



Guidelines on

Pain

Management &

Palliative Care

A. Paez Borda (chair), F. Charnay-Sonnek, V. Fonteyne,
E.G. Papaioannou

TABLE OF CONTENTS

PAGE

| | | |
|---------|--|----|
| 1. | INTRODUCTION | 6 |
| 1.1 | The Guideline | 6 |
| 1.2 | Methodology | 6 |
| 1.3 | Publication history | 6 |
| 1.4 | Level of evidence and grade of guideline recommendations* | 6 |
| 1.5 | References | 7 |
| 2. | PAIN MANAGEMENT IN UROLOGICAL CANCERS | 7 |
| 2.1 | Pain management in prostate cancer patients | 11 |
| 2.1.1 | Clinical presentation | 12 |
| 2.1.2 | Pain due to local impairment | 12 |
| 2.1.2.1 | Bladder outlet obstruction | 12 |
| 2.1.2.2 | Ureteric obstruction | 12 |
| 2.1.2.3 | Lymphoedema | 12 |
| 2.1.2.4 | Ileus | 12 |
| 2.1.3 | Pain due to metastases | 12 |
| 2.1.3.1 | Bone metastases | 12 |
| 2.1.3.2 | Systemic analgesic pharmacotherapy (the analgesic ladder) | 13 |
| 2.1.3.3 | Hormone therapy | 13 |
| 2.1.3.4 | Radiotherapy | 13 |
| 2.1.3.5 | Orthopaedic surgery | 13 |
| 2.1.3.6 | Radioisotopes | 13 |
| 2.1.3.7 | Bisphosphonates | 14 |
| 2.1.3.8 | Denosumab | 14 |
| 2.1.3.9 | Chemotherapy | 14 |
| 2.1.4 | Spinal cord compression | 14 |
| 2.1.5 | Hepatic invasion | 15 |
| 2.1.6 | Pain due to cancer treatment | 15 |
| 2.1.6.1 | Acute pain associated with hormonal therapy | 15 |
| 2.1.6.2 | Chronic pain associated with hormonal therapy | 15 |
| 2.1.7 | Recommendations on prostate cancer pain management | 15 |
| 2.2 | Pain management in transitional cell carcinoma patients | 15 |
| 2.2.1 | Clinical presentation | 16 |
| 2.2.2 | Origin of tumour-related pain | 17 |
| 2.2.2.1 | Bladder TCC | 17 |
| 2.2.2.2 | Upper urinary tract TCC | 17 |
| 2.2.3 | Pain due to local impairment | 17 |
| 2.2.3.1 | Bladder TCC | 17 |
| 2.2.3.2 | Upper urinary tract TCC | 17 |
| 2.2.4 | Pain due to metastases | 18 |
| 2.2.5 | Recommendations on transitional cell carcinoma pain management | 18 |
| 2.3 | Pain management in renal cell carcinoma patients | 18 |
| 2.3.1 | Clinical presentation | 19 |
| 2.3.2 | Pain due to local impairment | 19 |
| 2.3.3 | Pain due to metastases | 19 |
| 2.3.4 | Recommendations for renal cell carcinoma pain management | 19 |
| 2.4 | Pain management in patients with adrenal carcinoma | 20 |
| 2.4.1 | Malignant pheochromocytoma | 20 |
| 2.4.1.1 | Treatment of pain | 20 |
| 2.4.2 | Adrenocortical carcinomas | 20 |
| 2.4.2.1 | Treatment of the pain depending on its origin | 21 |
| 2.4.3 | Recommendations pain management adrenal carcinoma | 21 |
| 2.5 | Pain management in penile cancer patients | 21 |
| 2.5.1 | Clinical presentation | 22 |
| 2.5.2 | Pain due to local impairment | 22 |
| 2.5.3 | Lymphoedema | 22 |
| 2.5.4 | Pain due to metastases | 22 |
| 2.5.5 | Recommendations on penile cancer pain management | 23 |

| | | |
|---------|--|----|
| 2.6 | Pain management in testicular cancer patients | 23 |
| 2.6.1 | Clinical presentation | 23 |
| 2.6.2 | Pain due to local impairment | 23 |
| 2.6.3 | Pain due to metastases | 23 |
| 2.6.4 | Recommendations for testicular cancer pain management | 24 |
| 2.7 | References | 24 |
| 3. | PAIN MANAGEMENT AFTER UROLOGICAL OPERATIONS | 30 |
| 3.1 | Specific pain treatment after different urological operations | 30 |
| 3.1.1 | Extracorporeal shock wave lithotripsy | 30 |
| 3.1.2 | Endoscopic procedures | 31 |
| 3.1.2.1 | Transurethral procedures | 31 |
| 3.1.2.2 | Percutaneous endoscopic procedures | 31 |
| 3.1.2.3 | Laparoscopic and robotic procedures | 31 |
| 3.1.3 | Recommendations pain treatment after different urological operations | 31 |
| 3.1.4 | Open surgery | 31 |
| 3.1.4.1 | Minor operations of the scrotum/penis and the inguinal approach | 31 |
| 3.1.4.2 | Transvaginal surgery | 31 |
| 3.1.4.3 | Perineal open surgery | 31 |
| 3.1.4.4 | Transperitoneal laparotomy | 32 |
| 3.1.4.5 | Suprapubic/retropubic extraperitoneal laparotomy | 32 |
| 3.1.4.6 | Retroperitoneal approach - flank incision - thoracoabdominal approach | 32 |
| 3.1.5 | Recommendations for pain management after open surgery | 32 |
| 3.2 | Dosage and method of delivery of some important analgesics | 32 |
| 3.2.1 | NSAIDs | 32 |
| 3.2.2 | Opioids | 33 |
| 3.2.3 | Summary of recommendations for postoperative pain management in adults | 34 |
| 3.3 | Special populations | 34 |
| 3.3.1 | Ambulatory surgical patients | 34 |
| 3.3.2 | Geriatric patients | 34 |
| 3.3.3 | Obese patients | 34 |
| 3.3.4 | Drug- or alcohol-dependent patients | 35 |
| 3.3.5 | Other groups | 35 |
| 3.3.6 | Perioperative problems in children | 35 |
| 3.3.7 | Postoperative analgesia in children | 35 |
| 3.3.8 | Recommendations special populations | 36 |
| 3.4 | References | 36 |
| 4. | NON -TRAUMATIC ACUTE FLANK PAIN | 38 |
| 4.1 | Background | 38 |
| 4.2 | Initial diagnostic approach | 39 |
| 4.2.1 | Symptomatology | 39 |
| 4.2.2 | Laboratory evaluation | 39 |
| 4.2.3 | Diagnostic imaging | 39 |
| 4.2.3.1 | Computed tomography (CT) | 39 |
| 4.2.3.2 | Ultrasound imaging (US) | 39 |
| 4.2.3.3 | Intravenous urography and unenhanced helical CT | 39 |
| 4.3 | Initial emergency treatment | 41 |
| 4.3.1 | Systemic analgesia | 41 |
| 4.3.2 | Local analgesia | 41 |
| 4.3.3 | Supportive therapy | 41 |
| 4.3.4 | Upper urinary tract decompression | 41 |
| 4.3.5 | Recommendations non-traumatic acute flank pain | 42 |
| 4.4 | References | 42 |
| 5. | PALLIATIVE CARE | 44 |
| 5.1 | Introduction | 44 |
| 5.2 | Supportive care | 44 |
| 5.3 | Definition and aim of palliative care | 45 |
| 5.4 | General principles | 45 |

| | | |
|-----------|--|----|
| 5.4.1 | Communication | 45 |
| 5.4.2 | Patient-centered treatment | 46 |
| 5.4.3 | Cultural and spiritual approach | 47 |
| 5.4.4 | Setting for the provision of terminal care | 47 |
| 5.4.5 | Multidisciplinary approach | 47 |
| 5.4.6 | Can anyone provide palliative care? Health care staff and advanced urological diseases | 47 |
| 5.5 | Treatment of physical symptoms | 47 |
| 5.5.1 | Pain | 47 |
| 5.5.2 | Dyspnoea and respiratory symptoms | 47 |
| 5.5.3 | Cancer anorexia-cachexia syndrome | 48 |
| 5.5.4 | Vomiting | 48 |
| 5.5.5 | Other symptoms | 48 |
| 5.5.5.1 | Fatigue | 48 |
| 5.5.5.2 | Restlessness | 48 |
| 5.5.5.3 | Agitated delirium | 49 |
| 5.5.5.4 | Constipation | 49 |
| 5.5.5.5 | Anxiety | 49 |
| 5.5.6 | Recommendations treatment of physical symptoms | 49 |
| 5.6 | Terminal care | 49 |
| 5.6.1 | When and how to withdraw specific treatment | 50 |
| 5.6.2 | Parenteral hydration: should it be discontinued in the terminal phases? | 50 |
| 5.6.3 | Palliative sedation | 51 |
| 5.7 | Treatment of psychological aspects | 51 |
| 5.7.1 | Fear | 51 |
| 5.7.2 | Depression | 52 |
| 5.7.3 | Family care | 52 |
| 5.7.4 | Communication of bad news | 53 |
| 5.7.5 | Recommendations treatment of psychological aspects | 53 |
| 5.8 | References | 53 |
| ADDENDUM | | 59 |
| A.1 | PAIN MANAGEMENT (GENERAL) | 59 |
| A.1.1 | Pain evaluation and measurement | 59 |
| A.1.1.1 | Pain evaluation | 59 |
| A.1.1.2 | Assessing pain intensity and quality of life (QoL) | 59 |
| A.1.2 | References | 60 |
| A.2 | CANCER PAIN MANAGEMENT (GENERAL) | 61 |
| A.2.1 | Classification of cancer pain | 61 |
| A.2.2 | General principles of cancer pain management | 61 |
| A.2.3 | Non-pharmacological therapies | 62 |
| A.2.3.1 | Surgery | 62 |
| A.2.3.2 | Radionuclides | 62 |
| A.2.3.2.1 | Clinical background | 62 |
| A.2.3.2.2 | Radiopharmaceuticals | 62 |
| A.2.3.3 | Radiotherapy for metastatic bone pain | 63 |
| A.2.3.3.1 | Clinical background | 63 |
| A.2.3.3.2 | Radiotherapy scheme | 63 |
| A.2.3.3.3 | Spinal cord compression | 64 |
| A.2.3.3.4 | Pathological fractures | 64 |
| A.2.3.3.5 | Side effects | 64 |
| A.2.3.4 | Psychological and adjunctive therapy | 64 |
| A.2.3.4.1 | Psychological therapies | 64 |
| A.2.3.4.2 | Adjunctive therapy | 65 |
| A.2.4 | Pharmacotherapy | 65 |
| A.2.4.1 | Chemotherapy | 66 |
| A.2.4.2 | Bisphosphonates | 66 |
| A.2.4.3 | Denosumab | 66 |
| A.2.4.4 | Systemic analgesic pharmacotherapy - the analgesic ladder | 66 |

| | | |
|-------|---|----|
| | A.2.4.4.1 Non-opioid analgesics | 66 |
| | A.2.4.4.2 Opioid analgesics | 67 |
| | A.2.4.5 Treatment of neuropathic pain | 70 |
| | A.2.4.5.1 Antidepressants | 70 |
| | A.2.4.5.2 Anticonvulsant medication | 71 |
| | A.2.4.5.3 Local analgesics | 71 |
| | A.2.4.5.4 NMDA receptor antagonists | 71 |
| | A.2.4.5.5 Other drug treatments | 72 |
| | A.2.4.5.6 Invasive analgesic techniques | 72 |
| | A.2.4.6 Breakthrough cancer pain | 73 |
| | A.2.4.7 Recommendations pharmacotherapy | 74 |
| A.2.5 | Quality of life | 74 |
| A.2.6 | Conclusions | 75 |
| A.2.7 | References | 75 |
| A.3 | POSTOPERATIVE PAIN MANAGEMENT | 87 |
| A.3.1 | Background | 87 |
| A.3.2 | Importance of effective postoperative pain management | 87 |
| | A.3.2.1 Aims of effective postoperative pain management | 87 |
| A.3.3 | Pre- and postoperative pain management methods | 87 |
| | A.3.3.1 Preoperative patient preparation | 87 |
| | A.3.3.2 Pain assessment | 88 |
| | A.3.3.3 Pre-emptive analgesia | 88 |
| | A.3.3.4 Systemic analgesic techniques | 88 |
| | A.3.3.4.1 Non-steroidal anti-inflammatory drugs | 88 |
| | A.3.3.4.2 Paracetamol | 88 |
| | A.3.3.4.3 Metamizole (dipyrone) | 89 |
| | A.3.3.4.4 Opioids | 89 |
| | A.3.3.4.5 Patient-controlled analgesia | 89 |
| | A.3.3.4.6 Adjuncts to postoperative analgesia | 89 |
| | A.3.3.5 Regional analgesic techniques | 90 |
| | A.3.3.5.1 Local anaesthetic agents | 90 |
| | A.3.3.5.2 Epidural analgesia | 90 |
| | A.3.3.5.3 Patient-controlled epidural analgesia | 90 |
| | A.3.3.5.4 Neural blocks | 90 |
| | A.3.3.5.5 Wound infiltration | 91 |
| | A.3.3.5.6 Continuous wound instillation | 91 |
| | A.3.3.6 Multimodal analgesia | 91 |
| | A.3.3.7 Postoperative pain management teams | 91 |
| | A.3.3.8 Recommendations postoperative pain management\ | 91 |
| A.3.4 | References | 92 |
| 6. | ABBREVIATIONS USED IN THE TEXT | 95 |



1. INTRODUCTION

1.1 The Guideline

The 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. The panel composition has not changed since the last version of the guideline.

1.2 Methodology

The recommendations provided in the current guidelines are based on systematic literature searches using Embase/Medline and the Cochrane Central Register of Controlled Trials. PsychInfo and Eur-Lex were also used to obtain evidence related to psychological therapies and legal regulations on palliative care in the EU, respectively.

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 2013 edition contained 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.

The objective for 2014 was to restructure the entire guideline and to put the focus more on urological aspects and action based recommendations. Background and general information has been moved to Addenda A1, A2 and A3.

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 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).

1.5 References

1. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2009). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009.
<http://www.cebm.net/index.aspx?o=1025> [Access date February 2014]
2. Atkins D, Best D, Briss PA, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004 Jun;19;328(7454):1490.
<http://www.ncbi.nlm.nih.gov/pubmed/15205295>
3. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. Going from evidence to recommendations. *BMJ* 2008 May;10;336(7652):1049-51.
<http://www.ncbi.nlm.nih.gov/pubmed/18467413>
4. Guyatt GH, Oxman AD, Vist GE, et al; GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008 Apr;26;336(7650):924-6.
<http://www.ncbi.nlm.nih.gov/pubmed/18436948>

2. PAIN MANAGEMENT IN UROLOGICAL CANCERS

The prevalence of cancer pain is close to 25% for newly diagnosed cases (1) and > 75% for advanced disease (2,3). Half of the patients express neuropathic pain, which in 90% is caused by neurotoxic chemotherapy (4). A straightforward, comprehensive approach to treating cancer pain is mandatory.

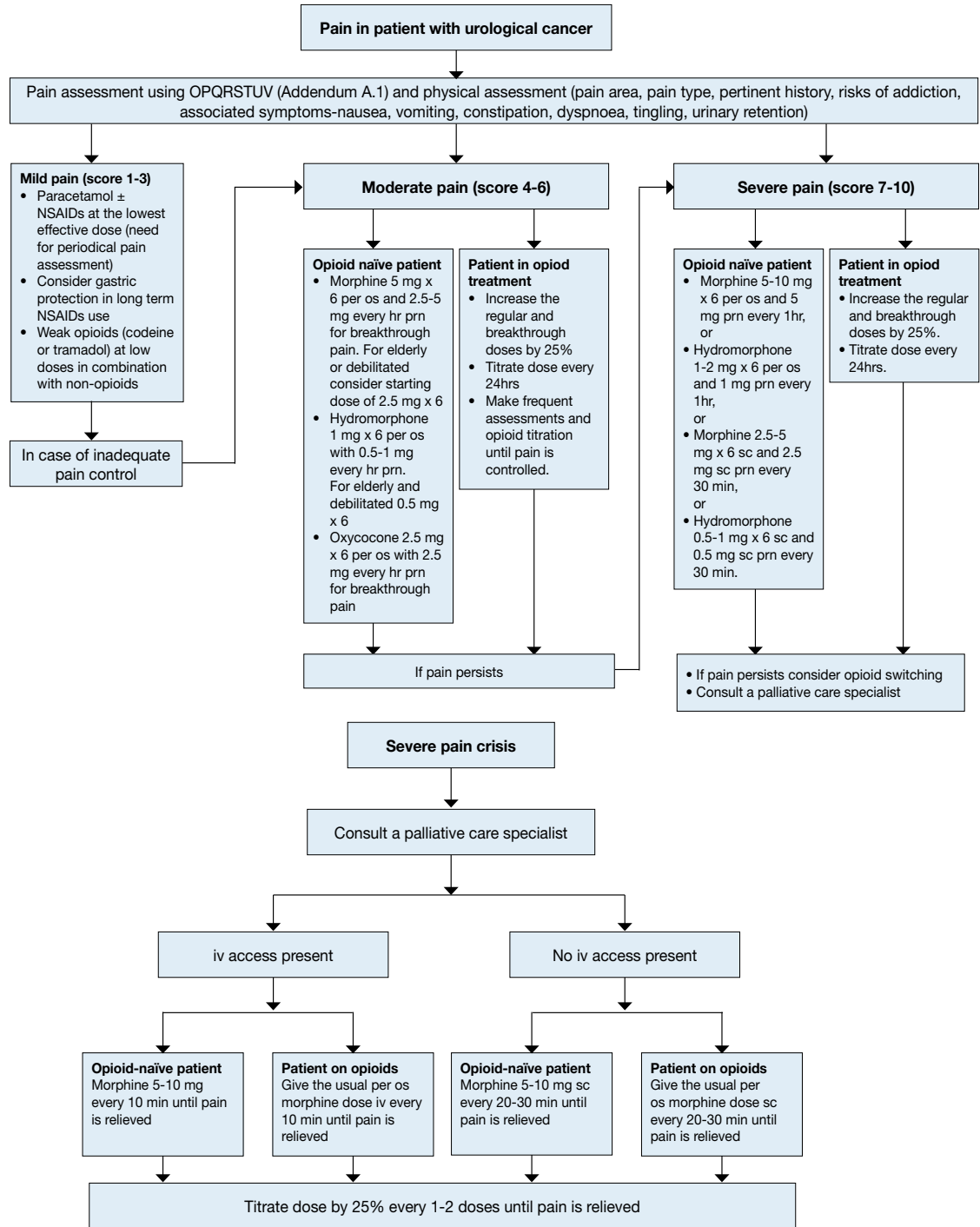
General concepts on palliative surgery, radionuclides and adjunctive and psychological therapies can be considered common to every urological tumour. Basic concepts in this respect are presented in Table 3. Figure 1 presents a general approach to the patient with urological cancer and pain. Figure 2 represents a general approach to the patient with urological cancer and metastatic bone pain. Figure 3 gathers the therapeutic options for neuropathic pain.

For a more detailed description, refer to addenda A. Pain Management (General) and B. Cancer pain management (General).

Table 3: General concepts on palliative surgery, radionuclides and adjunctive and psychological therapies

| Surgery | LE | GR |
|---|-----------|-----------|
| Palliation is not equivalent to minimal invasion. Consider aggressive surgery under certain circumstances. | 2b | B |
| Radionuclides | | |
| Radiopharmaceuticals are an option for patients with multifocal pain bone metastases when other treatments have failed. | 2b | B |
| Psychological | | |
| Always offer psychological support to cancer patients and their loved ones. | 1a | A |
| Adjunctive therapy | | |
| Moderate exercise can be an adjuvant and should be suggested in the treatment of cancer pain. | 1a | A |

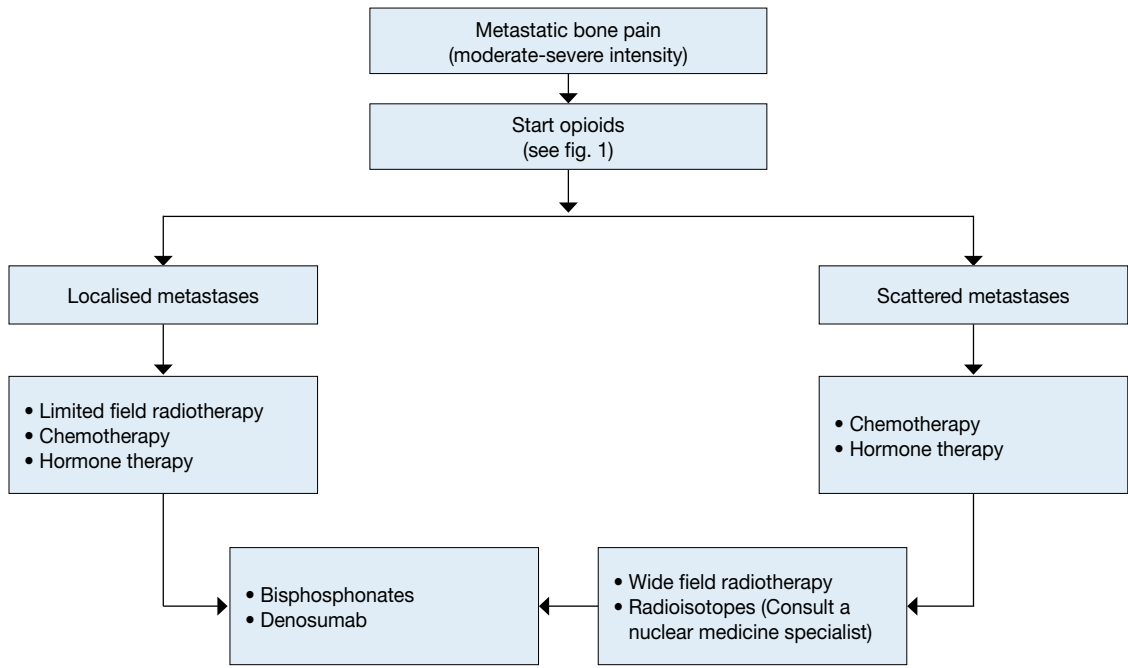
Figure 1: Cancer pain treatment in urology



Clinicians must be aware of the side-effects of opioids, if not confident, consulting a palliative care specialist is recommended

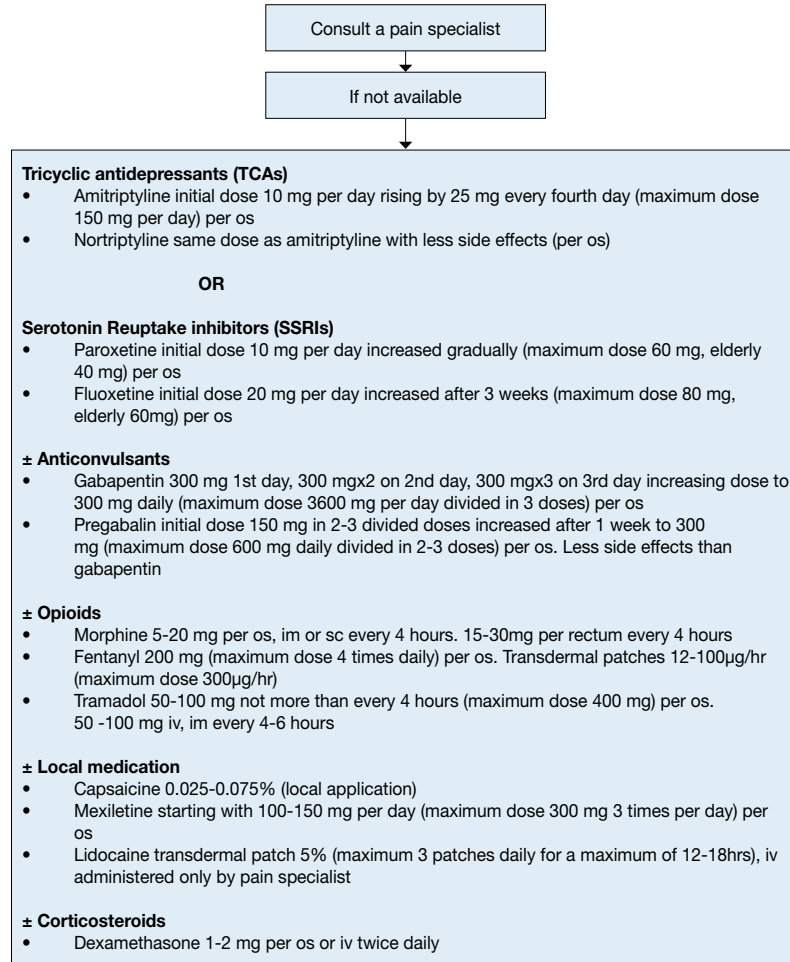
NSAIDs = non-steroidal anti-inflammatory drugs; iv = intravenous; sc = subcutaneous; prn = pro re nata (as needed)

Figure 2: Management of metastatic bone pain



Pain assessment (OPQRSTUV approach, see Addendum A.1) is mandatory before treating metastatic bone pain. All patients should be offered opioids (see Figure 1). Localised metastases are best treated with limited field radiotherapy (consult radiotherapist for dosage). Alternatively, chemo-sensitive and/or hormone-sensitive tumours can be treated with systemic chemotherapy or hormone therapy. Radio-resistant and/or chemo/hormone-refractory tumours are then best treated with bisphosphonates or denosumab. Scattered bone metastases in chemo-sensitive and/or hormone-sensitive tumours can be treated initially with systemic chemotherapy or hormone therapy. Chemo/hormone-refractory tumours are then best treated with wide field radiotherapy or radioisotopes. Patients failing wide field radiotherapy or radioisotopes can then be offered bisphosphonates or denosumab.

Figure 3: Management of neuropathic pain

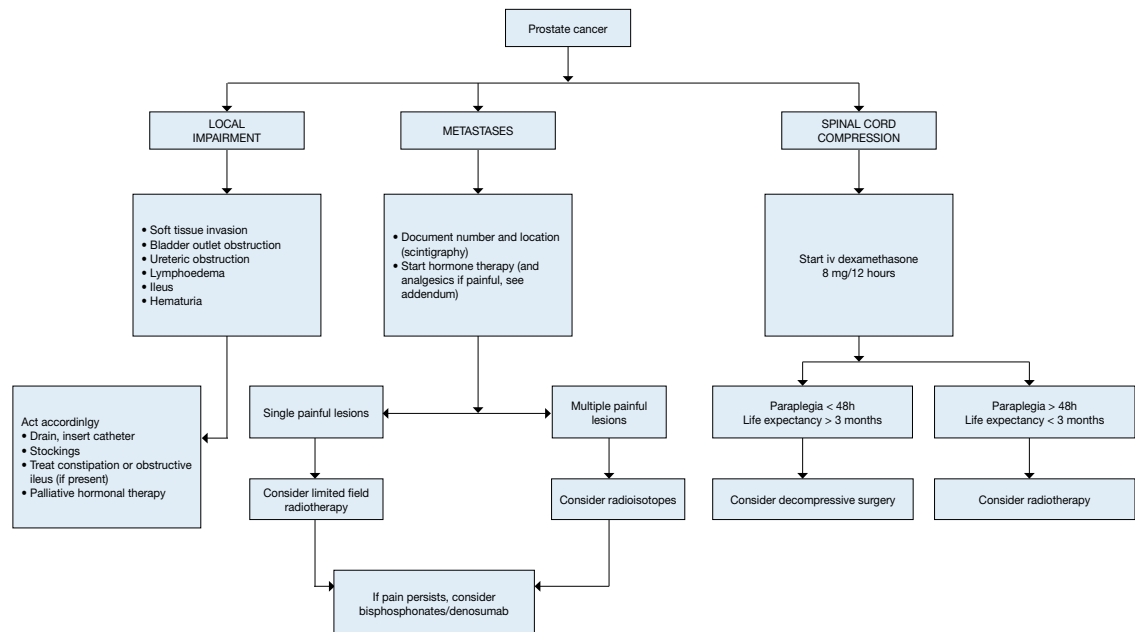


Note: there are no sufficient data relating to the kind of drug or dose administered according to neuropathic pain severity or type (eg. throbbing, cramping, piercing etc.)

2.1 Pain management in prostate cancer patients

For a complementary approach please refer to the EAU Guidelines on Prostate Cancer (5).

Figure 4: Pain management in PCa patients



Only the main clinical scenarios are addressed in Figure 4. For a wider approach please refer to the EAU Guidelines on Prostate Cancer.

2.1.1 **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%) (6). The overall incidence of chronic pain in PCa patients is about 30-50%, but as patients enter the terminal phase this rises to 90% (7).

2.1.2 **Pain due to local impairment**

2.1.2.1 *Bladder outlet obstruction*

Continuous growth of the prostate or local bleeding 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. If a bladder neoplasm can be reasonably excluded, the best method is to insert a suprapubic catheter and treat the tumour according to the stage (5). If the outlet obstruction persists, palliative transurethral resection of the prostate (TURP) is an option if no curative therapy can be offered. Palliative radiotherapy can relieve symptoms caused by bladder outlet obstruction in 63% of the patients (8).

2.1.2.2 *Ureteric obstruction*

Ureteric obstruction is most frequently caused by tumour compression or infiltration within the true pelvis (7-10). In most cases, obstruction is primarily asymmetrical. 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. Antegrade ureteral stenting through the nephrostomy site can also be attempted when the patient desires an internal diversion. Palliative radiotherapy can be offered as an alternative treatment for ureteric obstruction with a response rate of 62%.

2.1.2.3 *Lymphoedema*

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

2.1.2.4 *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.

2.1.3 **Pain due to metastases**

2.1.3.1 *Bone metastases*

- Bone metastases are the most common cause of chronic pain in patients with PCa (9,10).
- 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 (11).
- The factors that convert a painless lesion into a painful one are unknown.

The choice of treatment will depend on the site of the tumour, and on the patient's physical and emotional condition. 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:

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

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

2.1.3.2 Systemic analgesic pharmacotherapy (the analgesic ladder)

Metastatic bone pain usually needs a straightforward approach. 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 (12). Tramadol and dihydrocodeine extended-release tablets were effective for the management of chronic tumour pain due to bone metastases, with tramadol giving slightly better pain management and fewer side-effects, particularly constipation (13). 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 (14). Patients with inadequate pain control and intolerable opioid related toxicity/adverse effects may have to switch to an alternative opioid for symptomatic relief.

2.1.3.3 Hormone therapy

For more information on hormone therapy, refer to EAU Guidelines on Prostate Cancer (5). Hormone therapy 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) and 70% (17). Well-differentiated prostatic carcinoma is more likely to respond to hormones than poorly differentiated tumours. Manipulations that include replacement corticosteroid therapy or have additional corticoid effects seem to give higher response rates.

2.1.3.4 Radiotherapy

- The role of radiotherapy in the management of pain due to bone metastases is pivotal (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 e.g. 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 is close to 70% (21) (Section A.2.3.3).

2.1.3.5 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).

2.1.3.6 Radioisotopes

Widespread axial skeletal involvement in PCa has been successfully treated with systemically administered bone-seeking radioisotopes (see also Section A.2.3.2). Commonly used radionuclides are ⁸⁹Sr chloride and ¹⁵³Sm-EDTMP. The addition of ⁸⁹Sr 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 quality of life (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.

