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An Analysis of Laser Therapy for the Treatment of Nonmelanoma Skin Cancer

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Abstract

BACKGROUND—Skin cancer remains the most prevalent type of cancer in the United States, and its burden on the health care system remains substantial. Standard treatments such as cryosurgery, electrodessication and curettage, topical and photodynamic therapies, and surgical excision including Mohs micrographic surgery are not without inherent morbidity, including risk of bleeding, infection, and scar.

OBJECTIVE—Lasers may be an alternative for treatment of nonmelanoma skin cancer, and this paper reviews this therapeutic option.

METHODS—A comprehensive search in the Cochrane Library, MEDLINE, and PUBMED databases was performed to identify relevant literature investigating the role of laser therapy in the treatment of nonmelanoma skin cancer.

RESULTS—New literature regarding laser treatment of nonmelanoma skin cancer is emerging, demonstrating promising clinical outcomes. The greatest efficacy has been seen with vascular-selective and ablative lasers in the treatment of basal cell carcinomas. Some success has been reported for laser treatment of squamous cell carcinoma, but data are less convincing. In summary, laser therapy offers an alternative treatment option for nonmelanoma skin cancer; however, its clinical efficacy is variable and, at this time, remains less than currently accepted standards of care.

CONCLUSION—Further studies are needed to optimize parameters, determine maximum efficacy, and provide long-term follow-up.

Skin cancer remains the most common type of cancer in the United States.[1] Nonmelanoma skin cancers continue to be the most prevalent skin cancers diagnosed today, with nearly 3.5 million cases diagnosed in the United States annually.[1] Basal cell carcinomas (BCCs) account for approximately 75% to 80% of these cancers, and squamous cell carcinomas (SCCs) are second at approximately 25%.[1–4] Moreover, the numbers are increasing: The incidence of women diagnosed with a BCC under age 40 has more than doubled in the last 40 years, and the incidence of SCC diagnosed in both men and women under the age of 40

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has more than tripled.[1,2,4–8] Currently, the standard management of BCCs and SCCs includes cryosurgery, curettage (with or without electrodessication), topical immunomodulator therapies, and standard surgical excision including Mohs micrographic surgery. Whereas these primary treatment modalities have variable cure rates (reaching upwards of 99% with Mohs micrographic surgery), there is associated morbidity including risk of bleeding, infection, functional defects, and scarring. Further, recovery time and cost can be an issue for some patients.

Since the advent of the first lasers, their utility in medicine has been expanded significantly.[9,10] What initially precipitated from the need for a better treatment of port wine stains led to the development of "selective photothermolysis."[11,12] Selective photothermolysis was based on the concept that light passes through space until it is absorbed by a structure which contains light-absorbing molecules that coincide with the delivered wavelength. The delivery of short bursts of intense light at wavelengths preferentially absorbed by these "target" structures can cause selective thermal damage.[11,12] Confinement of thermal damage within the target lesion is achieved if a laser wavelength with selective absorption and sufficient (but not overwhelming) energy is delivered with pulse duration shorter than the time it takes for the target to lose 50% of its thermal energy as heat.[11,13] With careful selection of parameters, lasers can be used to target tumor components (hemoglobin in vasculature or tissue water) and can provide an alternative treatment option that minimizes the morbidity associated with current therapies used to treat nonmelanoma skin cancer. In this paper, the authors review the role of laser therapy in the treatment of nonmelanoma skin cancer.

Laser Therapy for the Treatment of Basal Cell Carcinomas

The clinical presentation of BCCs depends on subtype; however, the presence of telangiectatic vessels is a classic clinical feature. These microscopic feeding vessels are an integral part of the tumor's architecture and are both ectatic and fragile, making them an ideal target for selective damage.[13–17] It has been hypothesized that lasers can be used to selectively target the tumor's vascular supply. A potential advantage of this photothermal vascular targeting over conventional excisional treatments is greater preservation of normal tissue surrounding the tumor. This approach may be an effective alternative to minimizing morbidity. It is important to note that the targeting of hemoglobin in neoangiogenic tumor vessels has been proposed only as a hypothesized mechanism. Additionally, in the real-world setting, high energies are often used in combination with multiple passes and in some cases, without epidermal cooling, which could result in significant nonselective thermal injury.

