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Analysis Of The Effects Of Laser Therapy As A Therapy Modality In Melanoma

Review Article

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Abstract

Background: Malignant melanoma is a skin malignancy originating from melanocyte cells that are responsible for skin color. Treatment options for melanoma are wide excision surgery with tumor-free margin, systemic therapy with chemotherapeutic agents, and radiotherapy. The development of laser therapy for cosmetic and medical procedures related to skin malignancies has increased significantly over the last decade. The use of laser therapy for pigmented lesions is still controversial because can delay the diagnosis of melanoma and increase the risk of death.
Methods: A non-systematic literature review was conducted to answer the following three research questions: 1) The Usage of Laser Therapy in Melanoma, 2) The Effects of Using Laser Therapy on Malignant Melanoma. Literature was searched from the PubMed, Google Scholar,and Science Direct databases and then analyzed qualitatively.
Results: The use of laser therapy in the treatment of pigmented lesions without a definitive diagnosis by histopathological examination is controversial. It can delay the diagnosis of melanoma, recurrence of melanoma lesions, and can cause mortality
Discussion: Definitive conclusions about whether laser therapy for pigmented lesions without a definitive diagnosis of pre-existing melanoma or melanoma is still unknown.
Conclusion: Laser therapy can be given in specific melanoma cases, with laser subtypes, specific wavelengths, and after confirming the diagnosis by histopathological examination. Conventional therapy using surgical excision with free margins is currently preferred over laser therapy.

Background

Malignant melanoma is a skin malignancy originating from melanocyte cells that are responsible for skin color.[1, 2] Treatment options for melanoma are wide excision surgery with tumor-free margin, systemic therapy with chemotherapeutic agents, and radiotherapy.[2, 3] These therapeutic modalities can have a high cure rate, but morbidities include the risk of bleeding, infection, functional disability, and scarring.[1, 3] Other factors including effectiveness, simplicity of treatment, cost, and aesthetic outcome are also important considerations to ensure patient satisfaction.[4, 5]

The development of laser therapy for cosmetic and medical procedures related to skin malignancies has increased significantly over the last decade. With a careful selection of parameters, lasers can be used to target tumor components and can provide alternative treatment options that minimize morbidity.[5, 6] Laser therapy has now become a routine procedure not only in dermatological practice but also performed by cosmetologists and aesthetic institutes for pigmented lesions.[7] The use of laser therapy for pigmented lesions is still controversial because can delay the diagnosis of melanoma and increase the risk of death.[8] The purpose of this article is to review the role of laser therapy in the treatment of melanoma.

Malignant Melanoma

Melanoma is the third most common and aggressive skin malignancy after basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The incidence of melanoma is 5% of skin cancer and 65% of skin cancer-related deaths. In 2014 in America, there were 76,100 cases, and 9,710 people died that year due to melanoma. In the Caucasian race, the incidence of malignant melanoma has increased by 3-6% over the last few decades making

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melanoma one of the fastest-growing cancers worldwide.[1]

The main risk factors for melanoma include heredity, genetics, and environmental exposures. Light skin color, white race, family history of skin cancer or melanoma, female, age 40 years, exposure to ultraviolet light (especially UV-B), and exposure to tanning beds are important risk factors for the development of melanoma. Exposure to high intensity and intermittent UV light is one of the risk factors that play an important but modifiable role in the development of melanoma.[1, 2] UV exposure can cause mutagenic effects and tumorigenesis through DNA damage that causes excessive melanocyte cell proliferation.[1-3]

Melanoma is clinically characterized by brown or black-pigmented lesions. The most likely sign of melanoma is a new pigmented lesion that is found on the skin and has changed in size, shape, or color. Another important sign is that the lesion looks different compared to other skin lesions, called "The Ugly Duckling Sign". Melanoma-specific symptoms and signs that are widely known as ABCDE: 1) A for asymmetry, i.e. the shape of the tumor is not symmetrical; 2) B for border irregularity, an irregular border; 3) C for color variation, i.e. from colorless to deep black in one lesion; 4) D for diameter, i.e. the tumor is usually more than 6 mm in diameter; 5) E for evolution, namely changes in lesions that can be noticed by the patient or family. Several other signs, such as 1) The wound does not heal, 2) Pigmentation that extends from the border of the lesion to the surrounding skin, 3) Redness or swelling around the border of the lesion, 4) Changes in sensation such as itching and/or stinging; 5) Changes in the surface of the mole such as becoming scaly, bleeding, or looking like a lump.[1]

In clinical practice, without using dermoscopy and histopathological examination with biopsy, the diagnosis is often delayed and confused with other pigmented lesions.[7, 8] Melanoma often mimics the melanocytic and non-melanocytic benign lesions such as nevus, lentigo, dysplastic melanocytic nevus, melanoma, seborrheic keratosis, pigmented BCC, and pigmented actinic keratoses.3,9 Misdiagnosis of melanoma with other benign pigmented lesions can lead to an inappropriate choice of therapy. The therapeutic modality currently widely used in clinical practice for pigmented lesions and melanoma is laser therapy.[7-9]

