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Anesthesia and analgesia for cancer-related amputation

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Cancer-related amputations, although more and more infrequent, are responsible for a considerable amount of chronic pain that is often resistant to standard therapies and interventions. Cancer patients are particularly at risk of developing the common pain syndromes of phantom limb pain (PLP) and persistent stump pain, secondary to their underlying disease and side effects of the their treatment. A significant number of anesthetic and pharmacologic therapies have been trialed to eliminate these chronic pain conditions. Many techniques, including preemptive epidural analgesia and perineural blockade, have shown promise in eliminating the development of these conditions, but none has been definitively proven superior. Despite the interventions and multiple medications, this group of symptoms remains resistant and continues to drive the search for a panacea. This article reviews studies examining the effect of reducing PLP and persistent stump pain when specific regional anesthesia techniques, such as epidural anesthesia and perineural blocks, are used both preemptively and continued postoperatively. This article also reviews selected trials of pharmacologic therapies for the treatment of chronic postamputation pain in the cancer patient, such as opioids, select N-methyl d-aspartate antagonists, calcitonin, antidepressants, β-blockers, anticonvulsants, and botulinum toxin. Other therapies, such as mirror treatment, use for the alleviation of PLP, are covered as well. The selected key studies reviewed in this article reveal many promising techniques and pharmacologic modalities in the treatment of postamputation cancer pain, yet none has been reliably proven to completely block PLP or persistent stump pain once and for all. Though there have been no dramatic breakthroughs, it is evident that continued research, specifically for cancer patients, is more urgent than ever.

In 2009, an estimated 2570 new cases of primary bone cancer [1] and 10,660 new cases of soft-tissue cancer[2] will be diagnosed in the United States. Combined, these cancers will represent <1% of all types of new cancer diagnosed for the year. Most of these patients will be treated with a combination of chemotherapy and advanced limb salvage surgical technique. However, between 6% and 10% of these patients will ultimately undergo an amputation.[3] Although amputation may present a chance for disease control or even cure, it will likely present a new challenge to the postamputation cancer patient living with complex and often painful symptoms, such as chronic stump pain and phantom limb pain (PLP). Although 85% of patients with all types of cancer report good control with oral medication,[4,5] more than 80% of cancer patients with amputation complain of symptoms refractory to these conventional treatments.[6] For this group of cancer patients, a complex regimen of multimodal medications and interventions is often required.

In recent years, the overall 5-year survivability from all types of cancer has increased from 50% to 66%.[6] Survivability has increased even more dramatically for many of the cancers that result in amputation. For example, osteosarcoma, the most common type of bone sarcoma, has seen an increase in 5 year survivability in recent decades from a once dismal 20% to nearly 70%.[7] This increased survivability and a preponderance for occurrence in adolescents and

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young adults[8] make amputation pain a chronic pain condition rather than a malignant, end-of-life symptom in cancer patients.

As with amputees from trauma and vascular disease, cancer amputees will often suffer from the classic amputation pain syndromes of persistent stump pain and PLP. In addition, cancer patients with amputation frequently suffer from pain symptoms due not only to the amputation, but also possibly pain related to the underlying cancer, a more complicated prosthetic application, a stump weakened by direct radiotherapy, side effects of systemic chemotherapy, or emotional or psychosocial issues related to their disease. Just as the etiology of pain for patients with cancer amputation is multifaceted, so is the treatment. This article focuses on the causes and character of postamputation pain in the cancer patient and its current treatments options.

Characteristics of the cancer patient undergoing amputation

In recent years, treatment of soft-tissue sarcomas and primary bone tumors has shifted from amputation to limb salvage technique. Much of this change in management is due to advances in imaging, such as the development of computed tomography and magnetic resonance imaging, as well as the use of directed radiotherapy. Limb salvage, once considered a higher risk for local recurrence, metastatic disease, and lower overall survival has shown, with proper margins, to have comparable rates of disease-free survival and overall survival rates.[9] This surgical technique often involves very wide resection and requires complex reconstruction. Although this method presents an operative challenge, quality of life and patient satisfaction is clearly improved in upper limb disease[10,11] and equal to amputation in lower extremity disease.[12] The success of limb salvage, radiotherapy, and chemotherapy has dramatically reduced the number of initial amputations in most institutions from 40% to 5%.[13] Not surprisingly, because of the shift to limb salvage technique, amputation has gone from being the initial surgical intervention of choice to a technique reserved for tumors that are either locally recurrent, very large, or have significant and aggressive composite tissue involvement.[3] Such tumors are rare and as the technique has evolved, involvement of elements, such as major vascular structures, once thought to be an outright indication for amputation, have proven to be amenable to limb salvage.[14,15]

The most common malignant bony tumors occurring in population are conventional osteosarcoma, chondrosarcoma, and Ewing's sarcoma.[16] A majority, almost two-thirds, occurs in the pelvis or lower extremities.[12] Soft-tissue sarcomas, by definition, arise from soft tissue but may involve bone and represent many histologic subtypes. Most of the bony and soft-tissue cancers that lead to amputation have their highest incidence early in life. Osteosarcoma, for example, classically occurs in patients aged <30 years.[16] Pediatric patients, especially those aged <10 years, are particularly at risk for requiring an amputation as limb length inequality produced by limb salvage can be considerable. With acceptance of newer expandable prosthesis, however, this indication for amputation is decreasing.[7]

Characterization of pain in the cancer amputee

Pain is a common cancer symptom with a maximum of 75% of patients complaining of moderate to severe pain during the later phases of their disease.[17] The prevalence of pain and abnormal sensation in the cancer amputee is considerable. Most amputees of all cause will experience phantom sensation that is, a feeling of the amputated limb existing, sensing and moving in its previous form. Many of these patients, between 50% and 80%,[18] will also experience phantom sensations that are intense and interpreted as painful. This condition, termed PLP, occurs with varied character and intensity among cancer amputees. Amputees describe different qualities to PLP, such as burning, stabbing, throbbing, cramping, and tingling. These sensations are often reported with more intensity at the perceived distal end of the limb.[19] However, PLP is also notoriously resistant to conventional treatments, and peripheral regional anesthesia has shown only mixed results.

The underlying reasons for PLP are complex, and studies examining the incidence and intensity also point to a relation to gender, preamputation pain, level of amputation, prosthetic use, stump pain, and elapsed time since amputation.[18] Many authors point to a gradual disappearance in symptoms as time elapses[20,21]; however, others have found that although there is a diminution of pain symptom frequency or intensity over time, symptoms are persistent.[22] Still others have cast this temporal relationship in doubt, with findings of no change in pain symptoms or intensity over time.[23,24] There is no published data examining this relationship specifically in cancer amputees; however, with cancer survivability increasing, this is an area for future examination.

Cancer patients may be especially susceptible to developing PLP secondary to adjunctive chemotherapy use. A retrospective study examining PLP incidence in pediatric patients found an overall rate of 48% of PLP in cancer-related amputations vs 12% in trauma-related amputations.[25] This same study found an even higher rate of PLP in those patients who had undergone induction chemotherapy, suggesting that the long-lasting neurotoxic properties may contribute to the risk of PLP. Commonly used chemotherapeutic agents, such as vincristine, cisplatin, etoposide, methotrexate, and ifosfamide have been shown to cause peripheral neuropathy, and oxaliplatin has been implicated in causing severe muscle cramps when in contact with cold surfaces.[25-27]

Besides PLP, postamputation patients may also complain of stump pain which itself has an incidence between 39%