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Doctors McMichael and Dvorkin Wininger have reported no relationships with proprietary entities producing health care goods or services.

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Physiatric Approach to Cancer Rehabilitation

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Clinical Vignette

KM is a 51-year-old female with history of left gluteus maximus grade 3 spindle cell sarcoma diagnosed in July 2007. She had tumor excision complicated by a small laceration to the left sciatic nerve resulting in foot drop, and had brachytherapy radiation that was complicated by urinary and bowel incontinence. KM also had chemotherapy with doxorubicin and ifosfamide, after which she had worsening of her baseline peripheral neuropathy symptoms. Multiple comorbidities included obesity, idiopathic polyneuropathy, and lumbar stenosis status post left L4/L5 lumbar laminectomy.

When KM presented to the cancer rehabilitation clinic seven years after her initial treatment, her chief complaint was pain with sitting, standing, and walking for prolonged distance. She had sharp low back and left buttock pain radiating down her left leg. She also was bothered by bowel and bladder incontinence that prevented her from participating in community activities. Lastly, she had uncontrolled lymphedema in the left lower extremity, which impaired her mobility. While she is grateful that she has survived her cancer, she would like advice on whether or not her quality of life can be improved.

Definition of Cancer Rehabilitation

Cancer rehabilitation is defined as "any functional or rehabilitation intervention for any cancer patient at any point along the cancer continuum with a goal of increasing personal ability."[1] A cancer survivor is defined as a person who is alive from the time of cancer diagnosis to transition from active treatment to extended survival. There are approximately 14.5 million cancer survivors in the United States, and it is estimated that by 2024 the number of survivors will be nearly 19 million.[2] It is projected that the total cost of cancer care in 2020 will exceed $170 billion, a 39 percent increase from 2010.[3]

Rehabilitation after cancer has been recognized as a policy goal since the 1970s. The National Cancer Act of 1971 launched an ambitious national research program to improve cancer diagnosis, treatment, and care delivery. Initially, inpatient rehabilitation programs were developed at several large tertiary-care hospitals. With multimodal chemotherapy and radiotherapy, and generally less radical surgeries, survival has increased while at the same time toxicities and impairments have moderated. Also, cancer treatments have transitioned to outpatient settings, often with geographic decentralization improving patient convenience and decreasing treatment burden.[4]

Sarcoma: A Model of Cancer Rehabilitation

Sarcoma is a cancer that arises from the transformed cells of mesenchymal origin. The two major categories are bone and soft tissue, with the latter including tumors of cartilage, fat, muscle, vascular, and hematopoietic cell lines. Within these two categories, there are about 50 types of soft tissue sarcomas including spindle cell sarcoma. Spindle cell sarcoma is named based on the long, narrow appearance of the cells under the microscope. The American Cancer Society estimates that in 2014, approximately 12,204 new soft tissue sarcomas were diagnosed and 4,740 patients were expected to die from the disease. The growth rate of soft tissue sarcomas depends on the aggressiveness of the tumor, with low-grade tumors often mistaken for benign tumors. Clinically, the most common initial presentation is a painless, gradually enlarging mass.[5]

Treatment of Sarcoma

Treatment generally combines surgical excision, chemotherapy, and radiation. Soft tissue sarcomas expand spherically along tissue planes, and this centrifugal growth creates a pseudo-capsule of surrounding compressed tissue. This explains why, even after excision, there can be microscopic disease in situ requiring chemotherapy and radiation to fully eradicate the cancer. The main goal of surgery is resection of the tumor with a 2 to 3 cm disease-free margin by removing one uninvolved tissue plane circumferentially.[5]

Sarcoma can often lead to amputation if clean tissue margins cannot be obtained. Limb salvage is a technique to completely resect the tumor with adequate margins to avoid limb amputation. If limb salvage is possible, it is preferred over amputation even if, for example, a motor nerve is sacrificed during resection. The main nerves that can be sacrificed during lower limb salvage surgery include sciatic, femoral, fibular, and tibial nerves. This occurs if the tumor involves the actual nerve or if it is within the margin of tumor resection.

