PALLIATIVE CARE SECTION

Cancer Pain: Part 2: Physical, Interventional and Complimentary Therapies; Management in the Community; Acute, Treatment-Related and Complex Cancer Pain: A Perspective from the British Pain Society_Endorsed by the UK Association of Palliative Medicine and the Royal College of General Practitioners

Jon Raphael, MB, ChB, MSc, FRCA, MD, FFPMRCA,*
Joan Hester, MB, BS, FRCA, MSc, FFPMRCA,†
Sam Ahmedzai, BSc, MB, ChB, FRCP,‡
Janette Barrie, RN, MSc,§ Paul Farquhar-Smith,
MB, BCHir, FRCA, PhD, FFPMRCA,‡ John Williams,
MB, BS, FRCA, FFPMRCA,‡ Catherine Urch, BM,
MRCP, PhD,§ Michael I. Bennett, MB, ChB, MD,
FRCP, FFPMRCA,TT Karen Robb, BSc, PhD, MCSP,††
Brian Simpson, MA, MB, BCHir, MD, FRCS,***
Max Pittler, MD, PhD,TTTt, Barbara Wider, MA,TTT
Charlie Ewer-Smith, DipCOT, CMS,‡‡
James DeCourney, MBBS, FRCA,****
Ann Young, MB ChB,***** Christina Liossi, BA, MSc,
MPhil, DPsych,****** Renee McCullough, BM, BS,
MRCP, DIP, PAL, MED,***** Dilini Rajapakse, MBBS,
MSc, MRCPCH,***** Martin Johnson, MB, ChB,
MRCPG,** Rui Duarte, BSc,* and
Elizabeth Sparkes, BSc†††

*Faculty of Health, Birmingham City University,
Birmingham, UK;

†Pain Management, Kings College Hospital, London,
UK;

‡Anaesthetics, Royal Marsden Hospital, London, UK;

§Palliative Medicine, St. Marys Hospital, London, UK;

¶Physiotherapy, St. Bartholomews Hospital, London,
UK;

**Paediatric Palliative Medicine, Great Ormand Street
Hospital, London, UK;

††General Practice, Royal College of General
Practitioners, London, UK;

***Palliative Medicine, University of Sheffield, Sheffield,
UK;

§§Long Term Conditions, Lanarkshire Health,
Scotland;

TTEnd of Life Observatory, Lancaster University,
Lancaster, UK;

***Neurosurgery, University Hospital Wales, Cardiff;

TTTComplimentary Therapy, Peninsula Medical School,
Exeter, UK;

****Occupational Therapy, University Bristol Hospital,
Bristol, UK;

******Psychology, Southampton University, Southampton,
UK;

******Psychology, Coventry University, Coventry, UK;

TTTComplimentary Therapy, Gloucestershire Hospital,
Gloucester, UK;

TTTTScience, German Institute for Quality and
Efficiency in Health Care, Cologne, Germany

Reprint requests to: Jon Raphael, MSc, MD,
Birmingham City University, Faculty of Health,
Graduate School, Ravensbury House, Westbourne
Road, Westbourne Campus, Edgbaston, Birmingham
B15 3TN, UK. Tel: +44(0)1384 244809; Fax:
+44(0)1384 244025; E-mail: jon.raphael@bcu.ac.uk.
Abstract

Objective. This discussion document about the management of cancer pain is written from the pain specialists’ perspective in order to provoke thought and interest in a multimodal approach to the management of cancer pain, not just towards the end of life, but pain at diagnosis, as a consequence of cancer therapies, and in cancer survivors. It relates the science of pain to the clinical setting and explains the role of psychological, physical, interventional and complementary therapies in cancer pain.

Methods. This document has been produced by a consensus group of relevant healthcare professionals in the United Kingdom and patients’ representatives making reference to the current body of evidence relating to cancer pain. In the second of two parts, physical, invasive and complementary cancer pain therapies; treatment in the community; acute, treatment-related and complex cancer pain are considered.

Conclusions. It is recognized that the World Health Organization (WHO) analgesic ladder, whilst providing relief of cancer pain towards the end of life for many sufferers worldwide, may have limitations in the context of longer survival and increasing disease complexity. To complement this, it is suggested that a more comprehensive model of managing cancer pain is needed that is mechanism-based and multimodal, using combination therapies including interventions where appropriate, tailored to the needs of an individual, with the aim to optimize pain relief with minimization of adverse effects.

Key Words. Cancer Pain; Palliative Treatment

Preface

This discussion document, which can be more fully accessed at www.britishpainsociety.org/book_cancer_pain.pdf, about the management of cancer pain is written from the pain specialists’ perspective in order to provoke thought and interest in a multimodal approach to the management of cancer pain, not just toward the end of life, but pain at diagnosis, as a consequence of cancer therapies, and in cancer survivors. It relates the science of pain to the clinical setting and explains the role of psychological, physical, interventional and complementary therapies in cancer pain.

It is directed at physicians and other health care professionals who treat pain from cancer at any stage of the disease and it is hoped that it will raise awareness of the types of therapies that may be appropriate, heighten appreciation of the role of the pain specialist in cancer pain management, and lead to dialogue and liaison between oncology, specialist pain and palliative care professionals.

This document is accompanied by information for patients to help them and their carers understand the available techniques and to support treatment choices.

Methods

This document has been produced by a consensus group of relevant health care professionals and patients’ representatives making reference to the current body of evidence relating to cancer pain.

Executive Summary

- It is recognized that the World Health Organisation (WHO) analgesic ladder, whilst providing relief of cancer pain toward the end of life for many sufferers worldwide, may have limitations in the context of longer survival and increasing disease complexity. To complement this, it is suggested that a more comprehensive model of managing cancer pain is needed that is mechanism-based and multimodal, using combination therapies including interventions where appropriate, tailored to the needs of an individual, with the aim to optimize pain relief with minimization of adverse effects.
- The neurophysiology of cancer pain is complex; it involves inflammatory, neuropathic, ischemic, and compression mechanisms at multiple sites. Knowledge of these mechanisms and the ability to decide if a pain is nociceptive, neuropathic, visceral or a combination of all three will lead to best practice in pain management.
- People with cancer can report the presence of several different anatomical sites of pain that may be caused by the cancer, treatment of cancer, general debility or concurrent disorders. Accurate and meaningful assessment and reassessment of pain is essential and optimizes pain relief. History, examination, psychosocial assessment and accurate record keeping should be routine, with pain and quality of life measurement tools used where appropriate.
- Radiotherapy, chemotherapy, hormones, bisphosphonates and surgery are all used to treat and palliate cancers. Combining these treatments with pharmacological and nonpharmacological methods of pain control can optimize pain relief, but limitations of these treatments have also to be acknowledged.
- Opioids remain the mainstay of cancer pain management, but the long-term consequences of tolerance, dependency, hyperalgesia and suppression of the hypothalamic/pituitary axis should be acknowledged and managed in both noncancer and cancer pain, as well as the well known side-effects such as constipation. NSAIDs, anti-epileptic drugs, tricyclic antidepressants, NMDA antagonists, sodium channel blockers, topical agents and the neuraxial route of drug administration all have a place in the management of complex cancer pain.
- Psychological distress increases with intensity of cancer pain. Cancer pain is often under reported and undertreated for a variety of complex reasons partly due to a number of beliefs held by patients, families and health care professionals. There is evidence that cognitive behavioral techniques that address catastrophizing and...
promote self efficacy lead to improved pain management. Group format pain management programs could contribute to care of cancer survivors with persistent pain.

- Physiotherapists (PTs) and occupational therapists (OTs) have an important role in the management of cancer pain and have specific skills that enable them to be patient-focused and holistic. Therapists utilize strategies that aim to improve patient functioning and quality of life, but the challenge remains to practice in an evidence-based way and more research is needed in this field.

- Patient selection for an interventional procedure requires knowledge of the disease process, the prognosis, the expectations of patient and family, careful assessment and discussion with the referring physicians. There is good evidence for the effectiveness of coeliac plexus neurolysis and intrathecal drug delivery. Within the limitations of running randomized controlled trials (RCTs) for interventional procedures in patients with limited life expectancy and severe pain, there is a body of evidence of data over many years that supports an important role for some procedures (e.g., cordotomy). Safety, aftercare and management of possible complications have to be considered in the decision making process. Where applied appropriately and carefully at the right time, these procedures can contribute enhanced pain relief, reduction of medication use and markedly improved quality of life.

- There is a weak evidence base for the effectiveness of complementary therapies in terms of pain control, but they may improve well being. Safety issues are also a consideration.

- Patients with cancer pain spend most of their time in the community until the last month of life. Older patients and those in care homes may particularly have undertreated pain. Primary care teams supported by palliative care teams are best placed to initiate and manage cancer pain therapy, but education of patients, carers and health care professionals is essential to improve outcomes.

