REVIEW

Analgesia for patients with advanced disease: I

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This series of two articles explores the challenge of managing pain in patients with advanced malignant and non-malignant disease. Pain is a common symptom in advanced disease. Despite guidance from organisations such as the World Health Organisation, cancer pain is often inadequately managed. Managing pain in non-malignant conditions, such as end stage cardiac failure, presents an even greater challenge to healthcare professionals. This first article discusses epidemiology, definitions, pathophysiology, assessment, non-pharmacological approaches, the analgesic “ladder”, and opioids. The second article will examine the use of non-opioids, anaesthetic techniques, and analgesia in dying patients as well as discussing future directions.

Pain occurs in 40%–80% of patients with advanced progressive disease.^{1,2} Despite publication of the World Health Organisation (WHO) guidelines for managing cancer pain nearly two decades ago,³ management of pain still presents a challenge in everyday practice. Most of the available evidence for managing pain arises from studying cancer patients, but many of the basic principles can be applied to non-malignant as well as malignant disease.

EPIDEMIOLOGY

Prevalence studies have reported figures of 40%–80% for cancer pain. The prevalence rises with advancing disease and may be higher in certain types of cancer.¹ One of the challenges in managing pain is that patients may have more than one pain. For example, in a study of 200 patients presenting to a specialist cancer pain clinic, approximately 75% had multiple pains.⁴ Until recently, it was widely believed that patients dying from non-malignant disease did not have high levels of pain. However, it is now known that patients dying from cardiac failure or chronic airways disease suffer similar levels of pain² to those found in patients with malignant disease.

DEFINITION OF PAIN

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage”.⁵ The amount of suffering or “total pain” experienced by an individual patient will be determined by physical, psychological, social, and spiritual factors.

Pain can be classified broadly into two categories: nociceptive and neuropathic, which

are characterised by differing clinical presentations and underlying pathophysiological mechanisms. Breakthrough pain will also be defined and discussed in this section.

Nociceptive pain

Nociceptive pain encompasses visceral and somatic—for example, bone and soft tissue—pain. It is transmitted from peripheral nociceptors through mainly non-myelinated C sensory fibres and small diameter A fibres⁶ via the dorsal root ganglion and spinothalamic pathways in the spinal cord to the thalamus, periaqueductal grey, and various higher centres in the brain.

Visceral pain is often described by patients as diffuse aching—for example, the typical backache associated with carcinoma of the pancreas. Sometimes this pain can be intermittent or spasmodic in nature, as in gastrointestinal colic.

Bone pain can often be localised to an area of specific damage associated with tenderness on examination. In a load bearing bone, such as the femur, pain is exacerbated or initiated by movement; this is an example of incident pain.

Patients with motor neurone disease may have severe musculoskeletal pain due to joint strain and immobility. Spasms and stiffness associated with upper motor neurone signs in malignant spinal cord compression or in multiple sclerosis can also be extremely painful. In musculoskeletal pain specifically tender “trigger points” can be palpated.

Neuropathic pain

Neuropathic pain is pain transmitted from damaged neural tissue in either the peripheral or central nervous system. Structural changes at the cellular level are associated with aberrant nerve conduction^{7,8}: abnormal numbers and positioning of sodium channels in damaged neurones are responsible for reduced response thresholds and firing of action potentials even in the absence of a stimulus. Large diameter A nerve fibres are not usually associated with pain transmission but are thought to be “recruited” in neuropathic pain states.⁸

Typically, the patient describes neuropathic pain as burning or shooting. It can be intermittent, lasting only seconds, or continuous and may deprive the patient of sleep. Some patients report allodynia, which occurs when a normally non-painful stimulus, such as the touch of the

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patient's clothing, provokes severe pain. Autonomic changes, such as temperature and colour changes, may also be present. An example of malignant neuropathic pain is brachial plexopathy caused by metastatic lymph nodes in the axilla. Central post-stroke pain is an example in non-malignant disease.

Chemicals, channels, and receptors involved in pain transmission

The *N*-methyl-D aspartate (NMDA) channel–receptor complex is involved in the pathophysiology of neuropathic pain and in other chronic pain states. It is found predominantly in the spinal cord but is also thought to occur in the peripheral nervous system. The excitatory neurotransmitter glutamate is the natural ligand for the complex, and its physiological purpose is to play a part in the “memory” process of neural pain pathways. Magnesium ions also have an important role in the functioning of this complex. In pathological states, the channel is activated incorrectly, and this leads to a state of heightened excitability of pain pathways known as “wind-up”.⁸

Many other molecules are now thought to act as either neurotransmitters or neuromodulators in pain transmission pathways: substance P, neurokinin, bradykinin, adenosine, nitric oxide, prostanoids, serotonin, and cholecystokinin are just a few examples. These are all potential targets for the development of novel analgesics.