Vascular Lasers for Treatment of Basal Cell Carcinoma

Several studies have demonstrated the efficacy of vascular targeting lasers in the treatment of BCCs.[13,18–21] A pilot study investigated the role of pulsed dye laser (PDL) alone in the treatment of BCCs. Twelve patients with 21 biopsy-proven BCCs were treated with 4 sessions of 595 nm PDL at 2-week intervals.[18] A single pass with 10% overlap was performed with a 7 mm spot, 3 milliseconds pulse duration, energy density of 15 J/cm^2, and no cooling. Response rates were determined by histological clearance; after a minimum of 2

weeks after the final laser treatment, the BCC site with a 4-mm margin was surgically excised as a disk excision and analyzed histopathologically. Response rates were dependent on tumor size, with nearly 92% of BCCs <1.5 cm in diameter demonstrating complete response to PDL treatment, whereas only 25% of BCC >1.5 cm in diameter demonstrating complete response.[18] Tumor histologic types among the complete responders included superficial, nodular, micronodular, and "keratinizing."[18] However, in the larger incomplete responders, there was an estimated 71% to 99% reduction in tumor size after PDL.[18] Additionally, it was found that subtype was an important factor in determining outcomes, with complete response occurring more frequently in superficial BCCs as compared to all other subtypes (77% vs 50%, respectively).[18] The most notable clinical side effect was purpura followed by a gray discoloration of the skin (in some subjects) with subsequent formation of hemorrhagic scale crust. At 2 weeks after treatment, all patients demonstrated complete healing clinically.[18]

Another study looked at longer-term follow-up of PDL therapy for treatment of BCCs.[19] The study involved 14 patients with 20 biopsy-proven BCCs who were treated with 4 consecutive treatments of 595 nm PDL at 3- to 4-week intervals. Treatment was performed with 1 pass with 10% overlap using a 7 mm spot, 3 milliseconds pulse duration, 15 J/cm^2, and cryogen spraying cooling (Dynamic Cooling Device, 30 milliseconds/20 milliseconds).[19] Complete clinical response was seen in 95% of patients at the first follow-up visit (3–7 months after last PDL treatment) regardless of tumor size (ranging from 8 to 17 mm), or histologic subtype.[19] After a median follow-up of 18 months (range 12–21 months), 94.7% of the treated BCCs with complete initial response demonstrated no evidence of recurrence or residual tumor.[19] Treatment effect was preserved beyond the 18-month follow-up as well, with nearly 90% remaining tumor free up to 21 months after treatment.[19] The results were irrespective of subtype treated.[19] Regarding side effects, of the 20 BCCs treated, 15 displayed some degree of hypopigmentation. Some of this hypopigmentation may have resulted from the clearance of dermatoheliosis in these heavily sun-exposed areas. Other than hypopigmentation, no other side effect such as scarring, erythema, or textural change was noted. Excellent cosmesis (graded by patient self-evaluation) was achieved in 90% of treated sites.[19]

Another similar study investigated the role of PDL in the treatment of BCCs located on the face.[20] Twenty-nine patients with 39 total biopsy-proven BCCs underwent 1 to 4 (average 3) treatments with 595 nm PDL at 2- to 4-week intervals. Treatment was performed with 1 pass with 25% overlap using a 7 mm spot, 3 milliseconds, 15 J/cm^2, no cooling, and included a 3 to 5 mm margin around the tumor.[20] Local anesthesia was offered if the patients complained of significant pain. Complete clinical resolution was seen in 75% of treated facial BCCs at a mean follow-up time of 11 months.[20] Of note, 16% of tumors recurred, and 9% demonstrated incomplete resolution after 4 treatments.[20] Nodular, infiltrative, or mixed types of tumors were more likely to recur or did not respond to treatment.[20] Reported side effects after procedure included erythema, mild edema, and dusky purpura, which subsided in 1 week.[20] Scarring was not seen in any patients and all were pleased with the cosmetic results.[20]

