



European Association of Urology

GUIDELINES ON PAIN MANAGEMENT

**F. Francesca (chair), P. Bader, D. Echte, F. Giunta, J. Williams
M. Fall (chair), A. Baranowski, C. Fowler, V. Lepinard, J. Malone-Lee,
E.J. Messelink, F. Oberpenning, J.L. Osborne, S. Schumacher**

TABLE OF CONTENTS

PAGE

1	GENERAL INTRODUCTION	6
1.1	Background	6
1.1.1	Definition of pain	6
1.1.2	Nociception and innervation	6
1.1.3	Innervation of the urogenital system	8
1.1.4	References	9
1.2	Pain evaluation and measurement	12
1.2.1	Pain evaluation	12
1.2.2	Pain measurement	12
1.2.3	References	13
2	CANCER PAIN MANAGEMENT	16
2.1	Classification of cancer pain	16
2.1.1	References	16
2.2	General management of cancer pain	16
2.2.1	Principles in cancer pain management	16
2.2.2	Primary analgesic therapies	18
2.2.3	Pharmacotherapy	18
2.2.4	Systemic analgesic pharmacotherapy	18
2.2.4.1	Nonopioid analgesics	19
2.2.4.2	Opioid analgesics	19
2.2.4.3	Opioid administration	19
2.2.4.4	Adjuvant analgesics	22
2.2.5	Transcutaneous electrical nerve stimulation (TENS)	24
2.2.6	Invasive analgesic technique	24
2.2.7	Physical / psychological therapy	25
2.2.8	Conclusions	25
2.2.9	References	25
2.3	Pain management in prostate cancer patients	29
2.3.1	Clinical presentation	29
2.3.2	Pain due to local impairment	29
2.3.2.1	Soft-tissue and hollow-viscus invasion	29
2.3.3	Pain due to metastases	30
2.3.3.1	Bone metastases	30
2.3.3.2	Spinal cord compression	32
2.3.3.3	Hepatic invasion	32
2.3.4	Pain due to cancer treatment	32
2.3.4.1	Acute pain associated with hormonal therapy	32
2.3.4.2	Chronic pain associated with hormonal therapy	32
2.3.5	Conclusions	32
2.3.6	References	34
2.4	Pain management in transitional cell carcinoma patients	36
2.4.1	Clinical presentation	36
2.4.2	Pain due to local impairment	36
2.4.3	Pain due to metastases	37
2.4.4	References	37
2.5	Pain management in renal cell carcinoma patients	38
2.5.1	Clinical presentation	38
2.5.2	Pain due to local impairment	38
2.5.3	Pain due to metastases	38
2.5.4	References	39
2.6	Pain management in adrenal carcinoma patients	40
2.6.1	Malignant pheochromocytoma	40
2.6.2	Adrenocortical carcinomas	40
2.6.3	References	40

2.7	Pain management in penile cancer patients	41
2.7.1	Clinical presentation	41
2.7.2	Pain due to local impairment	41
2.7.3	Pain due to metastases	42
2.7.4	Conclusions	42
2.7.5	References	42
2.8	Pain management in testicular cancer patients	42
2.8.1	Clinical presentation	42
2.8.2	Pain due to local impairment	42
2.8.3	Pain due to metastases	42
2.8.4	References	42
2.9	Recommendations at a glance	43
3	POST-OPERATIVE PAIN MANAGEMENT	43
3.1	Background	43
3.2	Importance of effective postoperative pain control	43
3.3	Methods used in treating postoperative pain	44
3.3.1	Development of Acute Pain Teams	44
3.3.2	Pain assessment	45
3.3.3	Preoperative cognitive -behavioural interventions	45
3.3.4	Postoperative analgesic drugs	46
3.3.5	Pain prevention	49
3.4	Specific pain treatment after different urological operations	50
3.4.1	Extracorporeal Shock Wave Lithotripsy	50
3.4.2	Endoscopic procedures	50
3.4.3	Open surgery	51
3.4.4	References	53
3.5	Table of opioid equi-analgesic doses	55
3.6	Levels of evidence and grades of recommendation	56
3.6.1	References	56
4.	ABBREVIATIONS USED IN THE TEXT	57
5	CHRONIC PELVIC PAIN	
5.1	Background	4
5.1.1	Introduction	4
5.2	Definitions of chronic pelvic pain and terminology	4
5.3	Classification of chronic pelvic pain syndromes	6
	Appendix - IASP classification as relevant to chronic pelvic pain	7
5.4	References	8
5.5	Chronic prostatitis	8
5.5.1	Introduction	8
5.5.2	Definition	8
5.5.3	Pathogenesis	8
5.5.4	Diagnosis	9
5.5.5	Treatment	9
5.6	Interstitial Cystitis	10
5.6.1	Introduction	10
5.6.2	Definition	10
5.6.3	Pathogenesis	11
5.6.4	Epidemiology	12
5.6.5	Association with other diseases	13
5.6.6	Diagnosis	13
5.6.7	IC in children and males	13
5.6.8	Medical treatment	14
5.6.9	Intravesical treatment	15
5.6.10	Interventional treatments	16
5.6.11	Alternative and complementary treatments	17
5.6.12	Surgical treatment	18

5.7	Scrotal Pain	22
5.7.1	Introduction	22
5.7.2	Innervation of the scrotum and the scrotal contents	22
5.7.3	Clinical examination	22
5.7.4	Differential Diagnoses	22
5.7.5	Treatment	23
5.8	Urethral syndrome	23
5.9	References	24
6.	PELVIC PAIN IN GYNAECOLOGICAL PRACTICE	36
6.1	Introduction	36
6.2	Clinical history	36
6.3	Clinical examination	36
6.3.1	Investigations	36
6.4	Dysmenorrhoea	36
6.5	Infection	37
6.5.1	Treatment	37
6.6	Endometriosis	37
6.6.1	Treatment	37
6.7	Gynaecological malignancy	37
6.8	Injuries related to childbirth	37
6.9	Conclusion	38
6.10	References	38
7.	NEUROLOGICAL ASPECTS	38
7.1	Introduction	38
7.2	Pudendal nerve entrapment	39
7.3	Other neurogenic conditions	39
7.4	References.	39
8.	PELVIC FLOOR FUNCTION AND DYSFUNCTION	40
8.1	Introduction	40
8.2	Function	40
8.3	Dysfunction	40
8.4	Therapy	40
8.5	References	41
9.	PSYCHOLOGICAL FACTORS IN CHRONIC PELVIC PAIN	41
9.1	Introduction	41
9.2	Models of pain	41
9.2.1	Biomedical model	41
9.2.2	Psychodynamic model	41
9.2.3	Biopsychosocial model	41
9.2.4	Motoric pain behaviour	42
9.2.5	Cognitive processes	42
9.2.6	Psychophysiological reactivity	42
9.3	Chronic Pelvic Pain in a biopsychosocial model	42
9.4	Psychiatric disorders	42
9.4.1	Somatoform pain disorders	42
9.4.2	Depression	42
9.5	Abuse and Chronic Pelvic Pain	43
9.6	References	43

10.	GENERAL TREATMENT OF CHRONIC PELVIC PAIN	44
10.1	Analgesia	44
10.1.1	Non-acidic antipyretic analgesics	44
10.1.2	Acidic antipyretic analgesics	44
10.1.3	Guidelines for use	44
10.1.4	Opioids	44
10.1.5	Guidelines for use	45
10.1.6	Opioid like agents	46
10.1.7	Neuropathic analgesics	46
10.2	References	49
10.3	Nerve Blocks	51
10.4	Transcutaneous Electrical Nerve Stimulation (TENS)	52
10.4.1	Results of suprapubic TENS in IC	52
10.5	Sacral neuromodulation in pelvic pain syndromes	53
10.6	References	53
11.	LIST OF ABBREVIATIONS	56

1. GENERAL INTRODUCTION

1.1 Background

1.1.1 Definition of pain (WHO)

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

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

The International Association for the Study of Pain (IASP) has proposed a working definition: Pain is “an unpleasant sensory and emotional experience associated with either actual or potential tissue damage, or described in terms of such damage” (1).

Although we use the term of pain to define all sensations that hurt or are unpleasant, actually two quite different kinds of pain exist. The first is termed nociceptive, because of its direct link with noxious stimuli, or physiological because it is a key component of the body's normal defence mechanisms, protecting the body from a potentially hostile external environment by initiating reflex avoidance strategies. This pain is associated with tissue damage or inflammation, so is also called inflammatory pain. The second is termed neuropathic and results from a lesion to the peripheral or central nervous systems.

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

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

1.1.2 Nociception and innervation

Neural mechanisms of nociception

Structure of the peripheral neural apparatus

One of the vital functions of the nervous system is to provide information about the occurrence or threat of injury. The sensation of pain, by its inherent aversive nature, contributes to this function. The peripheral neural apparatus that responds to noxious (injurious or potentially injurious) stimuli provides a signal to alert the organism of potential injury. This apparatus must respond to the multiple energy forms that produce injury (such as heat, mechanical and chemical stimuli) and provide information to the central nervous system regarding the location and intensity of noxious stimuli.

The physiological pain is an important and adaptive element of the normal nervous system which, clinically, only needs to be temporarily suppressed or disabled during surgical procedures where damage is deliberately produced.

The protective mechanism operates as a result of the presence of a specific set of primary sensory neurones called nociceptors.

Sensory fibers

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

Nociceptors

Nociceptors are sub-classified with respect to three criteria:

1. Unmyelinated (C-fibre) versus myelinated (A-fibre) parent nerve fibre
2. Modalities of stimulation that evoke a response
3. Response characteristics.

Chemical sensitivity of nociceptors

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

therefore are directly involved in producing pain, while others lead to a sensitization of the nociceptor response to natural stimuli and therefore play a role in primary hyperalgesia.

Efferent functions of nociceptors

Cutaneous nerves have more than a fourfold higher number of small diameter A - and C-fibres than the larger, myelinated A - fibres (2). Nociceptors, apart from signalling pain, also serve other regulatory and trophic functions (3,4). An efferent role for nociceptors was suggested years ago by Lewis (5) to account for the flare that surrounds an acute injury. Experimental evidence suggests that small-diameter afferent fibres may have several effector functions such as regulation of blood flow and vascular permeability in somatic and visceral tissues; trophic functions, such as maintenance and repair of skin integrity; and immunological processes, such as emigration of leucocytes at sites of tissue injury (6,7). Afferent fibres are also considered to play a role in the regulation of activity of autonomic ganglia and visceral smooth muscles (8-10). Antidromic stimulation of dorsal roots induces plasma extravasation, not only in cutaneous tissues, but also in a wide variety of internal organs (11). The principal lines of evidence indicating that afferent neurons are involved in antidromic vasodilation, neurogenic inflammation and axon reflex flare are:

1. The responses are abolished by surgical or chemical ablation (e.g. with capsaicin) of the sensory innervation of the involved tissues (12-15).
2. The responses occur independently of the autonomic nervous system (16,17).

The fibres involved in the reflex vasodilation are polymodal nociceptive C-fibres that are capsaicin-sensitive (18,19). Low-firing frequencies (<1 Hz) in C-fibres can generate significant vasodilation (20). Recent reports indicate that stimulation of A δ -fibres may also result in a flare response (21).

Deep pain

Behavioural and clinical studies indicate that there are important differences between cutaneous and deep pain. For example, unlike cutaneous pain, deep pain is diffuse and poorly localized. Deep pain may be associated with strong autonomic responses such as sweating and changes in heart rate, blood pressure and respiration. In addition, deep pain may be produced by stimuli that are not tissue damaging, e.g. distension of bowel and bladder (22,23). Finally, visceral pains may be associated with referred pain as well as cutaneous and deep tissue hyperalgesia.

The role of the dorsal horn

The nociceptors terminate in a highly ordered way in the dorsal horn of the spinal cord with the thinly myelinated A-delta ending in laminae I and V and the unmyelinated C-fibres in lamina II. These high threshold sensory fibres activate a large number of second order interneurons and projection neurons in the spinal cord.

The activity generated by nociceptor input is transferred, after complex active processing in the dorsal horn, directly, or via brainstem relay nuclei, to the thalamus and then onto the cortex, where the sensation of pain is generated.

Parallel outputs from the dorsal horn go to the ventral horn and activate flexor motor neurons generating the withdrawal flexion reflex, so that both the sensation of physiological pain and the flexion withdrawal reflex occur together.

This consideration led Sherrington in his pioneering studies on pain to conclude that "pain seems the psychological adjunct to protective reflex".

Brain areas involved in nociception and pain

Numerous brain areas are involved in the various components of pain.

Nociceptive messages become more and more difficult to follow as they travel further along the central nervous system (CNS), and numerous brain areas are involved in the various components of pain. According to Melzack & Casey (24), these components include:

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

Modulation of pain

The transmission of pain from peripheral tissues through the spinal cord to the higher centres of the brain is clearly not a passive simple process using exclusive pathways. Rather, circuitry within the spinal cord has the potential to alter, dramatically, the relation between the stimulus and the response to pain in an individual.

The sensation of pain is subject not only to modulation during its ascending transmission from the periphery to the cortex but also to segmental modulation and descending control from higher centres.

This control is manifested via pathways that originate at the level of the cortex, the thalamus and the brainstem (the periaqueductal grey, raphe nuclei and locus coeruleus/subcoeruleus complex).

The main neurotransmitters implicated in descending pain control are serotonin, noradrenaline and the endogenous opioids, although others also play a role.

1.1.3 Innervation of the urogenital system

The differences between mechanisms of nociception in the skin and viscera are emphasized by studies on the response properties of visceral afferents from the urinary tract. There is ongoing controversy as to whether visceral pain is mediated by a specific subgroup of nociceptive fibres (specificity theory) or by the spatial and temporal patterns of discharges in non-specific afferent fibres (pattern theory) (25-27).

Ureter

There have been only a few studies on the properties of primary afferent neurons innervating the ureter (28-30). Ureteric afferents were thinly myelinated or unmyelinated, and responded to direct probing of a limited area of tissue. Two populations of afferents were distinguished by Cervero & Sann (30). The first responded to contractions of the ureter and could also be excited by low levels of distension (average threshold 8 mmHg). They appeared to encode levels of distension throughout and beyond the physiological range. The second group did not respond to peristaltic contractions of the ureter, but they could be excited by distension with a wide range of thresholds. The average stimulus-response curves showed a monotonic rise of discharge with increasing pressure. The large majority appeared to have low levels of ongoing activity. The authors claimed that this second group of neurons could be considered a class of specific visceral nociceptor, and suggested that the ongoing activity and relatively low-pressure thresholds seen in some afferents might be due to the anoxic state of the *in vitro* preparation. When ureters were perfused intraluminally, higher pressure thresholds were seen, although some at least still appeared to respond to distension to only 10 mmHg (30). The contraction-insensitive afferents were noted to respond to chemicals such as bradykinin and potassium.

Urinary bladder

Two distinct groups of afferent fibres capable of signalling noxious stimuli have been identified in the urinary bladder. Most visceral afferents from the urinary bladder are unmyelinated fibres, although a population of myelinated A - fibres is also present (31). The majority of visceral primary afferents from the bladder, urethra, and reproductive and other pelvic organs encode for both noxious and non-noxious stimuli (31-34). A subset of the unmyelinated fibres accurately encode intravesical pressure changes in the noxious range (31). In addition, a subpopulation of C-fibre visceral afferents has been identified that is not mechanically sensitive, but is excited by chemical irritants (31,36,37). Reflexes evoked by urinary bladder distention in rats are increased by mucosal inflammation. Thus, pain originating from the bladder may be intensified by the presence of inflammation (31,36,38,39).

Graded distension of the healthy urinary bladder in humans initially gives rise to a sensation of fullness and eventually pain as volume increases and intravesical pressure exceeds about 25-35 mmHg (40-44). In the inflamed bladder, the sensations during bladder emptying become unpleasant and painful. The qualitative change in the nature of sensations with cystitis suggests that new viscerosensory mechanisms may emerge with inflammation, induced experimentally with irritant chemicals such as turpentine, xylene and mustard oil (45-47). Nearly all afferents are small myelinated or unmyelinated, and travel with sympathetic (hypogastric) or parasympathetic (pelvic) nerves. Some exhibit a low level of ongoing discharge when the bladder is empty. Distension excited mainly thin myelinated afferents, with pressure thresholds corresponding to the values where humans report the first sensation of fullness. Nearly all units were activated by the intraluminal pressures reached during normal, non-painful micturition. All myelinated afferents responded in a graded fashion to increases of the intravesical pressure throughout the innocuous and into the suprphysiological, noxious, pressure range (28,48,49). These afferents reflected the magnitude and the temporal profile of intravesical pressure changes with high fidelity. There are only a few afferents that could be called specific nociceptors in the bladder, and which would signal only painful levels of distension at an intravesical pressure of 50 mmHg (50,51).

The activation of a numerically significant population of initially unresponsive afferents indicates that peripheral afferent mechanisms encoding pain from pelvic viscera are highly malleable and are strongly affected by the state of the tissue. These peripheral changes are obviously likely to be important for signalling pain and discomfort in inflammatory conditions.

Male reproductive organs

Free nerve endings derived from A - or C-fibres are abundant throughout the glans penis. The two fibre types

associated with these endings appear to be slowly adapting low-threshold stretch receptors and high-threshold mechanoreceptors (52,53).

The sensory innervation of the testes (dog model) show that more than 95% of the fibres of the superior spermatic nerve are unmyelinated with the great majority having polymodal properties (i.e. responding to mechanical, chemical and thermal stimuli) (54). Responses of the polymodal receptor are augmented by application of prostaglandins E2 and I2 (55) and of bradykinin acting via a B2 receptor (56). The prostaglandins are less potent in their ability to excite nociceptors as compared to their efficacy as potentiators of the response to bradykinin (55). The effects of analgesic substances on the testicular polymodal nociceptors may result from Ca²⁺ dependent membrane surface potential changes (57).

Afferent fibres form a homogeneous group with polymodal receptors in testis and/or epididymis. This applied to both myelinated and unmyelinated afferents. They could be excited in a slowly adapting fashion to stimuli applied to one or more sensitive spots, each only a millimetre or so in diameter. The threshold for activation varied over a wide range but 80% of afferents responded to mechanical stimuli of less than 17 g/mm². The afferents were polymodal in the sense that they responded to other forms of stimulation, notably algescic chemicals and heating. Bradykinin and hypertonic saline solutions were effective stimuli for the afferents. Prostaglandins did not excite but sensitised the afferents to other stimuli (58).

