Cancer Pain Syndromes

Kathleen M. Foley

One third to one half of cancer patients in active therapy, both adults and children, and about two thirds of those with far advanced disease have significant pain. In a terminal facility, this proportion may be as high as 80% or 90%. In countries with limited approaches for adequate pain management, prevalence of pain in advanced disease may be upwards of 95%. The data suggest that about 25 million patients worldwide die each year without adequate pain control. The evaluation and management of cancer pain is therefore a problem of immense importance.

The appropriate treatment of cancer pain begins with the evaluation of the pain complaint and pain syndrome. This process is crucial, often providing a new perspective to the patient's problem and leading to a change in management. Our sophistication in evaluating and treating these patients is now such that we should not simply manage pain, but should strive to understand both its genesis and implications.

Classification of Pain

Cancer patients have either acute pain or chronic pain. They can have either type of pain at many different times during the course of their illness. Typically, acute pain is a process occurring early, often as a presentation of the cancer. It is usually readily treated as the appropriate diagnosis is followed by specific anticancer therapy, and analgesics or anesthetics are supplemented transiently as needed. In contrast, chronic pain presents a more complex problem, which may profoundly complicate the cancer patient's psychological adjustment to illness.

In addition to this temporal classification—acute *v* chronic—the pain of cancer can also be divided by its presumed pathophysiology. Pain can be somatic, visceral or deafferentation (Table 1). The evidence suggests that both somatic and visceral pain can be treated by most of the wide variety of therapeutic approaches now available, while deafferentation pain is more difficult to treat.

Somatic pain usually is a well-localized, constant, aching or gnawing pain (Table 1). It results from ongoing activation of peripheral nociceptors. The pain from bone metastasis is a typical example.

Visceral pain tends to be constant and aching, but poorly localized. It is often referred to cutaneous sites. It results from activation of visceral nociceptors. Examples include back or epigastric pain from pancreatic cancer and shoulder or abdominal pain from metastases. This group of patients, like those with somatic pain, tend to do very well with treatment of their tumor and with analgesics, nerve blocks, or surgical techniques.

The third group of pain syndromes are those related to injury or afferent neural pathways. These deafferentation pains are characterized by paroxysmal or burning dysesthesias. Brachial and lumbosacral plexopathies constitute the major group of patients with this syndrome. Analgesics may work in these patients, but adjuvant analgesics, specifically the tricyclic antidepressants or anticonvulsants, seem to be of greater value. It is clear that this group of patients represents the most difficult to manage.

Classification of the Pain Patient

Additional perspective into the problem of cancer pain is gained by a classification of patient subtypes (Table 2). Patients with acute cancer-related pain, either associated with the diagnosis or with cancer therapy, will endure

Kathleen M. Foley, MD, is Chief of the Pain Service at Memorial Sloan-Kettering Cancer Center and an Associate Attending Neurologist. She is an Associate Professor of Neurology and Pharmacology at Cornell University Medical College. Other appointments include Consultant, World Health Organization Cancer Pain Relief Program and Member, Board of Directors of the American Pain Society, International Association for the Study of Pain, and the American Academy of Neurology.

Table 1
Types of Cancer-Related Pain

	Somatic	Visceral	Deafferentation
Characteristics of pain	constant, aching gnawing; well localized	constant; aching, poorly localized; often referred to cutaneous sites	paroxysms of pain "shooting or shock-like" on background of burning, aching sensations
Putative mechanisms	activation of nociceptors	activation of nociceptors	spontaneous and paroxysmal discharges in the PNS and CNS
Examples	bone metastasis	pancreatic cancer liver/lung mets with shoulder pain	metastatic brachial and lumbosacral plexopathies
Management of pain	treat tumor, analgesics, nerve blocks, cordotomy	treat tumor, analgesics, nerve blocks, cordotomy?	analgesics (especially adjuvants), sympathetic blocks, ? treat tumor ?TENS

Table 2
Types of Patients with Pain from Cancer

- Patients with acute cancer-related pain
  - Associated with the diagnosis of cancer
  - Associated with cancer therapy (surgery, chemotherapy, or radiation)
- Patients with chronic cancer-related pain
  - Associated with cancer progression
  - Associated with cancer therapy (surgery, chemotherapy, or radiation)
- Patients with pre-existing chronic pain and cancer-related pain
- Patients with a history of drug addiction and cancer-related pain
  - Actively involved in illicit drug use
  - In methadone maintenance programs
  - With a history of drug abuse
- Dying patients with cancer-related pain

an enormous amount of pain for promise of successful outcome. Often, they do not seek treatment and are able cognitively to manage their pain without assistance. They tend to be hopeful. In those successfully treated, acute cancer-related pain may be viewed as a harbinger of illness; any recurrence of pain is an immediate signal both to the patient and physician that recurrent disease may be present.

