Emerging Ionizing and Non-Ionizing Radiation for Treatment of Musculoskeletal Disorders and Malignancies

Narges Jokar[1*], Habibollah Dadgar[2], Ali Gholamrezanezhadi[3], Sana Salehi[4], and Majid Assadi[5]

1. *The Persian Gulf Nuclear Medicine Research Center, The Persian Gulf Biomedical Sciences Research Institute, Bushehr, Iran*
2. *Cancer Research Center, Razavi Hospital, Imam Reza International University, Mashhad, Iran*
3. *Department of Diagnostic Radiology, Keck Faculty of Medicine, University of Southern California (USC), Los Angeles, USA*
4. *Department of Interventional Radiology, Faculty of Medicine, Mercer University, Savannah, GA, USA*
5. *Department of Molecular Imaging and Radionuclide Therapy (MIRT), The Persian Gulf Nuclear Medicine Research Center, The Persian Gulf Biomedical Sciences Research Institute, Bushehr University of Medical Sciences, Bushehr, Iran*

*** Corresponding author**

Narges Jokar, MSc
The Persian Gulf Nuclear Medicine Research Center, The Persian Gulf Biomedical Sciences Research Institute, Bushehr University of Medical Sciences, Bushehr, Iran
Tel: +98 77 1258 0169
Email: nargesjokar97@yahoo.com

Received: 17 Apr 2019
Accepted: 8 Jun 2019

Citation to this article:
Jokar N, Dadgar H, Gholamrezanezhadi A, Salehi S, Assadi M. Emerging Ionizing and Non-Ionizing Radiation for Treatment of Musculoskeletal Disorders and Malignancies. *J Iran Med Counc*. 2019;2(4):54-65.

Abstract

The Musculoskeletal (MSK) system includes bone, cartilage, fat, muscles, blood vessels, neural tissue, and other connective tissues. As aging occurs, the incidence of musculoskeletal disorders increases. Benign bone and soft tissue pathologies are more common than malignant ones. Although some MSK abnormalities can be self-limited, in the cases of severe defects or impairment of the potential restoration, intervention by novel methods such as radiation therapy may be required along with the main treatment, which is surgery in most cases. Radiation is categorized as non-ionizing and ionizing. Non-ionizing radiation has longer wavelength, lower frequency, and lower energy, while ionizing radiation has short wavelength, high frequency, and higher energy. Utilizing these methods can have both symptom-relieving and curative effects.

One of the non-ionizing radiation types comes in the form of Low Level Laser Therapy (LLLT), which is a non-aggressive, non-ionizing, monochromatic and electromagnetic high-concentrated beam. LLLT has an essential role in ATP production, reducing inflammation, pain relief, wound healing, and muscle function. The development of ionization radiation therapy by radionuclides as a targeted therapy in nuclear medicine, boron capture neutron therapy and proton therapy as external radiation therapy can play a critical role in treating bone and soft tissue malignancies, especially in pediatric oncology. The purpose of this paper was to review the efficiency of LLLT, bone-seeking radiopharmaceuticals, proton, and boron capture neutron therapy for the treatment of bone and soft tissue sarcomas and malignancies.

Keywords: Fast Neutrons, Low Level Laser Therapy, Musculoskeletal System, Protons

Introduction

The Musculoskeletal (MSK) system includes bone, cartilage, muscles, fat, blood vessels, neural tissue, and other connective tissues. The most important primary lesions are originated from mesenchymal tissue, the same as the mesoderm of the embryo (1,2). As aging occurs, the incidence of MSK disorders increases. Over 20 million MSK injuries take place in the USA annually and the most common types include sprain, fractures, and contusion (3). Although some MSK abnormalities can be self-limited, in the cases of severe defects or impairment of the potential restoration, intervention by novel methods may be required. These novel techniques accelerate the repair and regeneration process of the musculoskeletal system. One of these methods used in musculoskeletal disorders is called Low Level Laser (Light) Therapy (LLLT). The term LASER stands for Light Amplification by Stimulated Emission of Radiations. This light stems from electromagnetic radiation (from radio waves to gamma rays) (4).

