Guidelines on

Pain Management & Palliative Care

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European Association of Urology

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1. INTRODUCTION

1.1 The Guideline

The new European Association of Urology (EAU) Guidelines expert panel for Pain Management and Palliative Care have prepared this guidelines document to assist medical professionals in appraising the evidence-based management of pain and palliation in urological practice. These guidelines include general advice on pain assessment and palliation, with a focus on treatment strategies relating to common medical conditions and painful procedures.

The multidisciplinary panel of experts responsible for this document include a urologist, a radiotherapist-oncologist, an anaesthesiologist and a nurse specialised in palliative care.

1.2 Methodology

The recommendations provided in the current guidelines are based on systematic literature search using Embase/Medline and the Cochrane Central Register of Controlled Trials.

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

1.3 Publication history

The Pain Management Guidelines were first published in 2003, with a partial update in 2007, followed by a full text update in 2009. In 2010 two new topics were added, Section 5.6 “Perioperative pain management in children” and Chapter 6 “Non-traumatic acute flank pain”. The quick reference guide was completely reworked. In the 2011 print all chapters were abridged.

The current 2013 edition contains partial updates based on the available literature. Section 3.5 on Palliative Care was moved and expanded to a new Chapter 7, which deals with the subject of Palliative Care.

A quick reference document presenting the main findings of the former Pain Management guidelines is also available. All texts can be viewed and downloaded for personal use at the EAU website: http://www.uroweb.org/guidelines/online-guidelines/

1.4 Acknowledgements

The Expert Panel would like to express its gratitude to Dr. Juan Guerra Martínez (JGM), medical oncologist at the University Hospital of Fuenlabrada, Spain, for his guidance on palliation matters. His assistance and expertise proved most valuable.

1.5 Level of evidence and grade of guideline recommendations*

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

Table 1: Level of evidence (LE)*

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

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

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

Alternatively, absence of high level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations where corroborating studies cannot be performed, perhaps for ethical or other reasons and in this case unequivocal recommendations are considered helpful for the reader. The quality of the underlying scientific evidence - although a very important factor - has to be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (2-4).

The EAU Guidelines Office does not perform cost assessments, nor can it address local/national preferences in a systematic fashion. However, whenever these data are available, the expert panels will include the information.

Table 2: Grade of recommendation (GR)*

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

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

1.6 References

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2. BACKGROUND

2.1 Definition of pain

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

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

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

2.2 Pain evaluation and measurement

*2.2.1 **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 pain involves the following steps:

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

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

O Onset: 'When did it start? How long does it last? How often does it occur?'
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?'
U Understanding/Impact on you
  - What do you believe is causing this symptom?
  - How is this symptom affecting you and/or your family?
V Values
  - What is your goal for this symptom?
  - What is your comfort goal or acceptable level for this symptom (on a scale of 0 - 10 with 0 being none and 10 being the worst possible)?
  - Are there any other views or feelings about this symptom that are important to you or your family?

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

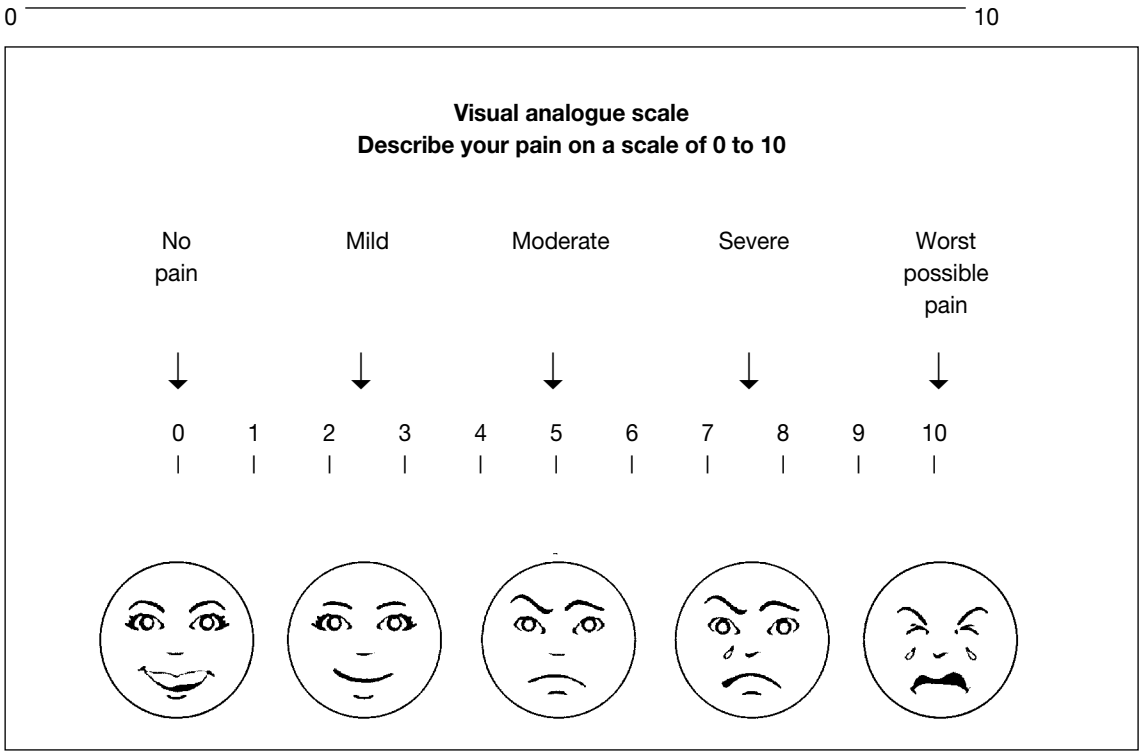
Pain in cancer patients could be caused by the cancer itself, be due to secondary muscular spasm, be secondary to cancer treatments, or have no relation to the cancer, e.g., arthritis.

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

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

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

Figure 1: Pain assessment scales



Other common ways of pain assessment are numerical scales (NRS rating 1-10, "Faces"- Wong Baker scale, mostly used in children and verbal scales (rating from absence to severe pain) (Figure 1). To study the effects of both physical and non-physical influences on patient wellbeing, an instrument must assess more dimensions than the intensity of pain or other physical symptoms. Several validated questionnaires to assess various QoL dimensions are available, including the Medical Outcomes Short-Form Health Survey Questionnaire 36 (SF-36), and the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) (6-10).

For cognitively impaired and elderly patients Doloplus-2 offers pain assessment by rating somatic, psychomotor and psychosocial behaviour. The tool consists of 10 items with four behavioural descriptions representing increasing severity of pain from 0 to 3. Individual item scores are summed to arrive at a total score ranging from 0 to 30 points. Five points is the threshold indicating pain (11).

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3. CANCER PAIN MANAGEMENT (GENERAL)

3.1 Classification of cancer pain

Cancer pain is classified as mild (1-3), moderate (4-6) and severe (7-10) (1).
The physical causes of pain are either nociceptive or neuropathic. In cancer patients, nociceptive pain tends to be caused by invasion of the bone, soft tissues or viscera (e.g. bowel, bladder), and neuropathic pain by nerve compression or infiltration.

Urogenital neoplasms frequently metastasise to bone (e.g., spine, pelvis, and skull). Bone metastases are associated with pathological fractures, hypercalcaemia and neurological deficits, leading to substantial impairment of QoL. The release of algogenic substances in the tissue, microfractures and periosteal tension are the main mechanism for pain sensation (2).

Pain caused by bone metastasis is nociceptive, but can become neuropathic if the tumour invades or compresses a nerve, neural plexus or spinal cord. One-third of patients with tumour-related pain are affected by neuropathic pain components (3). Nociceptive pain is well localised. Initially, it occurs on physical movement, but later might also occur at rest.

Neuropathic pain frequently has a constant 'burning' character. The efficacy of opioids may be diminished in neuropathic pain, making co-analgesia necessary (4). Patients with severe neuropathic pain are a special challenge. Psychological changes frequently occur, and specific therapeutic intervention may be necessary (5).

The World Health Organization (WHO) recommends a stepwise scheme for the treatment of cancer pain syndromes and neoplastic bone pain. Bisphosphonates and calcitonin are helpful for stabilising bone metabolism. Epidural and intrathecal opioids are sometimes useful in managing metastatic bone pain. Selected patients with neuropathic pain sometimes benefit from nerve destruction by intrathecal or epidural phenol (6).

3.2 General principles of cancer pain management

The four goals of care are:
- prolonging survival;
- optimising comfort;
- optimising function;
- relieving pain.

Pain leads to a vicious cycle of sleeplessness, worry, despair, isolation, hopelessness, depression, and escalation of pain. The following hierarchy of general treatment principles is useful in guiding the selection of pain management choices.
1. Individualised treatment for each patient.
2. Causal therapy to be preferred over symptomatic therapy.
3. Local therapy to be preferred over systemic therapy.
4. Systemic therapy with increasing invasiveness (the WHO ladder).
5. Conformance with palliative guidelines.
6. Both psychological counselling and physical therapy from the very beginning.

The fundamental principle is the individualisation of therapy. Repeated evaluations allow the selection and

administration of therapy to be individualised in order to achieve and maintain a favourable balance between pain relief and adverse effects.

The next steps in the hierarchy, especially points 2-4, necessitate a continuing risk-to-benefit assessment between therapeutic outcome versus tolerability and willingness to accept adverse effects. The more invasive the therapy, the more difficult the decisions become. This is particularly true with palliative medicine, where the prospects of healing are limited and there is the problem of working against time.

If local therapy is not feasible or cannot be well tolerated, then symptomatic measures are appropriate, although local therapy is to be preferred over systemic treatment. In simple cases, measures such as drainage and stenting can make analgesic medication redundant, e.g., gastric probe, ureteral stent, percutaneous nephrostomy, and bladder catheter. Patients with recurrent subileus caused by peritoneal carcinomatosis are immediately relieved of their pain when they are given an artificial anus.

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

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

- 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 (TENS).
- Use invasive analgesic techniques after careful evaluation of the likelihood and duration of the analgesic benefit, the immediate risks, and the morbidity of the procedure (epidural infusion).
- Use neurodestructive procedures (chemical or surgical neurolysis, coeliac plexus blockade).
- Some patients with advanced cancer and treatment refractory symptoms where comfort is the overriding goal can elect to be deeply sedated (see chapter 7, section 7.5.3 Palliative sedation).

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

3.3 Non-pharmacological therapies

*3.3.1 **Surgery***

Surgery may have a role in the relief of symptoms caused by specific problems, such as obstruction of a hollow viscus, unstable bony structures and compression of neural tissues or draining of symptomatic ascites (7-9). 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 (10-13).

Recommendation	LE	GR
Palliation is not equivalent to minimal invasion. Consider aggressive surgery under certain circumstances.	2b	B

*3.3.2 **Radionuclides***

3.3.2.1 Clinical background

For patients presenting with multiple painful bone metastases, both β- and α-emitting, radionuclides can be used to obtain pain relief.

3.3.2.2 Radiopharmaceuticals

β-Emitting isotopes

The most important β-emitting radiopharmaceuticals are: strontium-89 chloride (^{89}Sr) and samarium-153 lexidronam (^{153}Sm ethylenediaminetetramethylenephosphonate [EDTMP]) They are indicated for the treatment of bone pain resulting from skeletal metastases with an osteoblastic response on bone scan but without spinal cord compression (14-22) (LE: 2) or pathological fracture (14,17,23) (LE: 2).

These radiopharmaceuticals are delivered intravenously. The patient can pose a radiation exposure risk for 2-4 days after ^{153}Sm, and 7-10 days after ^{89}Sr (17,19-21,23-30) (LE: 2). Information about

radioprotection should be provided. If the pain responds to the initial treatment, administration of ^{153}Sm can be repeated at intervals of 8-12 weeks in the presence of recurrent pain (14,30,31) (LE: 2).The response rate for second and subsequent treatments may be lower than for the first (14,18,23,30) (LE: 2).

Side effects:
About 10% of patients experience a temporary increase in bone pain (pain flare) (32-35), generally 2-4 days after ^{153}Sm, and 1-2 weeks after ^{89}Sr (acute side effect) (17,18). Pain flare is associated with a good clinical response (LE: 2) (32-35), and sometimes requires a transient increase in analgesia. Pain reduction is unlikely to occur within the first week, and can occur as late as 1 month after injection. Late side effects include temporary myelosuppression (platelets and white blood cells). Recovery occurs 4-6 weeks later, depending on bone marrow reserve. There is generally no significant effect on haemoglobin.

Recommendations	**LE**	**GR**
Radiopharmaceuticals are an option for patients with multifocal pain bone metastases when other treatments such as radiotherapy, hormone therapy or bisphosphonates have failed.	2b	B
β-Emitting radiopharmaceutical are contraindicated within 4 weeks of myelotoxic chemotherapy (except for cisplatin), or within 12 weeks of hemi-body radiotherapy.	3	C
β-Emitting radiopharmaceuticals are mainly excreted in urine so precautions must be taken with urine or blood spills for the first 10 days after treatment.	4	A
β-Emitting radiopharmaceuticals provide an overall survival benefit in patients with CRPC and bone metastases.	1b	A

CRPC = castration-resistant prostate cancer

Absolute contraindications:
- During or within 4 weeks of myelotoxic chemotherapy (all compounds except cisplatin), or within 12 weeks of hemi-body external radiotherapy in order to avoid severe haematopoietic toxicity.
- Known hypersensitivity to EDTMP or similar phosphonate compounds for ^{153}Sm (14).
- Glomerular filtration rate (GFR) < 30 mL/min (14,31).
- Pregnancy; continued breastfeeding (31).

Relative contraindications:
- In acute or chronic severe renal failure (GFR 30-60 mL/min), the dose administered should be adapted.
- With a single painful lesion: external limited field radiotherapy should be performed (36,37).

Caution must be used in the following circumstances:
- Urinary incontinence: special recommendations apply, including catheterisation before administration of the radionuclide (32).
- White blood cell count of < 2500/µL (31).
- Platelets < 80,000/µL (31).
- Haemoglobin < 90 g/L (31).

α-Emitting isotopes: radium-223
α-Particle therapy represents a new concept that has also been successful in prolonging survival in phase III clinical trials (38). Unlike β-emitting radiopharmaceuticals, α-pharmaceuticals, such as ^{223}Ra, deliver an intense and highly localised radiation dose to bone surfaces (39). ^{223}Ra thus has potentially better efficacy and tolerability when compared to β-emitters.

In clinical trials, treatment is administered by iv injection once monthly for 4 or 6 months (40-42). No imaging dose or premedication are required. No radiation protection procedures are required.

Pain response was seen in up to 71% of the patients with a dose response observed 2 weeks after administration (43). ^{223}Ra has a favourable safety profile with little or no myelotoxic effect (44,45).

A recently completed phase III study has proven that ^{223}Ra provides an overall survival benefit in patients with CRPC and bone metastases (38). ^{223}Ra is expected to receive approval by various regulatory agencies in the near future.

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

3.3.3.1 Clinical background

Radiotherapy alleviates metastatic bone pain in approximately 70% of patients, with complete pain relief at the treated site in up to 40% of patients (46-48) (LE: 1a). The onset of pain relief varies from a few days to 4 weeks (48) (LE: 2b). The median duration of pain relief reported by most studies is 3-6 months (48) (LE: 1a).

3.3.3.2 Radiotherapy scheme

Single-fraction radiotherapy is as effective as multifraction radiotherapy in relieving metastatic bone pain (47-53) (LE: 1a). However, the rates of retreatment and pathological fractures are significantly higher after single-fraction radiotherapy (47,48,54) (LE: 1a).

Single-fraction radiotherapy remains the treatment of choice for alleviating bone pain because of its greater convenience for patients (LE: 1a), faster patient turnover for the radiotherapy unit (55) and lower costs (53,56) (LE: 3). The recommended dose is 8 Gy (48-53,57,58) (LE: 1a). Pain relief can be achieved with lower doses (1) (LE: 1b). These lower doses should be borne in mind if a third retreatment is necessary, or if there is concern about radiation tolerance (48) (LE: 2b).

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

3.3.3.3 Spinal cord compression

Metastatic epidural spinal cord compression (MSCC) is a common, severe complication of malignancy. The most common symptom is back pain (83-95%), and weakness is present in 35-75%. When spinal cord compression is suspected, magnetic resonance imaging (MRI) is currently the gold standard for detection and therapeutic management (59-63) (LE: 2b), with sensitivity of 93% (64) (LE: 3) and specificity of 96% (64) (LE: 3). The level of neurological function at the start of treatment determines the functional outcome (65).

Corticosteroids reduce oedema and may have an oncolytic effect on certain tumours. However, the extent of the benefit and the optimal dosage are unclear. High-dose corticosteroids carry a significant risk of adverse effects. One RCT of patients with MSCC showed significantly better functional outcome when radiotherapy was combined with dexamethasone (66) (LE: 1b).

Radiotherapy is generally the treatment of choice. A multifraction regimen (10 × 3 Gy) is preferable in these patients because it allows for a higher dose and thus greater reduction in tumour size. For patients whose chances of survival are estimated to be poor, a short course of radiotherapy is advised (67) (LE: 1b).

Several uncontrolled surgical trials (59,61,63) and one meta-analysis (60) have indicated that direct decompressive surgery is superior to radiotherapy alone with regard to regaining ambulatory and sphincter function, and obtaining pain relief (LE: 1a). However, the decision to pursue surgery must be tempered by awareness of the attendant significant morbidity and mortality risks. Careful patient selection is of utmost importance; the criteria are shown in Table 3 (LE: 3).

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

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

A randomised prospective trial has demonstrated that patients treated with a combination of surgery followed by radiotherapy can remain ambulatory longer, and those who are not ambulatory at presentation have a better chance of regaining ambulatory function than those treated with radiotherapy alone (62) (LE: 1b).

3.3.3.4 Pathological fractures

In patients with impending pathological fractures (e.g., femoral lesion with an axial cortical involvement > 30 mm), a prophylactic orthopaedic procedure should be considered (64).

3.3.3.5 Side effects

Side effects are related to the total dose, fractionation size, and the localisation of the metastases. Acute grade 2-4 toxicity is more frequent after multifraction radiotherapy regimens. The incidence of late toxicity is low (54). The side effects are mostly transient, lasting a few days and include:

1. Pain flare (within 24 h and due to oedema). Patients should be counselled accordingly and given breakthrough opioids. Patients receiving single-fraction radiotherapy may be at higher risk than those receiving multifraction radiotherapy (68). A small phase II study has shown that 8 mg dexamethasone is effective for prophylaxis of radiotherapy-induced pain flare after palliative radiotherapy for bone metastases (69) (LE: 3).
2. Symptoms depending on the treatment field and location: nausea (especially with larger fields), vomiting, diarrhoea, irritation of the throat and oesophagus.

3.3.4 ***Psychological and adjunctive therapy***

3.3.4.1 Psychological therapies

The perception of pain and the suffering it causes derive from a combination of physical, emotional, spiritual, and social constructs. Psychological assessment and support are an integral and beneficial part of treating pain in cancer patients (70-72).

There is evidence that highly emotional cancer patients, as detected through their own narratives, experience less pain than their less emotional counterparts (73). Cultural differences also play a role in pain perception (74).

Depression is the most prevalent psychiatric diagnosis in patients with cancer. Although there is no proof that psychotherapy is useful in non-cancer patients with depression, patients with incurable cancer can benefit from this type of treatment (75). In this setting, structured psychotherapy seems to be more effective than antidepressant medication (76). Interestingly, effective psychological management results in a reduction in depressive complaints, inflammatory markers, pain, and fatigue in cancer patients (77).

Cognitive behavioural therapy (CBT), such as relaxation and distraction, can provide pain relief (78-80). As expected, protocols tailored to individual patient characteristics can result in higher satisfaction in terms of pain relief, mood improvement and general well-being. The possibility of delivering CBT by home visits, telephone, or through the internet seems promising (81-83). Virtual consultation and automated symptom monitoring for cancer patients with depression can exceed all expectations (84). It has also been suggested that CBT may be particularly helpful for younger cancer patients (85).

More recently, the effects of dignity therapy on distress and end-of-life experience have been formally tested. Dignity therapy is based on a formal written narrative of the patient's life. Its benefits in terms of end-of-life experiences might support its clinical application (86). Families can be dysfunctional (e.g., emotionally and organisationally) during palliative care and bereavement. Family-focused grief therapy based on communication, cohesiveness, conflict resolution, and shared grief is effective in protecting family members against the drama of disease and death (87). Other psychological interventions that aim to minimise caregiver emotional distress have not been effective (88). Overall, educational programmes that aim to maximise family and patient satisfaction with pain treatment seem promising (89).

