



The Role of Ablation in Cancer Pain Relief

Dimitrios K. Filippiadis¹ · Steven Yevich² · Frederic Deschamps³ · Jack W. Jennings⁴ · Sean Tutton⁵ · Alexis Kelekis¹

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Abstract

Purpose of Review The purpose of this article is to describe the concepts of ablation techniques for pain relief in symptomatic oncologic patients. Controversies concerning techniques and products will be addressed.

Recent Findings Despite conventional pain palliative techniques, cancer patients often endorse unresolved somatic and neuropathic pain that can present as a great burden to quality of life. In non-operative patients, several techniques have been applied to minimize opioid dependence. While radiotherapy is often considered as a non-invasive option, percutaneous ablation has been advanced as a minimally-invasive alternative with clear procedural and outcome advantages. Similar to radiation therapy, percutaneous ablation techniques can act either upon nerve structures responsible for pain mediation signals (neurolysis) or directly upon the tumor to relieve tumor-mediated inflammation and decompress tumor compression of adjacent structures.

Summary Percutaneous ablation provides valuable neurolysis and tumor-directed pain palliative effects to be incorporated into clinical guidelines for pain reduction in oncologic patients. Selection among different ablation techniques should be based upon an individually tailored approach, to include consideration of all treatment modalities.

Keywords Pain · Oncology · Ablation · Neurolysis

Introduction

All phases of cancer can cause significant somatic and neuropathic pain that results in psychological and physical distress, and ultimately a reduction in quality of life [1, 2, 3]. Pain prevalence in oncologic patients is estimated at 51–66% with the vast majority of these patients (56% to 82.3%) remaining

undertreated [1, 2, 3]. Pathophysiology of pain is multifactorial including tumor invasion or displacement of pain-sensitive or pain-mediating structures, as well as from indirect iatrogenic causes including tissue destruction or inflammation from cancer therapies including radiotherapy, surgery or systemic chemotherapy and immunotherapy [1, 4]. An understanding of the etiology of pain is often important for effective treatment.

Tumor growth may cause pain from different mechanisms. Pain-sensitive or pain-mediating structures include spinal nerves, the ‘sympathetic axis’ and the osseous periosteum/bony trabeculae [1, 4]. Spinal nerves can be affected by direct tumor infiltration or from secondary compression due to vertebral collapse, which may affect sensory and motor function. Similarly, tumor infiltration may entrap sympathetic nerve fibers, resulting in nociceptive visceral pain. Tumor infiltration into osseous structures may result in micro-fractures and periosteal distortion that precipitate mechanical stress, pathologic fracture, and nociceptive stimulation associated with the periosteum [4]. As many cancer patients are not good surgical candidates due to age-related comorbidities, tumor progression, and concern for delays in systemic therapy, alternative non-surgical therapies are important for pain palliation [5].

Opioid therapy for cancer related pain according to the three-step analgesic ladder proposed by the World Health

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✉ Dimitrios K. Filippiadis
dfilippiadis@yahoo.gr

¹ 2nd Department of Radiology, University General Hospital “ATTIKON”, Medical School, National and Kapodistrian University of Athens, 1 Rimini str, 12462 Haidari, Athens, Greece

² Department of Interventional Radiology, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

³ Department of Interventional Radiology, Gustave Roussy Cancer Campus Grand Paris, Villejuif, France

⁴ Department of Musculoskeletal Radiology, Washington University School of Medicine, St Louis, MO, USA

⁵ Division of Vascular and Interventional Radiology, Medical College of Wisconsin, Wauwatosa, WI, USA

Organization (WHO) provides a simplified model of analgesics escalation. Despite the valuable contribution of opioid therapy for pain palliation, the administration of opioids is not free of health and financial costs [6–8]. Additionally, nearly one third of oncologic patients under opioid therapy complain of refractory or non-responsive pain [9].

Radiotherapy is a type of ablation technology that provides a non-invasive adjunctive treatment to complement opioid therapy. Although considered a gold standard therapy, radiation only achieves overall pain responses (complete and partial responses combined) up to 60% and 61%. The technique's efficacy and application is limited by factors including radio-resistant tumors, irradiated tissue dose limits, delayed onset of pain relief, and insufficient duration of symptom relief [5•, 10, 11•].