The group of patients with chronic cancer-related pain have pain associated with either progressive disease or with therapy. These two groups are of course very different. Those with pain due to cancer therapy, who have little or no active disease, are often dealing with the psychological components of their illness and the need to re-establish a functional life. Their attitude is in sharp contrast to the group of patients who have progressive disease, in whom hopelessness and helplessness may be overt.

A third important group with cancer pain comprise those with pre-existing chronic pain. The patient who has a long previous history of chronic illness behavior must be identified early. They often need intensive intervention and support, a continual focus on their psychological status, and accurate diagnosis of their cancer pain.

A fourth group of patients with pain includes those who remain actively involved in illicit drug use. This group is difficult to evaluate and difficult to treat. Pain and cancer may lead them to return to drugs to manage their anxiety and depression. Their every complaint is misinterpreted as a request for more drug.

Many of these patients must be taught the difference between management of their behavior and treatment of their pain. They may need to be treated in a setting in which experts in rehabilitation of the drug addict and experts in pain management work together. They should not be shunned or inadequately treated.

Lastly, there are the dying patients with cancer-related pain. In this group, inadequate management of pain has an enormous impact on both the patient and family. Families suffer greatly when a loved one dies in unrelieved pain. This is what is remembered and what is carried to the next fatal illness, either their own or in their family. The impact of inadequate pain control on bereavement is crucial in treating this group of patients.

Pain Assessment

The principles of evaluating cancer pain are shown in Table 3. One must clarify the complaint of pain and distinguish between pain and suffering. Understanding the extent of disease is crucial. It is important to examine where the patient hurts and understand the referred patterns of pain. If radiographs of the area of pain do not appear to delineate any cause, the physician should evaluate sites that may have referred the pain. Diagnostic studies must be reviewed personally. Appropriate analgesic control must be maintained during all diagnostic procedures.

Table 3
General Principles in Cancer Pain Evaluation

- Clarify the history of the complaint "pain."
- Delineate the extent of disease.
- Examine the site of pain and know referral patterns.
- Use the appropriate diagnostic tools: Plain X-rays, bone scan, tomography, CT scan.
- Review these studies *personally.*
- Treat the pain early with analgesics.

Pain Syndromes

Specific pain syndromes (Table 4) occur in the cancer patient. Syndromes associated with infiltration of bone are the most common and are often not recognized as early as they should be. Involvement of the base of skull, the vertebral bodies, and the sacrum represent the three

Table 4
Specific Pain Syndromes in Patients with Cancer

- Pain syndromes associated with direct tumor infiltration
  - Tumor infiltration of bone
    - Base of skull syndromes
      - Jugular foramen metastases
      - Clivus metastases
      - Sphenoid sinus metastases
    - Vertebral body syndromes
      - C2 metastases
      - C7, T1 metastases
      - L1 metastases
    - Sacral syndrome
  - Tumor infiltration of nerve
    - Peripheral nerve
      - Peripheral neuropathy
    - Plexus
      - Brachial plexopathy
      - Lumbar plexopathy
      - Sacral plexopathy
    - Root
      - Leptomeningeal metastases
    - Spinal cord
      - Epidural spinal cord compression
- Pain syndromes associated with cancer therapy
  - Post-surgery syndromes
    - Post-thoracotomy syndrome
    - Post-mastectomy syndrome
    - Postradical neck syndrome
    - Phantom limb syndrome
  - Post-chemotherapy syndromes
    - Peripheral neuropathy
    - Aseptic necrosis of the femoral head
    - Steroid pseudorheumatism
    - Postherpetic neuralgia
  - Post-radiation syndromes
    - Radiation fibrosis of brachial and lumbar plexus
    - Radiation myelopathy
    - Radiation-induced second primary tumors
    - Radiation necrosis of bone
- Pain syndromes not associated with cancer or cancer therapy
  - Cervical and lumbar osteoarthritis
  - Thoracic and abdominal aneurysms
  - Diabetic neuropathy

major groups. In each group, patients present with very typical symptomatology. For example, patients with disease at the C7 or T1 vertebral body will complain of pain in the paraspinal area, which then radiates down the posterior arm to the elbow. They will then complain of some paresthesias in the fourth and fifth fingers of the hand and will eventually demonstrate triceps weakness in the intrinsic muscles of the hand. This characteristic syndrome should be recognized before signs of radiculopathy develop.

There are typical pain syndromes that follow direct infiltration of nerve. For example, nerve compression in either the retroperitoneal or the intercostal areas first present with pain, with sensory and motor deficits developing later. These patients may need evaluation of contiguous structures. The CT scan and MRI are the diagnostic procedures of choice.