Breakthrough pain

Although there has been some confusion about the definition of breakthrough pain, for the purposes of this article it refers to an episodic surge in pain against a background of otherwise controlled pain. It may or may not be related to the controlled background pain and may last for anything from a few seconds to a few hours. Sometimes it can be due to “end-of-dose failure”—that is, an increase in the patient's usual pain just before the next dose of regular analgesic. Incident pain is defined by some authorities as a particular form of breakthrough pain bought about by movement. Spontaneous short lived neuropathic pain is sometimes considered to be another type of breakthrough pain.

ASSESSMENT

A prerequisite in the management of pain is to make an accurate assessment of the patient. A detailed history of the pain(s), including onset, characteristics, sites, previous medications, and disease-modifying treatment history, should be followed by a physical examination looking for

sites of tenderness (for example, a tender vertebra) infection, and neurological signs associated with neuropathic pain. It should be remembered that pain may be due to:

- The disease,
- Investigations—for example, bone marrow biopsies or lumbar punctures,
- Treatment—for example, oral mucositis induced by cytotoxic chemotherapy, or peripheral neuropathy secondary to antiretroviral treatment for HIV, or
- An unrelated problem.

In addition, it is helpful to establish what the patient's previous experiences of pain have been and to consider psychological, social, cultural, and spiritual factors that may affect not only the patient's experience of pain but also the approach to management.

Once an assessment has been made and a treatment plan discussed with the patient, it is useful to monitor outcomes of interventions. Several methods have been used in palliative care: visual analogue scales and five point Likert scales, such as those used in the palliative outcome score,⁹ are two examples.

APPROACH TO PAIN MANAGEMENT

Most of the available information on pain management pertains to advanced cancer, but many of the basic principles can be extended to advanced non-malignant disease. The experience of pain is highly individual, and the expertise of the multiprofessional team will be required, with potential involvement from clinical nurse specialists in palliative care and specialties related to non-malignant disease, palliative care physicians, physiotherapists, occupational therapists, general practitioners, district nurses, clinical psychologists, psychiatrists, pain anaesthetists, neurosurgeons, orthopaedic surgeons, general surgeons, oncologists, radiologists, complementary therapists, and a relevant religious adviser. These professionals work together using a variety of non-pharmacological and pharmacological approaches.

NON-PHARMACOLOGICAL APPROACHES TO PAIN MANAGEMENT

Surgery

Surgery may be useful for malignant bone pain—for example, prophylactic stabilisation of a femur containing a lytic metastasis. Patients who have this procedure have better outcomes than if the femur has actually fractured. Radiological criteria include thinning of the bone cortex by more than 50%.¹⁰

Vertebral metastases can lead to spinal instability and severe pain. A number of neurosurgical techniques to improve spinal stability have been developed and can be very effective at relieving pain.

Another effective surgical technique for treating malignant bone pain is the injection of acrylic cement into bones weakened by metastatic disease—for example, bones of the pelvis.¹¹

Radiotherapy

Palliative radiotherapy can provide excellent analgesia particularly for painful bone metastases. A single fraction of radiotherapy delivered to a painful site is usually as effective as multiple fractions while being much less burdensome.¹²

Whole brain radiotherapy is extensively used to palliate headache and other symptoms associated with raised intracranial pressure.¹³

Box 1: Summary of pain definitions

- Nociceptive pain.
  - Somatic (bone or soft tissue), localised.
  - Visceral, poorly localised.
- Neuropathic pain.
  - Damage to peripheral or central nervous system.
  - NMDA receptor–channel complex important in pathophysiology.
  - Burning, shooting, autonomic changes.
- Breakthrough pain.
  - Episodic surge in otherwise well controlled pain (may be unrelated to background pain).
- Incident pain.
  - Momentary pain usually due to voluntary movement.

Transcutaneous nerve stimulation and acupuncture

Transcutaneous nerve stimulation (TENS) is a non-invasive non-pharmacological method of pain control. There are no data from randomised controlled trials to support its effectiveness, but it has been used in a variety of pains, including neuropathic pain, bone pain, and generalised musculoskeletal pain, including spasticity. Some patients find TENS especially helpful possibly because adjusting the machine to individual requirements gives a sense of control over a difficult situation. TENS cannot be used in patients with pacemakers.