- Surgery, chemotherapy and radiotherapy are cancer treatments that can cause persistent pain in cancer survivors, up to 50% of whom may experience persistent pain that adversely affects quality of life. Awareness of this problem may lead to preventative strategies, but, at the moment, treatment is symptom based and often inadequate.

- Management of acute pain, especially postoperative pain, in patients on high dose opioids is a challenge that requires in-depth knowledge of pharmacokinetics and formulation of a careful management plan to avoid withdrawal symptoms and inadequate pain management.

- Chronic pain after cancer surgery may occur in up to 50% of patients. Risk factors for the development of chronic pain after breast cancer surgery include: young age, chemo and radiotherapy, poor postoperative pain control and certain surgical factors. Radiotherapy induced neuropathic pain has become less prevalent but can cause longstanding pain and disability.

- Patient education is an effective strategy to reduce pain intensity.

- Cancer pain is often very complex but the most intractable pain is often neuropathic in origin, arising from tumor invasion of the meninges, spinal cord and dura, nerve roots, plexuses and peripheral nerves. Multimodal therapies are necessary.

- The management of cancer pain can and should be improved by better collaboration between the disciplines of oncology, pain medicine and palliative medicine. This must start in the training programmes of doctors, but also in established teams in terms of funding, time for joint working, and education of all health care professionals involved with the treatment of cancer pain.

- The principles of pain management and palliative care in adult practice are relevant to pediatrics, but the adult model cannot be applied directly to children.

Part 2 of 2: Physical, Invasive and Complementary Cancer Pain Therapies; Treatment in the Community; Acute, Treatment-Related and Complex Cancer Pain

Physical Therapies in Cancer Pain

Summary

PTs and OT have an important role in the management of cancer pain and have specific skills which enable them to be patient-focused and holistic. Therapists utilize strategies that aim to improve patient functioning and quality of life but the challenge remains to practice in an evidence-based way. More research is needed in this field.

Introduction

PT and OT play an important role in the management of patients with cancer pain and may encounter these patients at various stages in the "cancer journey." Rehabilitation of cancer patients is gaining increasing recognition and is now considered an essential component in the delivery of care [1].

The main aims of therapy are to relieve pain (wherever possible) and to improve function and quality of life using treatments based on the best available evidence. Management should be patient-centered, collaborative and restorative and involve family and carers to ensure a coordinated approach to treatment planning and goal-setting. The patient’s engagement in the therapy partnership is vital.

Early referral to therapies is important not only with the palliative care patients, but also with others, to prevent chronicity and help anticipate future problems. With in-patients, early referral should result in better discharge planning that may stop bed blocking and help patients return to their preferred place of care.

Much can be learned from therapists who work with musculoskeletal pain and there is a plethora of literature exam-
ment of psychological comorbidities (e.g., anxiety or depression). Assessment will focus on a patient’s functional ability (e.g., their ability to transfer or mobilize). There are three components of assessment that must be considered in all patients: a description of the pain (including site, severity, irritability, nature); responses to the pain and the impact of pain on the person’s life [9].

Therapists must be aware of the dangers of placing too much attention on correction of physical impairments at the expense of function [10]. For many cancer patients (especially those with advanced disease) it will be more important to complete a task than to focus on correction of individual impairments.

Occupational Therapy Assessment

Occupational therapy assessment recognizes it is usual for cancer patients to identify and focus on those tasks and occupational roles that they are no longer able to manage or enjoy due to their pain. The OT will listen to the patient’s narrative and begin to identify aggravating, relieving factors; the beliefs held regarding pain; what the pain means to the patient, those around them; how the patient is currently managing their activities in relation to their pain.

The OT will identify which activities the individual needs to do, wants to do and is expected to do by others.

Evaluating Outcome

It is important to utilize reliable and valid outcome measures as well as utilizing patient’s subjective feedback. Outcome measures for use in clinical practice must be feasible (i.e., practical, inexpensive and easy to use), provide extra clinical information and be responsive to changes over time. A great variety of tools are now available but there are no published guidelines for therapists to assist selection of measures.

Outcome Measures

Both visual analog scales and numerical ratings scales (NRSs) are commonly used in clinical practice. Previous research has suggested cutoff points for mild, moderate and severe pain on a NRS, with 0–4 mild, 5–6 moderate, 7–10 severe. This is useful to consider when assessing whether improvements in pain report are clinically significant.

Example: A drop in pain report from 9/10 to 7/10 may be less clinically significant than a drop from 7/10 to 5/10, although the incremental change is the same.

The brief pain inventory [12] is a useful clinical tool for therapists as it reports both pain intensity and pain interference using a NRS.

It is important that the patient remains at the center of the treatment process. A measure that can be used to detect the impact of therapy intervention on the patient’s self-
perception of occupational performance is the Canadian Occupational Performance Measure [13]. It has also been demonstrated to empower and actively encourage patient participation in therapy interventions.

Other tools that can be used include pain drawings (often simple body charts) or descriptive questionnaires such as the McGill Pain Questionnaire [14].

**Therapy Management**

The ultimate aim is for the patient to achieve full functional potential and become autonomous in managing the impact of pain on their daily life. There is currently a lack of evidence for the use of therapy interventions for patients with cancer-related pain and research is required in this field. Interventions can be classified as physical, psychosocial, and lifestyle adjustment.

**Physical Approaches**

Some of these approaches are traditionally administered by PTs (e.g., therapeutic exercise and transcutaneous electrical nerve stimulation [TENS]) but other health care practitioners (HCPs) may have sufficient skills in this area (e.g., OT, clinical nurse specialists). Graded activity for return to function is inextricably linked with therapeutic exercise but may traditionally be considered the domain of the OT. When utilizing these approaches, a certain amount of manual handling is required and therapists must pay special attention to patient comfort and position at all times.

**Therapeutic Exercise**

The main goal of exercise is to address the problems associated with inactivity/immobility (specific or general) and fear of movement. The detrimental effects of immobilization are well documented and include muscle wasting/weakness, joint stiffness, reduced motor control, mood changes, decreased self-efficacy, reduced coping capacity, and cardiovascular deconditioning. Exercise programs must be tailored to the individual needs of the patient and should start cautiously, build up gradually and be within patients’ tolerance levels. There are now many reviews of exercise in cancer patients, some of which include guidance on specific precautions [15,16].

**Graded and Purposeful Activity**

Engagement in meaningful activities (which may include craft, recreation or work) has been shown to assist patients with cancer pain to improve their self-concept and task mastery [17]. Appropriately prescribed and graded activities, can be used to increase activity tolerance, autonomy, social integration, self-esteem, and competence, and decrease pain behaviors [18].

**Postural Re-education**

Postural re-education is appropriate in patients who have altered posture or movement secondary to pain. It is important to attempt correction of such postural abnormalities early in rehabilitation to avoid further dysfunctional movement patterns. Examples include breast cancer patients who develop chronic postsurgical pain following breast cancer treatment and adopt protective postures resulting in muscle spasm and muscle imbalances [19]. In head and neck cancer patients, there is growing evidence for the use of Progressive Resistive Exercise training to manage shoulder dysfunction and pain secondary to spinal accessory nerve damage. The importance of correcting posture and scapular stability prior to resistance exercise has been documented [20].

**Massage and Soft Tissue Mobilization**

Soft tissue mobilization is widely practiced in the management of pain and includes techniques such as scar mobilization/massage, myofascial techniques and connective tissue massage. A wealth of information is available on such approaches [21,22].

**TENS**

TENS is a noninvasive form of electrical stimulation that has been used for many years to treat a wide range of pain problems. Although experts suggest that TENS has an important role there are currently no formal guidelines on the use of TENS in cancer patients. Only two RCTs evaluating TENS use in cancer-related pain have been identified [23,24] and the effectiveness of TENS remains inconclusive [25]. Yet some patients may find it beneficial. Conventional TENS is the most common mode of delivery used in practice and should be the first treatment option in most situations. It is generally recommended to start with TENS electrodes in the painful area or an adjacent dermatome. The intensity should be “strong but comfortable” and patients can safely increase treatment time up to several hours as long as no side-effects occur and benefit continues.

**Heat and Cold Therapy**

Application of heat can be achieved from simple approaches (e.g., a hot bath to aid relaxation or more local applications such as heated packs). Cold can be delivered via ice packs and home remedies can be devised (e.g., using frozen peas, wrapped in a towel or protective fabric to prevent frost burn). All standard contraindications and precautions must be followed and choice of treatment will depend on pain presentation and the therapeutic effects needed.

**Lifestyle Adjustment**

Typically, it is the OT who addresses this aspect of management although the PT can also be involved in some
aspects (e.g., prescription of walking aids). Analysis of
tolerance levels and education in skills can enable
functional restoration without provoking painful episodes.
Techniques such as pacing, planning, prioritizing, energy
management, activity analysis, work simplification, time
management, compensatory techniques, ergonomic prin-
ciples, and the reorganization of routines can be taught to
provide the patient with skills to restructure their lifestyle,
thus minimizing painful episodes.