Although the studies mentioned above demonstrate promise, it is important to recognize that the settings used may go beyond the threshold for theorized vascular selectivity, especially when high fluences are used without epidermal cooling. However, these treatments may still provide a cosmetic advantage over other destructive modalities such as electrodessication and curettage. Furthermore, the duration of follow-up in the aforementioned studies may not capture all recurrence.[4,5,22] A follow-up period of 5 or more years, which has been used for some surgical trials, may provide a more complete picture of the potential for recurrence.[4,5,22,23]

Another important factor determining the efficacy of vascular lasers in the treatment of BCCs is the wave-length of the laser used. A few studies questioned the effectiveness of treating BCCs with vascular-selective lasers, citing incomplete responses and high recurrence rates in tumors treated with 585 nm pulsed dye lasers.[24,25] In 1 study, 7 patients with 7 total BCCs were treated with a 585 nm laser using a 5 mm spot size, 0.45 milliseconds pulse duration, 6.0 J/cm^2 energy density, and no mention of cooling.[24] The study reported a cure rate of only 14.3% (1/7) and a recurrence rate of 85.7% (6/7).[24] Based on these findings, the authors concluded that PDL treatment was not a realistic alternative to other current treatments for BCCs which yield much higher cure rates.[24] However, the settings used (lower energy and small spot size) likely contributed to the poor clinical results. In another similar study, 7 subjects with 9 biopsy-proven BCCs were treated with a 585 nm PDL using a 7 mm spot size, 0.45 milliseconds pulse, and 9.0 J/cm^2. A 4-mm margin of normal skin was treated as well.[25] The study reported a cure rate of 55.6% (5/9) and a recurrence rate of 44.4% (4/9).[25] Based on these results, the authors concluded that a persistence rate of 44.4% was unacceptably high and did not match the clearance rate that can be attained with current standard BCC treatment modalities.[25]

There are several important distinctions to be made between the studies investigating the utility of the 585 nm versus the 595 nm. In general, greater efficacy was observed when the 595 nm laser was used to treat small, superficial BCC tumors as compared to 585 nm lasers, with most incomplete responders being larger tumors. This is likely because the maximum coagulation depth of a 595 nm laser is deeper than that of 585 nm, at approximately 1.5 to 2 mm total depth of light penetration.[26,27] Therefore, it can be expected that a 595 nm wavelength would more adequately treat tumors in the upper 1 to 1.5 mm of skin. Furthermore, studies described above that demonstrated improved clearance rates with a 595 nm laser successfully used a higher fluence and longer pulse duration than the 585 nm laser studies.

As noted above, 1 issue with PDL treatment is the relatively shallow depth of light penetration.[26,27] Other vascular targeting wavelengths with greater depths of penetration can also induce BCC tumor regression. Lasers such as the long-pulsed 1,064 nm neodymium-doped yttrium aluminum garnet (Nd: YAG) and 755 nm Alexandrite lasers penetrate 50% to 75% deeper into the skin than the PDL.[13,26,28–30] Additionally, the conversion of oxyhemoglobin to methemoglobin after irradiation with PDL creates a second target chromophore for the Nd:YAG laser if PDL is used first followed by Nd:YAG. However, these lasers have a much lower absorption coefficient in blood than in PDL, requiring higher fluences and increasing the risk of adverse effects.[26]

A recent prospective, nonrandomized, open-label clinical trial looked at 10 subjects with 13 biopsy-proven nonfacial BCCs <1.5 cm and treated them with a single pass of 1,064 nm Nd:YAG laser using a 5 mm spot size, 10 milliseconds pulse duration, 80 to 120 J/cm^2 without cooling.[30] Standard excision was performed 1 month after laser treatment to confirm histologic clearance. The study demonstrated complete histologic clearance after 1 treatment in 92% of the BCC tumors, and at higher fluences, the study was able to demonstrate 100% histologic clearance after 1 treatment.[30] No significant adverse events were noted, including scarring.