Acupuncture has been used to treat musculoskeletal pain and central pain. The mechanism of action is thought to involve endogenous opioid activation and stimulation of neuropeptide genes.¹⁴ There is little evidence available of its effectiveness in pain caused by advanced disease.

Complementary therapies

Other complementary therapies, such as aromatherapy and massage, are widely used, but again there is limited evidence to support their effectiveness in pain control.¹⁵ Nevertheless, complementary therapies may improve pain relief by inducing relaxation in some patients, and these techniques are very popular with patients.

In advanced disease, it is unlikely that cognitive and behavioural approaches will be used in isolation but they may be helpful particularly when the pain is proving difficult to control, in terms of helping the patient to develop coping strategies.

PHARMACOLOGICAL APPROACHES TO PAIN MANAGEMENT

Chemotherapy and identifying easily treatable causes

Palliative chemotherapy is outside the scope of this article but, as a disease-modifying means of controlling pain, it should always be considered for patients with cancer. In addition, easily reversible causes of pain, such as infection, should be identified and treated where appropriate.

Clinical depression may increase the total suffering of patients who are in pain and should be treated pharmacologically if appropriate.

The WHO analgesic “ladder”

The WHO guidelines were first published in 1986³ and are considered to be the “gold standard” for managing the pain of advanced cancer. A schematic diagram of the analgesic “ladder” is shown in fig 1.

Non-opioids include non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and the adjuvant drugs. A wide variety of drugs can be considered as adjuvants—for example, antidepressants, anticonvulsants, antiarrhythmics, antispasmodics (skeletal and smooth muscle relaxants), steroids, and bisphosphonates. The second article in this series discusses non-opioids in detail.

Although several studies have attempted to show that the WHO analgesic ladder is an effective approach to managing

Figure 1 WHO analgesic ladder (adapted from *Cancer pain relief*. 2nd Ed. Geneva: WHO, 1996).

cancer pain, the evidence is conflicting. Although most studies claimed that 80% of cancer pain can be successfully managed using the WHO approach, a review of these studies¹⁶ concluded that the evidence was of insufficient quality to support this fact.

The management of pain in advanced non-malignant disease has been extrapolated from the WHO guidelines, although there is little evidence of efficacy and safety.

It should be noted that many of the drugs used for pain relief are used outside their product licence: some are prescribed by an unlicensed route and others for an unlicensed indication. The Association for Palliative Medicine and the Pain Society have recently published guidance on this issue,¹⁷ and it may be helpful to refer to this when prescribing outside a drug's usual licence.

OPIOIDS

Pharmacology

Opioids include all the drugs that act at opioid receptors (μ , κ , δ , and ORL-1), which are scattered throughout the brain, spinal cord, and peripheral nervous system, as well as in the skin and joints. It is likely that there are several subtypes of each receptor. Agonism at these receptors produces analgesic as well as undesirable effects. Opiates are those opioids that are derived from the opium poppy (morphine and codeine).

There are a number of opioids available for use in moderate to severe pain. Commonly used opioids are summarised in table 1.

Despite enthusiastic marketing of newer opioids by pharmaceutical companies, morphine remains the first line strong opioid recommended by the European Association of Palliative Care (EAPC) guidelines¹⁸ and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines.¹⁹ This is because of familiarity, cost, and the fact that to date there is no convincing evidence that alternative opioids have superior efficacy or side effect profiles.

However, pharmacological data suggest that different opioids may have differing affinities for the opioid receptor subtypes²⁰ and that humans may have unique receptor “profiles” as well as genetic differences in metabolic pathways.²¹ This genetic opioid “fingerprint” is currently under investigation but could explain why some people appear to have better analgesia or reduced side effects or both when their opioid is switched from morphine to an alternative.

In addition, some opioids may be less problematic than others in patients with renal impairment. Morphine, for example, relies on reasonable kidney function for efficient excretion of its metabolites, which are implicated in morphine toxicity.

The second step of the WHO ladder suggests using “weak” opioids, such as codeine and, more recently, tramadol. There is little evidence supporting the use of these drugs at their maximum doses in preference to the lowest doses of the third step opioids (for which there are no maximum or ceiling doses).

Box 2: Non-pharmacological approaches

- Orthopaedic techniques or neurosurgery to stabilise bones.
- Radiotherapy.
- TENS.
- Acupuncture.
- Aromatherapy or massage.
- Cognitive and behavioural techniques.

