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Management of pain associated with spinal tumor

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Epidemiology

The spine is the most frequent site of bony involvement in patients with malignant metastases [1]. Tumor of the vertebral bodies has been demonstrated in 25% to 70% of patients with metastatic cancer [2], and spinal metastases are present in 40% of patients who die from cancer [3]. Metastatic lesions are three to four times as common as primary bony tumors of the spine [4]. The major complications caused by malignant metastases of the spine are pain and neurologic injury. Pain and neurologic injury usually occur together and are the result of compression of neural structures, which may be caused directly by tumor mass or by displacement of vertebral fragments into the spinal canal.

In the United States, approximately 20,000 cancer patients are treated each year for malignant epidural spinal cord compression or cauda equina compression (MESCC). Virtually all patients with MESCC have severe pain. MESCC affects 5% to 10% of adult solid tumor patients and 5% of pediatric solid tumor patients [5,6]. This is corroborated by autopsy series [7,8]. Half of the patients presenting with MESCC are not known to have cancer at the time that pain or neurologic deficits begin [9].

Thoracic metastases occur twice as frequently as lumbar metastases and four times as frequently as cervical metastases [10]. Almost two thirds of metastatic spinal lesions present in the thoracic region [11]. The level of spinal involvement varies with tumor type. Breast and lung tumor metastases are equally distributed throughout the spine. Prostate, renal, and gastrointestinal metastases are more often found in the lower thoracic, lumbar, and sacral levels. Tumors of the uterus and cervix most commonly spread to the lower lumbar and sacral spine. Pancoast tumors of the apex of the lung extend directly into the cervicothoracic spine in 25% of cases [3]. Multiple noncontiguous levels of spinal tumor are present in 10% to 38% of cases [12]. This pattern is relatively less common in patients with lung cancer [9].

MESCC is caused by extension of tumor from the vertebral body in 85% to 90% of cases [11]. In pediatric patients, MESCC caused by tumor of the posterior elements is more likely, and intraforaminal spread of tumor from paraspinal sites also occurs more frequently than in adults [12]. Tumor metastases to the epidural space seldom breach the dura [3,13].

MESCC is the presenting sign of cancer in up to 30% of pediatric cases. The time interval to presentation with MESCC may be twice as long in children without known cancer compared with those already diagnosed with malignancy [13]. Children without a cancer history presenting with MESCC are often initially misdiagnosed [6]. MESCC is the most frequent neurologic complication of Ewing's sarcoma.

Undertreatment of pain in cancer patients persists despite decades of efforts to provide clinicians with information about analgesics. A recent retrospective record review done by researchers at the National Comprehensive Cancer Network (NCCN) showed that fully one quarter of breast cancer patients with bone metastases reporting moderate to severe pain do not seem to receive adequate pain relief [14]. Other studies also show a high prevalence of unrelieved pain across clinical settings [15].

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Differential diagnosis

The most common presenting symptom of MESCC is neck or back pain. Pain may precede other symptoms and signs by 1 year [12]. The differential diagnosis of neck or back pain with associated neurologic dysfunction secondary to MESCC includes many benign tumors. Meningiomas occur more frequently in patients with breast cancer [16]. Other nonmalignant conditions also occur. Coexisting nonmalignant disease of the spine may affect as many as 30% of patients with MESCC [17]. Degenerative, inflammatory, and infectious processes affect the spinal structures, and soft tissue injuries causing neck or back pain are common. Trauma is the most common cause of neck or back pain in children; other nonmalignant conditions, such as Scheuermann's disease and scoliosis, present in this age group [18]. Neck and back pain in cancer patients may also be treatment related, caused by vertebral osteoporosis or compression fractures as a result of radiation therapy or corticosteroids.

Spinal cord or cauda equina dysfunction may be related to tumor or treatment without MESCC. Leptomeningeal disease, intradural extramedullary or intramedullary spinal cord disease, paraneoplastic necrotizing myelopathy, and myelopathy induced by radiation or intrathecal chemotherapy should be considered if no epidural compressive lesion is identified. Myelopathy is a late complication of radiation. Epidural lipomatosis may be caused by corticosteroid therapy. Vascular events of the spinal cord may occur more often in the presence of malignant disease.

Pathogenesis of pain and neurologic dysfunction

Pain caused by malignancy of the spine may result from activation of afferent nociceptive neurons by mechanical distortion and inflammatory mediators (nociceptive pain) or from neural dysfunction (neuropathic pain). Nociceptors innervate the periosteum, soft tissues, facet articular cartilage, dura mater, nerve root sheaths, and blood vessels. Vertebral collapse and structural instability can give rise to mechanical pain via injury to these structures. Neuropathic pain results from altered peripheral and central neural activity, which may be induced by injury of the nerve roots, axonal injury, or other processes, such as deafferentation.

Spinal tumor may present with several patterns (Table 1). Specific physiologic features explain the high incidence of metastasis to the vertebrae, despite their poor blood supply. Metastases may occur more commonly in previously damaged bone [19]. This is important when evaluating the cancer patient with long-standing neck or back pain who presents with an increase in typical pain or a change in the character of pain.

Table 1
Patterns of spinal tumor involvement

Bone
Bone alone
Single site
Multiple contiguous sites
Multiple noncontiguous sites
Bone and paraspinal soft tissues
Bone, paraspinal tissues, and viscera
Bone and nerve roots
Bone and epidural space (without thecal compression)
Bone and epidural spinal cord compression
Bone and epidural cauda equina compression
Epidural
Intraforaminal
Isolated
Local extension
Epidural and spinal cord compression
Single site
Multiple contiguous sites
Multiple noncontiguous sites
Epidural and cauda equina compression
Single site
Multiple contiguous sites
Multiple noncontiguous sites
Diffuse

From Weinstein SM. Management of spinal cord and cauda equina compression. In: Berger AM, Portenoy RK, Weissman DE, editors. Principles and practice of palliative care and supportive oncology. 2nd edition. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 534; with permission.

Epidural tumors produce dysfunction of neural structures and pain by compression, demyelination, ischemia, and tissue edema. Inflammation may change vascular permeability and disrupt the blood-spinal barrier at the tumor site. The release of excitatory amino acids by injured neurons may further promote ischemia and cause pain.

In the initial stage of epidural cord compression, there may be white matter edema and axonal swelling with normal blood flow. These changes are caused by direct compression or venous congestion. Over time, progressive compression decreases blood flow and disturbs vascular autoregulation, leading to vasogenic edema and pain. Spinal cord infarction may result from interruption of venous outflow or occlusion of small

arteries or from interruption of the major arterial supply to the spinal cord, including the artery of Adamkiewicz or radicular arteries in the intervertebral foramina.