Usage of Laser Therapy in Melanoma

Different types of lasers can be used to treat pigmented lesions. Melanin absorbs a wide range of light at wavelengths around 1,000 nm.[7] The literature indicates that laser therapy options for skin cancer are generally divided into four main categories based on the type of laser medium: solid-state lasers, diode lasers, dye lasers, and gas lasers. Solid-state lasers use a solid-state amplification medium such as crystal or glass with transition metal ions. Diode lasers use p-n junctions of semiconductor diodes to form an active medium. The diode laser is one of the most common types of lasers used today. Dye lasers use organic dyes as reinforcing media. This type of laser allows for a wider wavelength range compared to solid-state or gas lasers. Gas lasers use an electric current released through the gas to produce coherent light. The gas laser is the first continuous-wave laser.[4]

Mirza and Khantri in 2017 conducted a literature review on melanoma therapy using solid-state lasers in two studies, diode lasers in one study, gas lasers in three studies, but no studies using dye lasers. Two solid-state laser studies were performed in vitro and ex vivo on melanoma lesions. In vivo studies were carried out using a laser with a sub-lethal wavelength of Alexandrite 755 nm in three human melanoma cell lineages. An ex vivo study was performed using a 694 nm Q-switched ruby laser (QSRL) to treat forty-two tissue biopsies from five common classifications of melanocytic lesions – cell nevi, pigmented dermal nevi, congenital nevi, lentigo malignant lesions, and superficial melanoma. Histopathological examination revealed photothermolysis of deep and superficial pigmented cells; single QSRL exposure to lightly pigmented lesions localized in and around the basal cell layer was sufficient for ablation, whereas ablation did not occur in more heavily pigmented lesions extending into the dermis persisting. They concluded that, due to the erratic nature of melanocyte malignancy, such as repigmentation and malignant transformation, as well as the need for multiple laser applications, melanocytic skin lesions should not be treated with QSRL.[4]

Therapy with a near-infrared diode laser produces light with a wavelength of 805 nm which is mainly absorbed by the locally injected indocyanine dye to generate heat and destroy the melanoma tissue. One patient treated with this laser showed recurrence and metastasis more frequently, occurring approximately one-sixth more frequently compared to more than 20 surgical excisions. In this study, all types of laser therapy still did not provide good therapeutic results in melanoma patients and still require a combination with systemic therapy using immunomodulatory agents.[4,10]

A study with a gas laser with CO_2 showed a 100% clearance rate in the treatment of malignant lentigo lesions with a lower recurrence rate than radiation therapy. Studies have also found a lower recurrence rate with laser therapy than with surgery, and a shorter disease-free interval after laser surgery compared with surgery for stage I malignant melanoma.[4] Austin et al.suggested that laser and light-based therapies (LLBT) is a safe, effective, and cost-effective palliative care option for patients with melanoma. The laser therapy uses a non-fractionated carbon dioxide (CO_2) gas laser with a wavelength of 10,600 nm to erode melanoma tissue through evaporation of water. In studies using non-fractionated CO_2 lasers, minimal morbidity and high patient satisfaction have been reported, however, these results vary depending on the laser and the parameters used. Many patients report no incident recurrence within more than one year however, there is minimal information to determine overall mortality. In patients with metastatic melanoma who were treated with fractionated CO_2 with a wavelength of 10,600 nm, three patients showed recurrence of melanoma at 2 to 9 years of follow-up and all patients were satisfied with the treatment. Lasers with fractionated CO_2 still left melanoma lesions in the laser-intervened tissue areas, compared to non-fractionated CO_2, Lasers with fractionated CO_2 are more effective in combination with systemic therapy using immunomodulatory agents. Laser therapy using a pulsed dye laser using a wavelength of 585 or 595 nm is used to treat vascular lesions.[10]

Pulsed dye laser provides some palliative improvement in combination with chemotherapy and immunotherapy, but cannot be highly recommended because of the low complete response rate in metastatic melanoma.

The Effects of Using Laser Therapy on Malignant Melanoma

Although some laser therapy interventions have shown promising results based on the level of patient satisfaction compared to conventional therapy, especially systemic therapy, there is no clear and recommended type of laser in melanoma lesions.[4, 10] The use of laser therapy in melanoma is not dependent on the type of laser but rather on the length of the laserwave used. Dye lasers have shorter wavelengths (500-700 nm) and gas has very long wavelengths (>10,000 nm). Shorter wavelength, more absorbed by pigmented lesions due to absorption of the red light spectrum which gives DNA level damage and selective photothermolysis of malignant lesions. Longer wavelengths function through the presence of a more generalized increase in temperature to be able to directly damage cells and activate anti-tumor immune responses, and non-selective photothermolysis. Solid-state and diode lasers show a wider spectrum, so the choice of laser type should be considered based on the case of malignant melanoma in the patient.[4]