Another study investigated the role of combination of 585 nm PDL and 1064 nm Nd:YAG laser in treatment of nonfacial BCCs.[13] Ten subjects with 13 biopsy-proven BCCs received four combined PDL and Nd: YAG treatments at 2- to 4-week intervals: The tumor and 4 mm of peripheral skin were treated with the following laser parameters: 585 nm PDL with a 7 mm spot, 2 milliseconds pulse duration, 8 J/cm^2 fluence followed by a 250 milliseconds delay and a pulse of 1,064 nm Nd:YAG laser at 15 milliseconds and 40 J/cm^2 (spot size not provided).[13] A single pass was performed with 10% overlap, and forced chilled air was used for parallel cooling. Standard excision was performed 2 to 4 weeks after the final treatment to confirm histologic clearance.[13] The study found that 58% of all tumors showed a complete clinical and histological response to the 4 combined laser treatments. However, when stratified by size, 75% of all tumors <1 cm in diameter showed complete response.[13] Interestingly, all subjects that had residual tumors on post-treatment evaluation were on some type of anticoagulation; it was theorized that this inhibited laser-mediated intravascular coagulation, and thus caused incomplete resolution of the BCC tumor.[13] This is important to note as many patients are on some form of anticoagulation. Blinded investigator evaluations of side effects revealed gradual decrease in erythema and purpura throughout the series of laser treatments. A subset of subjects developed transient hyperpigmentation, most notable at the completion of the series of laser treatments.[13]

In conclusion, vascular targeting lasers, particularly of the 595 nm wavelength, demonstrate promising clinical efficacy in their use for the treatment of BCCs. Greater success has been seen in the treatment of smaller and more superficial BCCs, as well as those located on the trunk or extremities as opposed to the face. As mentioned earlier, the fluence and pulse duration used to achieve adequate tumor control may exceed the energies that allow for “selective photothermolysis.” Thus, whereas the aforementioned studies demonstrated that vascular targeting lasers can be used for tumor control with good cosmetic outcomes, further work needs to be done, with long-term follow-up to assess complete recurrence rates, as compared with current surgical trial data. If vascular targeting lasers are to become a reasonable and commonly used alternative for the treatment of BCCs, clinical data should demonstrate consistent long-term cure rates that are at least as good as other currently accepted destructive modalities; or, alternatively, these lasers should be reserved for use in select patients where other current modalities cannot be used or are not likely to provide acceptable outcomes. Further randomized, controlled comparison trials are needed to evaluate laser therapy in the treatment of BCCs.

Ablative Lasers

Ablative lasers, consisting primarily of carbon dioxide (CO_2) and erbium yttrium aluminum garnet (Er:YAG) lasers, have wavelengths that lie within the infrared range (10,600 and 2,940 nm, respectively).[31] These lasers work by ablating tissue through the vaporization of tissue water. Their precision lies in the minimization of "spillover" damage of tissue not in the treatment area. Delivery of high fluences with a short pulse duration allows for more precise control of tissue vaporization with minimal nonspecific thermal damage to the surrounding tissue. The original ablative lasers were developed using a continuous wave (CW) mechanism of action. These lasers provided a continuous beam of light that had minimal variability in power output over time (a stable average beam power). Complications included nonselective thermal injury as heat spread from the periphery, causing unintended collateral damage. As ablative lasers improved, the development of quasi-continuous mode (QSM) and pulsed lasers emerged, largely replacing CW models. The QSM models are, in essence, CW lasers that are mechanically shuttered to deliver pulses.