Analyzing, grading and adapting activities allows patients
to continue managing them within their ability, tolerance
level and pain parameters [26,27]. The restructure of lifesty-
e and routine, environmental adaptation, task simplification,
fatigue management, appropriate equipment and orthotic
prescription and interventions regarding correct positioning
and pressure relief during activity facilitate independence,
conserve energy, minimize pain on exertion and enable valued activities to be continued.

Invasive Procedures in Cancer Pain

Summary

Patient selection for an interventional procedure requires
knowledge of the disease process, the prognosis, the
expectations of patient and family, careful assessment and
discussion with the referring physicians. There is good
evidence for the effectiveness of coeliac plexus block and
intrathecal drug delivery. Safety, aftercare and manage-
ment of possible complications have to be considered in
the decision making process. Where applied appropriately
and carefully at the right time, these procedures can con-
tribute enhanced pain relief, reduction of medication use
and markedly improved quality of life.

Introduction

This chapter focuses on the interventional procedures
considered the most effective. It deals with the pharma-
cological blockade of neural tissue by targeted injection
or infusion, their destruction by chemical, physical or sur-
gical methods and the fixation of vertebral compression
fractures.

For a few procedures (coeliac plexus ablation, intrathecal
infusions, see below) there is controlled trial evidence in
cancer populations. For most procedures there is less
robust evidence of largely uncontrolled case series.

A pragmatic approach is required when deciding whether
to offer such therapies. The likely benefits and possible
risks need to be considered and compared with those of
continuing with pharmacological management. Typically,
interventional management of cancer pain does not sub-
stitute for other modalities but can improve pain relief and
allow for a reduction in systemic medications and their
side-effects.

Careful assessment of the pain should be undertaken by
an interdisciplinary team usually including specialists in
pain, palliative care and nursing. The team might include
others. Practical factors should be considered, such as
discharge home, patient and family preferences. Complex situations will often require high level discussion.

It has been traditional to consider exhausting oral or
topical analgesia before considering invasive methods;
however, this is not always in the patients best interests.
Where there are unacceptable side-effects from opioids,
such as drowsiness, then invasive methods may be pre-
ferred or an implanted pump early in advanced cancer can
allow for the maximum benefit to be obtained.

This chapter aims to bring information related to benefits
and adverse effects for interventional procedures com-
monly used in cancer pain management.

Types of Interventional Procedures

These most typically involve interruption to or modification
of nerve conduction with the aim of diminishing pain from
a target area. The nerves involved include those of the
peripheral, autonomic and central nervous system.

The procedures may be considered as nondestructive or
destructive. In nondestructive procedures, nerve blockade
or modulation is achieved by the deposition of reversible
pharmaceutical agents. These may be provided by bolus
injection and most commonly involve local anesthetic
agents often supplemented by depot steroids. Alternatively
catheter placement allows for the continuous delivery of
agents. When placement is adjacent to peripheral or auto-
nomic nerves similar agents are used. For catheter place-
ment in the spinal canal with the aim of modulating neuronal
activity of the spinal cord, different agents are used. These
are most commonly opioids often supplemented by local
anesthetics and/or the alpha-2 adrenergic agonist, cloni-
dine. More recently, the voltage gated calcium channel
blocker, ziconotide has been introduced [28].

The destructive procedures involve the use of chemical
agents (alcohol 50–100% and phenol 6–10%), physical
methods of heat (radiofrequency) and cold (cryoablation)
and surgery.

Destructive procedures must only be provided by appro-
riately trained personnel, and are best offered within a
multidisciplinary framework of care recognizing the psy-
chosocial components of pain experience. Failure to do so
is likely to reduce the efficacy of such procedures.

Patients should be thoroughly informed about likely
sensory deficits and possible complications. In most
cases, destructive procedures should first be simulated
with local anesthetic to allow the patient to experience the
sensory changes that may occur [29].

The patient should be closely followed as an inpatient for
several days after the destructive procedure with close
monitoring and planned opioid reduction to avoid drowsi-
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ness and respiratory depression when the respiratory stimulation of pain is removed.

Peripheral Nerve Blockade

Peripheral nerve blocks have a limited role in cancer pain management. There is no controlled trial evidence but case series describe pain relief for a short time with local anesthetic blockade of the regional nerve supply of a target area. They may therefore be useful for peripерative pain, and other acute cancer pains such as pathological rib fracture (intercostal nerve blockade). This may be achieved by bolus injection of local anesthetic. It is often supplemented with depot steroid with the aim of providing longer term relief but there is no evidence to support this for peripheral nerves [30]. Alternatively, catheter infusions of local anesthetic adjacent to brachial plexus [31] or other nerves may prolong the pain relief [32,33].

Neurolytic blockade of peripheral nerves produces short-term relief, for example, intercostal neurolysis has a median duration of 3 weeks [34]. Although this study found no incidences of neuritis, the survival time was short, and others have reported an incidence of neuritis of 30% [35]. Neurolytic agents should be limited to those with short life expectancy.

Autonomic Nerve Blockade

It is known that the sympathetic nervous system carries pain afferents from the viscera and that blockade can reduce pain.

Coeliac Plexus Ablation

The coeliac plexus carries visceral afferents from several abdominal organs including the pancreas, liver, biliary tract, renal pelvis, ureter, spleen, and bowel up to the first part of the transverse colon.

Injection of a neurolytic medication around the coeliac plexus has been most investigated for pancreatic cancer pain but has found a role for other upper gastrointestinal malignancies such as gastric cancer, esophageal cancer, colorectal cancer, liver metastasis, gallbladder cancer and cholangiocarcinoma [36].

Access to the plexus is most commonly posterior with needle placement in front of or posterior to the crura of the diaphragm [37], but other approaches are used such as anterior [38], endoscopic [39] and transdiscal [40]. Imaging most commonly involves fluoroscopy but alternatives used include computerized tomography [41] and MRI [42]. While there is no apparent difference in outcome between these methods, they do allow for access in certain individuals where fibrous infiltration or tumor invasion may distort the anatomy affecting neurolytic spread [43,44] or may be valuable when patients cannot lie on their front [45].

In a single-blind RCT of 100 patients with pancreatic cancer, neurolytic plexus ablation was compared with pharmacological management together with sham procedure. Pain relief was better in the interventional group for 6 weeks [46]. A meta-analysis [47] of five RCTs of coeliac plexus ablation, found significantly improved pain relief when compared with pharmacological management or local blockade of the plexus for 8 weeks with reduced opioid consumption in the ablation group.

Up to 30% of patients experience hypotension after coeliac plexus block due to loss of sympathetic tone and splanchnic vasodilatation [48]. This reaction usually manifests itself within the first 12 hours. Up to 60% of patients report diarrhoea due to sympathetic blockade and unopposed parasympathetic efferent influence after coeliac plexus block, which usually resolves within 48 hours [49]. Neurologic complications, including paraplegia, leg weakness, sensory deficits, and paresthesias, have been reported after coeliac plexus ablation and with a large study reporting four cases of paraplegia after 2,730 coeliac plexus blocks [50]. Paraplegia was attributed to either direct injury of the spinal cord during the procedure or spinal infarction secondary to spasm of the spinal artery.

Theoretically, radiofrequency splanchnic denervation should avoid the risk of such paraplegia [51] but outcome is less studied. It may be an option when relative risks are discussed with the patient.

Superior Hypogastric Plexus Block

The superior hypogastric plexus carries afferent from the bladder, uterus, vagina, prostate, testes, urethra, descending colon and rectum. Superior hypogastric block may relieve pelvic pain and a block of these nerves has been described to reduce pain associated with pelvic malignancy [52]. Posterior approach is commonest but an anterior approach has been described [53].

Ganglion Impar Block

This is the most inferior sympathetic ganglion lying anterior to the sacrococcygeal junction. It has been shown in case series to provide pain relief for patients with advanced cancers of the pelvis and perineum, after abdomino-perineal resection for rectal cancer [52] and following radiation proctitis [54].

Neuraxial Blocks

Neuraxial blocks may be epidural (outside the theca or dura mater) or intrathecal (into the cerebrospinal fluid).

Epidural local anesthetic and steroid can provide temporary pain relief where a vertebral metastasis is associated with nerve compression.

Care should be exercised if impending cord compression or invasion of the epidural canal by tumor is suspected and imaging may be advisable in such circumstances.
Despite the lack of evidence to support these interventions, several experienced practitioners have and continue to use these techniques with reported benefit to patients. Epidurals with steroid and local anesthetic can provide temporary pain relief.

**Intrathecal and Spinal Nerve Root Neurolysis**

A saddle block with heavy intrathecal phenol can be used for perineal pain of somatic origin in advanced pelvic cancers, especially where bladder and bowel function are already compromised.

Chemical neurolysis of spinal nerve roots is used less frequently than in the past as safer interventions (e.g., neuraxial infusions have been developed). While there are case series describing effective relief of pain, the duration is limited and the incidence of neurological deficits is high [55].