1.1.4 REFERENCES

- 1 **Foley KM, Posner J.B.**
Pain and its management. In: Cecil Textbook of medicine. 18th edition. W. B. Saunders Company: 1988:104-112.
- 2 **Ochoa J, Mair WGP**
The normal sural nerve in man. In: Ultrastructure and numbers of fibres and cells. Acta Neuropathologica (Berlin) 1969; 13:197-216.
- 3 **Kruger L**
Morphological features of thin sensory afferent fibers: a new interpretation of 'nociceptor' function. In: Hamann W, Iggo A (eds) Progress in brain research. Elsevier: Amsterdam, 1988; p 253-257.
- 4 **McMahon SB, Koltzenburg M**
Novel classes of nociceptors: Beyond Sherrington. Trends in Neuroscience. 1990 13:199-201.
- 5 **Lewis T**
The nocifensor system of nerves and its reactions. Br Med J 1937; 431-435.
- 6 **Nilsson J, von Euler AM, Dalsgaard C-J**
Stimulation of connective tissue cell growth by substance P and substance K. Nature 1985; 315:61-63.
- 7 **Kjartansson J, Dalsgaard CJ, Jonsson CE**
Decreased survival of experimental critical flaps in rats after sensory denervation with capsaicin. Plastic and Reconstructive Surgery 1987; 79:218-221.
- 8 **Szolcsányi J**
Capsaicin and neurogenic inflammation: history and early findings. In: Chahl L A, Szolcsányi J, Lembeck F (eds) Antidromic vasodilatation and neurogenic inflammation. Akademiai Kiado, Budapest, 1984; p 7-25.
- 9 **Holzer P**
Local effector functions of capsaicin-sensitive sensory nerve endings: Involvement of tachykinins, calcitonin gene-related peptide and other neuropeptides. Neuroscience 1988; 24:739-768.
- 10 **Maggi CA, Meli A**
The sensory-efferent function of capsaicin-sensitive sensory neurons. General Pharmacology 1988; 19:1-43.
- 11 **Szolcsányi J**
Antidromic vasodilation and neurogenic inflammation. Agents Actions 1988; 23:4-11.
- 12 **Jansco G, Kiraly E, Jansco-Gabor A**
Pharmacologically induced selective degeneration of chemosensitive primary sensory neurones. Nature 1977; 270:741-743.
- 13 **Lembeck F, Holzer P**
Substance P as neurogenic mediator of antidromic vasodilation and neurogenic plasma extravasation. Naunyn-Schmiedeberg's Arch of Pharmacol 1979; 310:175-183.
- 14 **Gamse R, Holzer P, Lembeck F**
Decrease of substance P in primary afferent neurones and impairment of neurogenic plasma extravasation by capsaicin. Br J Pharmacol 1980; 68:207-213.
- 15 **Carpenter SE, Lynn B**
Vascular and sensory responses of human skin to mild injury after topical treatment with capsaicin. Brit J Pharmacol 1981; 73:755-758.
- 16 **Couture R, Cuello AC, Henry JL**
Trigeminal antidromic vasodilation and plasma extravasation in the rat: effects of sensory, autonomic, and motor denervation. Brain Res 1985; 346:108-114.

- 17 **Blumberg H, Wallin BG**
Direct evidence of neurally mediated vasodilatation in hairy skin of the human foot.
J Physiol (London) 1987; 382:105-121.
- 18 **Jansco N, Jansco-Gabor A, Szolcsanyi J**
Direct evidence for neurogenic inflammation and its prevention by denervation and by pretreatment with capsaicin. *Brit J Pharmacol and Chemotherapy* 1967; 31:138-151.
- 19 **Jansco N, Jansco-Gabor A, Szolcsányi J**
The role of sensory nerve endings in neurogenic inflammation induced in human skin and in the eye and paw of the rat. *Journal of Pharmacology and Chemotherapy* 1968; 32:32-41.
- 20 **Lynn B, Shakhaneh J**
Neurogenic inflammation in the skin of the rabbit. *Agents Actions* 1988; 25:228-230.
- 21 **Jänig W, Lisney JW**
Small diameter myelinated afferents produce vasodilation but not plasma extravasation in rat skin.
J Physiol 1989; 415:477-486.
- 22 **Dubner R**
Introductory remarks: Basic mechanisms of pain associated with deep tissues.
Can J Physiol Pharmacol 1991; 69:607-609.
- 23 **Ness TJ, Gebhart GF**
Visceral pain: A review of experimental studies. *Pain* 1990; 41:167-234.
- 24 **Darian-Smith I, Johnson KO, LaMotte C, Kenins P, Shigenaga P, Ming VC**
Coding of incremental changes in skin temperature by single warm fibers in the monkey.
J Neurophysiol 1979; 5:1316-1331.
- 25 **Cervero F, Jänig W**
Visceral nociceptors: A new world order. *Trend Neurosci* 1992; 15:374-378.
- 26 **Jänig W, Morrison JFB**
Functional properties of spinal visceral afferents supplying abdominal and pelvic organs, with special emphasis on visceral nociception. In: Cervero F, Morrison J F B (eds) *Progress in brain research: visceral sensation*. Elsevier, Amsterdam, 1986; p 87-114.
- 27 **Cervero F**
Visceral pain. In: Dubner R, Gebhart G F, Bond M R (eds) *Proceedings of the Vth World Congress on Pain*. Elsevier, Amsterdam, 1988; p 216-226.
- 28 **Beck PW, Handwerker HO, Zimmermann M**
Nervous outflow from the cat's foot during noxious radiant heat stimulation.
Brain Res 1974; 67:373-386.
- 29 **Neil A, Attal N, Guilbaud G**
Effects of guanethidine on sensitization to natural stimuli and self-mutilating behaviour in rats with a peripheral neuropathy. *Brain Res* 1991; 565:237-246.
- 30 **Wallin BG, Torebjörk E, Hallin RG**
Preliminary observations on the pathophysiology of hyperalgesia in the causalgic pain syndrome. In: Zotterman Y (ed) *Sensory functions of the skin of primates with special reference to man*. Pergamon, Oxford, 1976; p 489-499.
- 31 **Häbler H-J, Jänig W, Koltzenburg M**
Activation of unmyelinated afferent fibres by mechanical stimuli and inflammation of the urinary bladder in the cat. *J Physiol (London)* 1990; 425:545-562.
- 32 **Bahns E, Ernsberger U, Jänig W, Nelke A**
Functional characteristics of lumbar visceral afferent fibres from the urinary bladder and the urethra in the cat. *Pflügers Arch* 1986; 407:510-518.
- 33 **Bahns E, Halsband U, Jänig W**
Functional characteristics of sacral afferent fibres from the urinary bladder, urethra, colon, and anus. *Pflügers Arch* 1987; 410:296-303.
- 34 **Berkley KJ, Hotta H, Robbins A, Sato Y**
Functional properties of afferent fibers supplying reproductive and other pelvic organs in pelvic nerve of female rat. *J Neurophysiol* 1990; 63:256-272.
- 35 **Schaible HG, Schmidt RF**
Effects of an experimental arthritis on the sensory properties of fine articular afferent units.
J Neurophysiol 1985; 54:1109-1122.
- 36 **Häbler H-J, Jänig W, Koltzenburg M**
A novel type of unmyelinated chemosensitive nociceptor in the acutely inflamed urinary bladder.
Agents Actions 1988; 25:219-221.
- 37 **Koltzenburg M, McMahon SB**

- Plasma extravasation in the rat urinary bladder following mechanical, electrical and chemical stimuli: evidence for a new population of chemosensitive primary sensory afferents. *Neurosci Lett* 1986; 72:352-356.
- 38 **McMahon SB, Abel C**
A model for the study of visceral pain states: Chronic inflammation of the chronic decerebrate rat urinary bladder by irritant chemicals. *Pain* 1987; 28:109-127.
- 39 **McMahon SB**
Neuronal and behavioural consequences of chemical inflammation of rat urinary bladder. *Agents Actions* 1988; 25:231-233.
- 40 **Roberts WJ, Elardo SM**
Sympathetic activation of A-delta nociceptors. *Somato Res* 1985; 3:33-44.
- 41 **Seltzer Z, Devor M**
Ephaptic transmission in chronically damaged peripheral nerves. *Neurology* 1979; 29:1061-1064.
- 42 **Kruger L, Perl ER, Sedivec MJ**
Fine structure of myelinated mechanical nociceptor endings in cat hairy skin. *J Comp Neurol* 1981; 198:137-154.
- 43 **Treede R-D, Meyer RA, Raja S N, Campbell JN**
Peripheral and central mechanisms of cutaneous hyperalgesia. *Prog Neurobiol* 1992; 38:397-421.
- 44 **Davis KD, Treede RD, Raja SN, Meyer R A, Campbell JN**
Topical application of clonidine relieves hyperalgesia in patients with sympathetically-maintained pain. *Pain* 1991; 47:309-317.
- 45 **Raja SN, Treede R-D, Davis KD, Campbell JN**
Systemic alpha-adrenergic blockade with phentolamine: A diagnostic test for sympathetically maintained pain. *Anesthesiology* 1991; 74:691-698.
- 46 **Shea VK, Perl ER**
Failure of sympathetic stimulation to affect responsiveness of rabbit polymodal nociceptors. *J Neurophysiol* 1985; 54:513-519.
- 47 **Barasi S, Lynn B**
Effects of sympathetic stimulation on mechanoreceptive and nociceptive afferent units from the rabbit pinna. *Brain Res* 1986; 378:21-27.
- 48 **Kieschke J, Mense S, Prabhakar NR**
Influence of adrenaline and hypoxia on rat muscle receptors in vitro. In: Hamann W, Iggo A (eds) *Prog Brain Res*. Elsevier, Amsterdam: 1988; p 91-97.
- 49 **Sanjue H, Jun Z**
Sympathetic facilitation of sustained discharges of polymodal nociceptors. *Pain* 1989; 38:85-90.
- 50 **Melmon KL, Webster ME, Goldfinger SE, Seegmiller JE**
The presence of a kinin in inflammatory synovial effusion from arthritides of varying etiologies. *Arthritis Rheum* 1967; 10:13-20.
- 51 **Rocha e Silva M, Rosenthal SR**
Release of pharmacologically active substances from the rat skin in vivo following thermal injury. *Jour Pharmacol Exp Ther* 1961; 132:110-116.
- 52 **Kitchell RL, Gilanpour H, Johnson RD**
Electrophysiologic studies of penile mechanoreceptors in the rat. *Exp Neurol* 1982; 75:229-244.
- 53 **Johnson RD, Kitchell RL**
Mechanoreceptor response to mechanical and thermal stimuli in the glans penis of the dog. *J Neurophysiol* 1987; 57:1813-1836.
- 54 **Kumazawa T**
Sensory innervation of reproductive organs. In: Cervero F, Morrison J F B (eds) *Progress in brain research: visceral sensation*. Elsevier, Amsterdam, 1986; p 115-132.
- 55 **Mizumura K, Sato J, Kumazawa T**
Comparison of the effects of prostaglandins E2 and I2 on testicular nociceptor activities studied in vitro. *Naunyn Schmiedebergs Arch Pharmacol* 1991; 344:368-376.
- 56 **Mizumura K, Minagawa M, Tsujii Y, Kumazawa T**
The effects of bradykinin agonists and antagonists on visceral polymodal receptor activities. *Pain* 1990; 40:221-227.
- 57 **Sato J, Mizumura K, Kumazawa T**
Effects of ionic calcium on the responses of canine testicular polymodal receptors to algescic substances. *J Neurophysiol* 1989; 62:119-125.
- 58 **Meyer RA, Campbell JN, Raja SN**
Peripheral Neural Mechanisms of Nociception In: Wall PD, Melzack R (eds) *Textbook of Pain*, third edition, Churchill Livingstone, Edinburgh, UK, 1994.

1.2 PAIN EVALUATION AND MEASUREMENT

1.2.1 Pain Evaluation

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

Systematic evaluation of the pain involves the following;

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

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

P, Palliative or Provocative factors, 'what makes it less intense?'

Q, Quality, 'what is it like?'

R, Radiation, 'does it spread anywhere else?'

S, Severity, 'how severe is it?'

T, Temporal factors, 'is it there all the time, or does it come and go?'

Pain in patients with cancer is a complex phenomenon consisting of many different aspects. Not all pains will be of malignant origin, for example cancer patients may have pain from arthritis or cervical spondylosis. Frequently they may have more than one pain problem and each pain will need to be individually assessed and evaluated. Some pains may be due to muscular spasm rather than the cancer itself. A key principle is to constantly re-evaluate pain and the effect and side-effects of analgesic therapy.

Pain in cancer patients may be caused by the cancer itself (e.g. tumour pressure on nerve plexus or tumour infiltration), or may be due to secondary muscular spasm. Additionally pain may be secondary to cancer treatments e.g. radiation induced brachial plexopathy or may have no relation to the cancer e.g. arthritis.

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

1.2.2 Pain measurement

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

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

0 ----- 10

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

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

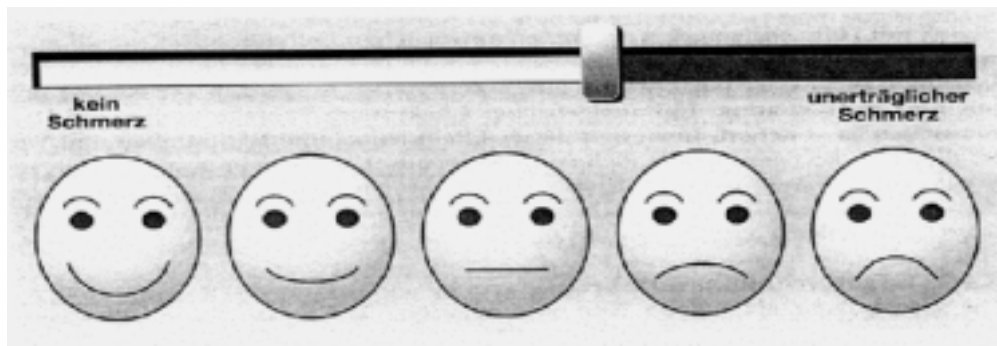


Figure 1: Visual analogue scale

1.2.3 REFERENCES

1. **Twycross R.**
Evaluation and Measurement of pain. In: Pain relief in Advanced cancer. Churchill Livingstone.
London, 1994
2. **Management of Cancer Pain.**
U.S. Department of Health and Human Services. AHCPR Publication No. 94-0592, 1994



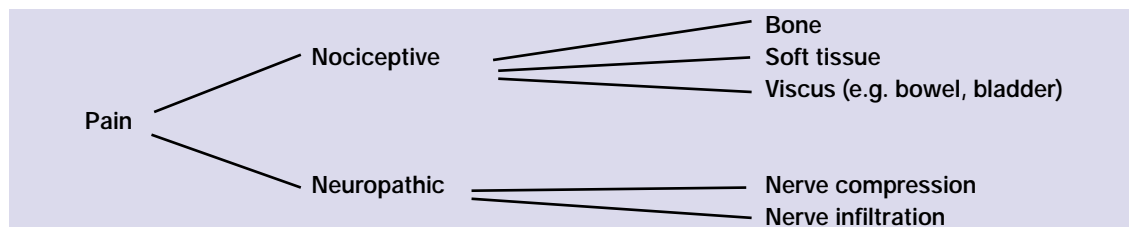
European Association of Urology

**GUIDELINES
ON
CANCER AND
POSTOPERATIVE
PAIN
MANAGEMENT**

F. Francesca (chair), P. Bader, D. Echtler, F. Giunta, J. Williams

2. CANCER PAIN MANAGEMENT

2.1 Classification of cancer pain



Urogenital neoplasms frequently metastasize to bone (e.g. spine, pelvis, skull) and such bone metastases are associated with pathological fractures, hypercalcaemia and neurological deficits, leading to substantial impairment of quality of life. The release of algogenic substances in the tissue, microfractures and periosteal tension are the main mechanism for pain sensation (1). Pain caused by bone metastases is nociceptive pain, but can become associated with neuropathic pain if the tumour invades or compresses a nerve, neural plexus or spinal cord. A third of patients with tumour-related pain are affected by neuropathic pain components (2). Nociceptive pain is well localised; initially it occurs on physical movement but later may occur also at rest. Neuropathic pain frequently has a constant „burning“ character. The efficacy of opioids may be diminished in neuropathic pain and hence additional co-analgesics are necessary (3). Patients with severe neuropathic pain are a special challenge. Psychological changes frequently occur and specific therapeutic intervention may be necessary (4).

The WHO recommends a stepwise scheme for treatment of cancer pain syndromes and for neoplastic bone pain.

Bisphosphonates and calcitonin are helpful for stabilising bone metabolism. Epidural and intrathecal opioids are sometimes useful in managing bone pain from metastases. Nerve destruction by intrathecal or epidural phenol is sometimes useful in selected patients with neuropathic pain (5).

2.1.1 References

1. **Mercadante S.**
Malignant-bone pain. Pathophysiology and treatment. *Pain* 1997; 69: 1-18
2. **Grond S, Zech D, Diefenbach C, Radbruch L, Lehmann KA.**
Assessment of cancer pain: a prospective evaluation of 2266 cancer patients referred to a pain service. *Pain* 1996; 64: 107-114
3. **Sindrup SH, Jensen TS.**
Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999; 83: 389-400
4. **Mercadante S, Portenoy RK.**
Opioid poorly responsive cancer pain. Part 3. Clinical strategies to improve opioid responsiveness. *J Pain Sympt Manage* 2001; 21: 338-354
5. **Stevens RA, Stotz A.**
Neurolytic blocks for management of oncologic pain. *Cancer Res Ther Control* 1999; 9: 345-353

2.2 GENERAL MANAGEMENT OF CANCER PAIN

2.2.1 Principles in cancer pain management

The therapeutic strategy depends on the four goals of care:

1. prolonging survival
2. optimising comfort
3. optimising function
4. relieving pain (figure 3)

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

- 1st Individualized treatment for each patient
- 2nd Causal therapy to be preferred over symptomatic therapy
- 3rd Local therapy to be preferred over systemic therapy
- 4th Systemic therapy with increasing invasiveness (WHO ladder)
- 5th Conformance with palliative guidelines
- 6th Both psychological counselling and physical therapy from the very beginning

The guiding principle of care is the individualisation of therapy. Through a process of repeated evaluations, the selection and administration of therapy is individualised so that a favorable balance between pain relief and adverse effects is achieved and maintained. The next steps in the hierarchy, especially points 2 to 4, necessitate a continuing risk-to-benefit assessment between therapeutic outcome versus tolerability and willingness to accept adverse effects.