2.1.3.7 *Bisphosphonates*

Bisphosphonates can be part of the supportive care for patients with bone metastases and pain. 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.

2.1.3.8 *Denosumab*

Compared to zoledronic acid and placebo, denosumab delays or prevents skeletal related events in bone metastases from solid tumours and as such prevents progression of pain severity (32). With regard to QoL, pain management and overall survival and safety, denosumab shows no benefits over other bone-targeting therapies.

2.1.3.9 *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 (33), particularly with docetaxel.

Trials using single-agent chemotherapy in advanced disease have shown poor results, but newer studies have 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. 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 (34). 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 (35). Docetaxel is the standard first-line chemotherapeutic agent (36). Despite a net survival benefit, the prognosis remains poor. 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 (36,37). 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) (37) (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 (38). Although most of these regimens are associated with side-effects such as fatigue, mild myelosuppression and gastrointestinal irritation, they are generally well tolerated in most patients (39).

2.1.4 *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% (40). Thoracic cord compression is the most common area (70%), and the incidence of multiple extradural sites can be as high as 18% (41). 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 (dexamethasone, 16 mg daily) are of only temporary use in cord oedema. There is evidence that decompressive surgery is superior to radiotherapy alone. Patients most suited for surgery are 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 (42).

2.1.5 **Hepatic invasion**

Hepatic invasion by secondary tumour is a common cause of severe hypochondrial pain, often radiating to the back and shoulder blades. Liver pain can often be controlled by conventional titration of appropriate analgesics or with corticosteroids.

Whole-liver palliative radiotherapy (30 Gy in 15 daily fractions) can also be useful in more than half of patients with refractory pain, giving far fewer side-effects than the alternatives of intra-arterial chemotherapy or hepatic artery embolisation (43).

2.1.6 **Pain due to cancer treatment**

2.1.6.1 *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 (44,45), presumably caused by an initial stimulation of LH release before suppression is achieved (46,47). The syndrome typically presents as an exacerbation of bone pain or urinary retention. Spinal cord compression and sudden death have also been reported (45). 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 (48).

2.1.6.2 *Chronic pain associated with hormonal therapy*

Gynaecomastia

Chronic gynaecomastia and breast tenderness are common complications of anti-androgen therapies for PCa. Frequently associated with diethylstilboestrol (49), it is less common with flutamide and cyproterone (50-52), and uncommon in patients receiving LHRH agonist therapy (53). In elderly patients, it must be distinguished from primary or secondary breast cancer (53). Tamoxifen and anastrozole (54-56), prophylactic radiotherapy (57,58) and mastectomy have been used to treat hormone-related gynaecomastia.

2.1.7 **Recommendations on prostate cancer pain management**

| | LE | GR |
|--|----|----|
| Systemic pain management | | |
| WHO analgesic ladder step 1: NSAID or paracetamol | 1a | A |
| Opioid administration | | |
| Opioids use (for dosing and titration refer to Chapter 3) | 1a | A |
| Access to breakthrough analgesia | 1b | A |
| Tricyclic antidepressant and/or anticonvulsant in case of neuropathic pain | 1a | A |
| Pain due to painful or unstable bony metastases (single lesions) | | |
| External beam irradiation | 1b | A |
| Pain due to painful bony metastases (widespread, opioid refractory) | | |
| Radioisotopes (⁸⁹ Sr or ¹⁵³ Sm-EDTMP) | 2 | B |
| Bisphosphonates | 1b | A |
| Denosumab | 1b | A |

2.2 **Pain management in transitional cell carcinoma patients**

Figure 5 represents a general approach to the patient with bladder cancer and pain. Figure 6 summarizes the therapeutic options for patients with UUTC and pain. For a more detailed description, refer to addenda A. Pain Management (General) and B. Cancer Pain Management (General).

For a complementary approach please refer to the EAU Guidelines on Renal Cell Carcinoma (59).

Figure 5: Pain management in bladder cancer patients

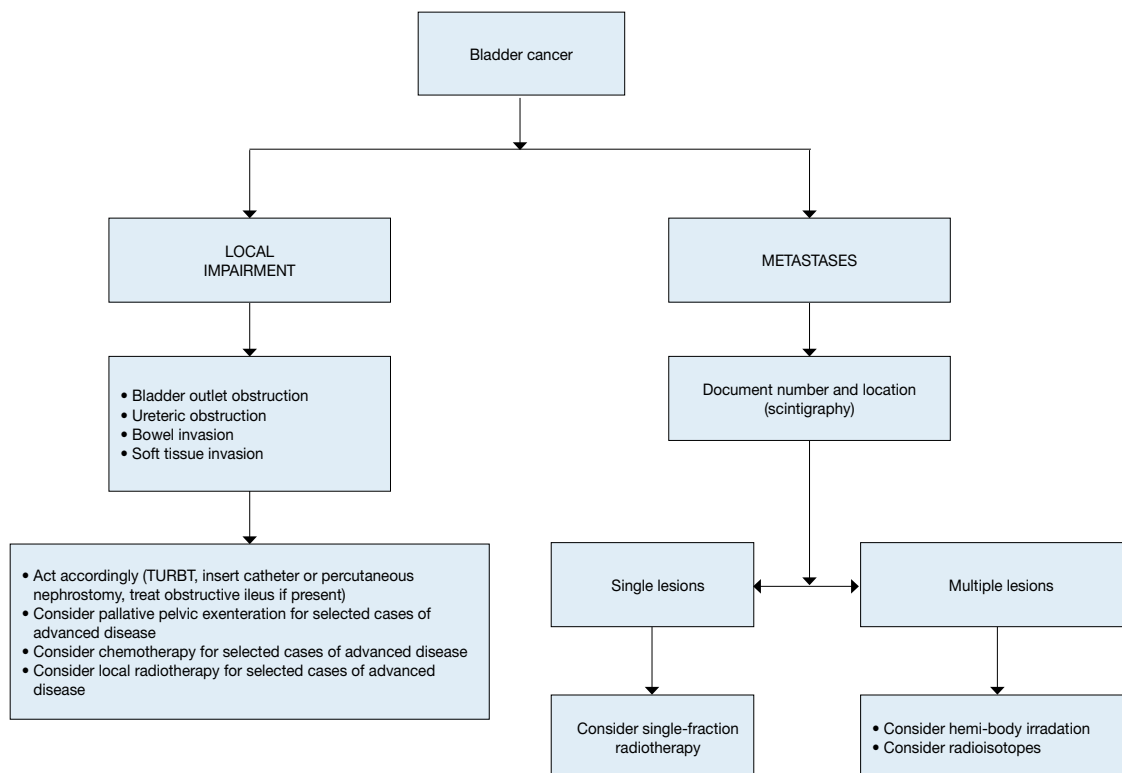
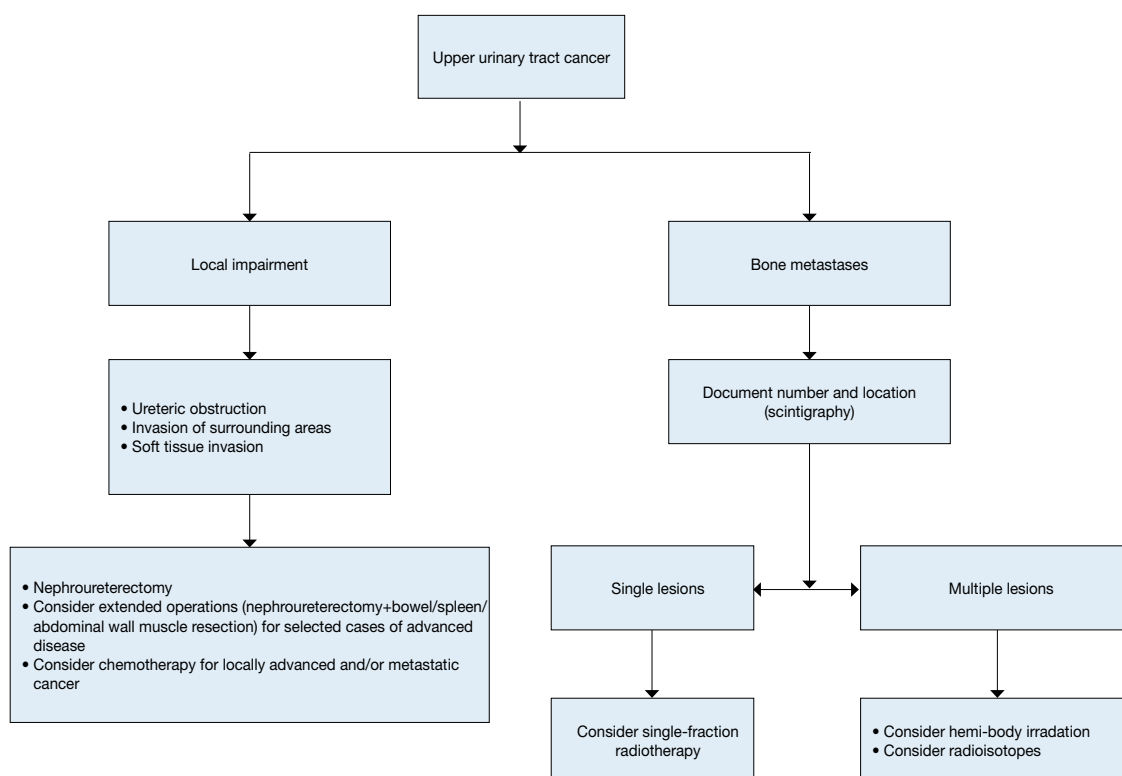


Figure 6: Pain management in UUTC patients



2.2.1 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 (60,61).

2.2.2 **Origin of tumour-related pain**

2.2.2.1 *Bladder TCC*

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

- bladder outlet obstruction, mainly due to haematuria;
- 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).

2.2.2.2 *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).

2.2.3 **Pain due to local impairment**

2.2.3.1 *Bladder TCC*

Bladder outlet obstruction due to tumour growth and/or hematuria can be the main complaint for most patients. Obstruction of the ureteral orifices by tumour infiltration may lead to hydronephrosis and consecutive flank pain due to ureteral distension (visceral pain). Cystoscopy and/or transurethral resection of the tumour may be effective in eliminating clots and bladder outlet and/or 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 (62).

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) (62).

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 (63). Extended operations, including excision of involved bowel, are sometimes indicated. Palliative surgery may be necessary in occlusive intestinal syndromes (64). 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 (65). 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% (66).

First-line chemotherapy strategies that are mainly based on platinum-containing regimens have some effect in 12-75% of patients with advanced disease (63). In a phase III trial, vinflunine, as a new second line chemotherapy agent, proved to be very effective in disease control (76%), but pain control was not an end point. Quality of life remained unchanged during chemotherapy despite drug toxicity (67).

Radiotherapy (21-35 Gy) can be effective in controlling pelvic pain and other symptoms such as frequency and haematuria due to local disease progression (68-70) (LE 1a). Acute bowel toxicity can be expected in one third of the patients.

2.2.3.2 *Upper urinary tract TCC*

Transitional cell carcinoma of the upper urinary tract often presents with microscopic or gross haematuria (70-80%), but flank pain can also occur due to obstruction or lumbar mass (61). Local symptoms do not confer worse prognosis compared to patients with incidentally detected upper urinary tract TCC (71). 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 and radiotherapy, the same considerations are valid for upper urinary tract TCC as for bladder TCC.

2.2.4 Pain due to metastases

No data are currently 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 (72) (LE: 1b). There are no specific trials studying the effect of radiotherapy on painful bone metastases in bladder cancer. Single-fraction radiotherapy is as effective as multi-fraction radiotherapy in relieving metastatic bone pain (LE: 1a). However, the rates of retreatment and pathological fractures are higher after single-fraction radiotherapy (21,73) (LE: 1a).

Radioisotope treatment or hemi-body irradiation can be used in patients with multiple bone metastases (72). There are no specific studies of radioisotope therapy for bone metastasis in TCC. Orthopaedic surgery can stabilise pathological fractures (see section A.2.3.3.4 Pathological fractures)

2.2.5 Recommendations on transitional cell carcinoma pain management

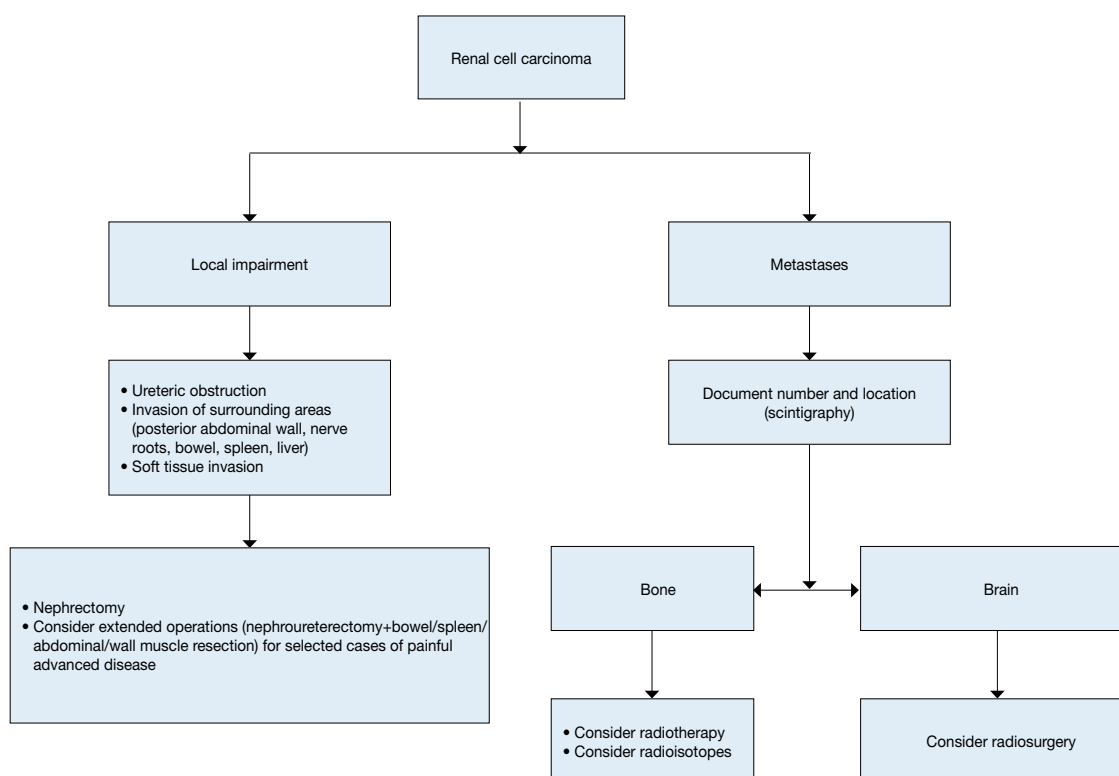
| Transitional cell carcinoma pain management | LE | GR |
|--|----|-----|
| Always disclose bladder outlet obstruction as source of local pain. | - | GCP |
| In locally advanced bladder cancer, palliative cystectomy or exenteration might be an option for symptom relief. | 3 | B |
| Use radiotherapy to reduce pain and symptoms of locally advanced bladder cancer. | 1a | B |
| Use radiotherapy to reduce pain due to bone metastases. | 1b | A |

GCP = good clinical practice

2.3 Pain management in renal cell carcinoma patients

Figure 7 represents a general approach to the patient with renal cancer and pain. For a more detailed description, refer to addenda A. Pain Management (General) and B. Cancer Pain Management (General). For a complementary approach please refer to the EAU Guidelines on Renal Cell Carcinoma (59).

Figure 7: Pain management in renal cell carcinoma patients



2.3.1 **Clinical presentation**

Renal cell carcinoma (RCC) is not painful unless the tumour invades adjacent areas or obstructs urine outflow. 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 metastases mainly to lung, bone, brain, liver and ipsilateral or contralateral adrenergic glands. Overall, 50-60% of patients may need treatment for the symptoms of metastatic disease, mainly pain.

2.3.2 **Pain due to local impairment**

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

Even in cases of metastatic disease, palliative nephrectomy is indicated for the control of severe symptoms such as haemorrhage, pain or paraneoplastic syndromes.

Standard pre-operative (30 Gy) or postoperative radiotherapy offers no survival benefit, and its role in delaying local progression is questionable (74). 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 (75).

In metastatic disease, the EORTC Genitourinary Group study 30947 demonstrated a significant increase in survival with palliative nephrectomy plus immunotherapy compared with immunotherapy (interferon-alpha) alone (median survival of 17 compared with 7 months) (76) (LE: 2b). There is no effect on pain relief from immunotherapy.

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

2.3.3 **Pain due to metastases**

Patients with bone metastases have a significantly better life expectancy (30 months) than those with visceral metastases (11.6 months) (77). Surgery is indicated for solitary bone metastases that can be resected completely, intractable bone pain, and impending or demonstrable pathological fracture. Surgery for bone metastases achieves a significant decrease in pain in 89-91% of patients (78-80) (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 (81,82) (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 (83-85) (LE: 3), and in 67% with general bone metastases (86) (LE: 2b). There is no impact on survival. Small studies of radionuclide therapy (e.g., ⁸⁹Sr) have shown good pain relief in bony metastases from RCC (87) (LE: 3). Also, some minimally invasive attempts to control bone metastases seem promising (88).

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 benefit in pain control. 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 what the ideal therapeutic schedule should be (89).

2.3.4 **Recommendations for renal cell carcinoma pain management**

| Renal cell carcinoma pain management | 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 quality of life, e.g., palliative nephrectomy in cases of metastatic tumour. | GCP |

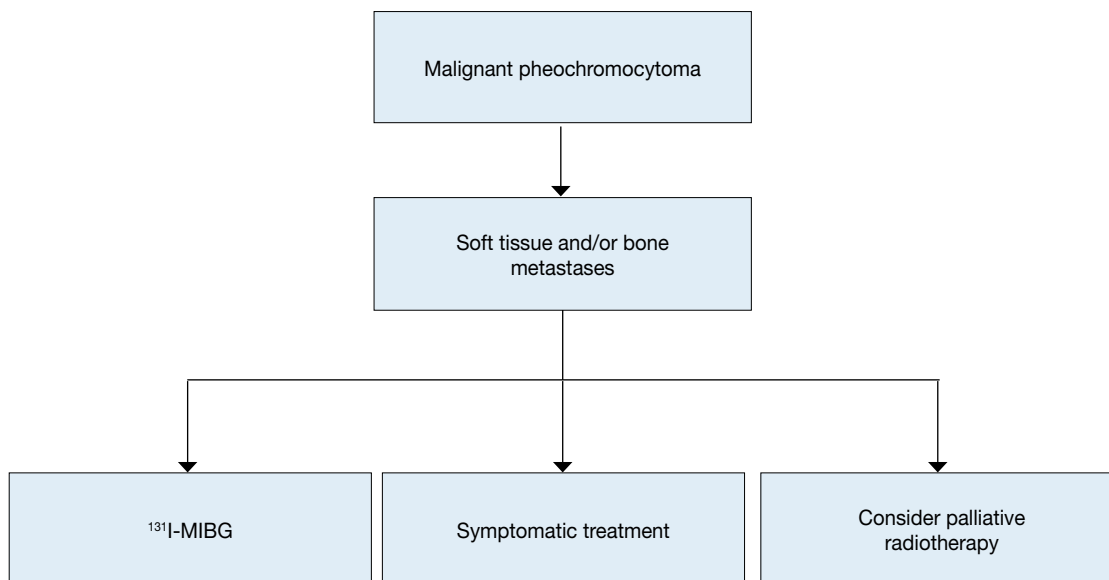
GCP = good clinical practice

2.4 Pain management in patients with adrenal carcinoma

Figure 8 represents a general approach to the patient with malignant pheochromocytoma and pain. For a more detailed description, refer to addenda A. Pain Management (General) and B. Cancer Pain Management (General).

For a complementary approach please refer to the EAU Guidelines on Renal Cell Carcinoma (59).

Figure 8: Pain management in patients with malignant pheochromocytoma



2.4.1 Malignant pheochromocytoma

Chemotherapy with cyclophosphamide, vincristine and dacarbazine has little effect on metastases (90) (LE: 2b), but therapeutic doses of ¹³¹I-MIBG (33 GBq = 900 mCi) may produce some results (91,92) (LE: 2b). The hormone response rate is 50%. There are no data on pain relief with ¹³¹I-MIBG in metastatic pheochromocytoma, but a response rate that is at least the same as for hormone levels should be expected.

Malignant pheochromocytomas are considered radioresistant, although there are some cases in which radiation therapy induced partial remission (93). There is no information about the efficacy of radiation concerning pain relief in cases of bone or soft tissue metastases.

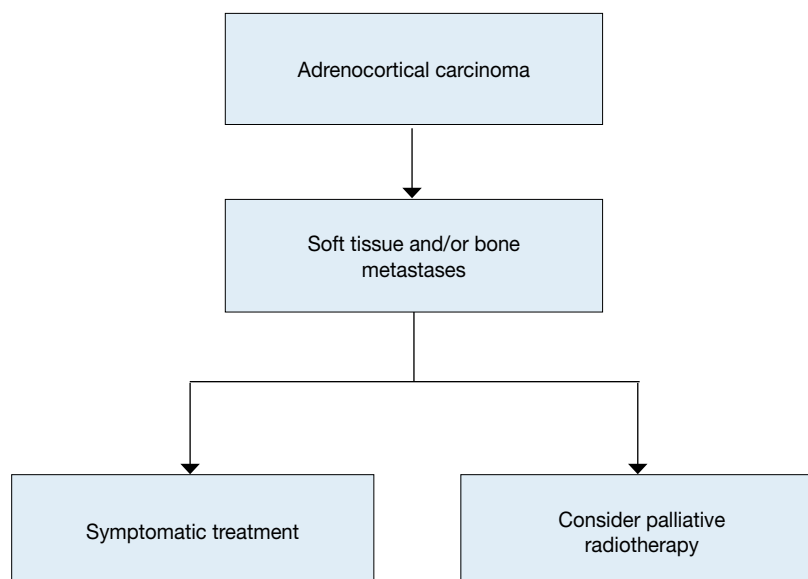
2.4.1.1 Treatment of pain

- Soft tissue and/or bone pain due to metastases are best treated by therapeutic doses of ¹³¹I-MIBG, if the pheochromocytoma takes up this radionuclide (94). There is no literature concerning chemotherapy or radiotherapy and pain relief in metastatic pheochromocytoma.
- Treat the pain symptomatically following the recommendations made in Section A.2.4.

2.4.2 Adrenocortical carcinomas

Figure 9 represents a general approach to the patient with adrenocortical carcinoma and pain. For a more detailed description, refer to addenda A. Pain Management (General) and B. Cancer Pain Management (General). For a complementary approach please refer to the EAU Guidelines on adrenal carcinoma (59).

Figure 9: Pain management in patients with 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 (95). Chemotherapy is of low efficacy. The most effective drug is mitotane, an adrenolytic. The tumour-response rate is 25-35% (95,96) (LE: 2a). Radiotherapy has not been useful except for palliation and pain management (97) (LE: 2b).

2.4.2.1 Treatment of the pain depending on its origin

- Abdominal symptoms are typical at first presentation of the tumour. The treatment is surgical removal of the primary tumour as well as resection of local lymph nodes.
- Soft tissue and/or bone metastases causing local symptoms can be treated by radiotherapy (94,97). 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 A.2.4.

2.4.3 Recommendations pain management adrenal carcinoma

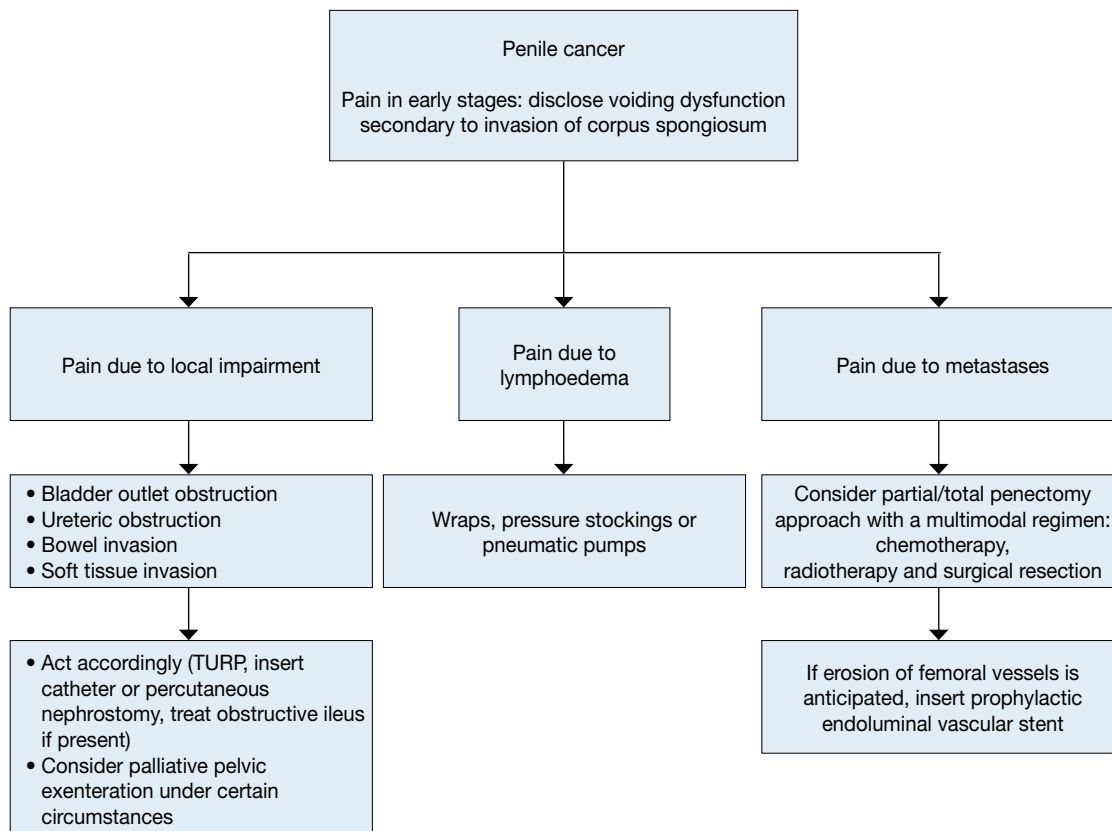
| Malignant pheochromocytoma | LE | GR |
|---|-----------|-----------|
| ¹³¹ I-MIBG may reduce pain. | 2b | B |
| Radiation therapy can induce partial remission. | 3 | C |
| Adrenocortical carcinoma | | |
| Surgical removal of the primary tumour and local lymph nodes can decrease pain. | 3 | C |
| Radiotherapy can be effective for palliation and pain management. | 2b | B |

2.5 Pain management in penile cancer patients

Figure 10 represents a general approach to the patient with penile carcinoma and pain. For a more detailed description, refer to addenda A. Pain Management (General) and B. Cancer Pain Management (General).

For a complementary approach please refer to the EAU Guidelines on Penile Cancer (98).

Figure 10: Pain management in penile cancer patients



2.5.1 **Clinical presentation**

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 (99). 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.

2.5.2 **Pain due to local impairment**

Bladder outlet and ureteric obstruction is managed in the same manner as that described in Section 2.1.2.2.

2.5.3 **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.

2.5.4 **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 and radiotherapy, followed by surgical resection (100).

The chemotherapy regimen that is so far most effective and well tolerated is paclitaxel, ifosfamide and cisplatin (TIP), although large randomised trials are lacking (101). The role of radiotherapy is mainly palliative. Radiotherapy can help in decreasing the pain from fixed inguinal nodes, bone metastases, spinal cord compression and paraplegia (102). When tumour erosion into femoral vessels is suspected, emergency intervention with endoluminal vascular stents or transobturator bypass graft should be undertaken (103,104).

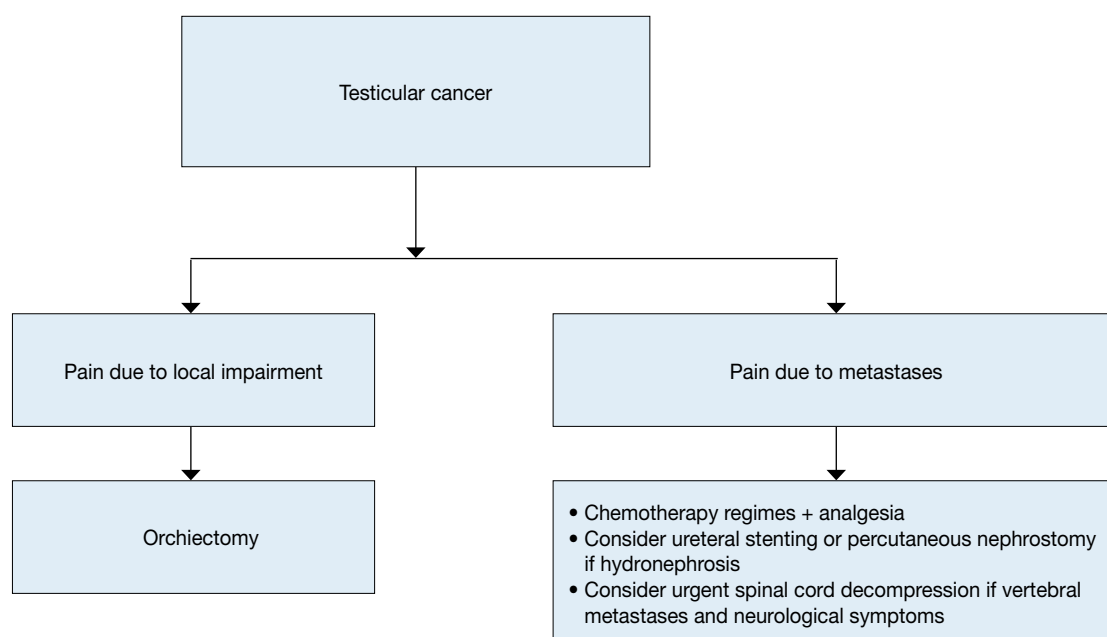
2.5.5 Recommendations on penile cancer pain management

| Penile cancer | LE | GR |
|--|----|----|
| Advanced penile cancer must be approached with a multimodal treatment regimen that includes neoadjuvant chemotherapy, radiotherapy and surgical resection. | 2b | B |
| Radiotherapy might decrease pain from fixed nodes and bone metastases. | 3 | C |

2.6 Pain management in testicular cancer patients

Figure 11 represents a general approach to the patient with Testicular Cancer and pain. For a more detailed description, refer to addenda A. Pain Management (General) and B. Cancer Pain Management (General). For a complementary approach please refer to the EAU Guidelines on Testicular Cancer (105).

Figure 11: Pain management in testicular cancer patients



2.6.1 Clinical presentation

Approximately 20% of patients present with scrotal or inguinal pain. Only 11% of patients complain of back or flank pain at first presentation (106). Primary advanced tumour with pain due to bone metastases is very rare (maximum 3% at first presentation). It should be treated causally by primary chemotherapy and adjuvant analgesics.