On the other hand, there are musculoskeletal malignancies as a heterogeneous tumor (1). Sarcomas are classified into two categories: 1- soft tissue sarcomas (blood vessels, fat, connective tissues, muscle, nerve and nerve sheath) and 2- bone sarcomas. In 2017, it is estimated that nearly 12,390 and 3260 new cases for soft tissue and bone sarcomas will be detected, respectively (5). Bone is considered the most common area of secondary metastases. But, benign bone and soft tissue pathologies are more prevalent than malignant tumors. The most important clinical symptoms of musculoskeletal disorders are inflammation, acute and chronic pain, and subsequent fractures (6,7). Acute and chronic impairment and deformities have undesirable effects on the patient's quality of life (8). These impairments are diagnosed based on histological characteristics and imaging modalities. Different types of sarcomas require multidisciplinary approaches. Surgery is considered the main treatment approach for sarcomas. Chemotherapy and radiation therapy are applied as adjuvant or neoadjuvant therapies in these patients (9,10). In this study, the effectiveness of non-ionization, laser, and ionization radiation including proton, neutron and radioactive exposure was evaluated in soft and hard tissue pathologies and malignancies.

Materials and Methods

This research was conducted by searching multiple electronic databases, such as Scopus, MEDLINE, Google Scholar, Web of Science, PubMed and handbooks. The keywords used for searching were musculoskeletal, MSK, muscle, bone, MSK disorders, MSK malignancy, soft tissue, sarcoma, LLLT, LASER, Low Level Laser Therapy, bone-seeking radionuclides, bone-seeking radiopharmacy, bone metastases, external beam radiation therapy, proton therapy, neutron therapy, BCNT, pediatric cancer, and bone malignancy. The obtained data with no restriction in date and language were examined by investigators and discussed as well. Exclusion criteria were unpublished doctoral theses and abstract article in poster format.

Low Level Laser Therapy

Biophysical and biochemistry studies have shown the biological effects of visible light on cellular function. The laser is a monochromatic, non-aggressive, non-ionizing, and electromagnetic centralized beam (11). Most of the performed studies demonstrated the efficacy of laser on animals, in which it had led to a rapid rate of wound healing and improved epithelial tissue proliferation (12). Significant biological effects caused by non-thermal devices include cell proliferation, collagen synthesis, release of intracellular growth factor from the vessels, activation of cells, stimulation of photoreceptor in mitochondrial respiratory chain, change in cellular ATP or cAMP level, enhancing muscle performance through metabolic photochemical effects, protein synthesis, reduction of fatigue index, tissue repair and tensile strength (11,13,14). Lasers have various types of Helium-Neon (HeNe), Indium, Gallium-Aluminum-Phosphide (InGaAlP), Gallium-Aluminum-Arsenide (GaAlAs), and Gallium-Arsenide (GaAs). The vast majority of therapeutic lasers are semiconductor lasers (15,16).

The total required dose prescribed to the patient is based on the time of treatment and the total applied energy to tissue. Generally, the greater power of the laser needs less time for delivering the same dose. The energy of LASER penetrates into the skin by three phenomena of absorption, transmission, and reflection, so these narrow beams spread in large diameter within the tissue, and lead to chemical changes. LLLT has shown the ability to adjust processes in many cells, such as stem cells, endothelial, macrophages, smooth muscle cells, monocytes, fibroblasts, lymphocyte, keratinocytes, and different cell lines (11,12,17,18).

LLLT and Musculoskeletal Disorders

Sport Medicine

Utilization of laser in sports medicine has a long history and plays an essential role in improving wound healing and pain management. LLLT accelerates the process of inflammation, pain reduction and tissue healing. The fundamental benefits are the proliferation of fibroblasts and enhancement of type I and III procollagens synthesis, increasing bone healing and helping with revascularization within wound's site (14,19,20). Also, LLLT decreases muscle atrophy and improves nerve operations. LLLT stimulates secretion of TNF-α and TGF-β in muscle and tendons, speeds up tissue repair and decreases the duration of inflammation (21).