A necrotic cavity, usually located in the ventral portion of the posterior columns or dorsal horn, has been visualized on MRI [12]. The effects of cord compression and resultant neuropathic pain may also be caused by coup and contrecoup injury. Demyelination as a mechanism is supported by a pathologic examination that demonstrates greater demyelination of white matter than gray matter, a pattern that does not conform to arterial supply [5]. Animal experiments show rapid ischemic change producing a greater degree of irreversible neurologic injury [20,21]. Similar observations have been made in human spinal cord. There is limited experimental work on the cauda equina syndrome.

As noted previously, patients with spinal tumors may present with several patterns of involvement, and they are also at risk for brain disease. The clinician should be familiar with all central nervous system complications associated with malignancy, and a complete evaluation should take into consideration risks for head, skull, brain, and leptomeningeal metastases.

Patient evaluation

Although it is widely recognized that pain is the cardinal symptom of spinal neoplasm, accurate assessment of neck and back pain in the cancer patient may present a challenge to even the experienced clinician. A complete history and physical examination, including a thorough neurologic examination, are essential to localize the underlying pathologic findings and to choose diagnostic and therapeutic interventions correctly. Fig. 1 outlines an algorithm approach to the diagnostic evaluation. In a retrospective survey of cancer patients presenting with back pain, misdiagnosis was attributed to poor history, inadequate physical examination, and insufficient diagnostic evaluation [22]. In one review of cancer pain consultations performed by a neurology-based pain service, the comprehensive evaluation of pain led to a new diagnosis in 65% of cases [23].

History

Up to 95% of adult patients and 80% of pediatric patients with MESCC present with pain [12,24]. The difference in pain prevalence between adults and children may reflect greater difficulty in pain assessment and underreporting of pain in children. As noted previously, pain may precede other symptoms and signs by 1 year [12]. This interval may vary by tumor type; it is generally shorter for lung cancer than for breast cancer [25]. Overall, patients experience pain for an average of 4 to 5 months before clinical presentation [3].

It is crucial to begin with a thorough pain history (Box 1). The patient's complaint is crucial information, because there are no objective ways to measure pain. The physiologic signs associated with acute pain, such as elevated blood pressure and pulse rate, are unreliable in subacute or chronic pain. Pain intensity rating scales should be used to establish a baseline against which the success of treatment may be judged (Fig. 2). Behavioral observations, such as facial grimacing or agitation, should be used to assess patients who are unable to communicate. Although there are standardized tools for preverbal children, they are not available for adults with impaired communication [26].

Pain may be local at the site of pathologic findings or referred in a nonradicular or radicular (dermatomal) distribution, or it may have combined features. Radicular or root pain is reported in 90% of lumbosacral MESCC, 79% of cervical MESCC, and 55% of thoracic MESCC [25]. Radicular pain may be bilateral in thoracic lesions and is often described as a tight band around the chest or abdomen. It is important to note that radicular pain may be experienced in only one part of a dermatome. When a nerve root lesion produces chest or abdominal pain, the complaint may be mistakenly identified as referred pain of visceral origin. Radicular lesions are usually associated with segmental findings on neurologic examination.

Pain may be continuous at rest and markedly aggravated by physical activity. Although local pain from a vertebral lesion is worsened with loading as a result of upright posture, pain caused by MESCC is often greatly increased by lying supine. A lesion confined to the vertebral body may also produce nonradicular referred pain. Disease at C7 may refer pain to the interscapular region, and disease at L1 may refer pain to the iliac crests, hips, or sacroiliac region. Sacral disease often causes midline pain radiating to the buttocks. Radicular pain may be paroxysmal, spontaneous, or provoked by movement or sensory stimulation. The Valsalva maneuver may produce or aggravate local and radicular pain. Pain on neck flexion or on raising a straight leg implies dural traction. Lhermitte's sign indicates