A second group of patients with direct infiltration of nerve are those who develop brachial plexopathy. Brachial plexopathy can occur in a variety of different settings and from a variety of different neoplasms, most often breast or lung cancer, or lymphoma. In a study of 100 patients with brachial plexopathy due to cancer, 78 patients demonstrated tumor infiltration, of whom 82% presented with pain. Pain was present for several weeks to months before the onset of objective neurologic findings in the arm. Typically, the pain was in the shoulder, upper arm and elbow, with radiation into the fourth and fifth fingers. Dysesthesias included a burning sensation in the fourth and fifth fingers and freezing sensations in the arm. With progression of the disease, the intensity of pain progressed; at the time of diagnosis, 98% of patients complained of severe pain. In those with progressive neurologic dysfunction, persistent pain developed, prior to institution of anticancer therapy. These patients must be distinguished from those previously irradiated who then develop neurologic signs due to radiation fibrosis of the brachial plexus. Pain is much less prominent in this syndrome; about 18% complain of pain, and only about 35% of these patients ever develop severe pain. When pain occurs, it is usually described as aching in the shoulder and tightness and heaviness in the arm. This group of patients has a high incidence of lymphedema (about 80%), while patients with tumor infiltration have a rather low prevalence of this complication.

Pain syndromes related to cancer therapy include those complicating surgery, radiotherapy, and chemotherapy. As noted, these may occur in the absence of an active tumor diagnosis and are therefore often associated with different sets of psychological concomitants than pain syndromes related to tumor infiltration.

The post-surgical pain syndromes, including post-thoracotomy, post-mastectomy, post-radical neck, and phantom limb pain, all share injury to peripheral nerve. The typical pain is characterized by pulling and burning dysesthesias often with associated lancinating pains.

Post-mastectomy pain can appear immediately after surgery or up to two to three months later. It follows any type of mastectomy, from lumpectomy to radical mastectomy. It is more prevalent in patients with postoperative complications, such as excessive serous drainage or local abscess. Pain is localized to the posterior arm, axilla and anterior chest wall. Patients describe a constricting, burning pain, a "hot poker" in the axilla, which is markedly exacerbated by movement. Some of the patients develop a shoulder-hand syndrome. Six to ten percent of women undergoing surgical procedures on the breast develop this syndrome, and the symptoms do not improve with breast reconstruction. The cause of this pain syndrome is interruption of the intercostobrachial nerve, which penetrates the anterior chest wall and is severed in any surgical procedure on the breast. As such, post-mastectomy pain is not a harbinger of recurrent disease.

Post-thoracotomy pain may occur following surgical procedures on the lung. It is characterized by burning in the area of the scar, depressed sensation, and local changes in autonomic function. Frozen shoulder and respiratory splinting may also complicate the pain. In contrast to those with post-mastectomy syndrome, patients whose pain worsens following surgery are at high risk for recurrence of disease.

Injury to the nerves involving the cervical and post-auricular areas may cause characteristic lancinating pain in patients following radical neck surgery. This pain syndrome may improve with anticonvulsant therapy, such as carbamazepine.

Another group of pain syndromes in patients with cancer follows chemotherapy (See Table 4). For example, the peripheral neur-

opathy that occurs from the vinca alkaloids may be characterized by continuous dysesthesias. This syndrome eventually improves in most patients and many benefit from temporary use of tricyclic antidepressants, sometimes supplemented by narcotic analgesics and intensive physical therapy. The pain associated with aseptic necrosis of the femoral head may be dramatically reversed by replacement of the femoral head. Steroid pseudorheumatism is diffuse aching pain associated with rapid withdrawal of steroids; this pain may be dramatically reversed by reinstitution of steroids. Postherpetic neuralgia is a common and distressing pain syndrome. Afflicted patients should be treated early and aggressively with a multimodal approach including physical therapy, tricyclic antidepressants, transcutaneous electrical nerve stimulation, and potentially, sympathetic blocks.

The incidence of post-radiation syndromes is increasing with the number of long-term survivors of cancer therapy. Radiation fibrosis of the brachial or lumbar plexus is not often associated with severe pain. More characteristic is a large edematous limb that may not function well. As always, the differential diagnosis from tumor has to be made. About 20% of patients with radiation myelopathy will present with a central pain syndrome. The pain is characteristically in the mid-back, occasionally with dysesthetic sensations in the leg. This pain may respond to steroids, anticonvulsant drugs or the tricyclic antidepressants. Radiation-induced second primary tumors and radiation necrosis of bone represent other types of potentially painful post-radiation syndromes. Both malignant schwannomas and new primary lung tumors have been reported to develop at the site of earlier radiotherapy. A patient with pain recurrence following radiotherapy must therefore undergo reassessment of the site to rule out the presence of a new primary.

Finally, patients may be afflicted with pain syndromes not associated with cancer or cancer therapy. For example, osteoporotic collapse of a vertebral body may develop intercurrently with cancer in the elderly bedridden patient receiving steroid therapy. The challenge in these patients lies in distinguishing malignant pain from that originating from non-neoplastic processes.

In summary, there is a wide variety of pain syndromes, knowledge of which is essential for the appropriate evaluation and treatment of cancer pain. Patients need to be assessed carefully even in the setting of far-advanced disease. The major goal is to understand the nature of pain, the type of patient experiencing it, and the implications for the course and prognosis of the illness.

Suggested Readings

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