ATP Production

When cells absorb the energy of the photon, this energy transmits into the adenosine triphosphate (ATP). ATP is the shape of energy that is used by all types of cells (including musculoskeletal system) to perform their activities. ATP production is done by the mitochondria. This action occurs with the help of oxygen as a primary cellular fuel, and through the oxidative phosphorylation process. Next, mitochondria react to the monochromatic light, make changes in the biological process, and activate several intracellular signaling pathways. In the skeletal muscles, it affects the amount of energy metabolism in mitochondria. The oxidation -reduction process and increase of electron transfer in the respiratory chain are some advantages of ATP production in muscles (22-24). Additionally, these effects of laser have been verified on various muscle functions such as performance, fatigue, and improved range of motion. The monochromatic properties of the laser affect the chromophores within the mitochondria. This process results in ATP production in various ways. Based on this property, researchers have focused on the positive effect on muscle function (6,8).

ATP production, as a precursor to cell division, leads to the synthesis of enzymes, RNA, and DNA. In the skeletal muscles, it affects the extent of energy metabolism in mitochondria. Also, the ability of oxi-reduction process and increase the electron transfer in the respiratory chain are some advantages of ATP production in muscles (25,26).

Anti-Inflammation

Recent studies have revealed the anti-inflammatory effect of laser on fibroblast stimulation. The laser prevents cyclooxygenase 2 in cells and reduces Prostaglandin E_2 (PGE_2), which are responsible for inflammation. Prostaglandins are one of the most important mediators of inflammation. Their production can be inhibited by Non-Steroidal Anti-Inflammatory (NSAI) drugs and inflammation reduction, subsequently. Prostaglandin E2 absorbs leucocytes and is responsible for increased vascular permeability (27,28).

Pain

The currently available therapy for musculoskeletal pain comprises surgery, relaxation, chiropractic actions, immobilization, medications, physical therapy, behavioral management, and injections. These conventional modalities have many systemic complications, such as heart disease, infection, digestive effects, addiction, neurological defects and surgical complications (6). Up to now, numerous studies have reported the ability of LLLT in chronic pain alleviation in musculoskeletal system (29,30). The typical chronic conditions include osteoarthritis (20), myofascial syndrome (31), rheumatoid arthritis, frozen shoulder (32), neck and back pain (33), joint pain (34,35), epicondylitis, carpal tunnel syndrome (36), tendinopathy, fibromyalgia (37), plantar fasciitis, post-surgery of tibia fracture and chronic regional pain syndrome, relief and recovery by LLLT. Chronic pains have effect on the quality of life and physical disability that relates to work activities (8,38). Some researchers have pointed to its effectiveness and the rest are against it. The exact mechanism of LLLT is equivocal. Radiation of lasers provokes the production of endogenous opioids, serotonin, nitric oxide, and acetylcholine that have a pain relieving effect. Moreover, it increases the threshold of pain (38,39). Another conceptual mechanism about LLLT-induced analgesia shows the direct effect on nerve conduction velocity and potentials to release somatostatin (8,24,32,33). For instance, LLLT is of promising potentials to heal temporomandibular disorders (TMDs), which is the most frequent facial pain, through a non-invasive, non-pharmaceutical, secure, and rapid intervention (40,41).

Wound Healing and Blood Circulation

The reports on satisfactory effect of LLLT on wound healing have increased recently. Researches showed the level of procollagen mRNA (type I and III) increases in wound healing. Different curative factors have been observed in healing lesions and injuries. Acute lesions respond to the treatment better than chronic ulcers. In chronic ulcers, more treatment sessions are required than acute wounds (13,24). Also, it has been discovered that the laser is effective in enhancing the blood circulation of soft tissue structures. Improvement in circulation leads to better healing as a result of controlling hypoxia, ischemia, and edema. Along with laser therapy, arterial dilatation occurs and continues for three days (15,42).