2.6.2 Pain due to local impairment

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

2.6.3 Pain due to metastases

- Back or flank pain due to retroperitoneal lymphadenopathy slowly disappears as chemotherapy causes the mass to decrease (105). 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/percutaneous nephrostomy.
- Bone pain due to bony metastases is very rare and occurs mainly in patients with primary advanced disease and relapse after chemotherapy (107,108). Treatment with chemotherapy or second-line chemotherapy may be possible (105). 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 (109).

2.6.4 Recommendations for testicular cancer pain management

| Testicular cancer pain | LE | GR |
|---|----|----|
| Systemic chemotherapy is effective for the back or flank pain due to retroperitoneal lymphadenopathy. | 2b | B |
| Back pain and neurological symptoms due to spinal cord compression may require urgent surgery. | 3 | C |

2.7 References

- Paice JA, Ferrell B. The management of cancer pain. *CA Cancer J Clin* 2011 May-Jun;61(3):157-82. <http://www.ncbi.nlm.nih.gov/pubmed/21543825>
- Swarm R, Pickar Abernethy A, Angheliescu DL, et al. National Comprehensive Cancer Network. Adult Cancer Pain. *J. Natl Compr Canc Netw* 2010;8;1046-1086 <http://www.jnccn.org/content/8/9/1046.full>
- Smith HS. Painful osseous metastases. *Pain Physician* 2011 Jul-Aug;14(4):E373-403. <http://www.ncbi.nlm.nih.gov/pubmed/21785487>
- Fallon MT. Neuropathic pain in cancer. *Br J Anaesth* 2013 Jul;111(1):105-11. <http://www.ncbi.nlm.nih.gov/pubmed/23794652>
- Heidenreich A, Bolla A, Joniau S, et al. EAU Guidelines on Prostate Cancer. <http://www.uroweb.org/guidelines/online-guidelines/>
- Foley KM. Pain syndromes in patients with cancer. In: Bonica JJ, Ventafridda V (eds). *Advances in Pain Research and Therapy 2*. New York, Raven Press, 1979, pp. 59-75.
- Twycross RG, Lack SA. Symptom control in far advanced cancer. In: *Pain relief*. London: Pitman, 1983, p. 6.
- Cameron MG, Kersten C, Guren MG, et al. Palliative pelvic radiotherapy of symptomatic incurable prostate cancer - A systematic review. *Radiother Oncol* 2013 Sep.[Epub ahead of print] <http://www.ncbi.nlm.nih.gov/pubmed/24044801>
- Banning A, Sjøgren P, Henriksen H. Pain causes in 200 patients referred to a multidisciplinary cancer pain clinic. *Pain* 1991 Apr;45(1):45-8. <http://www.ncbi.nlm.nih.gov/pubmed/1861877>
- Nielsen OS, Munro AJ, Tannock IF. Bone metastases: pathophysiology and management policy. *J Clin Oncol* 1991 Mar;9(3):509-24. <http://www.ncbi.nlm.nih.gov/pubmed/1705581>
- Wagner G. Frequency of pain in patients with cancer. *Recent Results Cancer Res* 1984;89:64-71. <http://www.ncbi.nlm.nih.gov/pubmed/6364273>
- Olson KB, Pienta KJ. Pain management in patients with advanced prostate cancer. *Oncology (Williston Park)*.1999 Nov;13(11):1537-49 <http://www.ncbi.nlm.nih.gov/pubmed/10581602>
- McNicol E, Strassels SA, Goudas L. NSAIDs or paracetamol, alone or combined with opioids, for cancer pain. *Cochrane Database Syst Rev* 2005 Jan;(1):CD005180. <http://www.ncbi.nlm.nih.gov/pubmed/15654708>
- Miles CL, Fellowes D, Goodman ML, et al. Laxatives for the management of constipation in palliative care patients. *Cochrane Database of Sys Rev* 2006 Oct;(4)CD003448. <http://www.ncbi.nlm.nih.gov/pubmed/17054172>
- Stoll BA. Hormonal therapy-pain relief and recalcification. In: Stoll BA, Parbhoo S (eds). *Bone*
- Stoll BA. Breast and prostatic cancer: Methods and results of endocrine therapy. In: Stoll BA (ed.). *Hormonal management of endocrine-related cancer*. London: Lloyd-Luke, 1981, pp. 77-91, 148-57.
- Pannuti F, Martoni A, Rossi AP, et al. The role of endocrine therapy for relief of pain due to advanced cancer. In: Bonica JJ, Ventafridda V (eds). *Advances in Pain Research and Therapy 2*. NY: Raven Press, 1979, pp. 145-165.
- Zeng L, Lutz S, Chow E, et al. Recent important developments in the management of nonspine bone metastases. *Curr Opin Support Palliat Care* 2012 Mar;6(1):80-4. <http://www.ncbi.nlm.nih.gov/pubmed/22123259>
- Porter AT, McEwan AJ, Powe JE, et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. *Int J Radiat Oncol Biol Phys* 1993 Apr;25(5):805-13. <http://www.ncbi.nlm.nih.gov/pubmed/8478230>
- Hegi-Johnson F. Outcomes of stereotactic ablative radiation therapy for vertebral metastases. *Journal of Medical Imaging and Radiation Oncology*, 2012. 56 (Journal Article): p. 266.

21. Sze WM, Shelley M, Held I, et al. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy--a systematic review of randomised trials. *Clin Oncol* 2003 Sep;15(6): 345-52.
<http://www.ncbi.nlm.nih.gov/pubmed/1452448>
22. (No authors listed) Pathological fractures due to bone metastases. *Br Med J (Clin Res Ed)*. 1981 Sep;283(6294):748.
<http://www.ncbi.nlm.nih.gov/pubmed/6791732>
23. Galasko CS. The management of skeletal metastases. *J R Coll Surg Edinb* 1980 May;25(3):144-61.
<http://www.ncbi.nlm.nih.gov/pubmed/6452521>
24. Ford HT, Yarnold JR. Radiation therapy - pain relief and recalcification. In: Stoll BA, Parbhoo S, eds. *Bone Metastasis: Monitoring and Treatment*. NY: Raven Press, 1983, pp. 343-54.
25. Lane MD, Le HB, Lee S, et al. Combination radiofrequency ablation and cementoplasty for palliative treatment of painful neoplastic bone metastasis: experience with 53 treated lesions in 36 patients. *Skeletal Radiol* 2011 Jan;40(1):25-32.
<http://www.ncbi.nlm.nih.gov/pubmed/20686765>
26. Roqué i Figuls M, Martínez-Zapata MJ, Alonso-Coello P, et al. Radioisotopes for metastatic bone pain. *Cochrane Database Syst Rev* 2003, issue 4, art. no.: CD003347. DOI:10.1002/14651858.CD003347.
<http://www.ncbi.nlm.nih.gov/pubmed/14583970>
27. Parker, C. Overall Survival Benefit and Impact on Skeletal-Related Events for Radium-223 Chloride (Alpharadin) in the Treatment of Castration-Resistant Prostate Cancer (CRPC) Patients With Bone Metastases: A Phase III Randomized Trial (ALSYMPCA), in 27th EAU Annual Congress. 2012: Paris, France.
28. Tu SM, Millikan RE, Mengistu B, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet* 2001 Feb;357(9253):336-41.
<http://www.ncbi.nlm.nih.gov/pubmed/11210994>
29. Wong RKS, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database Syst Rev* 2002, CD002068.
<http://www.ncbi.nlm.nih.gov/pubmed/12076438>
30. Yuen KK, Shelley M, Sze WM, et al. Bisphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev* 2006 Oct;(4): CD006250.
<http://www.ncbi.nlm.nih.gov/pubmed/17054286>
31. Smith MR. Zoledronic acid to prevent skeletal complications in cancer: corroborating the evidence. *Cancer Treat Rev* 2005;31(Suppl.3):19-25.
<http://www.ncbi.nlm.nih.gov/pubmed/16229955>
32. Ford JA, Jones R, Elders A, et al. Denosumab for treatment of bone metastases secondary to solid tumours: Systematic review and network meta-analysis. *Eur J Cancer* 2013 Jan;49(2):416-30.
<http://www.ncbi.nlm.nih.gov/pubmed/22906748>
33. Shelley M, Harrison C, Coles B, et al. Chemotherapy for hormone-refractory prostate cancer. *Cochrane Database Syst Rev* 2006 Oct;(4):CD005247.
<http://www.ncbi.nlm.nih.gov/pubmed/17054249>
34. Aljumaily R, Mathew P. Optimal management of bone metastases in prostate cancer. *Curr Oncol Rep*. 2011 Jun;13(3):222-30.
<http://www.ncbi.nlm.nih.gov/pubmed/21336561>
35. Bishr M, Lattouf JB, Gannon PO, et al. Updates on therapeutic targets and agents in castration-resistant prostate cancer. *Minerva Urol Nefrol* 2011 Jun;63(2):131-43.
<http://www.ncbi.nlm.nih.gov/pubmed/21623331>
36. Bahl A, Bellmunt J, Oudard S. Practical aspects of metastatic castration-resistant prostate cancer management: patient case studies. *BJU Int* 2012 Mar;109 Suppl 2:14-9.
<http://www.ncbi.nlm.nih.gov/pubmed/22257100>
37. de Bono JS, Oudard S, Ozguroglu M, et al. TROPIC Investigators: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010 Oct;376(9747):1147-54
<http://www.ncbi.nlm.nih.gov/pubmed/20888992>
38. Basch E, Bennett A, Scher H. Cabozantinib (XL184) reduces pain symptoms in patients (pts) with castration-resistant prostate cancer (CRPC) and bone metastases: Results from a phase 2 non randomized expansion cohort. *Mol Cancer Ther*, 2011. 10(11).
39. Kao SC, Hovey E, Marx G. Second-line therapy for castrate-resistant prostate cancer: a literature review. *Asia Pac J Clin Oncol* 2011 Sep;7(3):212-23.
<http://www.ncbi.nlm.nih.gov/pubmed/21884433>
40. Hoy AM, Lucas CF. Radiotherapy, chemotherapy and hormone therapy: treatment for pain. In: Wall PD, Melzack R (eds). *Textbook of Pain*, 3rd ed. Edinburgh: Churchill Livingstone, 1994.

41. Kramer JA. Spinal cord compression in malignancy. *Palliat Med* 1992;6:202-11.
42. George R, Jeba J, Ramkumar G, et al. Interventions for the treatment of metastatic extradural spinal cord compression in adults. *Cochrane Database Syst Rev* 2008 Oct, issue 4, art. no.:CD006716.
<http://www.ncbi.nlm.nih.gov/pubmed/18843728>
43. Borgelt BB, Gelber R, Brady LW, et al. The palliation of hepatic metastases: results of the Radiation Therapy Oncology Group pilot study. *Int J Radiat Oncol Biol Phys* 1981 May;7(5):587-91.
<http://www.ncbi.nlm.nih.gov/pubmed/6168623>
44. Chrisp P, Sorkin EM, Leuporelin. A review of its pharmacology and therapeutic use in prostatic disorders. *Drugs and Aging* 1991 Nov-Dec;1(6):487-509.
<http://www.ncbi.nlm.nih.gov/pubmed/1794035>
45. Thompson IM, Zeidman EJ, Rodriguez FR. Sudden death due to disease flare with luteinizing hormone-releasing hormone agonist therapy for carcinoma of the prostate. *J Urol* 1990 Dec;144(6):1479-80.
<http://www.ncbi.nlm.nih.gov/pubmed/2122011>
46. Crawford ED, Nabors W. Hormone therapy of advanced prostate cancer: where we stand today. *Oncology (Williston Park)* 1991 Jan;5(1):21-30.
<http://www.ncbi.nlm.nih.gov/pubmed/1828686>
47. Goldspiel BR, Kohler DR. Goserelin acetate implant: a depot luteinizing hormone-releasing hormone analog for advanced prostate cancer. *DICP* 1991 Jul-Aug;25(7-8):796-804.
<http://www.ncbi.nlm.nih.gov/pubmed/1835221>
48. Eberlein TJ. Gynecomastia. In: Harris J R, Hellman S, Henderson I C, Kinne D, eds. *Breast diseases*, 2nd ed. PA: Lippincott, 1991, pp. 46-50.
49. Delaere KP, Van Thillo EL. Flutamide monotherapy as primary treatment in advanced prostatic carcinoma. *Semin Oncol* 1991 Oct;18(5Suppl.6):13-8.
<http://www.ncbi.nlm.nih.gov/pubmed/1948117>
50. Goldenberg SL, Bruchofsky N. Use of cyproterone acetate in prostate cancer. *Urol Clin North Am* 1991 Feb;18(1):111-22.
<http://www.ncbi.nlm.nih.gov/pubmed/1825143>
51. Neumann F, Kalmus J. Cyproterone acetate in the treatment of sexual disorders: pharmacological base and clinical experience. *Exp Clin Endocrinol* 1991;98(2):71-80.
<http://www.ncbi.nlm.nih.gov/pubmed/1838080>
52. Ramamurthy L, Cooper RA. Metastatic carcinoma to the male breast. *Br J Radiol* 1991 Mar;64(759):277-8.
<http://www.ncbi.nlm.nih.gov/pubmed/2021802>
53. Cherny NI, Portenoy RK. Cancer Pain: Principles of Assessment and Syndromes. In: Wall PD, Melzack R(eds). *Textbook of Pain*, 3rd ed. Edinburgh: Churchill Livingstone, 1994.
54. Bedognetti D, Rubagotti A, Conti G, et al. An open, randomised, multicentre, phase 3 trial comparing the efficacy of two tamoxifen schedules in preventing gynaecomastia induced by bicalutamide monotherapy in prostate cancer patients. *Eur Urol* 2010 Feb;57(2):238-45.
<http://www.ncbi.nlm.nih.gov/pubmed/194813355>
55. Boccardo F, Rubagotti A, Battaglia M, et al. Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. *J Clin Oncol* 2005 Feb;23(4):808-15.
<http://www.ncbi.nlm.nih.gov/pubmed/15681525>
56. Fradet Y, Egerdie B, Andersen M, et al. Tamoxifen as prophylaxis for prevention of gynecomastia and breast pain associated with bicalutamide 150 mg monotherapy in patients with prostate cancer: a randomised, placebo-controlled, dose-response study. *Eur Urol* 2007 Jul;52(1):106-14.
<http://www.ncbi.nlm.nih.gov/pubmed/17270340>
57. Dicker AP. The safety and tolerability of low-dose irradiation for the management of gynecomastia caused by antiandrogen monotherapy. *Lancet Oncol* 2003 Jan;4(1):30-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12517537>
58. Van Poppel H, Tyrrell CJ, Haustermans K, et al. Efficacy and tolerability of radiotherapy as treatment for bicalutamide-induced gynecomastia and breast pain in prostate cancer. *Eur Urol* 2005 May;47(5):587-92.
<http://www.ncbi.nlm.nih.gov/pubmed/15826748>
59. Ljunberg B, Cowan N, Hanbury DC, et al. EAU Guidelines on renal cell carcinoma: the 2010 update. *Eur Urol* 2010 Sep;58(3):398-406.
<http://www.ncbi.nlm.nih.gov/pubmed/20633979>

60. Hall MC, Womack S, Sagalowsky A, et al. Prognostic factors, recurrence and survival in transitional cell carcinoma of the upper urinary tract: a 30-year experience in 252 patients. *Urology* 1998 Oct; 52(4):594-601.
<http://www.ncbi.nlm.nih.gov/pubmed/9763077>
61. Roupert M, Zigeuner R, Palou J, et al. European guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinomas: 2011 update. *Eur Urol* 2011 Apr;59(4):584-94.
<http://www.ncbi.nlm.nih.gov/pubmed/21269756>
62. Ok JH, Meyers FJ, Evans CP. Medical and surgical palliative care of patients with urological malignancies. *J Urol* 2005 Oct;174(4, pt.1): 1177-82.
<http://www.ncbi.nlm.nih.gov/pubmed/16145365>
63. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol* 2013 Oct;64(4):639-53.
<http://www.ncbi.nlm.nih.gov/pubmed/23827737>
64. Mount BM, Scott JF. Palliative care of the patients with terminal cancer. In: Skinner DG, Lieskovsky G (eds). *Diagnosis and Management of Genitourinary Cancer*, 1988, W.B. Saunders, Philadelphia, pp.842-863.
65. Kamat AM, Huang SF, Bermejo CE, et al. Total pelvic exenteration: effective palliation of perineal pain in patients with locally recurrent prostate cancer. *J Urol* 2003 Nov;170(5):1868-71.
<http://www.ncbi.nlm.nih.gov/pubmed/14532795>
66. Brophy PF, Hoffmann JP, Eisenberg BL. The role of palliative pelvic exenteration. *Am J Surg* 1994 Apr;167(4):386-90.
<http://www.ncbi.nlm.nih.gov/pubmed/7513967>
67. Bellmunt J, Theodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared to best supportive care alone after platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009 Sep;27(27):4454-61.
<http://www.ncbi.nlm.nih.gov/pubmed/19687335>
68. Duchesne GM, Bolger JJ, Griffiths GO, et al. A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09. *Int J Radiation Oncol Biol Phys* 2000 May;47(2):379-88.
<http://www.ncbi.nlm.nih.gov/pubmed/10802363>
69. Fletcher A, Choudhury A, Alam N. Metastatic bladder cancer: a review of current management. *ISRN Urol* 2011;545241.
<http://www.ncbi.nlm.nih.gov/pubmed/22084801>
70. Srinivasan V, Brown CH, Turner AG. A comparison of two radiotherapy regimens for the treatment of symptoms from advanced bladder cancer. *Clin Oncol (R Coll Radiol)* 1994;6(1):11-3.
<http://www.ncbi.nlm.nih.gov/pubmed/7513538>
71. Raman JD, Shariat SF, Karakiewicz PI, et al. Does preoperative symptom classification impact prognosis in patients with clinically localized upper-tract urothelial carcinoma managed by radical nephroureterectomy? *Urol Oncol* 2011 Nov;29(6):716-23.
<http://www.ncbi.nlm.nih.gov/pubmed/20056458>
72. McQuay HJ, Collins S, Carroll D, et al. Radiotherapy for the palliation of painful bone metastases. *Cochrane Database Syst Rev* 2000;(2):CD001793.
<http://www.ncbi.nlm.nih.gov/pubmed/10796822>
73. Wu JS, Wong R, Johnston M, et al. Cancer Care Ontario Practice Guidelines Initiative Supportive Care Group. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys* 2003 Mar;55(3):594-605.
<http://www.ncbi.nlm.nih.gov/pubmed/12573746>
74. Van de Werf-Messing B. Proceedings: carcinoma of the kidney. *Cancer* 1973 Nov;32(5):1056-61.
<http://www.ncbi.nlm.nih.gov/pubmed/4757899>
75. DiBiase SJ, Valicenti RK, Schultz D, et al. Palliative irradiation for focally symptomatic metastatic renal cell carcinoma: support for dose escalation based on a biological model. *J Urol* 1997 Sep;158 (3 Pt 1):746-9.
<http://www.ncbi.nlm.nih.gov/pubmed/9258072>
76. Mickisch GH, Garin A, van Poppel H, et al; European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. Radical nephrectomy plus interferon-alfabased immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 2001 Sep;358(9286):966-70.
<http://www.ncbi.nlm.nih.gov/pubmed/11583750>

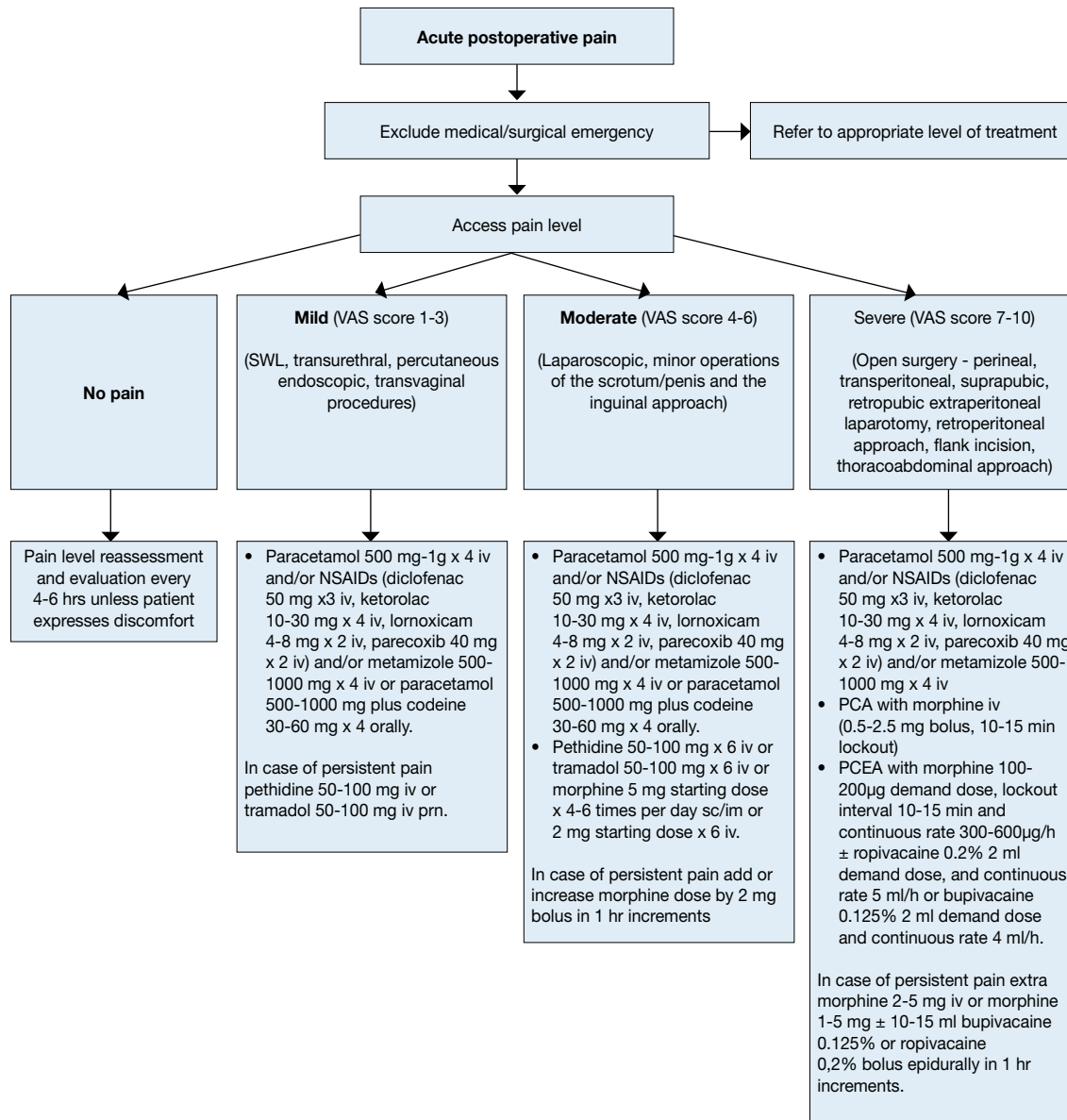
77. Bohnenkamp B, Romberg W, Sonnentag W, et al. (Prognosis of metastatic renal cell carcinoma related to the pattern of metastasis [author's transl.]). *J Cancer Res Clin Oncol* 1980 Jan;96(1):105-14. [Article in German]
<http://www.ncbi.nlm.nih.gov/pubmed/7358767>
78. Jackson RJ, Loh SC, Gokaslan ZL. Metastatic renal cell carcinoma of the spine: surgical treatment and results. *J Neurosurg* 2001 Jan;94(suppl.1):18-24.
<http://www.ncbi.nlm.nih.gov/pubmed/11147860>
79. Kollender Y, Bickels J, Price WM, et al. Metastatic renal cell carcinoma of bone: indications and technique of surgical intervention. *J Urol* 2000 Nov;164(5):1505-8.
<http://www.ncbi.nlm.nih.gov/pubmed/11025692>
80. Smith EM, Kursh ED, Makley J, et al. Treatment of osseous metastases secondary to renal cell carcinoma. *J Urol* 1992 Sep;148(3):784-7.
<http://www.ncbi.nlm.nih.gov/pubmed/1512825>
81. Gorich J, Solymosi L, Hasan I, et al. (Embolization of bone metastases). *Radiologe* 1995 Jan;35(1):55-9. [Article in German]
<http://www.ncbi.nlm.nih.gov/pubmed/7534427>
82. Layalle I, Flandroy P, Trotteur G, et al. Arterial embolization of bone metastases: is it worthwhile? *J Belge Radiol* 1998 Oct;81(5):223-5.
<http://www.ncbi.nlm.nih.gov/pubmed/9880954>
83. Forman JD. The role of radiation therapy in the management of carcinoma of the kidney. *Sem Urol* 1989 Aug;7(3):195-8.
<http://www.ncbi.nlm.nih.gov/pubmed/2481333>
84. Halperin EC, Harisiadis L. The role of radiation therapy in the management of metastatic renal cell carcinoma. *Cancer* 1983 Feb;51(4):614-7.
<http://www.ncbi.nlm.nih.gov/pubmed/6185207>
85. Onufrey V, Mohiuddin M. Radiation therapy in the treatment of metastatic renal cell carcinoma. *Int J Radiat Oncol Biol Phys* 1985 Nov;11(11):2007-9.
<http://www.ncbi.nlm.nih.gov/pubmed/2414257>
86. Chow E, Wong R, Hruba G, et al. Prospective patient-based assessment of effectiveness of palliative radiotherapy for bone metastases. *Radiother Oncol* 2001 Oct; 61(1):77-82.
<http://www.ncbi.nlm.nih.gov/pubmed/11578732>
87. Kloiber R, Molnar CP, Barnes M. Sr-89 therapy for metastatic bone disease: scintigraphic and radiographic follow-up. *Radiology* 1987 Jun;163(3):719-23.
<http://www.ncbi.nlm.nih.gov/pubmed/3575721>
88. Callstrom MR, Dupuy DE, Solomon SB, et al. Percutaneous image-guided cryoablation of painful metastases involving bone: Multicenter trial. *Cancer*. 2013 Mar;119:1033-41.
<http://www.ncbi.nlm.nih.gov/pubmed/23065947>
89. Zstovitch F, Lombardi G, Nicoletto O, et al. Second-line therapy for refractory renal-cell carcinoma. *Crit Rev Oncol Hematol* 2012 Jul;83(1):112-22.
<http://www.ncbi.nlm.nih.gov/pubmed/21944739>
90. Schlumberger M, Gicquel C, Lumbroso J, et al. Malignant pheochromocytoma: clinical, biological, histologic and therapeutic data in a series of 20 patients with distant metastases. *J Endocrinol Invest* 1992 Oct;15(9):631-42.
<http://www.ncbi.nlm.nih.gov/pubmed/1479146>
91. Mornex R, Badet C, Peyrin L. Malignant pheochromocytoma: a series of 14 cases observed between 1966 and 1990. *J Endocrinol Invest* 1992 Oct;15(9):643-9.
<http://www.ncbi.nlm.nih.gov/pubmed/1479147>
92. Proye C, Vix M, Goropoulos A, et al. High incidence of malignant pheochromocytoma in a surgical unit: 26 cases out of 100 patients operated from 1971 to 1991. *J Endocrinol Invest* 1992 Oct; 15(9):651-63.
<http://www.ncbi.nlm.nih.gov/pubmed/1479148>
93. Yu L, Fleckman AM, Chadha M, et al. Radiation therapy of metastatic pheochromocytoma: case report and review of the literature. *Am J Clin Oncol* 1996 Aug;19(4):389-93.
<http://www.ncbi.nlm.nih.gov/pubmed/8677912>
94. Kopf D, Goretzki PE, Lehnert H. Clinical management of malignant adrenal tumors. *J Cancer Res Clin Oncol* 2001;127(3):143-55.
<http://www.ncbi.nlm.nih.gov/pubmed/11260859>

95. Wooten MD, King DK. Adrenal cortical carcinoma. Epidemiology and treatment with mitotane and a review of the literature. *Cancer* 1993 Dec;72(11):3145-55.
<http://www.ncbi.nlm.nih.gov/pubmed/8242539>
96. Bukowski RM, Wolfe M, Levine HS, et al. Phase II trial of mitotane and cisplatin in patients with adrenal carcinoma: a Southwest Oncology Group study. *J Clin Oncol* 1993 Jan;11(1):161-5.
<http://www.ncbi.nlm.nih.gov/pubmed/8418229>
97. Percarpio B, Knowlton AH. Radiation therapy of adrenal cortical carcinoma. *Acta Radiol Ther Phys Biol* 1976 Aug;15(4):288-92.
<http://www.ncbi.nlm.nih.gov/pubmed/62490>
98. Pizzocaro G1, Algaba F, Horenblas S, et al. EAU penile cancer guidelines 2009. *Eur Urol* 2010 Jun;57(6):1002-12.
<http://www.ncbi.nlm.nih.gov/pubmed/20163910>
99. Margulis V, Sagalowsky AI. Penile Cancer: Management of Regional Lymphatic Drainage. *Urol Clin North Am* 2010 Aug;37(3):411-9.
<http://www.ncbi.nlm.nih.gov/pubmed/20674696>
100. Pagliaro LC, Crook J. Multimodality therapy in penile cancer: when and which treatments? *World J Urol* 2009 Apr;27(2):221-5.
<http://www.ncbi.nlm.nih.gov/pubmed/18682961>
101. Pagliaro LC, Williams DL, Daliani D, et al. Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: a phase II study. *J Clin Oncol* 2010 Aug;28(24):3851-7.
<http://www.ncbi.nlm.nih.gov/pubmed/20625118>
102. Ravi R, Chaturvedi HK, Sastry DV. Role of radiation therapy in the treatment of carcinoma of the penis. *Br J Urol* 1994 Nov;74(5):646-51.
<http://www.ncbi.nlm.nih.gov/pubmed/7530129>
103. Ferreira U, Reis LO, Ikari LY, et al. Extra-anatomical transobturator bypass graft for femoral artery involvement by metastatic carcinoma of the penis: report of five patients. *World J Urol* 2008 Oct;26(5):487-91.
<http://www.ncbi.nlm.nih.gov/pubmed/18581120>
104. Link RE, Soltes GD, Coburn M. Treatment of acute inguinal hemorrhage from metastatic penile carcinoma using an endovascular stent graft. *J Urol* 2004 Nov;172(5 Pt 1):1878-9.
<http://www.ncbi.nlm.nih.gov/pubmed/15540743>
105. Albers, P., et al., EAU guidelines on testicular cancer: 2011 update. *Eur Urol* 2011;60(2):304-19.
106. Hernes EH, Harstad K, Fosså SD. Changing incidence and delay of testicular cancer in southern Norway (1981-1992). *Eur Urol* 1996;30(3):349-57.
<http://www.ncbi.nlm.nih.gov/pubmed/8931969>
107. Hitchins RN, Philip PA, Wignall B, et al. Bone disease in testicular and extragonadal germ cell tumours. *Br J Cancer* 1988 Dec;58(6):793-6.
<http://www.ncbi.nlm.nih.gov/pubmed/3224081>
108. Merrick MV. Bone scintigraphy in testicular tumours. *Br J Urol* 1987 Aug;60(2):167-9.
<http://www.ncbi.nlm.nih.gov/pubmed/3664206>
109. Arnold PM, Morgan CJ, Morantz RA, et al. Metastatic testicular cancer presenting as spinal cord compression: report of two cases. *Surg Neurol* 2000 Jul;54(1):27-33.
<http://www.ncbi.nlm.nih.gov/pubmed/11024504>

3. PAIN MANAGEMENT AFTER UROLOGICAL OPERATIONS

A straight forward approach is provided to postoperative pain. Please note that opioid doses for opioid naïve patients should be lower than for cancer pain patients.