The impact of early detection of psychological distress may improve health outcomes (90). There is also a real need for screening the patient's desire for psychological support, as well as patient distress. This may include psychological interventions according to the patient's needs and desires (91). Different tools are available to better assess patients' needs, such as Palliative Care Needs Assessment Guidelines and Needs Assessment Tool (92) and the short form of the Supportive Care Needs Survey (SCNS-SF34) (93).

Recommendation	LE	GR
Always offer psychological support to cancer patients and their loved ones.	1a	A

3.3.4.2 Adjunctive therapy

A number of therapeutic strategies have been proposed as non-pharmacological adjunctives to medical and surgical procedures. To date, there is no conclusive evidence on the effect of reflexology and massage therapy (94-96). Nevertheless, certain manipulations (e.g., sciatic nerve press) seem to be effective for immediate pain relief in many oncological conditions (97). The notion that acupuncture may be effective for cancer patients is

not supported by the currently available data (98,99). However, modest although significant improvements in depression and pain scales have been confirmed by well-conducted studies on acupuncture (100).

Evidence from robust studies is still lacking on the effect of traditional Chinese medicine and complementary alternative medicine (101,102). The effect of cupping therapy - an ancient form of medicine in which suction is created on the skin - on pain needs to be more rigorously tested (103).
Physical exercise (short walks) can positively affect the pain experience of prostate cancer (PCa) patients (104). Similarly, moderate exercise positively affects cancer-related sleep disturbance (105). TENS might mitigate hyperalgesia in cancer patients. Unfortunately, reliable studies in this field are lacking (106).

Listening to music slightly reduces distress, pain intensity and opioid requirements in cancer patients (107,108). Music relaxation videos seem to positively affect pain severity, opioid consumption, and anxiety level in patients treated for some gynaecological tumours (109). It is likely that patients harbouring urological tumours could also benefit.

Strong evidence on the real potential of cannabis derivatives is lacking (110).

Evidence exists of the strong relationship between pain, anxiety and depression, and health-related QoL in cancer patients (111,112). Sexual dysfunction is a potential long-term complication of cancer treatment. Following treatment for PCa, transurethral alprostadil and vacuum constriction devices reduce sexual dysfunction, although negative effects are common. Vaginal lubricating creams are also effective, as are PDE5 inhibitors (PDE5Is) for sexual dysfunction secondary to prostate cancer treatment (113). Psychological interventions focused on sexual dysfunction following cancer can be considered as moderately effective (114).

Recommendations	LE	GR
Moderate exercise can be an adjuvant and should be suggested in the treatment of cancer pain.	1a	A
Acupuncture and traditional Chinese medicine have not been proven effective in the treatment of cancer pain.	1a	A

3.4 Pharmacotherapy

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

*3.4.1 **Chemotherapy***

A successful effect on pain is generally related to tumour response. There is a strong clinical impression that tumour shrinkage is generally associated with relief of pain, although there are some reports of analgesic benefit even in the absence of significant tumour shrinkage (115) (LE: 1a).

*3.4.2 **Bisphosphonates***

3.4.2.1 Mechanisms of action

- Inhibition of bone resorption: beginning 24-48 h after administration. Target cells are the osteoclasts. There are three different mechanisms of inhibition of bone resorption corresponding to the three generations of bisphosphonates. There are four distinct effects on osteoclasts:
  - reduction of osteoclastic activity
  - inhibition of osteoclast adhesion
  - decrease in number of osteoclasts
  - induction of osteoclast apoptosis.
- Inhibition of crystallisation and mineralisation: clinically not relevant.
- Promotion of osteoblastic bone formation and production of osteoclast resorption inhibitor.
- Anti-angiogenic effect and effect on tumour cells.

3.4.2.2 Effects and side effects

The main effects are:

- decrease of the risk of skeleton-related events (116) (LE: 1b);
- pain relief in 60-85% of patients (116-118) (LE: 1b).

The main side effects are:

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

Recommendations	LE	GR
Dehydration must be recognised and treated before administration.		B
When using zoledronate, reduce the dose in the event of impaired renal function (119).	2	B
Avoid simultaneous administration of aminoglycosides (120).		B
Perform clinical examination of the patient's mouth and jaws; avoid oral/dental surgery during administration of iv bisphosphonates (121-125).	2	B

*3.4.3 **Denosumab***

Histological findings and analysis of bone turnover markers support the view that bone metastases from PCa are characterised by an excess osteoclastic activity inducing bone destruction. This results in an increased risk of skeletal-related events (SREs), such as pathologic fractures, spinal cord compression, pain requiring radiotherapy or surgery, and hypercalcemia. The receptor activator of nuclear factor-kB ligand (RANKL), mediates the formation, function, and survival of osteoclasts. Tumour cells induce osteoclast activation, which then mediates bone resorption and releases growth factors, resulting in a cycle of bone destruction and tumour proliferation.

Denosumab is a fully human monoclonal antibody that specifically binds and neutralises RANKL, inhibiting osteoclastogenesis and decreasing osteoclast-mediated bone destruction (126). Improvement in bone-metastases-free-survival (4.3 months) and increased time to first bone metastasis (3.7 months) has been reported with denosumab in a phase III randomised placebo controlled trial (127).

Another recently published phase III study, randomised men with CRPC and no previous exposure to iv bisphosphonate between 120 mg subcutaneous denosumab plus iv placebo, or 4 mg iv zoledronic acid plus subcutaneous placebo, every 4 weeks until the primary analysis cut-off date. Denosumab significantly delayed the time to first onstudy skeletal-related event by 18% compared to zoledronic acid, with a between-group difference of 3-6 months (128). Occurrences of adverse events and serious adverse events were similar between groups. More events of hypocalcaemia occurred in the denosumab group (121 [13%]) than in the zoledronic acid group (55 (6%); p<0.0001). Osteonecrosis of the jaw was infrequent in both groups. The authors concluded that denosumab was better than zoledronic acid for prevention of skeletal-related events, and potentially represents a novel treatment option in men with bone metastases from CRPC (128).

A large randomised study (1432 patients) showed that denosumab significantly increased bone-metastasis-free survival by a median of 4.3 months compared to placebo (median 29.5 (95% CI 25.4-33.3) vs 25.2 (22.2-29.5) months; hazard ratio (HR) 0.85, 95% CI 0.73-0·98, P=0.028). Denosumab also significantly delayed time to first bone metastasis (33.2 (95% CI 29.5-38.0) vs 29.5 (22.4-33.1) months; HR 0.84, 95% CI 0.71-0.98, P=0.032). Overall survival did not differ between groups (denosumab, 43.9 (95% CI 40.1-not estimable) months vs placebo, 44.8 (40.1-not estimable) months; HR 1.01, 95% CI 0.85-1.20, P=0·91). Rates of adverse events and serious adverse events were similar in both groups (127).

Recommendation	LE	GR
Denosumab use increases bone-metastasis-free survival and delays time to first bone metastasis in prostate cancer patients.	1b	A

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

Analgesic pharmacotherapy is the mainstay of cancer pain management (129-131). Although concurrent use of other interventions is valuable in many patients, and essential in some, analgesic drugs are needed in almost every case. Based on clinical convention, analgesic drugs can be separated into three groups:

- Non-opioid analgesics.
- Opioid analgesics.
- Adjuvant analgesics.

Emphasising that pain intensity should be the prime consideration, the WHO has proposed a three-step approach to analgesic selection for cancer pain (129,131) (LE: 1a). Known as the analgesic adder, when

combined with appropriate dosing guidelines it can provide adequate relief in 70-90% of patients (132,133).

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

3.4.4.1 Non-opioid analgesics

- Non-opioid analgesics are paracetamol, metamizole (dipyrone) and non-steroidal anti-inflammatory drugs (NSAIDs).
- Can be useful alone for mild to moderate pain (step 1 of the analgesic ladder).
- May be combined with opioids.
- Have a ceiling effect of analgesic efficacy.
- No tolerance or physical dependence.
- Inhibit the enzyme cyclo-oxygenase and block the synthesis of prostaglandins.
- Involvement of central mechanisms is also likely in paracetamol analgesia (134).
- Potential adverse effects: bleeding diathesis due to inhibition of platelet aggregation, gastroduodenopathy (including peptic ulcer disease) and renal impairment are the most common; less common adverse effects include confusion, precipitation of cardiac failure and exacerbation of hypertension. Particular caution must be used in elderly patients and those with blood-clotting disorders, predisposition to peptic ulceration, impaired renal function and concurrent corticosteroid therapy (135).
- Non-acetylated salicylates (choline magnesium trisalicylate and salsalate) are preferred in patients who have a predilection to bleeding; these drugs have less effect on platelet aggregation and no effect on bleeding time at the usual clinical doses.
- Paracetamol rarely produces gastrointestinal toxicity, but, if this occurs, with no adverse effect on platelet function. Hepatic toxicity is possible, however, and patients with chronic alcoholism and liver disease can develop severe hepatotoxicity at the usual therapeutic doses (136).

3.4.4.2 Opioid analgesics

Cancer pain of moderate or severe intensity should generally be treated with a systemically administered opioid analgesic (137). Classification is based on interaction with the various receptor subtypes:

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

By convention, the relative potency of each of the commonly used opioids is based on a comparison with 10 mg parenteral morphine. Equianalgesic dose information provides guidelines for dose selection when the drug or route of administration is changed (138).

A trial of systemic opioid therapy should be administered to all cancer patients with moderate or severe pain (138-141). Patients who present with severe pain should be treated with a strong opioid from the outset. Patients with moderate pain are commonly treated with a combination drug containing paracetamol or aspirin plus codeine, tramadol, or propoxyphene, the dose of which can be increased until the maximum dose of the non-opioid co-analgesia is attained (e.g. 4000 mg paracetamol).

Factors to consider when selecting an opioid include:

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

Routes of administration

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

Non-invasive routes

- **Oral** routes are the preferred approach in routine practice. Alternative routes are necessary for patients who have impaired swallowing, gastrointestinal dysfunction, require a very rapid onset of analgesia, or cannot tolerate the oral route.
- **Rectal** suppositories containing oxycodone, hydromorphone, oxycodone and morphine in combination are available, and controlled-release morphine tablets can also be administered per rectum. The potency of rectally administered opioids is believed to approximate to oral dosing (142).
- **Transdermal** routes: fentanyl and buprenorphine have been demonstrated to be effective in postoperative and cancer pain (143). There is some interindividual variability in fentanyl bioavailability by this route, which, combined with large differences in elimination pharmacokinetics, necessitates dose titration in most cases (144). The efficacy of transdermal fentanyl is equal to morphine. The incidence of side effects such as sedation and constipation are lower than for morphine (145,146) (LE: 1b).
  - Transdermal patches able to deliver 12, 25, 50, 75 and 100 mg/h are available. Multiple patches can be used simultaneously for patients who require higher doses. Current limitations of the transdermal delivery system include costs, and the need for an alternative short-acting opioid for breakthrough pain.
  - Recently, buprenorphine has become available for transdermal administration. A high affinity partial μ-opioid agonist, it is in clinical use for the treatment of acute and chronic pain (147). Its analgesic effect is comparable with that of other opioids, and it shows no relevant analgesic ceiling effect throughout the therapeutic dose range (148). Unlike full μ-opioid agonists, buprenorphine's physiological and subjective effects, including respiratory depression and euphoria, reach a plateau at higher doses. This ceiling may limit the abuse potential, and might result in a wider safety margin (149).
- **Sublingual** absorption of any opioid is potentially clinically beneficial, but bioavailability is very poor with drugs that are not highly lipophilic, so the chances of an adequate response are low (150). Sublingual buprenorphine, a relatively lipophilic partial agonist, can provide adequate relief for mild to moderate cancer pain. Overall, this route has limited value due to the lack of formulations, poor absorption of most drugs, and the inability to deliver high doses or prevent swallowing of the dose. An oral transmucosal formulation of fentanyl (incorporated into a sugar base) is useful for the rapid relief of breakthrough pain (151,152). Fentanyl delivered by this means is more effective than oral morphine at relieving pain (LE: 2).

Recommendations	LE	GR
Transdermal fentanyl is equally effective to morphine. The incidence of side effects is lower than for morphine.	1b	A
Oral transmucosal administration of fentanyl should be used to provide rapid relief of breakthrough pain. The starting dose is 400 μg, or 200 μg in the elderly and those with a history of opioid sensitivity or underlying pulmonary disease.	2a	B

Invasive routes

For patients undergoing a trial of systemic drug administration, a parenteral route must be considered when the oral route is not available. Repeated parenteral bolus injections, which can be administered iv, intramuscularly (im) or subcutaneously (sc), may be useful in some patients, but are often compromised by the occurrence of prominent bolus effects (toxicity at peak concentration and/or pain breakthrough at the trough). Repeated im injections are common, but are painful and offer no pharmacokinetic benefit; their use is not recommended (153).

- **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 min for methadone, to 10-15 min for morphine ((154). This approach is appropriate in two settings:
  - To provide parenteral opioids, usually transiently, to patients who already have venous access and are unable to tolerate oral opioids.
  - To treat very severe pain, for which iv doses can be repeated at an interval as brief as that determined by the time to peak effect until adequate relief is achieved.
- **Continuous parenteral infusions** is mainly used in patients who are unable to swallow, absorb opioids or otherwise tolerate the oral route, but is also employed in patients whose high opioid requirement renders oral treatment impractical (155). Long-term infusions can be administered iv or sc.
  - Ambulatory patients can easily receive a continuous sc infusion using a 27-gauge butterfly

needle, which can be left in place for up to a week. A recent study demonstrated that the bioavailability of hydromorphone by this route is 78% (156), and clinical experience suggests that dosing can be identical to that for continuous iv infusion. A range of pumps is available to provide patient-controlled rescue doses (supplemental doses offered on an as-needed basis to treat pain that breaks through the regular schedule) as an adjunct to continuous basal infusion.

- Opioids suitable for continuous sc infusion must be soluble, well absorbed and non-irritant. Extensive experience has been reported with hydromorphone, oxycodone and morphine (157). Methadone appears to be relatively irritating and is not preferred (158). To maintain the comfort of an infusion site, the sc infusion rate should not exceed 5 mL/h.
- The infraclavicular and anterior chest sites provide the greatest freedom of movement for patients, but other sites can be used. A single infusion site can usually be maintained for 5-7 days.

Opioid switching

A systematic search was developed to include studies after 2004, with cancer patients switching between strong opioids and reporting pain control and adverse effects, usually from morphine or oxycodone to methadone. The search reviewed 288 papers, among which, only 11 (280 patients) met the inclusion criteria. Pain intensity was significantly reduced in the majority of studies, and there were fewer serious adverse effects (159).

Changing the route of administration

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

Dosing

- **A round-the-clock dosing**. Patients with continuous or frequent pain generally benefit from scheduled around-the-clock dosing, which provides continuous relief by preventing recurrence of the pain. This approach should be used only in patients with no previous opioid exposure. Patients should also be provided with a rescue dose. This combination offers gradual, safe and rational dose escalation that is applicable to all routes of opioid administration.
- **Controlled-release drug formulations**. These preparations of oral opioids can lessen the inconvenience of around-the-clock administration of drugs with a short duration of action. Numerous studies have demonstrated the safety and efficacy of these preparations in cancer patients with pain (160,161).
- **As-needed (prn) dosing**. This strategy is beneficial if rapid dose escalation is necessary or when beginning therapy with opioids with a long half-life (e.g., methadone or levorphanol). As-needed dosing may also be appropriate for patients who have rapidly decreasing analgesic requirements, or intermittent pains separated by pain-free intervals.
- **Patient-controlled analgesia (PCA)**. This is a technique of parenteral drug administration in which the patient controls an infusion device that delivers a bolus of analgesic drug on demand according to parameters set by the physician. Long-term PCA in cancer patients is most commonly sc using an ambulatory infusion device. PCA is usually added to a basal infusion rate and acts, in effect, as a rescue dose.

Adverse effects and their management

- **Tolerance.** There is great variation in the opioid dose required to manage pain (400-2000 mg im morphine per 24 h) (162). The induction of true analgesic tolerance that could compromise the utility of treatment can only be said to occur if a patient manifests the need for increasing opioid doses in the absence of other factors (e.g., progressive disease) that would be capable of explaining the increase in pain. Extensive clinical experience suggests that most patients who require dose escalation to manage increasing pain do have demonstrable disease progression (163). This suggests that true pharmacological tolerance to the analgesic effects of opioids is not a common clinical problem, and has two important implications:
  - Concern about tolerance should not impede the use of opioids early in the course of the disease.
  - Worsening pain in patients receiving a stable dose of opioids should not be attributed to tolerance, but be assessed as evidence of disease progression or, less commonly, increasing psychological distress.

- **Adverse drug interactions.** There is potential for cumulative side effects and serious toxicity to arise from combinations of drugs. The sedative effect of an opioid may add to that of other centrally acting drugs, such as anxiolytics, neuroleptics and antidepressants. Likewise, constipation produced by opioids is probably worsened by anticholinergic drugs.
- **Respiratory depression.** This is the most serious adverse effect of opioid therapy, which can impair all phases of respiratory activity (rate, minute volume and tidal exchange). Clinically significant respiratory depression is always accompanied by other signs of central nervous system depression, including sedation and mental clouding. Repeated administration of opioid drugs appears to produce a rapid tolerance to their respiratory depressant effects, however, so these drugs can be used in the management of chronic cancer pain without significant risk of respiratory depression. When this does occur in patients on chronic opioid therapy, administration of the specific opioid antagonist naloxone usually improves ventilation.
- **Sedation.** Tolerance to this effect usually develops within a period of days to weeks. Patients should be warned about it, to reduce anxiety and discourage activities that could be dangerous if sedation occurs (e.g., driving). Some patients have a persistent problem with sedation, particularly if other sedating drugs are also being taken or if there is comorbidity such as dementia, metabolic encephalopathy, or brain metastases.
- **Confusion and delirium.** Confusion is a greatly feared effect of opioid drugs, and mild cognitive impairment is common (164). However, similar to sedation, pure opioid-induced encephalopathy appears to be transient in most patients, persisting from days to 1-2 weeks. Although persistent confusion attributable to opioids alone does occur, it is usually related to the combined effect of the opioid and other factors, including electrolyte disorders, neoplastic involvement of the central nervous system, sepsis, vital organ failure and hypoxaemia (165). A stepwise approach to management often culminates in a trial of a neuroleptic drug. Haloperidol in low doses (0.5-1.0 mg orally or 0.25-0.5 mg iv or im) is most commonly recommended because of its efficacy and low incidence of cardiovascular and anticholinergic effects.
- **Constipation.** This is the most common adverse effect of chronic opioid therapy (166-168), and laxative medication should be prescribed prophylactically. Combination therapy is frequently used, particularly co-administration of a softening agent (e.g. docusate) and a cathartic (e.g., senna, bisocodyl or phenolphthalein). The doses should be increased as necessary, and an osmotic laxative (e.g. magnesium sulphate) should be added if required. Chronic lactulose therapy is an alternative that some patients prefer, and the occasional patient is managed with intermittent colonic lavage using an oral bowel preparation.
- **Nausea and vomiting.** Opioids may produce nausea and vomiting via both central and peripheral mechanisms. These drugs stimulate the medullary chemoreceptor trigger zone, increase vestibular sensitivity, and affect the gastrointestinal tract (increased gastric antral tone, diminished motility, delayed gastric emptying). The incidence of nausea and vomiting in ambulatory patients is estimated to be 10-40% and 15-40%, respectively (169), with the effects greatest at the start of therapy. Metoclopramide is the most reasonable initial treatment. Tolerance typically develops within weeks. Routine prophylactic administration of an anti-emetic is not necessary. Serotonin antagonists (e.g., ondansetron) are not likely to be effective with opioid-induced symptoms as they do not eliminate apomorphine-induced vomiting and motion sickness, which appear to be appropriate models for opioid effects. Clinical trials are needed to confirm this.
- **Addiction and dependence.** Confusion about physical dependence and addiction augments the fear of opioids and contributes substantially to the undertreatment of pain (170). Patients with chronic cancer pain have a so-called therapeutic dependence on their analgesic pharmacotherapy, which may or may not be associated with the development of physical dependence, but is seldom associated with addiction. The medical use of opioids is rarely associated with the development of addiction (171). There are no prospective studies in patients with chronic cancer pain, but extensive clinical experience affirms the low risk of addiction in this population (LE: 3). Healthcare providers, patients and families often require vigorous and repeated reassurance that the risk of addiction is small.