Quantum Treatment Device and LLLT

Quantum is the smallest quantity of energy which cannot be decomposed. The electromagnetic waves have constituted quantum or energy packages (43,44). Today, quantum medicine is utilized in the prevention and treatment of some diseases. Based on quantum theory, the body has a magnetic field with specific frequencies and the condition of these frequencies presents normal states or probable disorders. The body consists of a center-oriented and outlet center electric field. Maintaining a stable state for the body is vital and imbalance may cause abnormalities. In unfavorable condition for tissues, preserving the level of energy storage (Center-oriented electromagnetic field) reduces the electromagnetic energy of the evasion center. In the quantum treatment, a device with a frequency equal to the frequency in specific organs is used. Terra Quant devices are used for the wound healing, pain relief, and regeneration of tissue. In these devices, by using a Low Level Laser, the hypodermic cells will be affected and this results in releasing endorphin, increasing ATP production, pain reductions, and muscular relaxation. For chronic pain, using a laser with more frequencies may be beneficial (45,46).

Evolving Role of Proton Beam Therapy

As usual, the complete resection of musculoskeletal tumors without significant impairment seems to be not possible, and if the surgery is applied alone, tumor recurrence may occur in 85-90% of patients. For these reasons, radiation therapy and chemotherapy applications as adjuvant therapies are required to eliminate the possibility of local recurrence. The type and location of the tumor, accessibility, suitability of surgery and the effectiveness of chemotherapy are the factors that specify usage of radiotherapy as a definitive, preoperative and postoperative treatment (47). From decades, X-ray beam conventional radiotherapy was the best adjutant modality in cancer treatment, but in this technique, both cancer and normal tissues are simultaneously damaged even in different directions. Therefore, attention to the utilization of non-conventional radiation treatment has been increased. At this point, researchers suggest proton beam as a replacement for X-ray treatment procedures. The main benefit of this particle irradiation is the precise deposition of energy in a few penetration depths followed by a steep reduction in a dose named Bragg peak. The substantial clinical benefit of Bragg peak is optimum delivery and conformed distribution of dosage to the desired region in patient body with a drastic fall-off in surrounding normal tissues. These properties result in irradiation of low volume of normal-tissue that makes a significant subsequent reduction in the occurrence of second cancers (48-50). The Bragg peak region in the proton is too narrow (Figure 1), so in the clinical application, multiple superimposing Bragg peaks are used by multiple modulated beams to cover tumor volume in the depth of interest (9,51).

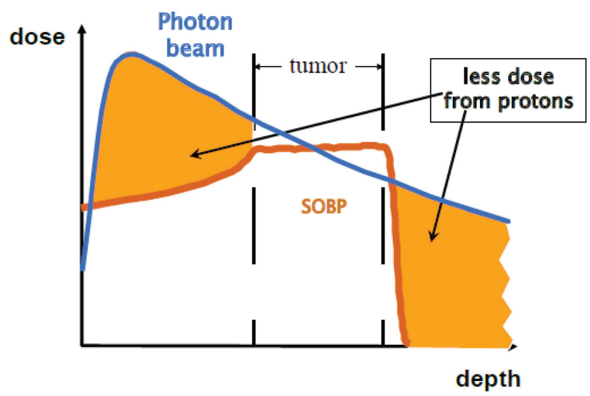

Figure 1. The exhibition of spread out Bragg peak (SOBP) of protons versus photons beam

Proton beam therapy as a kind of radiation therapy is recognized for its substantial advantages in different sarcomatous tumors including head and neck cancers and childhood tumors. The specific physical characteristics of proton result in a uniform dose distribution over the tumor volume versus dose sparing in normal adjacent tissues. These effects make better survival rates and local-regional control while reducing the risk of radiation sequel and secondary malignancies. There are some clinical trials about the treatment of most important sarcomas such as osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, chordoma, and chondrosarcoma (50).

The incidence rate of sarcoma malignancies in pediatrics is 15%, and these cancers are substantially challenged to be handled with radiotherapy due to the probability of late and secondary effects. Lee *et al* in 2005 compared the dose distributions between proton therapy, conformal radiation therapy of photon, electron therapy, and intensity modulated radiation therapy for retinoblastomas, medulloblastomas and pelvic sarcomas in pediatrics. They found that proton radiation therapy is the most optimal treatment that has high dose coverage in tumor volume plus and it preserves normal nearby tissues (2).