Figure 12: Postoperative pain management



SWL = extracorporeal shock wave lithotripsy; NSAIDs = non-steroidal anti-inflammatory drugs; iv = intravenous; sc = subcutaneous; im = intramuscular; prn = pro re nata (when needed)

3.1 Specific pain treatment after different urological operations

3.1.1 Extracorporeal shock wave lithotripsy

Many patients (33-59%) do not need any analgesia during or after extracorporeal shock wave lithotripsy (ESWL) (1-3) (LE: 2b). Post-treatment pain is unlikely to be severe, and oral analgesics are usually sufficient.

Analgesic plan

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 (4). 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% (5). After premedication with midazolam (2 mg iv, 5 min before treatment), diclofenac or tramadol was safe and effective, with fewer side-effects than fentanyl (6) (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.

3.1.2 **Endoscopic procedures**

3.1.2.1 *Transurethral procedures*

Analgesic plan

- Intraoperative: spinal (intrathecal or epidural) anaesthesia provides intraoperative analgesia and for 4-6 hrs postoperatively.
- Postoperative: after 4-6 hrs, mild oral analgesics such as NSAIDs or paracetamol ± codeine, or stronger opioids; also orally. In case of bladder discomfort from the indwelling catheter, metamizole (orally or iv), pethidine (iv) or piritramide (iv) are also effective. Antimuscarinic drugs such as oxybutynin (5 mg orally three times daily) are useful and reduce the need for opioids (7) (LE: 1b).

3.1.2.2 *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 administered locally into the skin incision.

3.1.2.3 *Laparoscopic and robotic procedures*

A particular problem after laparoscopic procedures 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 (8-10) (LE: 1b). The same could apply for some transabdominal urological laparoscopic interventions.

Analgesic plan

- The administration of local anaesthetic into the port incisions reduces pain after laparoscopy (11).
- 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 (11,12).

3.1.3 **Recommendations pain treatment after different urological operations**

| Extracorporeal shock wave lithotripsy | LE | GR |
|--|-----------|-----------|
| Administer NSAIDs or midazolam 30-45 min before SWL procedure to reduce the need for opioids | 2b | B |
| Transurethral procedures | 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 |
| Laparoscopic and robotic procedures | 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 |

NSAIDs = non-steroidal anti-inflammatory drugs; SWL = extracorporeal shock wave lithotripsy.

3.1.4 **Open surgery**

3.1.4.1 *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.

3.1.4.2 *Transvaginal surgery*

Paracetamol ± NSAIDs are usually sufficient for this kind of operations.

3.1.4.3 *Perineal open surgery*

Analgesic plan

- 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.

3.1.4.4 Transperitoneal laparotomy

Analgesic plan

- Sometimes an intrapleural catheter can be inserted.
- 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 (13).

3.1.4.5 Suprapubic/retropubic extraperitoneal laparotomy

Analgesic plan

- 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.

3.1.4.6 Retroperitoneal approach - flank incision - thoracoabdominal approach

Analgesic plan

- 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 (14,15). Once the patient is able to take oral analgesics (depending on bowel motility) paracetamol ± codeine or metamizole can be administered (to reduce the need for opioids) or used alone.

3.1.5 Recommendations for pain management after open surgery

| Minor operations of the scrotum/penis and the inguinal approach | 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 |
| Transvaginal surgery | | |
| NSAIDs are often sufficiently effective after minor or moderate surgery. | 2A | B |
| NSAIDs decrease the need for opioids. | 1b | B |
| Transperitoneal laparotomy | | |
| Consider continuous epidural infusion of a combination of opioids and local anaesthetic. Once the patient is able to take oral analgesics use metamizole, paracetamol ± codeine or tramadol. | 1b | A |
| Retroperitoneal approach - flank incision - thoracoabdominal approach | | |
| Consider continuous epidural infusion of a combination of opioids and local anaesthetic. Once the patient is able to take oral analgesics use metamizole, paracetamol ± codeine or tramadol. | 1b | A |

NSAIDs = non-steroidal anti-inflammatory drugs; PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia.

3.2 Dosage and method of delivery of some important analgesics

3.2.1 NSAIDs

Table 4: 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 5: 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 |

3.2.2 Opioids

Table 6: 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* | lv (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

*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 7: 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.

3.2.3 Summary of recommendations for postoperative pain management in adults

| Recommendations | LE | GR |
|---|----|----|
| Preoperative assessment and preparation of patients allow more effective pain management. | 1a | A |
| Adequate postoperative pain assessment can lead to more effective pain control and fewer complications. | 2a | B |
| 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 |
| 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 |
| 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 |
| 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 |
| Epidural analgesia, especially PCEA, provides superior postoperative analgesia, reducing complications and improving patient satisfaction, and is therefore preferable to systemic techniques. | A | 1b |

NSAIDs = non-steroidal anti-inflammatory drugs; PCEA = patient-controlled epidural analgesia.

3.3 Special populations

3.3.1 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 [(16,17), LE: 2a; (18), LE: 2b].

3.3.2 Geriatric patients

Pain perception appears to be reduced in geriatric patients, and requirement for analgesia generally decreases with increasing age (19,20). Geriatric patients can also suffer from emotional and cognitive impairment such as depression and dementia, which could affect adequate pain management (21). Postoperative delirium in elderly patients is a common complication and is often multifactorial. It may be associated with administration of pethidine (22). 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 (23) (LE: 2b). Epidural analgesia might diminish the risk of postoperative delirium and respiratory complications in elderly patients (24) (LE: 2b).

3.3.3 Obese patients

Obese patients appear to be at higher risk for certain postoperative complications, including respiratory,

cardiovascular and thromboembolic episodes, and wound infection (25,26). 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 (27,28) (LE: 2b).

If absolutely necessary, opioids should be used with caution under careful titration to avoid depression of the respiratory drive (28). Oxygen therapy should also be applied postoperatively to increase oxygen saturation (29).

3.3.4 **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 (30) (LE:1a).

3.3.5 **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).

3.3.6 **Perioperative problems in children**

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 (31) (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 8). The prior application of EMLA (2.5% lidocaine and 2.5% prilocaine) cream helps to reduce the pain of venipuncture (32) (LE: 1a). Atropine, 0.01-0.02 mg/kg iv, im, orally or rectally, prevents bradycardia during anaesthesia induction.

Table 8: 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 | 2-receptor agonist |
| Clonidine | 4 µg/kg | Oral | 2-receptor agonist |
| Pentobarbital | 4-6 mg/kg | im | Barbiturate |
| Chloral hydrate | 50-100 mg/kg | Oral | Barbiturate |
| Methohexital | 25-30 mg/kg | Rectally | Barbiturate |

3.3.7 **Postoperative analgesia in children**

Postoperatively, paracetamol, NSAIDs, opioids and their combinations are used according to the severity of the surgical procedure (Table 9).

Table 9: 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. Patient-controlled analgesia can be used safely in children older than 6 years. Nurse-controlled analgesia is effective in infants and children unable to use PCA (33).

Locoregional techniques such as wound infiltration, nerve blocks, and caudal and epidural analgesia are also successful (34,35). The most commonly used drugs are bupivacaine and ropivacaine (Table 10). Higher volumes of lower drug concentrations appear to be more effective than lower volumes of higher concentrations (36) (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 (37-39) (LE: 1a).

Table 10: Epidural dose of local anaesthesia

| Drug | Bolus 0-12 months | Bolus > 1 year | Infusion for 0-12 months | Infusion > 1 year |
|-------------|-------------------|----------------|--------------------------|-------------------|
| 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 |

3.3.8 Recommendations special populations

| Special populations | LE | GR |
|--|----|----|
| Ambulatory surgical patients | | |
| 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 |
| Geriatric patients | | |
| Multimodal and epidural analgesia are preferable for postoperative pain management in elderly patients because these techniques are associated with fewer complications. | 2b | B |
| Obese patients | | |
| 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 |
| Perioperative pain management in children | | |
| Apply EMLA locally to alleviate venipuncture pain in children. | 1b | A |

NSAIDs = non-steroidal anti-inflammatory drugs.

3.4 References

- Kraebber DM, SA Torres. Extracorporeal shock wave lithotripsy: review of the first 100 cases at the Kidney Stone Center of Southeast Georgia. *South Med J* 1988 Jan;81(1):48-51.
<http://www.ncbi.nlm.nih.gov/pubmed/3336800>
- Liston TG, Montgomery BS, Bultitude MI, et al. Extracorporeal shock wave lithotripsy with the Storz Modulith SL20: the first 500 patients. *Br J Urol* 1992 May;69(5):465-9.
<http://www.ncbi.nlm.nih.gov/pubmed/1623372>
- Voce S, Dal Pozzo C, Arnone S, et al. 'In situ' echo-guided extracorporeal shock wave lithotripsy of ureteral stones. Methods and results with Dornier MPL 9000. *Scand J Urol Nephrol* 1993;27(4):469-73.
<http://www.ncbi.nlm.nih.gov/pubmed/8159919>
- Tauzin-Fin P, Saumont S, Houdek MC, et al. (Analgesia by sublingual buprenorphine in extracorporeal kidney lithotripsy). *Ann Fr Anesth Reanim* 1993;12(3):260-4. (article in French)
<http://www.ncbi.nlm.nih.gov/pubmed/8250363>
- Dawson C, Vale JA, Corry DA, et al. Choosing the correct pain relief for extracorporeal lithotripsy. *Br J Urol* 1994 Sep;74(3):302-7.
<http://www.ncbi.nlm.nih.gov/pubmed/7953259>
- Ozcan S, Yilmaz E, Buyukkocak U, et al. Comparison of three analgesics for extracorporeal shock wave lithotripsy. *Scand J Urol Nephrol* 2002;36(4):281
- Tauzin-Fin P, Sesay M, Svartz L, et al. Sublingual oxybutynin reduces postoperative pain related to indwelling bladder catheter after radical retropubic prostatectomy. *Br J Anaesth* 2007 Oct;99(4):572-5.
<http://www.ncbi.nlm.nih.gov/pubmed/17681969>
- Barczynski M, Herman RM. A prospective randomized trial on comparison of low-pressure (LP) and standard-pressure (SP) pneumoperitoneum for laparoscopic cholecystectomy. *Surg Endosc* 2003 Apr;17(4):533-8.
<http://www.ncbi.nlm.nih.gov/pubmed/12582754>

9. Lindgren L, Koivusalo AM, Kellokumpu I. Conventional pneumoperitoneum compared with abdominal wall lift for laparoscopic cholecystectomy. *Br J Anaesth* 1995 Nov;75(5):567-72.
<http://www.ncbi.nlm.nih.gov/pubmed/7577282>
10. Sarli L, Costi R, Sansebastiano G, et al. Prospective randomized trial of low-pressure pneumoperitoneum for reduction of shoulder-tip pain following laparoscopy. *Br J Surg* 2000 Sep;87(9):1161-5.
<http://www.ncbi.nlm.nih.gov/pubmed/10971421>
11. Bisgaard T. Analgesic treatment after laparoscopic cholecystectomy: a critical assessment of the evidence. *Anesthesiology* 2006 Apr;104(4):835-46.
<http://www.ncbi.nlm.nih.gov/pubmed/16571981>
12. Neudecker J, Sauerland S, Neugebauer E, et al. The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. *Surg Endosc* 2002 Jul;16(7):1121-43.
<http://www.ncbi.nlm.nih.gov/pubmed/12015619>
13. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg* 2002 Jun; 183(6):630-41.
<http://www.ncbi.nlm.nih.gov/pubmed/12095591>
14. Block BM, Liu SS, Rowlingson AJ, et al. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA* 2003 Nov;290(18):2455-63.
<http://www.ncbi.nlm.nih.gov/pubmed/14612482>
15. Wu CL, Cohen SR, Richman JM, et al. Efficacy of postoperative patient-controlled and continuous infusion epidural analgesia versus intravenous patient-controlled analgesia with opioids: a metaanalysis. *Anesthesiology* 2005 Nov;103(5):1079-88; quiz 1109-10.
<http://www.ncbi.nlm.nih.gov/pubmed/16249683>
16. Beauregard L, Pomp A, Choinière M. Severity and impact of pain after day-surgery. *Can J Anesth* 1998 Apr;45(4):304-11.
<http://www.ncbi.nlm.nih.gov/pubmed/9597202>
17. Rawal N, Hylander J, Nydahl PA, et al. Survey of postoperative analgesia following ambulatory surgery. *Acta Anaesthesiol Scand* 1997 Sep;41(8):1017-22.
<http://www.ncbi.nlm.nih.gov/pubmed/9311400>
18. Crews JC. Multimodal pain management strategies for office-based and ambulatory procedures. *JAMA* 2002 Aug;288(5):629-32.
<http://www.ncbi.nlm.nih.gov/pubmed/12150675>
19. Gibson SJ, Helme RD. Age-related differences in pain perception and report. *Clin Geriatr Med* 2001 Aug;17(3):433-56.
<http://www.ncbi.nlm.nih.gov/pubmed/11459714>
20. Gloth FM 3rd. Geriatric pain. Factors that limit pain relief and increase complications. *Geriatrics* 2000 Oct;55(10):46-8.
<http://www.ncbi.nlm.nih.gov/pubmed/11054950>
21. Pickering G, Jourdan D, Eschalièr A, et al. Impact of age, gender and cognitive functioning on pain perception. *Gerontology* 2002 Mar-Apr;48(2):112-8.
<http://www.ncbi.nlm.nih.gov/pubmed/11867935>
22. Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA* 1994 Nov;272(19):1518-22.
<http://www.ncbi.nlm.nih.gov/pubmed/7966844>
23. Gloth FM 3rd. Principles of perioperative pain management in older adults. *Clin Geriatr Med* 2001 Aug;17(3):553-73.
<http://www.ncbi.nlm.nih.gov/pubmed/11459721>
24. Lynch EP, Lazor MA, Gellis JE, et al. The impact of postoperative pain on the development of postoperative delirium. *Anesth Analg* 1998 Apr;86(4):781-5.
<http://www.ncbi.nlm.nih.gov/pubmed/9539601>
25. Adams JP, Murphy PG. Obesity in anaesthesia and intensive care. *Br J Anaesth* 2000 Jul;85(1): 91-108.
<http://www.ncbi.nlm.nih.gov/pubmed/10927998>
26. Choban PS, Flancbaum L. The impact of obesity on surgical outcomes: a review. *J Am Coll Surg* 1997 Dec;185(6):593-603.
<http://www.ncbi.nlm.nih.gov/pubmed/9404886>
27. Choi YK, Brolin RE, Wagner BK, et al. Efficacy and safety of patient-controlled analgesia for morbidly obese patients following gastric bypass surgery. *Obes Surg* 2000 Apr;10(2):154-9.
<http://www.ncbi.nlm.nih.gov/pubmed/10782177>

28. Cullen DJ. Obstructive sleep apnea and postoperative analgesia: a potentially dangerous combination. *J Clin Anesth* 2001 Mar;13(2):83-5.
<http://www.ncbi.nlm.nih.gov/pubmed/11331164>
29. Rosenberg J, Pedersen MH, Gebuhr P, et al. Effect of oxygen therapy on late postoperative episodic and constant hypoxemia. *Br J Anaesth* 1992 Jan;68(1):18-22.
<http://www.ncbi.nlm.nih.gov/pubmed/1739560>
30. Collins ED, Kleber HD, Whittington RA, et al. Anesthesia-assisted vs buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. *JAMA* 2005 Aug;294(8):903-13.
<http://www.ncbi.nlm.nih.gov/pubmed/16118380>
31. Chundamala J, Wright JG, Kemp SM. An evidence-based review of parental presence during anesthesia induction and parent/child anxiety. *Can J Anaesth* 2009 Jan;56(1):57-70.
<http://www.ncbi.nlm.nih.gov/pubmed/19247779>
32. Möller C. A lignocaine-prilocaine cream reduces venipuncture pain. *Ups J Med Sci* 1985;90(3):293-8.
<http://www.ncbi.nlm.nih.gov/pubmed/3913095>
33. Monitto CL, Greenberg RS, Kost-Byerly S, et al. The safety and efficacy of parent-/nurse-controlled analgesia in patients less than six years of age. *Anesth Analg* 2000 Sep;91(3):573-9.
<http://www.ncbi.nlm.nih.gov/pubmed/10960379>
34. Matsota P, Papageorgiou-Brousta M, Kostopanagioutou G. Wound infiltration with levobupivacaine: an alternative method of postoperative pain relief after inguinal hernia repair in children. *Eur J Pediatr Surg* 2007 Aug;17(4):270-4.
<http://www.ncbi.nlm.nih.gov/pubmed/17806025>
35. Merguerian PA, Sutters KA, Tang E, et al. Efficacy of continuous epidural analgesia versus single dose caudal analgesia in children after intravesical ureteroneocystostomy. *J Urol* 2004 Oct;172(4 Pt 2):1621-5;discussion 1625.
<http://www.ncbi.nlm.nih.gov/pubmed/15371775>
36. Hong JY, Han SW, Kim WO, et al. A comparison of high volume/low concentration and low volume/high concentration ropivacaine in caudal analgesia for pediatric orchiopexy. *Anesth Analg* 2009 Oct;109(4):1073-8.
<http://www.ncbi.nlm.nih.gov/pubmed/19762734>
37. Akbas M, Titiz TA, Ertugrul F, et al. Comparison of the effect of ketamine added to bupivacaine and ropivacaine, on stress hormone levels and the duration of caudal analgesia. *Acta Anaesthesiol Scand* 2005 Nov;49(10):1520-6.
<http://www.ncbi.nlm.nih.gov/pubmed/16223400>
38. Castillo-Zamora C, Castillo-Peralta LA, Nava-Ocampo AA. Dose minimization study of single-dose epidural morphine in patients undergoing hip surgery under regional anesthesia with bupivacaine. *Paediatr Anaesth* 2005 Jan;15(1):29-36.
<http://www.ncbi.nlm.nih.gov/pubmed/15649160>
39. Tripi PA, Palmer JS, Thomas S, et al. Clonidine increases duration of bupivacaine caudal analgesia for ureteroneocystostomy: a double-blind prospective trial. *J Urol* 2005 Sep;174(3):1081-3.
<http://www.ncbi.nlm.nih.gov/pubmed/16094063>

4. NON -TRAUMATIC ACUTE FLANK PAIN

4.1 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 11).

Table 11: 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 | |

4.2 Initial diagnostic approach

4.2.1 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/mm³) (4).
- Because the signs and symptoms can be very similar, acute uncomplicated pyelonephritis should be immediately differentiated from complicated renal colic:
 - Concomitant fever (> 38°C) makes imaging obligatory (5). A radiological evaluation of the upper urinary tract should be offered to every patient presenting with flank pain and fever to rule out urinary tract obstruction irrespective of the accompanying symptoms, duration of the episode and urine macroscopic or microscopic findings.
 - Imaging is also imperative in patients with acute flank pain and a solitary kidney (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.

4.2.2 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.

4.2.3 Diagnostic imaging

4.2.3.1 Computed tomography (CT)

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 extrarenal 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).

4.2.3.2 Ultrasound imaging (US)

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.

4.2.3.3 Intravenous urography and unenhanced helical CT

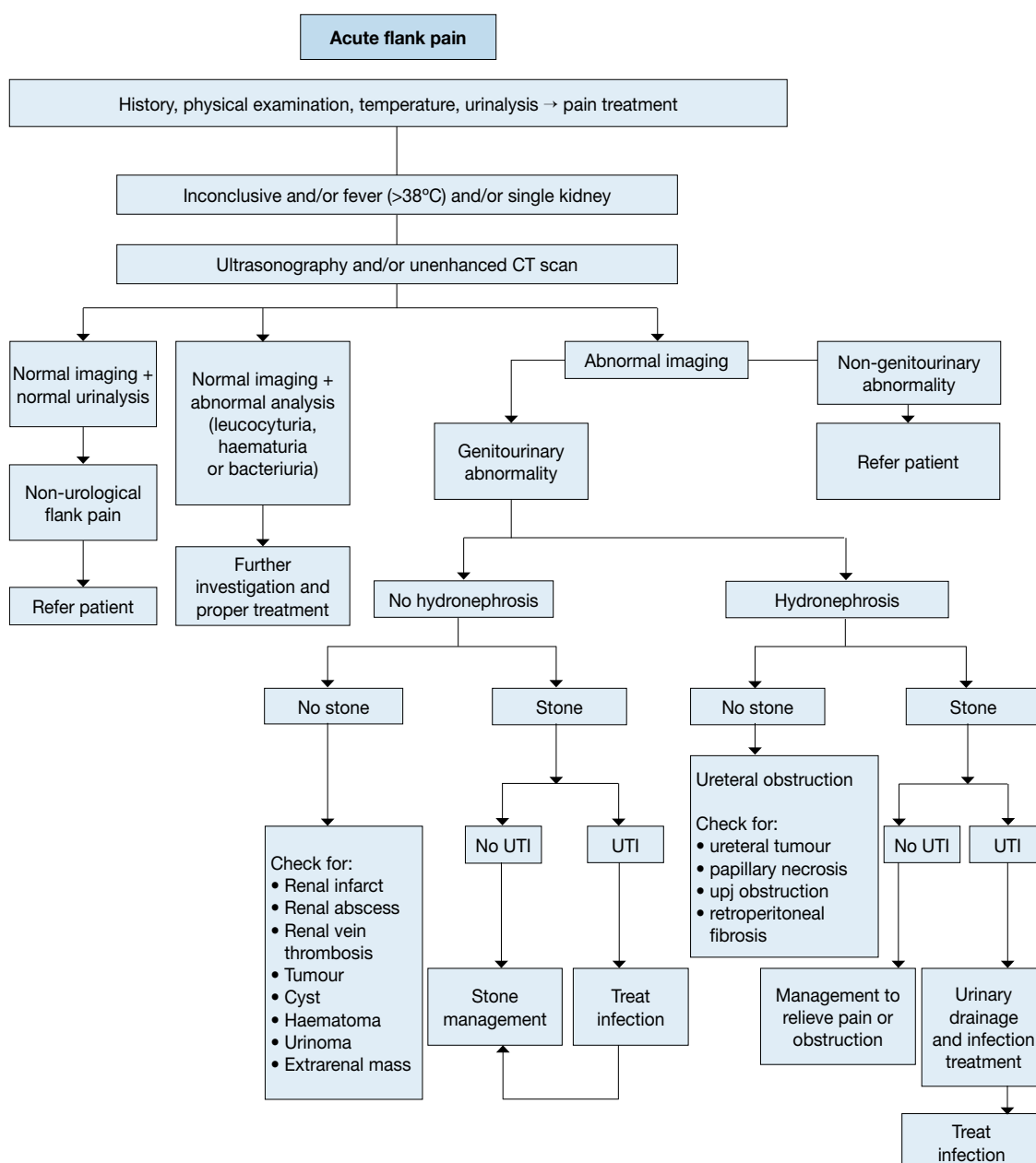
Intravenous urography (IVU) reliably provides information on the anatomy of the urinary collecting system

(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 12 shows comparative results of UHCT US and IVU in assessing acute flank pain and suspicion of ureterolithiasis (17-19). Figure 13 summarises the diagnostic approach to non-traumatic acute flank pain.

Figure 13: Diagnostic approach to non-traumatic acute flank pain



CT = computed tomography; UTI = urinary tract infection; UPJ = uretero pelvic junction

Table 12: 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 |

4.3 Initial emergency treatment

4.3.1 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 dipyron to be less effective than diclofenac, 75 mg (23) (LE: 1a), but a slow iv infusion of dipyron, 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.

4.3.2 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.

4.3.3 Supportive therapy

Patients with acute flank pain often present with moderate to severe dehydration. 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).

4.3.4 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 (21):

- 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 (31-33). New technological advances such as the antireflux JJ ureteral stents seem to minimise catheter-related pain (34,35) (LE: 1b).

4.3.5 Recommendations non-traumatic acute flank pain

| Non-traumatic acute flank pain | LE | GR |
|--|----|----|
| Febrile patients (> 38°C) with acute flank pain and/or with a solitary kidney need urgent imaging. | 4 | B* |
| 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 |
| In patients presenting with acute flank pain NSAIDs such as diclofenac (75 mg bolus) and dipyrrone (1-2 g slow iv injection) are the drugs of first choice. | 1a | A |

*Recommendation based on expert opinion

4.4 References

- Chen MY, Zagoria RJ, Saunders HS, et al. Trends in the use of unenhanced helical CT for acute urinary colic. *AJR Am J Roentgenol* 1999 Dec;173(6):1447-50.
<http://www.ncbi.nlm.nih.gov/pubmed/10584780>
- Dalrymple NC, Verga M, Anderson KR, et al. The value of unenhanced helical computerized tomography in the management of acute flank pain. *J Urol* 1998 Mar;159(3):735-40.
<http://www.ncbi.nlm.nih.gov/pubmed/9474137>
- Levine JA, Neitlich J, Verga M, et al. Ureteral calculi in patients with flank pain: correlation of plain radiography with unenhanced helical CT. *Radiology* 1997 Jul;204(1):27-31.
<http://www.ncbi.nlm.nih.gov/pubmed/9205218>
- Eskelinen M, Ikonen J, Lipponen P. Usefulness of history-taking, physical examination and diagnostic scoring in acute renal colic. *Eur Urol* 1998 Dec;34(6):467-73.
<http://www.ncbi.nlm.nih.gov/pubmed/9831787>
- Pearle M. Management of the acute stone event. *AUA Update Series* 2008. Vol 27. Lesson 30. American Urological Association, Education and Research Inc, Linthicum, MD.
- Roche-Nagle G, Rubin BB. Considerations in the diagnosis and therapy for acute loin pain. *Am J Emerg Med* 2009 Feb;27(2):254.e3-4.
<http://www.ncbi.nlm.nih.gov/pubmed/19371555>
- Catalano O, Nunziata A, Altei F, et al. Suspected ureteral colic: primary helical CT versus selective helical CT after unenhanced radiography and sonography. *AJR Am J Roentgenol* 2002 Feb;178(2):379-87.
<http://www.ncbi.nlm.nih.gov/pubmed/11804898>
- Worster A, Preyra I, Weaver B, et al. The accuracy of noncontrast helical computed tomography versus intravenous pyelography in the diagnosis of suspected acute urolithiasis: a meta-analysis. *Ann Emerg Med* 2002 Sep;40(3):280-6.
<http://www.ncbi.nlm.nih.gov/pubmed/12192351>
- Katz DS, Scheer M, Lumerman JH, et al. Alternative or additional diagnoses on unenhanced helical computed tomography for suspected renal colic: experience with 1000 consecutive examinations. *Urology* 2000 Jul;56(1):53-7.
<http://www.ncbi.nlm.nih.gov/pubmed/10869622>
- Heidenreich A, Desgrandschamps F, Terrier F. Modern approach of diagnosis and management of acute flank pain: review of all imaging modalities. *Eur Urol* 2002 Apr;41(4):351-62.
<http://www.ncbi.nlm.nih.gov/pubmed/12074804>
- Wang LJ, Ng CJ, Chen JC, et al. Diagnosis of acute flank pain caused by ureteral stones: value of combined direct and indirect signs on IVU and unenhanced helical CT. *Eur Radiol* 2004 Sep;14(9):1634-40.
<http://www.ncbi.nlm.nih.gov/pubmed/15060838>
- ACR Appropriateness Criteria. Acute onset flank pain, suspicion of stone disease. American College of Radiology-Medical Specialty Society, 1995 (revised 2007). NGC:005991
<http://www.acr.org/~media/ACR/Documents/AppCriteria/Diagnostic/AcuteOnsetFlankPainSuspicionStoneDisease.pdf>
- Gaspari R, Horst K. Emergency ultrasound and urinalysis in the evaluation of flank pain. *Acad Emerg Med* 2005 Dec;12(12):1180-4.
<http://www.ncbi.nlm.nih.gov/pubmed/16282510>
- Kartal M, Eray O, Erdogru T, et al. Prospective validation of a current algorithm including bedside US performed by emergency physicians for patients with acute flank pain suspected for renal colic. *Emerg Med J* 2006 May;23(5):341-4.
<http://www.ncbi.nlm.nih.gov/pubmed/16627832>

15. Noble VE, Brown DF. Renal ultrasound. *Emerg Med Clin North Am* 2004 Aug;22(3):641-59.
<http://www.ncbi.nlm.nih.gov/pubmed/15301843>
16. Pfister SA, Deckart A, Laschke S, et al. Unenhanced helical computed tomography vs intravenous urography in patients with acute flank pain: accuracy and economic impact in a randomized prospective trial. *Eur Radiol* 2003 Nov;13(11):2513-20.
<http://www.ncbi.nlm.nih.gov/pubmed/12898174>
17. Boulay I, Holtz P, Foley WD, et al. Ureteral calculi: diagnostic efficacy of helical CT and implications for treatment of patients. *AJR Am J Roentgenol* 1999 Jun;172(6):1485-90.
<http://www.ncbi.nlm.nih.gov/pubmed/10350277>
18. Liu W, Esler SJ, Kenny BJ, et al. Low-dose nonenhanced helical CT of renal colic: assessment of ureteric stone detection and measurement of effective dose equivalent. *Radiology* 2000 Apr;215(1): 51-4.
<http://www.ncbi.nlm.nih.gov/pubmed/10751467>
19. Ripollés T, Agramunt M, Errando J, et al. Suspected ureteral colic: plain film and sonography vs unenhanced helical CT. A prospective study in 66 patients. *Eur Radiol* 2004 Jan;14(1):129-36.
<http://www.ncbi.nlm.nih.gov/pubmed/12819916>
20. Holdgate A, Pollock T. Nonsteroidal anti-inflammatory drugs (NSAIDs) versus opioids for acute renal colic. *Cochrane Database Syst Rev* 2005 Apr;18(2):CD004137.
<http://www.ncbi.nlm.nih.gov/pubmed/15846699>
21. Tiselius H-G, Alken P, Buck C, et al. Guidelines on urolithiasis. Chapter 5. Treatment of patients with renal colic. In: *EAU Guidelines*. Edition presented at the 24th EAU Congress, Stockholm, 2009, pp. 21-2.
<http://www.uroweb.org/nc/professional-resources/guidelines/online/>
22. Cohen E, Hafner R, Rotenberg Z, et al. Comparison of ketorolac and diclofenac in the treatment of renal colic. *Eur J Clin Pharmacol* 1998 Aug;54(6):455-8.
<http://www.ncbi.nlm.nih.gov/pubmed/9776434>
23. Edwards JE, Meseguer F, Faura C, et al. Single dose dipyrrone for acute renal colic pain. *Cochrane Database Syst Rev* 2002(4):CD003867.
<http://www.ncbi.nlm.nih.gov/pubmed/12519613>
24. Collaborative Group of the Spanish Society of Clinical Pharmacology and García-Alonso F. Comparative study of the efficacy of dipyrrone, diclofenac sodium and pethidine in acute renal colic. *Eur J Clin Pharmacol* 1991;40(6):543-6.
<http://www.ncbi.nlm.nih.gov/pubmed/1884733>
25. Asgari, S.A., et al., Treatment of loin pain suspected to be renal colic with papaverine hydrochloride: a prospective double-blind randomised study. *BJU Int*, 2012. 110(3): p. 449-52.
26. Yencilek F, Aktas C, Goktas C, et al. Role of papaverine hydrochloride administration in patients with intractable renal colic: randomized prospective trial. *Urology* 2008 Nov;72(5):987-90.
<http://www.ncbi.nlm.nih.gov/pubmed/18789511>
27. Kober A, Dobrovits M, Djavan B, et al. Local active warming: an effective treatment for pain, anxiety and nausea caused by renal colic. *J Urol* 2003 Sep;170(3):741-4.
<http://www.ncbi.nlm.nih.gov/pubmed/12913687>
28. Iguchi M, Katoh Y, Koike H, et al. Randomized trial of trigger point injection for renal colic. *Int J Urol* 2002 Sep;9(9):475-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12410926>
29. Springhart WP, Marguet CG, Sur RL, et al. Forced versus minimal intravenous hydration in the management of acute renal colic: a randomized trial. *J Endourol* 2006 Oct;20(10):713-6.
<http://www.ncbi.nlm.nih.gov/pubmed/17094744>
30. Worster A, Richards C. Fluids and diuretics for acute ureteric colic. *Cochrane Database Syst Rev* 2005 Jul;20(3):CD004926.
<http://www.ncbi.nlm.nih.gov/pubmed/16034958>
31. Beddingfield R, Pedro RN, Hinck B, et al. Alfuzosin to relieve ureteral stent discomfort: a prospective, randomized, placebo controlled study. *J Urol* 2009 Jan;181(1):170-6.
<http://www.ncbi.nlm.nih.gov/pubmed/19013590>
32. Mokhtari G, Shakiba M, Ghodsi S, et al. Effect of terazosin on lower urinary tract symptoms and pain due to double-J stent: a double-blind placebo-controlled randomized clinical trial. *Urol Int* 2011;87(1):19-22.
<http://www.ncbi.nlm.nih.gov/pubmed/21597261>
33. Wang CJ, Huang SW, Chang CH. Effects of tamsulosin on lower urinary tract symptoms due to double-J stent: a prospective study. *Urol Int* 2009;83(1):66-9.
<http://www.ncbi.nlm.nih.gov/pubmed/19641362>

34. Ecke TH, Bartel P, Hallmann S, et al. Evaluation of symptoms and patients' comfort for JJ-ureteral stents with and without antireflux-membrane valve. *Urology* 2010 Jan;75(1):212-6. <http://www.ncbi.nlm.nih.gov/pubmed/19819529>
35. Ritter M, Krombach P, Knoll T, et al. Initial experience with a newly developed antirefluxive ureter stent. *Urol Res* 2012 Aug;40(4):349-53. <http://www.ncbi.nlm.nih.gov/pubmed/21850408>

5. PALLIATIVE CARE

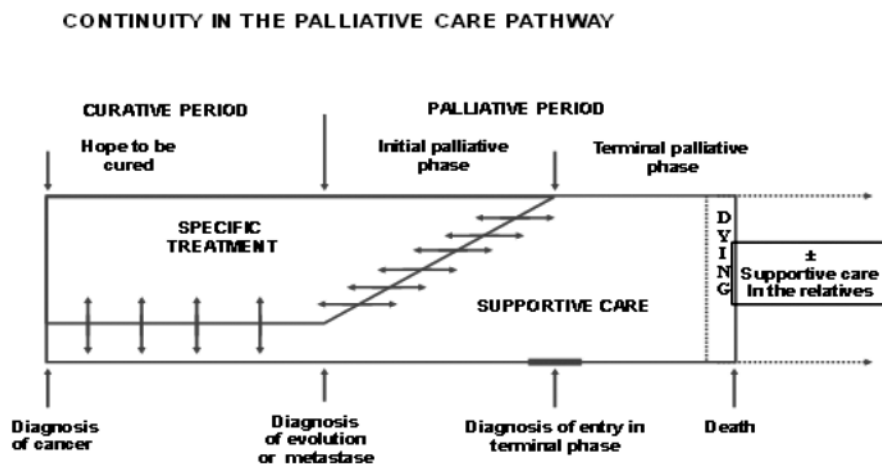
5.1 Introduction

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. An early collaboration between oncologist and palliative care team is recommended and supportive care (pain specialist, psychologist, nutritionist, physiotherapist) should be available throughout the patient's pathway.