Ideally, preserving one innervated muscle in a compartment results in better function than radical resection of the whole compartment. For example, the posterior thigh compartment contains biceps femoris, semitendinosus, and semimembranosus, which are innervated mainly by the tibial nerve. If possible, a tumor in this region is best treated by a resection that preserves some of the innervated muscles within the compartment, versus a total compartmental resection.[6]

Radiotherapy is recommended in high-grade and intermediate-grade tumors with the goal of local control. Radiotherapy can be subdivided as either external beam therapy or brachytherapy. Brachytherapy involves the insertion of radioactive seeds/wires into surgically placed catheters in the tumor bed.[5] Radiotherapy can significantly reduce muscle power and range of motion due to fibrosis, atrophy, spasm, pain, and decreased bone density.[7] Brachytherapy specifically to the rectum or pelvis can result in loss of bowel control. Radiotherapy presents a lifelong risk of developing complications secondary to fibrosis, which requires regular monitoring.

Unlike surgery and radiation therapy, the goal of chemotherapy is not local control but systemic control, which often leads to more side effects. Ifosfamide and doxorubicin are typical chemotherapeutic agents in the treatment of sarcoma.[5] Though these drugs are not implicated in chemotherapy-induced polyneuropathy, they can worsen nerve function in patients with underlying polyneuropathy from other causes.

Overall, limb salvage surgery and radiotherapy result in about 70 percent long term survival. However, more than half of these survivors will have some type of disability due to the deleterious effects of surgery, radiation, and chemotherapy.[8]

Role of the Physiatrist in Cancer Rehabilitation

Cancer survivors can face a broad assortment of functional impairments arising directly from the cancer itself or from treatments. Direct effects of cancer can include brain metastases, spinal cord compression, and paraneoplastic syndromes. Examples of functional impairment as a result of cancer treatments include limb-sparing tumor excision, chemotherapy-induced peripheral neuropathy, and radiation fibrosis syndrome (RFS). RFS is defined as the abnormal accumulation of thrombin in the intravascular and extra-vascular compartments that leads to progressive fibrotic sclerosis after specific doses and frequency of radiation treatments. It is a late complication and can manifest itself clinically years after treatment. RFS can affect any tissue type, including skin, nerve, muscle, ligament, and tendon.[9] Because these various conditions are often superimposed, it is necessary to obtain a full oncologic history incorporating all surgeries and chemotherapies that the patient received. In addition, radiation treatment history should include fields, doses, and fractions to help assess if RFS is present.

Sarcoma survivors have a wide range of musculoskeletal and neurological impairments that are often overlooked. These impairments include lymphedema, altered gait mechanics, low back pain, sacroiliac joint pain, and bursitis. The expertise of the physiatrist in coordinating care in medically complex patients with multiple care providers allows an opportunity to be a strong patient advocate.

Rehabilitation Treatment

One retrospective study by Alappattu et al. specifically focused on clinical characteristics of patients with cancer who are referred to outpatient physical therapy. Overall, 418 patients were examined and most had genitourinary, breast, or head and neck cancers, and were followed over a two-year period. Frequently cited musculoskeletal impairments included:

- Deficits with strength (83.6 percent) and soft tissue anatomy (71.3 percent)
- Incontinence (38.4 percent)
- Loss of joint range of motion (51.2 percent)
- Posture (40.2 percent)
- Pain (47.8 percent)
- Fatigue (31.1 percent)
- Lymphedema (27.6 percent)
- Fibrosis (21.2 percent)[10]

The authors reported that the odds of having impairments in posture, range of motion, lymphedema, and fatigue were greater in patients who underwent chemotherapy and/or radiation therapy than in those who did not undergo these interventions. Furthermore, patients who underwent radiation therapy were 4.7 times more likely to report complaints of pain. Patients who underwent surgical procedures were more likely to have soft tissue impairments.[10]

A physiatric evaluation should screen for lymphedema, deficits in range of motion, postural dysfunction, peripheral neuropathy, and impaired balance. If these symptoms are diagnosed early in the cancer care continuum, treatment has the potential not only to improve quality of life, but also to strengthen tolerance for additional oncologic treatments.