Table 1 Commonly used opioids and preparations (pethidine is not recommended for chronic pain because its duration of action is too short and toxic metabolites accumulate on repeated dosing, which can cause seizures)

Opioid	Equivalent dose to 10 mg of oral morphine (mg)*	Preparations	Comments
Codeine and dihydrocodeine	100	IR and SR tablets, liquid, injection	Ceiling dose and partial agonism limit its use
Tramadol	50	IR and SR tablets, injection	
Buprenorphine	0.1–0.2	Sublingual tablets, transdermal patch	
Morphine	10 (oral), 5 (parenteral)	IR tablets and liquid, SR tablets, sachets, and suppositories, injection	
Fentanyl	0.06–0.07 (injection), transdermal patch is more complex	Injection (large volume limits use), transdermal patch (avoid in unstable pain), OTFC (a lozenge preparation on a stick)	CyP450 interactions, may be less constipating than morphine
Alfentanil	0.33	Injection	Hepatic metabolism, CyP450 interactions
Diamorphine	3.3	Injection	Illegal in many countries outside UK
Hydromorphone	1.3 (oral)	IR and SR tablets, injection	Very similar to morphine, limited use
Oxycodone	5 (oral)	IR liquid and tablets, SR tablets, suppositories, injection	
Methadone	1–10 depending on whether dosing is acute or chronic	Tablets and liquid, injection	Difficult to use (complex pharmacokinetics), interactions with antiretroviral drugs

*Dose equivalences are a guide only and are often derived from single dose studies. Potency ratios in chronic dosing are likely to be very different, and changing from one opioid to another, particularly methadone, requires caution.

IR, immediate release; SR, slow release; OTFC, oral transmucosal fentanyl citrate; CyP450, cytochrome P450.

Uses

Opioids are used at steps two and three of the analgesic ladder for all types of pain. There is extensive evidence and clinical experience of the efficacy of opioids in cancer pain but little in pain occurring in advanced non-malignant disease.

It was thought until recently that neuropathic pain is not opioid responsive, but in fact there appears to be a spectrum of opioid responsiveness. A small randomised controlled trial in patients with postherpetic neuralgia demonstrated superior pain relief of oxycodone (a semisynthetic strong opioid) compared with a placebo.²²

There is a suggestion from single dose studies in cancer patients that opioid responsiveness in neuropathic pain is more likely if there is ongoing active nerve damage—for example, from nerve compression.²³

There are certain situations in which a particular opioid preparation or route may have advantages over others.

- For patients with dysphagia or nausea, transdermal fentanyl patches are useful, providing that the pain is stable.
- Incident pain and other short lived pains, such as that exacerbated by dressing changes, may be best relieved by oral transmucosal fentanyl citrate (OTFC), a fentanyl lozenge on a stick, which was developed for use in incident pain but has also been used in other short lived pains.²⁴ Rapid absorption occurs via the buccal mucosa, avoiding first pass metabolism. Onset of analgesia is claimed to occur within 10–15 min, while the duration of action is about two hours. OTFC therefore has a potential advantage over other immediate release opioids, which tend to cause side effects because the pain has stopped long before blood levels of the drug have dropped. OTFC is very expensive, and trials of cheaper opioids given by the intranasal or sublingual routes—for example, fentanyl, alfentanil, and sufentanil—are underway. The effects of intranasal diamorphine have been studied in children with fractures, and it provided a rapid onset non-invasive method of pain relief, when compared with diamorphine injections.²⁵ Dextromoramide is another cheap strong opioid used for short lived pain episodes, but it has recently been discontinued.
- Methadone theoretically has NMDA antagonist activity in addition to opioid agonism and has been used to relieve neuropathic pain, but results are variable and it is a

difficult drug to use owing to its pharmacokinetics, which can lead to accumulation.

- Topical opioids have been useful in the management of painful skin wounds.²⁶

Prescribing opioids

Many of the following recommendations for the prescription and titration of strong (step three of the WHO ladder) opioid analgesics can be found in the WHO,³ EAPC,¹⁸ and SIGN¹⁹ guidelines.