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

If local therapy is not feasible or cannot be well tolerated then symptomatic measures are appropriate, although local therapy is to be given preference over systemic treatment. In simple cases measures such as drainage and stenting can make analgesic medication redundant. Examples include inserting a gastric probe, a ureteral stent, a percutaneous nephrostomy, or a bladder catheter. To cite another example, patients who receive an artificial anus due to recurrent sub ileus caused by peritoneal carcinomatosis are relieved of their pain immediately.

The indication stands in direct relation to the severity of the disease and the operation, especially if there are no prospects of healing. Cases such as these, however, are sometimes in particular need of the invasive measures described above. This is not only to relieve pain for the rest of the patient's days, but also to improve the general quality of life, even though invasive operations may also negatively impact the patient's well-being. Examples can include evisceration to prevent cloaca in cervix carcinoma, or implanting a prosthetic hip due to a pathological fracture originating in metastatised bladder or kidney cancer.

A gradual strategy (Evidence level IV) can be considered when dose escalation of a systemically administered opioid fails to yield a satisfactory result:

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

As is widely discussed in pain-management literature the importance of physiotherapy and psychological counselling cannot be emphasized strongly enough. For further discussion of these points see the chapters above.

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

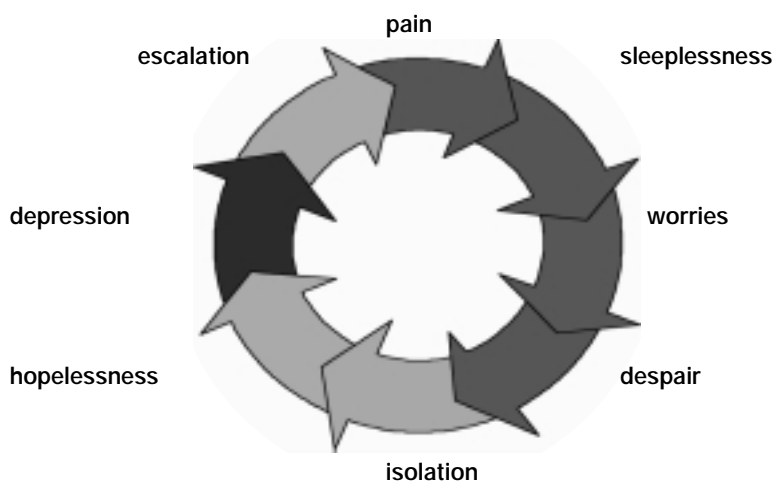


Figure 3: tumor pain helix

PAIN CAN BE OVERCOME

2.2.2 Primary analgesic therapies

- **Radiotherapy** has a pivotal role in the treatment of cancer pain and other oncological conditions. In some situations, such as the treatment of bone metastases, the value of radiotherapy is documented by abundant data and a favourable clinical experience (1,2,3). Evidence level I a.
- **Chemotherapy**. The likelihood of a successful effect on pain is generally related to the likelihood of tumour response. There is a strong clinical impression that tumour shrinkage is generally associated with relief of pain, although there are some reports of analgesic value even in the absence of significant tumour shrinkage (4). Evidence level 1a.
- **Surgery** may have a role in the relief of symptoms caused by specific problems, such as obstruction of a hollow viscus, unstable bony structures and compression of neural tissues or drain symptomatic ascites (5,6,7). The potential benefits must be weighed against the risks of surgery, the anticipated length of hospitalisation and convalescence, and the predicted duration of benefit. Radical surgery to excise locally advanced disease in patients with no evidence of metastatic spread may be palliative, and potentially increase the survival of some patients (8). Evidence level II b.
- **Antibiotics** may be analgesic when the source of the pain involves infection (e.g. pyonephrosis, abscess, and osteitis pubis). In some cases, infection may be occult and confirmed only by the symptomatic relief provided by empiric treatment with these drugs (9). Evidence level II b.

2.2.3 Pharmacotherapy

The success of cancer pain therapy depends on the ability of the clinician to assess the presenting problems, identify and evaluate pain syndromes and formulate a plan for comprehensive continuing care. This requires familiarity with a range of therapeutic options and an approach to long-term care that is responsive to the changing needs of the patient. This approach emphasises the need to incorporate pain treatment within a broader therapeutic agenda, in which tumour control, symptom palliation (physical and psychological) and functional rehabilitation are concurrently addressed.

2.2.4 Systemic analgesic pharmacotherapy

The 'analgesic ladder'

Analgesic pharmacotherapy is the mainstay of cancer pain management (10,11,12). Although concurrent use of other interventions is valuable in many patients, and essential in some, analgesic drugs are needed in almost every case. Based on clinical convention, analgesic drugs can be separated into three groups:

1. nonopioid analgesics
2. opioid analgesics
3. adjuvant analgesics, which are drugs with other primary indications that can be effective analgesics in specific circumstances.

An expert committee convened by the Cancer Unit of the World Health Organization (WHO) has proposed a useful approach to drug selection for cancer pain, which has become known as the 'analgesic ladder' (10,12). When combined with appropriate dosing guidelines, this approach is capable of providing adequate relief to 70-90% of patients (13,14). Emphasising that pain intensity should be the prime consideration in analgesic selection, the approach advocates three basic steps (Figure 1). Evidence level I a.

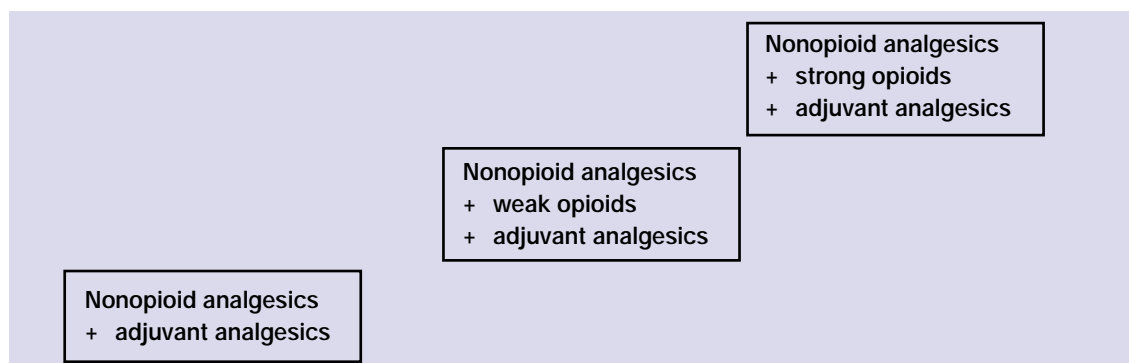


Figure 1: The 'analgesic ladder' according to WHO

Step 1 Patients with mild to moderate cancer-related pain should be treated with a nonopioid analgesic, which should be combined with an adjuvant analgesic if a specific indication for one exists.

Step 2 Patients who present with moderate to severe pain, or who fail to achieve adequate relief after a trial of a nonopioid analgesic, should be treated with a weak opioid. This treatment is typically accomplished

using a combination product containing a nonopioid (e.g. aspirin or acetaminophen) and an opioid (such as codeine, oxycodone or propoxyphene). This drug can also be co-administered with an adjuvant analgesic.

Step 3 Patients who present with severe pain, or who fail to achieve adequate relief following appropriate administration of drugs on the second rung of the 'analgesic ladder', should receive a strong opioid, such as morphine or hydromorphone. This drug may also be combined with a nonopioid analgesic or an adjuvant drug.

2.2.4.1 Nonopioid analgesics

- Nonopioid analgesics = aspirin, acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs)
- May be useful alone for mild to moderate pain (step 1 of the analgesic ladder)
- Provide analgesia when combined with opioids
- Have a *ceiling effect* of analgesic efficacy
- No tolerance or physical dependence
- Inhibit the enzyme cyclo-oxygenase and block the synthesis of prostaglandins
- Involvement of central mechanisms are also likely in acetaminophen analgesia (15)
- Potential adverse effects (16)
Most common: bleeding diathesis due to inhibition of platelet aggregation, gastro-duodenopathy (including peptic ulcer disease) and renal impairment are the most common. Less common: confusion, precipitation of cardiac failure and exacerbation of hypertension. Particular caution in elderly patients and those with blood-clotting disorders; predisposition to peptic ulceration, impaired renal function and concurrent corticosteroid therapy.
- Nonacetylated salicylates (choline magnesium trisalicylate and salsalate) are preferred in patients who have a predilection to bleeding; these drugs have less effect on platelet aggregation and no effect on bleeding time at the usual clinical doses. Acetaminophen also rarely produces gastrointestinal toxicity and there are no adverse effects on platelet function; hepatic toxicity is possible, however, and patients with chronic alcoholism and liver disease can develop severe hepatotoxicity at the usual therapeutic doses (17).

2.2.4.2 Opioid analgesics

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

Classification

Classification based on their interactions with the various receptor subtypes:

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

Relative potency and equianalgesic doses

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

Selecting Patients for Opioid Therapy

A trial of systemic opioid therapy should be administered to all cancer patients with moderate or severe pain. This is true regardless of the pain mechanism (18,19,20). Patients who present with severe pain should be treated with a 'strong' opioid from the start. Patients with moderate pain are commonly treated with a combination drug containing acetaminophen or aspirin plus codeine, oxycodone or propoxyphene. The dose of these combination products can be increased until the maximum dose of the nonopioid coanalgesic is attained (e.g. 4000 mg acetaminophen).

2.2.4.3 Opioid administration

A) Opioid selection

Factors to consider include the following.

- pain intensity
- patient age
- prior opioid therapy (response to previous trials of opioid therapy)
- coexisting disease
- influence of underlying illness and characteristics of the opioid and concurrent medications.

B) Routes of administration

Classification on the basis of degree of invasiveness. Opioids should be administered by the least invasive and safest route capable of providing adequate analgesia. In a survey of patients with advanced cancer, more than half required two or more routes of administration prior to death and almost a quarter required three or more.

Noninvasive Routes

- *Oral* routes are the preferred approach in routine practice. Alternative routes are necessary for patients who have impaired swallowing or gastrointestinal dysfunction, those who require a very rapid onset of analgesia and those who are unable to utilise or tolerate the oral route.

- *Rectal* suppositories containing oxycodone, hydromorphone, oxycodone and morphine have been formulated and controlled-release morphine tablets can also be administered per rectum. The potency of opioids administered rectally is believed to approximate to oral dosing (21).

- *Transferral* routes are not yet very common; fontanel is the only opioid available as a transferral preparation.

The fontanel transferral system consists of a drug reservoir that is separated from the skin by a copolymer membrane, which controls the rate of drug delivery to the skin surface such that the drug is released into the skin at a nearly constant amount per unit of time. The system has been demonstrated to be effective in postoperative pain and cancer pain (22). The dosing interval for each system is usually 72 hours, but some patients require a 48-hour schedule. There is some inter individual variability in fentanyl bioavailability by this route, and this phenomenon, combined with large differences in elimination pharmacokinetics, necessitates dose titration in most cases (23). Transdermal patches capable of delivering 25, 50, 75 and 100 mg/h are available. Multiple patches may be used simultaneously for patients who require higher doses. At the present time, the limitations of the transdermal delivery system include its cost and the requirement for an alternative short-acting opioid for breakthrough pain.

- *Sublingual* absorption of any opioid could potentially yield clinical benefits but bioavailability is very poor with drugs that are not highly lipophilic and the likelihood of an adequate response is consequently low (24).

Sublingual buprenorphine, a relatively lipophilic partial agonist, can provide adequate relief of mild to moderate cancer pain. Overall, however, the sublingual route has limited value due to the lack of formulations, poor absorption of most drugs and the inability to deliver high doses or prevent swallowing of the dose.

An oral transmucosal formulation of fentanyl, which incorporates the drug into a sugar base, is under evaluation. A pilot study in cancer patients suggested that it may be useful to provide rapid relief of breakthrough pain (25).

Invasive routes

For patients undergoing a trial of systemic drug administration, a parenteral route must be considered when the oral route is not available. Repeated parenteral bolus injections, which may be administered by the intravenous (iv), intramuscular (im) or subcutaneous (sc) routes, may be useful in some patients, but are often compromised by the occurrence of prominent 'bolus' effects (toxicity at peak concentration and/or pain breakthrough at the trough). Repetitive im injections are a common practice, but they are painful and offer no pharmacokinetic advantage; their use is not recommended (26).

- *Intravenous bolus* administration provides the most rapid onset and shortest duration of action. Time to peak effect correlates with the lipid solubility of the opioid and ranges from 2-5 minutes for methadone to 10-15 minutes for morphine (27). This approach is appropriate in two settings:

1. to provide parenteral opioids, usually transiently, to patients who already have venous access and are unable to tolerate oral opioids
2. to treat very severe pain, for which iv doses can be repeated at an interval as brief as that determined by the time to peak effect, if necessary, until adequate relief is achieved.

- *Continuous parenteral infusions* are useful for many patients who cannot be maintained on oral opioids.

Long-term infusions may be administered iv or sc. In practice, the major indication for continuous infusion occurs in patients who are unable to swallow or absorb opioids. Continuous infusion is also used in some patients whose high opioid requirement renders oral treatment impractical (28).

Ambulatory patients can easily use a continuous subcutaneous infusion using a 27-gauge 'butterfly' needle. The butterfly can be left under the skin for up to a week. A recent study demonstrated that the bioavailability of hydromorphone is 78% by this route (29) and clinical experience suggests that dosing may proceed in a manner identical to continuous iv infusion. A range of pumps is available, which vary in complexity, cost and ability to provide patient-controlled 'rescue doses' as an adjunct to a continuous basal infusion. Opioids suitable for continuous sc infusion must be soluble, well absorbed and non-irritant. Extensive experience has been reported with diamorphine, hydromorphone, oxycodone and morphine (30). Methadone appears to be relatively irritating and is not preferred (31). To maintain the comfort of an infusion site, the sc infusion rate should not exceed 5 cc/h. The infraclavicular and anterior chest sites provide the greatest freedom of movement for patients, but other sites may be used. A single infusion site can usually be maintained for 5-7 days.

Changing routes of administration

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

C). Dosing

- *'Around-the-clock' (ATC) dosing*

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

- *Controlled release drug formulations*

Controlled release preparations of oral opioids can lessen the inconvenience associated with the use of 'around-the-clock' administration of drugs with a short duration of action. Numerous studies have demonstrated the safety and efficacy of these preparations in cancer patients with pain (32,33).

- *'As needed' (PRN) dosing*

This strategy is beneficial when rapid dose escalation is needed or therapy is begun with a long half-life opioid such as methadone or levorphanol. 'As needed' dosing may also be appropriate for patients who have rapidly decreasing analgesic requirement or intermittent pains separated by pain free intervals.

- *Patient-controlled analgesia (PCA)*

This is a technique of parenteral drug administration in which the patient controls an infusion device that delivers a bolus of analgesic drug 'on demand' according to parameters set by the physician. Long-term PCA in cancer patients is most commonly accomplished via the subcutaneous route using an ambulatory infusion device. In most cases, PCA is added to a basal infusion rate and acts essentially as a rescue dose.

Adverse effects and their management

- *Tolerance*

Patients vary greatly in the opioid dose required to manage pain (400 - 2000 mg of intramuscular morphine per 24 hours) (34). The induction of true analgesic tolerance, which could compromise the utility of treatment, can only be said to occur if a patient manifests the need for increasing opioid doses in the absence of other factors (e.g. progressive disease) that would be capable of explaining the increase in pain. Extensive clinical experience suggests that most patients who require an escalation in dose to manage increasing pain have demonstrable progression of disease (35). These observations suggest that true pharmacological tolerance to the analgesic effects of opioids is not a common clinical problem. This conclusion has two important implications: 1. concern about tolerance should not impede the use of opioids early in the course of the disease and 2. worsening pain in a patient receiving a stable dose of opioids should not be attributed to tolerance, but should be assessed as presumptive evidence of disease progression or, less commonly, increasing psychological distress.

- *Adverse drug interactions*

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

- *Respiratory depression*

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

- *Sedation*

Sedation usually persists until tolerance to this effect develops, usually within a period of days to weeks. It is

useful to forewarn patients of this potential, and thereby reduce anxiety and encourage avoidance of activities, such as driving, that may be dangerous if sedation occurs. Some patients have a persistent problem with sedation, particularly in combination with other sedating drugs or coexistent diseases such as dementia, metabolic encephalopathy or brain metastases.

- *Confusion and delirium*

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

- *Constipation*

Constipation is the most common adverse effect of chronic opioid therapy (38,39,40). Laxative medications should be prescribed prophylactically. There are no controlled comparisons of the various laxatives for opioid-induced constipation, and published recommendations are based entirely on anecdotal experience. Combination therapy is frequently used, particularly coadministration of a softening agent (docusate) and a cathartic (e.g. senna, bisacodyl or phenolphthalein). The doses of these drugs should be increased as necessary, and an osmotic laxative (e.g. milk of magnesia) should be added if needed. Chronic lactulose therapy is an alternative that some patients prefer and occasional patients are managed with intermittent colonic lavage using an oral bowel preparation.

- *Nausea and vomiting*

Opioids may produce nausea and vomiting through both central and peripheral mechanisms. These drugs stimulate the medullary chemoreceptor trigger zone, increase vestibular sensitivity and have effects on the gastrointestinal tract (including increased gastric antral tone, diminished motility and delayed gastric emptying). In ambulatory patients, the incidence of nausea and vomiting has been estimated to be 10-40% and 15-40%, respectively (41). The likelihood of these effects is greatest at the start of opioid therapy. Metoclopramide is the most reasonable initial treatment. Tolerance typically develops within weeks. Routine prophylactic administration of an antiemetic is not necessary. The serotonin antagonists (e.g. ondansetron) are not likely to be effective with opioid induced symptoms since they do not eliminate apomorphine-induced vomiting and motion sickness, which appear to be appropriate models for opioid effects. Clinical trials of the latter agents are needed to confirm this conclusion.

- *Addiction and dependence*

Confusion about physical dependence and addiction augment the fear of opioid drugs and contribute substantially to the under treatment of pain (42). Patients with chronic cancer pain have a 'therapeutic dependence' to their analgesic pharmacotherapy. This relationship may or may not be associated with the development of physical dependence, but is virtually never associated with addiction. The medical use of opioids is very rarely associated with the development of addiction (43). Although there are no prospective studies in patients with chronic cancer pain, there is an extensive clinical experience that affirms the extremely low risk of addiction in this population. Health-care providers, patients and families often require vigorous and repeated reassurance that the risk of addiction is extremely small.