**Neuraxial Infusions**

Some patients with advanced cancer may have pain that cannot be controlled with systemic medications, or the use of these medications may be limited by unacceptable side-effects at doses below those required to give adequate relief. For these patients administration of drugs by the spinal route, either epidurally or intrathecally, may be required and gives good control in the majority of cases [56].

There are different types of procedures ranging from percutaneous lines to fully implanted programmable pumps. The fully implanted systems carry less risk of infection and have lower maintenance but the operation is more prolonged [57]. Costs of the therapy currently suggest implanted systems are more cost effective than the percutaneous after 3 months [58].

There is evidence from RCTs of improved pain relief and less drug related side-effects compared with medical therapy for fully implanted systems. The reversal of drowsiness associated with systemic opioids is of great practical significance [28,59,60].

These procedures carry a moderate level of minor adverse effects and a low level of serious adverse effects [57]. They should be reserved for those patients whose pain cannot be controlled with systemic analgesia and undertaken in centers experienced with the technique and its aftercare [61].

The most effective drugs are opioids, commonly morphine, and generally patients who respond to spinal morphine are those who respond to systemic morphine but only partially and/or are limited by dose related side-effects. Patients who are unresponsive to large doses of systemic opioids are unlikely to respond to spinal opioids. Other drugs that appear to be effective spinaly include local anesthetics (typically bupivacaine) [62], alpha-2 agonists (clonidine) [63] and ziconotide [28]. In a randomized placebo controlled study of Ziconotide in II patients, 50% on active therapy vs 17% on placebo achieved >30% pain relief. However, 30% on ziconotide vs 10% on placebo experienced “serious” side-effects, 38% of those on ziconotide discontinued treatment, and follow-up generally thought to be too short. Fuller details of the use of intrathecal therapies is found elsewhere [61].

Intraventricular opioids can be administered via an implanted pump and catheter for pain in the head and face. Cerebrospinal fluid diversion via a shunt or third ventriculostomy may be appropriate for palliation in some cases of obstructive hydrocephalus that are otherwise inoperable; craniotomy and subtotal removal of a malignant cerebral tumor is a routine neurosurgical palliative procedure.

**Domiciliary Management of Spinal Catheters**

Most patients want to die at home [64], and while the safe management of spinal drug infusions does present challenges to this, these can be overcome to facilitate this aim [65]. In addition, with percutaneous drug delivery, intracutaneous use allows lower dose and therefore longer intervals between infusion refilling of ambulatory pumps, facilitating home care and reducing the risk of infection. Intrathecal catheters may be less prone to dislodgement, and blockage due to fibrosis [66], and have been shown to be safer in the domiciliary setting [67].

**Preparation**

Full involvement of the primary care team in the management of pain is vital. If, when considering the use of spinal drug delivery, management at home is identified as a priority it is essential to establish that the patient and family are suitable and have appropriate goals and expectations. The community nursing and primary care teams should be happy to cooperate and be involved.

Psychological assessment should be considered once pain has been relieved, and sedation due to analgesics minimized, some patients may be less distracted from the other psychological aspects of their illness. This can lead to difficulties with good symptom control. Full discussion and consent from the patient and family, taking factors such as these into consideration, is essential.

**Procedure**

Percutaneous catheters, injection portals or fully implanted systems may be used, but a factor in patient selection is the shorter expectation of survival in this group compared with patients with nonmalignant pain. Percutaneous catheters may be tunneled or not tunneled; tunneled catheters are less prone to displacement and infection [56].

Implantation and other procedures are ideally done in a sterile facility with resuscitation facilities in a hospital or hospice. Insertion as a domiciliary procedure has been reported [68], but this does raise issues with sterility and the ability to resuscitate in the event of side-effects.
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Very compact and reliable battery-powered infusion pumps are available that allow both continuous and patient-controlled bolus drug administration.

Aftercare

It is imperative that those who will be involved in the patient’s management at home are fully trained and confident in the necessary techniques and knowledge before discharge. The patient’s management should also be stabilized as an inpatient or in hospice prior to discharge home, with titration down of systemic analgesics, in particular to avoid opioid overdosage [69]. The cooperation of the patient’s general practitioner and out of hours service is important, and this is supported by the availability of detailed guidelines or protocols, and back-up from members of the specialist pain or palliative care team is essential [61]. This should be recognized in job plans.

With appropriate training and compliance with competencies, refilling of infusion reservoirs can be performed by community nursing staff, as well as monitoring of the patient’s condition: particularly pain relief, temperature and the state of implantation sites. Again, guidelines or protocols should support this.

Anterolateral Cordotomy

This can be undertaken as a percutaneous or open procedure involving intervention on the side of the spinal cord opposite to that of the pain to ablate the spinothalamic tract fibers. Consequently, it reduces the sensation of touch and temperature in addition to pain.

The awake percutaneous procedure ablates the spinothalamic tract using radiofrequency lesioning through a needle inserted between the first and second cervical vertebrae. Its value in mesothelioma is well documented [70] and its use in other lateralized pains is recognized [71].

Immediate pain relief is achieved in the majority with 80% either stopping or reducing opioids but pain recurs in a third of these by 6–12 months [70]. The main risk is of weakness of the leg contralateral to the side of the pain through damage to the corticospinal tract, mild effects are seen in up to 8–10% in the first few days, but prolonged effects are reported in 1–2% [71]. This risk increases, for topographical reasons, when the lower sacral dermatomes are targeted. Painful dysesthesias occur in about 5% [70].

Whereas percutaneous cordotomy can only be performed in the cervical area, the spinothalamic fibers can be divided by open operation in the thoracic cord. This avoids the risk to respiration and to the upper limb when the pain is below the waist (e.g., secondary to invasion of the lumbosacral plexus and is recommended for bilateral procedures to avoid fatal sleep apnoea). In a small series [72], none of the patients experienced motor weakness and all had complete or nearly complete and sustained relief of the target pain, allowing a substantial reduction in medication for all but one. This released them from being closely tied to the hospital/hospice allowing greater freedom and independence that was dramatic in some cases (e.g., holidays abroad). There were no new sphincter disturbances reported.

Midline Myelotomy

Splitting the spinal cord in the midline posteriorly was intended to divide the spinothalamic fibers as they crossed, thereby controlling bilateral pain while avoiding the risks of bilateral cordotomy. Introduced in 1926, it was not particularly successful until the serendipitous observation in 1970 that a single level myelotomy at C1 produced analgesia over a wide body area. It was subsequently found that a limited midline myelotomy at T10 was effective against pelvic visceral cancer pain [73]. The recent discovery of a specific pathway in the medial dorsal columns which conducts visceral pain [74] provides a possible substrate for this operation that appears to be very effective and safe [75] but is rarely used.

Other Neurosurgical Procedures

In the past, many surgical targets in the brain have been tried with varying degrees of success and morbidity, but none is now used more than sporadically. This includes sites in the medulla,pons, midbrain, thalamus and hypothalamus, and the somatosensory and cingulate cortices. The pituitary gland provided one of the most useful targets; transnasal alcohol-induced hypophysectomy was very effective against hormone-dependant and diffuse cancer pain particularly when due to bone metastases from breast and prostate. Diabetes insipidus occurred in half the patients and visual disturbances were common; pharmacological hormonal manipulation has made it redundant. Dorsal root entry zone lesions are rarely used for cancer pain; an extensive laminectomy is required, the morbidity is relatively high, only paroxysmal pain responds well and cordotomy or rhizotomy are likely to be preferable.

Vertebroplasty

Painful pathological fractures of vertebra that do not respond to the conservative therapies of medications, TENS, steroid epidurals can be considered for fixation by cemented vertebroplasty. Open studies in myeloma and metastatic cancers report pain relief that is often complete in around 80% of patients [76–78]. Cement leak is the commonest risk at around 5%; however, complications from this are rare but are serious [79].

Complementary Therapies in Cancer Pain

Summary

There is a weak evidence base for the effectiveness of complementary therapies in terms of pain control, but they may improve well being. Safety issues are also a consideration.
Complementary and alternative medicine (CAM) refers to a diverse array of treatment modalities and diagnostic techniques. It has been defined as “diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, satisfying a demand not met by orthodoxy, or diversifying the conceptual framework of medicine” [80].

Large proportions of cancer pain patients are using CAM [81]. Reasons include dissatisfaction with conventional medicine, desperation, compatibility between the philosophy of CAM and patients’ own beliefs, and the wish for more control over one’s own health [82].

CAM therapies have the potential to increase well-being and thus influence pain. They are often employed in addition to conventional treatments in palliative and supportive cancer care.

**Acupuncture**

This is the insertion of needles into the skin and underlying tissues for therapeutic or preventive purposes at specific sites, known as acupuncture points.

A systematic review identified two RCTs and found no compelling evidence of acupuncture to control cancer pain [83] that was confirmed by other reviewers. Subsequent RCTs did not produce convincing evidence of effectiveness. It is effective in alleviating chemotherapy-related nausea and vomiting and may hence contribute to pain control [84].