- The drug should be given regularly, using an immediate release preparation. Immediate release oral morphine should be given every four hours (except in patients with severe renal failure, see next section).
- Oral administration is preferable.
- A “rescue” dose should be available for use between regular doses, if the pain returns.
- The “rescue” dose is commonly the same as the regular four hourly dose, although there is no evidence to support this.
- The total daily dose of opioid should be reviewed on a daily basis according to the number of rescue doses used in the preceding 24 hour period.
- It used to be common practice to prescribe a double dose of immediate release opioid at night to avoid the patient having to wake during the night. A recent study has suggested that patients experience more side effects and poorer analgesia using this method than if they are woken for their four hourly dose.²⁷
- Once pain control is achieved, the patient can use a slow release preparation, usually given once or twice a day. “Rescue” doses of the immediate release preparation can continue to be used. If the patient consistently requires two or more rescue doses per day, the slow release preparation should be increased accordingly.
- Stimulating and softening laxatives and antiemetics (metoclopramide or haloperidol, for example) should be made available at the same time as the initial opioid prescription.

Opioids in patients with renal and hepatic impairment

If the patient has coexisting renal failure, morphine may still be used, but the dose interval should be 6–8 hours

Box 3: Morphine: dispelling the myths

- Patients with advanced disease and pain do not become addicted to opioids.
- Opioids do not shorten life if used properly and if doses are titrated—in fact, controlling pain well may even lengthen life.
- Taking opioids does not delay diagnosis by “masking” pain.
- Prescribing opioids at an earlier stage of disease does not mean that options later in the disease trajectory will be “used up”.
- Patients on a stable dose of opioid are often able to drive and carry out normal activities.
- The sedation and nausea associated with opioids are usually transient (2–3 days).
- Respiratory depression is very rare. However, patients on a stable dose of opioid can occasionally develop respiratory depression after a nerve block or other pain relieving procedure or if their renal function deteriorates.

and the starting dose should be 30%–50% lower. Occasionally in patients with renal failure it may be necessary to use an opioid that is hepatically metabolised to inactive metabolites, such as alfentanil (parenteral use only). Methadone has been used successfully in patients with renal failure, but there are limited data on the safety of the other oral opioids in renal failure, particularly for patients undergoing dialysis, and they should all be used with caution in this situation.

Although hepatic impairment is usually irrelevant when prescribing morphine, oral bioavailability may dramatically increase in patients with liver failure owing to the loss of first pass metabolism, and unexpected toxicity may occur. This is rare in malignant liver disease but should be remembered when prescribing for patients with end stage viral or alcoholic liver disease.

Legal issues

It is important to remember that strong (step 3) opioids are controlled drugs, and prescriptions should be written giving the total amount of drug in words and figures. In addition, if a patient wishes to travel abroad with strong opioids then the prescribing doctor may be expected to apply on their behalf

for a Home Office export licence (depending on the amount). More information about prescribing strong opioids for overseas travel can be found in the *British National Formulary*.²⁸

Morphine myths

Many patients are frightened of strong opioids, particularly morphine, and it is vital to explore their fears before starting the drug (see box 3). Strategies for managing side effects should also be discussed at the outset.

Prescribing opioids for patients with a history of drug dependency

Drug dependent patients may develop life threatening illnesses and pain. Anxieties about potential opioid abuse should not preclude the assessment and treatment of pain in this group of patients; however, efficient communication between the local drug dependency unit, the general practitioner, and all potential prescribers is essential. Analgesic requirements should be treated completely separately from opioids used to control dependency syndromes. Patients do not necessarily require larger than average doses of opioids to control pain.

Opioid side effects

A recent evidence based report by an expert working party of the EAPC examined the approaches required to manage opioid side effects²⁹ and summarised the key points as follows:

- Reduce the dose if possible,
- Review the pain and consider the addition of non-opioids,
- Manage the side effect symptomatically,
- Change the route of administration of the opioid—for example, subcutaneous or spinal routes may have improved side effect profiles, and
- Change the opioid—opioid “switching” or “rotation”.

The key side effects of opioids are shown in table 2.

A few points on the management of side effects will be discussed.

Opioid induced constipation

There is no evidence to support the superiority of one laxative regimen over another. There is some evidence from crossover studies that transdermal fentanyl is less constipating than morphine.³⁰ Whether this is a property of the drug itself or of the route of delivery is unclear.

Table 2 Opioid side effects and toxicity

Side effect	Prevalence (%)	Comments
Constipation	Up to 80	Not transient
Nausea or vomiting	15–30	Often transient lasting 2–3 days
Sedation	20–60	Often transient at initiation or dose increase; psychostimulants may help
Confusion or hallucinations	No figures available	May herald toxicity
Myoclonic jerks	Up to 60 at doses over 500 mg/day	May herald toxicity, especially in patients with renal failure
Respiratory depression	Rare in chronic dosing	Stop opioid for a few hours, restart at 30%–50% of dose, use naloxone in 100–200 µg increments only if respiratory rate <8–10/min
Xerostomia	Common	Exclude candidiasis and other drugs; artificial salivas or pilocarpine may help
Urine retention	Rare	Usually transient; cholinergic agonists may help
Pruritus	2–10 for spinal route; rare for oral route	Often transient; ondansetron or paroxetine may help

Notes: most available data are for morphine; data are lacking for other opioids; the presence or absence of miosis is not reliable.