For a better understanding it is important to define the term supportive care.

5.2 Supportive care

According to the multinational association of supportive care, cancer supportive care can be defined as '... the prevention and management of the adverse effects of cancer and its treatment. This includes management of physical and psychological symptoms and side effects across the continuum of the cancer experience from diagnosis through anticancer treatment to post-treatment care. Enhancing rehabilitation, secondary cancer prevention, survivorship and end of life care are integral to Supportive Care...'



Source: I. Krakowski, in : *Oncologie* (2004) 6 :7-15

One of the pillars of supportive care is to establish good communication between patient and carer. 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 improve the experience of PCa patients (1).

5.3 Definition and aim of palliative care

According to the WHO definition (2), 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 (2).

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 (3).

5.4 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 (4,5).

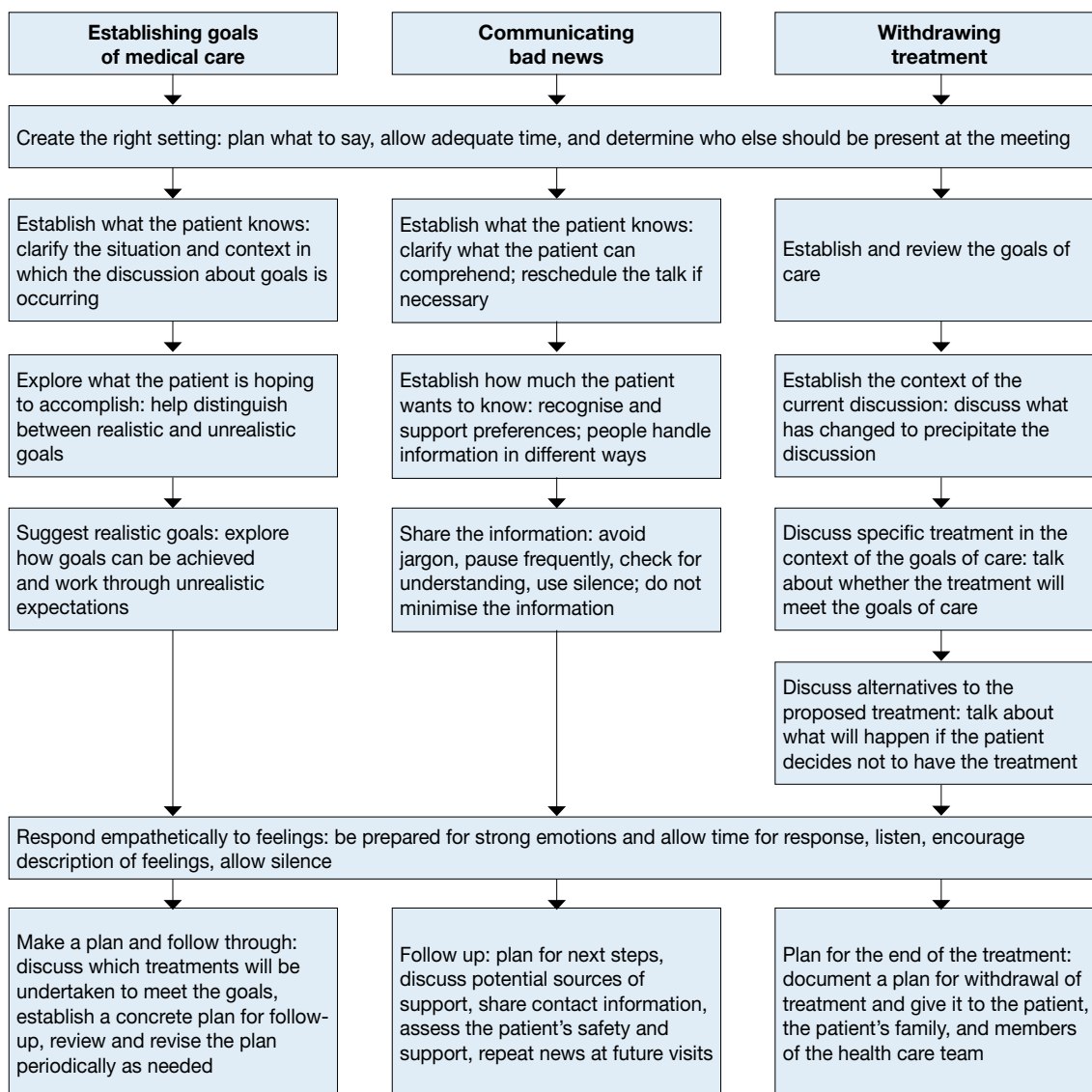
Palliation involves:

1. communication;
2. placing the patient at the centre of treatment;
3. cultural and spiritual approaches;
4. decision about the setting for the provision of terminal care;
5. multidisciplinary approach.

5.4.1 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. Communication skills include making eye contact with the patients, asking open-ended questions, responding to a patient's emotions, and showing empathy (6). Figure 14 illustrates the principles for communicating with patients about major topics in palliative care.

Figure 14: 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.

Terminal patients deserve specific information about their condition. This kind of information increases the quality of terminal care (7,8). 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).

5.4.2 Patient-centered treatment

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 (12).

5.4.3 **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 (13). 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 (14). 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 (15).

5.4.4 **Setting for the provision of terminal care**

Many patients with advanced cancer prefer not to stay in hospital despite being symptomatic. There are evidences proving that dying in a familiar setting can result in a better dying experience The European Legislation aims at providing specialised palliative care at the community level. Nevertheless, providing care tailored to the needs of patients can be a challenge since moves between home and institutions may be frequent. Nevertheless dying at home is becoming increasingly frequent (16). Homebased end-of-life (EoL) care and dying at home represent now the paradigm of palliative care.

5.4.5 **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).

5.4.6 **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).

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.

5.5 **Treatment of physical symptoms**

5.5.1 **Pain**

All the details concerning pain treatment are addressed in Chapter 2 and Addenda A1 an A2.

5.5.2 **Dyspnoea and respiratory symptoms**

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).

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. 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).

5.5.3 **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. 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 (31). More recently, a phase II RCT has shown that thalidomide (50 mg/day, orally, for 2 weeks) is effective against cancer-related anorexia (32).

5.5.4 **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 (33). 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 (34).

At the earlier stage of disease during cancer treatment, 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 fosaprepitant.

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 (35).

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 (36).

5.5.5 **Other symptoms**

5.5.5.1 **Fatigue**

Asthenia is an overwhelming, persistent feeling of tiredness in which normal activity becomes an effort. 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 (37). There is evidence suggesting reduction in fatigue and depression when compared with placebo. Standard oral doses are 10-40 mg/day (38). 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 (39).

Moreover, the use of IV Iron, in particular high molecular-weight iron dextran, added to erythropoiesis stimulating agent, results in an increase in haematopoietic response and reduction in the need of RBC transfusion (40,41). At the early stage of cancer treatment and of palliation, exercise is an effective intervention for patients with CRF (42). Like exercise, psychoeducational activity is a promising therapy for ameliorating CRF (43).

5.5.5.2 **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 (44).

5.5.5.3 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 (45,46). However, haloperidol (5-10 mg, intravenous) remains a useful drug for the treatment of many forms of delirium (47).

5.5.5.4 Constipation

Chronic constipation can be a serious problem for cancer patients taking opioids. Oral lactulose seems more effective than polyethylene glycol (48). Nevertheless, evidence on laxatives for management of constipation remains limited due to insufficient RCTs (48). Interestingly, subcutaneous methylnaltrexone seems effective in inducing laxation in patients with opioid-induced constipation when standard laxatives fail (49,50). 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).

5.5.5.5 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 (51).

5.5.6 Recommendations treatment of physical symptoms

| | LE | GR |
|--|----|----|
| Dyspnoea and respiratory symptoms | | |
| Benzodiazepines can be considered when opioids and non-pharmacological measures fail to control breathlessness. | 1a | A |
| Cancer anorexia-cachexia syndrome | | |
| Nutritional support is ineffective | 1b | A |
| Oral thalidomide (50 mg/day, 2 weeks) seems effective. | 1b | A |
| Vomiting | | |
| Dexamethasone is not effective in metoclopramide-refractory nausea. | 1b | A |
| Patients with a high risk of vomiting induced by chemotherapy are effectively treated with a combination of dexamethasone and 5-HT ₃ and neurokinin 1 receptor antagonists. | 1a | A |
| In patients with moderate risk of vomiting induced by chemotherapy, palonosetron combined with dexamethasone is recommended. | 1a | A |
| Patients receiving radiotherapy and experiencing emesis can be effectively treated with combined 5-HT ₃ receptor antagonist and dexamethasone. | 1a | A |
| Fatigue | | |
| For anaemic patients erythropoietin and darbopoetin have provided improvement. | 1b | B |
| Methylphenidate 10-40 mg/day, can reduce fatigue and depression. | 1b | B |
| Restlessness | | |
| Neuroleptics cannot be recommended for treatment of terminal restlessness. | 3 | C |
| Agitated delirium | | |
| Haloperidol (5-10 mg, intravenous) can be useful. | 2a | C |
| Constipation | | |
| No clear recommendations as to the use of a particular laxative can be made. | 1a | A |
| Anxiety | | |
| It is therefore not possible to draw conclusions about the effectiveness of pharmacotherapy in this setting. | 4 | A |

5.6 Terminal care

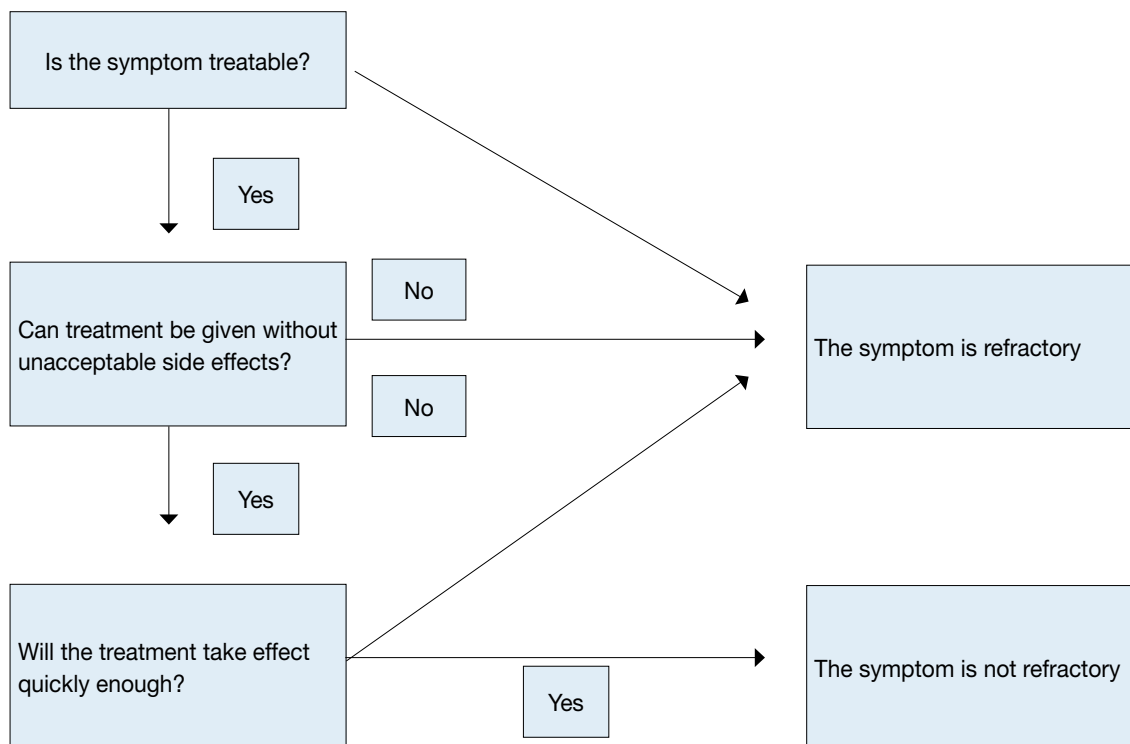
For medical practitioners who are trained to save lives, the end of life represents a completely different professional scenario in which personal skills give way to multidisciplinary, compassionate intervention.

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 (52).

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 (53). The aim of palliative sedation is never to hasten death and there is evidence that it does not jeopardise survival (54,55). Figure 15 is an aid for the recognition of refractory symptoms.

Figure 15: 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. 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 states in the United States of America (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 (56-63), thus making the approach to the final stages of life not always equitable.

5.6.1 **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 (64).

5.6.2 **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 (65).

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 (66). Nevertheless, it seems that parenteral hydration can improve many of the symptoms experienced by terminally ill, dehydrated cancer patients (67).

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 (4).

5.6.3 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 (4).

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 (4,68)-.

It is generally agreed that physicians and nurses should be present the moment palliative sedation begins (68). Subcutaneous administration is the preferred route and midazolam the drug of choice (2,69). Table 13 provides a suggestion for palliative sedation (4).

Table 13: Three steps approach to palliative sedation. In the hospital setting, Phase 3 can follow Phase 1 (2)

| | 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 every 15 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.

5.7 Treatment of psychological aspects

5.7.1 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 (70). 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 (71).

5.7.2 **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 (72). 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 (73,74).

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 (75).

Moreover, behavioural therapy, counselling, psychotherapy, education/information, relaxation and social support alleviate depression and anxiety (76). 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 (77).

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 (78).

5.7.3 **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 (79).

Patients and families need to be prepared for death. The process can then take place under good, serene conditions (80,81). 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 (80). 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 (82).

Table 14: Arresødal Hospice principles of management of intrafamilial conflicts (80)

| | |
|-------------------------------------|--|
| 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 monoor 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. |

5.7.4 **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 (83). Specific, patient-targeted information increases the quality of terminal care (8).

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 (84). 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 (85).

5.7.5 **Recommendations treatment of psychological aspects**

| Fear | LE | GR |
|--|-----------|-----------|
| Distress must be recognised, measured, treated and monitored at all stages of the disease. | 2b | A |
| Depression | | |
| Efforts should be made to detect hidden depression. | 2b | B* |

*Recommendation based on expert opinion.

5.8 **References**

1. Waldie M, Smylie J. Communication: the key to improving the prostate cancer patient experience. *Can Oncol Nurs J*. 2012 Spring;22(2):129-39.
<http://www.ncbi.nlm.nih.gov/pubmed/22764588>
2. World Health Organization. National cancer control programmes: policies and managerial guidelines, 2nd ed. Geneva. 2002.
<http://whqlibdoc.who.int/hq/2002/9241545577.pdf>
3. Van Mechelen W, Aertgeerts B, De Ceulaer K, et al. Defining the palliative care patient: A systematic review. *Palliat Med* 2012 Feb.
<http://www.ncbi.nlm.nih.gov/pubmed/22312010>
4. RDMA, C.o.N.G.f.P.S., Guideline for Palliative Sedation. Available from Utrecht: KNMG. 2009.
5. van der Heide A, Deliëns L, Faisst K, et al. End-of-life decision-making in six European countries: descriptive study. *Lancet* 2003 Aug;362(9381):345-50.
<http://www.ncbi.nlm.nih.gov/pubmed/12907005>
6. Morrison RS, Meier DE. Clinical practice. Palliative care. *N Engl J Med* 2004 Jun;350(25):2582-90.
<http://www.ncbi.nlm.nih.gov/pubmed/15201415>
7. Higginson IJ, Constantini M. Communication in end-of-life cancer care: a comparison of team assessments in three European countries. *J Clin Oncol* 2002 Sep;20(17):3674-82.
<http://www.ncbi.nlm.nih.gov/pubmed/12202669>
8. Nakajima N, Hata Y, Onishi H, et al. The Evaluation of the Relationship Between the Level of Disclosure of Cancer in Terminally Ill Patients With Cancer and the Quality of Terminal Care in These Patients and Their Families Using the Support Team Assessment Schedule. *Am J Hosp Palliat Care* 2012 Jul.
<http://www.ncbi.nlm.nih.gov/pubmed/22777409>
9. Alifrangis C, Koizia L, Rozario A, et al. The experiences of cancer patients. *QJM*. 2011 Dec;104(12):1075-81.
<http://www.ncbi.nlm.nih.gov/pubmed/21835781>
10. Arden-Close E, Moss-Morris R, Dennison L, et al. The Couples' Illness Communication Scale (CICS): development and evaluation of a brief measure assessing illness-related couple communication. *Br J Health Psychol*. 2010 Sep;15(Pt 3):543-59.
<http://www.ncbi.nlm.nih.gov/pubmed/19878621>

11. Manne S, Badr H, Zaider T, et al. Cancer-related communication, relationship intimacy, and psychological distress among couples coping with localized prostate cancer. *J Cancer Surviv.* 2010 Mar;4(1):74-85.
<http://www.ncbi.nlm.nih.gov/pubmed/19967408>
12. Peate I. Advanced prostate cancer: treatment and patient-centred care. *Br J Nurs.* 2012 Feb-Mar; 21(4):S24-30.
<http://www.ncbi.nlm.nih.gov/pubmed/22470904>
13. Smith AK, Sudore RL, Pérez-Stable EJ. Palliative care for Latino patients and their families: whenever we prayed, she wept. *JAMA.* 2009 Mar;301(10):1047-57, E1.
<http://www.ncbi.nlm.nih.gov/pubmed/19278947>
14. Surbone A, Baider L. The spiritual dimension of cancer care. *Crit Rev Oncol Hematol.* 2010 Mar;73(3):228-35.
<http://www.ncbi.nlm.nih.gov/pubmed/19406661>
15. Selman L, Harding R, Gysels M, et al. The measurement of spirituality in palliative care and the content of tools validated cross-culturally: a systematic review. *J Pain Symptom Manage.* 2011 Apr;41(4): 728-53.
<http://www.ncbi.nlm.nih.gov/pubmed/21306866>
16. Gomes B, Calanzani N, Higginson IJ. Reversal of the British trends in place of death: time series analysis 2004-2010. *Palliat Med* 2012 Mar;26(2):102-7.
<http://www.ncbi.nlm.nih.gov/pubmed/22258367>
17. Abdulrahman GO. The effect of multidisciplinary team care on cancer management. *Pan Afr Med J* 2011;9:20.
<http://www.ncbi.nlm.nih.gov/pubmed/22355430>
18. Sandgren A, Fridlund B, Nyberg P, et al. Symptoms, care needs and diagnosis in palliative cancer patients in acute care hospitals: a 5-year follow-up survey. *Acta Oncol* 2010 May;49(4):460-6.
<http://www.ncbi.nlm.nih.gov/pubmed/20121671>
19. Adolph MD, Frier KA, Stawicki SP, et al. Palliative critical care in the intensive care unit: A 2011 perspective. *Int J Crit Illn Inj Sci.* 2011 Jul;1(2):147-53.
<http://www.ncbi.nlm.nih.gov/pubmed/22229140>
20. Ross L, Petersen MA, Johnson AT, et al. Cancer patients' evaluation of communication: a report from the population-based study 'The Cancer Patient's World'. *Support Care Cancer.* 2013 Jan;21(1): 235-44.
<http://www.ncbi.nlm.nih.gov/pubmed/22678406>
21. Demirci S, Yildirim YK, Ozsaran Z, et al. Evaluation of burnout syndrome in oncology employees. *Med Oncol* 2010 Sep;27(3):968-74
<http://www.ncbi.nlm.nih.gov/pubmed/19784801>
22. Orzechowska A, Talarowska M, Drozda R, et al. (The burnout syndrome among doctors and nurses). *Pol Merkur Lekarski.* 2008 Dec;25(150):507-9.
<http://www.ncbi.nlm.nih.gov/pubmed/19205383>
23. Pisanti R, Lombardo C, Lucidi F, et al. Psychometric properties of the Maslach Burnout Inventory for Human Services among Italian nurses: a test of alternative models. *J Adv Nurs.* 2012 Aug. doi: 10.1111/j.1365-2648.2012.06114.x.
<http://www.ncbi.nlm.nih.gov/pubmed/22897490>
24. Pronost AM, Le Gouge A, Leboul D, et al. Relationships between the characteristics of oncohematology services providing palliative care and the sociodemographic characteristics of caregivers using health indicators: social support, perceived stress, coping strategies, and quality of work life. *Support Care Cancer.* 2012 Mar;20(3):607-14.
<http://www.ncbi.nlm.nih.gov/pubmed/21547448>
25. Bausewein C, Booth S, Gysels M, et al. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. *Cochrane Database Syst Rev.* 2008 Apr; (2):CD005623.
<http://www.ncbi.nlm.nih.gov/pubmed/18425927>
26. Ben-Aharon I, Gafter-Gvili A, Leibovici L, et al. Interventions for alleviating cancer-related dyspnea: A systematic review and meta-analysis. *Acta Oncol* 2012 Nov;51(8):996-1008.
<http://www.ncbi.nlm.nih.gov/pubmed/22934558>
27. Abernethy AP, McDonald CF, Frith PA, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet.* 2010 Sep;376(9743):784-93.
<http://www.ncbi.nlm.nih.gov/pubmed/20816546>

28. Wee B, Hillier R. Interventions for noisy breathing in patients near to death. *Cochrane Database Syst Rev.* 2008 Jan;(1):CD005177
<http://www.ncbi.nlm.nih.gov/pubmed/18254072>
29. Wildiers H, Dhaenekint C, Demeulenaere P, et al. Atropine, hyoscine butylbromide, or scopolamine are equally effective for the treatment of death rattle in terminal care. *J Pain Symptom Manage.* 2009 Jul;38(1):124-33.
<http://www.ncbi.nlm.nih.gov/pubmed/19361952>
30. Ovesen L, Allingstrup L, Hannibal J, et al. Effect of dietary counseling on food intake, body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy: a prospective, randomized study. *J Clin Oncol* 1993 Oct;11(10):2043-9.
<http://www.ncbi.nlm.nih.gov/pubmed/8410128>
31. Strasser F, Luftner D, Possinger K, et al. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *J Clin Oncol* 2006 Jul;24(21):3394-400.
<http://www.ncbi.nlm.nih.gov/pubmed/16849753>
32. Davis M, Lasheen W, Walsh D, et al., A Phase II dose titration study of thalidomide for cancer-associated anorexia. *J Pain Symptom Manage.* 2012 Jan;43(1):78-86.
<http://www.ncbi.nlm.nih.gov/pubmed/21640548>
33. Bruera E, Moyano JR, Sala R, et al. Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. *J Pain Symptom Manage.* 2004 Oct;28(4):381-8.
<http://www.ncbi.nlm.nih.gov/pubmed/15471656>
34. Dorman S, Perkins P. Droperidol for treatment of nausea and vomiting in palliative care patients. *Cochrane Database Syst Rev.* 2010 Oct;(10):CD006938.
<http://www.ncbi.nlm.nih.gov/pubmed/20927752>
35. Basch E, Hesketh PJ, Kris MG, et al., Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Oncol Pract.* 2011 Nov;7(6):395-8.
<http://www.ncbi.nlm.nih.gov/pubmed/22379425>
36. Ezzo JM, Richardson MA, Vickers A, et al., Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting. *Cochrane Database Syst Rev.* 2006 Apr;(2):CD002285.
<http://www.ncbi.nlm.nih.gov/pubmed/16625560>
37. Minton O, Richardson A, Sharpe M, et al. Drug therapy for the management of cancer-related fatigue. *Cochrane Database Syst Rev.* 2010 Jul;(7):CD006704.
<http://www.ncbi.nlm.nih.gov/pubmed/20614448>
38. Kerr CW, Drake J, Milch RA, et al. Effects of methylphenidate on fatigue and depression: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage.* 2012 Jan;43(1):68-77.
<http://www.ncbi.nlm.nih.gov/pubmed/22208450>
39. Portela MA, Rubiales AS, Centeno C. The use of psychostimulants in cancer patients. *Curr Opin Support Palliat Care.* 2011 Jun;5(2):164-8.
<http://www.ncbi.nlm.nih.gov/pubmed/21532350>
40. Gafter-Gvili A, Rozen-Zvi B, Vidal L, et al. Intravenous iron supplementation for the treatment of chemotherapy-induced anaemia - systematic review and meta-analysis of randomised controlled trials. *Acta Oncol* 2013 Jan;52(1):18-29.
<http://www.ncbi.nlm.nih.gov/pubmed/22877242>
41. Anthony LB, Nashat MD, Gabrail Y, et al. IV iron sucrose for cancer and/or chemotherapy-induced anemia in patients treated with erythropoiesisstimulating agents. Presented at the 43rd Annual Meeting of the American Society of Clinical Oncology; June 1-5, 2007 in Chicago.
<http://www.oncologypractice.com/communityoncology/single-view/iv-iron-sucrose-for-cancer-and-or-chemotherapy-induced-anemia-in-patients-treated-with-erythropoiesisstimulating-agents/1618af5853.html>
42. Mishra SI, Scherer RW, Snyder C, et al. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev.* 2012 Aug;8:CD008465.
<http://www.ncbi.nlm.nih.gov/pubmed/22895974>
43. Kangas M, Bovbjerg DH, Montgomery GH. Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients. *Psychol Bull.* 2008 Sep;134(5):700-41.
<http://www.ncbi.nlm.nih.gov/pubmed/18729569>
44. Kehl, K.A. Treatment of terminal restlessness: a review of the evidence. *J Pain Palliat Care Pharmacother.* 2004;18(1):5-30.
<http://www.ncbi.nlm.nih.gov/pubmed/15148006>