**Aromatherapy**

Controlled use of plant essences, applied either to the skin through massage, added to baths or inhaled with steaming water.

A Cochrane systematic review concluded that aromatherapy and/or massage has beneficial short-term effects on well-being in cancer patients [85]. It has, however, not been convincingly demonstrated whether it is associated with clinically relevant analgesic effects.

**Herbal Medicine**

Medical use of preparations, which contain exclusively plant material. There is no convincing evidence for any herbal medicine to suggest effectiveness for treating cancer pain [80].

**Homeopathy**

This is where diluted preparations of substances whose effects when administered to healthy subjects correspond to symptoms and clinical signs of the disorder in patients. A systematic review of six RCTs found no convincing evidence that homeopathic remedies have analgesic effects in cancer patients [86].

**Hypnotherapy**

This is the induction of a trance-like state to facilitate relaxation and enhance suggestibility for treating conditions and introduce behavioral changes.

Studies have suggested the usefulness of hypnotherapy in palliative cancer care. A systematic review found encouraging evidence that hypnotherapy can alleviate cancer pain [87]. Due to the often poor methodology of the primary data, this evidence was deemed inconclusive. Similar conclusions were reached in two systematic reviews for procedural pain in pediatric cancer patients [88,89].

**Massage**

This is the manipulation of the body's soft tissue using various manual techniques and applying pressure and traction.

Massage seems to increase well-being through reduction of stress and anxiety levels and thus may contribute to pain control. The evidence for analgesic effects in cancer patients is encouraging but not convincing [90].

**Music Therapy**

The use of receptive (passive) and/or active music therapy most commonly based on psychoanalytical, humanistic, cognitive behavioral or developmental theory.

There is no convincing evidence from RCT data to suggest effectiveness for pain control in cancer patients [80].

**Reflexology**

The use of manual pressure applied to specific areas, or zones, of the feet (and sometimes the hands or ears) that are believed to correspond to other body areas or organs.

A few small RCTs generated no convincing evidence that reflexology improves quality of life or pain of cancer patients [91].

**Relaxation**

Techniques for eliciting the relaxation response of the autonomic nervous system resulting in the normalizing of blood supply to the muscles, decrease in oxygen consumption, heart rate, respiration and skeletal muscle activity. Most commonly progressive muscle relaxation is used.

Relaxation techniques have the potential to increase well-being and thus may contribute to controlling pain.
Whether these techniques have direct analgesic effects remains, however, unknown.

**Supplements**

Oral medical use of preparations of herbal or nonherbal origin.

A systematic review of nine RCTs that tested cannabinoids concluded that they are not superior to codeine in controlling cancer pain. As cannabinoids cause central nervous depression their introduction into routine care was deemed undesirable [92].

**Safety Issues**

Complementary therapies are often used because they are erroneously considered safe and harmless, which can be dangerously misleading. Some treatments like homoeopathy, massage, music therapy, reflexology and relaxation are associated with only mild and rare direct risks if administered appropriately by a trained practitioner. Others have been associated with potentially serious risks: herbal medicines and supplements with herb-drug interactions, toxicity and contamination, acupuncture with pneumothorax, hypnosis with negative physiological and psychological effects. General safety issues include misdiagnosis, or delayed access to effective treatments. Self-medication is another problem due to the potential interactions with conventional cancer treatments. Also, patients often do not disclose their use of complementary medicines to their health care provider who needs to seek the relevant information.

**Cancer Pain Management in the Community**

**Introduction**

Managing patients with cancer pain in secondary or tertiary care settings has several advantages compared with management in community settings (defined as the patient’s home, care-homes or hospices). These advantages include more comprehensive assessment and observation, better access to investigations, and more direct influence on prescribing and administration of therapy.

Increasingly however, patient’s wishes and U.K. government policy advocates improved palliative care, and therefore cancer pain management, for patients in the community. Hospice patients consistently rate pain management as a top research priority within palliative care above other symptoms and aspects of care [93]. An understanding of cancer pain management in the community is therefore important for planning services and interventions.

**Epidemiology of Cancer Pain in the Community**

**Prevalence**

Systematic reviews [94,95] have demonstrated that cancer pain is common and its prevalence is related to the stage of illness: 48% of patients with early disease; 59% undergoing cancer treatment; 64–74% with advanced disease. These findings are in keeping with those in the recent European Pain in Cancer (EPIC) survey of 11 European countries, which indicated an overall pain prevalence of 72% of patients with cancer in the community. This was slightly higher in the United Kingdom at 77% [96].

**Pain Severity**

Most research on cancer pain severity has been conducted in secondary care settings [97,98]. Using a 0–10 numerical rating scale, hospitalized cancer patients typically report mean scores for worst pain 4.8, mean score for average pain 3.7, worse pain intensity greater than 5 in two thirds of patients.

There has been less research in community based patients with cancer pain. The EPIC survey invited patients with cancer pain in the community to participate that were specifically not recruited through palliative care or pain services [96]. For the 617 patients from the UK, the mean pain intensity was 6.4 (identical to the European average); over 90% rated their pain greater than 5 out of 10; a quarter were not receiving any analgesia.

This survey suggests that community based patients have greater, not less, pain intensity than those in secondary care and highlights the need for effective strategies in primary care.

**Effects of Age on Pain and Treatment**

Concerns exist that older people with cancer experience less effective pain management than younger people [99–101]. Recent research suggests that when older people with cancer are compared with a younger group there is no significant difference in pain intensity [98,102–105]; older people with cognitive impairment report greater intensity of cancer pain than those without [106]; older people are less likely to receive adequate analgesia than younger people [107,108] but importantly, these studies only compared the category of the analgesic prescribed for a given pain intensity, and not on the basis of whether the analgesic therapy was effective in reducing pain.
Further research into the differences in analgesic prescribing between older and younger people has shown that older people generally require lower doses of analgesia, especially opioids, than younger people even when controlling for pain intensity [102–104, 109]. This may be due to a physiological phenomenon, for example, impaired analgesic metabolism and excretion. Older people may sometimes need higher doses; 58 older people aged over 75 years attending a German pain clinic received higher doses of opioids than those aged under 65 years [110]. Older people do not experience more adverse effects, dose escalation or the need for opioid switching, than younger people [103,110]. Older people may have poorer attitudes and knowledge about pain and analgesia than younger people and therefore, are reluctant to have stronger analgesia [111,112].

In summary, age does not appear to impact upon pain intensity, but older age does appear to be associated with lower doses or potency of analgesic therapy in secondary care settings. These settings include hospital or hospice inpatient units and out-patient clinics. There is a paucity of research on community based patients with cancer pain.

### Time Spent by Patients in the Community

Patients with cancer pain spend most of their time in the community. RCTs from Italy and Norway that have examined the impact of home-based palliative care teams have shown that in the last 6 months of life patients referred to such teams spent between 65 and 81% of time at home compared with 65–70% of time in a control group; less time was spent at home and more time in hospital in the last month of life [113, 114].

Primary care teams supported by home-based palliative care teams are therefore usually best placed to initiate and manage cancer pain therapy for the majority of patients.

### Barriers to Pain Management

#### Patient Based Barriers

Attitudes or behaviors that prevent successful pain management are referred to as barriers and can be assessed using the Barriers Questionnaire (BQ) [115,116]. Research suggests that the most important of these barriers are fear of consequences of analgesic use (addiction and tolerance), fatalism about pain, inadequate communication with health care professionals, some religious and cultural beliefs may also impede effective pain control [117,118].

However, a U.K. study [112] which interviewed older and younger patients with cancer pain at home highlighted that knowing when to take and titrate analgesia was the most important barrier for all ages; older people found taking and titrating analgesia significantly more of a barrier than younger people; fear of adverse effects was an important barrier for both groups; fatalism and communication issues where of less importance.

### Role of Carers

Carers and family members are important sources of support for patients with cancer pain. However, carers can have a powerful influence on the management of pain in an individual patient. Carers’ barriers are often similar in nature to patient barriers but also include hesitancy to administer analgesia. Ethnicity of carers may also influence BQ scores.

High scores by carers on the Barriers Questionnaire have been shown to more strongly predict inadequate cancer pain management than patient scores (based on patient pain scores and level of analgesia); be associated with reports from carers that a patient's pain is uncontrolled [119,120].

### Health Care Professionals

Knowledge and attitudes of health care professionals toward cancer pain management vary. When these have been compared directly [121,122] nurses have been shown to have better pain assessment skills than doctors or pharmacists; doctors had better knowledge about clinical therapy; pharmacists had most knowledge about opioid pharmacology; all three professional groups scored poorly in some area.

These comparisons demonstrate the need for clinical teams rather than individuals to be involved in managing cancer pain.