Lymphedema

Lymphedema is defined as the accumulation of protein-rich lymph fluid in the interstitial tissues. It can occur as result of surgical destruction of the lymph nodes, lymphatic or major blood vessels, or damage from radiation fibrosis syndrome.[11] Accumulation of interstitial fluid leads to inflammation, adipose tissue hypertrophy, and fibrosis causing disfigurement. Increased protein concentration leads to increased colloid osmotic pressure, which drives fluid into the interstitium and

subsequently worsens swelling. Complications of lymphedema include recurrent skin infection, such as cellulitis, and skin changes, such as hyperkeratosis and papillomatosis.[11]

Lymphedema is a chronic condition, and there is no cure. However, there are methods to keep the fluid under control. Severity of lymphedema is rated from stage 0 to III by the International Society of Lymphology. Stage 0 is latent or subclinical lymphedema that can be present months prior to clinical presentation. Stage I is early accumulation of high protein fluid. Stage II is when tissue fibrosis develops, and stage III is when lymphostatic elephantiasis is noted. One study showed that in a cohort of 289 patients with soft tissue sarcoma, 9 percent developed stage II lymphedema. According to this study, risk factors included tumor size of greater than 5 cm and deep tumors, but not radiation dose.[11] If there is any question regarding the diagnosis, the gold standard test is lymphoscintigraphy or isotopic lymphography. During this test, an intradermal injection of radiolabeled colloid is injected into the distal part of the limb to examine the radiotracer transport through the lymphatic tissue.[12]

The most effective modality to treat lymphedema is complete decongestive therapy (CDT), also known as combined, complex, or comprehensive decongestive therapy. CDT programs have two phases: phase I focuses on the reduction of fluid volume, and phase II focuses on individualized long term self-management to maintain the gains from phase I. Phase I can occur up to five days a week for three to eight weeks, until reduction of fluid has reached a plateau. One of the main aspects of phase I is manual lymph drainage (MLD), which stimulates lymphatic vessels to remove excess interstitial fluid through subepidermal fluid channels that form after lymphatics are damaged. MLD is a light skin "massage technique" that is done by a certified lymphedema therapist. The goal is to mobilize the fluid from areas of congestion to lymph vessels that are working properly. Phase I also includes compression bandaging for gradient compression to mobilize fluid. Short stretch bandages can stretch about 40 to 60 percent from resting length, compared to long stretch bandages that can stretch to greater than 140 percent of resting length. Short bandages are applied with low-to-moderate tension using more layers at the distal portion of the extremity. Pressure within the bandages is low when the patient is at rest. Muscle contraction increases interstitial fluid pressure (working pressure) as muscles expand within the space of short bandages. This cycling from resting to working pressure creates an internal "pump." The overall goal of phase I is to move congested fluid into the vascular circulation. The short bandages also help to prevent fibrosis of the tissues. Patients must wear bandages during exercise since fluid load can increase temporarily.[13]

Phase II requires choosing an appropriate compression garment depending on the affected body part. If an off-the-shelf garment does not fit, a customized garment can be ordered especially if the patient has an irregularly shaped limb. If lymphedema is severe, night compression garments, such as velcro closure or foam garments, might be necessary to keep edema under control. Garments should be washed daily for hygiene and replaced every four to six months to maintain compression strength.[13]

FIGURE 1: **Example of IPC, Flexitouch® system.**
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Intermittent pneumatic compression therapy (IPC) or compression pump therapy can be used as an adjunct to phase I or II (see Figure 1). Single-chamber pumps are not used since they cause the fluid to move in both directions, as opposed to only away from the area of the congestion. The compression should occur in a specific pattern that is individualized for the patient, depending on the area of involvement. Pump pressure should be between 30 and 60 mmHg, and treatment should

last about one hour. One of the challenges with pumps is that the displayed pressure may not accurately correlate to the pressure delivered to the skin surface. Contraindications for IPC include acute infection, arterial vascular disease, deep venous thrombosis, superficial phlebitis, recurrent cancer in the affected area, or uncompensated heart failure. IPC is an adjunct to CDT and should not be performed without a comprehensive program.[13]

FIGURE 2:
Carbon Fiber AFO.
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Gait Impairment After Surgical Resection