2.2.4.4 Adjuvant analgesics

A 'adjuvant analgesic' is defined as a drug that has a primary indication other than pain but is analgesic in some conditions. These drugs may be combined with primary analgesics in any of the three steps of the 'analgesic ladder' to improve the outcome for patients who cannot otherwise attain an acceptable balance between relief and side-effects. In the management of cancer pain, adjuvant analgesics can be broadly classified based on conventional use. The following three groups are distinguished.

A) Multipurpose adjuvant analgesics

- *Corticosteroids*

Corticosteroids are among the most widely used adjuvant analgesics (44,45). They have been demonstrated to have analgesic effects; to improve quality of life significantly (46); and to have beneficial effects on appetite, nausea, mood and malaise in the cancer population (47). The mechanism of analgesia produced by these drugs may involve anti-oedema effects, antiinflammatory effects and a direct influence on the electrical activity in

damaged nerves. Patients with advanced cancer who experience pain and other symptoms may respond favourably to a relatively small dose of corticosteroid (e.g. dexamethasone 1-2 mg twice daily). Evidence level IIa.

- *Neuroleptics*

The role of neuroleptic drugs in the management of cancer pain is limited. Methotrimeprazine is a proven analgesic that has been very useful in bedridden patients with advanced cancer who experience pain associated with anxiety, restlessness or nausea. In this setting, the sedative, anxiolytic and antiemetic effects of this drug can be highly favourable, and side-effects, such as orthostatic hypotension, are less of an issue. A prudent dosing schedule begins with 5-10 mg every 6 hours, which is gradually increased as needed. Evidence level Ia.

- *Benzodiazepines*

Benzodiazepines have analgesic effects (48), but this must be balanced by the potential for side-effects, including sedation and confusion. With the important exception of clonazepam, which is widely accepted for the management of neuropathic pain, these drugs are generally used only if another indication exists, such as anxiety or insomnia. Evidence level IIb.

B) Adjuvants used for neuropathic pain

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

- *Antidepressants*

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

- *Anticonvulsants*

The anticonvulsants Carbamazepine, Phenytoin and Sodium valproate have been used for many years to treat neuropathic pain. Carbamazepine has a license for the treatment of trigeminal neuralgia. These drugs are prone to side-effects such as dizziness, drowsiness and Carbamazepine in particular may suppress bone marrow function and therefore requires regular monitoring. A newer anticonvulsant, Gabapentin has shown good efficacy in 2 large placebo-controlled RCT's. It is generally better tolerated than the older anticonvulsants and it has a licence in the UK for the treatment of all types of neuropathic pain. Evidence level Ia.

- *Clonidine*

Clonidine is an alpha-2 adrenergic agonist that has established analgesic effects (51). In the cancer population, a trial of oral or transdermal clonidine can be considered in the management of continuous neuropathic pain refractory to opioids and other adjuvants. Evidence level IIb.

C) Adjuvants used for bone pain

- *Anti-inflammatory Drugs*

Anecdotally, nonsteroidal anti-inflammatory drugs appear to be particularly efficacious for malignant bone pain. Corticosteroids are often advocated in difficult cases.

- *Bisphosphonates*

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

- *Radiopharmaceuticals*

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

2.2.5 *Transcutaneous electrical nerve stimulation (TENS)*

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

2.2.6 *Invasive analgesic techniques*

The results of the WHO 'analgesic ladder' validation studies suggest that 10-30% of patients with cancer pain do not achieve a satisfactory balance between relief and side-effects using systemic pharmacotherapy alone without unacceptable drug toxicity (13,14). Anaesthetic and neurosurgical techniques may reduce the requirement for systemically administered opioids to achieve adequate analgesia.

- *Epidural, intrathecal, and intraventricular opioid application*

The delivery of low opioid doses near the sites of action in the spinal cord may decrease supraspinally-mediated adverse effects. Compared to neuroablative therapies, spinal opioids have the advantage of preserving sensation, strength and sympathetic function. Contraindications include bleeding diathesis, profound leucopenia and sepsis. A temporary trial of spinal opioid therapy should be performed to assess the potential benefits of this approach before implantation of a permanent catheter. In some patients, the addition of a low concentration of a local anaesthetic, such as 0.125 - 0.25% bupivacaine, to an epidural opioid has been demonstrated to increase analgesic effect without increasing toxicity (64,65). The potential morbidity for these procedures indicates the need for a well-trained clinician and long-term monitoring. Evidence level III.

- *Chemical rhizotomy*, produced by the instillation of a neurolytic solution into either the epidural or intrathecal space, can be an effective method of pain control for patients with otherwise refractory localised pain syndromes. The technique is most commonly used in the management of chest-wall pain due to tumour invasion of somatic and neural structures. Other indications include refractory upper limb, lower limb, pelvic or perineal pain. Because of the significant risk of increased disability through weakness, sphincter incompetence and loss of positional sense, chemical rhizotomy of lumbosacral nerve roots is best reserved for patients with limited function and pre-existent urinary diversion. Adverse effects can be related to the injection technique (spinal headache, mechanical neural damage, infection and arachnoiditis) or to the destruction of non-nociceptive nerve fibres. Evidence level IV.

- During *cordotomy*, the anterolateral spinothalamic tract is sectioned to produce contralateral loss of pain and temperature sensibility. The patient with severe unilateral pain arising in the torso or lower extremity is most likely to benefit from this procedure. The percutaneous technique is generally preferred. Significant pain relief is achieved in more than 90% of patients during the period immediately following cordotomy. Of surviving patients 50% have recurrent pain after 1 year. Repeat cordotomy can sometimes be effective. The neurological complications of cordotomy include paresis, ataxia and bladder dysfunction (68).

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

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

2.2.7 Physical / psychological therapy

Physical therapies

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

Psychological therapies

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

- *Cognitive-behavioural interventions* can help some patients decrease the perception of distress engendered by the pain through the development of new coping skills and the modification of thoughts, feeling and behaviours.
- *Relaxation methods* may be able to reduce muscular tension and emotional arousal or enhance pain tolerance (60).
- *Other approaches* reduce anticipatory anxiety that may lead to avoidant behaviours or lessen the distress associated with the pain.

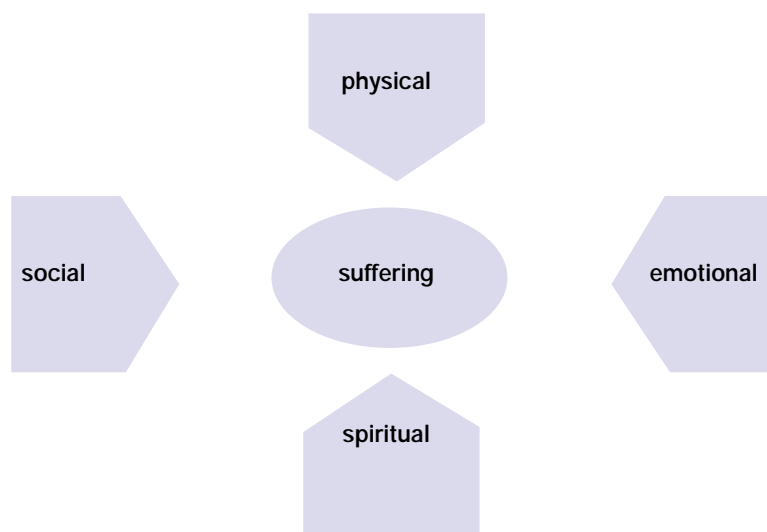


Figure 2: pain factors

2.2.8 Conclusions

The goal of analgesic therapy in cancer patients is to optimise analgesia with the minimum of side-effects. Currently available techniques can provide adequate relief for the vast majority of patients. Most will require ongoing analgesic therapy and requirements often change as the disease progresses. Patients with refractory pain should have access to specialists in pain management or palliative medicine who can provide an integrated multidisciplinary approach (78).

2.2.9 References

- 1 **Bates T**
A review of local radiotherapy in the treatment of bone metastases and cord compression. *Int J Radiat Oncol, Biology, Physics* 1992; 23:217-222.
- 2 **Bates T, Yarnold JR, Blitzer P, Nelson OS, Rubin P, Maher J**
Bone metastasis consensus statement. *Int J Radiat Oncol, Biology, Physics*, 1992; 23:215-216.
- 3 **Coia LR**
The role of radiotherapy in the treatment of brain metastases. *Int J Radiat Oncol, Biology*, 1992; 23:239-244.
- 4 **Patt YZ, Peters RE, Chuang VP, Wallace S, Claghorn L, Mavligit G**
Palliation of pelvic recurrence of colorectal cancer with intraarterial 5-fluorouracil and mitomycin. *Cancer* 1985; 56:2175-2180.
- 5 **Williams MR**
The place of surgery in terminal care. In: Saunders C (ed) *The management of terminal disease*. Edward

Arnold, London, 1984; p 148-153.

- 6 **Boraas M**
Palliative surgery. *Semin Oncol* 1985; 12:368-374.
- 7 **Sundaresan N, DiGiacinto GV**
Antitumor and antinociceptive approaches to control cancer pain. *Med Clin North Am* 1987; 71:329-348.
- 8 **Temple WJ, Ketcham AS**
Sacral resection for control of pelvic tumours. *Am J Surg* 1992; 163:370-374.
- 9 **Coyle N, Portenoy RK**
Infection as a cause of rapidly increasing pain in cancer patients.
J Pain Symptom Manage 1991; 6:266-269.
- 10 **World Health Organization**
Cancer pain relief and palliative care. World Health Organ, 1990 Geneva.
- 11 **Foley KM**
The treatment of cancer pain. *N Eng J Med* 1985; 313:84-95.
- 12 **World Health Organization**
Cancer pain relief. World Health Organ, 1986 Geneva.
- 13 **Schug SA, Zech D, Dorr U**
Cancer pain management according to WHO analgesic guidelines.
J Pain Symptom Manage 1990; 5:27-32.
- 14 **Grond S, Zech D, Schug SA, Lynch J, Lehman KA**
Validation of the World Health Organization guidelines for cancer pain relief during the last days and hours of life. *J Pain Symptom Manage* 1991; 6:411-422.
- 15 **Malmberg AB, Yaksh TL**
Hyperalgesia mediated by spinal glutamate and substance P receptors blocked by spinal cyclooxygenase inhibition. *Science* 1992; 92:1276-1279.
- 16 **Brooks PM, Wood AJ**
Nonsteroidal antiinflammatory drugs - differences and similarities. *N Eng J Med* 1991; 324:1716-1725.
- 17 **Seeff LB, Cuccherini BA, Zimmerman HI, Adler E, Benjamin S**
Acetaminophen hepatotoxicity in alcoholics. *Ann Intern Med* 1986; 104:399-404.
- 18 **Cherny NI, Thaler HT, Friedlander-Klar H, Lapin J, Portenoy RK**
Opioid responsiveness of neuropathic cancer pain: combined analysis of single-dose analgesic trials. *Proceedings of the American Society of Clinical Oncology* 1992; 11: abstract 1330.
- 19 **Jadad AR, Carroll D, Glynn CJ, Moore RA, McQuay HJ**
Morphine responsiveness of chronic pain: double blind randomised crossover study with patient controlled analgesia. *Lancet* 1992; 339:1367-1371.
- 20 **McQuay HJ, Jadad AR, Carnoll D et al**
Opioid sensitivity of chronic pain: a patient controlled analgesia method. *Anaesthesia* 1992; 47:757-767.
- 21 **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. Raven Press, New York, 1990; p 259-269.
- 22 **Calis KA, Kohler DR, Corso DM**
Transdermally administered fentanyl for pain management. *Clin Pharmacol* 1992; 11:22-36.
- 23 **Portenoy RK, Southam M, Gupta SK et al**
Transdermal fentanyl for cancer pain repeated dose pharmacokinetics. *Anesthesiology* 1993; 28:36-43.
- 24 **Weinberg DS, Inturrisi CE, Reidenberg B et al**
Sublingual absorption of selected opioid analgesics. *Clin Pharmacol Ther* 1988; 44:335-342.
- 25 **Fine PG, Marcus M, DeBoer AJ, Van der Oord B**
An open label study of oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough cancer pain. *Pain* 1991; 45:149-155.
- 26 **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. American Pain Society, Skokie, Illinois, 1992.
- 27 **Chapman CR, Hill HF, Saeger L, Gavrin J**
Profiles of opioid analgesia in humans after intravenous bolus administration: alfentanil, fentanyl and morphine compared on experimental pain. *Pain* 1990; 43:47-55.
- 28 **Storey P, Hill H, St Louis R, Tarver EE**
Subcutaneous infusions for control of cancer symptoms. *J Pain Symptom Man* 1990; 5:33-41.
- 29 **Moulin DE, Kreeft JH, Murray PN, Bouquillon AI**
Comparison of continuous subcutaneous and intravenous hydromorphone infusions for management of cancer pain. *Lancet* 1991; 337:465-468.

- 30 **Moulin DE, Johnson NG, Murray PN, Geoghegan MF, Goodwin VA, Chester MA**
Subcutaneous narcotic infusions for cancer pain: treatment outcome and guidelines for use.
Can Med Assoc J 1992; 146:891-7.
- 31 **Bruera E, Fainsinger R, Moore M, Thibault R, Spoldi E, Ventafridda V**
Local toxicity with subcutaneous methadone. Experience of two centers. Pain 1991; 45:141-145.
- 32 **Kaiko RF**
Clinical protocol and role of controlled release morphine the surgical patient. In: Stanley T H, Ashburn M A, Fine P G (eds) Anesthesiology in pain management. Kluwer Academic, Dordrecht, 1991; p 193-212.
- 33 **Walsh TD, MacDonald N, Bruera E, Shepard KV, Michaud M, Zanes R**
A controlled study of sustained-release morphine sulfate tablets in chronic pain from advanced cancer.
Am J Clin Oncol 1992; 15:268-272.
- 34 **Coyle N, Adelhardt J, Foley KM, Portenoy RK**
Character of terminal illness in the advanced cancer patient: pain and other symptoms during last four weeks of life. J Pain Symptom Man 1990; 5:83-89.
- 35 **Foley KM**
Clinical tolerance to opioids. In: Basbaum A I, Bessom J M (eds) Towards a new pharmacotherapy of pain. 1991, Dahlem Konferenzen. John Wiley, Chichester, p 181-204.
- 36 **Bruera E, Macmillan K, Hanson J, MacDonald RN**
The cognitive effects of the administration of narcotic analgesics in patients with cancer pain.
Pain 1989; 39:13-6.
- 37 **Breitbart W, Holland JC**
Psychiatric complications of cancer. Curr Ther in Hematol Oncol 1988; 3:268-275.
- 38 **Inturrisi CE**
Management of cancer pain. Cancer 1989; 63:2308-2320.
- 39 **Walsh TD**
Prevention of opioid side effects. J Pain Symptom Man 1990; 5:363-367.
- 40 **Sykes NP**
Oral naloxone in opioid associated constipation. Lancet 1991; 337:1475.
- 41 **Campora E, Merlini L, Pace M et al**
The incidence of narcotic induced emesis. J Pain Symptom Man 1991; 6:428-430.
- 42 **Schuster CR**
Does treatment of cancer pain with narcotics produce junkies? In: Hill C S, Fields W S (ed) Drug treatment of cancer pain in a drug oriented society. Advances in pain research and therapy, vol 11. Raven Press, New York, 1989; p 1-3.
- 43 **Chapman CR, Hill HF**
Prolonged morphine self-administration and addiction liability. Cancer 1989; 63:1636-1644.
- 44 **Walsh TD**
Adjuvant analgesic therapy in cancer pain. In: Foley K M, Bonica J J, Ventafridda V (eds) The Second International Conference on Cancer Pain. Advances in pain research and therapy, vol 16. New York, New York, 1990; p 155-168.
- 45 **Della Cuna GR, et al**
Effect of methylprednisolone sodium succinate on quality of life in pre terminal cancer patients. A placebo control multicenter study. Eur J Clin Oncol 1989; 29:1817-1821.
- 46 **Tannock I, Gospodarowicz M, Meakin W, Panzarella T, Stewart L, Rider W**
Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. J Clin Oncol 1989; 7:590-597.
- 47 **Wilcox JC, Corr J, Shaw J, Richardson M, Calman KC**
Prednisolone as appetite stimulant in patients with cancer. Br Med J 1984; 288:27.
- 48 **Fernandez F, Adams F, Holmes VF**
Analgesic effect of alprazolam in patients with chronic, organic pain of malignant origin.
J Clin Psychopharmacol 1987; 3:167-169.
- 49 **Panerai AE, Bianchi M, Sacerdote P, Ripamonti C, Ventafridda V, De Conno F**
Antidepressants in cancer pain. J Palliat Care 1991; 7:42-44.
- 50 **Portenoy RK**
Adjuvant analgesics. In: Doyle D, Hanks G W, MacDonald N (eds) Oxford textbook of palliative medicine. Oxford University Press, Oxford, 1993; p 187-203.
- 51 **Mok MS, Wang JJ, Chan JH, Liu SE, Lippmann M**
Analgesic effect of epidural clonidine and nalbuphine in combined use. Anesthesiology 1988; 69:A398.
- 52 **Clarke NW, Holbrook IB, McClure J, George NJ**
Osteoclast inhibition by pamidronate in metastatic prostate cancer: a preliminary study.