In melanoma lesions, the literature recommends the use of diode and gas lasers over solid-state lasers, and dye laser therapy is strongly discouraged.[4, 10] In diode lasers, excellent treatment results are limited because not all patients experience a complete improvement, but the use of this laser is more tolerable than chemotherapy. In gas lasers, the use of non-fractionated CO_2 is better because of the higher level of lesion eradication and longer healing time than diode lasers. Solid-state lasers are contraindicated because of their ineffectiveness and triggering unfavorable biochemical processes. There is no evidence of the efficacy of using dye laser dyes in the literature. In all laser treatments, the recurrence rate varies depending on the choice of laser subtype, stage of melanoma and metastases, and follow-up after laser therapy.[4, 10]

In an in vitro study, it was stated that laser therapy with low wavelengths can cause an increase in cell proliferation and laser therapy may aggravate the lesions.[6, 8, 11] A systematic review also showed an increase in the melanoma cell line A2058 increased within three days after laser therapy with a wavelength of 632.8 nm.[12] Andreeva et al. showed that low-intensity laser radiation at a wavelength of 835 nm can stimulate the proliferation of melanoma cell lines Mel IL and MeWo due to the role of cytochrome c oxidase in the multisubunit mitochondrial complex and initiation of cellular signaling. Laser radiation was found to induce phosphorylation of the receptor protein tyrosine kinase (TPKR; c-Met, hepatocyte growth factor receptor), which has previously been shown to activate the MAPK/ERK pathway and promote cell proliferation. Laser radiation can also promote endothelial cell proliferation, migration, nitric oxide secretion, and promote angiogenesis. In this process, low-power laser radiation will activate the PI3K/Akt pathway which then increases the expression of endothelial protein nitric oxide synthase (eNOS) in endothelial cells. Laser radiation also induced an immediate increase in mitochondrial membrane potential, ATP, and cAMP of melanoma cell line A2058 via increased cytochrome c oxidase activity. Laser radiation further increases the phosphorylation of Jun N-terminal kinase (JNK) resulting in the activation of transcription factor-1 (AP-1) activation protein. These findings suggest that the cytochrome c oxidase/mitochondrial membrane potential/ATP/cAMP/JNK/AP-1 signaling pathway is involved in the regulation of laser irradiation-induced melanoma cell proliferation. Low-power laser radiation can also induce the production of reactive oxygen species (ROS), which serve as major secondary messengers regulating the activity of various protein kinases. Non-receptor tyrosine kinases, in particular Src kinases, are targets of ROS and can be activated by oxidative events. Src kinases play important roles in regulating fundamental cellular processes, including cell proliferation, attachment, migration, and survival.[11, 12]

In addition, the use of laser therapy in the treatment of pigmented lesions without a definitive diagnosis by histopathological examination is controversial. It can delay the diagnosis of melanoma, recurrence of melanoma lesions, and can cause mortality. [6-8] True melanoma may be missed because of early detection error as benign tumors based solely on macroscopic presentation. [7] The systematic review of Zipster et al. demonstrated that laser treatment was performed without initial histologic examination, leading to a clinical misdiagnosis with 200 pigmented lesions without histologic examination that was considered to be melanocytic nevus turning out to be malignant melanomas.

Laser therapy of benign pigmented lesions based on histology can also induce melanoma in many cases. There are several possible explanations for the development of melanoma in patients with benign pigmented lesions based on the histopathological diagnosis, including the possibility of induction of melanoma by laser therapy. Laser therapy of an inappropriate wavelength may not be sufficient to destroy the lesion and promote the growth of a melanoma lesion. Areas of lesion tissue selected for biopsy may fail to reveal foci of invasive melanoma within the lesion.[8]

Laser therapy can lead to the elimination of clinically undetectable pigmented lesions. In particular, the deeper dermal or intrafollicular components of proliferative melanoma can be missed and thus have the potential for recurrence, especially in ablative laser therapy using a CO_2 laser. Histologically evaluating the recurrence of recurrent melanoma lesions can be very challenging and increase the risk of misdiagnosis.[7, 8]

Definitive conclusions about whether laser therapy for pigmented lesions without a definitive diagnosis of preexisting melanoma or melanoma is still unknown. Whether laser therapy cannot eliminate melanoma lesions is also still unknown.[6] Laser therapy is possible to treat skin cancer lesions but is very limited because it has not there are no methods that determine with certainty whether a melanoma lesion has completely disappeared compared to treatment of melanoma using excision.[8] The lack of evidence and the difficulty in obtaining more relevant in vivo data suggest that laser treatment of melanoma should be avoided and more conventional treatment methods preferred.[6]

Conclusion

Laser therapy for melanoma still gives mixed results. Laser therapy can be given in specific melanoma cases, with laser subtypes, specific wavelengths, and after confirming the diagnosis by histopathological examination. Conventional therapy using surgical excision with free margins is currently preferred over laser therapy.

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