Complete resection of spinal and paraspinal tumors is almost impossible; on the other hand, due to the crucial function of nerve roots and spinal cord, the management of this region is significant. The limited effective dose for spinal cord tumors is 45 to 50 Gy. In addition, definite control and treatment of sarcomas require high doses (52). So, researchers used new strategies to employ curative doses. The implemented strategy for spinal and paraspinal sarcoma patients combines high dose proton and photon radiation with biopsy or surgical resection. Delaney *et al* achieved promising results for local control of spinal and paraspinal tumors with high dose photon and proton radiation therapy in most of the patients and observed that the spinal cord is safen (53). Up to now, promising results of proton therapy in local control rates, survival, and minimal toxicity has been approved for sarcoma and pediatric tumors. But, restrictions in prior study designs such as lack of suitable and long follow up, Health-related Quality of Life (HQL) evaluation studies and large cohort, using different proton delivery techniques prevent generalizing the results. Hence, clinical strong evidence of this interesting field is still limited to date (48,51,54).

Boron Neutron Capture Therapy as a Targeted Form of Radiotherapy

Recently, clinical reports on Boron Neutron Capture Therapy (BNCT) have been published by in vivo and ex vivo researches. BNCT is as an innovative binary therapeutic modality that involves radiation treatment of different types of cancers (55). BNCT is a kind of external radiotherapy that includes nuclear capture and fission reactions of $^{10}B(n,\alpha)^{7}Li$ (see equation 1). This reaction happens when injected ^{10}B, a non-radioactive stable particle, is bombarded with low energy thermal neutrons. α particle and recoiling ^{7}Li nuclei as a production of this reaction have high linear energy transfer characteristics (E 150$keV\ \mu m^{-1}$, E 175$keV\ \mu m^{-1}$, respectively) (56). The pathlength of the particles is in the range of 4–10 μm. Therefore, deposition energy is approximately the same order as the single cell diameter. Hence, there is a possibility to select irradiation cancer cells that absorb the proper amount of ^{10}B, versus sparing normal tissues (57). Relative biological effectiveness in BNCT is more than conventional radiation techniques. BNCT has the potential to selectively destroy neoplastic cells with the utilization of p-borono-L-phenylalanine (L-BPA) and sodium borocaptate (BSH) as boron delivery agents (58-60).

$$^{10}B + {}^{1}_{0}n \longrightarrow {}^{11}B \longrightarrow {}^{4}_{2}\alpha + {}^{7}Li + \gamma \qquad (1)$$

Glioblastoma, brain metastases, and soft tissue sarcoma are candidate tumors for BCNT. There have been a few preclinical studies with the focus on BNCT research about soft tissue sarcoma. Clear cell sarcoma (CCS) malignancies are rare. This tumor has been derived from aponeuroses and tendons (61). The only effective treatment for this disease is surgical resection (62). Possibility of metastases (especially to the lung) is more than 50% in these patients, so it requires a new effective treatment method. In a study, researchers surveyed boron neutron as a novel clinical approach using L-BPA delivery agent. They observed the tumor volume in CCS decreased significantly, and it can be the promising curative selection for lung metastases in CCS, as well (63). Also, in another study, BNCT led to the elimination of tumor growth in various rat models, suggesting its potency as a substitute, or supplementary option for the treatment of CCS (64). Moreover, peripheral nerve sheath tumors (MPNST) are uncommon sarcoma with no suitable treatment. In a study using the MPNST animal model, the effectiveness of BNCT for treating this tumor has been clearly shown. Nevertheless, experimental results exclusively confirmed the therapeutic potency of BNCT for the treatment of these patients. Additional clinical studies are necessary for evaluation of the therapeutic effectiveness of BNCT to treat patients with MPNST. It is proposed to select more eligible patients in undergoing MPNST treatment (64,65). In addition, a case study reported treatment of a 54-year-old Japanese female with recurrent osteosarcoma by boron neutron capture therapy. BNCT showed an evident initial therapeutic result without skin damages. This procedure seems to be a very effective and safe modality in controlling radiation-induced osteosarcomas that are not suitable for surgery and other treatment methods (66).

