laparoscopic lymph node dissection
- Diagnostic laparoscopy
- Laparoscopic removal of organ or tumour.

In most cases patients will not be able to take oral medication for 4-6 hours postoperatively. It will therefore be necessary to use intramuscular or subcutaneous analgesia during this period.

A particular consideration is the development of pain in the shoulder due to diaphragmatic irritation following the pneumoperitoneum.

Analgesic plan

- Preoperative assessment
- Intraoperative: use of intravenous opioids +/- NSAIDs by the anaesthesiologist
- Postoperative: Initial use of systemic strong opioid given intramuscularly, intravenously or subcutaneously on either an ‘as needed’ or time contingent basis depending on the severity of the pain. After 4-6 hours patients may be able to take oral medications such as NSAIDs, paracetamol, codeine, or morphine.
Analgesic drug options after laparoscopic surgery

- Morphine intermittent intramuscular 10 mg/3 h
- PCA morphine, 1 mg bolus, 5 minute lockout
- Diclofenac 50 mg /8 h orally, 100 mg/16 h rectally
- Co-proxamol, co-dydramol, 2 tablets/6 h
- Tramadol 50-100 mg/6 h
- Paracetamol 1g/6 h

3.4.3 Open surgery

a. Minor operations of the scrotum/penis
b. Inguinal approach

These surgical operations are relatively minor and nearly all patients will be able to take oral analgesia following the operation. Often the operation will be performed under local anaesthesia or with the aid of an ilio-inguinal or ilio-hypogastric nerve block.

Analgesic options after surgery are outlined below:

<table>
<thead>
<tr>
<th>Analgesic drug options after minor surgery on scrotum, penis, and inguinal region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac 50 mg orally/8 h</td>
</tr>
<tr>
<td>Diclofenac 100 mg rectally/16 h</td>
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<td>Morphine 10 mg im/3 h</td>
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</tbody>
</table>

c) Transvaginal surgery

- Pelvic floor surgery
- Stress incontinence surgery.

Local or regional anaesthetic may be used for these operations.

After surgery the following analgesic options are possible:

<table>
<thead>
<tr>
<th>Analgesic drug options after transvaginal urological surgery</th>
</tr>
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<tbody>
<tr>
<td>Diclofenac 50 mg orally/8 h</td>
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<td>Morphine 10 mg im/3 h</td>
</tr>
</tbody>
</table>

d) Perineal open surgery

- Perineal radical prostatectomy (PRP)
- Posterior urethroplasty.

Analgesic plan

- Preoperative assessment
- Intraoperative: General anaesthetic and regional technique, sometimes an intrathecal catheter can be sited. General anaesthesia is usually used, particularly for PRP, because of the uncomfortable exaggerated lithotomy position on the operating table
- Postoperative: Combined opioid and local anaesthetic continuous epidural infusion. When the patient is able to take oral analgesics, usually after 3-4 days paracetamol +/- codeine could be used.
After surgery the following analgesic options are possible:

| Continuous epidural infusion of bupivacaine 0.25% + fentanyl 2 µg/mL, 5-15 mL/h |
| Intravenous morphine infusion, 1-10 mg/h + bolus doses 1-2 mg as required |
| PCA morphine, 1 mg bolus, 5 minute lockout |
| Diclofenac 50 mg /8 h orally, 100 mg/16 h rectally |
| Co-proxamol, co-dydramol, 2 tablets/6 h |
| Tramadol 50-100 mg/6 h |
| Paracetamol 1g/6 h |

### e) Transperitoneal Laparotomy
- Retroperitoneal lymph node dissection - RPLND
- Radical nephrectomy +/- caval thrombectomy
- Cystectomy + urinary diversion.

Patients will usually be managed postoperatively in an intensive care unit. A combined general anaesthetic and regional technique will usually be used.