Percutaneous ablation techniques provide a minimally invasive palliation alternative to minimize opioid dependence and improve patient quality of life without drug effects and minimal other complications related to morbidity [1•, 12, 13]. Ablation techniques as palliative therapy for pain reduction can be used for destruction of nerves mediating pain signals (percutaneous neurolysis) or for tumor destruction and decompression acting either indirectly (regional anesthesia from neurolysis) or directly upon the tumor, inhibiting its local growth [1•, 12, 13]. The purpose of this article is to describe the basic concepts of percutaneous ablation techniques for pain relief in symptomatic oncologic patients. Controversies concerning techniques and products will be addressed.

Ablation Techniques

A variety of ablation techniques apply energy through different mechanisms of action to achieve cell destruction. The most commonly applied ablation techniques include cryoablation, radiofrequency, and microwave ablation. Another emerging image-guided ablation technology that will be described is MR-guided High Intensity Focused Ultrasound (HIFU). All treatments rely on image guidance, and can be repeated.

Cryoablation During cryoablation, a needle probe is introduced into the tumor. Passage of Argon gas through the probe achieves an extreme cold temperature at the tip that destroys tumors. The Joule-Thompson effect governs the rapid expansion/compression of a gas with resultant temperature change based on the atomic properties of the gas [14]. Cell lysis occurs from the rapid alteration between freeze and thaw. The mechanisms of action include direct physical damage (shearing of cell membranes and organelles resulting in cellular death) and vascular mediated toxicity (with permanent microvascular occlusion and ischemic damage). In addition, there is hypothesis that cryoimmunological modulation may result during cryoablation, which is currently under investigation [14, 15].

Radiofrequency Ablation During radiofrequency ablation, the needle probe functions by application of a closed circuit applied through a generator. Grounding pads are not necessary in bipolar radiofrequency electrodes where both the anode and cathode of the circuit are included in the tip of the device [11]. Focal ionic agitation in the target tissues around the tip of the electrode is caused by high frequency alternating current (400 and 500 kHz) resulting in heat generation and lethal temperatures over 60 °C [5•]. The tissue impedance, perfusion and ventilation highly affect the volume and size of the ablation zone [11].

Microwave Ablation Application of microwave energy through a needle probe results in the creation of an oscillating microwave field that causes polar molecules to continuously realign increasing kinetic energy and tissue temperature [16]. During agitation of water molecules, friction and heat are produced with resultant cellular death via coagulation necrosis. All microwave antennas are linear in configuration differing in diameter (13–18 gauge) and in the length of the active tip (1–4 cm).

MR-Guided High Intensity Focused Ultrasound (HIFU) This noninvasive ablation technique functions through the concentration of acoustic energy on the target tissue. The focused ultrasound energy produce a rapid temperature increase that mediates critical thermal damage [17]. Magnetic Resonance Imaging provides three-dimensional treatment planning and thermometry for continuous temperature mapping. There is no ionizing radiation associated to the acoustic ultrasound energy application [17].

Other Ablation Techniques Interstitial laser photocoagulation uses laser photons but the resultant ablation zone is smaller compared to other technique and up to now it has been used mostly for ablation of benign lesions [18]. Irreversible electroporation (IRE) uses short intense electrical pulses to destabilize cellular membrane by creation of nanopores inducing cellular death through apoptosis [19]. Application of IRE for pain reduction requires further investigation lacking at the moment robust literature support.

Each of the aforementioned techniques has separate advantages and disadvantages. Cryoablation is governed by low levels of peri-procedural pain and results in larger ablation volumes that are visible under imaging with predefined size and shape depending on the number and location of the cryoprobes used. Radiofrequency ablation is faster than cryoablation, but the technique's efficacy can be limited by the presence of cortical or very sclerotic bone or by the “heat-sink” effect caused by vessels located close by. High power microwave generators (≥ 100 watts - frequency of 2.45 GHz) with internal fluid cooling of the antenna can generate higher temperatures than RF ablation with larger ablation volumes in

shorter time that are less affected by “heat-sink” effect and any kind of impedance-driven performance and less procedural pain [20]. Both radiofrequency and microwave energies result in ablation zones not visible under axial imaging during the therapeutic session.

Percutaneous Neurolysis

Percutaneous neurolysis uses chemical or thermal means to achieve pain reduction in oncologic patients [1•]. Extreme heat by means of radiofrequency or microwave or cold by means of cryoablation is applied for nerve destruction. Percutaneous ablation techniques manage nociceptive and neuropathic pain secondary to malignancies by destruction of nerves mediating pain signals. Indications for percutaneous neurolysis in oncologic patients include cancer pain arising from direct invasion of pain-sensitive structures or as a post-therapeutic insult [1•, 21]. Criteria for patient selection include cases of advanced, progressive cancer with a life expectancy of 6–12 months; contraindications include significant hemorrhage risk as in cases of coagulopathy, thrombocytopenia, or anticoagulant therapy, systematic or local infection, lack of a safe pathway and any kind of location specific contraindications [1•]. Potential target locations in oncologic patients include but are not limited to: stellate ganglion, thoracic intercostal, celiac and lumbar plexuses, splanchnic nerves and superior hypogastric plexus [1•, 22–25].