Recommendation	LE	GR
Inform the patient that the use of morphine has a small risk of addiction.	3	A

Adjuvant analgesics

Defined as a drug that has a primary indication other than pain but is analgesic in some conditions,. These drugs may be combined with primary analgesics on any of the three steps of the analgesic ladder to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side effects. In

the management of cancer pain, adjuvant analgesics are conventionally categorised as follows.

- **Corticosteroids.** Widely used as adjuvant analgesics (172,173), this group has been demonstrated to have analgesic effects, to improve QoL significantly (174), and to have beneficial effects on appetite, nausea, mood and malaise in patients with cancer (175). The mechanism of analgesia may involve anti-oedemic and anti-inflammatory effects, plus a direct influence on the electrical activity in damaged nerves. (i.e., reduction of neuropathic pain). Patients with advanced cancer who experience pain and other symptoms may respond favourably to a relatively small dose of corticosteroids (e.g. dexamethasone 1-2 mg twice daily) (LE: 2a).
- **Benzodiazepines.** These drugs have a small analgesic effect (176), and must be balanced by the potential for side effects, including sedation and confusion. Benzodiazepines are generally used only if another indication exists, such as anxiety or insomnia (LE: 2b).

Recommendation	LE	GR
Dexamethasone 1-2 mg twice daily can be a valuable adjuvant in the treatment of pain in advanced cancer.	2a	B

*3.4.5 **Treatment of neuropathic pain***

Numerous options are available for relieving neuropathic pain, including opioids, which give patients significant pain reduction with greater satisfaction than antidepressants (177,178). However, the potential complications of opioids mean that they are not always a satisfactory option (179). Beside opioids, effective therapies for managing neuropathic pain include antidepressants, anticonvulsants, topical treatments (lidocaine patch, capsaicin), N-methyl-D-aspartate (NMDA) receptor antagonists, baclofen, local anaesthetics, and clonidine (180,181).

3.4.5.1 Antidepressants

There is clear evidence for the effectiveness of antidepressants in the treatment of neuropathic pain (180). Antidepressants which work primarily via interaction with pathways running through the spinal cord from serotoninergic and noradrenergic structures in the brain stem and mid-brain.

Tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline (metabolite of amitriptyline), imipramine, and desipramine (metabolite of imipramine) are often the first drugs selected to alleviate neuropathic pain (182,183) (LE: 1a). The mechanism of action is predominantly by blocking the reuptake of norepinephrine and serotonin (dual acting), together with a blockade of neuronal membrane ion channels (reducing neuronal influx of $Ca2^{+}$ or Na^{+}), and interaction with adenosine and NMDA receptors. However, treatment with these analgesics may be compromised (and outweighed) by their side effects. TCAs must be used cautiously in patients with a history of cardiovascular disorders, glaucoma, and urine retention. In addition, combination therapy with monoamine-oxidase inhibitors could result in the development of serotonin syndrome.

Duloxetine enhances both serotonin and norepinephrine function in descending modulatory pathways. It has weak affinity for the dopamine transporter and insignificant affinity for several neurotransmitters, including muscarinic, histamine, glutamate, and gamma-aminobutyric acid (GABA) receptors. Duloxetine has demonstrated a significant pain-relieving effect with a generally favourable side-effect profile in painful diabetic neuropathy (182) (LE: 1b).

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

Recommendations	LE	GR
Offer amitriptyline and nortriptyline as a first line treatment for neuropathic pain, with nortriptyline associated with fewer side effects.	1b	A
TCAs must be used cautiously in patients with a history of cardiovascular disorders, glaucoma, and urine retention.	1b	A
Duloxetine is first-line treatment for neuropathic pain due to diabetic polyneuropathy.	2a	A
Duloxetine may be tried as an analgesic in other neuropathic pain syndromes.	3	C

3.4.5.2 Anticonvulsant medication

The rationale for the use of anticonvulsant drugs in treating neuropathic pain is the reduction of neuronal hyperexcitability, one of the key processes in the development and maintenance of neuropathic pain (184).

Different anticonvulsants have demonstrated pain relief by a blockade of neuronal membrane ion channels (reducing neuronal influx of $Ca2^{+}$ or Na^{+}), and effects on neurotransmitters (enhancement of GABA, inhibition of glutamate release) and/or neuromodulation systems (blocking the NMDA receptor) (185,186). Carbamazepine and phenytoin were initially used for the treatment of trigeminus neuralgia. Although both drugs reduce neuropathic pain, their attendant side effects and complicated pharmacokinetic profile limit their use.

Despite the introduction of newer anticonvulsants with better side effect profiles, carbamazepine remains the drug of choice for treating trigeminus neuralgia (187) (LE: 1a). However, oxcarbazepine (10-keto analogue of carbamazepine), a new anticonvulsant with a similar mechanism of action to that of carbamazepine but with a better side effect profile, may replace carbamazepine for this purpose (188).

Gabapentin and pregabalin are first-line treatments for neuropathic pain (reducing elements of central sensitisation), especially in post-zoster neuralgia and diabetic polyneuropathy (189-191) (LE: 1a). The combination of gabapentin with opioids seems to display synergistic effects in relieving neuropathic pain (192,193). Gabapentin has a favourable safety profile with minimal concern for drug interactions and no interference with hepatic enzymes. However, renal failure results in higher gabapentin concentrations and a longer elimination half-life, making dose adjustments necessary. Pregabalin (3-isobutyl GABA) is a structural analogue of gabapentin, but shows greater analgesic activity in rodent models of neuropathic pain than did gabapentin (194). Recent studies confirm the effectiveness of pregabalin in peripheral (including post-herpetic neuralgia and diabetic polyneuropathy) and central neuropathic pain (195).

Recommendation	LE	GR
Offer gabapentin and pregabalin as first-line treatment for neuropathic pain, especially if tricyclic antidepressants are contraindicated.	1b	A

3.4.5.3 Local analgesics

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

Local treatments for neuropathic pain include the 5% lidocaine patch, and capsaicin. The 5% lidocaine patch, a targeted peripheral analgesic, is effective in the treatment of post-herpetic neuralgia and a variety of other focal peripheral neuropathies (196,197) (first-line pharmacological treatment; LE: 1b). Once a day, up to three patches are applied to the painful skin, covering as much of the affected area as possible.

Capsaicin causes pain due to release of substance P from the nociceptive terminals, initiating nociceptive firing. An analgesic response follows because prolonged exposure to capsaicin desensitises the nociceptive terminals and elevates the pain threshold. Capsaicin (third-line pharmacological treatment) reduces pain in a variety of neuropathic pain conditions (including post-herpetic neuralgia, diabetic neuropathy and painful polyneuropathy). It is applied in a 0.075% concentration (198) (LE: 3).

Recommendations	LE	GR
Topical lidocaine 5% should be used as an adjuvant in patients suffering from post-herpetic neuralgia.	1b	A
Transdermal capsaicin may be used as an adjuvant in patients with neuropathic pain.	3	C

3.4.5.4 NMDA receptor antagonists

Within the dorsal horn, ionotropic glutamate receptors (NMDA, 2-amino-3-(3-hydroxyl-5-methyl-4-Isoxazole) propionate (AMPA), and kainate) and metabotropic glutamate receptors are all involved in neuropathic pain (170,199). However, the actions of excitatory amino acids (glutamate) on the NMDA receptor is considered a pivotal event in the phenomenon of wind-up and neuronal hyperexcitability (enhancement and prolongation of sensory transmission) that eventually leads to allodynia, and primary and secondary hyperalgesia.

Subanaesthetic doses of ketamine, and its active enantiomer S(+)-ketamine, given parenterally, neuraxially, nasally, transdermally or orally, alleviate pain postoperatively and in a variety of neuropathic pain syndromes, including central pain (200) (LE: 2b). However, ketamine may result in unwanted changes in mood, conscious perception, and intellectual performance, as well as psychomimetic side effects (including visual and auditory hallucinations, dissociation and nightmares), limiting its use for neuropathic pain (199). It must therefore be

reserved as a third-line option when other standard analgesic treatments are exhausted (201,202).

The primary role of low-dose systemic ketamine (bolus 0.25 mg/kg followed by continuous administration at 0.1-0.4 mg/kg/h) is as an antihyperalgesic, antiallodynic, or tolerance-protective compound in patients with severe acute pain, chronic or neuropathic pain, opioid tolerance, or those at risk for developing chronic postsurgical pain (following laparotomy, thoractomy, breast surgery, and nephrectomy) (203,204). In the acute setting ketamine is effective as a rescue analgesic (0.25 mg/kg, iv) for acute pain that is not, or poorly, responsive to opioids (205).

Despite improved and prolonged analgesia following caudal administration of ketamine in paediatric anaesthesia, there remains a controversy in the preclinical (animal) and clinical literature as to the safety and justifiability of this compound for neuraxial administration. In a case report, as well as in an animal study, severe histological abnormalities indicating neurotoxicity were observed following neuraxial administration of ketamine (206,207).

Recommendation	LE	GR
Ketamine is effective as an analgesic in neuropathic pain, but may be responsible for severe life-threatening side effects and should be reserved for specialised pain clinics and as a last resort (third-line treatment).	2b	B

3.4.5.5 Other drug treatments

Baclofen, a muscle relaxant, is analgesic due to its agonistic effect on the inhibitory $GABA_B$ receptors. Baclofen is efficacious in patients with trigeminal neuralgia, but not in those with other neuropathic pain conditions (208). However, this analgesic also has antispasticity properties and may induce analgesia by relieving muscle spasms, a frequent accompaniment of acute neuropathic pain. Baclofen can be considered a second-line agent for trigeminus neuralgia, or a third-line agent in neuropathic pain syndromes (LE: 3).

Clonidine, an α2-adrenoreceptor agonist, is available as a patch for transdermal administration and has been used in neuropathic pain states. When used locally, it seems to enhance the release of endogenous encephalin-like substances, but its use in the treatment of neuropathic pain is focused on intrathecal or epidural administration in combination with opioids and/or local anaesthetics. This delivery improves pain control because of a possible supra-additive effect during neuropathic pain treatment (209) (LE: 2b).

Summary: treatment of neuropathic pain

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

3.4.5.6 Invasive analgesic techniques

Studies suggest that 10-30% of patients with cancer pain do not achieve a satisfactory balance between relief and side effects using systemic pharmacotherapy alone without unacceptable drug toxicity (132,133). Anaesthetic and neurosurgical techniques may reduce the need for systemically administered opioids, while achieving relief.

Peripheral nerve catheterisation in the management of cancer pain

Tumour infiltration or compression of a peripheral nerve or plexus can result in severe neuropathic pain resistant to pharmacological treatment. In these patients invasive analgesic techniques may be emphasised (210,211).

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

GCP = good clinical practice

Neurolytic blocks to control visceral cancer pain

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

Different neurolytic blockades have been described (212,213). A coeliac plexus block is indicated to treat pain secondary to malignancies of the retroperitoneum or upper abdomen (distal part of the stomach, pancreas, liver, gall bladder) (214) (LE: 1b). A superior hypogastric plexus block has proven utility for pelvic pain (rectum, vaginal fundus, bladder, prostate, testes, seminal vesicles, uterus and ovaries) due to a neoplasm that is refractory to pharmacological treatment (215-217) (LE: 3).

Neuraxial administration of opioids

The delivery of low-dose opioids near the sites of action in the spinal cord may decrease supraspinally mediated adverse effects. Compared with neuroablative therapies, spinal opioids have the advantage of preserving sensation, strength and sympathetic function (218,219). Contraindications include bleeding diathesis, profound leukopenia and sepsis. A temporary trial of spinal opioid therapy should be performed to assess the potential benefits of this approach before implantation of a permanent catheter.

The addition of a low concentration of a local anaesthetic, such as 0.125-0.25% (levo)bupivacaine, to an epidural/intrathecal opioid increases the analgesic effect without increasing toxicity (220,221). The potential morbidity of these procedures requires well-trained clinicians and long-term monitoring (LE: 2).

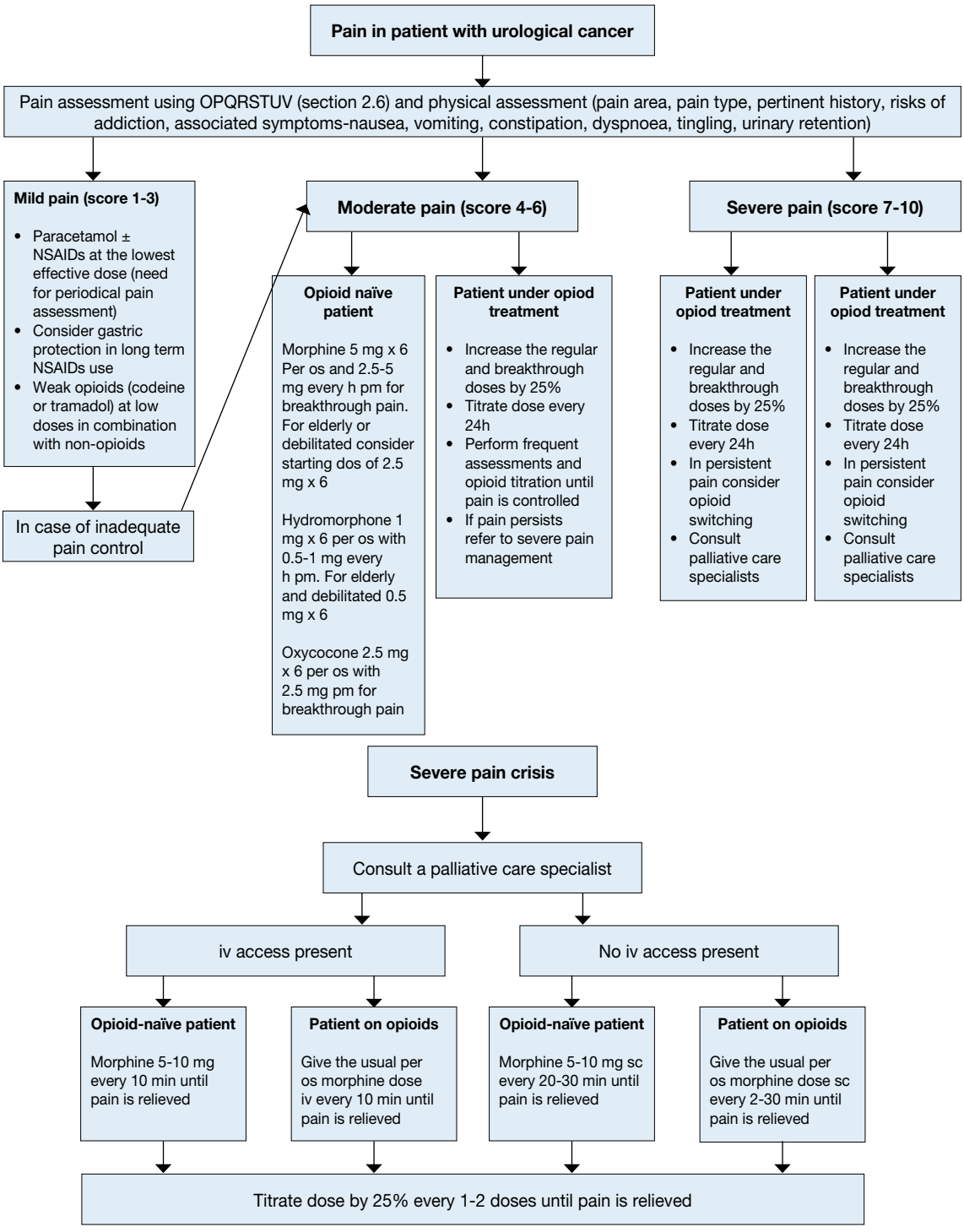
Recommendation	**GR**
Continuous intrathecal or epidural administration of morphine may be considered in patients with inadequate pain relief despite escalating doses with sequential strong opioids, or the development of side effects (nausea, vomiting, constipation, drowsiness, sedation) limiting further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

3.4.6 ***Breakthrough cancer pain***

Breakthrough cancer pain (BTCP) is a common and debilitating problem (222). It has been defined as an increase in pain intensity in patients on regularly administered analgesia. Due to their slow onset of action, oral opioids are not considered to be an efficient treatment for BTCP. Transmucosal, buccal, sublingual and intranasal fentanyl preparations have shown adequate rapid analgesia. Evidence suggests that oral transmucosal fentanyl citrate is effective for BTCP, giving more rapid relief than morphine (223).

All the studies performed have shown that these drugs should be administered to opioid-tolerant patients receiving at least 60 mg/day morphine or its equivalent (224). Proper assessment and classification of BTCP could improve care and support of patients with this syndrome (225) (LE: 1a).

Figure 2: Cancer pain treatment in urology



3.5 Quality of life (QoL)

Patients facing advanced stages of PCa frequently experience 'total pain', a mix of physical, psychological, spiritual and social suffering (226). Information about the illness and the process of care has proven to reduce distress (227,228). Treatment should include both psychological and somatic symptoms (226).

Physical activities adapted to the patient's condition are beneficial in the treatment of fatigue (229-231). Family caregivers and support groups are crucial components of the patient support system. Members of PCa self-help groups provide each other with various types of assistance, usually non-professional and non-material, for a particular shared, usually burdensome, characteristic (228). Help may involve provision and evaluation of relevant information, relating personal experiences, listening to, and accepting the experiences of others, providing sympathetic understanding, and establishing social networks. A supportive self-help group may also inform the public or engage in advocacy. All efforts should be aimed at improvement of QoL (228).

3.6 Conclusions

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

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4. PAIN MANAGEMENT IN UROLOGICAL CANCERS

The prevalence of cancer pain approaches 25% for newly diagnosed cases (1) and > 75% for advanced disease (2,3). This evidence will substantiate the next update on pain management in urological cancers.

4.1 Pain management in prostate cancer patients

For a complementary approach please refer to the EAU Guidelines on Prostate Cancer (4).

*4.1.1 **Clinical presentation***

Pain in both early and advanced PCa can be caused directly by the cancer (77%), be related to the treatment (19%), or be unrelated to either (3%) (5). Management must focus on symptomatic patients with locally advanced disease or metastases.

The overall incidence of chronic pain in PCa patients is about 30-50%, but as patients enter the terminal phase this rises to 90% (6). Pain may be directly attributable to tumour infiltration of and growth in three main areas: bone, nerve or a hollow viscus.

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

4.1.2.1 Invasion of soft tissue or a hollow viscus

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

4.1.2.2 Bladder outlet obstruction

Continuous growth of the prostate can lead to an outlet obstruction. Lower urinary tract symptoms (LUTS) can occur, especially stranguria and an inability to void. Acute pain requires prompt relief. The best method is to insert a suprapubic catheter and treat the tumour according to the stage (4). If the outlet obstruction persists, palliative transurethral resection of the prostate (TURP) is an option if no curative therapy can be offered.

4.1.2.3 Ureteric obstruction

Ureteric obstruction is most frequently caused by tumour compression or infiltration within the true pelvis (7-10). Less commonly, obstruction can be more proximal, associated with retroperitoneal metastases. In most cases, obstruction is primarily asymmetrical. Untreated progressive ureteric obstruction results in bilateral hydronephrosis and subsequent renal failure. It is good practice to drain symptomatic hydronephrosis at once, and to drain only one kidney (the less dilated and better appearing kidney or the one with the better function, if known) in asymptomatic patients. A nephrostomy tube is superior to a double-J stent for drainage because the subsequent routine endoscopic replacement of the stent could be increasingly difficult in a continuously growing prostate gland, and a nephrostomy tube can be changed without anaesthesia. Anterograde ureteral stenting through the nephrostomy site can also be attempted when the patient desires an internal diversion.

4.1.2.4 Lymphoedema

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

4.1.2.5 Ileus

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

4.1.3 ***Pain due to metastases***

4.1.3.1 Bone metastases

- Bone metastases are the most common cause of chronic pain in patients with PCa (11,12) as a result of:
  - endosteal or periosteal nociceptor activation (mechanical distortion or release of chemical mediators);
  - tumour growth into adjacent soft tissues or nerves;
  - other complex mechanisms (12).
- Widespread bony metastases frequently cause multifocal pain. Patients with multiple bony metastases typically report pain in only a few sites.
- More than 25% of patients with bony metastases are pain free (13).
- The factors that convert a painless lesion into a painful one are unknown.