### Place of Care

Primary care or community settings include care homes (nursing or residential) and patients with cancer pain in this context can sometimes be at a disadvantage. There is a high prevalence of daily pain in nursing home residents with cancer and this is often untreated, particularly in older patients [108]. Nursing homes can vary in their level of staffing and equipment (e.g., syringe drivers) necessary for effective cancer pain management particularly at the very end of life.

### Access to Opioids

Opioids are central to effective cancer pain management but access to opioids in the community may be an additional barrier faced by patients. In the United States, pharmacies in predominantly ethnic minority areas are significantly less likely to carry sufficient opioids than in other areas [123,124]. There is no comparative data specific to the UK.

### Patient-Based Educational Interventions

### Types of Interventions

Interventions designed to improve knowledge and attitudes toward cancer pain and analgesia have been studied extensively. These have been a combination of a
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brief coaching session (20–40 minutes) in which patient or carer barriers are identified and addressed, with advice on using analgesia; supported by written material and occasionally audiovisual material that patients and carers can review at home. Some studies have examined more intensive interventions that consist of repeated coaching and support by a nurse or researcher. Comparators in these randomized trials have included either usual care or a placebo such as a booklet on nutrition.

Evidence of Effectiveness

A recent meta-analysis of 21 clinical trials [125] has shown that educational interventions for community patients with cancer pain significantly improve knowledge and attitudes toward pain and analgesia, and reduce pain intensity. Compared with control, educational interventions resulted in a mean reduction of around 1 point on a 0–10 numerical rating scale for both worst and average pain intensity; produced a similar effect to that seen when adding paracetamol or gabapentin to patients already treated with opioids [126,127].

Patient and carer education is therefore an important, though probably under-used, component of successful cancer pain management.

Pain Related to Cancer Treatments

Summary

Chemotherapy, surgery and radiotherapy are cancer treatments that can cause persistent pain in cancer survivors, up to 50% of whom may experience persistent pain that adversely affects quality of life. Awareness of this problem may lead to preventative strategies, but at the moment, treatment is symptom based and often inadequate.

Introduction

Chemotherapy, surgery and radiotherapy are cancer treatments that can cause persistent pain in cancer survivor patients and adversely affect quality of life and function.

Up to 50% of cancer survivors may experience chronic pain secondary to treatment yet this is under recognized and under reported [128]. Pain in cancer survivors has an additional burden in that it is often perceived to be indicative of disease recurrence.

Painful Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Neurotoxicity is a dose limiting side-effect of many chemotherapies and biological therapies (also known as biological response modifiers that modulate the natural response to tumor cells) used in the treatment of cancer. Peripheral neuropathy is the most prevalent form of neurotoxicity.

Risk Factors for Development of CIPN

Longer duration of therapy; high cumulative dose; type of chemotherapeutic agent (e.g., vincristine, cisplatin, paclitaxel); pre-existing neuropathy (including CIPN).

Common Features of CIPN

Symmetrical symptoms; length dependency; “stocking-glove” distribution, distal limb long nerves affected; signs and symptoms of neurosensory dysfunction; onset related to administration of neurotoxic therapy; rapid, or delayed or even after therapy has finished; relative sparing of motor function [129].

In addition to interference with microtubular mediated axonal transport and anatomical damage, alterations in nerve function mediated by pro-inflammatory cytokines, immune cells and mitochondria have been postulated as important in CIPN [130,131]. Pain is not synonymous with neuropathy but is associated with higher grades of peripheral neuropathy.

Assessment

Several assessment tools have been used and validated [132]. Many are clinician rather than patient based and do not all include assessment of pain, function and quality of life. A specific CIPN pain scale could reduce underreporting and therefore undertreating of CIPN pain.

Quantitative sensory testing (QST) does not always reflect symptoms or correlate with chemotherapy dose nor does it identify neuropathy earlier than clinical history and examination [129]. However, QST is an objective assessment that is useful for surveillance of recovery (Table 1).

Prevention and Treatment

Modification and refinement of chemotherapy dosage schedules (especially in palliative setting) can reduce CIPN. Specific preventative treatments such as amifostine, glutathione, N acetyl carnitine, N acetyl cysteine, glutamine/glutamate have been studied in humans and animal models with variable success. Vitamin E can reduce cisplatin and paclitaxel induced neuropathy [136,137]. More research is needed to ascertain effective agents without appreciable side-effects or affecting anti-cancer efficacy.

Supportive education and nonpharmacological treatments are important. Simple strategies to reduce the impact of numb and painful hands and feet, such as reducing water temperature, using aids to help holding cups and utensils, are important. Psychological support, physiotherapy and occupational therapies are part of a multidisciplinary approach.

There is few data on effective pharmacological treatments of CIPN. Current management is predominantly based on evidence from other neuropathic pain. Although
GABAPENTIN was effective in an animal model of CIPN [138], it had no effect in humans in a controlled, randomized crossover trial [139]. Until there is more data, current neuropathic pain treatment guidelines may be used [140–142]. However, mechanisms of CIPN may be different to other neuropathic pain and more research is needed.

**Post Cancer Surgical Pain**

Pain syndromes after cancer surgery are found following breast, thoracic, head and neck surgery.

**Post Breast Cancer Surgical Pain (PBSCP)**

Chronic pain following surgery for breast cancer has been reported with an incidence of over 50%. Similar to other pain in cancer survivors, it is under-reported, under-recognized, and undertreated. Classification is varied and potentially confusing. Risk factors. Various risk factors predicting the development of PBSCP have been suggested, although data are conflicting. Young age (although associated with more aggressive disease and treatment), previous chemotherapy and radionotherapy, poorly controlled post-operative pain, pre-existing anxiety and depression, and surgical factors. Post-PBSCP pain can occur in the scar, arm, chest wall, or breast, and is commonly associated with sensory and dysesthetic qualities. Pain often interferes with function and quality of life.

**Risk Factors**

Various risk factors that have been suggested include:

- Young age
- Previous chemotherapy and radiation
- Poorly controlled post-operative pain
- Pre-existing anxiety and depression
- Surgical factors

Reconstructive surgery may be an additional risk factor. Post-PBSCP pain is less common after less radical surgery, such as breast conserving therapy compared to mastectomy.

**Surgical Factors**

Damage and dysfunction of the intercostobrachial nerve has been proposed as the main mechanism for PBSCP. Some studies showed lower incidence of pain after preservation of the nerve. Thirty percent still develop pain after preservation, and 30% do not develop PBSCP after the nerve is cut. Pain is less common after sentinel node biopsy compared with axillary dissection [143].

**Treatment and Prevention**

Reduction of risk factors for the development of PBSCP, such as attention to good post-operative pain control, careful choice of surgical procedure, and meticulous technique could reduce PBSCP.

**Table 1** Neuropathies associated with specific chemotherapies and biological therapies

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Type of Neuropathy (Incidence)</th>
<th>Onset Time (Coasting)</th>
<th>Duration/Recovery</th>
<th>Other Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin (carboplatin)</td>
<td>Chronic</td>
<td>c. 1 month (+)</td>
<td>Some resolution in 80% over months/years</td>
<td>Carboxplatin less CIPN</td>
</tr>
<tr>
<td>Oxaliplatin [133]</td>
<td>Acute (90%) and chronic</td>
<td>Acute: hours Chronic: c. 1 month (+)</td>
<td>Acute: Chronic: as cisplatin</td>
<td>Acute pain in up to 90%, cold induced</td>
</tr>
<tr>
<td>Vincristine [132] (vinblastine)</td>
<td>Chronic (30% severe)</td>
<td>Peak 2–3 weeks (+)</td>
<td>Some recovery 1–3 months, longer recovery into years</td>
<td>Paresthesias common, vinblastine less CIPN</td>
</tr>
<tr>
<td>Paclitaxel (docetaxel) [129]</td>
<td>Chronic</td>
<td>Within days (+)</td>
<td>@6/12 19% complete recovery, 25% no recovery [134]</td>
<td>More CIPN with more frequent dosing; docetaxel less CIPN</td>
</tr>
<tr>
<td>Bortezomib (Velcade®) [135]</td>
<td>Chronic (35%)</td>
<td>Any time (+)</td>
<td>Recovery less likely [135]</td>
<td>High incidence of neuropathy before starting bortezomib</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Chronic</td>
<td>Any time (+)</td>
<td>Recovery less likely [135]</td>
<td>No cumulative dose response, daily dose</td>
</tr>
</tbody>
</table>

CIPN = chemotherapy-induced peripheral neuropathy.
A few small trials of treatments for PBSCP have demonstrated modest and variable benefits from capsaicin and EMLA cream, gabapentin, amitriptyline and venlafaxine. Nevertheless, treatment includes best practice for general neuropathic pain management in a multidisciplinary approach.

Post Thoracotomy Pain

Persistent pain following thoracotomy for malignant and nonmalignant indication may occur in more than 50% of patients [146] and as for other types of chronic postoperative pain may be related to perioperative nerve damage [147]. Similarly, postoperative pain is a risk factor for chronic pain. Video-assisted thoracoscopic lung surgery (VATS) is associated with a lower incidence of persistent pain.