- Br J Cancer 1991; 63:420-423.
- 53 **Ernst DS, MacDonald RN, Paterson AHG, Jensen J, Brasher P, Bruera E**
A double blind, crossover trial of IV clodronate in metastatic bone pain.
J Pain Symptom Manage 1992; 7:4-11.
- 54 **Silberstein EB, Elgazzar AH, Kapilivsky A**
Phosphorus-32 radiopharmaceuticals for the treatment of painful osseous metastases. Seminars in Nuclear Medicine 1992; 22:17-327.
- 55 **Turner JH, Claringbold BG**
A phase II study of treatment of painful multifocal skeletal metastases with single and repeated dose samarium-153 ethylenediaminetetramethylene phosphonate. Eur J Cancer 1991; 27(9):1084-1086.
- 56 **Maxon H, Thomas SR, Hertzberg VS et al**
Rhenium-186 hydroxyethylidene diphosphonate for the treatment of painful osseous metastases. Seminars in Nuclear Medicine 1992; 22:33-40.
- 57 **Robinson RG, Preston DF, Spicer JA, Baxter KG**
Radionuclide therapy of intractable bone pain: emphasis on strontium-89. Seminars in Nuclear Medicine 1992; 22:28-32.
- 58 **Gobelet C, Waldburger M, Meier JL**
The effect of adding calcitonin to physical treatment on reflex sympathetic dystrophy. Pain 1992; 48:171-5.
- 59 **Fishman B**
The treatment of suffering in patients with cancer pain: cognitive behavioral approaches. In: Foley K M, Bonica J J, Ventafrida V (eds) Second International Congress on Cancer Pain. Advances in pain research and therapy, 1990; vol 16. Raven Press, New York, p 301-316.
- 60 **Linton SL, Melin L**
Applied relaxation in the management of cancer pain. Behav Psychother 1983; 11:337-350.
- 61 **Turk D, Meichenbaum D, Genest M**
Pain and behavioral medicine. 1983 Guilford Press, New York.
- 62 **Bushnell MC, Marchand S, Tremblay N, Duncan GH**
Electrical stimulation of peripheral and central pathways for the relief of musculoskeletal pain. Can J Physiol Pharmacol 1991; 69:697-703.
- 63 **Long DM**
Fifteen years of transcutaneous electrical stimulation for pain control. Stereotactic and Functional Neurosurgery 1991; 56:2-19.
- 64 **Hogan Q, Haddox JD, Abram S, Weissman D, Taylor ML, Janjan N**
Epidural opiates and local anesthetics for the management of cancer pain. Pain 1991; 46:271-279.
- 65 **Sjoberg M, Appelgren L, Einarsson S et al**
Long-term intrathecal morphine and bupivacaine in 'refractory' cancer pain. Results from the first series of 52 patients. Acta Anaesthesiol Scand 1991; 35:30-43.
- 66 **Sandouk P, Serrie A, Urtizberea M, Debray M, Got P, Scherrmann MJ**
Morphine pharmacokinetics and pain assessment after intracerebroventricular administration in patients with terminal cancer. Clin Pharmacol Ther 1991; 49:422-448.
- 67 **Robertson DH**
Transsacral neurolytic nerve block. An alternative approach to intractable perineal pain. Br J Anaesth 1983; 55:873-875.
- 68 **Arbit E**
Neurosurgical management of cancer pain. In: Foley K M, Bonica J J, Ventafrida V (eds) Second international congress on cancer pain. Advances in pain research and therapy, 1990; vol 16. Raven Press, New York, p 289-300.
- 69 **Levin AB, Ramirez LL**
Treatment of cancer pain with hypophysectomy: surgical and chemical. In: Benedetti C, Chapman C R, Moricca G (eds) Recent advances in the management of pain. Advances in pain research and therapy, vol 7. Raven Press, New York, 1984; p 631-645.
- 70 **Hassenbusch SJ, Pillay PK, Barnett GM**
Radiofrequency cingulotomy for intractable cancer pain using stereotaxis guided by magnetic resonance imaging. Neurosurgery 1990; 27:220-223.
- 71 **Ventafrida V, Ripamonti C, De Conno F, Tamburini M, Cassileth BR**
Symptom prevalence and control during cancer patients' last days of life. J Palliat Care 1990; 6:7-11.
- 72 **Latimer EJ**
Ethical decision-making in the care of the dying and its applications to clinical practice. J Pain Symptom Manage 1991; 6:329-336.
- 73 **Edwards RB**

Pain management and the values of health care providers. In: Hill C S, Fields W S (eds) Drug treatment of cancer pain in a drug-oriented society. Advances in pain research and therapy, Raven Press, New York, 1989; vol 11. p 101-112.

74 Wanzer SH, Federman DD, Adelstein SJ et al

The physician's responsibility toward hopelessly ill patients-a second look. N Eng J Med 1989; 120:844-849.

75 Martin RS

Mortal values: healing, pain and suffering. In: Hill C S, Fields W S (eds) Drug treatment of cancer pain in a drug-oriented society. Advances in pain research and therapy, Raven Press, New York, 1989; p 19-26.

76 Burke AL, Diamond PL, Hulbert J, Yeatman J, Farr EA

Terminal restlessness - its management and the role of midazolam. Med J Aust vol 11. 1991; 155:485-487.

77 Greene WR, Davis WH

Titration intravenous barbiturates in the control of symptoms in patients with terminal cancer. South Med J 1991; 84:332-7.

78 Cherny NI, Portenoy RK

Practical Issues in the Management of Cancer Pain In: Wall PD, Melzack R (eds) Textbook of Pain, third edition, 1994, Churchill Livingstone, Edinburgh, UK.

2.3 Pain management in prostate cancer patients

2.3.1 Clinical presentation

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

Pain is more common and a real challenge in advanced disease. Therefore pain management has to focus on the symptomatic patient with metastases. The overall incidence of chronic pain in prostate cancer patients is about 30-50%, but as patients enter the terminal phase of their illness this figure rises to 90% (3). Pain may be directly attributable to tumour growth in three main areas which include tumour infiltration of bone, nerve or a hollow viscus.

2.3.2 Pain due to local impairment

2.3.2.1 Soft-tissue and hollow-viscus invasion

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

Bladder outlet obstruction

Continuous growth of the prostate can lead to an outlet obstruction. Lower urinary tract symptoms (LUTS) can occur, especially stranguria and an inability to void. In these cases of acute pain prompt relief is necessary. The best method is inserting a suprapubic catheter and starting with hormonal treatment in case of advanced disease. If after 3 months the outlet obstruction persists, a transurethral palliative resection (TURP) could be performed for palliative reasons.

Ureteric obstruction

Ureteric obstruction is most frequently caused by tumour compression or infiltration within the true pelvis (4-7). Less commonly, obstruction can be more proximal, associated with retroperitoneal metastases. In most cases obstruction is typically asymmetric. Untreated progressive ureteric obstruction results in bilateral hydronephrosis and subsequent renal failure. In terminal cancer patients the decision to drain the kidneys can be difficult. It is good practise to drain symptomatic hydronephrosis at once and to drain only one kidney (the one with the better function) in asymptomatic patients. For drainage a nephrostomy tube is superior to a DJ-stent, because the endoscopic routine changes of the stent in the following months could be more and more difficult in a continuously growing prostate gland. Another reason is that changing the nephrostomy tube can be performed without any anesthesia.

Lymphoedema

Patients with a huge prostate mass and/or lymph node metastases in the pelvis very often show lymphoedema of the legs. The treatment of lymphoedema are physiatric techniques including use of wraps, pressure stockings or pneumatic pump devices. These can both improve function and relieve pain and heaviness.

Ileus

Local obstruction of the rectum occurs commonly in advanced cancer of the prostate and can lead to abdominal pain caused by ileus. Peritoneal involvement, which is rare, can also result in ileus. Surgery has to be performed in case of mechanical obstruction. Paralytic ileus due to tumour infiltration of a nerve plexus or secondary to analgesics may require laxatives for opioid-induced constipation to improve motility and reduce pain.

2.3.3 Pain due to metastases

2.3.3.1 Bone metastases

The following should be recognized.

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

The choice of treatment will depend on the tumour site, histology, stage and the patient's physical and emotional condition. Although therapies are being developed which will target tumour cells specifically, the most commonly used techniques will continue to result in a degree of damage to normal tissues with consequent side-effects. In each case the benefits and side-effects should be considered. Therapeutic options with fewer side-effects should be administered first. Options are hormone therapy, radiotherapy, isotopes, and systemic analgesic pharmacotherapy (the 'analgesic ladder'). Other tools in pain management such as nerve blocks are rarely used.

Hormone therapy

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

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

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

Problem. To date most patients with adenocarcinoma of the prostate present in early tumour stages and undergo radical surgery or less often radiotherapy. In case of PSA recurrence and/or symptoms they undergo hormone therapy. For years they could be asymptomatic. Pain is associated with a hormone resistant tumour in progression. Therefore other treatment options in pain management have to be administered.

Radiotherapy

External radiotherapy for metastatic bone pain is beneficial in the majority of patients. This effect does not appear to be significantly influenced by dose-time relationships or histology. The proportion of patients achieving complete pain relief approaches 80% (16).

- The role of radiotherapy in the management of pain due to bone metastases is unquestioned.
- Radiotherapy techniques vary widely - from a large dose given as a single treatment to as many as 20 smaller treatments given over 4 weeks.
- Dose-time factors: The biological effect of the radiation depends not only on the total dose delivered but also on the number of separate treatments and the total time over which the irradiation therapy is administered.
- Standard palliative treatment has been 20 Gy in 5 fractions over 5 days for a small volume, but for larger volumes (such as a hemipelvic field, where there is closely related bowel) 30 Gy in 10 fractions over 12 days has been used (17).
- If the bone to be treated is superficial (e.g. ribs, scapula) then a single field using orthovoltage (300 kV) gives a sufficient tumour dose without irradiating underlying tissues too heavily.
- Palliative doses are smaller than maximum tolerance doses.
- Field size is a compromise
- Avoid treating larger volumes than necessary in order to minimise morbidity
- Bear in mind that radiological evidence of a deposit may considerably underestimate the extent of disease

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

Orthopaedic surgery

If more than 50% of the thickness of the cortex of a long bone is eroded by metastasis, prophylactic fixation rather than radiotherapy alone should be considered to avoid pathological fractures. Internal fixation should be followed by postoperative radiotherapy because there is a real danger of continued tumour growth and further structural weakness (23,24). Radiotherapy should not be withheld for fear of inhibiting bone healing and re growth. There is good evidence that palliative doses of radiotherapy are associated with recalcification (25).

Radioisotopes

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

Comparison of radioisotope vs. hemibody irradiation

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

Chemotherapy

The role of chemotherapy in prostate cancer has been very limited until now, because the progression rate is relatively low. In advanced disease previous clinical trials using single-agent chemotherapy have shown poor results. Newer studies suggest multiagent chemotherapies may be more effective. They may prolong survival, and relieve pain as well as other symptoms which are associated with progressive disease. Numerous studies have documented not only subjective responses to chemotherapy, in terms of decreased pain and improved quality of life, but also observed objective measures of responses, such as a decrease in tumour markers and stabilization or improvement of metastatic bone lesions, soft-tissue tumours, and lymphadenopathy. Currently, five chemotherapeutic regimens for advanced hormone-refractory prostate cancer are recommended by the National Comprehensive Cancer Network (NCCN) of the US, a consortium of 17 major cancer centres.

The PSA response rates are mentioned.

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

Although most of these regimens have associated side-effects, such as fatigue, mild myelosuppression, and gastro-intestinal irritation, they are generally well tolerated by the majority of patients (28).

Soft-tissue lesions could be influenced to a greater extent than bony metastases. Pain management by chemotherapy could be effective, however it is much more cost intensive than the administration of opioids.

Systemic analgesic pharmacotherapy (the 'analgesic ladder')

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

2.3.3.2 Spinal cord compression

Spinal cord compression may be due to collapse of a vertebral body or to pressure from an extradural tumour within the spinal canal and prodromal pain is a feature in 96% of these patients. The overall incidence in prostate cancer patients is less than 10% (29). Thoracic cord compression is the most common area (70%) and the incidence of multiple extradural sites may be as high as 18% (30). Definitive treatment with surgery (anterior decompression with spinal stabilisation) or radiotherapy should be considered. Sometimes the symptom of local back pain disappears despite increasing motor deficits. This is due to the evolving sensory component of the paraplegia. The use of corticosteroids (typically dexamethasone 16 mg daily) to treat oedema of the cord is temporary.

2.3.3.3 Hepatic invasion

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

Whole liver palliative radiotherapy can also be useful in carefully selected patients with refractory pain, with far fewer side-effects than the alternatives of intra-arterial chemotherapy or hepatic artery embolisation.

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

2.3.4 Pain due to cancer treatment

2.3.4.1 Acute pain associated with hormonal therapy

Luteinizing hormone releasing hormone (LHRH) tumour flare in prostate cancer

Initiation of LHRH therapy for prostate cancer produces a transient symptom flare in 5% - 25% of patients (32,33).

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

2.3.4.2 Chronic pain associated with hormonal therapy

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

2.3.5 Conclusions

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

required because there is still much to be learned about the indications, dose, frequency and optimal administration of anti-cancer therapies for the relief of pain.

Surgery, radiotherapy, chemotherapy, and hormone therapy are mainly used as anti-tumour treatment in the relief of pain. The rational use of any of these types of treatment demands knowledge both of tumour biology and also of the mechanisms of action of these specific oncological techniques. The therapeutic aim should be clearly understood prior to starting treatment. Radical treatment should be given if the disease is potentially curable, but the intent should be symptomatic or palliative if the tumour is advanced or widely disseminated (41). The various regimens employed to treat pain in prostate cancer patients have been described above and the scientific basis for their use have been explained. However, the importance of early intervention needs to be emphasized. Education of the patient is crucial. He must be aware of the early signs and symptoms of metastatic disease which do not necessarily involve pain.

Recommendations at a glance (stage M1)

Grades of recommendation (A, B, C, GPP) and levels of evidence (Ia, Ib, IIa, IIb, III, IV)

Additional references (42-47)

Anti cancer treatment

- A, Ia Hormonal therapy (Orchiectomy, LHRH analogues, diethylstilbestrol equivalent)
- B, IIb Total androgen blockade: flare prevention, second line
- B, III Intermittent androgen suppression experimental
- A, Ib To date monotherapy with antiandrogen not recommended
- A, Ib First line treatment controls disease for 12 to 18 months, second line individualized
- Supportive care
- A, Ib Low-dose glucocorticoids
- Chemotherapy
- B, Ib Mitoxantrone plus prednisolone
- B, IIb Estramustine + vinblastine or etoposide or paclitaxel

Pain management

- B Pain assessment (localisation, type, severity, overall distress)
- Pain due to painful or unstable bony metastases (some spots)
- C External beam irradiation
- Pain due to painful bony metastases (widespread)
- C Primary hormone therapy, maximum androgen blockade in case of worsening
- Hemibody irradiation
- B Radioisotopes (Strontium-89 or Samarium-153)
- Pain due to painful metastases (many spots)
- B, IIb Biphosphonates
- Systemic pain management
- B Around-the-clock dosing, not as 'required'
- Mild pain
- A World Health Organisation analgesic ladder step 1: NSAID or paracetamol
- Moderate pain
- B codeine, dihydrocodeine or dextropropoxyphene plus paracetamol or NSAID
- Severe pain
- B (C) Morphine or diamorphine (oral route)
- Opioid administration
- B Dose titration
- C Access to breakthrough analgesia
- B Prophylactic laxatives
- B Subcutaneous route when parenteral required: transdermal fentanyl equi effective
- A Tricyclic antidepressant and/or anticonvulsant in case of neuropathic pain
- C High dose dexamethasone in case of severe bone pain, nerve infiltration, spinal cord compression, hepatic capsular pain
- Psychological therapies and psychiatric techniques

2.3.6 References

- 1 **Saunders CM**
Appropriate treatment, appropriate death. In: Saunders C M (ed) The management of terminal malignant disease, 2nd edn. Edward Arnold, London, 1984; p 1.
- 2 **Foley KM**
Pain syndromes in patients with cancer. In: Bonica J J, Ventafridda V (eds) Advances in pain research and therapy 2. Raven Press, New York, 1979; p 59-75.
- 3 **Twycross RG, Lack SA**
Symptom control in far advanced cancer: pain relief. Pitman, London, 1983; p 6.
- 4 **Fair WR**
Urologic emergencies. In: DeVita V T, Hellman S, Rosengerg S A (eds). Cancer principles and practice of oncology, 3rd edn. Lippincott, Philadelphia, 1989; p 2016-2028.
- 5 **Greenfield A, Resnick MI**
Genitourinary emergencies. Seminars in Oncology 1989; 16:516-520.
- 6 **Talner LB**
Specific causes of obstruction. In: Pollack H M (ed) Clinical urography, Saunders, Philadelphia, 1990; vol 2. p 1629-1751.
- 7 **Cherny NI, Portenoy RK**
Cancer Pain: Principles of Assessment and Syndromes In: Wall PD, Melzack R (eds) Textbook of Pain, third edition, 1994 Churchill Livingston, Edinburgh, UK.
- 8 **Banning A, Sjogren P, Henriksen H**
Pain causes in 200 patients referred to a multidisciplinary cancer pain clinic. Pain 1991; 45:45-48.
- 9 **Nielsen OS, Munro AJ, Tannock IF**
Bone metastases: pathophysiology and management policy. J Clin Oncol 1991; 9:509-524.
- 10 **Wagner G**
Frequency of pain in patients with cancer. Recent Results in Cancer Research 1984; 89:64-71.
- 11 **Huggins C, Hodges VC**
Studies on prostatic cancer. Cancer Research 1941; 1:293-297.
- 12 **Powles TJ, Smith IE, Coombes RC**
Endocrine therapy. In: Halnan K E (ed) Treatment of cancer. Chapman & Hall, London, 1982; p 103-117.
- 13 **Stoll BA**
Hormonal therapy-pain relief and recalcification. In: Stoll B A, Parbhoo S (eds) Bone metastasis: monitoring and treatment. 1983; Raven Press, New York, p 321-342.
- 14 **Stoll BA**
Breast and prostatic cancer: methods and results of endocrine therapy. In: Stoll B A (ed) Hormonal management of endocrine-related cancer. Lloyd-Luke, London, 1981; p 77-91, 148-157.
- 15 **Pannuti F, Martoni A, Rossi AP, Piana E**
The role of endocrine therapy for relief of pain due to advanced cancer. In: Bonica J J, Ventafridda V (eds) Advances in pain research and therapy 2. 1979 Raven Press, New York, p 145-165.
- 16 **Bates TD**
Radiotherapy, chemotherapy and hormone therapy in the relief of cancer pain. In: Swerdlow M, Charlton J E (eds) Relief of intractable pain. 1989 Elsevier, Amsterdam, p 329-347.
- 17 **Ford HT, Yarnold JR**
Radiation therapy - pain relief and recalcification. In: Stoll B A, Parbhoo S (eds) Bone metastasis: monitoring and treatment. 1983 Raven Press, New York, p 343-354.
- 18 **Qasim MM**
Half body irradiation (HBI) in metastatic carcinomas. Clin Radiol 1981; 32:215-219.
- 19 **Salazar OM, Rubin P, Hendrickson FR et al**
Single-dose half-body irradiation for the palliation of multiple bone metastases from solid tumours: a preliminary report. J Radiat Oncol Biol Phys 1981; 7:773-781.
- 20 **Wilkins MF, Keen CW**
Hemi-body radiotherapy in the management of metastatic carcinoma. Clin Radiol 38:267-268.
- 21 **Danjoux CE, Rider WD, Fitzpatrick PJ**
The acute radiation syndrome. Clin Radiol 1979; 30:581-584.
- 22 **Fryer CJH, Fitzpatrick PJ, Rider WD, Poon P**
Radiation pneumonitis: experience following a large single dose of radiation. J Radiat Oncol Biol Phys 1978; 4:931-936.
- 23 **British Medical Journal Editorial:**
Pathological fracture due to bone metastasis. Br Med J 1981; 283:748.
- 24 **Galasko CSB**