Davis et al. demonstrated that with respect to the Toronto Extremity Salvage Score, patients with sciatic nerve resection were able to perform 70 percent of their activities of daily living. An ankle-foot orthosis (AFO) is the most common bracing required if the sciatic nerve is resected (see Figure 2). Special consideration should be given to ankle stabilization in patients with marked ankle proprioceptive deficits.[14] The subcategories of AFOs include carbon fiber designs instead of plastic fabrication. Some advantages of carbon fiber designs include that they are light weight, they provide energy at toe-off, and they contribute to a more normal gait pattern. Carbon fiber orthoses are contraindicated in patients with spasticity or severe contracture, since they can not be custom-molded. If hip flexion and knee extension are functionally intact, then inclusion of knee bracing, such as knee-ankle-foot orthosis (KAFO), is unnecessary.

Gluteal muscle resection causes pelvic obliquity and results in compensatory gait patterns. These patterns include compensated and uncompensated Trendelenburg gait postures (the former with a truncal lean to the ipsilateral stance leg) and gluteus maximus gait patterns with trunk extension on heel-strike on the weakened side, which compensates for ipsilateral hip extension weakness. Compensatory gait patterns can inflame the greater trochanteric and pes anserine bursae, and contribute to piriformis syndrome and chronic back pain.

Pain Management

The prevalence of pain in patients with sarcoma is estimated at 53 percent, and the incidence of inadequately treated pain was reported as 63 percent.[15]

Non-opioid analgesics such as acetaminophen and NSAIDs play an important role in treating mild pain. Acetaminophen can be effective in mild cancer pain, but there is limited evidence regarding the synergistic benefit with opioids based on a review of five randomized controlled trials.[16] NSAIDs were found to be beneficial for cancer pain compared to placebos in a meta-analysis of 25 studies.[16] Eight studies compared NSAIDs versus NSAIDs combined with an opioid. Four of these studies found that the combination provided marginally better pain relief. Unfortunately, most of the literature on acetaminophen and NSAIDs in cancer has small sample sizes, and none included selective COX-2 inhibitors.[16]

Antidepressant and anticonvulsant medications can be used in cancer-related neuropathic pain. Neuropathic pain is present in about 40 percent of patients with cancer, and up to 40 percent of survivors reported neuropathic pain at five years after treatment.[16] Pain can be from surgical treatment (mastectomy or amputation), chemotherapy-induced peripheral neuropathy, or radiation-induced plexopathy or myelopathy. Opioid analgesia is insufficient as monotherapy to control neuropathic pain.

Bisphosphonates are another group that has been shown to improve pain from bony metastases. Pain from bony metastases occurs due to upregulated osteoclastic activity and increased bone resorption. Bisphosphonates work by inhibiting osteoclastic bone resorption. Several meta-analyses as well as a Cochrane review have shown a decrease in skeletal related events in patients receiving bisphosphonates.[16] There are two classes of bisphosphonates. The first is a non-nitrogenous and older class (i.e., etidronate and clodronate) and the second class contains nitrogen (i.e., pamidronate and zoledronate). In the non-nitrogenous group, the osteoclast initiates apoptosis and dies, leading to decreased bone breakdown. Nitrogenous bisphosphonates act on bone metabolism by binding and

blocking an enzyme in the HMG-CoA reductase pathway and therefore slowing down bone resorption to allow bone remodeling to occur. The risk of osteonecrosis of the jaw is between 0.7 and 12 percent using these medications, and is more likely to occur in patients with metastatic disease, poor oral hygiene, or after dental surgery.[16]

To address pain management in the oncology population, the World Health Organization developed an analgesic ladder that provides guidelines based on pain severity. Non-opioids like acetaminophen are recommended for mild pain, with low-potency opioids, such as tramadol, codeine, and hydrocodone indicated for moderate pain. Stronger opioids, such as morphine, hydromorphone, methadone, fentanyl, and oxycodone, are reserved for severe pain. Drugs that have a different mechanism of action should be combined to improve analgesia and reduce opioid requirements.[16] However, it is important to make sure that opioids are initiated at an appropriate time to improve function and quality of life. They should not be withheld until the terminal stages of cancer care.