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

The treatment options are:

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

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

4.1.3.2 Hormone therapy

Huggins and Hodges (14) first noted the effect of exogenous oestrogen administration on prostatic carcinoma. A variety of additive or ablative hormone manipulations have been employed, including oestrogen, anti-androgen (cyproterone, flutamide), oestrogen-mustine complex (estramustine), progestogens, aminoglutethimide, gonadotrophin-releasing hormone (GnRH) analogues, orchidectomy, adrenalectomy and hypophysectomy. Corticosteroids are also used for the palliation of pain, particularly pain due to bone deposits.

For more information on hormone therapy, refer to EAU Guidelines on Prostate Cancer (4). Hormone therapy is generally much better tolerated than chemotherapy. It can cause a temporary exacerbation of pain (pain flare), which is generally predictive of a subsequent response (15). In a collected series of protocols, pain relief has been estimated at 35% (16) to 70% (17). This difference may have been due to patient selection and problems with pain measurement. Well-differentiated prostatic carcinoma is more likely to respond to hormones than are poorly differentiated tumours. Manipulations that include replacement corticosteroid therapy or have additional corticoid effects seem to give higher response rates. Corticosteroids are also used for the palliation of pain, particularly in bone metastases.

To date, most patients with adenocarcinoma of the prostate present with early-stage tumours and undergo treatment with curative intent. In cases of disease progression and symptoms, hormone therapy is indicated, with patients remaining asymptomatic for several years.

4.1.3.3 Radiotherapy

- The role of radiotherapy in the management of pain due to bone metastases is unquestionable (18).
- Radiotherapy techniques vary widely, from a large dose given as a single treatment to as many as 20 smaller treatments given over 4 weeks.
- The biological effect of the radiation depends not only on the total dose delivered, but also on the number of separate treatments and the total time over which the irradiation therapy is administered.
- Palliative doses are smaller than maximum tolerance doses.
- It should be noted that radiological evidence of a deposit may considerably underestimate the extent of disease.

In metastatic adenocarcinoma of the prostate, radiotherapy is associated with palliation of pain from bony metastases and improved QoL. Radiation therapy is effective at treating painful sites, and might also be effective at reducing the propensity for adjuvantly treated disease to become symptomatic in most patients (19). New organ limited approaches as the stereotactic ablative radiation therapy (SABR) of vertebral metastases can result in excellent local control (20). This effect does not appear to be significantly influenced by dose-time relationships or histology. The proportion of patients achieving complete pain relief approaches (70%) (21) (Section 3.3.3).

4.1.3.4 Orthopaedic surgery

If more than 50% of the thickness of the cortex of a long bone is eroded by metastasis, prophylactic fixation rather than radiotherapy alone should be considered. Internal fixation should be followed by postoperative radiotherapy because there is a real danger of continued tumour growth and further structural weakness (22,23). 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 (24). The sequential combination of radiofrequency and cementoplasty seems promising for the treatment of painful osseous metastases (25).

4.1.3.5 Radioisotopes

Widespread axial skeletal involvement in PCa has been successfully treated with systemically administered bone-seeking radioisotopes (see also Section 3.3.2). Commonly used radionuclides are ^{89}Sr chloride and ^{153}Sm-EDTMP. The addition of ^{89}Sr as a single injection of 10.8 mCi (399.6 MBq) is an effective adjuvant therapy to local field radiotherapy, reducing disease progression, the requirement for further radiotherapy and analgesic support (26), and improving QoL.

Some evidence suggests that radioisotopes could give complete relief from pain over 1-6 months, with no increase in analgesia, although adverse effects, specifically leukocytopenia and thrombocytopenia, have been reported (26). α-Particle therapy represents a new concept that has been successful in prolonging survival in phase III clinical trials (27). Unlike β-emitting radiopharmaceuticals, α-pharmaceuticals, such as ^{223}Ra, deliver an intense and highly localised radiation dose to bone surfaces (28). ^{223}Ra thus has potentially better efficacy and tolerability when compared with β-emitters.

4.1.3.6 Bisphosphonates

Bisphosphonates can be part of the supportive care for patients with bone metastases and pain (29). Improvement in pain control has been demonstrated (29). They should be considered for the treatment of refractory bone pain in metastatic PCa (30). Zoledronic acid (4 mg intravenously over 15 min every 3-4 weeks) decreased the frequency of skeleton-related events, delayed the time to the first occurrence, and reduced pain (31). Studies are needed to determine the optimal timing, schedule and duration of treatment in men with bone metastases.

4.1.3.7 Denosumab

Denosumab reduces the risk of skeletal events in men with castration-resistant bone-metastatic PCa (32).

4.1.3.8 Calcitonin

Current evidence does not support the use of calcitonin to control pain arising from bone metastases (33).

4.1.3.9 Chemotherapy

In about 80% of men with metastatic PCa, primary androgen ablation leads to symptomatic improvement. The disease eventually becomes refractory to hormone treatment. Systemic chemotherapy should be reserved for this patient group. Recent data have shown encouraging signs in overall survival, palliation of symptoms and improvements in QoL (34), particularly with docetaxel.

Trials using single-agent chemotherapy in advanced disease have shown poor results, but newer studies confirmed that multiagent chemotherapies are more effective. Other studies have confirmed the symptomatic effect of mitoxantrone plus low-dose prednisone, but none found improved survival.

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

A major proportion of the morbidity and mortality related to chemotherapy can be traced to the burden of bone metastases (35). Any effective hormone therapy or chemotherapy is generally suited to relieve metastatic pain, or to limit, at least. Over the last decade, several new agents for metastatic castration-resistant prostate cancer (mCRPC) targeting different mechanisms of progression have been applied successfully: docetaxel, cabazitaxel, sipuleucel-T, denosumab, and abiraterone acetate, among others (36). Docetaxel is the standard first-line chemotherapeutic agent (37).

Despite a net survival benefit, the prognosis remains poor. Second-line therapeutic options are limited. Results from recently completed trials show a statistically and clinically significant improvement in pain relief and overall survival with cabazitaxel compared with mitoxantrone. Cabazitaxel has been shown to be well tolerated and has been approved as second-line chemotherapy for mCRPC (37,38). Also, a significant reduction of tumor associated pain and a survival advantage of 4.6 months compared to placebo following docetaxel-based chemotherapy has already been shown for abiraterone (phase III study) (38) (LE: 1b)

Cabozantinib is a potent inhibitor of tyrosine kinase c-Met and vascular endothelial growth factor receptor (VEGFR2) and seems to reduce pain and opioid consumption in patients with mCRPC (39). Denosumab is a human monoclonal anti-RANKL antibody but it does not reduce pain severity in patients with mCRPC (40). Although most of these regimens are associated with side effects such as fatigue, mild myelosuppression and gastrointestinal irritation, they are generally well tolerated by most patients (41). Pain management by chemotherapy could be effective, although it is much more cost-intensive than the administration of opioids, and the survival advantage is limited.

4.1.3.10 Systemic analgesic pharmacotherapy (the analgesic ladder)

If the treatments described above provide insufficient pain relief, systemic analgesic pharmacotherapy should be administered. In most cases, the drug selection scheme proposed by the WHO, the analgesic ladder, is recommended. Short-term studies have shown that NSAIDs alone are effective in managing cancer pain, with side effects similar to those with placebo. In about 50% of studies, increasing the dose of NSAIDs increased efficacy but not the incidence of side effects.

No large clinical difference has been demonstrated between combining an NSAID with an opioid vs either medication alone (42). Tramadol extended-release tablets and dihydrocodeine extended-release tablets were effective for the management of chronic tumour pain associated with PCa with bone metastasis on step 2 of the WHO ladder, with tramadol giving slightly better pain management and fewer side effects, particularly constipation (43).

The treatment of constipation in palliative care is based on experimental evidence, and uncertainty persists about its optimum management in this group of patients (44).

Oral morphine is an effective analgesic for cancer pain, with qualitative evidence showing that it compares well with other opioids. Morphine is the gold standard for moderate to severe cancer-related pain. Alternatives such as hydromorphone are available, but no clinically significant difference has been shown compared to other strong opioids such as morphine (45).

Patients with inadequate pain control and intolerable opioid related toxicity/adverse effects may have to switch to an alternative opioid for symptomatic relief, although the evidence to support opioid switching is largely anecdotal, observational or from uncontrolled studies (46).

4.1.4 ***Spinal cord compression***

Spinal cord compression can occur due to the collapse of a vertebral body or to pressure from an extradural tumour within the spinal canal. Prodromal pain is a feature in 96% of these patients. The overall incidence in PCa patients is less than 10% (47). Thoracic cord compression is the most common area (70%), and the incidence of multiple extradural sites can be as high as 18% (48).

Definitive treatment with surgery (anterior decompression with spinal stabilisation) or radiotherapy should be considered. The symptom of local back pain sometimes disappears, despite an increase in motor deficits, because of the evolving sensory component of the paraplegia.

Corticosteroids (typically dexamethasone 16 mg daily) are of only temporary use in cord oedema. There is evidence that decompressive surgery benefits ambulant patients with poor prognostic factors for radiotherapy, and non-ambulant patients with a single area of compression, paraplegia of < 48 h duration, non-radiosensitive tumours and predicted survival of > 3 months. There is a significant risk of serious adverse effects from high-dose corticosteroids (49).

4.1.5 ***Hepatic invasion***

Hepatic invasion by secondary tumour is a common cause of severe hypochondrial pain, often radiating to the back and shoulder blade. The mechanism may be the stretching of nerve endings in the liver capsule, diaphragmatic irritation, or haemorrhage into a necrotic area of tumour. Liver pain can often be controlled by conventional titration of appropriate analgesics or with corticosteroids.

Whole-liver palliative radiotherapy can also be useful in carefully selected patients with refractory pain, giving far fewer side effects than the alternatives of intra-arterial chemotherapy or hepatic artery embolisation. Hepatic irradiation can improve abdominal pain with little toxicity in more than half of patients (50). Doses should not exceed 30 Gy in 15 daily fractions or its equivalent if radiation hepatitis is to be avoided.

4.1.6 ***Pain due to cancer treatment***

4.1.6.1 Acute pain associated with hormonal therapy

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

Initiation of LHRH therapy for PCa produces a transient symptom flare in 5-25% of patients (51,52), presumably caused by an initial stimulation of LH release before suppression is achieved (53,54). The syndrome typically presents as an exacerbation of bone pain or urinary retention. Spinal cord compression and sudden death have also been reported (52). Symptom flare is usually observed within the first week of therapy, and lasts 1-3 weeks. Co-administration of an androgen antagonist at the start of LHRH agonist therapy can prevent this (55).

4.1.6.2 Chronic pain associated with hormonal therapy

Gynaecomastia

Chronic gynaecomastia and breast tenderness are common complications of anti-androgen therapies for PCa, the incidence varying between drugs. Frequently associated with diethylstilboestrol (56), it is less common with flutamide and cyproterone (57-59), and uncommon in patients receiving LHRH agonist therapy (7). In elderly patients, it must be distinguished from primary breast cancer or secondary cancer in the breast (7).

4.1.7 *Recommendations at a glance (stage M1) (60-65)*

ANTICANCER TREATMENT		
Recommendation	**LE**	**GR**
Hormonal therapy (orchiectomy, LHRH analogues, diethylstilboestrol equivalent)	1a	A
Total androgen blockade: flare prevention, second-line	2b	B
Intermittent androgen suppression experimental	3	B
Monotherapy with anti-androgen is an option	2	B
First-line treatment controls disease for 12-18 months, second-line individualised	1b	A
Supportive care		
Low-dose glucocorticoids	1b	A
Chemotherapy		
Mitoxantrone plus prednisolone	1b	B
Estramustine + vinblastine or etoposide or paclitaxel	2b	B

PAIN MANAGEMENT		
Recommendation	**LE**	**GR**
Pain assessment (localisation, type, severity, overall distress)		B
Pain due to painful or unstable bony metastases (single lesions)		
External beam irradiation	1b	A
Pain due to painful bony metastases (widespread)		
Radioisotopes (^{89}Sr or ^{153}Sm-EDTMP)	2	B
Pain due to painful metastases (many spots)		
Bisphosphonates	1b	A
Denosumab	1b	A
Systemic pain management		
WHO analgesic ladder step 1: NSAID or paracetamol	1a	A
Opioid administration		
Dose titration	2	B
Access to breakthrough analgesia	1b	A
Tricyclic antidepressant and/or anticonvulsant in case of neuropathic pain	1a	A

4.2 Pain management in transitional cell carcinoma patients

4.2.1 *Clinical presentation*

From the perspective of pain, there are no differences between transitional cell carcinoma (TCC) and other histotypes of urothelial malignant tumour. In bladder carcinoma, pain can be present at an early stage as a burning pain (dysuria), together with irritative symptoms (urgency and frequency), or late in advanced disease due to obstruction of the upper urinary tract, or local invasion of neighbouring tissues causing pelvic or metastatic organ invasion. In upper urinary tract TCC, pain is an initial symptom in 18-30% of cases (66,67).

4.2.2 *Origin of tumour-related pain*

4.2.2.1 *Bladder TCC*

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

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

4.2.2.2 *Upper urinary tract TCC*

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

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

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

4.2.3.1 Bladder TCC

Obstruction of the ureteral orifices by tumour infiltration may lead to hydronephrosis and consecutive flank pain due to ureteral distension (visceral pain). Transurethral resection of the tumour may be effective in eliminating ureteral obstruction, but in palliative situations, hydronephrosis is mainly treated by temporary or permanent ureteral stenting or percutaneous/open nephrostomy, similar to the treatment of obstruction caused by PCa (68).

In locally advanced disease, symptoms are comparable with those caused by T4 PCa. Infiltration of the contiguous soft tissue and neighbouring organs can cause acute burning pain by infiltration of the pelvic nerves (neuropathic pain), sometimes associated with paraesthesia irradiating to the lower limb, or motor deficit. If the tumour invades adjacent organs (small bowel or rectum), there can be obstruction, and visceral pain due to distension of hollow organs. Growing bladder tumour can cause complete bladder outlet obstruction, with hypogastric abdominal pain from bladder distension. Obstruction of the lymphatic vessels by lymphadenopathy can cause lymphoedema of the lower limbs with pain due to distension of muscle fascia (somatic pain) (68).

In infiltrating and advanced bladder cancer, radical or debulking cystectomy and urinary diversion have a positive impact on pain, by removing the neoplastic mass invading the surrounding tissues (EAU Guidelines on Muscle Invasive Bladder Cancer, Chapter 8.1). Extended operations, including excision of involved bowel, are sometimes indicated. Palliative surgery may be necessary in occlusive intestinal syndromes (69). In a small retrospective study of patients with tumour infiltration of the rectum by locally recurrent PCa, total exenteration resulted in significant pain reduction in all patients, and 79% were completely pain free (70). In a mixed group of cancer patients (colorectal, urinary or gynaecological) with different symptoms such as bleeding, fistula, or pelvic pain or obstruction, palliative pelvic exenteration improved QoL in 88% (71).

First-line chemotherapy strategies that are mainly based on platinum-containing regimens have some effect in 12-75% of patients with advanced disease (EAU Guidelines on Muscle Invasive Bladder Cancer Guidelines, Chapter 12). It probably relieves pain by decreasing the neoplastic mass in respondent patients (72-76) (LE: 1a), but pain control was one of the study end points in only one small study (77).

In a phase III trial, vinflunine, as new second line chemotherapy agent, proved to be very effective in disease control with 76%, but pain control was not an end point. Quality of life stayed unchanged during chemotherapy despite drug toxicity (78).

Radiotherapy can be effective in controlling pelvic pain and other symptoms such as frequency and haematuria due to local disease progression. In a large randomised study with 500 participants, two radiotherapy schedules (35 Gy in 10 fractions and 21 Gy in three fractions) were compared for symptomatic improvement of bladder-related symptoms. Sixty-eight percent of the participants achieved symptomatic improvement, 71% with 35 Gy radiotherapy and 64% with 21Gy. Acute bowel toxicity was noticed in one third of the patients. There was no significant difference between the two study arms (79) (LE 1a). Some smaller studies have shown comparable results with respect to improvement of QoL by local radiotherapy (80,81).

4.2.3.2 Upper urinary tract TCC

Transitional cell carcinoma of the upper urinary tract often presents with microscopic or gross haematuria (70-80%), but flank pain also occurs in 20-40% of patients due to obstruction or lumbar mass (EAU Guidelines on Upper Urinary Tract Urothelial Cell Carcinomas, Chapter 3.4). A multi-institutional study with 654 patients has shown that local symptoms do not confer worse prognosis compared to patients with incidentally detected upper urinary tract TCC (82). Locally advanced primary tumours are usually managed by radical nephroureterectomy. Extended operations including excision of involved bowel, spleen or abdominal wall muscle are sometimes indicated.

With regard to chemotherapy, the same considerations are valid for upper urinary tract TCC as for bladder TCC (compare with EAU Guidelines on Upper Urinary Tract Urothelial Cell Carcinomas, Chapter 3.7.2). The standard chemotherapy regimens that moderately extend survival are MVAC (methotrexate, vinblastin, adriamycin, cisplatin) and gemcitabine/cisplatin as first-line drugs, as in bladder cancer (83). In a phase II study of 151 patients with locally advanced or metastatic urothelial cancer, 45 patients (29%) with upper urinary tract carcinoma were included, and vinflunine as second-line chemotherapy demonstrated moderate activity in these patients (84)

4.2.4 ***Pain due to metastases***

Haematogenous metastases to the bone are often found in advanced bladder or upper urinary tract TCC. No

data are available in the literature concerning the specific effect of chemotherapy on bone metastases alone.

Radiotherapy has a palliative analgesic role in bone metastases (Chapter 3.3.3) and pain reduction > 50% can be achieved in 50% of patients (85) (LE: 1b). All the data concerning radiotherapy or radionuclide therapy of bone metastases have been taken from series including different carcinomas such as prostate, breast or kidney cancer. There are no specific trials studying the effect of radiotherapy on painful bone metastases in bladder cancer. Single-fraction radiotherapy is as effective as multifraction radiotherapy in relieving metastatic bone pain (21,86) (LE: 1a). However, the rates of retreatment and pathological fractures are higher after single fraction radiotherapy (21,86) (LE: 1a).

Radioisotope treatment (Chapter 3.3.2) or hemi-body irradiation can be used in patients with multiple bone metastases (85). There are no specific studies of radioisotope therapy for bone metastasis in TCC. Orthopaedic surgery can stabilise pathological fractures, as for those from PCa (Section 3.3.3.4 Pathological fractures)

Recommendations	LE	GR
In locally advanced bladder cancer, palliative cystectomy or exenteration might be an option for symptom relief.	3	B
Use radiotherapy to reduce pain and symptoms of locally advanced bladder cancer.	1a	B
Use radiotherapy to reduce pain due to bone metastases.	1b	A

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

- Chemotherapy in urothelial cell carcinoma is effective in terms of disease control (LE 1b).
- There is a correlation between pain control and quality of life (LE 2a).

4.3. Pain management in renal cell carcinoma patients

*4.3.1 **Clinical presentation***

Renal cell carcinoma (RCC) is not painful unless the tumour invades adjacent areas or obstructs urine outflow due to haemorrhage and blood clot formation. Some 20-30% of patients present with metastases, and 30% of patients, primarily presenting with a localised kidney tumour, develop them during follow-up. Renal cell carcinoma metastasises mainly to lung, bone, brain, liver and ipsilateral or contralateral adrenergic glands. Such patients have a maximal 2-year survival rate of 20%. Overall, 50-60% of patients may need treatment for the symptoms of metastatic disease, mainly pain.

The main origins of tumour-related pain are:

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

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

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

Extended operations that include excision of involved bowel, spleen or abdominal wall muscle are sometimes indicated.

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

Standard pre-operative (30 Gy) or postoperative radiotherapy offers no survival benefit, and its role in delaying local progression is questionable (87).

Low dose radiotherapy of soft tissue has no proven benefit for pain or tumour control. However, there are emerging data indicating that a complete palliative response is more likely when higher biologically effective doses of irradiation are delivered, especially to patients with a relatively high performance status (88).

In metastatic disease, the EORTC Genitourinary Group study 30947 demonstrated a significant increase in

survival with palliative nephrectomy plus immunotherapy compared with immunotherapy (interferon-α) alone (median survival of 17 compared with 7 months) (89) (LE: 2b). There is no special effect on pain relief from immunotherapy.

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

GCP = good clinical practice

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

*4.3.3 **Pain due to metastases***

Patients with bone metastases have a significantly better life expectancy (30 months) than those with visceral metastases (11.6 months) (90).