Bone-Seeking Radionuclide Therapy

A frequent site for metastatic malignant tumors such as prostate, lung and breast cancers is skeletal system (67). These advanced cancers are the cause of different diseases, poor quality of life and mortality (68). Previous treatment techniques such as whole-body external beam radiation therapy have many side effects, so it is better to apply specific bone-seeking agents that cure multifocal masses of tumors (69,70). Internal radiation therapy using radionuclides has increased for many years. The significant advantage of this technique is the minimum and maximum radiation to healthy and malignant tissues, respectively (71). The most important beta and alpha-emitters for osseous metastases are in the below table (Table 1). Alpha particle is more destructive than a beta particle and able to induce double-strand breaks even in quiescent and hypoxic cells. Researches showed that osteoblastic metastases compared with osteolytic metastases have a markedly and better response to bone-targeted therapies. Also, multiple treatment sessions showed to be more successful compared with a single injection. There are various studies about these radionuclides and drug conjugates. For example, in 2007, Liepe and Kotzerke carried out a comparative study about potency and toxicity of ^{188}Re-HEDP, ^{153}Sm-EDTMP, and ^{186}Re-HEDP for pain alleviation, bone marrow function and quality of life in 79 patients with bone metastases. They concluded all radiopharmaceuticals were effective in pain reduction, without causing severe side effects or considerable differences in toxicity or curative efficacy (72). Sharma *et al* in a prospective study compared the therapeutic efficacy of ^{177}Lu-EDTMP and ^{153}Sm-EDTMP in 30 metastatic prostate and breast patients. The mean absorbed doses of these radiopharmaceutical agents in other organs were similar. The complete response for each radioactive nuclide was evaluated as 80.0%.

Table 1. Summary of key radionuclides for the treatment of bone metastases

Radionuclides	Type of Emission	Half-Life
Rhenium-186 hydroxyethylidene diphosphonate (^{186}Re-HEDP)	Beta - Gamma	89.3 hour
188-Re-HEDP	Beta - Gamma	16.9 hour
Samarium-153 ethylenediamine tetramethylene phosphonate (^{153}Sm-EDTMP)	Beta - Gamma	46.3 hour
89-Sr-HEDP	Beta	50.5 day
32-Phosphorus (^{32}P)	Beta	14.3 day
177- Lutetium EDTMP (^{177}Lu-EDTMP)	Beta - Gamma	6.73 day
^{177}Lu-BPAMD	Beta - Gamma	6.73 day
223-Radium (^{223}Ra)	Alpha- Gamma	11.4 day
^{177}Lu-PSMA	Beta - Gamma	6.73 day
^{177}Lu-DOTATE	Beta - Gamma	6.73 day

Unexpected reactions and notable trouble in blood parameters were not observed (73).

Role of imaging in bone-targeted therapy is quantitative assessment of lesions, treatment planning, response rate, and patient follow up. These techniques include bone scintigraphy, single photon emission computed tomography (SPECT), positron emission tomography (PET), and recently hybrid modality including PET-computed tomography (CT) and PET-magnetic resonance imaging (MRI). These techniques use a little dose of the radiopharmaceutical for diagnosis application. ^{18}F-fludeoxyglucose (FDG) PET plays a major role in the skeletal metastases detection level compared with bone scintigraphy in a large number of tumors. Prostate-Specific Membrane Antigen (PSMA) PET together with bone scintigraphy can be used as a good guide for selecting eligible patients in bone-seeking radionuclide therapy in osseous metastatic prostate cancer. The extent of bony tumor and prognostication of clinical outcome is measured through fluoride PET and it correlates with overall survival in patients who receive bone-targeted radionuclide therapies. There will be good overall survival and pain reduction when a bone-targeted therapy is combined with hormone therapy (50).