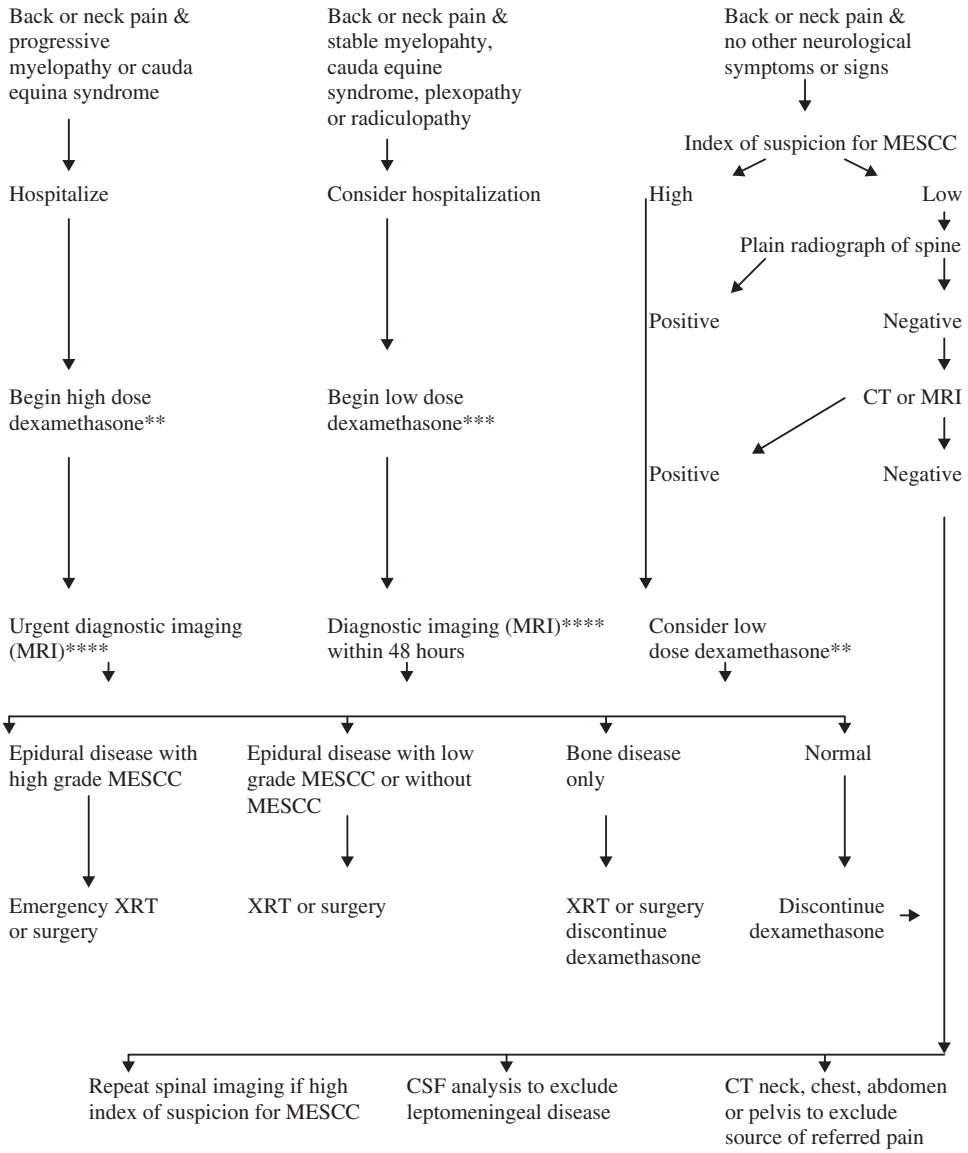

Fig. 1. Cancer patient with back or neck pain*. *Candidate for external beam radiotherapy or surgery. **High-dose dexamethasone (100 mg), followed by 24 mg every 6 hours with taper over weeks. ***Low-dose dexamethasone (20 mg), followed by 4 mg every 6 hours with taper over weeks. ****MRI; suggest sagittal screen of vertebral column with expanded imaging of affected areas or CT myelography (see text). MESCC, malignant epidural spinal cord or cauda equine compression; CSF, cerebrospinal fluid. (*From* Weinstein SM. Management of spinal cord and cauda equina compression. In: Berger AM, Portenoy RK, Weissman DE, editors. Principles and practice of palliative care and supportive oncology. 2nd edition. Lippincott Williams & Wilkins; 2002. p. 536; with permission.)

a spinal cord lesion. Compression of the cervical spinal cord rarely produces funicular pain, which is referred to the lower extremities, thorax, or abdomen as a band of paresthesias. Pseudoclaudication of legs may be an isolated symptom of lumbar nerve root irritation [27].

The neurologic findings associated with MESCC vary. Upper motor neuron weakness may occur with lesions of the spinal cord (above the L1 level). This finding is present in 75% of patients with MESCC at diagnosis [11]. Sensory changes occur in about half of patients at pre-

Box 1. Features of the pain history: PQRST

P: Provocative factors, palliative factors
Q: Quality or characteristics
R: Region, radiation, and referral (radicular, nonradicular)
S: Severity, intensity
T: Temporal factors: onset, duration, time to maximum intensity, frequency, variation

sentation, including paresthesias and sensory loss, which can be segmental or below the level of injury. Bladder and bowel dysfunction are evident in more than half of patients on presentation with spinal cord or cauda equina compression. Constipation usually precedes urinary retention or incontinence [28].

Examination

The physical examination begins with observation of posture; spinal curvature; and symmetry of the paraspinal muscles, extremities, and skin. The clinician may appreciate tenderness of the spinous processes on palpation or percussion, although this may not correlate with the level of spinal disease. Gibbus deformity and vertebral misalignments are frequently palpable. Tenderness and spasm of the paraspinal muscles may also be noted. Urinary retention may be demonstrated by bladder percussion. Laxity of the anal sphincter may be apparent on digital rectal examination. Specific areas of sacral or coccygeal tenderness may be identified by external palpation or rectal or pelvic examination.

Spinal maneuvers to elicit pain should be carefully performed. Thoracic and abdominal radicular pain may be provoked on lateral flexion and rotation of the trunk. Increased pain on neck flexion and raising a straight leg may be pseudomeningeal signs of dural traction caused by epidural tumor. If neck rigidity is present, the clinician should use extreme caution with range-of-motion maneuvers. Muscle spasm may be triggered by bony instability of the cervical spine, and forced movements may dislodge bony fragments, causing acute spinal cord or brain stem injury.

The neurologic examination reveals positive findings in most patients with MESCC. The examination should include assessment of mental status, cranial nerves, motor function, reflexes, sensation, coordination, and gait. Proximal lower extremity weakness may be initially evident only as difficulty in rising from a chair. Although weakness caused by upper motor neuron dysfunction is usually associated with increased tone and hyperreflexia, acute spinal shock can cause a flaccid areflexic paralysis. In the subacute phase of recovery from spinal shock, mass reflexes appear, consisting of flexor spasms, hyperhydrosis, and piloerection caused by autonomic dysfunction. Lower motor neuron weakness may be accompanied by flaccidity, atrophy, muscle fasciculations, and hyporeflexia. A cervical lesion can produce segmental hyporeflexia in the arms. Lesions above the pyramidal decussation of the corticospinal tracts in the lower brain stem may be associated with loss of contralateral abdominal reflexes; lesions below the decussation produce loss of ipsilateral abdominal reflexes. Segmental motor dysfunction caused by thoracic nerve root disease may produce asymmetric abdominal muscle contraction and loss of abdominal reflexes. Beevor's sign (upward movement of the umbilicus on attempted flexion of the trunk) indicates a lesion at or near the T10 level. Lesions of the roots of the upper lumbar plexus produce hip flexion weakness and a dropped knee jerk reflex; lesions of the roots to the lower lumbar plexus may produce foot drop and diminished ankle jerk reflex. Hand atrophy without weakness is considered a false

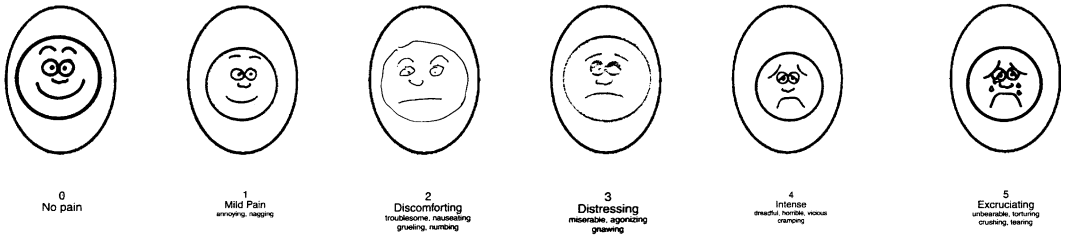

Fig. 2. Pain intensity rating scales used to establish a baseline against which treatment results are measured; the faces scale.

localizing sign when caused by upper cervical pathologic findings [29]. Loss of bulbocavernosus and anal reflexes may accompany conus and cauda equina lesions [28].

Although the sensory examination may help in determining the level of epidural disease, MESCC results in a broad variation of sensory dysfunction, with incomplete lesions being the rule. The level of reduced sensation may be determined to be up to five segmental levels below or one to two segments above the level of cord compression. A sensory level on the trunk sparing the sacral dermatomes may occur in up to 20% of patients with thoracic or high lumbar spinal cord compression [30]. Suspended partial sensory levels or unilateral bands of sensory loss may be seen with spinal cord lesions up to the brain stem. Compression of the conus of the spinal cord may produce sensory loss in the saddle area (buttocks and perineum). Facial numbness may be caused by upper cervical lesions. Lesions of the upper thoracic nerve roots may result in Horner's syndrome, with autonomic dysfunction of the face and upper extremity.