- The management of skeletal metastases.
Journal of the Royal College of Surgeons of Edinburgh 1980; 3:148-151.
- 25 **Ford HT, Yarnold JR**
Radiation therapy - pain relief and recalcification. In: Stoll B A, Parbhoo S (eds) Bone metastasis: monitoring and treatment. 1983 Raven Press, New York, p 343-354.
- 26 **Dearnaley DP, Bayly RJ, A'Hern RP et al**
Palliation of bone metastases in prostate cancer. Hemibody irradiation or Strontium-89. Clin Oncol 1992; 4:101-107.
- 27 **Kraeber-Bodere F, Campion L, Rousseau C, Bourdin S, Chantal JF, Resche I**
Treatment of bone metastases of prostate cancer with strontium-89 chloride: efficacy in relation to the degree of bone involvement. Eur J Med 2000 Oct; 27 (10): 1487-1493.
- 28 **Olson KB, Pienta KJ**
Pain Management in Patients With Advanced Prostate Cancer Oncology (Huntingt) 1999 Nov;13(11):1537-1549;discussion 1549-1550 passim.
- 29 **Hoy AM, Lucas CF**
Radiotherapy, Chemotherapy and Hormone Therapy: Treatment for Pain In: Wall PD, Melzack R (eds) Textbook of Pain, third edition, 1994 Churchill Livingstone, Edinburgh, UK.
- 30 **Kramer JA**
Spinal cord compression in malignancy. Palliat Med 1992; 6:202-211.
- 31 **Borgelt BB, Gelber R, Brady LW, Griffin T, Hendrickson FR**
The palliation of hepatic metastases: results of the Radiation Therapy Oncology Group pilot study. J Radiat Oncol Biol Phys 1981; 7:587-591.
- 32 **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; 144:1479-1480.
- 33 **Chrisp P, Sorkin EM**
Leuporelin. A review of its pharmacology and therapeutic use in prostatic disorders. Drugs and Aging 1991; 1:487-509.
- 34 **Goldspiel BR, Kohler DR**
Goserelin acetate implant: a depot luteinizing hormone-releasing hormone analogue for advanced prostate cancer. DICP 1991; 25:796-804.
- 35 **Crawford ED, Nabors W**
Hormone therapy of advanced prostate cancer: where we stand today. Oncology 1991; 5:21-30.
- 36 **Eberlein TJ**
Gynecomastia. In: Harris J R, Hellman S, Henderson I C, Kinne D (eds) Breast diseases, 2nd ed. 1991 Lippincott, Philadelphia, p 46-50.
- 37 **Delaere KP, Van Thillo E**
Flutamide monotherapy as primary treatment in advanced prostatic carcinoma. Seminars in Oncology 1991; 5:13-18.
- 38 **Goldenberg SL, Bruchovsky N**
Use of cyproterone acetate in prostate cancer. Urologic Clinics of North America 1991; 18:111-122.
- 39 **Neumann F, Kalmus J**
Cyproterone acetate in the treatment of sexual disorders: pharmacological base and clinical experience. Exp Clin Endocrinol 1991; 98:71-80.
- 40 **Ramamurthy L, Cooper RA**
Metastatic carcinoma to the male breast. Br J Radiol 1991; 64:277-278.
- 41 **Cherny NI, Portenoy RK**
Cancer Pain: Principles of Assessment and Syndromes In: Wall PD, Melzack R (eds) Textbook of Pain, third edition, 1994 Churchill Livingstone, Edinburgh, UK.
- 42 **National Committee on Cancer Care Workgroup on Prostate Cancer**
Treatment of Metastatic Prostate Cancer (M1) In: Ministry of Health (Singapore): Prostate cancer 2000, National Guideline Clearinghouse, <http://www.ngc.gov>.
- 43 **Scottish Intercollegiate Guidelines Network (SIGN)**
Control of pain in patients with cancer. A national clinical guideline 2000, National Guideline Clearinghouse, <http://www.ngc.gov>.
- 44 **American College of Radiology**
ACR Appropriateness Criteria(tm) for bone metastases In: American College of Radiology: ACR Appropriateness Criteria(tm) for metastatic bone disease, 1995 (revised 1999), National Guideline Clearinghouse, <http://www.ngc.gov>.
- 45 **Cancer Care Ontario (CCO)**

Use of strontium-89 in patients with endocrine-refractory carcinoma of the prostate metastatic to bone, 1997 (updated online 2001), National Guideline Clearinghouse, <http://www.ngc.gov>.

46 Schröder FH

Hormonal Therapy of Prostate Cancer In: Walsh, Retik, Vaughan, Wein (eds), Kavoussi, Novick, Partin, Peters (associate eds): *Campbell's Urology*, 8th edition, vol. 4, 3182-3208.

47 Eisenberger MA

Chemotherapy for Hormone-Resistant Prostate Cancer In: Walsh, Retik, Vaughan, Wein (eds), Kavoussi, Novick, Partin, Peters (associate eds): *Campbell's Urology*, 8th edition, vol. 4, 3209-3226.

2.4. Pain management in transitional cell carcinoma patients

2.4.1 Clinical presentation

Urothelial cancer is the fourth most common cancer in men and the ninth in women (1). Transitional cell carcinoma (TCC) is the most frequent cancer of the bladder and upper urinary tract. It arises much more frequently in the bladder than in the collecting system - calices, renal pelvis and ureter. From the perspective of the pain no differences can be made between the transitional cell carcinoma (TCC) and other histotypes of urothelial malignant tumours. In terms of bladder carcinoma pain can be present during the natural history of the disease - early as a burning pain together with irritative symptoms, or late in the advanced disease due to local invasion of neighbouring tissues or metastatic organ invasion.

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

Origin of tumour related pain

Bladder TCC

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

Upper urinary tract TCC

- 1) Obstruction of the upper urinary tract (presenting symptom in around 30% of cases)
- 2) Acute obstruction due to blood clots
- 3) Invasion of the surrounding areas by a locally advanced tumour (posterior abdominal wall, nerve roots, paraspinous muscles, other organs like bowel, spleen, liver)
- 4) Bone metastases
- 5) Soft tissue metastases (seldom painful)

2.4.2 Pain due to local impairment

Bladder TCC

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

In locally advanced disease infiltration of the contiguous soft tissue and neighbouring organs can determine acute burning pain by infiltration of the pelvic nerves (neuropathic pain). This pain is sometimes associated with paraesthesia irradiating to the lower limb or with motor deficit. If the tumour invades adjacent organs - small bowel, rectum - obstruction of these organs could appear and visceral pain due to distension of hollow organs.

Additionally, growing bladder tumour can cause complete bladder outlet obstruction with hypo gastric abdominal pain due to bladder distension. Obstruction of the lymphatic vessels by lymphadenopathy can cause lymphoedema of the lower limbs with pain due to distension of muscle fascia (somatic pain).

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

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

Radiotherapy can be effective in controlling pelvic pain due to local disease progression. Using 40-45 Gy on

target volume RT can reduce the local painful symptoms but it can also worsen the irritative bladder symptoms and can induce proctitis (Evidence level IIb) (10).

Upper tract TCC

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

2.4.3 Pain due to metastases

In advanced disease of bladder or upper urinary tract TCC haematogenous metastases to the bone are often found. No data are available in the literature concerning the specific effect of chemotherapy on bone metastases only. Radiotherapy has a palliative analgesic role in bone metastases. Using ten fractionated doses of 30 - 35 Gy it rapidly reduces if not eliminates pain in 80-90% of cases (Evidence level IIb) (10). Also hemibody irradiation can be used in diffuse bone metastases (10). No specific studies exist on the radioisotope therapy of bone metastasis in transitional cell carcinoma.

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

2.4.4 References

- 1 **Wingo PA, Tong T, Bolden S**
Cancer Statistics 1995. *CA Cancer J Clin* 1995; 45: 45 - 48.
- 2 **Fraley EE**
Cancer of the renal pelvis. In *Genitourinary cancer*. Skinner DG, De Kernion JB (eds). W.B. Saunders: Philadelphia, 1978: 134.
- 3 **Huben RP, Mounzer AM, Murphy GP**
Tumor grade and stage as prognostic variables in upper tract urothelial tumors. *Cancer* 1988; 62: 2016-2020.
- 4 **Mount BM, Scott JF**
Palliative care of the patients with terminal cancer. In : *Diagnosis and management of genitourinary cancer*. Skinner DG, Lieskovsky G (eds.). W.B. Saunders : Philadelphia 1988; 842-863
- 5 **Ricci S, Galli L, Chioni A, Iannopolo M, Antonuzzo A, Francesca F, Selli C, Orlandini C, Conte PF**
Gemcitabine plus epirubicin in patients with advanced urothelial carcinoma not eligible for platinum-based regimens. *Cancer* 2002; 95: 1444-1450.
- 6 **Sternberg C, Yagoda A, Scher HI, Watson RC, Geller N, Herr HW, Morse MJ, Sogani PC, Vaughan ED, Bander N et al.**
Methotrexate, vinblastine, doxorubicin and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and pattern of response and relapse. *Cancer* 1989; 12: 2448-2458.
- 7 **Loehrer PJ, Einhorn LH, Elson P, Crawford ED, Kuebler P, Tannock I, Raghavan D, Stuart- Harris R, Sarosdy MF, Lowe BA et al.**
A randomized comparison of cisplatin alone or combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1992; 10: 1066-1072.
- 8 **Logothetis C, Dexeus F, Finn L, Sella A, Amato RJ, Ayala AG, Kilbourn RG**
A prospective randomized trial comparing M-VAC and CISCA chemotherapy for patients with metastatic urothelial tumors. *J Clin Oncol* 1990; 8: 1050-1055.
- 9 **Van der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Mooer MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, Kerbrat P, Sanchez Rovira P, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Grul CM, Conte PF**
Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomised, multinational, multicenter, Phase III study. *J Clin Oncol* 2000; 18: 3068-3077.
- 10 **Friedland J**
Local and systemic radiation for palliation of metastatic disease. *Urol Clin North Am* 1999; 26: 391 - 402.

2.5. Pain management in renal cell carcinoma patients

2.5.1 Clinical presentation

Renal cell carcinoma is mainly diagnosed incidentally. Pain cannot be expected unless a tumour invades surrounding areas or obstructs the outflow of urine owing to haemorrhage and subsequent formation of blood clots.

20-30% of the patients present with metastatic disease and 30% of the patients primary presenting with a localised kidney tumour develop metastases during follow-up. That means 50-60% of all patients with renal cell carcinoma develop metastases during their life and may have to be treated because of symptoms, mainly pain. Renal cell carcinoma spreads mainly to lung, bone, brain, liver and ipsilateral or contralateral adrenergic gland. Patients with metastases have a 2-year survival rate of maximal 20%, which has to be considered in case of palliative treatment.

Origin of tumour related pain:

- 1) Invasion of the surrounding areas by a locally advanced tumour (posterior abdominal wall, nerve roots, paraspinal muscles, other organs like bowel, spleen, liver)
- 2) Obstruction of the upper urinary tract due to haemorrhage and subsequent formation of blood clots
- 3) Bone metastases
- 4) Soft tissue metastases (seldom painful)

2.5.2 Pain due to local impairment

Patients with *invasion of the surrounding areas* by a locally advanced primary tumour (e.g. invasion of the posterior abdominal wall, nerve roots, paraspinal muscles, other organs like bowel, spleen, liver) without metastases usually present with pain. Surgical management is the only effective management of this type of tumour. Sometimes extended operations including excision of involved bowel, spleen or abdominal wall muscle are indicated. Adjuvant immunotherapy or radiotherapy is without proven benefit with regard to recurrence. Even in case of metastatic disease, palliative nephrectomy is indicated for the control of severe symptoms like haemorrhage, pain or paraneoplastic syndromes (GPP). The frequency with which each of these symptoms is controlled, however, is unclear and there are no data in the literature comparing efficacy of nephrectomy in palliative situations to other therapies like angioinfarction of the tumour.

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

In metastatic disease, EORTC study 30947 demonstrated significant increase in survival with palliative nephrectomy plus immunotherapy compared to immunotherapy (interferon-alpha) alone (median survival of 17 compared to 7 months) (evidence level Ib) (2). There is no special effect on pain relief by immunotherapy.

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

There are no data in the literature concerning the efficacy of alternative therapies like angioinfarction of the tumour in regard to haemorrhage and pain relief in palliative situations.

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

2.5.3 Pain due to metastases

Patients with *bone metastases* have a significantly better life expectancy (30 months) than those with visceral metastases (11,6 months) (3).

Indications for surgery for bone metastases are solitary metastases that can be resected completely, intractable bone pain, impending or demonstrated pathologic fracture. In cases of bone metastases with extensive soft tissue involvement and corresponding severe pain sometimes amputation of a leg or arm is required to maintain a certain quality of life. With surgery of bone metastases a significant pain decrease is achieved in 89 - 91 % (Evidence level IIb/III) (4-6). Additionally, surgery prevents pathologic fractures and spinal compression, and there is a significant impact on survival.

Preoperative embolization of bone metastases or embolization alone achieves good pain relief in hypervascular bone metastases (Evidence level III) (7,8).

High dose radiation therapy for palliation of painful bony metastases has shown to be effective in 50-75% of all renal cancer patients (Evidence level III) (9-11) and in 67% for bone metastases in general (Evidence level IIb) (12). There is no impact on survival.

In small studies radionuclide therapy, e.g. Sr-89 therapy, seems to achieve good pain relief in bone metastases

from renal cell carcinoma (Evidence level III) (13). Large prospective studies in regard to long term pain relief are missing.

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

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

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

Immunotherapy alone achieves an overall response in 15-27% (14). Immunotherapy in combination with chemotherapy (IL-2 + interferon-alpha + 5-fluorouracil) is the most effective immunotherapy with partial tumour response in up to 46% and complete response in maximal 15% of the patients. However, these response rates are observed nearly exclusively for lung and lymph node metastases (15). Pain due to soft tissue metastases probably behaves in a manner analogue to the tumour response, but there are no data concerning pain control by immunotherapy.

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

2.5.4 References

- 1 **Van de Werf-Messing B**
Proceedings: Carcinoma of the kidney. *Cancer* 1973; 32: 1056-1061.
- 2 **Mickisch GA, Garin A, van Poppel H, de Prijck L, Sylvester R**
Radical nephrectomy plus interferon-alpha-based immunotherapy compared with interferon-alpha alone in metastatic renal cell carcinoma: A randomised trial. *Lancet* 2001; 358: 966-970.
- 3 **Bohnenkamp B, Romberg W, Sonnentag W, Feldmann U**
Prognosis of metastatic renal cell carcinoma related to the pattern of metastasis. *J Cancer Res Clin Oncol* 1980; 96: 105-114.
- 4 **Smith EM, Kursh ED, Makley J, Resnick MI**
Treatment of osseous metastases secondary to renal cell carcinoma. *J Urol* 1992; 148: 784-787.
- 5 **Kollender Y, Bickels J, Price WM, Kellar KL, Chen J, Merimsky O, Meller I, Malawer MM**
Metastatic renal cell carcinoma of bone: Indications and technique of surgical intervention. *J Urol* 2000; 164: 1505-1508.
- 6 **Jackson RJ, Loh SC, Gokaslan ZL**
Metastatic renal cell carcinoma of the spine: surgical treatment and results. *J Neurosurg* 2001; 94 (Suppl 1): 18-24.
- 7 **Gorich J, Solymosi L, Hasan I, Sittek H, Majdali R, Reiser M**
Embolization of bone metastases. *Radiologe* 1995; 35: 55-59.
- 8 **Layalle I, Flandroy P, Trotteur G, Dondelinger RF**
Arterial embolization of bone metastases: is it worthwhile? *J Belge Radiol* 1998; 81(5): 223-225.
- 9 **Halperin EC and Harisiadis L**
The role of radiation therapy in the management of metastatic renal cell carcinoma. *Cancer* 1983; 51: 614-617.
- 10 **Onufrey V and Mohiuddin M**
Radiation therapy in the treatment of metastatic renal cell carcinoma. *Int J Rad Oncol Biol Phys* 1985; 11: 2007-2009.
- 11 **Forman JD**
The role of radiation therapy in the management of carcinoma of the kidney. *Sem Urol* 1989; 7: 195-198.
- 12 **Chow E, Wong R, Hruby G, Connolly R, Franssen E, Fung KW, Andersson L, Schueller T, Stefaniuk K, Szumacher E, Hayter C, Pope J, Holden L, Loblaw A, Finkelstein J, Danjoux C**
Prospective patient-based assessment of effectiveness of palliative radiotherapy for bone metastases. *Radiother Oncol* 2001; 61(1): 77-82.
- 13 **Kloeber R, Molnar CP, Barnes M**
Sr-89 therapy for metastatic bone disease: scintigraphic and radiographic follow-up. *Radiology* 1987; 163(3): 719-723.
- 14 **Figlin RA**
Renal cell carcinoma: management of advanced disease. *J Urol* 1999; 161: 381-386.
- 15 **Kankuri M, Pelliniemi TT, Pyrhonen S, Nikkannen V, Helenius H, Salminen E**
Feasibility of prolonged use of interferon-alpha in metastatic kidney carcinoma: a phase II study. *Cancer* 2001; 92(4): 761-767.

2.6. Pain management in adrenal carcinoma patients

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

2.6.1 Malignant pheochromocytoma

Pheochromocytomas result from pheochromocytes, which are the predominant cells of the adrenal medulla and are also found in the paraganglia near the aorta and in lesser quantities in the ganglia of the sympathetic nervous system (2). When correctly diagnosed and treated the disease is curable unless there are metastases. The highest sensitivity in detecting the tumour has CT scan or MRI with 94-100%. ¹³¹J-MIBG (¹³¹J-metaiodo-benzylguanidine) scan is positive in approximately 87% (3).

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

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

Treatment of pain

- a) Soft tissue and/or bone pain due to metastases are best treated by therapeutic doses of ¹³¹J-MIBG, if the pheochromocytoma takes up this radionuclide (Evidence level IIb) (8). There is no literature concerning chemotherapy or radiotherapy and pain relief in metastatic pheochromocytoma.
- b) Symptomatic treatment of the pain with drugs etc. according to chapter 2.