For CO_2 lasers, depth of tissue ablation per pass is superficial, in the 20 mm range.[31–35] At distances where adequate fluence is reached for the heat vaporization of water, tissue is precisely ablated. As heat radiates out and fluence decreases, tissue is no longer vaporized, but is instead coagulated, which provides associated hemostasis and collagen synthesis stimulation.[31,32] For Er: YAG lasers, depth of tissue ablation per pass is less, at approximately 2 mm in depth for a single pulse, although multiple pulses can be delivered.[36] The water affinity of the Er:YAG laser is roughly 15 times greater than that of the CO_2 laser, [31] which allows for greater tissue vaporization, but minimal coagulation. Hemostasis, and to a lesser extent collagen stimulation, may be significantly reduced with Er:YAG as compared to CO_2 lasers.[31]

A prospective investigational trial studied the clinical efficacy of CO_2 laser treatment of BCCs, demonstrating excellent clinical response with a reported 100% cure rate and 0% recurrence after 3 years of follow-up.[37] In the study, 140 patients with single or multiple superficial or nodular BCCs <1.5 cm in diameter were treated with a super-pulsed CO_2 laser at 1 to 3 mm spot size, 2 to 3 milliseconds pulse duration, and 10 Hz frequency.[37] Intraoperative cytology or histopathology was used to assess efficacy of treatment, akin to Mohs micrographic technique. In total, an average of three scrape biopsies were taken for intraoperative cytological examination for each patient: 1 immediately before laser vaporization, 1 after the first pass, and 1 after the second pass once "deep dermis" was reached. All subjects were cytologically "clear" by the final sample.[37] The authors reported an average healing time of 7 to 10 days, with "good aesthetic outcomes" in all, though no further elaboration on cosmetic results were provided. At 3 years follow-up, the authors reported no evidence of recurrence by clinical examination; however, cure was not documented by histologic confirmation at the final follow-up.[37]

In another similar study, 74 patients with 113 biopsy-confirmed BCCs were treated with curettage and super-pulsed CO_2 laser.[38] Tumors were initially debulked by curettage, followed by 2 to 4 passes of super-pulsed CO_2 laser treatment at 600 to 800 μs pulse duration and 8 to 12 watts. The study demonstrated a 93.7% cure rate after 1 session of treatment, with "good to excellent" cosmetic outcomes achieved in 85.8% of treated cases.[38]

The authors reported that given the tissue alteration induced at the treatment site, postoperative histopathological evaluation was not accurate. However, a biopsy was performed during the follow-up period in the presence of any clinical suspicion of recurrence.[38] The study demonstrated that 85.8% of lesions had an excellent cosmetic outcome, 12.4% displayed moderate-to-good cosmetic outcome, and 1.6% displayed a poor cosmetic outcome.[38] Of the BCCs treated, 67 were nodular sub-type, and 40 were located in the nasal area. Only 1 patient with a significant scar in the nasal area needed further treatment and underwent surgical repair.[38] Importantly however, this study did not demonstrate any significant advantage in tumor control rates compared with studies using simple curettage alone (93.7% vs 96.03%, respectively).[23,38] However, in cosmetically sensitive areas such as the central face, eyelids, and vermilion lip, curettage may result in unacceptable outcomes such as wide, atrophic or hypertrophic scarring, dyspigmentation, and potential distortion of normal anatomic contours.[23,38]

A follow-up study evaluated treatment of difficult-to-manage periorbital BCCs. Twenty patients with a total of 21 biopsies confirmed that lesions were treated with debulking by curettage followed by 4 passes of super-pulsed CO_2 laser using a 600 to 800 μs pulse duration at 12 watts.[39] After the initial 4 passes of the ablative laser, a histopathological sample was obtained by curettage. In the presence of residual disease, retreatment was performed by CO_2 laser. This cycle was performed until no malignant cells were seen.[39] Of the 21 lesions, 15 were nodular, and 12 were found on the lower lid. A cure rate of 95.2% and a recurrence rate of 4.8% (1 lesion) were observed.[39] Other than mild disruption to the eyelash in 2 patients, the authors reported excellent cosmetic outcomes.[39] This study concluded that CO_2 lasers could be an alternative tool for treating difficult-to-manage periorbital BCCs while maintaining excellent oncological and cosmetic results.