Diagnostic evaluation

Several imaging methods are available to confirm the etiology of neck and back pain and to evaluate for MESCC. Because the correct interpretation of symptomatic and asymptomatic lesions on diagnostic imaging studies requires thorough knowledge of the patient's clinical presentation, it is strongly recommended that clinicoradiographic correlation be made by the examining clinician.

Plain radiographs can confirm tumor and assess the structural stability of the spine. In the cancer patient with pain and at risk for spinal metastases with neck, shoulder, or upper extremity pain, flexion and extension views of the cervical spine should not be forced. Although plain radiographs are more than 90% sensitive and 86% specific for demonstrating abnormalities in the patient with symptomatic spinal metastases, autopsy series suggest that up to 25% of spinal lesions are invisible on plain radiography [31]. False-negative results may occur because of a mild degree of pathologic change or poor visualization; the abnormality may be missed on interpretation. The false-positive rate for interpreting collapsed vertebrae as pathologic may be as high as 20% [32]. It is estimated that a 30% to 50% change in bone mass is needed before plain films become abnormal [33]. On the anterior/posterior view, spinal radiographs may show pedicle erosion (the "winking owl"), increased interpeduncular distance, paraspinal widening, or paraspinal soft tissue shadow. On the lateral view, vertebral collapse, scalloped bodies, disk space destruction, a narrow spinal canal, hypertrophied facets, and disk calcification may be seen. Oblique views are needed to discriminate spondylolytic osteophytic encroachment from tumor causing foraminal abnormality [5]. Greater than 50% vertebral collapse and pedicle erosion are especially predictive of MESCC. On plain radiography, multiple vertebral involvement is noted in up to 86% of patients with spinal tumor and in greater than 30% of patients with MESCC [5].

CT may be useful to delineate pathologic findings using restricted fields of view [31]. CT and CT myelography are superior to other imaging techniques for demonstrating cortical bone architecture [34].

MRI is considered the imaging procedure of choice for MESCC. In the patient with neck or back pain and radicular symptoms but no bony tumor on plain radiographs, gadolinium-enhanced MRI is indicated to identify intraforaminal disease such as occurs in lymphoma and sometimes solid tumors [24]. MRI without and with contrast excludes vertebral metastases, paravertebral lesions, MESCC, intramedullary tumor, and many leptomeningeal processes.

In the cancer patient with neck or back pain and suspected MESCC, complete spine MRI is indicated, because there is high risk of noncontiguous or skip lesions. A full spine sagittal screening image to identify targets for more detailed imaging is suggested [5]. Failure to identify multiple levels of MESCC may compromise radiotherapy if untreated lesions become symptomatic and are detected at a later time.

Cerebrospinal fluid examination is not usually required for the diagnosis of epidural tumor, and dural puncture may pose some risk to the patient with MESCC.

Management of acute malignant epidural spinal cord compression or cauda equina compression

Pharmacologic interventions

Corticosteroids are the mainstay of pharmacologic therapy for acute MESCC and the treatment of associated pain. The administration of these agents prevents lipid peroxidation of neuronal cell membranes, ischemia, and increased intracellular calcium [35]. Vasogenic edema in MESCC

has been demonstrated to be responsive to corticosteroids.

The timing of administration and dosage of corticosteroids may affect neurologic outcome, and there is some evidence for a therapeutic window [27,35] A better analgesic effect of higher dose regimens has been demonstrated [33] Many authors favor a prolonged course of high-dose corticosteroids (eg, the equivalent of a bolus of dexamethasone, 100 mg, followed by 96 mg/d in divided doses tapered over a few weeks) for high-grade MESCC and a lower dosage (eg, dexamethasone, 20 mg, followed by 16 mg/d in divided doses with a taper) for low-grade MESCC [5,35,36]. High-dose therapy may be more analgesic but increases the risk of side effects. Side effects depend on duration of drug administration, cumulative dose, and regimen. In one prospective study of MESCC patients treated with high-dose corticosteroids, it was noted that depressive symptoms and disorders were more common than in similar patients not receiving such treatment [37]. Suppression of the hypothalamic-pituitary-adrenal axis occurs with sustained dosing. Steroid-induced osteoporosis may be reversible in young patients [38]. Other corticosteroid withdrawal symptoms, including *Pneumocystis* infection, have been reported. Corticosteroids are metabolized by the cytochrome P450 system, which has implications for drug interactions [35]. Clinicians should be aware that rapid administration of steroids causes severe burning pain in the perineum and that it is preferable that doses not be given as an intravenous push. Corticosteroids should be held before making the cancer diagnosis if lymphoma is suspected because of the immediate oncolytic effect that would impede diagnosis.

Virtually all patients presenting with MESCC have severe pain requiring opioid analgesics. During the acute phase, concurrent with bolus high-dose corticosteroids, many patients require rapid titration of an opioid agonist. Some patients require doses of intravenous morphine equivalent up to 30,000 mg/d [39]. Morphine doses are usually limited by the concentration of drug available and the delivery system available. With the use of medications like fentanyl, much higher equivalent doses can be delivered. The need for high-dose opioids reflects the severity of acute neuropathic pain. In some settings, this may be best accomplished with an intravenous patient-controlled pump or patient-controlled analgesia (PCA). PCA facilitates the quick adjustment of dose in both directions and allows the patient a rapid bolus for severe pain. The PCA pump is a programmable delivery system that allows the practitioner to deliver a continuous infusion (basal rate), a patient-administered dose (bolus dose), and a nurse-administered bolus dose. The clinician should be prepared to titrate the opioid to effect rapidly [40].

Nonpharmacologic interventions

Radiation therapy

Radiation therapy for MESCC is chosen to treat pain, inhibit tumor growth, restore and preserve neurologic function, and improve quality of life. The course of external beam radiotherapy (XRT) for spinal metastases and MESCC depends on the radiosensitivity of the tumor and its extent. XRT is considered by many clinicians to be the primary treatment for MESCC. XRT alone is more than 85% effective for MESCC in radiosensitive tumors [3]. Motor improvement is seen in 49% of cases, and stabilization of function is seen in another 31%. Less than 50% of patients regain lost function, however [3].

Surgery

The goals of surgery are to treat pain, resect pathologic findings, restore load-bearing capacity, decompress neural structures, maintain stability, and improve quality of life. Indications for surgery have been established by clinical consensus to be (1) to establish the cancer diagnosis, (2) to achieve surgical cure, (3) to treat prior irradiated tumor with symptomatic progression of MESCC, (4) to decompress neural structures and stabilize the spine, (5) to halt rapid clinical deterioration, and (6) to treat radioresistant tumor with symptomatic progression of MESCC [3,41,42]. Surgery may be considered for stabilization when pain occurs as a result of bony instability of the spine [17] or if instability is associated with greater than 50% collapse of the vertebral body [43]. In a recent experience, a small group of patients not considered candidates for major surgical procedures benefited from limited resection of lateral epidural tumor. Surgery was preceded by careful correlation of symptoms with tumor mass, and good outcomes, including pain relief, were recorded in all eight patients [44].