Both radiofrequency ablation and cryoablation have been applied for neurolysis. The most commonly applied protocols apply radiofrequency in two sessions of heat-based thermocoagulation performed at 75–90 degrees for 60–90 s [1•]. There is no well-established protocol for the application of cryoablation during percutaneous neurolysis; some authors propose a single freezing cycle with temperatures of –140 degrees centigrade followed by a 2 min thawing cycle whilst others propose 2 alternating freeze-thaw cycles ranging from 6 to 10 min and from 3 to 5 min, respectively [1•, 26]. Microwave ablation is rarely used for percutaneous neurolysis due to higher cost and lack of specific thermocoagulation protocol.

Percutaneous neurolysis is usually performed under local anesthesia and intravenous analgesia or conscious sedation, since real time neurologic control is often helpful to ensure safe and efficacious therapeutic session. Imaging guidance and stimulation tests performed prior to thermocoagulation increase safety and efficacy of the technique. Imaging guidance may include fluoroscopy, ultrasound (incl. endoscopic) computed tomography and Magnetic Resonance Imaging [1•, 27–32]. Positive sensory test (the response’s location is concordant with the distribution of the patient’s usual pain) governs the efficacy of thermocoagulation while positive motor

testing (lack of motor response in a threshold below 2.0 V) is associated with procedural safety.

When compared to chemical neurolysis by means of alcohol or phenol, thermocoagulation of nerves seems to be more effective acting faster with longer analgesic duration under a better safety profiles. Specifically cryoneurolysis has been associated with lower or no rates of post-therapeutic neuritis [25, 33, 34]. When compared to conservative pain therapy with opioids consumption, percutaneous neurolysis does not have the same side effects of related to long-term analgesic effect and can help reduce opioid consumption [35].

Percutaneous Ablation

The pathophysiology of cancer pain reduction after percutaneous ablation is multifactorial including among others resultant necrosis between the tumor and the pain-sensitive periosteum, tumor volume decompression to relieve compression on surrounding structures, reduction in nerve-stimulating cytokines, and inhibition of osteoclast activity [36–39]. Decisive factors for proper patient selection include the tumor characteristics and histology, the patient’s general health status, and the degree of bone destruction that might result in impending or pathologic fracture [40]. The main indication for the application of thermal ablation as palliative therapy for pain reduction in oncologic patients includes treatment of painful metastases refractory or unsuitable to conventional therapies [5•]. In case of impending pathologic fracture or necessity for fracture stabilization, percutaneous ablation can be combined in a single session with percutaneous bone consolidation therapies such as cementoplasty or percutaneous screw fixation that complements ablation therapy by providing structural osseous support [5•, 18, 36].

Percutaneous ablation should be performed under imaging guidance with antibiotic prophylaxis. The use of procedural anesthesiologic may be applied for patient comfort. Cryoablation is often performed under conscious sedation or local anesthetic due to the low peri-operational pain [Fig. 1]. MR-guided HIFU requires general anesthesia in all cases to ensure the patient maintains position as procedure requires prolonged time in one position.

Multiple techniques have been developed to advance the ablation tools into the specified location. For instance, intact cortical bone can be pierced with access trocars as the ablation probes are not of sufficient durability. Other techniques have been developed to protect surrounding structures from the thermal energy to minimize risks of complications [36, 41•, 42]. For example, ablations near nerves are carefully performed as the safety threshold to avoid nerve tissue damage is below 44 over 10 °C [42]. These protective measures include displacement techniques using fluid, (Dextrose 5% in case of Radiofrequency energy), balloons, or gas (Carbon