As discussed earlier, depth of treatment is an important factor affecting efficacy of treatment. One study investigated the role of ablation depth in the efficacy of CO_2 lasers for the treatment of BCCs. In this study, 35 patients with 51 biopsy-confirmed BCCs ranging from 4 to 35 mm were ablated with a CO_2 laser using a microprocessor optomechanical flash scanner.[40] The methods of this study were unique as compared with others, and focused primarily on determining the ability of the CO_2 laser to completely ablate BCCs. A preoperative 2 mm punch biopsy was taken for histological confirmation, and then the tumor site was treated with a CO_2 laser with the Swiftlase scanner (Swiftlase by Sharplan, Germany) at a power of 10 watts (additional settings were not provided). Tumor subtypes consisted of 21 superficial, 28 nodular, and 2 infiltrative. The authors assessed tumor eradication using visual assessment during laser ablation. After adequate ablation as assessed by clinical appearance of the ablated tumor, the ablated tissue and the surrounding rim were excised, and the defect was reconstructed as a normal excisional biopsy.[40] The excised ablated specimen was then sent for histological assessment of residual tumor. The study demonstrated an overall cure rate of 67%, with superficial tumors demonstrating the highest cure rate of 86% and nodular tumors demonstrating complete removal in only 50%.[40] Increasing the ablation depth from upper, middle, lower dermis, and subcutaneous tissue resulted in clear margins of 40%, 66%, 93%, and 92%, respectively.[40] The study concluded that tumor depth, which could be inferred by BCC subtype, was very important in

determining appropriateness of laser treatment and anticipating clinical efficacy after therapy.[40] There was no discussion of cosmetic outcomes in this study.

Clinical data investigating the role of Er:YAG laser in the treatment of BCCs are limited. The authors found only 1 study that researched the role of Er:YAG laser involvement in treatment of BCCs. In this study, 286 patients with an average of 4.2 BCCs each underwent 1 of 3 treatment modalities for recurrent nodular BCCs: The first method used photodynamic therapy (PDT) with topical application of methyl aminolevulinic acid (mALA) followed by LED light irradiation at a dosage of 37 J/cm^2 (Aktilite Cl128; Photocure, Denmark). The second method used only Er:YAG laser ablation with 600 to 1,000 mJ of energy at 7 Hz frequency (no other settings noted). The third method combined Er:YAG laser ablation (same settings) to reduce the tumor size <2 mm followed by mALA PDT. All 3 methods were used to treat each patient (1 BCC allocated to Method A, 1 to Method B, and 1 to Method C). Patients were examined at 3, 6, and 12 months, with final dermoscopic and histological evaluation performed at the 12-month mark. Excellent efficacy, defined as histological clearance, was seen with all treatments, with the greatest efficacy seen in the combination therapy group; combination therapy demonstrated a final efficacy of 98.97% versus 94.85% for PDT only and 91.75% for Er:YAG laser only.[41] The combined method also provided the best aesthetic results as determined by clinician assessment.[41] The Er:YAG only group had a slightly reduced clearance rate as compared to the PDT only group, although this was not statistically significant.