For pain that is intractable and not responsive to oral analgesics, consultation should be sought with an interventional pain management physiatrist for selective nerve blocks, neurolysis, and intraspinal devices. Some examples include celiac plexus block or splanchnic nerve radiofrequency neurotomy for longer-lasting pain relief, respectively.[17]

These procedures are targeted for visceral analgesia for upper abdominal organs. Ganglion of impar block can be performed for visceral analgesia to the rectal vault. Superior hypogastric plexus block can be useful for visceral analgesia for patients with ovarian, uterine, testicular, and cervical cancers. Intercostal nerve blocks are indicated for acute and chronic pain of skin, chest, muscles, or rib metastases. Sympathetic nerve blocks, including stellate ganglion (upper extremity) and lumbar sympathetic ganglion (lower extremity) blocks, can be useful for patients with complex regional pain syndrome secondary to nerve injury from nerve resection/transection or from any injury to the extremity[17] (see Table 1).

An important aspect of treating a patient with a history of cancer is to monitor for any new symptoms that could be concerning for recurrent tumors. These findings include new pain (especially thoracic pain), pain when supine at night, pain with transition of movement (mechanical pain indicative of spine instability), or radicular pain (from nerve root invasion) that could be indicative of spinal metastasis. Levack et al. demonstrated that patients with a history of cancer had a two- to three-month delay in diagnosis of metastatic spine disease despite complaining of new pain.[19] By the time there are signs of spinal cord compression such as hyper-reflexia, bowel and bladder issues, falls, or weakness, the damage is often irreversible. MRI is the gold standard imaging test in a patient with a history of cancer who presents with new symptoms.[19]

TABLE 1: **Examples of Interventional Pain Management Procedures**[17,18]

Pain Site	Type of Interventional Procedure	Site of Procedure
Visceral Analgesia for Upper Abdominal Organs (Liver, Small Bowel, Pancreas Omentus, Pancreas)	Celiac Plexus Block	Retroperitoneal — At Level of T12-L1 Surrounds Abdominal Aorta
Rectum, Coccydenia, Pelvic Rim	Ganglion of Impar Block	Retroperitoneal — Sacrococcygeal Junction
Visceral Analgesia for Pelvic Organs (Ovaries, Uterus, Cervix, Testes)	Superior Hypogastric Plexus Block	Retroperitoneal — Extends Bilaterally, Lower Third of L5 to Upper Third of S1 Vertebral Body
Skin, Chest, Muscles, Ribs	Intercostal Nerve Blocks	Between the Internal and Innermost Intercostal Muscle Layer of the Thorax and in the Intercostal Space Deep to the Subcostal Groove at the Angle of the Rib
Complex Regional Pain Syndrome	Sympathetic Nerve Block	Stellate Ganglion Block: Level of C7 Vertebra, Anterior to C7 Transverse Process, Below Subclavian Artery Lumbar Sympathetic Block: In Horizonal Plane, 0-0.5 cm Posterior to Anterior Border of L3 Vertebrae

Clinical Outcome

We developed a treatment plan for KM that included injecting her sacroiliac joint and pes anserine bursa, which provided relief of pain. She also had CRPS in her left lower extremity that was subsequent to sciatic nerve injury, and had been unresponsive to escalating doses of opioids. We ordered a sympathetic nerve block, but the injection did not provide benefit.

With regards to lymphedema, KM opted to wear compressive bandages during the day before going back for more therapy due to limited finances. She already used a carbon fiber AFO that was appropriately fitted and did not cause discomfort or skin breakdown.

KM's main barrier was her urinary and fecal incontinence that was subsequent to radiation fibrosis syndrome. She was not able to leave her house or participate in community or family functions because she was embarrassed that she might have an episode of incontinence. Furthermore, the only therapy she tolerated well was aquatic therapy, which was a challenge due to fecal and urinary incontinence.

Because KM was not able to return to work, she could not afford physical therapy copays. At our last visit, we suggested one to two visits with a pelvic floor specialist to be fitted for an anal plug that would allow her to participate in the community more often without bowel incontinence. At seven years from cancer diagnosis, she has not shown any recurrence of her sarcoma, but she continues to experience the additive consequences of her cancer treatments.

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