There has been a steady evolution in the concepts and execution of surgical management for MESCC [45]. The decision to recommend initial radiation therapy versus surgical intervention must be individualized. It has been suggested

that without bony instability, the speed of progression of neurologic deficit and radiosensitivity of the tumor are the main factors to consider. Randomized prospective trials are in progress to compare radiation therapy and surgery for MESCC. It is anticipated that the indications for primary surgery versus radiotherapy for MESCC will be better defined in the future.

Nonsurgical stabilization of the bony spine can be accomplished with a cervical collar or body bracing. Cancer patients with neck pain and suspected cervical spine disease should be placed in a collar during diagnostic evaluation.

Ongoing care

Integration of pharmacologic and nonpharmacologic analgesic therapies is needed for most patients with MESCC and associated pain.

Pharmacologic interventions

The World Health Organization (WHO) has published a three-step ladder outlining the use of nonopioid analgesics, opioid analgesics, and adjuvant medications for the treatment of progressively severe pain (Fig. 3) [45]. According to this system, a nonopioid analgesic, such as acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs (NSAIDs), should be tried first. If pain is not controlled, an opioid analgesic should be added. If the pain remains uncontrolled, a strong opioid analgesic should be prescribed. At all levels of the ladder, adjuvant drugs may be added to treat specific types of pain [26]. Extended corticosteroid administration has not been well studied but is common in clinical practice. This practice has been discouraged unless there is evidence of ongoing steroid-reversible neurologic deficits.

Guidelines for the use of NSAIDs, opioids, and adjuvant analgesics for neuropathic pain have been published in recent years [46–48]. NSAIDs are efficacious for bone pain [49]. In an evidence-based review, the first-line treatments for neuropathic pain have been determined to be gabapentin, the 5% lidocaine patch, opioid analgesics, and tricyclic antidepressants (TCAs) [50]. These treatments provide statistically significant outcomes.

Gabapentin is the first-line anticonvulsant for neuropathic pain. The recommended dose is from 1800 to 3600 mg/d, although some patients experience incremental analgesia with higher doses [50]. Gabapentin is generally well tolerated, and there are few drug interactions. The most frequent side effects of gabapentin are somnolence and dizziness. Peripheral edema is rarely seen but is a contraindication. In elderly patients or patients with renal insufficiency, gabapentin may cause gait and balance problems as well as cognitive impairment. To decrease adverse effects, gabapentin should be started at a low dose: 100 to 300 mg in a single dose at bedtime is recommended. It is recommended that dosing titration occur over 3 to 8 weeks to allow the development of tolerance to adverse effects [50]. Second-line anticonvulsant medications that are well-established with evidence of efficacy include lamotrigine and carbamazepine. Other anticonvulsants used for pain include levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide. Anti-

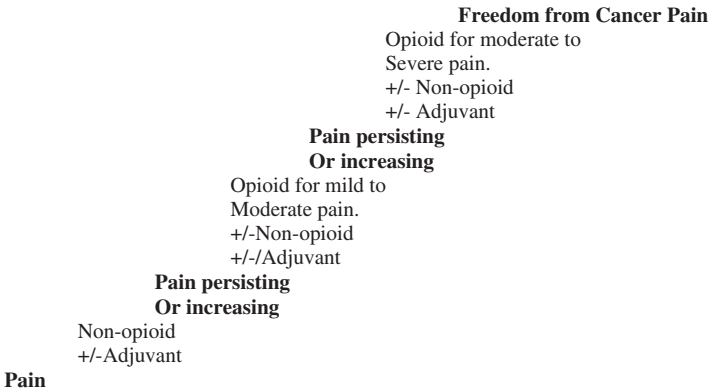

Fig. 3. World Health Organization analgesic ladder. (*From* World Health Organization cancer relief and palliative care. Geneva: World Health Organization; 1990; with permission.)

convulsants are effective by means of several different mechanisms, and nonresponse to one anticonvulsant does not predict nonresponse to the whole category [50].

The 5% lidocaine patch is a topical preparation with little systemic absorption. Systemic absorption should be monitored in patients on oral class 1 antiarrhythmic drugs. Skin reactions are rare. Treatment with the 5% lidocaine patch consists of the application of one to three patches daily for 12 hours on and 12 hours off. It is recommended that the patch be applied daily for 2 weeks to accomplish an adequate therapeutic trial. The patch is applied directly to the area of maximal pain [50].

Opioid analgesics are extremely effective in reducing neuropathic pain. Common adverse effects of opioid analgesics include constipation, sedation, and nausea. In elderly patients treated with opioid analgesics, gait disturbance and cognitive impairment can occur. Most patients become tolerant to these adverse effects, although constipation often persists. Therefore, regular laxative therapy is recommended. All patients taking regular opioid analgesics develop physical dependence, which is associated with withdrawal symptoms after abrupt discontinuation of the drug or rapid dose reduction. Physical withdrawal is not medically dangerous, but patients should be advised not to discontinue their medication abruptly without medical advice [50]. Guidelines for the use of opioid analgesics are shown in Box 2 [26].

Opioid analgesics are classified as either pure agonists, partial agonists, or mixed agonist-antagonists based on their activity at receptor sites. Partial agonists and mixed agonist-antagonists are not generally recommended as first-line analgesics. Pure agonists, such as codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, methadone, morphine, oxycodone, and oxymorphone, closely mimic the action of endogenous opioids and are most effective as analgesics. Their effectiveness is dose related, and there is no ceiling effect for analgesia. There is no stated maximum dose for full agonists; dosing is guided by efficacy and tolerability. Tablets combining an NSAID or acetaminophen with opioid analgesics are limited according to the nonopioid component. Fig. 5 provides specific directions on drug selection, relative potency, and equivalence of drugs compared with morphine. The oral route is preferred, but if the patient is unable to swallow or systemic side effects on oral medications are uncontrollable, alternative routes are indicated.

Box 2. Guidelines for the use of opioid analgesics

- Start with an analgesic with the potential to provide relief
- Know the essential pharmacology of the analgesic:
  - Analgesic type
  - Pharmacokinetics
  - Influences of coadministered drugs, disease, or age on analgesic disposition and response
  - Equianalgesic starting dose for the drug route to be used
  - Route of administration and a dosage form to fit the patient's needs
- Individualize/titrate the dosage
- Administer analgesics regularly after the initial dose titration
- Provide for breakthrough pain
- Use drug combinations that enhance analgesia
- Recognize and treat side effects
- Make conversions from one route to another or from one agent to another using known equianalgesic doses
- Prevent physical withdrawal

Adapted from Inturrisi C. Guidelines for opioid analgesics. Cancer 1989;63(Suppl):2308.