In summary, clinical efficacy has been demonstrated with ablative CO_2 laser therapy in the treatment of BCCs. Ablative CO_2 lasers can effectively provide good oncological and cosmetic outcomes with reduced morbidity and complications such as bleeding, infections, and scarring. Studies involving Er:YAG laser in the treatment of BCCs are far more limited but warrant further exploration. Many of the aforementioned studies demonstrating cure rates in the >90% range used a technique combining multiple “stages” of laser passes and intraoperative evaluation, with subsequent histological confirmation of tumor eradication. It seems that this approach can significantly increase the likelihood of complete resolution and minimize the chance of recurrence. Currently, however, ablative laser treatment of BCCs, with or without intraoperative histopathology has not demonstrated a significant benefit in tumor control rates over current standard of care options. Though there may be a cosmetic advantage using ablative lasers, to date, there are no direct comparison studies to confirm this. Additionally, cosmetic outcomes depend on the size, location, and especially the depth of the tumor treated. Further randomized, controlled side-by-side comparison trials are needed to evaluate laser therapy as compared with current standard treatment modalities, with more appropriate, longer follow-up times needed to fully evaluate the incidence of recurrence.

Laser Therapy for the Treatment of Squamous Cell Carcinomas

SCCs are the second most common type of skin cancer with an estimated annual incidence of 700,000.[4] Although prognosis is generally excellent, approximately 4% metastasize, and 1.5% to 2% result in mortality.[4] The literature investigating the role of laser therapy in the treatment of SCCs is far more limited. The authors did not find any studies that

demonstrated the successful treatment of true invasive SCCs with laser therapy, and this was corroborated by a recently published systematic review and pooled analysis of treatment options for non-metastatic invasive SCCs of the skin.[42] The review, however, did find literature demonstrating the successful treatment of SCCs-in-situ with ablative laser therapy.[33,43–52]

In the largest case series of its kind, 44 patients with 48 SCCs-in-situ were treated with one or more passes of super-pulsed CO_2 laser at 2 W/cm^2 (no other parameters were noted). The number of passes needed was determined intraoperatively, based on the clinical appearance of treated skin. The study demonstrated a 97.7% total clearance rate after a mean follow-up of 18 months (range 8–52 months).[47] Of these 44 patients, 91% had solitary lesions, with the vast majority being found on the legs. Several passes, according with the depth of lesion, were performed to remove entirely, the affected skin. Clinical assessment was performed at 2 and 4 weeks, and then every 6 months for a mean follow-up of 18.8 6 21.2 months (range 8–52 months). Clinical results after laser treatment were classified into three categories: “Clearance after 1 treatment,” defined as clinical clearance with total healing after only 1 laser session (achieved in 86.3% of cases), “Clearance after more than 1 treatment,” defined as partial clearance after the first laser treatment with total clearance after subsequent treatments (an additional 11.3% achieved, range 2–4 treatment sessions), and “No response,” defined as no clinical resolution to the first laser treatment (2.4% of cases) There was no postoperative histopathological confirmation of tumor eradication. A total response rate of 97.6% and a recurrence rate of 6.8% were noted (3 patients in total, with 1 on immunosuppressive treatment as a solid-organ transplant recipient).[47] Side effects of laser treatment were seen in 31.8% of patients, with the majority consisting of minimal erythema, and hypopigmentation and hyperpigmentation; 1 patient developed a keloid scar.[47]

Several smaller case series have demonstrated the efficacy of CO_2 lasers in the treatment of SCCs-in-situ. The response rates have ranged from 80% to 100% (the number of patients within the various studies has been small, generally <10, and thus the difference between 0% recurrence and 20% recurrence has been 1 patient, e.g.).[44,46,48–50,52,53] In these studies, side effects have been similar, with mild hypopigmentation, atrophic changes, or persistent erythema reported in the minority of patients treated. Postprocedural histopathologic confirmation of tumor clearance was not performed in any of these studies.[44,46,48–50,52,53]

One of the most important limiting factors preventing adequate tumor control of invasive SCCs is tumor size. SCCs are often thicker and more dysplastic than BCCs, with a wider spread of atypical keratinocytes within the epidermis and dermis.[54] Cornification, a common histopathological finding of SCCs, is generally absent in BCCs and further adds to SCC tumor thickness.[54] Because of this inherent histological difference in tumor architecture, treatment methods that do not provide margin control may have more limited efficacy. Furthermore, not all laser devices, settings, or techniques will provide adequate depth of removal to achieve tumor clearance. These observations have important implications: One would expect superficial BCCs, for example, to be more effectively treated by lasers as compared to invasive SCCs, unless care is taken to achieve adequate depth of removal.