#### Analgesic plan
- **Preoperative assessment**
- **Intraoperative:** General anaesthetic and regional technique, sometimes an intrapleural catheter can be sited
- **Postoperative:** Combined opioid and local anaesthetic continuous epidural infusion. When the patient is able to take oral analgesics, usually after 3-4 days paracetamol +/- codeine could be used.

| Continuous epidural infusion of bupivacaine 0.25% + fentanyl 2 µg/mL, 5-15 mL/h |
| Intravenous morphine infusion, 1-10 mg/h + bolus doses 1-2 mg as required |
| PCA morphine, 1 mg bolus, 5 minute lockout |
| Diclofenac 50 mg /8 h orally, 100 mg/16 h rectally |

### f) Extraperitoneal Laparotomy Suprapubic/retropubic
- Open prostatectomy
- Radical retropubic prostatectomy.

Patients will usually be managed postoperatively in an intensive care unit. A combined general anaesthetic and regional technique will usually be used. It will be possible to use the oral route early after this type of surgery. Oral opioids or paracetamol +/- NSAIDs could be used.

#### Analgesic plan
- **Preoperative assessment**
- **Intraoperative:** General anaesthetic and regional technique, sometimes an intrapleural catheter can be sited
- **Postoperative:** Combined opioid and local anaesthetic continuous epidural infusion. When the patient is able to take oral analgesics, usually after 3-4 days paracetamol +/- codeine, +/- NSAIDs could be used.

| Continuous epidural infusion of bupivacaine 0.25% + fentanyl 2 µg/mL, 5-15 mL/h |
| Intravenous morphine infusion, 1-10 mg/h + bolus doses 1-2 mg as required |
| PCA morphine, 1 mg bolus, 5 minute lockout |
| NSAIDs such as Diclofenac 50 mg po /8 h |
| Paracetamol 1 g 6 h orally |
| Diclofenac 50 mg /8 h orally, 100 mg/16 h rectally |

### g) Retroperitoneal approach - flank Incision (early oral intake)
- Nephrectomy
- Pyeloplasty
- Pyelonephrolithotomy.
Patients will usually be managed postoperatively in an intensive care unit. A combined general anaesthetic and regional technique will usually be used.

Analgesic plan

- **Preoperative assessment**
- **Intraoperative**: General anaesthetic and regional technique, sometimes an intrapleural catheter can be sited
- **Postoperative**: Combined opioid and local anaesthetic continuous epidural infusion. When the patient is able to take oral analgesics, usually after 3-4 days paracetamol +/- codeine could be used.

**Analgesic options after retroperitoneal approach - flank incision**

- Continuous epidural infusion of bupivacaine 0.25% + fentanyl 2 µg/mL, 5-15 mL/h
- Intravenous morphine infusion, 1-10 mg/h + bolus doses 1-2 mg as required
- PCA morphine, 1 mg bolus, 5 minute lockout
- Diclofenac 50 mg /8 h orally, 100 mg/16 h rectally
- Co-proxamol, co-dydramol, 2 tablets/6 h
- Tramadol 50-100 mg/6 h
- Paracetamol 1 g/6 h

3.4.4 REFERENCES


   http://lib.leeds.ac.uk/search/a?a


3.5 **Opioid equi-analgesic doses**

<table>
<thead>
<tr>
<th></th>
<th>Parenteral</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (10 mg)</td>
<td>1 : 3</td>
<td></td>
</tr>
<tr>
<td>Methadone (10 mg)</td>
<td>1 : 2</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone (1.5 mg)</td>
<td>1 : 5</td>
<td></td>
</tr>
<tr>
<td>Oxycodone (15 mg)</td>
<td>1 : 2</td>
<td></td>
</tr>
<tr>
<td>Pethidine (100 mg)</td>
<td>1 : 3</td>
<td></td>
</tr>
<tr>
<td>Codeine (130 mg)</td>
<td>1 : 1.6</td>
<td></td>
</tr>
<tr>
<td>PO</td>
<td>IV</td>
<td>SC</td>
</tr>
<tr>
<td>Morphine 5-10 mg</td>
<td>3-5:1</td>
<td>3:1</td>
</tr>
</tbody>
</table>

The opioid tolerance is not a complete cross tolerance. When opioid is changed, a lower than equi-analgesic dose is recommended.
3.6. Levels of evidence and grades of recommendation