These include intravenous and subcutaneous, transdermal, transmucosal, rectal, and neuraxial infusion [26]. Intraspinal administration of opioids produces pain relief in the absence of changes in motor, sympathetic, and sensory function. Dilute local anesthetics may be added in patients with refractory pain or to enhance analgesia. Intraspinal analgesia is nondestructive and reversible [26].

TCAs were the first medications approved for the treatment of neuropathic pain. TCAs have a significant adverse effect profile. TCAs must be used cautiously in patients with a history of cardiovascular disease, glaucoma, urinary retention, or autonomic neuropathy. Almost 20% of patients treated with nortriptyline after a myocardial infarction developed adverse cardiac events. Consequently, a screening electrocardiogram to check for cardiac conduction abnormalities is recommended before beginning treatment with TCAs. TCAs should be used cautiously if there is a risk

of accidental overdose or suicide attempt. TCAs interact with drugs metabolized by cytochrome P4502D6, including the commonly prescribed selective serotonin reuptake inhibitors. In elderly patients, TCAs may cause balance problems and cognitive impairment. Other adverse effects include sedation, anticholinergic effects, postural hypotension, and weight gain. Nortriptyline and desipramine hydrochloride have fewer adverse effects and are usually better tolerated then amitriptyline. To increase patient adherence to treatment, patients must understand that TCAs have a distinct analgesic effect that has been demonstrated to be independent of their antidepressant effect. TCAs should be initiated at a low dose (10–25 mg in a single dose at bedtime) and then titrated every 3 to 7 days by 10 to 25 mg as tolerated. TCAs may be titrated to a dose of 75 to 150 mg/d as tolerated [50]. Second-line antidepressants that may be effective in treating pain include venlafaxine and olanzapine.

Anesthetic and surgical interventions

Neuroablative procedures are considered when the benefit-to-risk ratio favors analgesia over the potential for further neurologic compromise. Destruction of nervous tissue may be accomplished by anesthetic or surgical means. Chemical epidural neurolysis may be chosen to effect single or multiple nerve root interruption. Intrathecal neurolysis would be anticipated to achieve analgesia over a wider territory and may be selected when the epidural space is compromised. Both approaches entail risk of acute neurologic deterioration, which may be irreversible [51].

Neurosurgical ablation of nerve roots (rhizotomy) involves major surgery. Midline myelotomy may be indicated for patients with severe midline sacral pain and bladder or bowel compromise caused by tumor of the sacrum. Spinothalamic tractotomy or cordotomy, although more easily performed as a percutaneous procedure, is not generally useful for pain in association with spine disease or MESCC. Hypophysectomy for diffuse pain may yield success rates as high as 90% in some endocrine-responsive tumors [52].

Rehabilitation

Each patient's rehabilitation program must be individually tailored and continually reassessed and modified. For some patients, comprehensive care may be best accomplished in a formal rehabilitation setting [53]. Specific rehabilitation goals are to reduce pain, improve ambulation, achieve weight bearing and transfers, restore bladder and bowel function, and protect the skin. Approximately 50% of patients require urinary catheterization before and after XRT for MESCC [3]. Sexual dysfunction in women and men may be treatable with specific pharmacologic and nonpharmacologic interventions.

Spinal orthotics stabilize the spine and may decrease spinal pain by limiting motion. Physical therapy techniques for pain include massage, ultrasound, hydrotherapy, electroacupuncture, trigger point manipulation, and transcutaneous electrical nerve stimulation. Skillful soft tissue manipulation is probably underused.

A number of medical problems common to the cancer population may limit aggressive rehabilitation efforts. Organ failure caused by the disease or its treatment, poor nutrition, and multiple physical and psychologic symptoms may complicate rehabilitation. The risk of fracture in osteoporotic or tumor-laden bones should be carefully evaluated before initiating a mobility program. In paraparetic or paraplegic patients, prophylactic fixation of upper extremity lesions may be considered to aid mobility and weight bearing. In bedridden patients with multiple impending fractures, positioning and transfers must be undertaken with great caution.

Chronic musculoskeletal problems may occur in children after spine irradiation during growth because of the development of secondary spinal deformities.

The goals of physical medicine and rehabilitation in the patient with MESCC range from active programs to supportive care [54]. Continued encouragement for the effort required in aggressive rehabilitation is needed for a successful outcome. Supportive rehabilitation therapy attempts to help patients adapt to a progressive decline in function as a result of advancing disease. For patients with a limited prognosis, usually considered as life expectancy less than 6 months, family participation receives more emphasis. The needs of the patient trend toward more dependent care as cancer progresses.

Psychologic interventions

Patients with metastatic spine disease are at high risk for intracrainal disease and neurotoxicities related to cancer treatment. In the psychologic evaluation of the patient, organic causes of neuropsychiatric manifestations should be considered.

There are known interactions between pain intensity, pain unpleasantness, and the affective experience of pain. Spinal pathways to limbic structures and medial thalamic nuclei provide inputs to central areas involved in the affective experience of pain. This central network of brain structures processes nociceptive information and converges on the anterior cingulate gyrus, the function of which is believed to be to establish emotional valence and response related to pain [55].

Ongoing psychologic support of the patient with metastatic spine disease is essential. Caring for this patient population entails recognizing the complexity of a person as a physical, intellectual, social, emotional, and spiritual being [26]. Issues of coping with pain, loss of independence, loss of control over bodily functions, and loss of sexual function require compassionate attention. Pain may be an unwelcome reminder of the presence and progression of disease. Fear, anger, frustration, disappointment, and other negative emotions are all closely tied to physical pain. ''Existential distress may bridge an undesirable transition from hopeful coping with pain to hopeless suffering from it'' [26]. Achieving relief from psychologic suffering is likely to enhance the effects of pain medications and other treatments. Professional mental health assistance is often indicated. Medication, counseling, clergy visits, and support groups may all be beneficial to the patient and family [26].