45. Jackson KC, Lipman AG. Drug therapy for delirium in terminally ill patients. *Cochrane Database Syst Rev.* 2004;(2):CD004770.
<http://www.ncbi.nlm.nih.gov/pubmed/15106261>
46. Lonergan E, Luxenberg J, Areosa Sastre A. Benzodiazepines for delirium. *Cochrane Database Syst Rev.* 2009 Oct;(4):CD006379.
<http://www.ncbi.nlm.nih.gov/pubmed/19821364>
47. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry.* 1996 Feb;153(2):231-7.
<http://www.ncbi.nlm.nih.gov/pubmed/8561204>
48. Lee-Robichaud H, Thomas K, Morgan J, et al. Lactulose versus Polyethylene Glycol for Chronic Constipation. *Cochrane Database Syst Rev.* 2010 Jul;(7):CD007570.
<http://www.ncbi.nlm.nih.gov/pubmed/20614462>
49. Candy B, Jones L, Goodman ML, et al. Laxatives or methylalntrexone for the management of constipation in palliative care patients. *Cochrane Database Syst Rev.* 2011 Jan;(1):CD003448.
<http://www.ncbi.nlm.nih.gov/pubmed/21249653>
50. Thomas J, Karver S, Cooney GA, et al. Methylalntrexone for opioid-induced constipation in advanced illness. *N Engl J Med* 2008 May;358(22):2332-43.
<http://www.ncbi.nlm.nih.gov/pubmed/18509120>
51. Candy B, Jackson KC, Jones L, et al. Drug therapy for symptoms associated with anxiety in adult palliative care patients. *Cochrane Database Syst Rev.* 2012 Oct;10:CD004596.
<http://www.ncbi.nlm.nih.gov/pubmed/23076905>
52. Temel JS, Greer JA, Admane S, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *J Clin Oncol* 2011 Jun;29(17):2319-26.
<http://www.ncbi.nlm.nih.gov/pubmed/21555700>
53. González Barón M, Gómez Raposo C, Pinto Marín A. Sedation in clinical oncology. *Clin Transl Oncol* 2005 Aug;7(7):295-301.
<http://www.ncbi.nlm.nih.gov/pubmed/16185591>
54. Claessens P, Menten J, Schotsmans P, et al. Palliative Sedation, Not Slow Euthanasia: A Prospective, Longitudinal Study of Sedation in Flemish Palliative Care Units. *J Pain Symptom Manage.* 2010 Sep.
<http://www.ncbi.nlm.nih.gov/pubmed/20832985>
55. Maltoni M, Pittureri C, Scarpi E, et al., Palliative sedation therapy does not hasten death: results from a prospective multicenter study. *Ann Oncol* 2009 Jul;20(7):1163-9.
<http://www.ncbi.nlm.nih.gov/pubmed/19542532>
56. Bendiane MK, Bouhnik AD, Galinier A, et al. French hospital nurses' opinion about euthanasia and physician-assisted suicide: a national phone survey. *J Med Ethics.* 2009 Apr;35(4):238-44.
<http://www.ncbi.nlm.nih.gov/pubmed/19332581>
57. Chen CH, Tang ST, Chen CH. Meta-analysis of cultural differences in Western and Asian patient perceived barriers to managing cancer pain. *Palliat Med* 2012 Apr;26(3):206-21.
<http://www.ncbi.nlm.nih.gov/pubmed/21474622>
58. Fainsinger RL, Waller A, Bercovici M, et al. A multicentre international study of sedation for uncontrolled symptoms in terminally ill patients. *Palliat Med* 2000 Jul;14(4):257-65.
<http://www.ncbi.nlm.nih.gov/pubmed/10974977>
59. Gysels M, Evans N, Meñaca A, et al. Culture is a priority for research in end-of-life care in Europe: a research agenda. *J Pain Symptom Manage.* 2012 Aug;44(2):285-94.
<http://www.ncbi.nlm.nih.gov/pubmed/22672921>
60. Rietjens JA, Deschepper R, Pasman R, et al. Medical end-of-life decisions: does its use differ in vulnerable patient groups? A systematic review and meta-analysis. *Soc Sci Med* 2012 Apr;74(8):1282-7.
<http://www.ncbi.nlm.nih.gov/pubmed/22401644>
61. Toscani F, Di Giulio P, Brunelli C, et al. How people die in hospital general wards: a descriptive study. *J Pain Symptom Manage.* 2005 Jul;30(1):33-40.
<http://www.ncbi.nlm.nih.gov/pubmed/160430>
62. Verloo H, Mpinga EK, Ferreira M, et al. Morphinephobia: the situation among the general population and health care professionals in North-Eastern Portugal. *BMC Palliat Care.* 2010 Jun;9:15.
<http://www.ncbi.nlm.nih.gov/pubmed/20569454>
63. Volker DL. Control and end-of-life care: does ethnicity matter? *Am J Hosp Palliat Care.* 2005 Nov-Dec;22(6):442-6.
<http://www.ncbi.nlm.nih.gov/pubmed/16329196>

64. Sykes N, Thorns A. The use of opioids and sedatives at the end of life. *Lancet Oncol* 2003 May;4(5):312-8.
<http://www.ncbi.nlm.nih.gov/pubmed/12732169>
65. Good P, Cavenagh J, Mather M, et al. Medically assisted hydration for adult palliative care patients. *Cochrane Database of Systematic Reviews*, Oct 2008(2) Assessed as up-to-date: 13 Feb 2011 DOI: 10.1002/14651858.CD006273.pub2
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006273.pub2/abstract>
66. Morita T, Hyodo I, Yoshimi T, et al. Artificial hydration therapy, laboratory findings, and fluid balance in terminally ill patients with abdominal malignancies. *J Pain Symptom Manage*. 2006 Feb;31(2):130-9.
<http://www.ncbi.nlm.nih.gov/pubmed/16488346>
67. Bruera E, Sala R, Rico MA, et al. Effects of parenteral hydration in terminally ill cancer patients: A preliminary study. *J Clin Oncol* 2005 Apr;23(10):2366-71.
<http://www.ncbi.nlm.nih.gov/pubmed/15800328>
68. Cherny NI, Radbruch L. Board of the European Association for Palliative, European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. *Palliat Med* 2009 Oct;23(7):581-93.
<http://www.ncbi.nlm.nih.gov/pubmed/19858355>
69. Mercadante S, Intravaia G, Villari P, et al. Controlled sedation for refractory symptoms in dying patients. *J Pain Symptom Manage*. 2009 May;37(5):771-9.
<http://www.ncbi.nlm.nih.gov/pubmed/19041216>
70. Penson RT, Partridge RA, Shah MA, et al. Fear of death. *Oncologist*. 2005 Feb;10(2):160-9.
<http://www.ncbi.nlm.nih.gov/pubmed/15709218>
71. Bidstrup PE, Johansen C, Mitchell AJ. Screening for cancer-related distress: Summary of evidence from tools to programmes. *Acta Oncol* 2011 Feb;50(2):194-204.
<http://www.ncbi.nlm.nih.gov/pubmed/21231781>
72. Rayner L, Price A, Hotopf M, et al. The development of evidence-based European guidelines on the management of depression in palliative cancer care. *Eur J Cancer*. 2011 Mar;47(5):702-12.
<http://www.ncbi.nlm.nih.gov/pubmed/21211961>
73. Fulcher CD, Badger T, Gunter AK, et al. Putting evidence into practice: interventions for depression. *Clin J Oncol Nurs*. 2008 Feb;12(1):131-40.
<http://www.ncbi.nlm.nih.gov/pubmed/18258583>
74. Kelly BJ, Turner J. Depression in advanced physical illness: diagnostic and treatment issues. *Med J Aust*. 2009 Apr;190(7 Suppl):S90-3.
<http://www.ncbi.nlm.nih.gov/pubmed/19351301>
75. Brelin S, Loge JH, Skurtveit S, et al. Antidepressants to cancer patients during the last year of life—a population-based study. *Psychooncology*. 2012 Mar. doi: 10.1002/pon.3059. (Epub ahead of print)
<http://www.ncbi.nlm.nih.gov/pubmed/22392773>
76. Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. *Med J Aust*. 2009 Apr;190(7 Suppl):S54-60.
<http://www.ncbi.nlm.nih.gov/pubmed/19351294>
77. Kroenke K, Theobald D, Wu J, et al. Effect of telecare management on pain and depression in patients with cancer: a randomized trial. *JAMA*. 2010 Jul;304(2):163-71.
<http://www.ncbi.nlm.nih.gov/pubmed/20628129>
78. Braun UK, Kunik ME, Pham C. Treating depression in terminally ill patients can optimize their physical comfort at the end of life and provide them the opportunity to confront and prepare for death. *Geriatrics*. 2008 Jun;63(6):25-7.
<http://www.ncbi.nlm.nih.gov/pubmed/18512998>
79. Tang ST, Chang WC, Chen JS, et al. Course and predictors of depressive symptoms among family caregivers of terminally ill cancer patients until their death. *Psychooncology*. 2012 Jul.
<http://www.ncbi.nlm.nih.gov/pubmed/22836818>
80. Holst L, Lundgren M, Olsen L, et al. Dire deadlines: coping with dysfunctional family dynamics in an end-of-life care setting. *Int J Palliat Nurs*. 2009 Jan;15(1):34-41.
<http://www.ncbi.nlm.nih.gov/pubmed/19234429>
81. Wentlandt K, Burman D, Swami N, et al. Preparation for the end of life in patients with advanced cancer and association with communication with professional caregivers. *Psychooncology*. 2011 Jun. doi: 10.1002/pon.1995. (Epub ahead of print)
<http://www.ncbi.nlm.nih.gov/pubmed/21648015>
82. Chan EK, O'Neill I, McKenzie M, et al. What works for therapists conducting family meetings: treatment integrity in family-focused grief therapy during palliative care and bereavement. *J Pain Symptom Manage*. 2004 Jun;27(6):502-12.
<http://www.ncbi.nlm.nih.gov/pubmed/15165648>

83. Li J, Yuan XL, Gao XH, et al. Whether, when, and who to disclose bad news to patients with cancer: a survey in 150 pairs of hospitalized patients with cancer and family members in China. *Psychooncology*. 2012 Jul;21(7):778-84.
<http://www.ncbi.nlm.nih.gov/pubmed/21509902>
84. Hottensen D. Anticipatory grief in patients with cancer. *Clin J Oncol Nurs*. 2010 Feb;14(1):106-7.
<http://www.ncbi.nlm.nih.gov/pubmed/20118035>
85. Baile WF, De Panfilis L, Tanzi S, et al. Using Sociodrama and Psychodrama To Teach Communication in End-of-Life Care. *J Palliat Med* 2012 Sep;15(9):1006-10.
<http://www.ncbi.nlm.nih.gov/pubmed/22799884>

ADDENDUM

A.1 PAIN MANAGEMENT (GENERAL)

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).

A.1.1 Pain evaluation and measurement

A.1.1.1 Pain evaluation

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.
- 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 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.

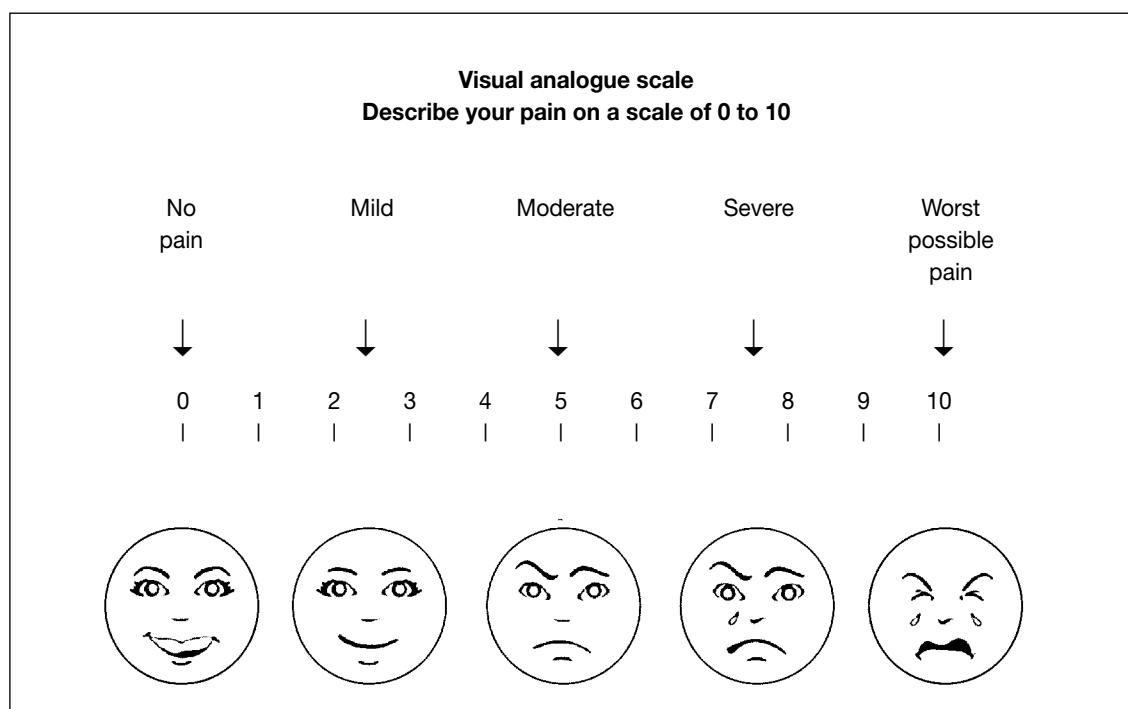
A.1.1.2 Assessing pain intensity and quality of life (QoL)

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 16: Pain assessment scales

0

10



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 16). 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.

For assessment, evaluation and measurement of neuropathic pain several questionnaires have been used. The most common and established one is the McGill Short Form Questionnaire (12).

A.1.2 References

1. Merskey H, Bogduk N (eds). Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. Seattle: IASP Press, 1994.
2. Jacobson L, Mariano AJ. General considerations of chronic pain. In: Loeser JD, ed. Bonica's Management of Pain. Philadelphia: Lippincott Williams & Wilkins, 2001, pp. 241-254.
3. Scholtz J, Woolf CJ. Can we conquer pain? Nat Neurosci 2002 Nov;5 Suppl:1062-7. <http://www.ncbi.nlm.nih.gov/pubmed/12403987>
4. Wiertelak EP, Smith KP, Furness L, et al. Acute and conditioned hyperalgesic responses to illness. Pain 1994 Feb;56(2):227-34. <http://www.ncbi.nlm.nih.gov/pubmed/8008412>
5. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004 Mar;140(6):441-51. <http://www.ncbi.nlm.nih.gov/pubmed/15023710>
6. Fosnocht DE, Chapman CR, Swanson ER, et al. Correlation of change in visual analog scale with pain relief in the ED. Am J Emerg Med 2005 Jan;23(1):55-9. <http://www.ncbi.nlm.nih.gov/pubmed/15672339>
7. Graham B. Generic health instruments, visual analog scales, and the measurement of clinical phenomena. J Rheumatol 1999 May;26(5):1022-3. <http://www.ncbi.nlm.nih.gov/pubmed/10332963>

8. Jensen MP. The validity and reliability of pain measures in adults with cancer. *J Pain* 2003 Feb;4(1): 2-21.
<http://www.ncbi.nlm.nih.gov/pubmed/14622723>
9. Rosier EM, Iadarola MJ, Coghill RC. Reproducibility of pain measurement and pain perception. *Pain* 2002 Jul;98(1-2):205-16.
<http://www.ncbi.nlm.nih.gov/pubmed/12098633>
10. Scott DL, Garrod T. Quality of life measures: use and abuse. *Ballieres Best Pract Research Clinical Rheumatol* 2000 Dec;14(4):663-87.
<http://www.ncbi.nlm.nih.gov/pubmed/11092795>
11. Lefebvre-Chapiro, S. The DOLOPLUS® 2 scale - evaluating pain in the elderly. *European Journal of Palliative Care*, 2001. 8(5): p. 191.
http://www.haywardpublishing.co.uk/year_search_review.aspx?JID=4&Year=2001&Edition=233
12. McGill Short form questionnaire.
http://www.npcrc.org/files/news/mcgill_pain_inventory.pdf

A.2 CANCER PAIN MANAGEMENT (GENERAL)

A.2.1 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).

A.2.2 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.

A.2.3 Non-pharmacological therapies

A.2.3.1 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).

A.2.3.2 Radionuclides

A.2.3.2.1 Clinical background

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

A.2.3.2.2 Radiopharmaceuticals

β^- -Emitting isotopes

The most important β^- -emitting radiopharmaceuticals are strontium-89 chloride (^{89}Sr) and samarium-153 lexidronam. 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). 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 one 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.

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).

β -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 4-6 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.

A.2.3.3 Radiotherapy for metastatic bone pain

A.2.3.3.1 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).

A.2.3.3.2 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 (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 highdose radiotherapy to postpone systemic treatments (LE: 3).

A.2.3.3.3 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 (57-61) (LE: 2b), with sensitivity of 93% (62) (LE: 3) and specificity of 96% (62) (LE: 3). The level of neurological function at the start of treatment determines the functional outcome (63).

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 (64) (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 (57,59,61) and one meta-analysis (58) 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 15 (LE: 3).

Table 15: 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 (60) (LE: 1b).

A.2.3.3.4 Pathological fractures

In patients with impending pathological fractures (more than 50% of the thickness of the cortex of a long bone affected), a prophylactic orthopaedic procedure should be considered (62). If is eroded by metastasis, prophylactic fixation rather than radiotherapy alone should be considered.

A.2.3.3.5 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 (65). 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 (66) (LE: 3).
2. Symptoms depending on the treatment field and location: nausea (especially with larger fields), vomiting, diarrhoea, irritation of the throat and oesophagus.

A.2.3.4 Psychological and adjunctive therapy

A.2.3.4.1 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 (67-69). There is evidence that highly emotional cancer patients, as detected through their own narratives, experience less pain than their less emotional counterparts (70). Cultural differences also play a role in pain perception (71). Depression is the most prevalent psychiatric diagnosis in patients with cancer. In this setting, structured psychotherapy seems to be more effective than antidepressant medication (72).

Cognitive behavioural therapy (CBT), such as relaxation and distraction, can provide pain relief (73-75). The possibility of delivering CBT by home visits, telephone, or through the Internet seems promising (76-78). Virtual consultation and automated symptom monitoring for cancer patients with depression can exceed all expectations (79). It has also been suggested that CBT may be particularly helpful for younger cancer patients (80).

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 (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 (82). Other psychological interventions that aim to minimise caregiver emotional distress have not been effective (83). Overall, educational programmes that aim to maximise family and patient satisfaction with pain treatment seem promising (84).

The impact of early detection of psychological distress may improve health outcomes (85). 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 (86). Different tools are available to better assess patients' needs, such as Palliative Care Needs Assessment Guidelines and Needs Assessment Tool (87) and the short form of the Supportive Care Needs Survey (SCNS-SF34) (88).

A.2.3.4.2 Adjunctive therapy

To date, there is no conclusive evidence on the effect of reflexology and massage therapy (89-91). Nevertheless, certain manipulations (e.g., sciatic nerve press) seem to be effective for immediate pain relief in many oncological conditions (92). The notion that acupuncture may be effective for cancer patients is not supported by the currently available data (93,94). However, modest although significant improvements in depression and pain scales have been confirmed by well-conducted studies on acupuncture (95).

Evidence from robust studies is still lacking on the effect of traditional Chinese medicine and complementary alternative medicine (96,97). 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 (98). Physical exercise (short walks) can positively affect the pain experience of prostate cancer (PCa) patients (99). Similarly, moderate exercise positively affects cancer-related sleep disturbance (100). TENS might mitigate hyperalgesia in cancer patients. Unfortunately, reliable studies in this field are lacking (101).

Listening to music slightly reduces distress, pain intensity and opioid requirements in cancer patients (102,103). Music relaxation videos seem to positively affect pain severity, opioid consumption, and anxiety level in patients treated for some gynaecological tumours (104). It is likely that patients harbouring urological tumours could also benefit.

Strong evidence on the real potential of cannabis derivatives is lacking (105).

Evidence exists of the strong relationship between pain, anxiety and depression, and health-related QoL in cancer patients (106,107). 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 (108). Psychological interventions focused on sexual dysfunction following cancer can be considered as moderately effective (109).

A.2.4 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.

A.2.4.1 **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 (110) (LE: 1a).

A.2.4.2 **Bisphosphonates**

The main effects are:

- decrease of the risk of skeleton-related events (111) (LE: 1b);
- pain relief in 60-85% of patients (111-113) (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%).

A.2.4.3 **Denosumab**

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 (114).

Another recently published phase III study 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 (115).

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 (114).

A.2.4.4 **Systemic analgesic pharmacotherapy - the analgesic ladder**

Analgesic pharmacotherapy is the mainstay of cancer pain management (116-118). 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 (117,118) (LE: 1a). Known as the analgesic ladder, when combined with appropriate dosing guidelines it can provide adequate relief in 70-90% of patients (119,120).

- **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).

A.2.4.4.1 **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 (121).
- 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 (122).
- 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, and patients with chronic alcoholism and liver disease can develop severe hepatotoxicity at the usual therapeutic doses (123).

A.2.4.4.2 Opioid analgesics

Cancer pain of moderate or severe intensity should generally be treated with a systemically administered opioid analgesic (124). 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 (125).

A trial of systemic opioid therapy should be administered to all cancer patients with moderate or severe pain (125-127). 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 (128).
- **Transdermal** routes: fentanyl and buprenorphine have been demonstrated to be effective in postoperative and cancer pain (129). 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 (130). The efficacy of transdermal fentanyl is equal to morphine. The incidence of side effects such as sedation and constipation are lower than for morphine (131, 132) (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 (133). Its analgesic effect is comparable with that of other opioids, and it shows no relevant analgesic ceiling effect throughout the therapeutic dose range (134). 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 (135).
- **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 (136). 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 (137,138). Fentanyl delivered by this means is more effective than oral morphine at relieving pain (LE: 2).

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 (139).

- **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 (140). 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 (141). 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% (142), 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 (143). Methadone appears to be relatively irritating and is not preferred (144). 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 (145).

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 (146,147).
- **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) (148). 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 (149). 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 (150). 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 (151). 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 (152-154), 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, bisacodyl 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 (155), 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 (156). 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 (157). There are no prospective studies in patients with chronic cancer pain, but extensive clinical experience affirms the low risk of addiction in this population (LE: 3). Healthcare providers, patients and families often require vigorous and repeated reassurance that the risk of addiction is small.

Adjuvant analgesics

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

- **Corticosteroids.** Widely used as adjuvant analgesics (158,159), this group has been demonstrated to have analgesic effects, to improve QoL significantly (160), and to have beneficial effects on appetite, nausea, mood and malaise in patients with cancer (161). 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 (162), 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).

A.2.4.5 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 (163,164). However, the potential complications of opioids mean that they are not always a satisfactory option (165). 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 (166,167).

A.2.4.5.1 Antidepressants

There is clear evidence for the effectiveness of antidepressants in the treatment of neuropathic pain (166). Antidepressants which work primarily via interaction with pathways running through the spinal cord from serotonergic 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 (168,169) (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 (168,169) (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).

A.2.4.5.2 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 (170). 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) (171,172). Carbamazepine and phenytoin were initially used for the treatment of trigeminal 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 trigeminal neuralgia (173) (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 (174).

Gabapentin and pregabalin are first-line treatments for neuropathic pain (reducing elements of central sensitisation), especially in post-zoster neuralgia and diabetic polyneuropathy (175-177) (LE: 1a). The combination of gabapentin with opioids seems to display synergistic effects in relieving neuropathic pain (178,179). 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 (180). Recent studies confirm the effectiveness of pregabalin in peripheral (including post-herpetic neuralgia and diabetic polyneuropathy) and central neuropathic pain (181).

A.2.4.5.3 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 (182,183) (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 (184) (LE: 3).

A.2.4.5.4 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 (156,185). 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 (186) (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 (185). It must therefore be reserved as a third-line option when other standard analgesic treatments are exhausted (187,188).

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) (189,190). 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 (191).

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 (192,193).

A.2.4.5.5 Other drug treatments

Baclofen, a muscle relaxant, is analgesic due to its agonistic effect on the inhibitory GABAB receptors. Baclofen is efficacious in patients with trigeminal neuralgia, but not in those with other neuropathic pain conditions (192). 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 trigeminal neuralgia, or a third-line agent in neuropathic pain syndromes (LE: 3).

Clonidine, an α_2 -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 enkephalin-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 (194) (LE: 2b).

Summary: treatment of neuropathic pain

- **First-line agent:**
 - nortirpyline, 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).

A.2.4.5.6 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 (3,120). 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 (195,196).

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 (197,198). 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) (199) (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 (200-202) (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 (203,204). 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 (205,206). The potential morbidity of these procedures requires well-trained clinicians and long-term monitoring (LE: 2).

A.2.4.6 Breakthrough cancer pain

Breakthrough cancer pain (BTCP) is a common and debilitating problem (207). 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 (208).

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 (209). Proper assessment and classification of BTCP could improve care and support of patients with this syndrome (210) (LE: 1a).

A.2.4.7 Recommendations pharmacotherapy

| Bisphosphonates | 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 |
| Denosumab | | |
| Denosumab use increases bone-metastasis-free survival and delays time to first bone metastasis in prostate cancer patients. | 1b | A |
| Opioids | | |
| 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 |
| Inform the patient that the use of morphine has a small risk of addiction. | 3 | A |
| Adjuvant analgesics | | |
| Dexamethasone 1-2 mg twice daily can be a valuable adjuvant in the treatment of pain in advanced cancer. | 2a | B |
| Neuropathic pain | | |
| Antidepressants | | |
| Offer amitriptyline and nortriptyline as a first line treatment for neuropathic pain, with nortriptyline associated with fewer side effects. | 1b | A |
| TCA's 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 |
| Offer gabapentin and pregabalin as first-line treatment for neuropathic pain, especially if tricyclic antidepressants are contraindicated. | 1b | A |
| Local analgesics | | |
| 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 |
| NMDA receptor antagonists | | |
| 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 |
| Invasive analgesic techniques | | |
| Reversible regional anaesthetic techniques must be considered for the management of neuropathic pain. | | GCP |
| Neuraxial administration of opioids | | |
| 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 |

GCP = good clinical practice; TCA = tricyclic antidepressants.

A.2.5 Quality of life)

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 (211,212). Treatment should include both psychological and somatic symptoms (213).

Physical activities adapted to the patient's condition are beneficial in the treatment of fatigue (214-216). Family caregivers and support groups are crucial components of the patient support system. Members of PCa selfhelp groups provide each other with various types of assistance, usually non-professional and non-material, for a particular shared, usually burdensome, characteristic (212). 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 (212).

A.2.6 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.

A.2.7 References

1. Knudsen AK, Brunelli C, Kaasa S, et al. Which variables are associated with pain intensity and treatment response in advanced cancer patients?--Implications for a future classification system for cancer pain. *Eur J Pain* 2011 Mar;15(3):320-7.
<http://www.ncbi.nlm.nih.gov/pubmed/20822941>
2. Mercadante S. Malignant bone pain: pathophysiology and treatment. *Pain* 1997 Jan;69(1-2):1-18.
<http://www.ncbi.nlm.nih.gov/pubmed/9060007>
3. Grond S, Zech D, Diefenbach C, et al. Assessment of cancer pain: a prospective evaluation of 2266 cancer patients referred to a pain service. *Pain* 1996 Jan;64(1):107-14.
<http://www.ncbi.nlm.nih.gov/pubmed/8867252>
4. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999 Dec;83(3):389-400.
<http://www.ncbi.nlm.nih.gov/pubmed/10568846>
5. Mercadante S, Portenoy RK. Opioid poorly-responsive cancer pain. Part 3. Clinical strategies to Improve opioid responsiveness. *J Pain Symptom Manage* 2001 Apr;21(4):338-54.
<http://www.ncbi.nlm.nih.gov/pubmed/11312049>
6. Candido K, Stevens RA. Intrathecal neurolytic blocks for the relief of cancer pain. *Best Pract Res Clin Anaesthesiol* 2003 Sep;17(3):407-28.
<http://www.ncbi.nlm.nih.gov/pubmed/14529011>
7. Boraas M. Palliative surgery. *Semin Oncol* 1985 Dec;12(4):368-74.
<http://www.ncbi.nlm.nih.gov/pubmed/2417321>
8. Sundaresan N, DiGiacinto GV. Antitumor and antinociceptive approaches to control cancer pain. *Med Clin North Am* 1987 Mar;71(2):329-48.
<http://www.ncbi.nlm.nih.gov/pubmed/2881035>
9. Williams MR. The place of surgery in terminal care. In: Saunders C (ed) *The management of terminal disease*. London: Edward Arnold, 1984; pp. 148-53.
10. Anast JW, Andriole GL, Grubb RL 2nd. Managing the local complications of locally advanced prostate cancer. *Curr Urol Rep* 2007 May;8(3):211-6.
<http://www.ncbi.nlm.nih.gov/pubmed/17459270>
11. Ferenschild FT, Vermaas M, Verhoef C, et al. Total pelvic exenteration for primary and recurrent malignancies. *World J Surg* 2009 Jul;33(7):1502-8.
<http://www.ncbi.nlm.nih.gov/pubmed/19421811>
12. Kamat AM, Huang SF, Bermejo CE, et al. Total pelvic exenteration: effective palliation of perineal pain in patients with locally recurrent prostate cancer. *J Urol* 2003 Nov;170(5):1868-71.
<http://www.ncbi.nlm.nih.gov/pubmed/14532795>
13. Temple WJ, Ketcham AS. Sacral resection for control of pelvic tumours. *Am J Surg* 1992 Apr;163(4):370-4.
<http://www.ncbi.nlm.nih.gov/pubmed/1373043>
14. Ackery D, Yardley J. Radionuclide-targeted therapy for the management of metastatic bone pain. *Semin Oncol* 1993 Jun;20(3)(Suppl 2):27-31.
<http://www.ncbi.nlm.nih.gov/pubmed/7684862>
15. Collins C, Eary JF, Donaldson G, et al. Samarium-153 -EDTMP in bone metastases of hormone refractory prostate carcinoma: a phase I/II trial. *J Nucl Med* 1993 Nov;34(11):1839-44.
<http://www.ncbi.nlm.nih.gov/pubmed/8229221>
16. Crawford ED, Kozlowski JM, Debruyne FM, et al. The use of strontium 89 for palliation of pain from bone metastases associated with hormone-refractory prostate cancer. *Urology* 1994 Oct;44(4):481-5.
<http://www.ncbi.nlm.nih.gov/pubmed/7524233>
17. Giammarile F, Mognetti T, Resche I. Bone pain palliation with strontium-89 in cancer patients with bone metastases. *Q J Nucl Med* 2001 Mar;45(1):78-83.
<http://www.ncbi.nlm.nih.gov/pubmed/11456379>