Results and Discussion

As aging occurs, the incidence of MSK disorders and injuries increases. Low level laser irradiation promotes bone repair, production of VEGF by fibroblasts, ATP stimulation, blood circulation, range of motion in musculoskeletal disorders, secretion of TNF-α and TGF-β in muscle and tendons as well as muscle function, tissue repair, and decreases the pain and duration of inflammation through an anti-inflammatory effect. Therapeutic effects of Low Level Laser for neoplasm and malignant tumors have not been determined yet, but there are many studies and discussions about the curative and palliative effect on non- malignant disorders. Nevertheless, despite extensive studies about the effectiveness of photobiostimulation in the musculoskeletal system, its mechanism and the efficiency is not still evident clearly, and there are ambiguous results due to the biochemical mechanism, treatment factors (the wavelength, severity, dosage, the total and interval treatment sessions), and application mode. So, these factors cause neutral and undesirable therapeutic results (8,11,20,74-79). In addition, because of different treatment factors and standardization problems, lack of control group, scales of assessment test and statistical analysis, the comparison of results is not possible (12,80). Researchers must mention the type of laser, power, total output and modulation of it in their studies (24,27,81-83). And more importantly, a significant fact in laser therapy is the use of a well-informed therapist to select optimum treatment factors (such as wavelength, power, beam profile, energy, energy density, number of the treatment sessions, etc.).

New techniques of external beam radiation therapy such as proton therapy and BCNT are novel challenging modalities and they have the potential influence to be more practical in the clinical application of malignancies, especially for the treatment of pediatric sarcomas. These particles have various advantages compared to photon radiation therapy. The entering dose in proton therapy is minimum, the exit dose is nearly nil, and most of the radiation energy is delivered to a certain interested depth. However, according to continuous uncertainties regarding proton beam treatment planning and delivery techniques, the high expenditure in proton therapy, the absence of adequate supporting evidence about the usage of protons over photons in some tumors, and insufficient access to and expertise with proton techniques, result in failure of protons in comparison to current photons radiation procedures. Proton radiation treatment is an expensive procedure, in spite of the fact that the costs may be outweighed by enhancing the quality of life for patients and decreasing the expenditure related to relieving the late adverse effects of radiations. The good physical aspects of protons have been greatly investigated. It must be noted that novel radiotherapy techniques like Pencil Beam Scanning (PBS) and intensity modulation are increasingly arranged in proton therapy. But, more investigations are required to understand the absolute advantage and limitations of protons. Other researches must develop proton technology, focus on clinical trial assays, their biological effects and more clinical applications in more cancers (84).

Clinical and preclinical BNCT studies have shown the potentials but no reliable therapeutic benefit has been investigated. Therefore, more researches should be carried out to better evaluate this recent treatment method. One important purpose is to make boron targeting more efficient in the cancer cell through an enhanced understanding of the radiobiological biodistribution of delivered ^{10}B with clinically prevalent appropriate ^{10}B compounds (85).

The last explained method, internal radiation therapy in nuclear medicine field as a molecular and targeted therapy, has an effective sequel in musculoskeletal tumors. 50% of patients have shown pain relief response in treatment with radionuclides for painful skeletal metastases. Multiple ß-emitters and one α-emitter (^{223}Ra) currently exist for the treatment of metastatic osseous pain. All showed high therapeutic effects and low bone marrow toxicity. There are important studies that confirmed overall survival benefit for patients who treated with the α-emitter. Other radiopharmaceuticals including b-emitters mentioned in this review (Table 1) have not still been tested with large numbers of patients as well as prospective multicenter trials (86-87).

Conclusion

Our study showed positive efficacy of LLLT in musculoskeletal disorders and also the curative role of boron neutron capture therapy, proton beam treatment and bone-seeking radionuclides in bone and soft tissue malignancies. Other researches in the field of boron capture neutron therapy, proton therapy, and bone-seeking radiopharmacy must focus on curative effect of them as a definitive treatment with no complication alone or in combination with other modalities such as chemotherapy or hormone therapy.

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