Progression and prognostication

The potential for recovery of function in patients with tumor involvement of the spine and associated neurologic structures varies by tumor type, the number of vertebrae involved, the nature and degree of neurologic involvement, the oncologic status, and general medical condition. In most series, approximately 50% of patients with metastatic spine tumors are ambulatory at presentation, 35% are paretic, and 15% are plegic [27]. Up to 30% of patients with weakness become plegic within the first week of presentation [5]. The prognosis for regaining ambulatory status in MESCC patients who begin therapy while ambulatory is 75%; the prognosis declines to 30% to 50% for patients who begin therapy paretic and to 10% for those who begin therapy plegic [24]. The duration of neurologic symptoms before treatment also affects the prognosis for neurologic recovery. If paraplegia has been present for days or urinary retention has been present for more than 30 hours, the likelihood of recovery is decreased [56]. Rapidly progressing symptoms confer a worse prognosis. Survival rates for patients with MESCC are 40% at 1 year if ambulatory before and after radiation treatment and 30% at 1 year and 20% at 3 years for patients who are nonambulatory before and ambulatory after treatment. The prognosis falls to 7% at 1 year for patients who are nonambulatory after treatment [3].

The survival prognosis for all patients treated for MESCC is less than 50% at 2 months [11]. Definitive intervention for MESCC must therefore be considered in the context of the patient's overall disease status. Systemic antineoplastic therapy may at times precede or entirely supplant intervention targeted at MESCC. In patients with advanced cancer, the burden of intervention to reverse MESCC often outweighs minimal potential gains in function. Although few studies of quality-of-life issues have been conducted in this population, pain control should remain a high priority regardless of the survival prognosis. The clinician caring for patients with spinal neoplasm and its complications must carefully select medical interventions to achieve therapeutic goals for each patient and family.

Pain outcome variables

It is crucial that the efficacy and side effects of pain treatment be monitored on an ongoing basis. When focusing on clinical management, the clinician should follow pain intensity, pain relief, side effects of treatment, adverse effects of treatment, functional status, and quality-of-life variables. This is best done by clinical assessment. There are formal tools available to measure these outcomes; further discussion of these is beyond the scope of this article [14].

Special populations

Pediatric patients

There are many misconceptions about assessing and managing pain in the pediatric population (Box 3) [57]. Pain in children is underreported and should be elicited using age-appropriate assessment tools. There are standardized tools for assessing pain in infants, children, and adolescents (see Fig. 2). The clinician should be aware that the same pharmacologic and nonpharmacologic pain treatments are available for

Box 3. Misconceptions about assessing and managing pain in the pediatric population

- Children either do not feel pain in the same way as adults, or they remember it differently.
- A valid assessment of pain and other symptoms in children is not usually possible.
- The risks of respiratory depression and other opioid-induced side effects are generally more profound in children then adults.
- The risks of causing addiction outweigh the benefits of using opioids in children.
- Pain in pediatric patients cannot be managed effectively due to lack of effective medications.

From Storey R, Knight CF, Schonwetter RS. Approach to caring for pediatric patients. In: Hospice/palliative care training for physicians: pocket guide to hospice/palliative medicine. Glenview, IL: American Academy of Hospice and Palliative Medicine; 2003. p. 158; with permission.

the pediatric population. As with adults, there should be a continuum of curative and supportive care. The child and the parents benefit from clear compassionate communication. The clinician should understand the sick child's acquisition of information and understanding of information about his or her condition.

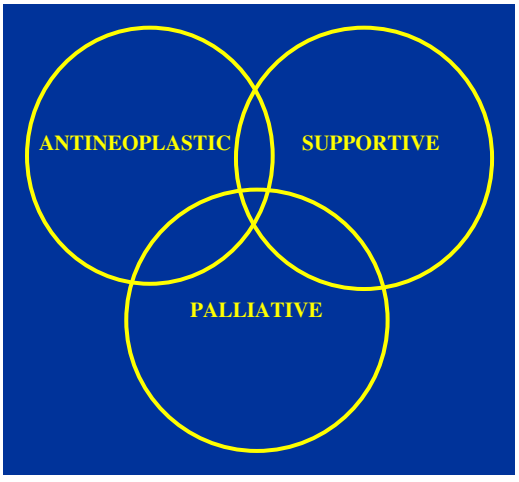

Fig. 4. Integrated approach to palliative care.

Patients with concurrent substance abuse

Opioid analgesics can be used in patients with a history of substance abuse or misuse but doing so requires close monitoring. Mental health consultation is recommended for assistance in treating those patients with substance abuse disorders. Concerns about causing a substance abuse disorder when there is no history of substance abuse do not justify refraining from using opioid analgesics in patients with pain. Substance abuse develops only rarely in patients with pain who do not have a history of substance abuse. Clinicians are often concerned by drug-seeking behaviors and must carefully distinguish opioid abuse or misuse from the appropriate desire to continue taking medications that effectively relieve pain [50,58].

Patients at end of life

As a terminally ill patient with cancer moves from the ambulatory setting toward death, the patient's progressing symptomatology requires intensification of care. This is a time of dynamic physiologic and psychologic changes, which requires an integrated palliative care approach. This requires frequent comprehensive assessment and demands that medical decisions be considered thoughtfully. The goals of end-of-life care for terminally ill patients with cancer shift away from the standard cure-oriented medical treatment. Care should focus on the patient and address family concerns. As families watch loved ones suffer, it is paramount that clinicians understand what the family is observing, because the pathologic grief often experienced by the family can affect end-of-life decisions.

In the Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatment, at least 50% of patients were reported by their families to have had severe pain in their last 4 weeks of life [59]. The prevalence rates of pain and suffering during the last weeks of life ranged from 20% to 87% [60–62]. Severe symptoms include pain, which is one of the most predominant symptoms that patients with terminal cancer experience and is likely the most feared symptom. The symptom complex is not limited to pain, however. Suffering is a mixture of pain and other physical symptoms, such as delirium and psycho-

CANCER PAIN RELIEF-UTAH: Analgesic Conversion Guide

Oral and Parenteral Opioid Equivalences and Relative Potency of Drugs Compared with Morphine

	Parenteral (mg)	Oral (mg)	Factor (IV to PO)	Duration of Action[1]
Opioid Agonists				
Morphine[2]	10	30	3	3-4 hours
Controlled Release Morphine (MS Contin, Oramorph SR)	-	30	-	8-12 hours
(Kadian)	-	30	-	24 hours
Methadone (Dolophine)[3]	10	3- 20[4]	2	4-8 hours
Hydromorphone (Dilaudid)	1.5	7.5	5	2-3 hours
Fentanyl (Duragesic,Actiq)[5]	100 µg	200 µg	2	1-3 hours
Levorphanol (Levo-Dromoran)[3]	2	4	2	3-6 hours
Oxymorphone (Numorphan)	1	6 (rectal)	6	3-6 hours
Codeine	130	200	1.5	3-4 hours
Oxycodone (Roxicodone, Percocet, Tylox,OxyIR etc.)[6]	-	15-20	-	3-5 hours
Controlled Release Oxycodone (OxyContin)	-	15-20	-	12 hour
Hydrocodone[7] (Vicodin, Lortab, Vicoprofen)[6]	-	30-200	-	3-5 hours
Tramadol (Ultram)[8]	-	*50-100*	-	*3-7 hours*
Not Recommended:				
Meperidine (Demerol)[9]	75	300	4	2-3 hours
Propoxyphene (Darvon Darvocet etc.)[3,6,9]	-	200	-	3-6 hours

Partial Agonist

Buprenorphine (Buprenex)[10]	0.4	-	-	6-8 hours

Mixed Agonist-Antagonists
Pentazocine (Talwin)
Nalbuphine (Nubain)
Butorphanol (Stadol)
Dezocine (Dalgan)

Special Note: Partial agonists and mixed agonist-antagonists have limited usefulness in cancer pain. They should NOT be used in combination with opioid agonist drugs. Converting from an agonist to an agonist-antagonist could precipitate a withdrawal crisis in the opioid-dependent patient.