Levels of evidence

1a Evidence obtained from meta-analysis of randomised controlled trials.
1b Evidence obtained from at least one randomised controlled trial.
2a Evidence obtained from at least 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 descriptive studies, such as comparative studies, correlation studies and case studies.
4 Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nature of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>(1a, 1b) Requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.</td>
</tr>
<tr>
<td>B</td>
<td>(2a, 2b, 3) Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.</td>
</tr>
<tr>
<td>C</td>
<td>(4) Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.</td>
</tr>
<tr>
<td>GPP</td>
<td>Good Practice Points Recommended best practice based on the clinical experience of the guideline development group.</td>
</tr>
</tbody>
</table>

3.6.1 REFERENCES

   http://www.sign.ac.uk/guidelines/published/index.html
   http://www.cancercare.on.ca/index_genitourinaryCancerguidelines.htm
4. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPROVe</td>
<td>Data and Safety Monitoring Board of the Adenomatous Polyp Prevention on Vioxx</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anaesthesiology</td>
</tr>
<tr>
<td>ATC</td>
<td>around-the-clock</td>
</tr>
<tr>
<td>BPI</td>
<td>Brief Pain Inventory</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>COX</td>
<td>Cyclo-Oxygenase</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>ESWL</td>
<td>extracorporeal shock wave lithotripsy</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (US Dept of Health and Human Services consumer protection agency)</td>
</tr>
<tr>
<td>FSH</td>
<td>follicle-stimulating hormone</td>
</tr>
<tr>
<td>GnRH</td>
<td>gonadotrophin-releasing hormone</td>
</tr>
<tr>
<td>GPP</td>
<td>good practice points</td>
</tr>
<tr>
<td>GR</td>
<td>grade of recommendation</td>
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<tr>
<td>HBI</td>
<td>hemibody irradiation</td>
</tr>
<tr>
<td>IASP</td>
<td>International Association for the Study of Pain</td>
</tr>
<tr>
<td>im</td>
<td>intramuscular</td>
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<tr>
<td>iv</td>
<td>intravenous</td>
</tr>
<tr>
<td>131J-MIBG</td>
<td>131J-metaiodobenzylguanidine</td>
</tr>
<tr>
<td>LE</td>
<td>level of evidence</td>
</tr>
<tr>
<td>LH</td>
<td>luteinising hormone</td>
</tr>
<tr>
<td>LHRH</td>
<td>Luteinizing hormone releasing hormone</td>
</tr>
<tr>
<td>LUTS</td>
<td>lower urinary tract symptoms</td>
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<tr>
<td>mg</td>
<td>milligramme</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>NSAID</td>
<td>nonsteroidal antiinflammatory drugs</td>
</tr>
<tr>
<td>PCA</td>
<td>patient-controlled analgesia</td>
</tr>
<tr>
<td>PCa</td>
<td>prostate cancer</td>
</tr>
<tr>
<td>po</td>
<td>per os</td>
</tr>
<tr>
<td>PRN</td>
<td>pain management 'as needed'</td>
</tr>
<tr>
<td>PRP</td>
<td>perineal radical prostatectomy</td>
</tr>
<tr>
<td>PSA</td>
<td>prostatic specific antigen</td>
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<tr>
<td>RCC</td>
<td>renal cell carcinoma</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>186Re-HEDP</td>
<td>rhenium-186-hydriethylidene diphosphonates</td>
</tr>
<tr>
<td>RPLND</td>
<td>retroperitoneal lymphnode dissection</td>
</tr>
<tr>
<td>sc</td>
<td>subcutaneous</td>
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<tr>
<td>153Sm-EDTMP</td>
<td>samarium-153-ethylenediaminetetramethylene phosphonic acid</td>
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<tr>
<td>89Sr</td>
<td>strontium-89 chloride</td>
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<tr>
<td>TCC</td>
<td>transitional cell carcinoma</td>
</tr>
<tr>
<td>TENS</td>
<td>transcutaneous electrical stimulation</td>
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<tr>
<td>TUIP</td>
<td>transurethral Incision of the Prostate</td>
</tr>
<tr>
<td>TURBN</td>
<td>transurethral Resection of the Bladder Neck</td>
</tr>
<tr>
<td>TURP</td>
<td>transurethral Resection of the Prostate</td>
</tr>
<tr>
<td>TURBT</td>
<td>transurethral Resection of Bladder Tumour</td>
</tr>
<tr>
<td>µg</td>
<td>microgramme</td>
</tr>
<tr>
<td>VAS</td>
<td>visual analogue scale</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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