18. Krishnamurthy GT, Krishnamurthy S. Radionuclides for metastatic bone pain palliation: a need for rational re-evaluation in the new millennium. *J Nucl Med* 2000 Apr;41(4):688-91.
<http://www.ncbi.nlm.nih.gov/pubmed/10768570>
19. Laing AH, Ackery DM, Bayly RJ, et al. Strontium-89 chloride for pain palliation in prostatic skeletal malignancy. *Br J Radiol* 1991 Sep;64(765):816-22.
<http://www.ncbi.nlm.nih.gov/pubmed/1717094>
20. Lee CK, Aeppli DM, Unger J, et al. Strontium-89 chloride (Metastron) for palliative treatment of bony metastases. The University of Minnesota experience. *Am J Clin Oncol* 1996 Apr;19(2):102-7.
<http://www.ncbi.nlm.nih.gov/pubmed/8610630>
21. Lewington VJ. Targeted radionuclide therapy for bone metastases. *Eur J Nucl Med* 1993 Jan;20(1):66-74.
<http://www.ncbi.nlm.nih.gov/pubmed/7678397>
22. Roque M, Martinez MJ, Alonso P, et al. Radioisotopes for metastatic bone pain. *Cochrane Database Syst Rev* 2003;(4): CD003347.
<http://www.ncbi.nlm.nih.gov/pubmed/14583970>
23. Ahonen A, Joensuu H, Hiltunen J, et al. Samarium-153-EDTMP in bone metastases. *J Nucl Biol Med* 1994 Dec;38(4 Suppl1):123-7.
<http://www.ncbi.nlm.nih.gov/pubmed/7543288>
24. Eary JF, Collins C, Stabin M, et al. Samarium-153-EDTMP biodistribution and dosimetry estimation. *J Nucl Med* 1993 Jul;34(7):1031-6.
<http://www.ncbi.nlm.nih.gov/pubmed/7686217>
25. Farhanghi M, Holmes RA, Volkert WA, et al. Samarium-153-EDTMP: pharmacokinetic, toxicity and pain response using an escalating dose schedule in treatment of metastatic bone cancer. *J Nucl Med* 1992 Aug;33(8):1451-8.
<http://www.ncbi.nlm.nih.gov/pubmed/1378887>
26. McEwan AJ, Porter AT, Venner PM, et al. An evaluation of the safety and efficacy of treatment with strontium-89 in patients who have previously received wide field radiotherapy. *Antibody Immunoconjug Radiopharm* 1990;3(2):91-8.
27. McEwan AJ, Amyotte GA, McGowan DG, et al. A retrospective analysis of the cost effectiveness of treatment with Metastron (89Sr-chloride) in patients with prostate cancer metastatic to bone. *Nucl Med Commun* 1994 Jul;15(7):499-504.
<http://www.ncbi.nlm.nih.gov/pubmed/7970425>
28. Nightengale B, Brune M, Blizzard SP, et al. Strontium chloride Sr 89 for treating pain from metastatic bone disease. *Am J Health Syst Pharm* 1995 Oct;52(20):2189-95.
<http://www.ncbi.nlm.nih.gov/pubmed/8564588>
29. Pons F, Herranz R, Garcia A, et al. Strontium-89 for palliation of pain from bone metastases in patients with prostate and breast cancer. *Eur J Nucl Med* 1997 Oct;24(10):1210-4.
<http://www.ncbi.nlm.nih.gov/pubmed/9323260>
30. Sartor O, Reid RH, Bushnell DL, et al. Safety and efficacy of repeat administration of samarium Sm-153 lexidronam to patients with metastatic bone pain. *Cancer* 2007 Feb;109(3):637-43.
<http://www.ncbi.nlm.nih.gov/pubmed/17167764>
31. Bodei L, Lam M, Chiesa C, et al. EANM procedure guidelines for treatment of refractory metastatic bone pain. *Eur J Nucl Med Mol Imaging* 2008 Oct;35(10):1934-40.
<http://www.ncbi.nlm.nih.gov/pubmed/18649080>
32. Finlay IG, Mason MD, Shelley M. Radioisotopes for the palliation of metastatic bone cancer: a systematic review; *Lancet Oncol* 2005 Jun;6(6):392-400.
<http://www.ncbi.nlm.nih.gov/pubmed/15925817>
33. Lewington VJ. Bone-seeking radiopharmaceuticals. *J Nucl Med* 2005 Jan;46 Suppl 1:38S-47S.
<http://www.ncbi.nlm.nih.gov/pubmed/15653650>
34. Resche I, Chatal JF, Pecking A, et al. A dose-controlled study of 153Sm-ethylenediaminetetramethylenephosphonate (EDTMP) in the treatment of patients with painful bone metastases. *Eur J Cancer* 1997 Sep;33:1583-91.
<http://www.ncbi.nlm.nih.gov/pubmed/9389919>
35. Taylor AR Jr. Strontium-89 for the palliation of bone pain due to metastatic disease. *J Nucl Med* 1994 Dec;35(12):2054.
<http://www.ncbi.nlm.nih.gov/pubmed/7527458>
36. Porter AT, McEwan AJ, Powe JE, et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. *Int J Radiat Oncol Biol Phys* 1993 Apr;25(5):805-13.
<http://www.ncbi.nlm.nih.gov/pubmed/8478230>

37. Quilty PM, Kirk D, Bolger JJ, et al. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol* 1994 Apr;31(1):33-40.
<http://www.ncbi.nlm.nih.gov/pubmed/7518932>
38. Parker C, et al. Overall Survival Benefit and Impact on Skeletal-Related Events for Radium-223 Chloride (Alpharadin) in the Treatment of Castration-Resistant Prostate Cancer (CRPC) Patients With Bone Metastases: A Phase III Randomized Trial (ALSYMPCA), in 27th EAU Annual Congress. 2012: Paris, France.
39. Tu SM, Millikan RE, Mengistu B, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet* 2001 Feb;357(9253):336-41.
<http://www.ncbi.nlm.nih.gov/pubmed/11210994>
40. Bruland, O. and R. Larsen, Radium revisited. In: Bruland O, Flaegstad T, editors. Targeted Cancer Therapies. An Odyssey. 2003, Ravnetrykk: University Library of Troms.
41. Henriksen G, Fisher DR, Roeske JC, et al. Targeting of osseous sites with alpha-emitting 223Ra: comparison with the beta-emitter 89Sr in mice. *J Nucl Med* 2003 Feb;44(2):252-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12571218>
42. Kvinnsland Y, Skretting A, Bruland OS. Radionuclide therapy with bone-seeking compounds: Monte Carlo calculations of dose-volume histograms for bone marrow in trabecular bone. *Phys Med Biol* 2001 Apr;46(4):1149-61.
<http://www.ncbi.nlm.nih.gov/pubmed/11324957>
43. Nilsson S, Strang P, Aksnes AK, et al. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. *Eur J Cancer* 2012 Mar;48(5):678-86.
<http://www.ncbi.nlm.nih.gov/pubmed/22341993>
44. Nilsson S, Franzen L, Parker C, et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. *Lancet Oncol* 2007 Jul; 8(7):587-94.
<http://www.ncbi.nlm.nih.gov/pubmed/17544845>
45. Parker CC, Pascoe S, Chodacki A, et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (ra 223) in patients with bone metastases and castration-resistant prostate cancer. *Eur Urol* 2013 Feb;63(2):189-97.
<http://www.ncbi.nlm.nih.gov/pubmed/23000088>
46. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: A systematic review. *J Clin Oncol* 2007 Apr;25(11):1423-36.
<http://www.ncbi.nlm.nih.gov/pubmed/17416863>
47. Sze WM, Shelley M, Held I, et al. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy--a systematic review of randomised trials. *Clin Oncol* 2003 Sep;15(6): 345-52.
<http://www.ncbi.nlm.nih.gov/pubmed/14524489>
48. Wu JS, Wong R, Johnston M, et al. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys* 2003 Mar;55(3):594-605.
<http://www.ncbi.nlm.nih.gov/pubmed/12573746>
49. Foro Arnalot P, Fontanals AV, Galceran JC, et al. Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction. *Radiother Oncol* 2008 Nov;89(2):150-5.
<http://www.ncbi.nlm.nih.gov/pubmed/18556080>
50. Hamouda WE, Roshdy W, Teema M. Single versus conventional fractionated radiotherapy in the palliation of painful bone metastases. *Gulf J Oncolog* 2007 Jan;1(1):35-41.
<http://www.ncbi.nlm.nih.gov/pubmed/20084712>
51. Kaasa S, Brenne E, Lund JA, et al. Prospective randomised multicenter trial on single fraction radiotherapy (8 Gy x1) versus multiple fractions (3 Gy x10) in the treatment of painful bone metastases. *Radiother Oncol* 2006 Jun;79(3):278-84.
<http://www.ncbi.nlm.nih.gov/pubmed/16793155>
52. Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011 Mar;79(4):965-76.
<http://www.ncbi.nlm.nih.gov/pubmed/21277118>
53. Sande TA, Ruenes R, Lund JA, et al. Long-term follow-up of cancer patients receiving radiotherapy for bone metastases: Results from a randomised multicentre trial. *Radiother Oncol* 2009 May;91(2):261-6.
<http://www.ncbi.nlm.nih.gov/pubmed/19307034>
54. Hartsell W, Konski A, Scott C, et al. Randomized trial of short versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst* 2005 Jun;97(11):798-804.
<http://www.ncbi.nlm.nih.gov/pubmed/15928300>

55. Ozsaran Z, Yalman, Anacak Y, et al. Palliative radiotherapy in bone metastases: Results of a randomized trial comparing three fractionation schedules. *Journal of B.U.ON.* (2001) 6:1 (43-48).
56. Van den Hout WB, van der Linden YM, Steenland E, et al. Single- versus multiple-fraction radiotherapy in patients with painful bone metastases: Cost-utility analysis based on a randomized trial. *J Natl Cancer Inst* 2003 Feb;95(3):222-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12569144>
57. Fourney DR, Abi-Said D, Lang FF, et al. Use of pedicle screw fixation management of malignant spinal disease: experience in 100 consecutive procedures. *J Neurosurg* 2001 Jan;94(1Suppl):25-37.
<http://www.ncbi.nlm.nih.gov/pubmed/11147865>
58. Klimo P, Thompson CJ, Kestle JRW, et al. A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro Oncol* 2005 Jan;7(1):64-76.
<http://www.ncbi.nlm.nih.gov/pubmed/15701283>
59. North RB, LaRocca VR, Schwartz J, et al. Surgical management of spinal metastases: analysis of prognostic factors during a 10-year experience. *J Neurosurg* 2005 May;2(5):564-73.
<http://www.ncbi.nlm.nih.gov/pubmed/15945430>
60. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet* 2005 Aug; 366(9486):643-8.
<http://www.ncbi.nlm.nih.gov/pubmed/16112300>
61. Wang JC, Boland P, Mitra N, et al. Single-stage posterolateral transpedicular approach for resection of epidural metastatic spine tumors involving the vertebral body with circumferential reconstruction: results in 140 patients. *J Neurosurg* 2004 Oct;1(3):287-98.
<http://www.ncbi.nlm.nih.gov/pubmed/15478367>
62. Van Der Linden YM, Kroon HM, Dijkstra SP, et al. Simple radiographic parameter predicts fracturing in metastatic femoral bone lesions: Results from a randomised trial. *Radiother Oncol* 2003 Oct;69(1): 21-31.
<http://www.ncbi.nlm.nih.gov/pubmed/14597353>
63. Rades D, Fehlauer F, Hartmann A, et al. Reducing the overall treatment time for radiotherapy of metastatic spinal cord compression (MSCC): 3-year results of a prospective observational multi-center study. *J Neurooncol* 2004 Oct;70(1):77-82.
<http://www.ncbi.nlm.nih.gov/pubmed/15527111>
64. Sorensen PS, Helweg-Larsen S, Mouridsen H, et al. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomized trial. *Eur J Cancer* 1994;30A(1):22-7.
<http://www.ncbi.nlm.nih.gov/pubmed/8142159>
65. Loblaw DA, Wu JSY, Kirkbride P, et al. Pain flare in patients with bone metastases after palliative radiotherapy. A nested randomized control trial. *Support Care Cancer* 2007 Apr;15(4):451-5.
<http://www.ncbi.nlm.nih.gov/pubmed/17093912>
66. Hird A, Zhang L, Holt T, et al. Dexamethasone for the Prophylaxis of Radiation-induced Pain Flare after Palliative Radiotherapy for Symptomatic Bone Metastases: a Phase II Study. *Clin Oncol (R Coll Radiol)* 2009 May;21(4):329-35.
<http://www.ncbi.nlm.nih.gov/pubmed/19232483>
67. Candy B, Jackson KC, Jones L, et al. Drug therapy for symptoms associated with anxiety in adult palliative care patients. *Cochrane Database Syst Rev* 2012 Oct;10:CD004596.
<http://www.ncbi.nlm.nih.gov/pubmed/23076905>
68. Minton O, Stone P, Richardson A, et al. Drug therapy for the management of cancer related fatigue. *Cochrane Database Syst Rev* 2008 Jan;(1):CD006704.
<http://www.ncbi.nlm.nih.gov/pubmed/18254112>
69. Sheinfeld Gorin S, Krebs P, Badr H, et al. Meta-analysis of psychosocial interventions to reduce pain in patients with cancer. *J Clin Oncol* 2012 Feb;30(5):539-47.
<http://www.ncbi.nlm.nih.gov/pubmed/22253460>
70. Cepeda MS, Chapman CR, Miranda N, et al. Emotional Disclosure Through Patient Narrative May Improve Pain and Well-Being: Results of a Randomized Controlled Trial in Patients with Cancer Pain. *J Pain Symptom Manage* 2008 Jun;35(6):623-31.
<http://www.ncbi.nlm.nih.gov/pubmed/18359604>
71. Chen CH, Tang ST, Chen CH. Meta-analysis of cultural differences in Western and Asian patient perceived barriers to managing cancer pain. *Palliat Med* 2012 Apr;26(3):206-21.
<http://www.ncbi.nlm.nih.gov/pubmed/21474622>

72. Ell K, Xie B, Quon B, et al. Randomized controlled trial of collaborative care management of depression among low-income patients with cancer. *J Clin Oncol* 2008 Sep;26(27):4488-96.
<http://www.ncbi.nlm.nih.gov/pubmed/18802161>
73. Anderson KO, Cohen MZ, Mendoza TR, et al. Brief cognitive-behavioral audiotape interventions for cancer-related pain: Immediate but not long-term effectiveness. *Cancer* 2006 Jul;107(1):207-14.
<http://www.ncbi.nlm.nih.gov/pubmed/16708359>
74. Devine EC. Meta-analysis of the effect of psycho-educational interventions on pain in adults with cancer. *Oncol Nurs Forum* 2003 Jan-Feb;30(1):75-89.
<http://www.ncbi.nlm.nih.gov/pubmed/12515986>
75. Tsai PS, Chen PL, Lai YL, et al. Effects of electromyography biofeedback-assisted relaxation on pain in patients with advanced cancer in a palliative care unit. *Cancer Nurs* 2007 Sep-Oct;30(5):347-53.
<http://www.ncbi.nlm.nih.gov/pubmed/17876179>
76. Dalton JA, Keefe FJ, Carlson J, et al. Tailoring cognitive-behavioral treatment for cancer pain. *Pain Manag Nurs* 2004 Mar;5(1):3-18.
<http://www.ncbi.nlm.nih.gov/pubmed/14999649>
77. Osborn RL, Demoncada AC, Feuerstein M. Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: Meta-analyses. *Int J Psychiatry Med* 2006;36(1):13-34.
<http://www.ncbi.nlm.nih.gov/pubmed/16927576>
78. Sherwood P, Given BA, Given CW, et al. A cognitive behavioral intervention for symptom management in patients with advanced cancer. *Oncol Nurs Forum* 2005 Nov;32(6):1190-8.
<http://www.ncbi.nlm.nih.gov/pubmed/16270114>
79. Kroenke K, Theobald D, Wu J, et al. Effect of telecare management on pain and depression in patients with cancer: A randomized trial. *JAMA* 2010 Jul;304(2):163-71.
<http://www.ncbi.nlm.nih.gov/pubmed/20628129>
80. Doorenbos A, Given B, Given C, et al. Reducing symptom limitations: A cognitive behavioral intervention randomized trial. *Psycho-Oncology* 2005 Jul;14(7):574-84.
<http://www.ncbi.nlm.nih.gov/pubmed/15643674>
81. Chochinov HM, Kristjanson LJ, Breitbart W, et al. Effect of dignity therapy on distress and end-of-life experience in terminally ill patients: a randomised controlled trial. *Lancet Oncol* 2011 Aug;12(8):753-62.
<http://www.ncbi.nlm.nih.gov/pubmed/21741309>
82. Chan EKH, O'Neill I, McKenzie M, et al. What works for therapists conducting family meetings: Treatment integrity in family-focused grief Therapy during palliative care and bereavement. *J Pain Symptom Manage* 2004 Jun;27(6):502-12.
<http://www.ncbi.nlm.nih.gov/pubmed/15165648>
83. Kurtz ME, Kurtz JC, Given CW, et al. A randomized, controlled trial of a patient/caregiver symptom control intervention: Effects on depressive symptomatology of caregivers of cancer patients. *J Pain Symptom Manage* 2005 Aug;30(2):112-122.
<http://www.ncbi.nlm.nih.gov/pubmed/16125026>
84. Chou PL, Lin CC. A pain education programme to improve patient satisfaction with cancer pain management: a randomised control trial. *J Clin Nurs*. 2011 Jul;20(13-14):1858-69.
<http://www.ncbi.nlm.nih.gov/pubmed/21615576>
85. Gold JI, Douglas MK, Thomas ML, et al. The relationship between posttraumatic stress disorder, mood states, functional status, and quality of life in oncology outpatients. *J Pain Symptom Manage* 2012 Oct;44(4):520-31.
<http://www.ncbi.nlm.nih.gov/pubmed/22743157>
86. Merckaert I, Libert Y, Messin S, et al. Cancer patients' desire for psychological support: prevalence and implications for screening patients' psychological needs. *Psychooncology* 2010 Feb;19(2):141-9.
<http://www.ncbi.nlm.nih.gov/pubmed/19382112>
87. Waller A, Girgis A, Johnson C, et al. Implications of a needs assessment intervention for people with progressive cancer: impact on clinical assessment, response and service utilisation. *Psychooncology* 2012 May;21(5):550-7.
<http://www.ncbi.nlm.nih.gov/pubmed/22517737>
88. Girgis A, Stojanovski E, Boyes A, et al. The next generation of the supportive care needs survey: a brief screening tool for administration in the clinical oncology setting. *Psychooncology*. 2011 Apr.
<http://www.ncbi.nlm.nih.gov/pubmed/21484938>
89. Ernst E. Is reflexology an effective intervention? A systematic review of randomised controlled trials. *Med J Aust* 2009 Sep;191(5):263-6.
<http://www.ncbi.nlm.nih.gov/pubmed/19740047>

90. Ernst E. Massage therapy for cancer palliation and supportive care: A systematic review of randomised clinical trials. *Supportive Care Cancer* 2009 Apr;17(4):333-7.
<http://www.ncbi.nlm.nih.gov/pubmed/19148685>
91. Jane SW, Wilkie DJ, Gallucci BB, et al. Systematic review of massage intervention for adult patients with cancer: a methodological perspective. *Cancer Nurs* 2008 Nov-Dec;31(6):E24-35.
<http://www.ncbi.nlm.nih.gov/pubmed/18987505>
92. He J, Zhao T, Zhang W, et al. A new analgesic method, two-minute sciatic nerve press, for immediate pain relief: A randomized trial. *BMC Anesthesiol* 2008 Jan;8:1.
<http://www.ncbi.nlm.nih.gov/pubmed/18221518>
93. Choi TY, Lee MS, Kim TH, et al. Acupuncture for the treatment of cancer pain: a systematic review of randomised clinical trials. *Support Care Cancer* 2012 Jun;20(6):1147-58.
<http://www.ncbi.nlm.nih.gov/pubmed/22447366>
94. Lee H, Schmidt K, Ernst E. Acupuncture for the relief of cancer-related pain: a systematic review. *Eur J Pain* 2005 Aug;9(4):437-44.
<http://www.ncbi.nlm.nih.gov/pubmed/15979024>
95. Mehling WE, Jacobs B, Acree M, et al. Symptom Management with Massage and Acupuncture in Postoperative Cancer Patients: A Randomized Controlled Trial. *J Pain Symptom Manage* 2007 Mar;33(3):258-66.
<http://www.ncbi.nlm.nih.gov/pubmed/17349495>
96. Bardia A, Barton DL, Prokop LJ, et al. Efficacy of complementary and alternative medicine therapies in relieving cancer pain: a systematic review. *J Clin Oncol* 2006 Dec;24(34):5457-64.
<http://www.ncbi.nlm.nih.gov/pubmed/17135649>
97. Manheimer E, Wieland S, Kimbrough E, et al. Evidence from the Cochrane Collaboration for traditional Chinese medicine therapies. *J Altern Complement Med* 2009 Sep;15(9):1001-14.
<http://www.ncbi.nlm.nih.gov/pubmed/19757977>
98. Kim JI, Lee MS, Lee DH, et al. Cupping for treating pain: a systematic review. *Evid Based Complement Alternat Med* 2011;2011:467014.
<http://www.ncbi.nlm.nih.gov/pubmed/19423657>
99. Griffith K, Wenzel J, Shang J, et al. Impact of a walking intervention on cardiorespiratory fitness, self reported physical function, and pain in patients undergoing treatment for solid tumors. *Cancer* 2009 Oct;115(20):4874-84.
<http://www.ncbi.nlm.nih.gov/pubmed/19637345>
100. Tang MF, Liou TH, Lin CC. Improving sleep quality for cancer patients: benefits of a home-based exercise intervention. *Support Care Cancer* 2010 Oct;18(10):1329-39.
<http://www.ncbi.nlm.nih.gov/pubmed/19834744>
101. Hurlow A, Bennett MI, Robb KA, et al. Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults. *Cochrane Database Syst Rev* 2012 Mar;3:CD006276.
<http://www.ncbi.nlm.nih.gov/pubmed/22419313>
102. Cepeda MS, Carr DB, Lau J, et al. Music for pain relief. *Cochrane Database Syst Rev* 2006 Apr;2: CD004843.
<http://www.ncbi.nlm.nih.gov/pubmed/16625614>
103. Huang ST, Good M, Zauszniewski JA. The effectiveness of music in relieving pain in cancer patients: a randomized controlled trial. *Int J Nurs Stud* 2010 Nov;47(11):1354-62.
<http://www.ncbi.nlm.nih.gov/pubmed/20403600>
104. Chi GC, Young A, McFarlane J, et al. Music Relaxation Video and Pain Control: A Randomized Controlled Trial for Women Receiving Intracavitary Brachytherapy for Gynecological Cancer. *Int J Radiat Oncol Biol Phys* 2011 Oct; 81(2): S189.
[http://www.redjournal.org/article/S0360-3016\(11\)01159-X/fulltext](http://www.redjournal.org/article/S0360-3016(11)01159-X/fulltext)
105. Zhornitsky, S. and S. Potvin, Cannabidiol in humans-The quest for therapeutic targets. *Pharmaceuticals* 2012;5(5):529-52.
www.mdpi.com/1424-8247/5/5/529/pdf
106. Brown LF, Kroenke K, Theobald DE, et al. The association of depression and anxiety with health related quality of life in cancer patients with depression and/or pain. *Psychooncology* 2010 Jul;19(7):734-41.
<http://www.ncbi.nlm.nih.gov/pubmed/19777535>
107. Kroenke K, Theobald D, Wu J, et al. The association of depression and pain with health-related quality of life, disability, and health care use in cancer patients. *J Pain Symptom Manage* 2010 Sep;40(3): 327-41.
<http://www.ncbi.nlm.nih.gov/pubmed/20580201>

108. Miles CL, Candy B, Jones L, et al. Interventions for sexual dysfunction following treatments for cancer. *Cochrane Database Syst Rev* 2007;(4):CD005540
<http://www.ncbi.nlm.nih.gov/pubmed/17943864>
109. Brotto LA, Yule M, Breckon E. Psychological interventions for the sexual sequelae of cancer: a review of the literature. *J Cancer Surviv* 2010 Dec;4(4):346-60.
<http://www.ncbi.nlm.nih.gov/pubmed/20602188>
110. Patt YZ, Peters RE, Chuang VP, et al. Palliation of pelvic recurrence of colorectal cancer with Intraarterial 5-fluorouracil and mitomycin. *Cancer* 1985 Nov;56(9):2175-80.
<http://www.ncbi.nlm.nih.gov/pubmed/2996749>
111. Coleman RE, McCloskey EV. Bisphosphonates in oncology. *Bone* 2011 Jul;49(1):71-6.
<http://www.ncbi.nlm.nih.gov/pubmed/21320652>
112. Heidenreich A, Hofmann R, Engelmann U. The use of bisphosphonates for the palliative treatment of painful bone metastasis due to hormone refractory prostate cancer. *J Urol* 2001 Jan;165(1):136-40.
<http://www.ncbi.nlm.nih.gov/pubmed/11125382>
113. Weinfurt K, Anstrom K, Castel L, et al. Effect of zoledronic acid on pain associated with bone metastasis in patients with prostate cancer. *Ann Oncol* 2006 Jun;17(6):986-9.
<http://www.ncbi.nlm.nih.gov/pubmed/16533874>
114. Smith MR, Saad R, Coleman R, et al. Denosumab and bone-metastases free survival in men with castration-resistant prostate cancer: results of a phase III randomized, placebo controlled trial. *Lancet* 2011 Nov.
<http://www.ncbi.nlm.nih.gov/pubmed/22093187>
115. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011 Mar;377(9768):813-22.
<http://www.ncbi.nlm.nih.gov/pubmed/21353695>
116. Foley KM. The treatment of cancer pain. *N Eng J Med* 1985 Jul;313(2):84-95.
<http://www.ncbi.nlm.nih.gov/pubmed/2582259>
117. Stjernsward J. WHO cancer pain relief programme. *Cancer Surv* 1988;7(1):195-208.
<http://www.ncbi.nlm.nih.gov/pubmed/2454740>
118. World Health Organization. Cancer pain relief and palliative Care. Report of a WHO expert committee. World Health Organization Technical Report Series, 804. Geneva, Switzerland: World Health Organization, 1990.
<http://apps.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=10&codcch=804>
119. Grond S, Zech D, Schug SA, et al. Validation of the World Health Organization guidelines for cancer pain relief during the last days and hours of life. *J Pain Symptom Manage* 1991 Oct;6(7):411-22.
<http://www.ncbi.nlm.nih.gov/pubmed/1940485>
120. Schug SA, Zech D, Dorr U. Cancer pain management according to WHO analgesic guidelines. *J Pain Symptom Manage* 1990 Feb;5(1):27-32.
<http://www.ncbi.nlm.nih.gov/pubmed/2324558>
121. Malmberg AB, Yaksh TL. Hyperalgesia mediated by spinal glutamate and substance P receptor blocked by spinal cyclooxygenase inhibition. *Science* 1992 Aug;92(5074):1276-9.
<http://www.ncbi.nlm.nih.gov/pubmed/1381521>
122. Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs - differences and similarities. *N Eng J Med* 1991 Jun;324(24):1716-25.
<http://www.ncbi.nlm.nih.gov/pubmed/2034249>
123. Seeff LB, Cuccherini BA, Zimmerman HJ, et al. Acetaminophen hepatotoxicity in alcoholics. A therapeutic misadventure. *Ann Intern Med* 1986 March;104(3):399-404.
<http://www.ncbi.nlm.nih.gov/pubmed/3511825>
124. Hanks GW, Conno F, Cherny N, et al; Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001 Mar;84(5):587-93.
<http://www.ncbi.nlm.nih.gov/pubmed/11237376>
125. Cherny NI, Thaler HT, Friedlander-Klar H, et al. Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms: a combined analysis of controlled, single-dose studies. *Neurology* 1994 May;44(5):857-61.
<http://www.ncbi.nlm.nih.gov/pubmed/7514771>
126. Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. *JAMA* 2005 Jun;293(24):3043-52.
<http://www.ncbi.nlm.nih.gov/pubmed/15972567>

127. Jadad AR, Carroll D, Glynn CJ, et al. Morphine responsiveness of chronic pain: double blind randomised crossover study with patient controlled analgesia. *Lancet* 1992 Jun;339(8806):1367-71. <http://www.ncbi.nlm.nih.gov/pubmed/1350803>
128. Hanning CD. The rectal absorption of opioids. In: Benedetti C, Chapman C R, Giron G, eds. *Opioid analgesia. Advances in pain research and therapy*, vol 14. NY: Raven Press, 1990, pp. 259-269.
129. Calis KA, Kohler DR, Corso DM. Transdermally administered fentanyl for pain management. *Clinical Pharm* 1992 Jan;11(1):22-36. <http://www.ncbi.nlm.nih.gov/pubmed/1730176>
130. Portenoy RK, Southam MA, Gupta SK, et al. Transdermal fentanyl for cancer pain. Repeated dose pharmacokinetics. *Anesthesiology* 1993 Jan;78(1):36-43. <http://www.ncbi.nlm.nih.gov/pubmed/8424569>
131. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. *J Pain Symptom Manage* 1997 May;13(5):254-61. <http://www.ncbi.nlm.nih.gov/pubmed/9185430>
132. Clark AJ, Ahmedzai SH, Allan LG, et al. Efficacy and safety of transdermal fentanyl and sustained release oral morphine in patients with cancer and chronic noncancer pain. *Curr Med Res Opin* 2004 Sep;20(9):1419-28. <http://www.ncbi.nlm.nih.gov/pubmed/15383190>
133. Koppert W, Ihmsen H, Korber N, et al. Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. *Pain* 2005 Nov;118 (1-2):15-22. <http://www.ncbi.nlm.nih.gov/pubmed/16154698>
134. Sittl R. Transdermal buprenorphine in the treatment of chronic pain. *Expert Rev Neurother* 2005 May;5(3):315-23. <http://www.ncbi.nlm.nih.gov/pubmed/15938664>
135. Johnson RE, Fudala PJ, Payne R. Buprenorphine: considerations for pain management. *J Pain Symptom Manage* 2005 Mar;29(3):297-326. <http://www.ncbi.nlm.nih.gov/pubmed/15781180>
136. Weinberg DS, Inturrisi CE, Reidenberg B, et al. Sublingual absorption of selected opioid analgesics. *Clin Pharmacol Ther* 1988 Sep;44(3):335-42. <http://www.ncbi.nlm.nih.gov/pubmed/2458208>
137. Coluzzi PH, Schwartzberg L, Conroy JD, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain* 2001 Mar; 91(1-2):123-30. <http://www.ncbi.nlm.nih.gov/pubmed/11240084>
138. Fine PG, Marcus M, DeBoer AJ, et al. An open label study of oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough cancer pain. *Pain* 1991 May;45(2):149-53. <http://www.ncbi.nlm.nih.gov/pubmed/1876422>
139. American Pain Society. *Principles of analgesic use in the treatment of acute pain and chronic cancer pain. A concise guide to medical practice*, 3rd edn. Skokie, IL: American Pain Society, 1992.
140. Chapman CR, Hill HF, Saeger L, et al. Profiles of opioid analgesia in humans after intravenous bolus administration: alfentanil, fentanyl and morphine compared on experimental pain. *Pain* 1990 Oct;43(1):47-55. <http://www.ncbi.nlm.nih.gov/pubmed/1980537>
141. Storey P, Hill HH Jr, St Louis RH, et al. Subcutaneous infusions for control of cancer symptoms. *J Pain Symptom Manage* 1990 Feb;5(1):33-41. <http://www.ncbi.nlm.nih.gov/pubmed/1969887>
142. Moulin DE, Kreeft JH, Murray-Parsons N, et al. Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. *Lancet* 1991 Feb;337(8739):465-8. <http://www.ncbi.nlm.nih.gov/pubmed/1704089>
143. Moulin DE, Johnson NG, Murray-Parsons N, et al. Subcutaneous narcotic infusions for cancer pain: treatment outcome and guidelines for use. *CMAJ* 1992 Mar;146(6):891-7. <http://www.ncbi.nlm.nih.gov/pubmed/1371946>
144. Bruera E, Fainsinger R, Moore M, et al. Local toxicity with subcutaneous methadone. Experience of two centers. *Pain* 1991 May;45(2):141-3. <http://www.ncbi.nlm.nih.gov/pubmed/1876420>
145. Dale O, Moksnes K, Kaasa S. European Palliative Care Research Collaborative pain guidelines: opioid switching to improve analgesia or reduce side effects. A systematic review. *Palliat Med* 2011 Jul;25(5):494-503. <http://www.ncbi.nlm.nih.gov/pubmed/21708856>