Surgery is indicated for solitary bone metastases that can be resected completely, intractable bone pain, and impending or demonstrable pathological fracture. In bone metastases with extensive soft tissue involvement and severe pain, amputation of a limb is sometimes required to maintain quality of life. Surgery for bone metastases achieves a significant decrease in pain in 89-91% of patients (91-93) (LE:3). Additionally, surgery prevents pathological fractures and spinal compression, and there is a significant impact on survival.

Preoperative embolisation of bone metastases or embolisation alone achieves good pain relief in hypervascular bone metastases (94,95) (LE: 3).

High-dose radiotherapy for palliation of painful bony metastases has been shown to be effective in 50-75% of all renal cancer patients (96-98) (LE: 3), and in 67% with general bone metastases (99) (LE: 2b). There is no impact on survival. Small studies of radionuclide therapy (e.g., ^{89}Sr) have shown good pain relief in bony metastases from RCC (100) (LE: 3). Also, some minimally invasive attempts to control bone metastases seem promising (101).

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

Immunotherapy alone achieved an overall response in 15-27% of patients (102). Immunotherapy in combination with chemotherapy (interleukin-2 + interferon-α + 5-fluorouracil) is the most effective therapy, achieving partial tumour response in up to 46% of patients and complete response in a maximum of 15%, although these rates are mainly for lung/lymph node metastases (103).

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

New inhibitors of the VEGF/VEGFR and mammalian target of rapamycin (mTOR) pathways (sorafenib, sunitinib, temsirolimus, bevacizumab, everolimus and pazopanib) are changing the second-line therapy to advanced renal cancer. Nevertheless, it is not clear yet what the ideal therapeutic schedule could be (104).

Renal cell carcinoma tends to spread to the brain. Radiosurgery seems to be an effective treatment modality for patients with brain metastases from RCC, and early significant tumour volume reduction after radiosurgery seems to result in long-term survival in RCC patients with brain metastases (105). Further randomised trials comparing whole brain radiation therapy (WBRT) alone versus WBRT plus stereotactic radiosurgery in treating patients with radioresistant brain metastases are needed.

4.4 Pain management in patients with adrenal carcinoma

Adrenal carcinoma is a rare disease and has a poor prognosis. Non-functional adrenal lesions of more than 5 cm in diameter should be removed because there is a high probability of malignancy (106).

*4.4.1 **Malignant phaeochromocytoma***

Phaeochromocytomas result from phaeochromocytes, which are the predominant cells of the adrenal medulla and are also found in the paraganglia near the aorta and in lesser numbers in the ganglia of the sympathetic nervous system (107). When correctly diagnosed and treated, the disease is curable, unless there are metastases.

Computed tomography (CT) and MRI have the highest sensitivity in detecting the tumour, achieving 94-100%. A ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) scan is positive in approximately 87% of cases (108).

Chemotherapy with cyclophosphamide, vincristine and dacarbazine has little effect on metastases (109) (LE: 2b), but therapeutic doses of ^{131}I-MIBG (33 GBq = 900 mCi) may produce some results (110,111) (LE: 2b). The hormone response rate is 50%. There are no data on pain relief with ^{131}I-MIBG in metastatic phaeochromocytoma, but a response rate that is at least the same as for hormone levels should be expected.

Malignant phaeochromocytomas are considered radioresistant, although there are some cases in which radiation therapy induced partial remission (112) (LE: 3). There is no information about the efficacy of radiation concerning pain relief in cases of bone or soft tissue metastases.

*4.4.2 **Treatment of pain***

- Soft tissue and/or bone pain due to metastases are best treated by therapeutic doses of ^{131}I-MIBG, if the phaeochromocytoma takes up this radionuclide (113) (LE: 2b). There is no literature concerning chemotherapy or radiotherapy and pain relief in metastatic phaeochromocytoma.
- Treat the pain symptomatically following the recommendations made in Section 3.4.

4.4.2.1 Adrenocortical carcinomas

Carcinoma of the adrenal cortex is highly malignant, with local and haematogenous metastasis, and 5-year survival rates of 25-43% for all treatments. Patients with distant metastases have a mean survival of only 4 months (114). An autopsy study showed metastasis to lung (60%), liver (50%), lymph nodes (48%), bone (24%) and pleura/heart (10%) (115). These tumours often extend directly into adjacent structures, especially the kidney.

Chemotherapy is of low efficacy. The most effective drug is mitotane, an adrenolytic. The tumour-response rate is 25-35% (114,116) (LE: 2a). It remains to be proven whether chemotherapy prolongs survival. Radiotherapy has not been useful except for palliation and pain management (117) (LE: 2b).

4.4.2.2 Treatment of the pain depending on its origin

- Abdominal symptoms are typical on first presentation of the tumour. The treatment is surgical removal of the primary tumour, with attempts to remove the entire lesion even if resection of adjacent structures is necessary, as well as resection of local lymph nodes.
- Soft tissue and/or bone metastases causing local symptoms can be treated by radiotherapy (113,117). There are no data on chemotherapy or radiotherapy for pain relief in metastatic adrenocortical carcinomas.
- Treat the pain symptomatically following the recommendations given in Section 3.4.

4.5 Pain management in penile cancer patients

*4.5.1 **Clinical presentation***

Penile cancer is rare in Europe, with an annual incidence of 0.3-1.0 new cases per 100,000 men (118). It mostly affects men between the ages of 50 and 70 years, with only 19% of cases in those aged < 40 years and 7% in those < 30 years (119). The penile lesion itself usually alerts the patient to the presence of a penile cancer but there is often a delay in seeking medical attention.

Lymph node involvement is a critical component of treatment planning and prognosis. Up to 60% of the patients at the time of presentation have palpable inguinal lymphadenopathy, and up to 85% of men will be found to have metastatic disease (120). Pain can occur in both early and advanced penile cancer. In the early stages, acute pain is expressed mainly by voiding dysfunction (infravesical obstruction) due to invasion of the corpus spongiosum. In advanced disease, pain is also caused by enlarged inguinal or pelvic node metastases and lymphoedema of the scrotum and lower limbs. Azotemia can develop secondary to nodal obstruction of the ureters. Hypercalcemia was reported in 17-21% of patients in two series (121). This was attributed to the parathyroid-hormone-like substances secreted by bulky metastases that stimulate osteoclastic bone resorption.

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

Soft tissue and hollow-viscus invasion

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

*4.5.3 **Lymphoedema***

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

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

*4.5.4 **Pain due to metastases***

Pain management begins with antitumour treatment; usually surgery that includes partial/total penectomy, and inguinal and pelvic lymphadenectomy, depending on the clinical stage of the disease. Advanced penile cancer has a poor prognosis and must be approached with a multimodal treatment regimen that includes neoadjuvant chemotherapy, radiotherapy, followed by surgical resection (122).

The chemotherapy regimen that is so far most effective and well tolerated is paclitaxel, ifosfamide and cisplatin (TIP), although large randomised trials are lacking (123). The role of radiotherapy is mainly palliative because its use after chemotherapy might decrease the pain from fixed inguinal nodes, bone metastases, spinal cord compression and paraplegia (124). Treatment of hypercalcemia consists of administration of iv saline for volume expansion, furosemide to promote diuresis and bisphosphonates to prevent osteoclastic bone resorption. When tumour erosion into femoral vessels is suspected, emergency intervention with endoluminal vascular stents or transobturator bypass graft should be undertaken (125,126).

*4.5.5 **Conclusions***

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

4.6 Pain management in testicular cancer patients

*4.6.1 **Clinical presentation***

Testicular cancer generally affects men in the third or fourth decade of life. It is mainly diagnosed causally as an intrascrotal mass. Approximately 20% of patients present with scrotal or inguinal pain, which disappears after orchiectomy. Only 11% of patients complain of back or flank pain at first presentation (127). Primary advanced tumour with pain due to bone metastases is very rare, maximally 3% at first presentation. It should be treated causally by primary chemotherapy and adjuvant analgesics.

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

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

*4.6.3 **Pain due to metastases***

- Back or flank pain due to retroperitoneal lymphadenopathy slowly disappears as chemotherapy causes the mass to decrease (128) (LE: 2b). Temporary analgesia is advisable (see Section 3.4.4).
- Retroperitoneal lymph node metastases can also cause obstruction of the ureter, leading to a symptomatic hydronephrosis with back or flank pain and perhaps additional fever. The therapy of choice is the immediate treatment of the hydronephrosis by ureteral stenting or the insertion of a percutaneous nephrostomy.
- Bone pain due to bony metastases is very rare and occurs mainly in patients with primary advanced disease and relapse after chemotherapy (129,130). Treatment with chemotherapy or second-line chemotherapy may be possible (128). There is no literature on radiotherapy in cases of relapse and limitation of further chemotherapy.
- Back pain and neurological symptoms due to spinal cord compression by vertebral metastases may require urgent surgery (131) (LE: 3).

4.7 Recommendations at a glance

Table 4: Efficacy of the therapeutic options in pain relief (expert opinion)

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

? = no conclusive data on pain control; - = no pain control; + = low pain control;
++ = moderate pain control; +++ = good pain control.
! Although studies are lacking, patients presenting with bone metastases or soft tissue metastases should not be refused for radiotherapy as an antalgic effect can be expected.

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5. POSTOPERATIVE PAIN MANAGEMENT

5.1 Background

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

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

5.2 Importance of effective postoperative pain management

The physiological consequences of postoperative pain are shown in Table 5. All of these can delay or impair postoperative recovery and increase the economic cost of surgery (longer hospitalisation) (8,9) (LE: 3). Inadequate postoperative pain control may also lead to development of chronic pain (6,10) (LE: 2b).

Table 5: Physiological consequences of postoperative pain

Condition	Consequences	Ref.	LE
Stress response to surgery	Tissue trauma results in release of mediators of inflammation and stress hormones Activation of this stress response leads to: - retention of water and sodium - increase in metabolic rate	(11)	2a
Respiratory complications	Shallow breathing Cough suppression Lobular collapse Retention of pulmonary secretions Infections	(12)	2b
Cardiovascular complications	Hypertension Tachycardia Increased myocardial work, - myocardial ischaemia - angina - infarction	(13)	2b

Thromboembolic complications	Reduced mobility due to inadequate pain management can lead to thromboembolic episodes	(14)	2a
Gastrointestinal complications	Gastric stasis Paralytic ileus mostly after open urological operations	(15)	2b
Musculoskeletal complications	Prolonged confinement to bed: - reduced mobility - muscle atrophy	(9)	3
Psychological complications	Perioperative pain may provoke fear and anxiety, which can lead to: - anger - resentment - hostility to medical and nursing personnel - insomnia	(8,9)	3

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

- To improve patient comfort and satisfaction.
- To facilitate recovery and functional ability.
- To reduce morbidity.
- To promote rapid discharge from hospital (1,2,4) (LE: 1a).

5.3 Pre- and postoperative pain management methods

*5.3.1 **Preoperative patient preparation***

- Patient evaluation.
- Adjustment or continuation of medication to avoid abstinence syndrome.
- Premedication as part of multimodal analgesia.
- Behavioural-cognitive interventions for patients and families to alleviate anxiety and fear of postoperative pain reduce postoperative analgesic requirements and result in better pain management (1) (LE: 1a).

Recommendation	LE	GR
Preoperative assessment and preparation of patients allow more effective pain management.	1a	A

*5.3.2 **Pain assessment***

Careful pain assessment by the surgeon or the acute pain team before and after treatment can lead to more efficient pain control, and diminished morbidity and mortality (1,3) (LE: 2a). In the post-anaesthesia care unit, pain should be evaluated, treated and re-evaluated initially every 15 min and then every 1-2 h. After discharge to the surgical ward, pain should be assessed every 4-8 h before and after treatment (16,17).

Various rating scales have been described to measure postoperative pain, but their major disadvantage is that they are all subjective, making their results difficult to evaluate, especially in patients with communication
difficulties (16).

Recommendation	LE	GR
Adequate postoperative pain assessment can lead to more effective pain control and fewer complications.	2a	B

*5.3.3 **Pre-emptive analgesia***

Pre-emptive or preventive analgesia is defined as the administration of analgesia before surgical incision to prevent central sensitisation from incision or inflammatory injury, to achieve optimal postoperative pain control (18). The results of clinical trials on its efficacy are controversial (18,19) (LE: 2b).

*5.3.4 **Systemic analgesic techniques***

5.3.4.1 Non-steroidal anti-inflammatory drugs

NSAIDs act by inhibiting cyclo-oxygenase (COX) and the subsequent production of prostaglandins. The main advantages of NSAIDs are that they do not produce respiratory depression or sedation, and seem to decrease the need for opioids (20). However, their analgesic effect is not strong enough for the management of severe postoperative pain (21). For NSAID dosage and administration, see Table 12, section 5.5.

Intravenous administration of NSAIDs should start 30-60 min before the estimated end of surgery, and oral administration should start as soon as possible. Intramuscular administration of analgesic drugs for postoperative pain control is generally avoided because of variability of serum drug concentrations (22).

Their main adverse effects are (21):

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

COX-2 selective inhibitors are associated with fewer gastrointestinal complications and better bone healing. In addition, they cause minimal platelet inhibition compared with non-selective COX inhibitors (23). However, COX-2 inhibitors are contraindicated for long-term use in patients with cardiovascular problems (24). The use of COX-2 inhibitors is approved only for short-term postoperative pain therapy.

Recommendations	LE	GR
NSAIDs are often effective after minor or moderate surgery.	2a	B
NSAIDs often decrease the need for opioids.	1b	B
Avoid long-term use of COX inhibitors in patients with atherosclerotic cardiovascular disease.	2a	B

5.3.4.2 Paracetamol

Paracetamol (acetaminophen) is a relatively safe and effective antipyretic and analgesic for mild to moderate postoperative pain. In cases of severe postoperative pain, co-administration of paracetamol with strong opioids seems to reduce the consumption of opioids (25) (LE: 2). Its exact mode of action is unclear, although it may act by centrally inhibiting COX production (26).

Dosage and routes of administration

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

Adverse effects

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

Combinations of paracetamol with opioids

Paracetamol in combination with an opioid provides adequate postoperative analgesia for mild to moderate pain without the adverse effects of strong opioids. For dosage and administration of paracetamol/opioid combinations, see Table 11, Section 5.5.

Recommendations	LE	GR
The use of paracetamol is recommended for postoperative pain management because it reduces consumption of opioids.	1b	B
Administer paracetamol as a single therapy to alleviate mild postoperative pain without major adverse effects.	2a	B

5.3.4.3 Metamizole (dipyrone)

Metamizole is an effective antipyretic and analgesic drug used for mild to moderate postoperative pain and renal colic. Its use is prohibited in the USA and some European countries because of single reported cases of neutropenia and agranulocytosis. Elsewhere, it is considered to be a useful analgesic and antipyretic drug for moderate pain. Long-term use of metamizole is best avoided (27,28) (LE: 2b).

Dosage and route of administration

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

Adverse effects

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

5.3.4.4 Opioids

Opioids are the first-line treatment for severe acute postoperative pain. Correct dose titration can minimise their unwanted effects (29). Opioid dosage and administration can be found in Tables 12 and 13, section 5.5.

5.3.4.5 Patient-controlled analgesia

Systemic administration of opioids may follow the "as needed" schedule or "around-the-clock" dosing. The most effective mode is PCA (30,31) (LE: 1a) (Table 6).

Table 6: Typical PCA dosing schedule

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

Recommendation	LE	GR
The use of intravenous patient controlled analgesia is recommended because it provides superior postoperative analgesia, improving patient satisfaction and decreasing risk of respiratory complications.	1b	A

Opioids adverse effects are:

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

5.3.4.6 Adjuncts to postoperative analgesia

Adjuncts to postoperative analgesia in low doses, such as ketamine, $\alpha 2$ agonists (clonidine or dexmedetomidine), or gabapentinoids (gabapentin or pregabalin), in appropriate doses and monitored care are beneficial in improving analgesic efficacy and reducing opioid-related side effects, with good safety and tolerability (32,33).

Low-dose ketamine is defined as a bolus dose < 2 mg/kg when given im or < 1 mg/kg when administered via the iv or epidural route. For continuous iv administration, low-dose ketamine is defined as a rate of ≤ 20 g/kg/min (34). Its use is contraindicated in patients with coronary disease, uncontrolled hypertension, congestive heart failure and arterial aneurysms. There are insufficient data to confirm the neurotoxicity of ketamine, even though some animal studies have shown some degree of neurodegeneration after continuous use (35) (LE: 2b).

Clonidine when given preoperatively, or epidurally postoperatively (1 µg/kg) can reduce opioid requirements (36).

More clinical evidence on dexmedetomidine is necessary to confirm its definite role in acute postoperative pain control (37).

In 17 studies up to 2007, patients received a single preoperative dose of 300-1200 mg gabapentin, 30 min-2 h before surgery in the remaining studies, the drug was administered at a dose of 1200-1800 mg/day at 1-24 h before the procedure and continued for 10 days. Gabapentin, used before as well as after surgery, decreases pain severity and the need for analgesic supplementation (38).

Perioperative pregabalin (300 mg/day) reduces opioid consumption and opioid-related adverse effects after surgery, however postoperative pain intensity is not reduced by pregabalin (39).

Single-injection caudal blocks with clonidine or ketamine are beneficial in paediatric patients (40).

Recommendations	LE	GR
Administer adjuncts in appropriate doses and monitored care to improve analgesic efficacy and reduce opioid-related side effects.	1a	A
Administer clonidine preoperatively or epidurally postoperatively to reduce opioid requirements.	1a	A
Gabapentin can be administered before as well as after surgery to decrease pain severity and need for analgesic supplementation.	1a	A

5.3.5 ***Regional analgesic techniques***

5.3.5.1 Local anaesthetic agents

The most commonly used local anaesthetics are:

- bupivacaine;
- l-bupivacaine;
- ropivacaine.

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

5.3.5.2 Epidural analgesia

Epidural analgesia provides excellent postoperative pain relief for extended periods after major surgery, and reduces postoperative complications and consumption of opioids (1,2) (LE: 1a) (Table 7).

Table 7: Typical epidural dosing schemes*

Drug	Single dose	Continuous infusion
Morphine	1-5 mg	0.1-1 mg/h
Fentanyl	50-100 µg	25-100 µg/h
Sufentanil	10-50 µg	10-20 µg/h
Pethidine	10-30 mg	10-60 mg/h
Bupivacaine 0.125% or ropivacaine 0.2% + fentanyl 2 µg/mL	10-15 mL	2-6 mL/h

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

5.3.5.3 Patient-controlled epidural analgesia

Patient-controlled epidural analgesia (PCEA) has become very common because it allows individualisation of dosage, decreased drug use, and greater patient satisfaction. It also seems to provide better analgesia than intravenous PCA (41,42) (LE: 1a) (Table 8).

Table 8: Typical PCEA dosing schemes

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

Recommendation on epidural analgesia	LE	GR
Epidural analgesia, especially PCEA, provides superior postoperative analgesia, reducing complications and improving patient satisfaction, and is therefore preferable to systemic techniques (41).	A	1b

5.3.5.4 Neural blocks

Local anaesthetic blocks (intermittent and continuous) can be used after urological surgical operations to supplement postoperative analgesia (43) (LE: 2a) (Table 9).

Table 9: Examples of neural blocks

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

5.3.5.5 Wound infiltration

Intraoperative wound infiltration with local anaesthetic (usually 10-20 mL ropivacaine or 0.25-0.5% bupivacaine) can provide some postoperative analgesia and may reduce the requirement for systemic analgesia (44) (LE: 2b).

5.3.5.6 Continuous wound instillation

Continuous postoperative wound instillation of a local anaesthetic via a multi-hole catheter placed intraoperatively by the surgeon has been shown to provide satisfactory analgesia for moderate to severe postoperative pain, reducing consumption of systemic analgesics (45-47) (LE: 2b).

*5.3.6 **Multimodal analgesia***

The concept of multimodal (balanced) analgesia is that combining different doses and routes of administration of analgesics improves the effectiveness of pain relief after surgery and reduces the maximal dosage and adverse effects (48) (LE: 2b). It seems to be more effective when different drugs are administered via different routes than when different drugs are administered via a single route (1) (LE: 2b).