The clinical literature seems to corroborate these concepts. A published case series investigated the histopathological outcomes of SCC tumors treated with ablative CO_2 laser therapy. In this study, 13 SCCs were treated with either 2 or 3 passes of a pulsed CO_2 laser using a 3-mm collimated handpiece at 500 mJ and 2 to 4 W/cm^2; the treated sites and 1-mm margins were then excised and submitted for histological evaluation. Incomplete vaporization of the SCC depth was seen in 3 of 7 patients treated with 3 passes and in 2 of 6 patients treated with 2 passes.[33] SCCs incompletely treated were significantly thicker than those completely ablated (0.65 vs 0.41 mm, respectively).[33] The average depth of residual tumor beneath the ablated surface was 0.41 mm.[33] Examination of treated specimens with residual tumor revealed areas of incomplete ablation of a hyperplastic atypical epidermis, thick stratum corneum still intact with no ablation of underlying SCC or residual atypia extending to follicular epithelium intact below the level of ablation.[33] It is likely that additional passes would have achieved improved clearance, but may increase side effects or decrease cosmetic acceptability of the outcome.

In another prospective case series, the authors initially published the successful treatment of 16 patients with 25 biopsy-proven SCCs-in-situ on the legs treated with pulsed CO_2 laser, demonstrating a 100% cure rate at 6 months with no recurrences noted.[45] However, at the 12-month follow-up, the authors noted that 12% of patients returned with recurrent lesions which, on subsequent biopsies, demonstrated the presence of invasive SCC. The authors further reported concern regarding progression to invasive SCC. The previously reported incidence of SCC-in-situ progressing to invasive malignancy was approximately 3% per year,[45] whereas in this case series, the observed rate was four fold higher.[45] The investigators presumed that in these three cases, there were unidentified foci of malignant change lying more deeply than in their original treatment plane, and had no reason to believe that laser treatment caused malignant transformation, but could not exclude this possibility.[45] Laser parameters were not provided.

In summary, ablative CO_2 lasers have been employed successfully as a treatment method for SCC-in-situ in some cases. They provide the potential for decreased associated morbidity compared with other established treatment modalities. However, although the limited tissue injury may allow for better healing and reduced morbidity, it may also be associated with inferior tumor control, especially if the tumor is deeper or wider than expected. Concern over residual tumor burden or recurrence has limited the current use of CO_2 laser ablation of SCCs and even SCCs-in-situ. Thus, further studies and head- to-head comparisons with histopathological confirmation of treatment adequacy are needed to determine the clinical utility of lasers for SCC as compared with other well-established treatment methods. Use of fractional ablative lasers to improve efficacy of PDT may offer promise[51] and should be further explored.

Conclusion

The use of vascular targeting and ablative lasers for the treatment of BCCs offers the potential benefits of reduced collateral tissue destruction, decreased bleeding, shorter healing time, and less scarring, making them a promising alternative treatment option for patients who are unable to tolerate or who fail current standards of care. However, tumor recurrence

rates are higher than most current standard of care options, especially micrographic surgery. The literature investigating the use of laser therapy for cutaneous SCCs is far more limited. Preliminary data have demonstrated promising results for the treatment of SCCs-in-situ; however, success has not been demonstrated for the treatment of invasive SCC. In summary, laser therapy offers an alternative treatment option for nonmelanoma skin cancer; however, its clinical efficacy is variable and, at this time, remains less than currently accepted standards of care. Further studies are needed to optimize parameters, determine maximum efficacy, and provide long-term follow-up.

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