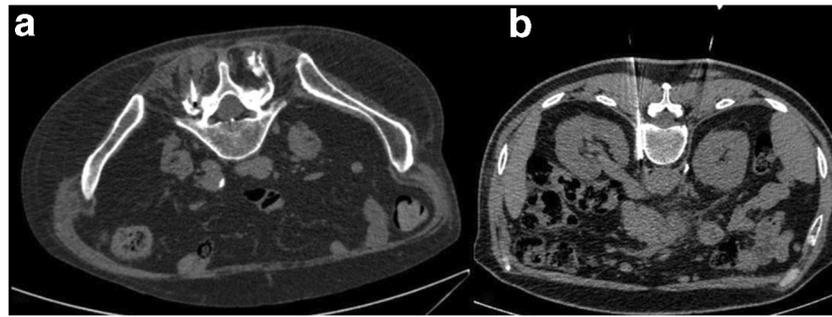


Fig. 1 A: A 68 y-o male patient with Renal Cell Carcinoma metastatic disease. Multiple lytic lesions in thoracic and lumbar vertebrae. Patient is complaining of low back pain in the right side at the level of L5-S1 facet joint where a soft tissue mass is depicted. Cryoablation was performed under Computed Tomography guidance. Patient was pain free from the

morning post ablation session B: A 72 y-o male patient with pancreatic adenocarcinoma complaining of intractable pain was treated with splanchnic nerves neurolysis. Radiofrequency electrodes were bilaterally placed at T12 level

dioxide is the most preferable gas). In addition, thermal couples may be used to monitor ablation size. Lastly, intra-procedural imaging, neurophysiologic monitoring, and skin protection through dissection techniques can also be employed to minimize risks [36, 41, 42].

Several studies apply ablation techniques in symptomatic patients with at least moderate pain severity and report a high efficacy (68–100%) and high safety rates (Table 1), [50–54]. Zugaro et al. compared cryoablation to radiofrequency as pain palliation techniques in symptomatic patients with osteolytic osseous metastases to find improved outcome with cryoablation [55]; however there is no compelling literature to prove superiority of one ablation technique over others [54].

In the peripheral skeleton, specifically in weight bearing bones, ablation should be combined with bone consolidation techniques for the necessary structural support [36, 45, 46]. Even in large-sized bone lesions percutaneous ablation by means of cryoablation combined with bone augmentation results in marked pain as well as mobility and quality of life improvements [47].

Whenever spine is concerned combining ablation to radiotherapy and cement injection has been reported to provide superior pain reduction results even in patients with radiotherapy resistant tumor subtypes [56, 57]. In peripheral skeleton combining percutaneous ablation (no matter which energy applied) to radiotherapy, seems to result in significantly better results of pain alleviation concerning overall response, complete pain relief, time to pain relief, recurrent pain retreatment need and post-therapeutic narcotic medications need [58*, 59].

Conclusion

Percutaneous ablation techniques may act either indirectly by regional neurolysis or directly upon the tumor to inhibit tumor growth through tumor necrosis. Ablation techniques provide significant pain alleviation and improve quality of life. Thorough knowledge of nervous anatomy and pain transmission pathways are fundamental for proper patient and technique selection, and to maximize efficacy and safety. Percutaneous ablation techniques can be combined with

Table 1 Recent studies applying ablation modalities for pain reduction in metastatic bone disease

Author (year)	Number of patients (Lesions)	Location	Tumor Substrate	Ablation Modality Used	Pain Reduction Score (NVS units)
Vaswani et al. (2018) [43]	41 (64)	Peripheral skeleton	Sarcoma	CWA or RFA	8 → 3
Ma et al. (2018) [44]	45 (76)	Peripheral skeleton	NSCLC	CWA or RFA	7.5 → 3.7
Deib et al. (2019) [45]	65 (77)	Peripheral skeleton	Metastatic disease of various substrate	MWA	6.32 → 2.01
Pusceddu et al. (2016) [46]	35 (37)	Peripheral skeleton	Metastatic disease of various substrate	MWA	6.8 → 0.7
Coupal et al. (2017) [47]	48 (48)	Pelvis	Metastatic disease of various substrate	CWA	7.9 → 1.2
Gallucher et al. (2019) [48]	16 (18)	Peripheral skeleton	Metastatic disease of various substrate	CWA	3.3 → 1.2
Cazzato et al. (2018) [49]	11(11)	Spine	Metastatic disease of various substrate	Bipolar RFA	7.8 → 3.5

radiotherapy for a more significant pain reduction effect even in radio-resistant tumor subtypes, and/or combined with bone consolidation techniques that augment treatment by providing structural support in weight-bearing osseous structures.

Compliance with Ethical Standards

Conflict of Interest Dimitrios K. Filippiadis declares that he has no conflict of interest.

Steven Yevich declares that he has no conflict of interest.

Frederic Deschamps declares that he has no conflict of interest.

Jack W. Jennings has received compensation from Merit Pharmaceuticals, Medtronic, and BTG plc for service as a consultant.

Sean Tutton declares that he has no conflict of interest.

Alexis Kelekis declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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