Recommendation	LE	GR
Multimodal pain management should be used whenever possible because it helps to increase efficacy while minimising adverse effects.	2b	B

*5.3.7 **Special populations***

5.3.7.1 Ambulatory surgical patients

A multimodal analgesic plan uses a combination of NSAIDs or paracetamol plus local anaesthetics used as peripheral nerve blocks, tissue infiltration, or wound instillation so as to avoid the use of opioids, which can prolong hospital stay ([49,50], LE: 2a; [51], LE: 2b).

Recommendations	LE	GR
For postoperative pain control in outpatients, multimodal analgesia with a combination of NSAIDs or paracetamol plus local anaesthetics should be used.	2b	B
If possible, avoid opioids.	3	B

5.3.7.2 Geriatric patients

Pain perception appears to be reduced in geriatric patients, and requirement for analgesia generally decreases with increasing age (52,53). Geriatric patients can also suffer from emotional and cognitive impairment such as depression and dementia, which could affect adequate pain management (54). Postoperative delirium in elderly patients is a common complication and is often multifactorial. It may be associated with administration of pethidine (55). Multimodal postoperative analgesia may be the pain management technique of choice in elderly patients, as the drug doses required are lower. However, it is important to be vigilant for adverse reactions, because they tend to increase in number in the geriatric population (56) (LE: 2b). Epidural analgesia might diminish the risk of postoperative delirium and respiratory complications in elderly patients (57) (LE: 2b).

Recommendation	LE	GR
Multimodal and epidural analgesia are preferable for postoperative pain management in elderly patients because these techniques are associated with fewer complications.	2b	B

5.3.7.3 Obese patients

Obese patients appear to be at higher risk for certain postoperative complications, including respiratory, cardiovascular and thromboembolic episodes, and wound infections (58,59). Administration of opioids to obese patients is associated with sudden respiratory arrest, therefore, a combination of NSAIDs or paracetamol with an epidural local anaesthetic might be the safest analgesic solution (60,61) (LE: 2b).

If absolutely necessary, opioids should be used with caution under careful titration to avoid depression of the respiratory drive (61). Oxygen therapy should also be applied postoperatively to increase oxygen saturation (62).

Recommendations	LE	GR
Postoperative use of opioids should be avoided in obese patients unless absolutely necessary.	2b	B
An epidural local anaesthetic in combination with NSAIDs or paracetamol is preferable.	2b	B

5.3.7.4 Drug- or alcohol-dependent patients

It has been proved that regional anaesthesia and analgesia are preferable to opioids in drug addicts. Moreover, clonidine is beneficial in those with withdrawal syndrome due to opioid or alcohol abstinence and postoperative delirium tremens (63) (LE:1a).

5.3.7.5 Other groups

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

5.3.8 ***Postoperative pain management teams***

The importance of efficient postoperative pain management has led to the development of acute postoperative pain management teams, which generally consist of nursing and pharmacy personnel led by an anaesthesiologist. They have been shown to improve pain relief, decrease analgesic side effects, improve patient satisfaction, and decrease overall costs and morbidity rates (64-66) (LE: 2b). Improved pain control can lead to shorter hospitalisation and fewer unscheduled readmissions after day surgery (67) (LE: 3).

5.4 Specific pain treatment after different urological operations

5.4.1 ***Extracorporeal shock wave lithotripsy***

Extracorporeal shock wave lithotripsy (SWL) is a minimally invasive treatment, during and after which 33-59% of patients do not need any analgesia (68-70) (LE: 2b). Post-treatment pain is unlikely to be severe and oral analgesics are usually sufficient.

Analgesic plan

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

NSAIDs or midazolam given 30-45 min before treatment reduces the need for opioids during the procedure (LE: 2b). With diclofenac premedication (100 mg rectally), only 18% of patients needed pethidine during lithotripsy (71). After premedication with 5 mg midazolam orally, 70% of patients were completely free of pain during treatment, and if buprenorphine was added, this proportion rose to 87% (72). After premedication with midazolam (2 mg iv, 5 min before treatment), diclofenac or tramadol was safe and effective, with fewer side effects than fentanyl (73) (LE: 1b). Other effective regimes for intraoperative pain treatment are fentanyl (1 µg/kg iv [74]), sufentanil or remifentanil. These drugs are usually given by the anaesthesiologist because of the risk of respiratory depression, which was significantly lower (20% vs 53%) after the procedure if remifentanil was used instead of sufentanil (75,76) (LE: 1b).

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

Recommendations	LE	GR
Analgesics should be given on demand during and after SWL because not all patients need pain relief.	3	B
Premedication with NSAIDs or midazolam often decreases the need for opioids during the procedure.	2b	B
iv opioids and sedation can be used in combination during SWL; dosage is limited by respiratory depression.	3	C
Post-SWL, analgesics with a spasmolytic effect are preferable.	3	C

SWL = extracorporeal shock wave lithotripsy.

*5.4.2 **Endoscopic procedures***

5.4.2.1 Transurethral procedures

Transurethral operations are usually performed under spinal anaesthesia (epidural or subarachnoid block) with the patient awake or mildly sedated, and usually with analgesia for 4-6 h after surgery. Pain is generally caused by the indwelling catheter or the double-J (ureteral stent following ureterorenoscopy), which mimics overactive bladder syndrome. Drugs with an antimuscarinic effect have been proven to be useful in addition to the opioids (77) (LE: 1b).

Analgesic plan

- Preoperative assessment: see Section 5.3.
- Intraoperative: spinal (intrathecal or epidural) anaesthesia provides intraoperative analgesia and last for 4-6 h postoperatively.
- Postoperative: after 4-6 h, mild oral analgesics such as NSAIDs or paracetamol ± codeine, or stronger opioids; also orally. In the case of bladder discomfort from the indwelling catheter, metamizole (orally or iv), pethidine (iv) or piritramide (iv) is also effective. Antimuscarinic drugs such as oxybutynin (5 mg orally three times daily) are useful and reduce the need for opioids (77) (LE: 1b).

Recommendations	**LE**	**GR**
Postoperative analgesics with spasmolytic effect or mild opioids are preferable.	3	C
Antimuscarinic drugs could be helpful in reducing discomfort resulting from the indwelling catheter.	3	B
Antimuscarinic drugs may reduce the need for opioids.	3	B

5.4.2.2 Percutaneous endoscopic procedures

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

5.4.2.3 Laparoscopic procedures

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

A particular problem after laparoscopic cholecystectomy is the development of shoulder pain as a result of diaphragmatic irritation following pneumoperitoneum. This seems to be dependent on the intra-abdominal pressure used during the procedure, because reduced CO2 insufflation reduces postoperative shoulder pain (78-80) (LE: 1b). The same could apply for some transabdominal urological laparoscopic interventions.

Analgesic plan

- Preoperative assessment: Section 5.3.
- Intraoperative: iv opioids ± NSAIDs, paracetamol or metamizole administered by an anaesthesiologist. The infiltration of local anaesthetic into the port incisions reduces pain after laparoscopy (81).
- Postoperative: administration of systemic opioids iv (im or sc), is very effective in the immediate postoperative period. NSAIDs (e.g., paracetamol and/or metamizole) and incisional local anaesthetics (multimodal concept) can be given to reduce the need for opioids (81,82).

Recommendations	**LE**	**GR**
Low intra-abdominal pressure and good desufflation at the end of the procedure reduces postoperative pain.	1b	A
NSAIDs are often sufficient for postoperative pain control.	2a	B
NSAIDs decrease the need for opioids.	1b	B

*5.4.3 **Open surgery***

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

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

Recommendations	LE	GR
For postoperative pain control, multimodal analgesia with a combination of NSAIDs or paracetamol plus local anaesthetics should be used.	3	B
If possible, avoid opioids for outpatients.	3	C

5.4.3.2 Transvaginal surgery

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

Recommendations	LE	GR
NSAIDs are often sufficiently effective after minor or moderate surgery.	2A	B
NSAIDs decrease the need for opioids.	1b	B

5.4.3.3 Perineal open surgery

Analgesic plan

- Preoperative assessment: Section 5.3.
- Intraoperative: general anaesthesia is usually used, particularly for perineal radical prostatectomy, because of the uncomfortable exaggerated lithotomy position. Sometimes an intrathecal catheter (epidural) can be sited for intra- and postoperative pain control.
- Postoperative: continuous epidural infusion of a combination of opioids and local anaesthetic or PCA is usually used. When systemic opioids are required, it is advisable to use them in combination with NSAIDs so as to reduce their dose and side effects. When the patient is able to take oral analgesics, metamizole or paracetamol ± codeine can be used.

5.4.3.4 Transperitoneal laparotomy

Analgesic plan

- Preoperative assessment: see Section 5.3.
- Intraoperative: general anaesthetic and regional technique; sometimes an intrapleural catheter can be sited.
- Postoperative: continuous epidural infusion of a combination of opioids and local anaesthetic. Once the patient is able to take oral analgesics (depending on bowel motility) metamizole, paracetamol ± codeine or tramadol can be used. Multimodal concepts (combining NSAIDs with opioids, fast-track strategies, keeping abdominal and urinary drainage as short as possible) are useful in reducing the need for analgesia (48).

Recommendations	LE	GR
The most effective method for systemic administration of opioids is PCA (see Section 5.3.4.5), which improves patient satisfaction and decreases the risk of respiratory complications.	1b	A
Epidural analgesia, especially PCEA, provides superior postoperative analgesia, reducing complications and improving patient satisfaction, and is preferable to systemic techniques (see Sections 5.3.5.2 and 5.3.5.3).	1b	A

PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia.

5.4.3.5 Suprapubic/retropubic extraperitoneal laparotomy

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

Analgesic plan

- Preoperative assessment: see Section 5.3.
- Intraoperative: general anaesthetic and regional technique.
- Postoperative: continuous epidural infusion of a combination of opioids and local anaesthetic. Once the patient is able to take oral analgesics metamizole, paracetamol ± codeine, ± NSAIDs can be used.

5.4.3.6 Retroperitoneal approach - flank incision - thoracoabdominal approach

Analgesic plan

- Preoperative assessment: see Section 5.3.
- Intraoperative: general anaesthetic and regional technique; sometimes an intrapleural catheter can be inserted.
- Postoperative: continuous epidural infusion of a combination of opioids and local anaesthetic gives significantly better pain control compared with iv analgesics (83,84). If epidural analgesia is

not possible or refused, PCA should be provided. Once the patient is able to take oral analgesics (depending on bowel motility) paracetamol ± codeine or metamizole can be associated (to reduce the need for opioids) or used alone.

Recommendation	LE	GR
Epidural analgesia, especially PCEA, provides superior postoperative analgesia, reducing complications and improving patient satisfaction and is therefore preferable to systemic techniques (see Sections 5.3.5.2 and 5.3.5.3).	1b	A

PCEA = patient-controlled epidural analgesia.

5.5 Dosage and method of delivery of some important analgesics

5.5.1 ***NSAIDs***

Table 10: Dosage and delivery of NSAIDs

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

Table 11: Dosage and delivery of paracetamol, metamizole and its combinations with opioids

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

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

5.5.2 ***Opioids***

Table 12: Dose and delivery of opioids

Drug	Method of administration	Common single dose (mg)	Maximal dose (mg)
Tramadol	Orally	50	400-600
Tramadol	iv	50-100	400-600
Dihydrocodeine	Orally	60-120	240
Piritramid	sc/im	15-30	120
Pethidine	Orally	25-150	500
Pethidine	Rectally	100	500
Pethidine	sc/im	25-150	500
Pethidine	iv	25-100	500
Morphine*	Orally	Starting with 10	No maximal dose
Morphine*	Rectally	Starting with 10	No maximal dose
Morphine*	sc/im	Starting with 5	No maximal dose
Morphine*	iv	Starting with 2	No maximal dose
Morphine*	Iv (PCA)	0.5-2.5 mg bolus	
10-15 min lockout	No maximal dose		

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

Table 13: Common equi-analgesic doses for parenteral and oral administration of opioids*

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

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

5.6 Perioperative pain management in children

*5.6.1 **Perioperative problems***

The main preoperative problems in children are fear of surgery, anxiety about separation from their parents, and the pain of procedures such as venipuncture. Contrary to the popular belief, the presence of parents during anaesthesia induction does not alleviate children's anxiety (85) (LE: 1a). The preoperative use of oral morphine sulphate, 0.1 mg/kg, can help to prevent crying in children and thereby reduce oxygen consumption and pulmonary vasoconstriction (Table 16). The prior application of EMLA (2.5% lidocaine and 2.5% prilocaine) cream helps to reduce the pain of venipuncture (86) (LE: 1a). Atropine, 0.01-0.02 mg/kg iv, im, orally or rectally, prevents bradycardia during anaesthesia induction.

Table 14: Premedication drugs in children

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

Recommendation	LE	GR
Apply EMLA locally to alleviate venipuncture pain in children.	1b	A

*5.6.2 **Postoperative analgesia***

Postoperatively, paracetamol, NSAIDs, opioids and their combinations are used according to the severity of the surgical procedure (Table 15).

Table 15: Dosage of analgesics in children for postoperative analgesia

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

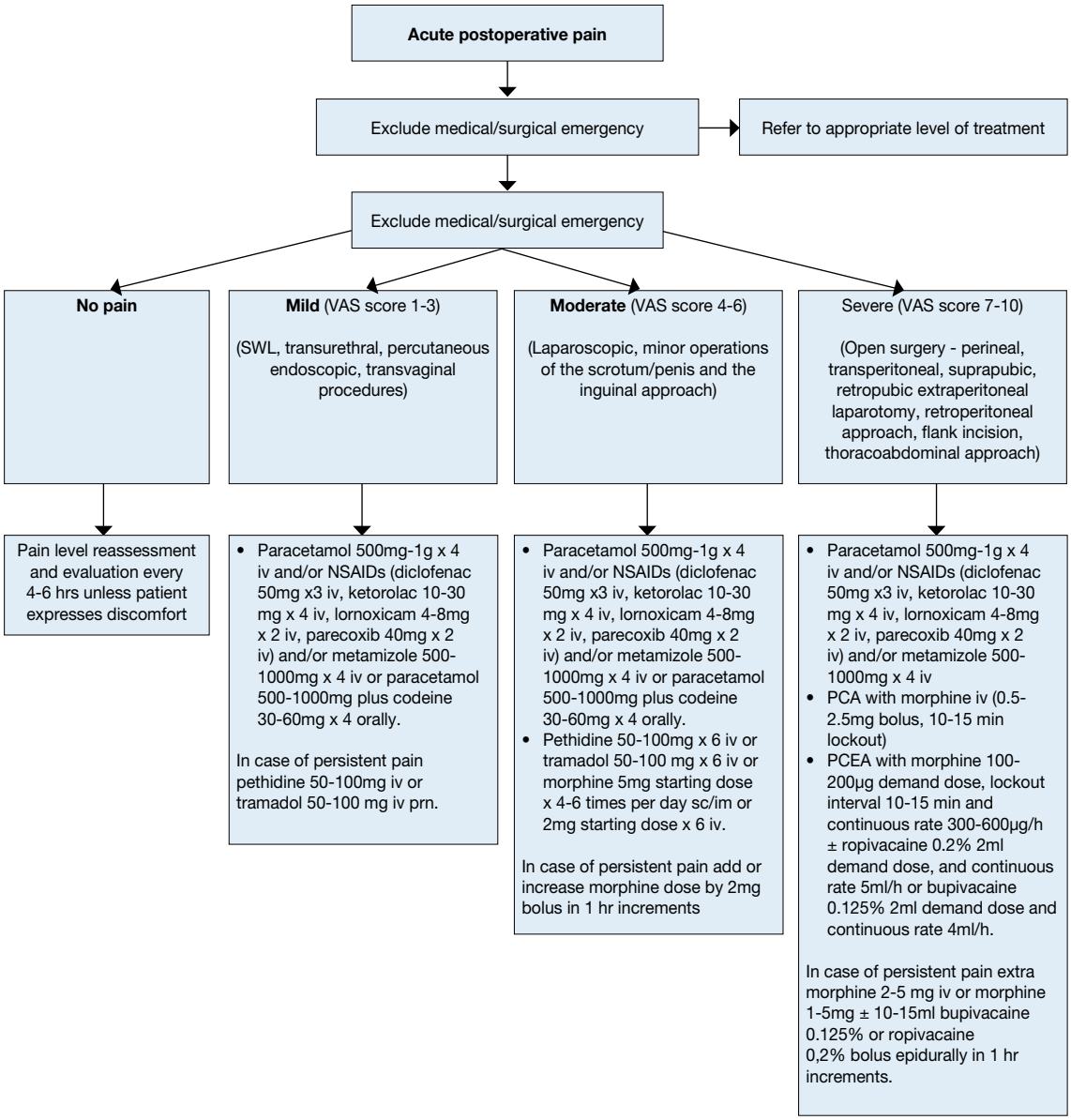
The postoperative use of COX-2 inhibitors in children is still controversial. PCA can be used safely in children older than 6 years. Nurse-controlled analgesia is effective in infants and children unable to use PCA (87).

Locoregional techniques such as wound infiltration, nerve blocks, and caudal and epidural analgesia are also successful (88,89). The most commonly drugs used are bupivacaine and ropivacaine (Table 16). Higher volumes of lower drug concentrations appear to be more effective than lower volumes of higher concentrations (90) (LE: 1a). The addition of opioids, ketamine or clonidine increases the duration of pain relief and reduces the need for rescue analgesia, thus providing more effective pain relief than local anaesthesia alone in caudal analgesia (91-93) (LE: 1a).

Table 16: Epidural dose of local anaesthesia

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

Figure 3: Postoperative pain management



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6. NON-TRAUMATIC ACUTE FLANK PAIN

6.1 Background

Acute flank pain is a frequently occurring and complex medical problem. Ureterolithiasis is the most common non-traumatic cause. However, half of all renal colics are not caused by urolithiasis (1-3) (Table 17).

Table 17: Main urological and non-urological causes of flank pain

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

6.2 Initial diagnostic approach

*6.2.1 **Symptomatology***

History and physical examination, including body temperature, can be very helpful in the differential diagnosis

of acute flank pain (4).

- Acute renal colic is indicated by pain of short duration (< 12 h), nausea, vomiting, loin tenderness and haematuria (erythrocytes > 10,000/mm^3) (4).
- Because the signs and symptoms can be very similar, acute uncomplicated pyelonephritis should be immediately differentiated from complicated renal colic:
  - Concomitant fever (> 38°C) makes imaging obligatory (5). A radiological evaluation of the upper urinary tract should be offered to every patient presenting with flank pain and fever to rule out urinary tract obstruction irrespective of the accompanying symptoms, duration of the episode and urine macroscopic or microscopic findings.
  - Imaging is also imperative in patients with acute flank pain and a solitary kidney (5) (LE: 4).
- Acute flank pain in patients with an increased risk for thromboembolic events should raise the suspicion of renal infarction (6).
- Careful abdominal examination can reveal an abdominal aortic aneurysm (misdiagnosed in 30% of patients).
- Renal vein thrombosis (RVT) may often present with symptoms of acute flank pain, proteinuria, haematuria, hypotension and renal insufficiency.
- Obstruction of the ureteropelvic junction can result in acute flank or abdominal pain after a high fluid volume intake, especially in paediatric patients.
- Renal papillary necrosis is not uncommon in the course of systemic diseases such as diabetes mellitus or analgesic nephropathy; the passage of sloughed papillae down the ureter may cause flank pain and haematuria.
- Testicular torsion should always be excluded in children with acute abdominal/flank pain.
- Torsion of the appendix testis can also result in abdominal pain or radiate to the flank.
- Spontaneous bleeding either within the kidney or to the retroperitoneum can be caused by kidney tumours (including angiomyolipomas), bleeding disorders or anticoagulation; acute flank pain is sometimes the presenting symptom.

Recommendation	LE	GR
Febrile patients (> 38°C) with acute flank pain and/or with a solitary kidney need urgent imaging.	4	B*

**Recommendation based on expert opinion.*

*6.2.2 **Laboratory evaluation***

All patients with acute flank pain require a urine test (red and white cells, bacteria or urine nitrite), blood cell count, and serum creatinine measurement. In addition, febrile patients with flank pain require C-reactive protein and urine culture. Pyelonephritis ± obstructive uropathy should be suspected when the white blood count exceeds 15,000/mm3.