146. Kaiko RF. Clinical protocol and role of controlled release morphine the surgical patient. In: Stanley TH, Ashburn MA, Fine PG, eds. Anesthesiology in pain management. Dordrecht, The Netherlands: Kluwer Academic, 1991, pp. 193-212.
147. Walsh TD, MacDonald N, Bruera E, et al. A controlled study of sustained-release morphine sulfate tablets in chronic pain from advanced cancer. *Am J Clin Oncol* 1992 Jun;15(3):268-72.
<http://www.ncbi.nlm.nih.gov/pubmed/1590284>
148. Coyle N, Adelhardt J, Foley KM, et al. Character of terminal illness in the advanced cancer patient: pain and other symptoms during last four weeks of life. *J Pain Symptom Manage* 1990 Apr;5(2):83-93.
<http://www.ncbi.nlm.nih.gov/pubmed/2348092>
149. Foley KM. Clinical tolerance to opioids. In: Basbaum AI, Bessom JM, eds. Towards a new pharmacotherapy of pain. Chichester, UK: Dahlem Konferenzen, John Wiley, 1991, pp. 181-204.
150. Bruera E, Macmillan K, Hanson J, et al. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain* 1989 Oct;39(1):13-6.
<http://www.ncbi.nlm.nih.gov/pubmed/2812850>
151. Breitbart W, Holland JC. Psychiatric complications of cancer. *Curr Ther in Hematol Oncol* 1988;3:268-75.
152. Inturrisi CE. Management of cancer pain. Pharmacology and principles of management. *Cancer* 1989 Jun;63(11 Suppl):2308-20.
<http://www.ncbi.nlm.nih.gov/pubmed/2566371>
153. Sykes NP. Oral naloxone in opioid- associated constipation. *Lancet* 1991 Jun;337(8755):1475.
<http://www.ncbi.nlm.nih.gov/pubmed/1675336>
154. Walsh TD. Prevention of opioid side effects. *J Pain Symptom Manage* 1990 Dec;5(6):362-7.
<http://www.ncbi.nlm.nih.gov/pubmed/1980127>
155. Campora E, Merlini L, Pace M, et al. The incidence of narcotic induced emesis. *J Pain Symptom Manage* 1991 Oct;6(7):428-30.
<http://www.ncbi.nlm.nih.gov/pubmed/1940487>
156. Schuster CR. Does treatment of cancer pain with narcotics produce junkies? In: Hill CS, Fields WS, eds. Drug treatment of cancer pain in a drug oriented society. Advances in pain research and therapy, vol 11. NY: Raven Press, 1989; pp. 1-3.
157. Chapman CR, Hill HF. Prolonged morphine self-administration and addiction liability. Evaluation of two theories in a bone marrow transplant unit. *Cancer* 1989 Apr;63(8):1636-44.
<http://www.ncbi.nlm.nih.gov/pubmed/2466551>
158. Della Cuna GR, Pellegrini A, Piazzini M. Effect of methylprednisolone sodium succinate on quality of life in preterminal cancer patients. A placebo controlled multicenter study. The Methylprednisolone Preterminal Cancer Study Group. *Eur J Cancer Clin Oncol* 1989 Dec;25(12):1817-21.
<http://www.ncbi.nlm.nih.gov/pubmed/2698804>
159. Walsh TD. Adjuvant analgesic therapy in cancer pain. In: Foley KM, Bonica JJ, Ventafridda V (eds). The Second International Conference on Cancer Pain. Advances in pain research and therapy, vol 16. New York, NY: Raven Press, 1990, pp. 155-168
160. Tannock I, Gospodarowicz M, Meakin W, et al. Treatment of metastatic prostatic cancer with lowdose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 1989 May;7(5):590-7.
<http://www.ncbi.nlm.nih.gov/pubmed/2709088>
161. Wilcox JC, Corr J, Shaw J, et al. Prednisolone as appetite stimulant in patients with cancer. *Br Med J (Clin Res Ed)* 1984 Jan;288(6410):27.
<http://www.ncbi.nlm.nih.gov/pubmed/6418303>
162. Fernandez F, Adams F, Holmes VF. Analgesic effect of alprazolam in patients with chronic, organic pain of malignant origin. *J Clin Psychopharmacol* 1987 Jun;7(3):167-9.
<http://www.ncbi.nlm.nih.gov/pubmed/3597802>
163. Ballantine JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med* 2003 Nov;349(20):1943-53.
<http://www.ncbi.nlm.nih.gov/pubmed/14614170>
164. Namaka M, Gramlich CR, Ruhlen D, et al. A treatment algorithm for neuropathic pain. *Clin Ther* 2004 Jul;26(7):951-79.
<http://www.ncbi.nlm.nih.gov/pubmed/15336464>
165. Rowbotham MC, Twilling L, Davies PS, et al. Oral opioid therapy for chronic peripheral and central neuropathic pain. *N Engl J Med* 2003 Mar;348(13):1223-32.
<http://www.ncbi.nlm.nih.gov/pubmed/12660386>
166. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* 2003 Nov;60(11):1524-34.
<http://www.ncbi.nlm.nih.gov/pubmed/14623723>

167. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007 Dec;132(3):237-51.
<http://www.ncbi.nlm.nih.gov/pubmed/17920770>
168. Kakuyama M, Fukuda K. The role of antidepressants in the treatment of chronic pain. *Pain Rev* 2000;7:119-128.
169. Sindrup SH, Otto M, Finnerup NB, et al. Antidepressants in the treatment of neuropathic pain. *Basic Clin Pharmacol Toxicol* 2005 Jun;96(6):399-409.
<http://www.ncbi.nlm.nih.gov/pubmed/15910402>
170. Jensen TS. Anticonvulsants in neuropathic pain: rationale and clinical evidence. *Eur J Pain* 2002; 6(Suppl.A):61-8.
<http://www.ncbi.nlm.nih.gov/pubmed/11888243>
171. Rogawski MA, Loscher W. The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions. *Nat Med* 2004 Jul;10(7):685-92.
<http://www.ncbi.nlm.nih.gov/pubmed/15229516>
172. Vinik A. Clinical review: use of antiepileptic drugs in the treatment of chronic painful diabetic neuropathy. *J Clin Endocrinol Metab* 2005 Aug;90(8):4936-45.
<http://www.ncbi.nlm.nih.gov/pubmed/15899953>
173. Collins SL, Moore RA, McQuay HJ, et al. Antidepressants and Anticonvulsants for Diabetic Neuropathy and Postherpetic Neuralgia: A Quantitative Systematic Review. *J Pain Symptom Manage* 2000 Dec;20(6):449-58.
<http://www.ncbi.nlm.nih.gov/pubmed/11131263>
174. Guay DR. Oxcarbazepine, topiramate, levetiracetam, and zonisamide: potential use in neuropathic pain. *Am J Geriatr Pharmacother* 2003 Sep;1(1):18-37.
<http://www.ncbi.nlm.nih.gov/pubmed/15555463>
175. Nicholson B. Gabapentin use in neuropathic pain syndromes. *Acta Neurol Scand* 2000 Jun;101(6): 359-71.
<http://www.ncbi.nlm.nih.gov/pubmed/10877151>
176. Spina E, Perugi G. Antiepileptic drugs: indications other than epilepsy. *Epileptic Disord* 2004 Jun;6(2):57-75.
<http://www.ncbi.nlm.nih.gov/pubmed/15246950>
177. Vranken JH, Dijkgraaf MG, Kruis MR, et al. Pregabalin in patients with central neuropathic pain: A randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain* 2008 May; 136(1-2):150-7.
<http://www.ncbi.nlm.nih.gov/pubmed/17703885>
178. Bennett MI, Simpson KH. Gabapentin in the treatment of neuropathic pain. *Palliat Med* 2004 Jan;18(1):5-11.
<http://www.ncbi.nlm.nih.gov/pubmed/14982201>
179. Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. *N Eng J Med* 2005 Mar;352(13):1324-34.
<http://www.ncbi.nlm.nih.gov/pubmed/15800228>
180. Frampton JE, Foster RH. Pregabalin in the treatment of postherpetic neuralgia. *Drugs* 2005;65(1); 111-8;discussion 119-20.
<http://www.ncbi.nlm.nih.gov/pubmed/15610058>
181. Ryvlin P. Defining success in clinical trials - profiling pregabalin, the newest AED. *Eur J Neurol* 2005 Nov;12 Suppl 4:12-21.
<http://www.ncbi.nlm.nih.gov/pubmed/16144536>
182. Galer BS, Jensen MP, Ma T, et al. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. *Clin J Pain* 2002 Sep-Oct;18(5):297-301.
<http://www.ncbi.nlm.nih.gov/pubmed/12218500>
183. Meier T, Wasner G, Faust M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. *Pain* 2003 Nov; 106(1-2):151-8.
<http://www.ncbi.nlm.nih.gov/pubmed/14581122>
184. Sindrup SH, Jensen TS. Pharmacologic treatment of pain in polyneuropathy. *Neurology* 2000 Oct; 55(7):915-20.
<http://www.ncbi.nlm.nih.gov/pubmed/11061244>
185. Fisher K, Hagen NA. Analgesic effect of oral ketamine in chronic neuropathic pain of spinal origin: a case report. *J Pain Symptom Manage* 1999 Jul;18(1):61-6.
<http://www.ncbi.nlm.nih.gov/pubmed/10439575>

186. Vranken JH, Dijkgraaf MG, Kruis MR, et al. Iontophoretic administration of S(+)-ketamine in patients with intractable central pain: a placebo-controlled trial. *Pain* 2005 Nov;118(1-2):224-31.
<http://www.ncbi.nlm.nih.gov/pubmed/16202531>
187. Enarson MC, Hayes H, Woodroffe MA. Clinical experiences with oral ketamine. *J Pain Symptom Manage* 1999 May;17(5):384-6.
<http://www.ncbi.nlm.nih.gov/pubmed/10355218>
188. Hocking G, Cousins MJ. Ketamine in chronic pain: an evidence-based review. *Anesth Analg* 2003 Dec;97(6):1730-9.
<http://www.ncbi.nlm.nih.gov/pubmed/14633551>
189. Himmelseher S, Durieux ME. Ketamine for perioperative pain management. *Anesthesiology* 2005 Jan;102(1):211-20.
<http://www.ncbi.nlm.nih.gov/pubmed/15618805>
190. Stubhaug A, Breivik H, Eide PK, et al. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol.Scand.* 1997 Oct;41(9):1124-32.
<http://www.ncbi.nlm.nih.gov/pubmed/9366932>
191. Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. *Anesth.Analg.* 2003 Mar;96(3):789-95.
<http://www.ncbi.nlm.nih.gov/pubmed/12598264>
192. Fromm GH, Terrence CF, Chatta AS. Baclofen in the treatment of trigeminus neuralgia: double blind study and long term follow up. *Ann Neurol* 1984 Mar;15(3):240-4.
<http://www.ncbi.nlm.nih.gov/pubmed/6372646>
193. Vranken JH, Troost D, de Haan P, et al. Severe toxic damage to the rabbit spinal cord after intrathecal administration of preservative-free S(+)-ketamine. *Anesthesiology* 2006 Oct;105(4):813-8.
<http://www.ncbi.nlm.nih.gov/pubmed/17006081>
194. Eisenach JC, De Kock M, Klimscha W. Alpha 2 adrenergic agonists for regional anesthesia: a clinical review of clonidine (1984-1995). *Anesthesiology* 1996 Sep;85(3):655-74.
<http://www.ncbi.nlm.nih.gov/pubmed/8853097>
195. Bride (eds). *Neural Blockade in Clinical Anesthesia and Management of Pain*, 3rd ed. 1998, Philadelphia: Lippincott-Raven, pp. 373-394.
196. Vranken JH, Zuurmond WW, de Lange JJ. Continuous brachial plexus lock as treatment for the Pancoast's syndrome. *Clin J Pain* 2000 Dec;16(4):327-33.
<http://www.ncbi.nlm.nih.gov/pubmed/11153789>
197. Eisenberg E, Carr DB, Chalmers TC. Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. *Anesth Analg* 1995 Feb;80(2):290-5.
<http://www.ncbi.nlm.nih.gov/pubmed/7818115>
198. Plancarte R, de Leon-Casasola O, El-Helaly M, et al. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. *Reg Anesth* 1997 Nov-Dec;22(6):562-8.
<http://www.ncbi.nlm.nih.gov/pubmed/9425974>
199. Kawamata M, Ishitani K, Ishikawa K, et al. Comparison between celiac plexus block and morphine treatment on quality of life in patients with pancreatic cancer pain. *Pain* 1996 Mar;64(3):597-602.
<http://www.ncbi.nlm.nih.gov/pubmed/8783327>
200. de Leon Casasola OA, Kent E, Lema MJ. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. *Pain* 1993 Aug;54(2):145-51.
<http://www.ncbi.nlm.nih.gov/pubmed/8233527>
201. Lillemo K, Cameron JL, Kaufman HS, et al. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. *Ann Surg* 1993 May;217(5):447-55; discussion 456-7.
<http://www.ncbi.nlm.nih.gov/pubmed/7683868>
202. Suleyman Ozyalcin N, Talu GK, Camlica H, et al. Efficacy of coeliac plexus and splanchnic nerve blockades in body and tail located pancreatic cancer pain. *Eur J Pain* 2004 Dec;8(6):539-45.
<http://www.ncbi.nlm.nih.gov/pubmed/15531222>
203. Ballantyne JC, Carwood CM. Comparative efficacy of epidural, subarachnoid, and intracerebroventricular opioids in patients with pain due to cancer. *Cochrane Database Syst Rev* 2005 Jan;(1):CD005178.
<http://www.ncbi.nlm.nih.gov/pubmed/15654707>

204. Smith TJ, Staats PS, Deer T, et al; Implantable Drug Delivery Systems Study Group. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol* 2002 Oct;20(19):4040-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12351602>
205. Deer TR, Caraway DL, Kim CK, et al. Clinical experience with intrathecal bupivacaine in combination with opioid for the treatment of chronic pain related to failed back surgery syndrome and metastatic cancer pain of the spine. *Spine J* 2002 Jul-Aug;2(4):274-8.
<http://www.ncbi.nlm.nih.gov/pubmed/14589479>
206. van Dongen RTM, Crul BJP, von Egmond J. Intrathecal coadministration of bupivacaine diminishes morphine dose progression during longterm intrathecal infusion in cancer patients. *Clin J Pain* 1999 Sep;15(3):166-72.
<http://www.ncbi.nlm.nih.gov/pubmed/10524468>
207. Quigley C. Opioid switching to improve pain relief and drug tolerability. *Cochrane Database of Systematic Reviews* 2004, issue 3, art. no.: CD004847.
<http://www.ncbi.nlm.nih.gov/pubmed/15266542>
208. Zeppetella G, Ribeiro MDC. Opioids for the management of breakthrough (episodic) pain in cancer patients. *Cochrane Database of Systematic Reviews* 2006 Jan, issue 1, art. no.: CD004311.
<http://www.ncbi.nlm.nih.gov/pubmed/16437482>
209. Mercadante S. Managing breakthrough pain. *Curr Pain Headache Rep* 2011 Aug;15(4):244-9.
<http://www.ncbi.nlm.nih.gov/pubmed/21424673>
210. Haugen DF, Hjermstad MJ, Hagen N, et al. Assessment and classification of cancer breakthrough pain: a systematic literature review. *Pain* 2010 Jun;149(3):476-82.
<http://www.ncbi.nlm.nih.gov/pubmed/20236762>
211. Nanton V, Docherty A, Meystre C, et al. Finding a pathway: information and uncertainty along the prostate cancer patient journey. *Br J Health Psychol.* 2009 Sep;14(Pt 3):437-58.
<http://www.ncbi.nlm.nih.gov/pubmed/18718111>
212. Thaxton L, Emshoff JG, Guessous O. Prostate cancer support groups: a literature review. *Oncol* 2005;23(1):25-40
<http://www.ncbi.nlm.nih.gov/pubmed/16492642>
213. Saunders C. The philosophy of terminal cancer care. *Ann Acad Med Singapore.* 1987 Jan;16(1):151-4.
<http://www.ncbi.nlm.nih.gov/pubmed/3592584>
214. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev* 2012 Nov;11:CD006145.
<http://www.ncbi.nlm.nih.gov/pubmed/23152233>
215. Segal RJ, Reid RD, Courneya KS, et al. Resistance Exercise in Men Receiving Androgen Deprivation Therapy for Prostate Cancer. *J Clin Oncol* 2003 May;21(9):1653-9.
<http://www.ncbi.nlm.nih.gov/pubmed/12721238>
216. Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, et al. The effect of physical exercise on cancer related fatigue treatment: a meta-analysis of randomised controlled trials. *Clin Oncol (R Coll Radiol).* 2010 Apr;22(3):208-21.
<http://www.ncbi.nlm.nih.gov/pubmed/20110159>

A.3 POSTOPERATIVE PAIN MANAGEMENT

A.3.1 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).

A.3.2 Importance of effective postoperative pain management

The physiological consequences of postoperative pain are shown in Table 16. 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 16: 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 |

A.3.2.1 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).

A.3.3 Pre- and postoperative pain management methods

A.3.3.1 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).

A.3.3.2 **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).

A.3.3.3 **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).

A.3.3.4 **Systemic analgesic techniques**

A.3.3.4.1 **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 4, section 3.2.

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.

A.3.3.4.2 **Paracetamol**

Paracetamol (acetaminophen) is a relatively safe and effective antipyretic and analgesic for mild to moderate postoperative pain, although a risk of rare but reactions skin reactions have been reported by the U.S. Food and Drug Administration (FDA) (<http://www.fda.gov/drugs/drugsafety/ucm363041.htm>). 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 5, Section 3.2.

A.3.3.4.3 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).

A.3.3.4.4 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 6 and 7, section 3.2.

A.3.3.4.5 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 17).

Table 17: 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 | - |

Opioids adverse effects are:

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

A.3.3.4.6 Adjuncts to postoperative analgesia

Adjuncts to postoperative analgesia in low doses, such as ketamine, α 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).

A.3.3.5 Regional analgesic techniques

A.3.3.5.1 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.

A.3.3.5.2 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 18).

Table 18: 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.

A.3.3.5.3 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 19).

Table 19: Typical PCEA dosing schemes

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

A.3.3.5.4 Neural blocks

Local anaesthetic blocks (intermittent and continuous) can be used after urological surgical operations to supplement postoperative analgesia (43) (LE: 2a) (Table 20).

Table 20: 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 |

A.3.3.5.5 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).

A.3.3.5.6 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).

A.3.3.6 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).

A.3.3.7 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 (49-51) (LE: 2b). Improved pain control can lead to shorter hospitalisation and fewer unscheduled readmissions after day surgery (52) (LE: 3).

A.3.3.8 Recommendations postoperative pain management

| Recommendation | LE | GR |
|---|----|----|
| Preoperative assessment and preparation of patients allow more effective pain management. | 1a | A |
| Adequate postoperative pain assessment can lead to more effective pain control and fewer complications. | 2a | B |
| 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 |
| 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 |
| 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 |
| 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 |
| Epidural analgesia, especially PCEA, provides superior postoperative analgesia, reducing complications and improving patient satisfaction, and is therefore preferable to systemic techniques (41). | A | 1b |

A.3.4 References

1. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an update report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2004 Jun;100(6):1573-81. <http://www.ncbi.nlm.nih.gov/pubmed/15166580>
2. Rosenquist RW, Rosenberg J; United States Veterans Administration. Postoperative pain guidelines. *Reg Anesth Pain Med* 2003 Jul-Aug;28(4):279-88. <http://www.ncbi.nlm.nih.gov/pubmed/12945020>
3. Apfelbaum JL, Chen C, Mehta SS, et al. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg* 2003 Aug;97(2):534-40. <http://www.ncbi.nlm.nih.gov/pubmed/12873949>
4. Neugebauer EA, Wilkinson RC, Kehlet H, et al; PROSPECT Working Group. PROSPECT: a practical method for formulating evidence-based expert recommendations for the management of postoperative pain. *Surg Endosc* 2007 Jul;21(7):1047-53. <http://www.ncbi.nlm.nih.gov/pubmed/17294309>
5. Pavlin DJ, Chen C, Penaloza DA, et al. Pain as a factor complicating recovery and discharge after ambulatory surgery. *Anesth Analg* 2002 Sep;95(3):627-34. <http://www.ncbi.nlm.nih.gov/pubmed/12198050>
6. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology* 2000 Oct;93(4):1123-33. <http://www.ncbi.nlm.nih.gov/pubmed/11020770>
7. Wu CL, Naqibuddin M, Rowlingson AJ, et al. The effect of pain on health-related quality of life in the immediate postoperative period. *Anesth Analg* 2003 Oct;97(4):1078-85. <http://www.ncbi.nlm.nih.gov/pubmed/14500161>
8. Kehlet H, Holte K. Effect of postoperative analgesia on surgical outcome. *Br J Anaesth* 2001 Jul; 87(1):62-72. <http://www.ncbi.nlm.nih.gov/pubmed/11460814>
9. Wilmore DW, Kehlet H. Management of patients in fast track surgery. *BMJ* 2001 Feb;332:473-6. <http://www.ncbi.nlm.nih.gov/pubmed/11222424>
10. Macrae WA. Chronic pain after surgery. *Br J Anaesth* 2001 Jul;87(1):88-98. <http://www.ncbi.nlm.nih.gov/pubmed/11460816>
11. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000 Jul;85(1):109-17. <http://www.ncbi.nlm.nih.gov/pubmed/10927999>
12. Sydow FW. The influence of anesthesia and postoperative analgesic management of lung function. *Acta Chir Scand Suppl* 1989;550:159-65. <http://www.ncbi.nlm.nih.gov/pubmed/2652967>
13. Wartier DC, Pagel PS, Kersten JR. Approaches to the prevention of perioperative myocardial ischemia. *Anesthesiology* 2000 Jan;92(1):253-9. <http://www.ncbi.nlm.nih.gov/pubmed/10638923>
14. Rosenfeld BA. Benefits of regional anesthesia on thromboembolic complications following surgery. *Reg Anesth* 1996 Nov-Dec;21(6 Suppl):9-12. <http://www.ncbi.nlm.nih.gov/pubmed/8956414>
15. Livingston EH, Passaro EP Jr. Postoperative ileus. *Dig Dis Sci* 1990 Jan;35(1):121-32. <http://www.ncbi.nlm.nih.gov/pubmed/2403907>
16. Herr K. Pain assessment in cognitively impaired older adults. *Am J Nurs* 2002 Dec;102(12):65-7. <http://www.ncbi.nlm.nih.gov/pubmed/12473932>
17. Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In *Handbook of Pain Assessment*. Turk DC and Melzack R, eds. NY: Guilford Press, 1992, pp. 135-151.
18. Kissin I. Preemptive analgesia. *Anesthesiology* 2000 Oct;93(4):1138-43. <http://www.ncbi.nlm.nih.gov/pubmed/11020772>
19. Kissin I. Preemptive analgesia. Why its effect is not always obvious. *Anesthesiology* 1996 May;84(5):1015-19. <http://www.ncbi.nlm.nih.gov/pubmed/8623993>
20. White PF. The role of non-opioid analgesic techniques in the management of pain after ambulatory surgery. *Anesth Analg* 2002 Mar;94(3):577-85. <http://www.ncbi.nlm.nih.gov/pubmed/11867379>
21. Souter AJ, Fredman B, White PF. Controversies in the perioperative use of nonsteroidal anti-inflammatory drugs. *Anesth analg* 1994 Dec;79(6):1178-90. <http://www.ncbi.nlm.nih.gov/pubmed/7978444>

22. Brose WG, Cohen SE. Oxyhemoglobin saturation following cesarean section in patients receiving epidural morphine, PCA, or IM meperidine analgesia. *Anesthesiology* 1989 Jun;70(6):948-53.
<http://www.ncbi.nlm.nih.gov/pubmed/2729636>
23. Fitzgerald GA. Cardiovascular pharmacology of nonselective nonsteroidal anti-inflammatory drugs and coxibs: clinical considerations. *Am J Cardiol* 2002 Mar;89(6A):26D-32D.
<http://www.ncbi.nlm.nih.gov/pubmed/11909558>
24. Bresalier RS, Sandler RS, Quan H, et al. Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005 Mar;352(11):1092-102.
<http://www.ncbi.nlm.nih.gov/pubmed/15713943>
25. Schug SA, Sidebotham DA, Mc Guinness M, et al. Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain. *Anesth Analg* 1998 Aug;87(2):368-72.
<http://www.ncbi.nlm.nih.gov/pubmed/9706932>
26. Bannwarth B, Demotes-Mainard F, Schaeferbeke T, et al. Central analgesic effects of aspirin-like drugs. *Fundam Clin Pharmacol* 1995;9(1):1-7.
<http://www.ncbi.nlm.nih.gov/pubmed/7768482>
27. Hedenmalm K, Spigset O. Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole). *Eur J Clin Pharmacol* 2002 Jul;58(4):265-74.
<http://www.ncbi.nlm.nih.gov/pubmed/12136373>
28. Maj S, Centkowski P. A prospective study of the incidence of agranulocytosis and aplastic anemia associated with the oral use of metamizole sodium in Poland. *Med Sci Monit* 2004 Sep;10(9):PI93-5.
<http://www.ncbi.nlm.nih.gov/pubmed/15328493>
29. McQuay H, Moore A, Justins D. Treating acute pain in hospital. *BMJ* 1997 May;314(7093):1531-5.
<http://www.ncbi.nlm.nih.gov/pubmed/9183203>
30. Ballantyne JC, Carr DB, Chalmers TC, et al. Postoperative patient controlled analgesia: meta-analyses of initial randomized control trials. *J Clin Anesth* 1993 May-Jun;5(3):182-93.
<http://www.ncbi.nlm.nih.gov/pubmed/8318237>
31. Walder B, Schafer M, Henzi I, et al. Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review. *Acta Anaesthesiol Scand* 2001 Aug;45(7):795-804.
<http://www.ncbi.nlm.nih.gov/pubmed/11472277>
32. Lui F, Ng KF. Adjuvant analgesics in acute pain. *Expert Opin Pharmacother*. 2011 Feb;12(3):363-85.
<http://www.ncbi.nlm.nih.gov/pubmed/21254945>
33. Vadivelu N, Mitra S, Narayan D. Recent advances in postoperative pain management. *Yale J Biol Med* 2010 Mar;83(1):11-25.
<http://www.ncbi.nlm.nih.gov/pubmed/20351978>
34. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. *Anesth Analg*. 2004 Aug;99(2):482-95
<http://www.ncbi.nlm.nih.gov/pubmed/15271729>
35. Wang C, Slikker W Jr. Strategies and experimental models for evaluating anesthetics: effects on the developing nervous system. *Anesth Analg*. 2008 Jun;106(6):1643-58.
<http://www.ncbi.nlm.nih.gov/pubmed/18499593>
36. Farmery AD, Wilson-MacDonald J. The analgesic effect of epidural clonidine after spinal surgery: a randomized placebo-controlled trial. *Anesth Analg*. 2009 Feb;108(2):631-4.
<http://www.ncbi.nlm.nih.gov/pubmed/19151300>
37. Chan AK, Cheung CW, Chong YK. Alpha-2 agonists in acute pain management. *Expert Opin Pharmacother*. 2010 Dec;11(17):2849-68.
<http://www.ncbi.nlm.nih.gov/pubmed/20707597>
38. Clivatti J, Sakata RK, Issy AM. Review of the use of gabapentin in the control of postoperative pain. *Rev Bras Anestesiol*. 2009 Jan-Feb;59(1):87-98.
<http://www.ncbi.nlm.nih.gov/pubmed/19374220>
39. Zhang J, Ho KY, Wang Y. Br J Anaesth. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. *Br J Anaesth*. 2011 Apr;106(4):454-62.
<http://www.ncbi.nlm.nih.gov/pubmed/21357616>
40. Lonnqvist PA, Morton NS. Paediatric day-case anaesthesia and pain control. *Curr Opin Anaesthesiol*. 2006 Dec;19(6):617-21
<http://www.ncbi.nlm.nih.gov/pubmed/17093365>

41. Mann C, Pouzeratte Y, Boccara G, et al. Comparison of intravenous or epidural patient-controlled Analgesia in the elderly after major abdominal surgery. *Anesthesiology* 2000 Feb;92(2):433-41.
<http://www.ncbi.nlm.nih.gov/pubmed/10691230>
42. Yardeni IZ, Shavit Y, Bessler H, et al. Comparison of postoperative pain management techniques on endocrine response to surgery: a randomised controlled trial. *Int J Surg* 2007 Aug;5(4):239-43.
<http://www.ncbi.nlm.nih.gov/pubmed/17660130>
43. Liu SS, Salinas FV. Continuous plexus and peripheral nerve blocks for postoperative analgesia. *Anesth Analg* 2003 Jan;96(1):263-72.
<http://www.ncbi.nlm.nih.gov/pubmed/12505964>
44. Mulroy MF, Burgess FW, Emanuelsson BM. Ropivacaine 0.25% and 0.5%, but not 0.125% provide effective wound infiltration analgesia after outpatient hernia repair, but with sustained plasma drug levels. *Reg Anesth Pain Med* 1999 Mar-Apr;24(2):136-41.
<http://www.ncbi.nlm.nih.gov/pubmed/10204899>
45. Bianconi M, Ferraro L, Ricci R, et al. The pharmacokinetics and efficacy of ropivacaine continuous wound instillation after spine fusion surgery. *Anesth Analg* 2004 Jan;98(1):166-72.
<http://www.ncbi.nlm.nih.gov/pubmed/14693613>
46. Bianconi M, Ferraro L, Traina GC, et al. Pharmacokinetics and efficacy of ropivacaine continuous wound instillation after joint replacement surgery. *Br J Anaesth* 2003 Dec;91(6):830-5.
<http://www.ncbi.nlm.nih.gov/pubmed/14633754>
47. Gupta S, Maheshwari R, Dulara SC. Wound instillation with 0.25% bupivacaine as continuous infusion following hysterectomy. *Middle East J Anesthesiol* 2005 Oct;18(3):595-610.
<http://www.ncbi.nlm.nih.gov/pubmed/16381265>
48. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg* 2002 Jun; 183(6):630-41.
<http://www.ncbi.nlm.nih.gov/pubmed/12095591>
49. Miaskowski C, Crews J, Ready LB, et al. Anesthesia-based pain services improve the quality of postoperative pain management. *Pain* 1999 Mar;80(1-2):23-9.
<http://www.ncbi.nlm.nih.gov/pubmed/10204714>
50. Rawal N. 10 years of acute pain services: achievements and challenges. *Reg Anesth Pain Med* 1999 Jan-Feb;24(1):68-73.
<http://www.ncbi.nlm.nih.gov/pubmed/9952098>
51. Stamer UM, Mpasios N, Stuber F, et al. A survey of acute pain services in Germany and a discussion of international survey data. *Reg Anesth Pain Med* 2002 Mar-Apr;27(2):125-31.
<http://www.ncbi.nlm.nih.gov/pubmed/11915057>
52. Fancourt-Smith PF, Hornstein J, Jenkins LC. Hospital admissions from the Surgical Day Case Centre of Vancouver General Hospital 1977-1987. *Can J Anesth* 1990 Sep;37(6):699-704.
<http://www.ncbi.nlm.nih.gov/pubmed/2208546>

6. 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 |
| ¹³¹ J-MIBG | ¹³¹ J-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 |
| ¹⁵³ Sm | samarium-153 |
| ⁸⁹ Sr | 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

All members of the General Pain and Palliative Care Guidelines expert panel have provided disclosure statements on all relationships that they have and that might be perceived to be a potential source of conflict of interest. This information is publicly accessible through the European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