1. Shorter time generally refers to parenterally administered opioids (except for controlled-release products which have some variability); longer time generally applies to oral dosing
2. Conversion factor listed for chronic dosing - single doses may require 6:1 factor; avoid using morphine in renal failure due to accumulation of m6G metabolite.
3. Long half-life, observe for drug accumulation and side effects after 2-5 days. May need to be dosed q 4h initially then changed to q 6-8h after steady state achieved (1-2 weeks).
4. With higher doses of morphine, the oral conversion ratio may be closer to 10 to 1 rather than 3 to 2. Caution and consultation are advised.
5. Available in transdermal system (Duragesic) for sustained dosing (see instructions on back) and an oral transmucosal system (Actiq) for breakthrough pain.
6. With the exception of plain oxycodone and propoxyphene, these opioids are combined with ASA or acetominophen in doses from 325 to 750 mg. **Dosage must be monitored for safe limits of ASA or acetominophen.**
7. Equivalence data not substantiated. Clinical experience suggests use as a mild, initial use opioid but effective dose may vary. Dose listed refers only to opioid portion.
8. Weak µ agonist with some antidepressant activity. For mild to moderate pain. Maximum recommended daily dose is 400mg to avoid CNS toxicity. Don't combine with other agonists – may have some antagonist activity if combined with pure agonist.
9. Not recommended for long term or high dose use because of CNS toxic metabolites (normeperidine, norpropoxyphene).
10. Partial agonist may produce withdrawal in opioid -dependent patients.

Fig. 5. Analgesic conversion guide.

To convert from another narcotic to morphine:

1. Total the amount taken in a 24-hour period that **effectively** controls pain.
2. Multiply by the conversion factor in the table.
3. If pain was **effectively** controlled, reduce the dose by 25-50% to allow for incomplete cross-tolerance between different opioids. During the first 24 hours, titrate **liberally and rapidly** to analgesic effect. If previous dose was **ineffective**, increase the calculated dose by 25%.
4. Lastly, divide by the number of doses per day to determine the individual dose (e.g., 6 doses for regular PO morphine q 4 hrs; 2 doses for controlled release morphine q 12 hours.)

Conversion Factors (Other opioid to morphine)

From Oral	To Oral Morphine	From Parenteral	To Parenteral Morphine
Methadone	0.15-1.5[4]	Methadone	1
Hydromorphone	4	Hydromorphone	6.7
Meperidine	0.1	Meperidine	0.13
Levorphanol	7.5	Levorphanol	5
Codeine	0.15	Codeine	0.08
Oxycodone	1.5-2	Oxymorphone	10
Hydrocodone	0.15 – 1[7]	Buprenorphine	25
Oxymorphone (rectal)	5		

To Convert to Transdermal Fentanyl (Duragesic)

1. Pain should be realitively well-controlled on a short acting opioid prior to initiating the patch. Patches are NOT recommended for unstable pain requiring frequent dose changes.
2. Determine 24 hour parenteral morphine equivalent requirement using the above table. Do not use manufacturer's published oral conversion recommendations which is based on 6:1 conversion ratio. Clinical experience suggests the conversion ratio of 3:1 is more accurate.
3. Select the μg per hour dose according to the ranges listed below. For dosage requirements >100μg/hr multiple patches can be used.
4. The patch duration is usually 72 hours. Duration in some may be only 48 hours: fever and heat from heat lamps, electric blankets etc. may accelerate drug release.
5. A p.r.n. dose of morphine or other short-acting opioid should be prescribed and may be needed particularly during the first 8-24 hours. Increase the patch dosage based on the average amount of additional opioid required over the 72 hour period. Continue breakthrough medication once the patch dose is stabilized.

Oral Morphine (mg/24hrs)	Parenteral Morphine (mg/24 hrs.)	Duragesic Equivalent (μg/hr.)
25-65	8-22	25
65-115	23-37	50
116-150	38-52	75
151-200	53-67	100
201-225	68-82	125
226-300	83-97	150

Note: *Due to patient variability the doses suggested in this guide are approximate and clinical judgment must be used to titrate to the desired response.*

Fig. 5 (*continued*)

logic or existential issues. A position statement from the American Academy of Neurology, Ethics and Humanities Subcommitee, on Palliative Care in Neurology defines commanding symptoms during the end of life as "distressing physical symptoms such as pain, dyspnea, cough, agitation, anxiety, nausea, vomiting, anorexia, constipation; and feelings such as fear, anger, indignation, hopelessness, powerlessness, loneliness, and isolation" [63].

Fear to treat end-of-life symptoms exists for many clinicians because they are not prepared formally to manage suffering and death as normal processes. This is partly because of an aversion to treat dying patients differently from those whom we are trying to heal or cure and to accept that

priority of care shifts to the relief of suffering [64,65].

Integrated palliative care

The Expert Committee on Cancer Pain Relief and Active Supportive Care of the WHO has stated that pain and symptom control should be of high priority in cancer care, and it has recommended greater allocation of resources to palliative interventions. The WHO defines palliative care as "active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social, and spiritual problems is paramount. The goal for palliative care is the achievement of the best quality of life for patients and their families" [45,66]. From the diagnosis of MESCC through treatment to cure, in relapse, or in disease progression to the terminal phase, patients require interventions that are directed against the disease (surgical intervention, radiation, and antineoplastic treatment), medically supportive of the cancer treatment (supportive care), and aimed at relief of symptoms (pain and symptom control or palliative care). This approach is independent of prognosis and primary treatment goals and recognizes that these elements of care overlap (Fig. 4) [66].

Summary

Metastatic spinal disease is common in cancer patients, and it is a frequent source of pain and disability. Expert management of the patient's pain and neurologic dysfunction is required. Neurosurgical advances have afforded the patient the opportunity to have improved symptom management and improved quality-of-life outcomes. Patients and their families are best served by the provision of supportive care by specialty pain medicine and palliative care services (especially neurology based) working with the primary neurosurgical team in an integrated model.

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