*6.2.3 **Diagnostic imaging***

6.2.3.1 Ultrasonography

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

6.2.3.2 Intravenous urography

The use of US in the management of acute flank pain has been increasing. If the findings of pelvic and/or ureteral dilatation, stone visualisation and the absence of ureteral ejaculation are combined, sensitivity to ureteral dilatation can be 96% (7,10,11) (LE: 2a). Together with a plain abdominal radiograph, US can be accepted when computed tomography (CT) is not available (7,12-16) (LE: 1b).The disadvantages of US include inability to differentiate dilatation from true obstruction and the need for highly specialised personnel (12). Sensitivity varies from 58 to 96% in untrained staff in emergency rooms (14), but evidence suggests that, with even short training, non-specialists can be highly effective at excluding disorders such as abdominal aortic aneurysm, free abdominal fluids, gallstones and obstructive uropathy (14) (LE: 2b). US is the diagnostic imaging modality of choice during pregnancy.

6.2.3.3 Unenhanced helical CT

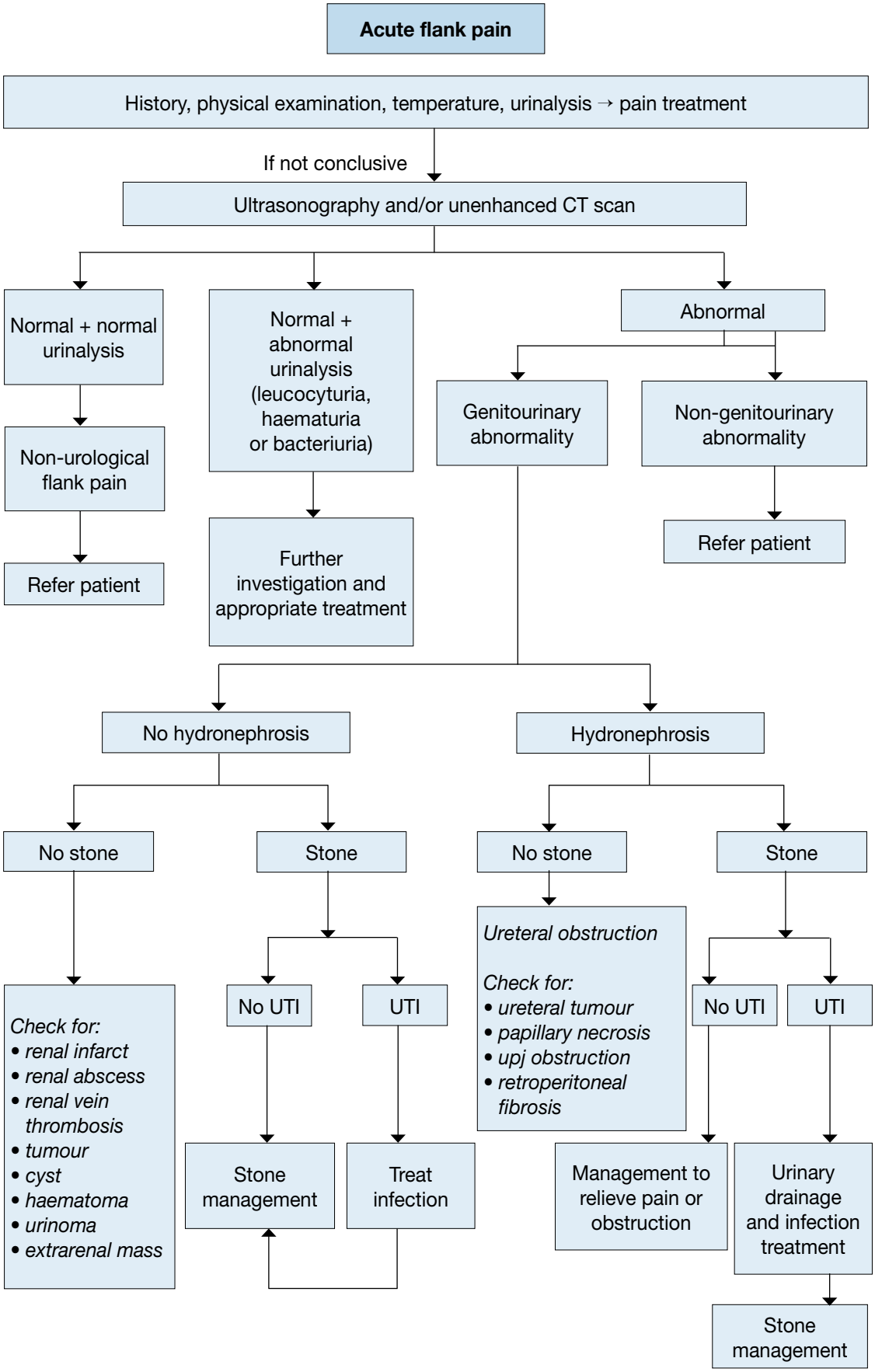
Intravenous urography (IVU) reliably provides information on the anatomy of the urinary collecting system (ureteral and renal pelvic dilatation) in 80-90% of cases and can identify ureteral calculi in 40-60% of cases.

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

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

Table 18 shows comparative results of UHCT US and IVU in assessing acute flank pain and suspicion of ureterolithiasis (17-19). Figure 4 summarises the diagnostic approach to non-traumatic acute flank pain.

Figure 4: Diagnostic approach to non-traumatic acute flank pain



CT = computed tomography; UTI = urinary tract infection.

Recommendations	LE	GR
Unenhanced helical computed tomography is the diagnostic imaging modality with the highest sensitivity and specificity for evaluation of non-traumatic acute flank pain.	1a	A
Ultrasound can be an alternative to unenhanced helical computed tomography in the initial approach to non-traumatic acute flank pain.	1b	A

Table 18: Comparative results of UHCT, US and IVU in assessment of acute flank pain and suspected ureterolithiasis (12)

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

6.3 Initial emergency treatment

*6.3.1 **Systemic analgesia***

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

- Intravenous NSAIDs are very effective in most cases, e.g., a bolus of diclofenac sodium, 75 mg (20) (LE: 1a); a slow iv injection of ketorolac, 30 mg, four times daily, is equivalent to diclofenac in the treatment of renal colic (22).
- Tests have shown a single dose of dipyrone to be less effective than diclofenac, 75 mg (23) (LE: 1a), but a slow iv infusion of dipyrone, 1 or 2 g, is just as effective as diclofenac (24).
- In cases of unresponsiveness to diclofenac (25) (LE: 1b), or contraindication of NSAIDs (24) (LE: 1b), iv papaverine hydrochloride (120 mg) is a safe and effective alternative.
- Large-scale studies have shown that NSAIDs and opioids are both effective analgesics, but vomiting is more prevalent with opioids (particularly pethidine) (20).
- The combination of iv morphine + ketorolac seems superior to either drug alone, and appears to be associated with a decrease in the need for rescue doses of analgesia (26).
- Antimuscarinics are often used in acute renal colic; there is no evidence that hyoscine butylbromide reduces opioid requirements in this condition (26) (LE: 1b).

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

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

*6.3.2 **Local analgesia***

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

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

*6.3.3 **Supportive therapy***

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

6.3.4 *Upper urinary tract decompression*

If pain relief cannot be achieved using medical therapy and there are signs of infection and impaired renal function, upper urinary tract drainage should be undertaken. The main indications for stenting for urgent relief of obstruction include (31):

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

Catheter-derived symptoms such as flank pain, pain during voiding, frequency, nocturia and urgency can be effectively treated with terazosin and tamsulosin (32-34).
New technological advances such as the antireflux JJ ureteral stents seem to minimise catheter-related pain (35,36) (LE: 1b).

6.4 Aetiological treatment

6.4.1 *Urolithiasis*

Treatment of urolithiasis is discussed in the EAU Guidelines on Urolithiasis (37).

6.4.2 *Infectious conditions*

Infectious uncomplicated conditions (i.e. acute pyelonephritis in otherwise healthy individuals) should be treated with appropriate antibiotics and analgesics according to the EAU Guidelines on Urological Infections (38).

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

6.4.3 *Other conditions*

6.4.3.1 *Ureteropelvic junction obstruction*

Ureteropelvic junction obstruction can result in intermittent flank or abdominal pain. Symptoms may worsen during brisk diuresis (after consumption of caffeine or alcohol). Dismembered or non-dismembered pyeloplasty is standard. A ureteral stent can help to relieve pain in very symptomatic patients prior to definitive surgery. Outcomes are excellent, with resolution of the obstruction in 90-95% of cases, including newborns (39).

6.4.3.2 *Papillary necrosis*

Papillary necrosis commonly presents as painless macroscopic haematuria, but can be complicated by ureteral obstruction. As well as symptomatic treatment, treatment should be given for the underlying cause of papillary necrosis, such as interstitial nephritis, acute pyelonephritis, diabetes mellitus, analgesic abuse or sickle cell disease. Ureteral obstruction due to sloughed papillae can be successfully treated with ureteroscopy or temporary ureteral stenting (40).

6.4.3.3 *Renal infarction*

There is no specific treatment for acute renal infarction, but the underlying disease (atrial fibrillation, left ventricular thrombus or a hypercoagulable state) may require anticoagulation with iv heparin followed by warfarin to prevent future events (41).

6.4.3.4 *Renal vein thrombosis*

Renal vein thrombosis is often clinically silent, but can present with acute flank pain. Systemic anticoagulation with heparin to prevent further propagation of thrombus or other thromboembolic phenomena (42) is standard, but the successful use of fibrinolytic agents in selected patients without clinical contraindications has been reported (43). Thrombectomy or nephrectomy is reserved for cases refractory to medical therapy.

6.4.3.5 *Intra- or perirenal bleeding*

Acute spontaneous intra- or perirenal bleeding often results in acute flank pain. Spontaneous renal haemorrhage (Wunderlich's syndrome), is an unusual and life-threatening cause of acute abdomen. Nephrectomy is usually the only therapeutic alternative (44,45).

6.4.3.6 Testicular cord torsion

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

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7. PALLIATIVE CARE

7.1 Background

The inevitable progression of certain diseases frequently results in unbearable suffering. When cure is no longer possible, palliation and compassion are mandatory. In the following section the reader will find a straightforward approach to the treatment of many psychological and physical symptoms. Unfortunately, the level of evidence for the proposed interventions is poor. Nevertheless, a well-structured map should be applied to provide the most effective and compassionate care for patients and their loved ones. Also, healthcare providers deserve particular care because the extent of professional anxiety and frustration can be significant in this clinical scenario.

7.2 Definition and aim of palliative care

According to the WHO definition (1), palliative care is "*an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual*." The goal of palliative care is to obtain the highest QoL for patients and their loved ones.

Palliative care:

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten nor postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;
- offers a support system to help the family cope during the patient's illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;

- enhances QoL, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiotherapy, and includes investigations needed to understand and manage better distressing clinical complications (1).

The readiness of patients to accept palliative care and a vision of palliative care shared by the patient and all caregivers involved are potentially important elements in this definition (2).

7.3 General principles

The panel assumes that the ethics of disease palliation are beyond doubt. Hence, a discussion on ethical principles is omitted from this document. Legislation on palliative and end-of-life care across Europe is variable. This panel considered it pointless to address that particular topic in depth. The panel also decided not to address physician-assisted suicide. Details about this and euthanasia can be found elsewhere (3,4). The current document focuses on interventions that can be applied in institutions. Home palliation is not addressed because few patients require this type of care are in the urological setting.

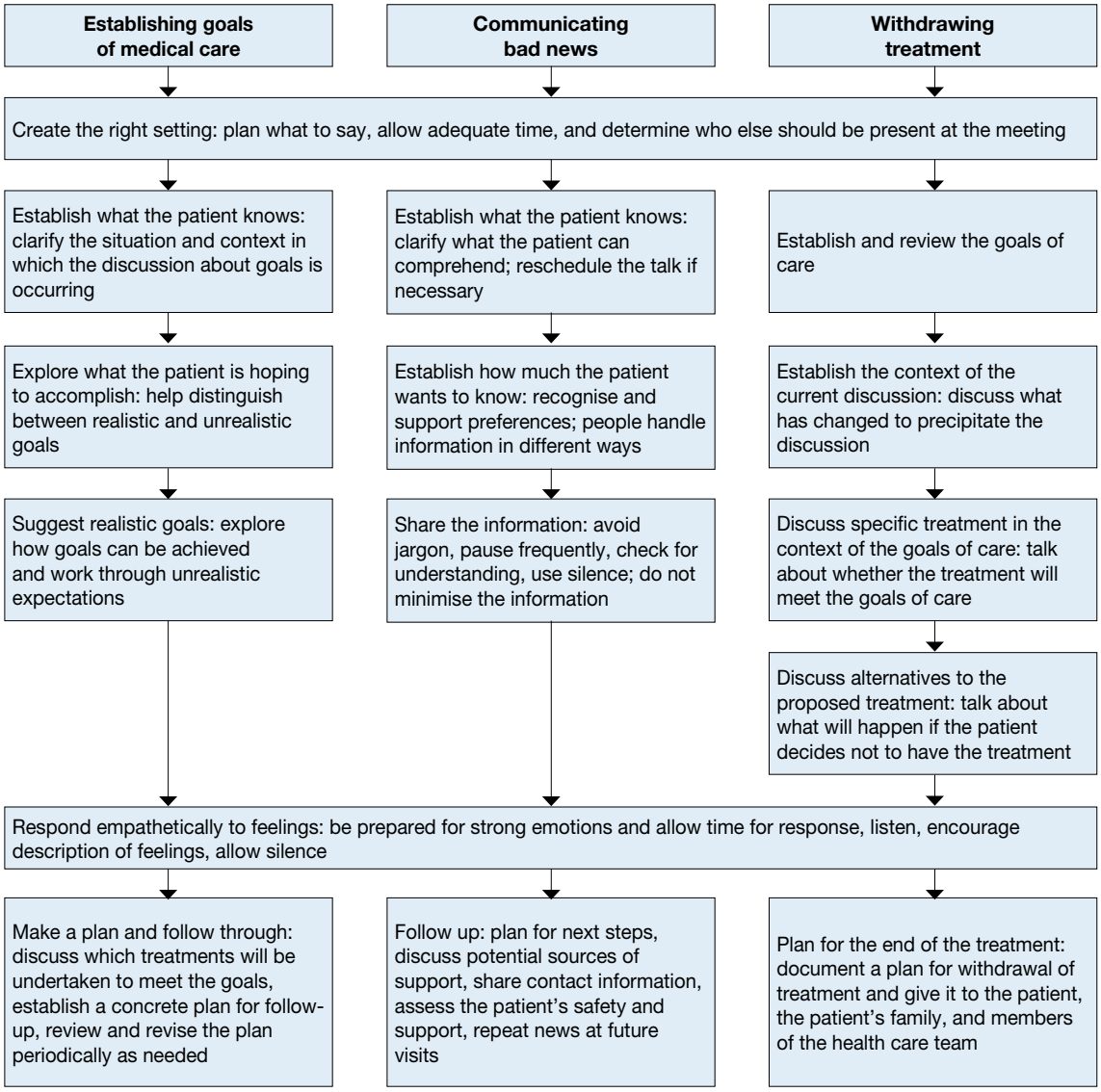
Palliation involves:

- communication;
- placing the patient at the centre of treatment;
- cultural and spiritual approaches;
- multidisciplinary approach.

*7.3.1 **Communication***

Communication is one of the cornerstones in palliative care. Good communication skills are relevant not only in the relationship between caregivers and patient and families, but also with all professionals inside and outside the hospital. Specific communication skills allow a better assessment of patients‘ needs and improve patient wellbeing and adherence to treatment. Communication skills include making eye contact with the patients, asking open-ended questions, responding to a patient’s emotions, and showing empathy (5). Figure 5 illustrates the principles for communicating with patients about major topics in palliative care.

Figure 5: Protocols for communicating with patients about major topics in palliative care



Adapted from the Education on Palliative and End-of-life Care Project.
Curriculum Emanuel LL, von Gunten CF, Ferris FD, eds. The Education in Palliative and End-of-life Care (EPEC) Curriculum: © The EPEC Project, 1999, 2003.

Communication skills are important at every stage of the disease. Terminal patients deserve specific information about their condition. This kind of information increases the quality of terminal care (6,7). Several guidelines have been established to help physicians and nurses improve their communication skills (5,8).

Moreover, it seems important to tailor information to the needs of the individual patient. Difficult discussions should be personalised to the individual patient. These can vary dramatically both in the area of disclosure of bad news about prognosis and end-of-life decision making. This also requires proper advanced care planning at an early stage in the management of patients with terminal cancer (9).

Communication is also part of the relationship between partners, when one member of the couple has a chronic illness such as cancer. When communication between the couple fails, it is more difficult to address the patient's needs. The Couples' Illness Communication Scale (CICS) is a simple tool for the clinical setting and can provide a springboard for addressing difficulties with illness-related communication between couples. It can be an aid for decision making in couple counselling. Relationship intimacy and how patients and partners communicate to achieve this intimacy is important for the psychological adjustment of early-stage PCa survivors and their partners (10,11).

Many initiatives provide patient guidance and education, from assessment to diagnosis and treatment planning. For example, at the Prostate Cancer Assessment Clinic, Ottawa Hospital, Canada, a nurse-led initiative has shown that effective communication between physicians, nurses, patients and families, and the interdisciplinary team and community partners is the key to improving the experience of PCa patients (12).

7.3.2 ***Patient-centred treatment***

Patient-centred treatment is another aspect of palliative care. There is evidence about the benefit of involving the patient in making any decisions. The patient must be at the heart of every decision and be provided with greater choice and control (13).

7.3.3 ***Cultural and spiritual approach***

The profound influence of personal circumstances on patients' experiences of illness, expectations of medical interventions, communication styles, and ways of coping should be considered, because it can lead to misunderstanding, conflict, anger, resentment, and lower quality of care (14).

Spirituality is also an important aspect that should be taken into account. Cancer patients do not expect spiritual solutions from oncology team members, but they wish to feel comfortable enough to raise spiritual issues and not be met with fear, judgmental attitudes, or dismissive comments. Spirituality can be a major resource for both patients and physicians, yet it can never be imposed but only shared (15).

In addition, it may be of interest to assess spiritual outcomes in palliative care. Nine tools have been identified in a review that has been validated in cross-cultural palliative care populations, and subject to appraisal of their psychometric properties, they may be suitable for cross-cultural research (16).

7.3.4 ***Multidisciplinary approach***

One of the main principles of palliative care is a multidisciplinary approach. All professions are concerned and the treatment decision (either palliation or terminal disease management) should be taken on a multidisciplinary basis (physicians, nurses, social workers, dieticians and psychologists). This is not always easy but it is effective (17). Multidisciplinary care is based on strong collaboration between acute, hospice and home care. It has been shown that the problems of many palliative cancer patients would be more appropriately addressed by advanced home care instead of acute hospital care (18).

7.3.5 ***Can anyone provide palliative care? Health care staff and advanced urological diseases***

Palliative care is practised everywhere and not only in palliative care units or hospices. For various reasons, people tend to delay facing questions associated with the end of life, and fear of the unknown often creates an environment of avoidance and an atmosphere of taboo (19). Healthcare professionals who are not used to working in palliative care often feel helpless. Often, there is a lack of communication with, and active listening to, patients and their families. This is not well received by patients who need communication with doctors and nurses (20).

Healthcare professionals caring for patients with advanced cancer are often exposed to burnout syndrome. It is important to detect signs of this condition at an early stage in order to prevent it from progressing (21,22). The tool mostly used is the Maslach Burnout Inventory (23).

The way that services are managed influences the occupational wellbeing of healthcare professionals. Also, services organised around an effective social support system enhance the quality of work life among caregivers, influencing their perceived stress and their coping strategies. Quality of life of the caregivers affects the quality of care (24).

Irrespective of the reasons for embarking on palliative care, once it has been decided upon, the professionals involved should commit themselves to respect the agreed interventions and implement them in every clinical situation. Clear policies on place of care (hospital, hospice or home), urinary diversions, and resuscitation are needed. Before assuming professional responsibility for terminal care, practices for parenteral hydration and antibiotic use should be clarified.

7.4 Treatment of physical symptoms

7.4.1 ***Pain***

All the details concerning pain treatment have been previously addressed in Chapters 3 and 4.

7.4.2 ***Dyspnoea and respiratory symptoms***

Breathlessness is common and very disturbing for patients with many types of advanced cancer. In this setting, the use of morphine and other opioids is not supported by research studies. Breathing training, walking, chest wall vibration, and electrical muscle stimulation, are effective non-pharmacological measures for relieving breathlessness (25).

When compared with placebo, benzodiazepines can cause more adverse effects (such as drowsiness), but fewer adverse effects are expected when compared to morphine. Despite the lack of evidence from well-conducted RCTs, benzodiazepines can be considered when opioids and non-pharmacological support measures fail to control breathlessness (26). Oxygen provides no symptomatic relief of dyspnoea compared with room air (27) (LE:1b).