Box 4: Summary of opioids

- Morphine is the first choice strong opioid.
- Opioids can be used for all types of pain, but consider NSAIDs and other non-opioids as well.
- Patient should be given information about side effects and to dispel "myths".
- At commencement make antiemetics and laxatives available.
- Consider switching to an alternative opioid if the side effects are unacceptable or there is inadequate analgesia, but reassess the pain first.
- The transdermal route is useful if there is poor compliance or the oral route is unavailable, but only if the pain is stable.
- Respiratory depression is rare during chronic dosing, if it occurs it should be treated by:
  - Stopping the opioid for a few hours,
  - Restarting at a reduced dose, and
  - Prescribing naloxone in 100–200 µg increments if the respiratory rate is <8/min.

Oral naloxone (a mu receptor antagonist) was studied in cancer patients with opioid induced constipation.³¹ Used orally, naloxone theoretically antagonises gut opioid effects without antagonising analgesia. Although it appeared to be effective in this study, unpleasant withdrawal symptoms were noted in a small number of patients, suggesting that naloxone given orally is still capable of crossing into the central nervous system. Methylnaltrexone, another oral opioid mu antagonist, which does not enter the central nervous system, has shown some preliminary promise³² and is undergoing further investigation.

Opioid induced sedation

Psychostimulants have shown some benefit in opioid induced sedation. One small crossover placebo study examined the use of methylphenidate in cancer patients taking opioids and found reduced levels of somnolence compared with baseline and with a placebo.³³ These drugs may also enhance analgesia for a given opioid dose.

Opioid induced pruritus

Opioid induced pruritus is unusual, except when the spinal route is used. Ondansetron has been shown in a randomised controlled trial to be effective in spinal opioid induced pruritus³⁴ and has also been used for oral opioid induced itch. An alternative opioid may be required if the itch does not resolve.

Opioid "switching" or "rotation"

There have been case reports and retrospective surveys describing improved analgesia or side effect profiles or both as a result of "switching" or "rotating" opioids.³⁵ It is not clear whether switching the opioid is merely equivalent to a dose reduction, since the equianalgesic potency ratios are not always accurate. There have been no randomised controlled trials comparing opioid switching with other techniques for reducing side effects, and indeed it would be very difficult to undertake such a trial.

SUMMARY

This paper has covered background information on pain epidemiology and mechanisms and has described in detail the use of opioids as per the second and third steps of the

Box 5: Key references for parts I and II

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WHO analgesic ladder. A second paper will examine non-opioid drugs, including future possibilities, anaesthetic interventions, and an approach to managing pain in dying patients.³⁶

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IMAGES IN MEDICINE

Fungal empyema thoracis complicating treatment of oesophageal carcinoma

Figure 1 Computer tomogram demonstrating pathology, aetiology, and treatment.

A 56 year old man with locally advanced oesophageal carcinoma was admitted with neutropenic ($0.6 \times 10^9/l$) sepsis 10 days after chemotherapy with etoposide, cisplatin, and capecitabine. At presentation there was evidence of marked respiratory compromise and subsequent chest radiography demonstrated a large right sided pleural effusion. Diagnostic thoracentesis revealed frank malodorous pus from which *Candida albicans* was repeatedly isolated. A large bore (32F) chest tube was inserted and he was started on intravenous broad spectrum antibiotics and fluconazole.

At initial diagnostic biopsy of malignancy a mediastinal perforation occurred which necessitated placement of a covered oesophageal stent. Consequently, there was a high clinical suspicion of abnormal oesophageal-mediastinal-pleural connection. Gastrografin swallow confirmed the presence of contrast extrinsic to the stent in its lower third. Computer tomography of the thorax is of interest because one image slice demonstrates pathology, aetiology, and treatment (see fig 1).

Despite recovery of his neutrophil count and aggressive intervention the patient succumbed to ongoing sepsis and respiratory compromise.

The case illustrates an unusual and fatal complication of an oesophageal stent perforation in a patient undergoing chemotherapy.

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