Post Head and Neck Surgery Pain

Surgery, in addition to chemotherapy and radiotherapy, is associated with chronic long-term pain for patients with head and neck cancer. Pain can occur in the oral cavity, face neck or shoulder. The incidence of chronic pain after surgery is similar to other post cancer surgery pain, about 40% at 1 year and 15% at 5 years [128]. Of the 33% of patients who had pain 1 year after neck dissection, most had features of neuropathic pain [148]. Treatment depends on careful assessment, providing information to patients and a combination of physical and pharmacological approaches.

Radiotherapy Induced Pain

Radiotherapy is used as a primary adjunctive treatment for many types of cancer. Certain tissue such as skin, mucous membranes and nerves, are more susceptible to damage.

Radiation-Induced Brachial Plexus Neuropathy (BPN)

Radiation-induced BPN was associated with breast conservation strategies and deep delivery of radiotherapy in the 1960s and 1970s. Modification of radiotherapy treatments have reduced the incidence of BPN [149,150]. BPN usually occurs at least 6 months after therapy, although higher doses may have a reduced latency. The major differential diagnosis is tumor related plexopathy. In addition to clinical factors, MRI may aid diagnosis.

Features Suggestive of Radiation-Induced Neuropathy. Progressive forelimb weakness (upper or lower arm depending on which roots are involved), pain less common, initial involvement of upper plexus divisions, slow progression and long duration, and incidence increases with time.

Treatment. There are no standard treatments for radiation-induced BPN but opioids may be beneficial [151]. Other nonpharmacological treatments such as chemical sympathectomy have been used, but evidence is limited. Current therapies are also based upon existing treatments for other neuropathic pain.

Pelvic Pain after Radiotherapy

Radiotherapy for pelvis malignancy can also lead to radiation-induced chronic pain syndromes. Pain results from multiple mechanisms, including effects on gut, nerves and pelvic and hip fractures. Dysuria may occur in 20% of patients 1 year after pelvic radiation [128]. In one study, nearly 50% of patients reported pain in back and lower extremities which was poorly controlled with analgesics and had a negative influence on quality of life [152]. Treatment is symptom-based although, as for BPN, preventative strategies are being explored.

Management of Acute Pain in Cancer Patients

Summary

Management of acute pain, especially postoperative pain, in patients on high dose opioids is a challenge that requires in depth knowledge of pharmacokinetics and formulation of a careful management plan to avoid withdrawal symptoms and inadequate pain management.

Introduction

Patients with cancer who present for surgery on high dose opioids are a heterogeneous group with a number of complex perioperative analgesic management problems. The main issues include: physical dependence and the precipitation of withdrawal symptoms if insufficient postoperative opioid is prescribed, and tolerance to the effect of postoperative opioids. Additionally there may be difficulties in calculating dosage conversions between different types of opioid and different routes of administration.

Tolerance

Tolerance is a phenomenon in which exposure to a drug results in the diminution of an effect or the need for a higher dose to maintain an effect. It may develop 1–2 weeks or more after initiation of opioid therapy. A larger dosage of opioid will be required to achieve the desired effect. Short-acting opioids should be titrated to effect in a controlled, monitored environment.

Tolerance also develops to some of the side-effects of opioids making patients less likely to suffer from respiratory depression, itching and nausea than opioid naïve patients.

Acute Pain Management

Management of pain in this population of patients is of increasing importance as the cancer survivor population grows and as greater numbers of patients are using convenient sustained release opioid preparations and transdermal delivery systems.
In general the issues of physical dependence, withdrawal and tolerance, only relate to patients who have been on WHO Step 3 strong opioids such as morphine or oxycodone for more than 1–2 weeks preoperatively. These issues are not likely to be a problem in patients taking WHO Step 2 analgesics such as codeine or tramadol unless the patient is taking larger than normal doses.

It is common to underestimate and undertreat pain in opioid dependent patients, because most postoperative analgesic regimes are based on the opioid naïve patient. Opioid dependent patients should be identified preoperatively and a perioperative analgesic plan should be devised after discussions with the patients’ opioid prescriber and with the pain team. The aim is to achieve effective analgesia without precipitation of withdrawal phenomena.

Opioid Management

Management involves the regular provision of the pre-existing opioid supplemented with additional short-acting opioid, local anesthetic, nonsteroidal anti-inflammatory drug and paracetamol. Patient-controlled analgesia with a short lock-out and higher bolus dose may be useful. Neuaxial and regional analgesia is recommended where appropriate.

Patients will present for surgery having been on many different types of opioid for varying periods of time (e.g., morphine, oxycodone, methadone, hydromorphone, pethidine, etc.) which may be modified release (e.g., MST, fentanyl patch) or immediate release preparations (e.g., immediate release morphine). The route of delivery may be oral, subcutaneous via a syringe pump or transdermal. Dosages range from MST 10 mg twice a day to very large doses such as MST 1 g per day or more.

Standard postoperative opioid regimes are generally developed for the opioid naïve patient. Patients on high dose opioids may have developed a physiological dependence and if managed using standard postoperative analgesia regimes may not receive adequate analgesia and develop a “withdrawal syndrome.” This results in adrenergic hyperactivity and common symptoms such as fatigue, generalized malaia, abdominal cramps, perspiration, fever, piloerection, dehydration and restless sleep.

Patients will require a baseline opioid dosage postoperatively—referred to as the baseline opioid requirement—calculated using their preoperative opioid dosage. This can either be given using the same opioid or using an alternative opioid in an equi-analgesic dosage. A continuous parenteral infusion may be needed if the patient is unable to take oral drugs. Provision will need to be made for “as required” dosing for breakthrough pain. Patient controlled analgesia machines have been successfully used in opioid dependent patients, their advantage is that dosages and lock-out intervals can be adjusted according to need.

In the preoperative and perioperative period regular opioids (usually oral) may be discontinued for several hours which amounts to the opioid “debt.” This should be replaced with systemic opioids during the operation.

Parenteral Opioid Delivery. Transdermal drug delivery systems have the disadvantage of being relatively inflexible in their dosage delivery, with clinically relevant dosages still being absorbed for up to 12 hours. One strategy is to leave the patch in place and to titrate to analgesic effect using immediate release opioids. Similarly, it may be appropriate to leave implanted analgesic pumps throughout the perioperative period and use additional short acting opioid and nonopioids used to control breakthrough pain.

Nonopioid Analgesia

Nonopioid analgesic drugs and local anesthetic procedures will have the effect of reducing opioid requirements—“opioid sparing effect” (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], paracetamol and clonidine). Local anesthetic blocks such as epidurals, brachial plexus block, paravertebral or iliinguinal blocks will also have an “opioid sparing” effect.

Effects of Surgery

Surgery itself will have a variable effect on opioid requirements and parenteral routes will have to be considered if the oral route is not available. It is difficult to predict the precise postoperative analgesic requirements as the effect of surgery may be to increase (if the surgery results in pain due to local tissue trauma) or decrease opioid requirements. Increases of 20% or more above the baseline opioid requirement have been reported, depending on the surgical procedure. However, surgery may alleviate pain due to removal of direct tumor pressure effects on local structures (e.g., removal of a retroperitoneal sarcoma tumor pressing on the lumbosacral plexus). In this group of patients opioid requirements may reduce but they will still need baseline opioid administration.

Complex Problems in Cancer Pain

Summary

Cancer pain is often very complex but the most intractable pain is often neuropathic in origin, arising from tumor invasion of the meninges, spinal cord and dura, nerve roots, plexuses and peripheral nerves. Accurate diagnosis of the causes of pain is necessary with the use of multimodal therapies. Case studies illustrating some of these points are found in the British Pain Society document (http://www.britishpainsociety.org).

Introduction

Cancer pain can be complex and difficult to treat. Up to 50% of patients may have pain at diagnosis and greater than 75% may experience pain with advanced cancer.
Pain may occur in more than one site in over half of cases and may have different etiologies. Such complexity can be challenging and require a truly multidisciplinary approach. As for nonmalignant pain, management of cancer pain can be challenging for the very young or old, for patients with medical problems such as heart disease, respiratory disease, renal or liver compromise and those with mental health issues. Often these factors may present in combination and generate demanding clinical problems.

Certain pain problems related to the nature of the pain or patient factors, may make the conventional WHO ladder approach to pharmacological therapy difficult to utilize and in some cases this approach may not be totally effective. Other pharmacological or more invasive treatments may be required.

To exemplify such complex issues we will discuss case studies concerning problems of breakthrough pain; cancer pain control in patients addicted to opioids; treatment of pain of mucositis; cancer pain in patients with dementia; alternatives to the conventional WHO ladder approach; interventional procedures; ketamine.