Noisy breathing (death rattles) occurs in most people who are dying. The cause of death rattle

remains unclear but is presumed to be due to air passing over upper airways secretions. It can be treated physically or pharmacologically. Although distressing for some professionals and most families, there is no evidence to suggest that any pharmacological (anticholinergic drugs) or non-pharmacological intervention is superior to placebo. Nevertheless, atropine 0.5 mg, hyoscine butylbromide 20 mg, and scopolamine 0.25 mg (subcutaneous, followed by continuous administration) can be moderately effective for treatment of death rattles (28,29).

Recommendation	LE	GR
Benzodiazepines can be considered when opioids and non-pharmacological measures fail to control breathlessness.	1a	A

*7.4.3 **Cancer anorexia-cachexia syndrome***

Cancer anorexia-cachexia syndrome (CACS) is frequent in patients with advanced cancer. Nutritional support in this setting seems to be ineffective (30) (LE: 1b), as does drug therapy. In a few selected cases, dexamethasone (4 mg/day) or progesterone analogues (megestrol acetate, 480-800 mg/day) can be considered, because it is thought that they have a significant effect on appetite and weight gain. A patient-doctor shared decision seems necessary before opting for treatment, considering that no gain in survival or QoL can be expected (31,32). The effect of orally administered cannabis extract (CE) on appetite and QoL in patients with CACS has been rigorously tested. Although CE is well tolerated, its effect on appetite did not clearly differ from that with placebo (33).

More recently, a phase II RCT has shown that thalidomide (50 mg/day, orally, for 2 weeks) is effective against cancer-related anorexia (34).

*7.4.4 **Vomiting***

Chronic nausea occurs in most patients with advanced cancer, and in many cases, it is refractory to metoclopramide. In this setting, dexamethasone does not seem superior to placebo (32).

Droperidol is an antipsychotic drug that has been used as an antiemetic in the management of postoperative and chemotherapy-induced nausea and vomiting. Unfortunately, there is insufficient evidence to advise its use in the management of nausea and vomiting in palliative care (35).

Patients with a high incidence of emesis - usually post-chemotherapy - should receive a serotonin 5-hydroxytryptamine (5-HT3) receptor antagonist (ondansetron, tropisetron, granisetron, dolasetron or palosetron), dexamethasone, and a neurokinin 1 receptor antagonist such as aprepitant or forsaprepitant. Preferential use of palonosetron is recommended for moderate emetic risk regimens, combined with dexamethasone. Patients undergoing high emetic risk radiotherapy should receive a 5-HT3 receptor antagonist before each fraction and for 24 h after treatment, and may receive a 5-day course of dexamethasone during fractions 1 to 5 (36).

Electroacupuncture is beneficial for chemotherapy-induced acute vomiting, but studies combining electroacupuncture with state-of-the-art antiemetics, and in patients with refractory symptoms, are needed to determine clinical relevance. Self-administered acupressure appears to be protective against acute nausea and can readily be taught to patients, although this has not been subjected to placebo-controlled studies. Non-invasive electrostimulation appears unlikely to have a clinically relevant impact when patients are given state-of-the-art antiemetic drug therapy (37).

Recommendations	LE	GR
Dexamethasone is not effective in metoclopramide-refractory nausea.	1b	A
Patients with a high risk of vomiting are effectively treated with a combination of dexamethasone and 5-HT3 and neurokinin 1 receptor antagonists.	1a	A
In patients with moderate risk of vomiting, palonosetron combined with dexamethasone is recommended.	1a	A
Patients receiving radiotherapy and experiencing emesis can be effectively treated with combined 5-HT3 receptor antagonist and dexamethasone.	1a	A

*7.4.5 **Other symptoms***

7.4.5.1 Fatigue

Asthenia is an overwhelming, persistent feeling of tiredness in which normal activity becomes an effort. Cancer-related fatigue (CRF) can be a significant problem with a serious impact on QoL. There are several tools to measure fatigue such as the Brief Fatigue Inventory (BFI), Numeric Rating Scale (NRS), and Revised Piper Fatigue Scale (PFS). The BFI includes nine items that measure the severity and impact of fatigue. It has adequate reliability with an established validity (38). The NRS has only one item: fatigue intensity. It is easy and

quick to use but less reliable (38). The Revised PFS has 22 items plus five additional open-ended items that measure four dimensions of subjective fatigue: behaviour/severity, affective meaning (mental aspect of fatigue), sensory, cognition/mood. It is an adequate and reliable measuring tool with established validity (39).

Trials of erythropoietin and darbopoetin (for anaemic patients) and psychostimulants have provided evidence for improvement in CRF. There are no data to support the use of paroxetine or progestational steroids for treatment of CRF. The amphetamine methylphenidate (standard treatment for attention deficit hyperactivity disorder) has been proposed for treatment of asthenia in patients with advanced cancer (40). There is evidence suggesting reduction in fatigue and depression when compared with placebo. Its effect on fatigue seems dose-dependent and sustained over time. Standard oral doses are 10-40 mg/day (41). Data from a phase III RCT suggest that modafinil - another psychostimulant - can be effective for the treatment of anorexia and depression in patients with advanced cancer (42) .

Exercise is an effective intervention for patients with CRF (43). Like exercise, psychoeducational activity is a promising therapy for ameliorating CRF (44).

7.4.5.2 Restlessness

Most patients in the final stages of their lives experience restlessness. Although neuroleptics have been widely used in this setting, there is insufficient evidence to suggest that a single drug or class of medication is appropriate for terminal restlessness (45).

Recommendation	LE	GR
Neuroleptics cannot be recommended for treatment of terminal restlessness.	3	C

7.4.5.3 Agitated delirium

There is limited high quality evidence on the role of drug therapy for delirium in terminal patients. Although benzodiazepines have been widely used, it has not been possible to assess the effectiveness of treatment options (46,47). However, haloperidol (5-10 mg, intravenous) remains a useful drug for the treatment of many forms of delirium (48).

7.4.5.4 Constipation

Chronic constipation can be a serious problem for cancer patients taking opioids. Oral lactulose seems more effective than polyethylene glycol (49). Nevertheless, evidence on laxatives for management of constipation remains limited due to insufficient RCTs (49).

Interestingly, subcutaneous methylnaltrexone seems effective in inducing laxation in patients with opioid-induced constipation when standard laxatives fail (50,51). Its safety, however, has to be proven in properly organised RCTs. No clear recommendations as to the use of a particular laxative can be made (LE: 1a).

7.4.5.5 Anxiety

Anxiety is a common symptom in patients near the end of life. A myriad of drugs has been used to calm anxiety in terminally ill patients (including anxiolytics, antidepressants, antipsychotics, benzodiazepines, butyrophenones, phenothiazines and thienobenzodiazepines). There is currently insufficient evidence on the role of this type of drug in patients with terminal illness, and it is therefore not possible to draw any conclusions about the effectiveness of pharmacotherapy in this setting (52).

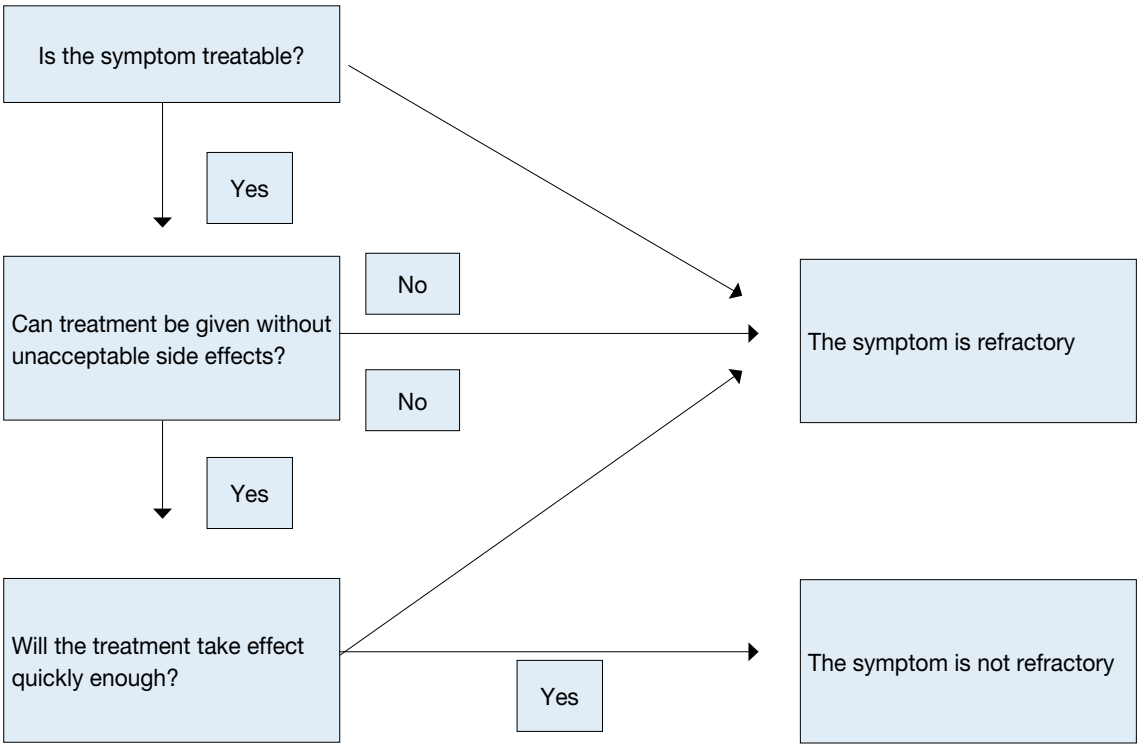
7.5 Terminal care

For medical practitioners who are trained to save lives, the end of life represents a completely different professional scenario in which personal skills give way to multidisciplinary, compassionate intervention. Relieving suffering requires well-trained teams and clearly established goals. It seems clear that early identification of patients needing palliative care can effectively improve QoL (53).

Recognition of intolerable refractory symptoms, standardised monitoring of disease progress, and availability of terminal care pathways are crucial for supporting patients and families with terminal disease.

In addition to the above-mentioned interventions, palliative sedation is one of the alternatives to keep in mind when dealing with terminally ill patients. Patients experiencing refractory symptoms (e.g., pain, vomiting, delirium and dyspnoea) can be considered for palliative sedation. It consists of the deliberate administration of drugs in minimum doses and combinations required not only to reduce the consciousness of the patients but also to achieve adequate alleviation of one or more refractory symptoms, and with the prior consent given by the patient explicitly, or implicitly, or delegated (54). The aim of palliative sedation is never to hasten death and there is evidence that it does not jeopardise survival (55,56). Figure 6 is an aid for the recognition of refractory symptoms.

Figure 6: Algorithm for treatment decisions for refractory symptoms



Source: Royal Dutch Medical Association (KNMG). Guideline for Palliative Sedation. Utrecht, 2009.

Although physicians are responsible for the objective evaluation of symptoms, fully competent patients have the right to prompt interventions or to refuse any kind of treatment. When the patient is mentally incapable, the nearest relative can make decisions. For certain complicated cases, physicians might seek the help of their ethics committee or ask for a legal consultation. Nevertheless, it should always be kept in mind that doubt should not be expressed in front of a suffering patient.

The ethics of palliative treatment at the end of life seem beyond question. Nevertheless, a few countries in Europe (Netherlands, Belgium and Switzerland) and some of the United States (Oregon and Washington) have clear regulations on the right to terminal sedation. Cultural and ethnic differences in the approach to the end of life are also prominent (57-64), thus making the approach to the final stages of life not always equitable.

*7.5.1 **When and how to withdraw specific treatment***

With every single intervention, the ethical principles of beneficence, non-maleficence, autonomy and justice should be considered. Relieving suffering - rather than sustaining life at any cost - might be sensible in patients with advanced disease. Patients (or relatives when they are incompetent) have the right to ask for treatment cessation at any time. It will always be taken into account that proxies are supposed to interpret the patient's wishes and not their own. Artificial ventilation, haemodialysis, parenteral nutrition, blood transfusion and chemotherapy can all be stopped at the patient's request (65).

Recommendation	LE	GR
The patient (or relatives if incompetent) should be able to decide on every single intervention.	4	A*

**Recommendation based on expert opinion.*

*7.5.2 **Parenteral hydration: should it be discontinued in the terminal phases?***

There is an interesting controversy about forced hydration in terminally ill patients. At present, good quality studies on this topic are lacking, making recommendations for practice pointless (66).

There is scientific evidence to show that artificial hydration provides no clear benefit in relation to normalising renal function and electrolyte levels compared with non-hydrated patients (67). Nevertheless, it seems that parenteral hydration can improve many of the symptoms experienced by terminally ill, dehydrated cancer patients (68).

The decision should be taken on an individual basis, but it is suggested that patients who cease drinking are close to death and will gain little from artificial hydration (3).

*7.5.3 **Palliative sedation***

Considering the lack of randomised trials on palliative sedation, the panel decided to stick to the principles of the Royal Dutch Medical Association (KNMG) in this respect (3).

As mentioned earlier, palliative sedation is the deliberate lowering of the level of consciousness in the last stages of life. As such, it can only be considered in the context of a palliative care plan. The object of palliative sedation is to relieve suffering, and lowering consciousness is the means to that end. Palliative sedation never aims to hasten death. Deciding whether the indications for palliative sedation are met is always a medical task, but not necessarily a matter for specialised physicians. The untreatable nature of the symptoms must be demonstrated beyond reasonable doubt. Besides the presence of medical indications in the form of one or more refractory symptoms, another precondition is the expectation that death will ensue in the reasonably near future – that is, within 1-2 weeks (3,69).

It is generally agreed that physicians and nurses should be present the moment palliative sedation begins (69). Subcutaneous administration is the preferred route and midazolam the drug of choice (1,70). Table 19 provides a suggestion for palliative sedation (3).

Table 19: Three steps approach to palliative sedation. In the hospital setting, Phase 3 can follow Phase 1 (1)

	Drug	Bolus	Continuous administration
Phase 1	Midazolam	Start with 10 mg s.c. If necessary, 5 mg every 2 h s.c.	Initial dose 1.5-2.5 mg/h sc/iv. If the desired effect is not achieved, increase the dose by 50% after a minimum of 4 h, always in combination with a bolus of 5 mg sc. If risk factors are present (age > 60 years, weight < 60 kg, severe kidney or liver dysfunction, very low serum albumin, and/ or co-medication that could exacerbate the effect of sedation): - lower initial dose (0.5-1.5 mg/h), and - lengthen interval (6-8 h) before increasing maintenance dose. In the case of doses > 20 mg/h, see Phase 2.
Phase 2	Levomepromazine	25 mg sc/iv, possibly 50 mg after 2 h	0.5-8 mg/h sc/iv in combination with midazolam. After 3 days, halve the dose to prevent drug accumulation. If the desired effect is not achieved, stop administering midazolam and levomepromazine; see Phase 3.
Phase 3	Propofol	20-50 mg iv	20 mg/h iv, increase by 10 mg/h every15 min. Administration under supervision of an anaesthesiologist is advisable. In hospital, this may be considered for Phase 2.

Source: Royal Dutch Medical Association (KNMG). Guideline for Palliative Sedation. Utrecht, 2009.

7.6 Treatment of psychological aspects

*7.6.1 **Fear***

While improvements in screening, prevention and treatment are encouraging, cancer is still related to very intensive treatment, and finally to death in many patients. It may cause deep fear and depression. The role of the healthcare giver is important in this process (71). Measuring distress should be a major part of assessing patient emotional disturbance. Different tools are available such as the Hospital Anxiety and Depression Scale and the Distress Thermometer. Successful implementation of a screening procedure depends on its acceptability to patients and clinicians, as well as the clinicians' perception of the added value. Distress is often related to the physical complications of cancer and its treatment, therefore, the approach should include psychological and physical well-being (72).

Recommendation	LE	GR
Distress must be recognised, measured, treated and monitored at all stages of the disease.	2b	A

*7.6.2 **Depression***

There is a strong correlation between physical disease and depression but there is no evidence that depression may cause cancer. Depression is associated with adverse outcomes such as increased pain, disability and poor prognosis (73).

The effectiveness of pharmacological agents for anxiety has not yet been proved. Nevertheless, both psychosocial and pharmacological interventions have been shown to be efficacious in treating depression in cancer patients (74,75).

One study has shown that prescription prevalence among cancer patients in the last year of life is almost four times higher than in the general population. One out of 10 patients is prescribed with antidepressants so close to death that the clinical effects can be questioned (76).

Moreover, behavioural therapy, counselling, psychotherapy, education/information, relaxation and social support alleviate depression and anxiety (77). Centralised telecare management coupled with automated symptom monitoring can improve pain and depression outcomes in cancer patients receiving care in geographically dispersed urban and rural oncology practices (78).

Screening for depression in terminally ill patients can optimise their physical comfort at the end of life and provide them with the opportunity to confront and prepare for death (79).

Recommendation	LE	GR
Efforts should be made to detect hidden depression.	2b	B*

**Recommendation based on expert opinion.*

*7.6.3 **Family care***

Family and relatives have an important role to play in the care of patients with advanced disease and they should be involved in decision-making about where the patient should be cared for (e.g., home or hospice). Nevertheless, the patient's views should always be kept in mind. In addition, the family is emotionally affected by the disease, and their emotional distress may influence the patient's mood. It is important to screen for depressive symptoms and predictors of depression among family caregivers, especially in the dying process and after death (80).

Patients and families need to be prepared for death. The process can then take place under good, serene conditions (81,82). Otherwise, it can lead to dysfunctional family dynamics that can be disturbing to the staff members in their efforts to provide optimal palliative care, and to the patient (81). Family-focused grief therapy based on communication, cohesiveness, conflict resolution, and shared grief is effective in protecting family members against the drama of disease and death (83).

Table 20: Arresødal Hospice principles of management of intrafamilial conflicts (81)

Maintain the palliative perspective	Consider the possibility and implementation of palliative management perspective strategies in certain subtypes of family dysfunction and to extend beyond this (if favourable circumstances allow), incorporate a more long-term outlook for future rehabilitation of the surviving relatives.
Maintain flexibility	Take into account the strengths, psychological resources, level of intellect and emotional state of conflicting family members before deciding whether to use interpretive or supportive techniques. Be prepared to reflect over strategies that have not been optimal, and modify as necessary.
Maintain neutrality	Current information for all staff members involved through mono- or multidisciplinary meetings is essential. It is important to handle conflicting family dynamics in an open, transparent and professional way, not to be unexpectedly absorbed as an active part of the conflict, and to avoid covert behaviour. The principle of neutrality applies to this strategy in that involvement in long-term prior conflicts is to be avoided.
Avoid splitting	Avoid, or at least identify and understand splitting between members of staff by recognizing that dysfunctional families with conflicting dynamics may display completely opposing attitudes within short periods of time, which can be challenging to staff. In the worst case scenarios, relatives in conflict may project their issues onto others as a way to control fragmented or distressed parts of themselves.
Avoid demonising	Encourage and enable staff to share awkward, challenging and/or negative feelings brought on by sudden or inadvertent involvement in conflicting family dynamics.

Set necessary limits	Limits need to be identified and maintained consistently if behaviour of a family member threatens the integrity or safety of the patient, other relatives, staff or the palliative-therapeutic relationship.
Intervention	Encourage staff members to maintain the professional/personal balance through multidisciplinary discussions, counselling and prompt debriefing.

7.6.4 ***Communication of bad news***

Informing patients of bad news about malignancies is a difficult task; bad prognosis for some cancers and severe symptoms and treatment side effects make it painful for health professionals. It may be easier not to inform the patient. Nevertheless, disclosure will emphasise uncertainty and anxiety. In addition, patients have the right to be informed and the right to choose non-disclosure (84). Specific, patient-targeted information increases the quality of terminal care (7).

Patients' families often experience anticipatory grief when learning of a diagnosis of advanced or terminal cancer. Anticipatory grief can be a response to threats of loss of ability to function independently, loss of identity, and changes in role definition, which underlie fear of death. When an oncologist delivers bad news, the patient and family members often hear the same discussion through different filters, which can lead to conflict and dysfunction. It is then important to provide a supportive and safe environment, and to help the patients reframe "hope" realistically so that they may have the opportunity for personal growth as well as reconciliation of primary relationships toward the end of life (85).

In such situations, good communication skills are needed. There are methods to help health care professionals deliver information about bad news, such as using sociograms and psychodrama (86).

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8. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

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

Conflict of interest

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