2.6.2 Adrenocortical carcinomas

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

Chemotherapy is of low efficacy. The most effective drug is mitotane, an adrenolytic drug. The tumour response rate is 25-35 % (Evidence level IIa) (9,11). If there is a prolonged survival by using chemotherapy remains unproven.

Radiation therapy has not been useful except for palliation and pain management (Evidence level IIb) (12).

Treatment of the pain depending on its origin

- a) Abdominal symptoms are typical symptoms when first presenting with the tumour. The treatment is surgical removal of the primary tumour with attempting to remove the entire lesion even if resection of adjacent structures is necessary as well as resection of the local lymph nodes.
- b) Soft tissue and/or bone metastases causing local symptoms can be treated by radiation therapy (8,12). There is no literature concerning chemotherapy or radiotherapy and pain relief in metastatic adrenocortical carcinomas.
- c) Symptomatic treatment of the pain with drugs etc. correspond to chapter 2.

2.6.3 References

- 1 **Cerfolio RJ, Vaughan ED Jr.; Brennan TG, Hirvela ER**
Accuracy of computed tomography in predicting adrenal tumor size. Surg Gynecol Obstet 1993; 176: 307-309.
- 2 **Goldfien A**
Pheochromocytoma - diagnosis and management. Clin Endocr Metab 1991; 10: 606.
- 3 **Lucon AM, Pereira MAA, Mendonca BB, Halpern A, Wajchenbeg BL and Arap S**
Pheochromocytoma: Study of 50 cases. J Urol 1997; 157: 1208-1212
- 4 **Schlumberger M, Gicquel C, Lumbroso J, Tenenbaum F, Comoy E, Bosq J, Fonseca E, Ghillani PP, Aubert B, Travagli JP, et al.**
Malignant pheochromocytoma: clinical, biological, histological and therapeutic data in a series of 20 patients with distant metastases. J Endocr Invest 1992; 15: 631-642.
- 5 **Mornex R, Badet C and Peyrin L**
Malignant pheochromocytoma: a series of fourteen cases observed between 1966 and 1991. J Endocr Invest 1992; 15: 643-649.

- 6 **Proye C, Vix M, Goropoulos A, Kerlo P and Lecomte-Houcke M**
High incidence of malignant pheochromocytoma in a surgical unit: 26 cases out of 100 patients operated from 1971 to 1991. *J Endocrinol Invest* 1992; 15: 651-663.
- 7 **Yu L, Fleckman AM, Chadha M, Sacks E, Levetan C, Vikram B**
Radiation therapy of metastatic pheochromocytoma: case report and review of the literature. *Am J Clin Oncol* 1996; 19: 389-393.
- 8 **Kopf D, Goretzki PE, Lehnert H**
Clinical management of malignant adrenal tumors. *J Cancer Res Clin Oncol* 2001; 127: 143-155.
- 9 **Wooten MD and King DK**
Adrenal cortical carcinoma. Epidemiology and treatment with mitotane and a review of the literature. *Cancer* 1993; 72: 3145-3155.
- 10 **Didolkar MS, Berscher AR, Elias EG, Moore RH.**
Natural history of adrenal cortical carcinoma: A clinical pathologic study of 42 patients. *Cancer* 1981; 47: 2153-2161.
- 11 **Bukowski RM, Wolfe M, Levine HS, Crawford DE, Stephens RL, Gaynor E, Harker WG**
Phase II trial of mitotane and cisplatin in patients with adrenal carcinoma: a Southwest oncology group study. *J Clin Oncol* 1993; 11: 161-165.
- 12 **Percarpio GT, and Knowlton AH.**
Radiation therapy of adrenal cortical carcinoma. *Acta Radiol* 1976; 15: 288-292.

2.7. Pain management in penile cancer patients

2.7.1 *Clinical presentation*

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

Until now there is no consensus about the therapeutic management of metastatic disease, and there are few controlled studies of statistical significance that study both penile carcinoma and cancer-related pain. Most of the principles about dealing with pain management in prostatic carcinoma are valid here as well; however, the following aspects should also be taken into consideration.

Pain can occur in both early and advanced stages of penile cancer. In early stages, acute pain could be the result of a voiding dysfunction (subvesical obstruction); details are given in chapter 4 on management of bladder outlet obstruction in prostate cancer. In advanced stages of the disease pain is usually caused by metastases or lymph node involvement. Inguinal lymph node involvement plays an important role. Positive lymph nodes are relatively common in penile cancer; inguinal or pelvic lymph nodes are most frequently affected. Positive nodes could be found in about 50% of cases, and systematic lymphadenectomy is curative in about 50% of these patients. Among all the possible complications after inguinal and ilioinguinal lymphadenectomy permanent and disabling lymphoedema of the scrotum and lower limbs are frequent.

Pain can ensue from:

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

2.7.2 *Pain due to local impairment*

Soft-tissue and hollow-viscus invasion

Bladder outlet and ureteric obstruction is managed analogously to that described in the chapter 'prostatic carcinoma' (chapter 3.2.1).

Lymphoedema

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

2.7.3 Pain due to metastases

Anti cancer management for pain relief

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

2.7.4 Conclusions

Until there is some sort of guideline about treating metastatic penile carcinoma, there will not be any conclusive or universally applicable recommendations about managing this kind of pain. To date treatment has been experimental in nature; findings from other cancer treatment regimes must be adapted for want of a more well-documented strategy. As is the case elsewhere, attention is paid to the guidelines that are appropriate for treating metastases and the involved organs (chapter 2).

2.7.5 References

1 Lynch DF Jr, Pettaway CA

Tumours of the Penis. In: Walsh, Retik, Vaughan, Wein (eds), Kavoussi, Novick, Partin, Peters (associate eds): Campell's Urology, 8th Edition, Vol. 4, 2945-2982.

2.8. Pain management in testicular cancer patients

2.8.1 Clinical presentation

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

2.8.2 Pain due to local impairment

Local pain due to the scrotal mass is effectively treated by orchiectomy.

2.8.3 Pain due to metastases

- a) Back or flank pain due to retroperitoneal lymphadenopathy will slowly disappear under chemotherapy with decrease of the mass (Evidence level IIb) (see guidelines to testicular cancer). Temporary analgesics are advisable (chapter 2 of these guidelines).
- b) Retroperitoneal lymph node metastases can also cause obstruction of the ureter leading to a symptomatic hydronephrosis with back or flank pain and perhaps additional fever. Therapy of choice is the immediate treatment of the hydronephrosis by ureteral stenting or inserting a percutaneous nephrostomy.
- c) Bone pain due to bone metastases is very rare and mainly occurs in patients with primary advanced disease and relapse after chemotherapy (2,3). Treatment may be possible by chemotherapy or second line chemotherapy (see guidelines for "Testicular cancer"). There is no literature considering radiotherapy in case of relapse and limitation for further chemotherapy.
- d) Back pain and neurological symptoms due to spinal cord compression by vertebral metastases may require urgent surgery (Evidence level III) (4).

2.8.4 References

1 Hermes ER, Harstad K, Fossa SD

Changing incidence and delay of testicular cancer in Southern Norway (1981-1992).
Eur Urol 1996; 30: 349-357.

2 Hitchins RN, Philip PA, Wignall B, Newlands ES, Begent RH, Rustin GJ, Bagshawe KD

Bone disease in testicular and extragonadal germ cell tumours. Br J Cancer 1988; 58: 793-796.

3 Merrick MV

Bone scintigraphy in testicular tumours. Br J Urol 1987; 60: 167-169.

4 Arnold PM, Morgan CJ, Morantz RA, Kepes JJ

Metastatic testicular cancer presenting as spinal cord compression: report of two cases.
Surg Neur 2000; 54: 27-33.

2.9. RECOMMENDATIONS AT A GLANCE

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

?	no conclusive data	
-	no	
+	low	
++	moderate	
+++	good	

Origin of pain / Therapeutic options	RCC	TCC	PCA	Penile cancer	Adrenergic cancer	Testicular cancer
Bone metastases						
surgery	+++	?	+	?	?	+
radiation	++	++	+++	?	+	?
radionuclide	+	?	+++	?	++	-
chemotherapy	-	?	+	?	-	+++
immunotherapy	-	-	-	?	?	?
hormone therapy	-	-	++	-	-	-
analgetics	+++	+++	+++	+++	+++	+++
Soft tissue infiltration						
surgery	+++	+++	-	?	?	+
radiation	-	+	++	?	+	?
chemotherapy	+	++	+	?	++	+++
immunotherapy	+	-	-	?	?	?
hormone therapy	-	-	++	-	-	-
analgesics	+++	+++	+++	+++	+++	+++
Nerve compression / nerve infiltration						
surgery	+++	+++	++	?	?	++
radiation	+	+	++	?	+	?
chemotherapy	+	++	+	?	?	+++
immunotherapy	+	-	-	?	?	?
hormone therapy	-	-	++	-	-	-
analgesics	+++	+++	+++	+++	+++	+++

3. POSTOPERATIVE PAIN MANAGEMENT

3.1. Background

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

All dosages refer to an average weight of 70 Kg.

These are approximate dose ranges. Actual selected dose depends on individual patient assessment.

3.2. Importance of effective postoperative pain control

Stress response to surgery

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

Poor postoperative pain control

Pain associated with these responses is unpleasant for the patient. Numerous reports have appeared in the medical literature describing the unacceptability of poorly controlled postoperative pain in hospitals (4,5). One

survey found that 77% of adults believed that postoperative pain is to be expected, with almost 60% regarding this as their primary fear before surgery (6). The traditional and common practice of giving 'as required' intramuscular opioids has been reported to lead to unrelieved pain in over 50% of patients (7).

EVIDENCE LEVEL III

Surgical morbidity

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

EVIDENCE LEVEL IIb

Economic cost

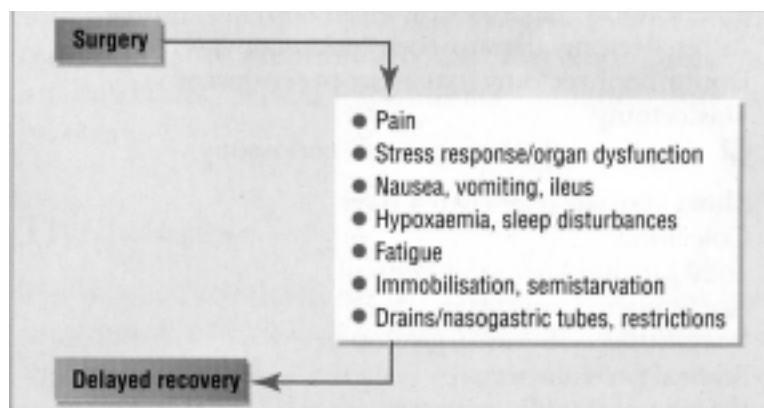
In addition, poor pain control may delay discharge from hospital, and lead to unplanned hospital admission following ambulatory surgery thus increasing medical costs (9).

EVIDENCE LEVEL III

Postoperative rehabilitation

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

EVIDENCE LEVEL IIb



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

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

3.3.1 Development of Acute Pain Teams

The importance of effective pain control and recognition of the inadequacy of treatment was appreciated by surgeons and anesthesiologists in the 1980's. This led to a number of changes including the development of Acute Pain Teams within hospitals to oversee effective postoperative pain control (12-16)

EVIDENCE LEVEL III

Many hospitals now unite the different postoperative analgesic techniques such as epidurals and Patient Controlled Analgesia (PCA) under the common management of an Acute Pain Team. These multidisciplinary teams are usually led by an anesthesiologist and consist of nursing and pharmacy personnel (17). Their aim is to treat pain, introduce systematic pain assessment, introduce new techniques such as PCA and epidurals, and to teach medical and nursing staff. In addition they are responsible for the audit of their services and for research.

EVIDENCE LEVEL III

Such acute pain services have been shown to improve pain relief and postsurgical outcomes (12,13). There is some evidence that 'low tech,' low cost approaches such as regular pain assessment, easy access to strong opioid drugs and teaching and education, are just as important as 'high tech' approaches such as PCA and

epidurals (18). In addition, improved pain control may lead to shorter hospital stays and fewer unscheduled admissions after day-case surgery (19).

EVIDENCE LEVEL III

The main aims of effective postoperative pain treatment (12,13);

- to reduce the incidence and severity of patients' postoperative pain
- to educate patients about the need to communicate unrelieved pain so they can receive prompt evaluation and effective treatment
- to enhance patient comfort and satisfaction
- to contribute to fewer postoperative complications and, in some cases, shorter stays after surgical procedures
- to introduce proper assessment of postoperative pain
- to introduce planning for effective postoperative pain control
- to promote nursing and medical staff training and education
- to provide patient comfort with minimal sedation and impairment of respiratory function

EVIDENCE LEVEL III

3.3.2 Pain assessment

The subject of postoperative pain and its control should be part of the surgeons initial review of all relevant aspects of the planned procedure (20).

EVIDENCE LEVEL III

RECOMMENDATIONS

The surgeon should discuss this with the patient and the family. A more detailed pain history should then be obtained by the anesthesiologist to include an assessment of;

- preoperative pain,
- previously used analgesic methods
- patients knowledge of, expectations of, and preferences for pain management methods

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

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

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

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

EVIDENCE LEVEL IIb

3.3.3 Preoperative cognitive - behavioural interventions

These aim to reduce pain, anxiety and the amount of drugs needed for pain control. Techniques include relaxation, distraction, and imagery. Preparation before surgery may reduce the amount of analgesia required postoperatively (22).

EVIDENCE LEVEL IIb

RECOMMENDATIONS

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

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

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

3.3.4 Postoperative analgesic drugs;

- *Non steroidal anti-inflammatory drugs (NSAID's) (23)*

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

EVIDENCE LEVEL Ia

A recent meta-analysis of 3453 postoperative patients rated NSAIDs highly as effective analgesics (27). Paracetamol and codeine combinations were the next most efficacious group followed by paracetamol alone and tramadol (28). The following recommendations on NSAID use have been based on a summary of recent published information (13);

- NSAIDs are not sufficiently effective as the sole agent after major surgery
- NSAIDs are often effective after minor or moderate surgery
- NSAIDs often decrease opioid requirement

Adverse effects of NSAIDs are potentially serious and it is essential that contraindications are respected (29).

Main adverse effects include:

- Gastric irritation, ulcer formation + bleeding
- Renal impairment
- Worsening of asthma
- Platelet inhibition

NSAIDs could be used after major urological surgery operations in combination with more powerful analgesics as part of a multimodal or balanced analgesic approach. After minor urological surgery NSAIDs may be sufficiently effective to be the sole agent used.

EVIDENCE LEVEL Ib

RECOMMENDATIONS

Typical dosing schedules include the following;

- Diclofenac (Voltarol Voltaren) 50mg 3 x per day orally (max 200 mg per day), or 100mg per rectum every 16hours
- Ibuprofen (Brufen) 400mg 3x per day orally
- Ketorolac (Toradol) 10-30mg orally or intravenously every 6hours
- Rofecoxib (Vioxx) 25mg orally 1x per day (max 50 mg per day)

THERAPY HAS TO BE STARTED BY ORAL ROUTE

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

- METAMIZOLE / DYPİRONE

It is prohibited in USA and UK because of reported single cases of agranulocytic neutropenia.

EVIDENCE LEVEL III

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

EVIDENCE LEVEL Ib

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

RECOMMENDATIONS

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

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

It is indicated in moderate severe post-operative pain.

Reference: Edwards JE et al. Cochrane Database Syst Rev 2001 3 003227

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

Paracetamol (acetaminophen) has been widely used in the treatment of postoperative pain. Its precise mode of action is unclear but it may work by inhibiting centrally produced COX (30). It is effective as an analgesic on its own or in combination with weak opioids such as codeine, dihydrocodeine or dextropropoxyphene (28) and tramadol (31).

EVIDENCE LEVEL Ia

These drugs are commonly prescribed after minor urological procedures when the patient is able to take oral medications. Alternatively a rectal preparation is available.

EVIDENCE LEVEL III

Contraindications are relatively few, some patients may be allergic to these preparations or sensitive to the constipating effects of codeine. Overdosing with paracetamol (more than 6g per day) may lead to liver impairment.

Typical dosing schedules include the following:

- Paracetamol 1g orally or rectally every 6 hours
- Co-codamol (Tylex) codeine + 500mg paracetamol) 2 tablets every 6 hours
- Co-proxamol((32.5mg dextropropoxyphene + 325mg paracetamol) 2 tablets every 6 hours

- *Tramadol (Tramal, Zydol)*

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

EVIDENCE LEVEL IIa

Efficacy in post operative pain has been widely reported (28). Tramadol has been reported to be less efficacious than NSAID's.

EVIDENCE LEVEL IIb

Combination of Tramadol plus paracetamol shows comparable efficacy to Ibuprofen.

EVIDENCE LEVEL Ib

Adverse effects include dizziness, sleepiness and nausea.

Tramadol may be useful in managing pain after minor to intermediate urological surgery.

EVIDENCE LEVEL III

Typical dosing schedules;

- Tramadol 50-100mg orally or intravenously, every 6 hours or continuously.
- Loading dose 100mg + 0.2mg/kg/hr as maintainance.

- *Opioids: oral, intravenous, subcutaneous and intramuscular.*

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

The subcutaneous route is comparable to intravenous.

EVIDENCE LEVEL Ia

Oral route is the most feasible, easy and efficacious.

EVIDENCE LEVEL Ia

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

RECOMMENDATIONS

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

Typical dosing schedules;

The dosage schedule for opioids needs to be individualised. The patient's response to opioids must be determined in relation to both efficacy of analgesia and the occurrence of side effects.

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

EVIDENCE LEVEL IIa

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

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

Different major and minor opioids are interchangeable.

EVIDENCE LEVEL Ia

Equianalgesic dosing tables helps the conversion of drug and route of administration

- *Patient controlled analgesia (PCA)*

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

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

Adverse effects include excessive sedation, respiratory depression and nausea.

Dosing schedule

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

Morphine loading dose 0.05-0.2 mg/kg

RECOMMENDATIONS

Dose should be titrated individually.

ASA III, background infusion and high dosage cancer therapy should be assisted in hospital.

- *Epidurals*

Continuous epidural infusions of local anaesthetic drug (typically Bupivacaine/Maracaine) and opioid (typically morphine or diamorphine) have been used to effectively relieve postoperative pain.

EVIDENCE LEVEL Ia

Epidurals have been shown to provide superior analgesia compared to PCA and other analgesic techniques such as intermittent intramuscular opioid (38).