**Breakthrough Pain**

Breakthrough pain has been referred to as a brief exacerbation of pain on a well controlled baseline. The terminology of “breakthrough pain” in undergoing subtle revisions but is made up of many different types of pain. Breakthrough pain can be of any etiology. Certain authors feel that “breakthrough pain” does not include exacerbations of pain in the titration phase, nor should end of dose exacerbation of pain be called “breakthrough” [153].

Breakthrough pain can be divided into spontaneous: no obvious cause; incident pain: clear cause evident; nonvolitional: pain caused by involuntary act; volitional: pain caused by voluntary act; procedural: pain caused by therapeutic procedure.

As for any cancer pain, treatment relies on detailed assessment and formulation of a multidisciplinary therapy plan. Rapid acting opioids have been successfully used to treat breakthrough pain, but it remains a difficult therapeutic problem. Newer preparations of rapid release opioids are being developed.

**Pain in Opioid Addiction and Substance Misuse**

In the United Kingdom, the prevalence of drug misuse is around 9 per 1,000 of the population aged 15–64 years, and around 3 per 1,000 inject drugs, in most cases opioids. Opioid abuse and dependence are associated with a wide range of problems, including overdose, HIV infection, hepatitis B or C, thrombosis, anemia, poor nutrition, dental disease, infections and abscesses, criminal behavior, relationship breakdown, unemployment, imprisonment, social exclusion and prostitution.

**Pain from Cancer in People Who are Addicted to Opioids may be Undertreated for the Following Reasons**

Lack of understanding of opioid addiction and methadone maintenance; lack of training on prescribing analgesia in this group of patients; attitude of health care professionals about illicit drug users (fear of diversion); failure to recognize the potential for tolerance to other opioids in Methadone-maintained patients; acute pain may be undertreated leading to misunderstandings, patient anxiety, depression, dissatisfaction and complaints.

**Principles of Giving Analgesia in Opioid-Addicted Patients**

Prevent withdrawal symptoms/complications; assess opioid load (in an intravenous [i.v.] drug user this is difficult; withdrawal symptoms can be prevented with low doses of opioids).

Diagnose the cause of the pain: nociceptive, inflammatory, neuropathic, visceral, mixed. Use balanced analgesia wherever possible (NSAIDs, paracetamol, local anesthetics, tricyclic antidepressants, anticonvulsants). Use oral/transdermal/subcutaneous routes, not i.v. (consider epidural or intrathecal drug delivery systems, remembering infection risk).

Use long acting opioids and minimize analgesia for breakthrough, as this may be rapidly escalated. Set a limit and review frequently. Use tablets (sevredol, oxynorm) for breakthrough pain, not oramorph.

Make a “contract” with the patient before starting therapy, explaining the limitations, and setting a clearly defined upper limit of opioids before next review. Write clear instructions for the whole team.

Use a sole prescriber (usually GP). Prescriptions may have to be issued daily, every 2–3 days, or weekly.

Use psychological therapies and treat anxiety and depression.

**Maintenance Therapy**

Methadone substitution is the primary maintenance treatment in the UK, usually 60–120 mg daily. There may be tolerance to other opioids, and rapid escalation of doses can be dangerous, especially when combined with alcohol or other sedative drugs.

Naltrexone (opioid antagonist) is used in detoxification programmes to help maintain abstinence. It is long acting (>48 hours) and will lead to opioid resistance and then opioid sensitivity when it has been eliminated systemically.

Buprenorphine (partial agonist) is also used to prevent withdrawal symptoms in opioid dependent patients. Its action on the μ receptors reduces the effects of any...
additional opioids. Average maintenance doses range between 12 and 24 mg daily. Patients with severe cancer pain may have to be changed from buprenorphine to methadone.

Mucositis
Mucositis is the painful inflammation and ulceration of the mucous membranes usually in the mouth but can affect other areas of the mucosa in the gastrointestinal tract [154,155]. It can be caused by radiation therapy or chemotherapy and very common after radiotherapy for cancer of the head and neck and after certain types of chemotherapy such as 5-fluorouracil. High dose chemotherapy and hematopoietic stem cell transplantation have especially high incidence of oral mucositis [155,156].

Nonpharmacological treatment strategies include meticulous oral hygiene, gel-based barrier protection, reduction of known painful precipitants (e.g., alcohol), local anesthetic mouthwashes and other oral lubricants. Opioids provide the mainstay of pharmacological treatment but newer anti-inflammatory therapies are being developed. However, severe oral mucositis often causes difficulties in swallowing precluding the use oral medication.

Pain in Dementia Sufferers
Adults with dementia will probably express their pain in ways that are quite different from their cognitively intact counterparts that can result in inadequate pain assessment and consequently poor pain management.

The processing of sensory-discriminative aspects of pain in the brain are thought to occur in the lateral pain system, whereas motivational-affective aspects are processed by the medial system. The recognition of these two systems is important with patients with dementia. Pain thresholds (that are the sensory-discriminative aspects) do not differ between patients with Alzheimer’s disease and those older adults without dementia, although pain tolerance (motivational-affective aspect) does. Older adults with Alzheimer’s disease perceive the presence of pain, but the intensity and affective aspects are different to that experienced by their cognitively intact counterparts. This might explain the atypical behavioral responses observed in this group.

Observation of behavior for pain assessment in patients who do not have the ability to communicate their pain can be helpful but typical pain behaviors may be absent or difficult to interpret. Involvement of health care professionals, informal care providers and the family in the identification of pain is essential.

The American Geriatric Society [157] list six categories of pain behaviors and indicators for older people with dementia: facial expressions; verbalizations and vocalizations; body movements; changes in interpersonal interactions; changes in activity patterns or routines; mental status changes.

A number of behavioral pain assessment tools for detecting the presence of pain in patients with dementia exist. Care providers are advised to select a tool that is appropriate to the patient that can be used for initial and ongoing assessments. However, the assessment of behavioral pain indicators should consider only one strategy to identify pain in patients with dementia and should be used in conjunction with other pain assessment strategies and the evaluation of pain relieving interventions.

Atypical Pharmacological Treatments: Ketamine
The N-methyl-D-aspartate (NMDA) receptor has been implicated in mechanisms of neuropathic and inflammatory chronic pain. It is one of the key components of central sensitization that contributes to increased pain and abnormal pain perception. It is also thought to be involved in many cancer pains. When the conventional WHO ladder approach fails, NMDA receptor antagonists could provide a novel and powerful site of analgesia.

There is evidence for the efficacy of NMDA receptor antagonists in many chronic pains (including cancer pain), yet the situation is not so clear clinically. There are few NMDA receptor antagonists available. Dextromethorphan has been used for acute pain. Methadone also has some NMDA antagonist activity and may help in some cases of opioid refractory pain. However, ketamine is the most used NMDA receptor antagonist for cancer pain.

Ketamine is an anesthetic, but in smaller doses appears to have analgesic properties. There are many case reports and case series demonstrating significant efficacy in refractory cancer pain either alone or concomitantly with opioids. However, there is little higher quality evidence (such as RCTs) at present. The lack of data is reflected in the variability of suggested protocols in both dose and route of administration. Side effects are potentially problematic including tachycardia and cognitive disturbances such as hallucinations. Nevertheless, ketamine may provide some empirical benefit in refractory cancer pain.

Pain in Children and Adolescents with Cancer
Pain in children and adolescents with cancer is a significant, debilitating, acute and chronic symptom, during or after treatment that affects the quality of life of young patients and their families. In recent years, advances in pain management have been made, however, still pain is often undertreated and there is a need for improvement.

The principles of pain management and palliative care in adult practice are relevant to pediatrics, nevertheless, the adult model cannot be applied directly to children for the following reasons [158]: 1) the types of malignancy and disease trajectory in children are different from those in adults; 2) special considerations are required when selecting analgesics, doses and modalities during childhood. Factors that influence prescribing are quite distinctive from adults and include metabolism, renal clearance, changing size and surface area, and the ability to manage medica-
tion, among others; 3) a child’s family and social context is different to that of an adult: relationships with parents and siblings, school and friends, extended family network are of paramount importance when treating young patients; 4) children’s developmental stage and continuous psychological, spiritual and cognitive development need to be taken into account when treating their pain (e.g., a child’s conceptualization of what causes and eases pain, understanding of time, ability to implement behavioral and cognitive strategies for coping with pain) and 5) the legal and moral positions regarding the decision-making ability of both those with parental responsibility and the child/young person themselves is very different to that of an adult.

Effective pain management in children and young people with cancer requires that pediatric health care providers take into account the multitude of physiological and psychological changes that occur from infancy through adolescence, including changes in relationships with parents [159]. The multidisciplinary approach to providing pain management for children and adolescents includes integrating pharmacological and psychosocial care in the context of each patient’s physical, cognitive, emotional and spiritual level of development [160].

Every child/young person with pain management and palliative care needs should have access to universal pediatric services, core palliative care services (hospice, community palliative care nurses) and specialist palliative care support when required [161].

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Cancer Pain Management: A perspective from the British Pain Society, supported by the Association for Palliative Medicine and the Royal College of General Practitioners

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