EVIDENCE LEVEL Ib

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

EVIDENCE LEVEL Ia

Potential adverse effects include;

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

RECOMMENDATIONS

The epidural route could be used in patients after major urological operations such as nephrectomy, radical prostatectomy, where extensive postoperative analgesia is required for 3-4 days.

Typical dosing schedule

- Epidural bupivacaine 0.125% (maximal dosage 175-250 mg/die)+ 2 microgrammes of fentanyl/ml or sufentanyl 0.3-1microg/ml, run at 5-15mls/hr
- Ropivacaine 0.1-0.2 % (maximal dosage 500-700) + 2 microg of fentanyl/ml or Sufentanyl 0.3-1 microg/ml, run at 5-15 mls/hr

- *Intermittent or continuous local neural blockade*

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

Typical nerve blocks could include the following;

- Wound infiltration with 10-20mls of 0.25-0.5% bupivacaine
- Iliohypogastric or ilioinguinal nerve infiltration after hernia repair, using 10-20mls of 0.25-0.5% bupivacaine
- Intercostal nerve infiltration with 5-10mls of 0.25% bupivacaine

Intrapleural catheters after intrathoracic surgery, continuous infusion of 10mls/hr of 0.1% bupivacaine

3.3.5 Pain prevention

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

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

EVIDENCE LEVEL IIb

Balanced analgesia

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

EVIDENCE LEVEL IIb

3.4 Specific pain treatment after different urological operations

3.4.1 Extracorporeal Shock Wave Lithotripsy (ESWL)

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

Analgesic plan

- **Preoperative assessment**
- **Intraoperative:** Opioids such as morphine or fentanyl +/- NSAIDs could be used intravenously by the anesthesiologist.
- **Postoperative:** Most patients will be able to tolerate oral analgesics following this procedure. NSAIDs, paracetamol, codeine and paracetamol combination preparations (Co-proxamol, co-dydramol, Tylex) or tramadol could all be used. These drugs could be prescribed on an 'as needed' or a time-contingent basis.

If pain is more severe or persistent then oral strong opioid preparations such as morphine could be considered.

If the oral route is not available then intramuscular or subcutaneous strong opioid could be prescribed e.g.

morphine i.m. 10mg every 3 hours.

Analgesic drug options after ESWL

Diclofenac 50mg orally/8hrs

Diclofenac 100mg rectally/16hrs

Paracetamol 1g orally/6hours

Co-proxamol, Co-dydramol, 2 tablets/6hrs

Tramadol 50-100mg/6hrs

Morphine 10mg im/3hrs

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

3.4.2 Endoscopic procedures

a) Transurethral procedures

- transurethral resection of bladder tumour - TURBT
- transurethral resection of bladder neck - TURBN
- transurethral incision of prostate - TUIP
- transurethral resection of prostate- TURP
- retrograde ureteroscopy (diagnostic and/or operative)

These operations are usually performed under spinal anesthesia (epidural or subarachnoid block) with the patient awake or mildly sedated. These regional anaesthetic techniques will usually provide postoperative analgesia for 4-6 hours following surgery. After this time oral analgesics could be used.

Analgesic plan

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

Analgesic drug options after transurethral procedures

Diclofenac 50mg orally/8hrs

Diclofenac 100mg rectally/16hrs

Paracetamol 1g orally/6hours

Co-proxamol, Co-dydramol, 2 tablets/6hrs

Tramadol 50-100mg/6hrs

Morphine 10mg im/3hrs

b) Percutaneous endoscopic procedures e.g.

- percutaneous nephrolithotomy
- percutaneous endopyelotomy
- percutaneous resection of pyelocaliceal tumors
- antegrade ureteroscopy

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

c) Laparoscopic procedures e.g.

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

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

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

Analgesic plan

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

Analgesic drug options after laparoscopic surgery

Morphine intermittent intramuscular 10mg-3hrs

PCA morphine, 1mg bolus, 5 minute lockout

Diclofenac 50mg /8hrs orally, 100mg/16hrs rectally

Co-proxamol, Co-dydramol, 2 tablets/6hrs

Tramadol 50-100mg/6hrs

Paracetamol 1g/6hrs

3.4.3 Open surgery

a. Minor operations of the scrotum/penis

b. Inguinal approach

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

Analgesic options after surgery are outlined below;

Analgesic drug options after minor surgery on scrotum, penis, and inguinal region

Diclofenac 50mg orally/8hrs

Diclofenac 100mg rectally/16hrs

Paracetamol 1g orally/6hours

Co-proxamol, Co-dydramol, 2 tablets/6hrs

Tramadol 50-100mg/6hrs

Morphine 10mg im/3hrs

c) Transvaginal surgery

- Pelvic floor surgery
- Stress incontinence surgery

Local or regional anaesthetic may be used for these operations.

After surgery the following analgesic options are possible;

Analgesic drug options after transvaginal urological surgery

Diclofenac 50mg orally/8hrs

Diclofenac 100mg rectally/16hrs

Paracetamol 1g orally/6hours

Co-proxamol, Co-dydramol, 2 tablets/6hrs

Tramadol 50-100mg/6hrs

Morphine 10mg im/3hrs

d) Perineal open surgery

- perineal radical prostatectomy (PRP)
- posterior urethroplasty

Analgesic plan

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

After surgery the following analgesic options are possible;

Analgesic options after major perineal open surgery

Continuous epidural infusion of bupivacaine 0.25% + fentanyl 2 microgrammes/ml, 5-15mls/hr

Intravenous morphine infusion, 1-10mg/hr + bolus doses 1-2mg as required

PCA morphine, 1mg bolus, 5 minute lockout

Diclofenac 50mg /8hrs orally, 100mg/16hrs rectally

Co-proxamol, Co-dydramol, 2 tablets/6hrs

Tramadol 50-100mg/6hrs

Paracetamol 1g/6hrs

e) Transperitoneal Laparotomy

- retroperitoneal lymph node dissection-RPLND
- radical nephrectomy +/- caval thrombectomy
- cystectomy + urinary diversion

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

Analgesic plan

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

Analgesic options after transperitoneal laparotomy

Continuous epidural infusion of bupivacaine 0.25% + fentanyl 2 microgrammes/ml, 5-15mls/hr

Intravenous morphine infusion, 1-10mg/hr + bolus doses 1-2mg as required

PCA morphine, 1mg bolus, 5 minute lockout

Diclofenac 50mg /8hrs orally, 100mg/16hrs rectally

f) Extraperitoneal Laparotomy Suprapubic/retropubic

- open prostatectomy
- radical retropubic prostatectomy

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

Analgesic plan

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

Analgesic options after extraperitoneal laparotomy suprapubic/retropubic

Continuous epidural infusion of bupivacaine 0.25% + fentanyl 2 microgrammes/ml, 5-15mls/hr

Intravenous morphine infusion, 1-10mg/hr + bolus doses 1-2mg as required

PCA morphine, 1mg bolus, 5 minute lockout

NSAID's such as Diclofenac 50mg po /8hrs

Paracetamol 1g 6 hrly orally

Diclofenac 50mg /8hrs orally, 100mg/16hrs rectally

g) Retroperitoneal Approach - Flank Incision (Early oral intake)

- nephrectomy
- pyeloplasty
- pyelonephrolithotomy

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

Analgesic plan

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

Analgesic options after retroperitoneal Approach - Flank Incision

Continuous epidural infusion of bupivacaine 0.25% + fentanyl 2 microgrammes/ml, 5-15mls/hr

Intravenous morphine infusion, 1-10mg/hr + bolus doses 1-2mg as required

PCA morphine, 1mg bolus, 5 minute lockout

Diclofenac 50mg /8hrs orally, 100mg/16hrs rectally

Co-proxamol, Co-dydramol, 2 tablets/6hrs

Tramadol 50-100mg/6hrs

Paracetamol 1g/6hrs

3.4.4 REFERENCES

1. **Kehlet H, Brandt MR, Rem J.**
Role of neurogenic stimuli in mediating the endocrine- metabolic response to surgery. Journal of Parenteral & Enteral Nutrition, 1980, 4, 152-6.
2. **Fong TM, Yu H, Cascieri MA et al.**
Interaction of glutamine 165 in the fourth transmembrane segment of the human neurokinin-1 receptor with quinuclidine antagonists. J Bio Chem 1994; 269 (21): 957-61.
3. **Kehlet H.**
The endocrine metabolic response to postoperative pain. Acta Anaesthesi Scand, 1982; 74 (Suppl): 173-175.
4. **Marks RM, Sachar EJ.**
Undertreatment of medical inpatients with narcotic analgesics. Ann Intern Med 1973; 78: 173-181.
5. **Donovan M, Dillon P, McGuire L**
Incidence and characteristics of pain in a sample of medical-surgical inpatients. Pain 1987;30: 69-78.
6. **Warfield CA, Kahn CH**
Acute pain management: programs in US hospitals and experiences and attitudes among US adults. Anesthesiology 1995;83: 1090-94.
7. **Oden R**

Acute postoperative pain: incidence, severity and etiology of inadequate treatment. *Anesthesiology Clinics N America* 1989;7: 1-5.

8. **Sydow FW.**
The influence of anesthesia and postoperative analgesic management on lung function. *Acta Chir Scand.*1989; 550 (Suppl): 159-165.
9. NHS Management Executive. Value for Money Unit. *Day Surgery: making it happen.* London HMSO, 1991.
10. **Wilmore DW, Kehlet H.**
Management of patients in fast track surgery. *BMJ* 2001;322:473-6.
11. **Brodner G, Van Aken H, Herle L, et al.**
Multimodal perioperative management-combining thoracic epidural analgesia, forced mobilisation, and oral nutrition- reduces hormonal and metabolic stress and improves convalescence after major urologic surgery. *Anesth Analg* 2001;92: 1594-1600.
12. **Acute pain management: Operative or Medical Procedures and Trauma.**
Clinical Practice Guideline. AHCPR Pub. No. 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services. Feb.1992.
13. **Acute pain management: scientific evidence.**
National Health and Medical Research Council. Commonwealth of Australia, Canberra, Australia 1999.
14. **Phillips GD, & Cousins MJ. (1986)**
Practical decision making. In: Cousins JM & Phillips GD (Eds), *Acute Pain Management* (pp 275-290). New York: Churchill Livingstone.
15. **Royal College of Surgeons of England, the College of Anaesthetists.**
Report of the Working Party on Pain after Surgery. London: Royal College of Surgeons 1990.
16. **American Pain Society (1989)**
Principles of analgesic use in the treatment of acute pain and chronic cancer pain: A concise guide to medical practice (2nd ed) Skokie, IL: American Pain Society.
17. **Ready LB, Oden R, Chadwick HS, Benedetti C, Rooke GA, Caplan R et al.**
Development of an anesthesiology based postoperative pain management service. *Anesthesiology* 1988; 68: 100-6.
18. **Rawal N, Berggren L.**
Organisation of acute pain services: a low cost model. *Pain* 1994; 18: 94.
19. **Fancourt-Smith PF, Hornstein J et al.**
Hospital admissions from the Surgical Day Case Centre of Vancouver General Hospital 1977-1987. *Can J Anaesth.* 1990; 37: 699-704.
20. **Dick MJ.**
Assessment and measurement of acute pain. *J Obstet, Gynaecol Neonatal Nurs* 199;24(9):843-8.
21. **Gould TH, Crosby DL, Harmer M, Lloyd SM, Lunn JN, Rees GAD.**
Policy for controlling pain after surgery; effect of sequential changes in management. *BMJ* 1992; 305: 1187-93.
22. **Justins DM, Richardson PH.**
Clinical management of acute pain. *Br Med Bull* 1991; 47: 561-83.
23. **Royal College of Anaesthetists (1988).**
Guidelines for the use of non steroidal anti-inflammatory drugs in the perioperative period. Royal College of Anaesthetists, UK.
24. **The HSG, Lund B, Distel MR**
A double-blind, randomised trial to compare meloxicam 15mg with diclofenac 100mg in the treatment of osteoarthritis of the knee. *Osteoarthritis & Cartilage* 1977;5: 283-88.
25. **Power I, Chambers WA, Greer IA.**
Platelet function after intramuscular diclofenac. *Anaesthesia* 1990; 45: 916-19.
26. **Cepeda SM, Vargas L, Ortegón G.**
Comparative analgesic efficacy of patient controlled analgesia with ketorolac versus morphine after elective intr-abdominal operations. *Anaesthesia & Analgesia* 1995;80: 1150-53.
27. **Moore RA, McQuay HJ.**
Single-patient data met-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. *Pain* 1997;69: 287-94.
28. **McQuay H, Moore A (eds).**
An evidence-based resource for pain relief. Oxford University Press, Oxford.
29. **Merry A, Power I.**
Perioperative NSAID's : towards greater safety. *Pain Reviews* 1995; 2: 268-91.
30. **Bannwart B, Demotesmainard F, Schaefferbeke T.**

- Central analgesic effects of aspirin-like drugs. *Fundam Clin Pharmacol* 1995; 9: 1-7.
31. **Edwards JE, McQuay HJ, Moore RA.**
Combination analgesic efficacy: individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. *J Pain Symptom Manage.* 2002; Feb;23(2):121-30.
 32. **Besson J, Vickers MD.**
Tramadol Analgesia: synergy in research and therapy. *Drugs* 1994; 47;1:1-2.
 33. **McQuay HJ, Moore A, Justins DM.**
Treating acute pain in hospital. *BMJ.* 1997;314: 1531-5.
 34. **Ballantyne JC.**
Postoperative patient-controlled analgesia compared with intramuscular analgesia: meta-analyses of initial randomised control trials. *J Clin Anesth* 1993; 5 (3) 179-181.
 35. **McArdle**
CS Continuous and patient controlled analgesic infusions. In: Doyle (ed) 1986 International Symposium on Pain Control. Royal Society of Medicine International Congress and Symposium Series No. 123: 17-22.
 36. **Stacey BR, Rudt TE, Nelhaus D.**
Management of patient controlled analgesia; a comparison of primary surgeons and a dedicated pain service. *Anaesthesia and Analgesia* 1997; 85; 130-34.
 37. **Wieblack A, Bridner G, Van Aken H.**
The effects of adding sufentanil to bupivacaine for postoperative patient controlled epidural analgesia. *Anaesthesia & Analgesia* 1997; 85: 124-29.
 38. **Ballantyne JC, Carr DB, deFerranti S et al.**
The comparative effects of postoperative analgesic therapies on pulmonary outcome; cumulative meta-analyses of randomised, controlled trials. *Anaesthesia and Analgesia* 1998; 86: 598-612.
 39. **Wheatley RG, Schug SA, Watson D.**
Safety and efficacy of postoperative epidural analgesia. *Br J Anaesth* 2001;87:47-61.
 40. **Cousins MJ, Bridenbaugh PO.**
Neural Blockade, J.B. Lipincott Co. Philadelphia.
 41. **Chizh BA, Dickenson AH, Wnendt S.**
The race to pain control; more participants, more targets. *Trends Pharm Sci* 1999;20:354-7.
 42. **Bach S, Noreng MF, Tjellden NU.**
Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. *Pain* 1988;33:297-301.
 43. **McQuay HJ.**
Pre-emptive analgesia: a systematic review of clinical studies. *Ann Med* 1995; 27: 249-56.
 44. **McQuay HJ, Carroll D, Moore RA.**
Postoperative orthopaedic pain-the effect of opiate premedication and local anaesthetic blocks. *Pain* 1988; 33:291-5.
 45. **Wilmore DW, Kehlet H.**
Management of patients in fast track surgery. *BMJ* 2001;322: 473-6.
 46. **Kehlet H, Wilmore DW**
Multimodal strategies to improve surgical outcome. *Am J Surg* 2002;183:630-41.

3.5 TAB. Opioid equi-analgesic doses

	Parenteral	Oral
Morphine (10mg)	1	3
Methadone (10mg)	1	2
Hydromorphone (1,5mg)	1	5
Oxycodone (15mg)	1	2
Pethidine (100mg)	1	3
Codeine (130mg)	1	1,6

The opioid tolerance is not a complete cross tolerance.

When opioid is changed, lower than equi-analgesic dose is recommended.

	PO	IV	SC	
Morphine	5:1 (range 11-3:1)	1:1	5:1	Methadone
Morphine	3-5:1	3,5:1	5:1	Hydromorphone

3.6. LEVELS OF EVIDENCE AND GRADES OF RECOMMENDATION

Levels of evidence

- Ia** Evidence obtained from meta-analysis of randomised controlled trials.
- Ib** Evidence obtained from at least one randomised controlled trial.
- IIa** Evidence obtained from at least one well-designed controlled study without randomisation.
- IIb** Evidence obtained from at least one other type of well-designed quasi-experimental study.
- III** Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
- IV** Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendation

Grade	evidence levels
A Ia,Ib	Requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B IIa,IIb,III	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C IV	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.
GPP = Good Practice Points	Recommended best practice based on the clinical experience of the guideline development group.

3.6.1 References

- 1** **Scottish Intercollegiate Guidelines Network (SIGN)**
Control of pain in patients with cancer. A national clinical guideline 2000, National Guideline Clearinghouse, <http://www.ngc.gov>.
- 2** **American College of Radiology**
ACR Appropriateness Criteria(tm) for bone metastases In: American College of Radiology: ACR Appropriateness Criteria(tm) for metastatic bone disease, 1995 (revised 1999), National Guideline Clearinghouse, <http://www.ngc.gov>.
- 3** **Cancer Care Ontario (CCO)**
Use of strontium-89 in patients with endocrine-refractory carcinoma of the prostate metastatic to bone, 1997 (updated online 2001), National Guideline Clearinghouse, <http://www.ngc.gov>.

4. ABBREVIATIONS USED IN THE TEXT

ASA	American Society of Anaesthesiology
BPI	Brief Pain Inventory
CNS	Central Nervous System
Cox	Cyclo-Oxygenase
ESWL	Extracorporeal Shock Wave Lithotripsy
FSH	follicle-stimulating hormone
GPP	Good practice points
IASP	International Association for the Study of Pain
im	intramuscular
iv	intravenous
LH	luteinising hormone
mg	milligramme
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCA	Patient-controlled analgesia
PCa	Prostate cancer
po	Per os
PSA	Prostatic Specific Antigen
RPLND	Retroperitoneal Lymph Node Dissection
sc	subcutaneous
TCC	Transitional cell carcinoma
TUIP	Transurethral Incision of the Prostate
TURBN	Transurethral Resection of the Bladder Neck
TURP	Transurethral Resection of the Prostate
TURBT	Transurethral Resection of Bladder Tumour
VAS	Visual analogue scale

