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ECP versus PUVA for the Treatment of Cutaneous T-Cell Lymphoma

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ABSTRACT

Extracorporeal photopheresis (ECP) and psoralen plus ultraviolet A therapy (PUVA) are widely accepted types of photochemotherapy used for the treatment of cutaneous T-cell lymphomas (CTCL). PUVA and ECP utilize a photosensitizing agent, that can be taken orally (PUVA) or added to the concentrated sample of white blood cells extracorporeally (ECP) prior to UVA exposure. Both therapies have been shown to be safe and effective for the treatment of CTCL. As a monotherapy, PUVA is preferentially used for treatment of patients at earlier stages with skin involvement alone (T1 and T2). ECP is usually used for patients with erythrodermic skin involvement (T4) in advanced stages (Stage III and IVA) with peripheral blood involvement as in Sézary syndrome (SzS). Use of ECP in earlier stages is controversial and is currently under investigation. Both PUVA and ECP are rarely used as monotherapy, though long-term remissions after PUVA monotherapy for early disease have been reported. CTCL is a rare disease and randomized prospective clinical trials are difficult. The best efficacy data derived from prospective case studies and meta-analysis are reviewed here.

Key Words: *ECP, PUVA, Extracorporeal Photopheresis, CTCL, Cutaneous T-cell Lymphoma, Psorlen + UVA Therapy*

Cutaneous T-cell lymphomas (CTCL) are a group of skin homing non-Hodgkin's lymphomas of T-cell origin. Mycosis fungoides (MF) and Sézary syndrome (SzS) are two of the most common variants. Survival of patients with MF is highly variable depending on the stage of the disease. Whereas life expectancy in the earliest stage (IA) is the same as age-matched controls, it is significantly reduced in advanced disease (1.5 years for Stage IV patients).[1] Because of the rarity of MF/SzS, no prospective, placebo-controlled, randomized clinical trials have been performed to evaluate the impact of treatment on survival, and comparisons have usually been made with "historic controls". Considering the good prognosis in earlier stages, and an assumption that "there is no cure", choices of therapy are largely directed towards induction of long-term remissions and palliation in early, as well as in later, stages of the disease. Quality of life is of utmost importance when considering treatment options for CTCL. The choices of therapy in early stages are usually reflective of good prognosis with a low risk/benefit ratio. In general, skin directed therapies are used for early stage disease, and systemic therapies are reserved for advanced stages.

PUVA

Efficacy

The mechanism of action for both skin-directed and extracorporeal photochemotherapies is thought to be related to the covalent photoadduction of methoxsalen molecules to pyrimidine bases in DNA, leading to impaired T-cell function or survival on the cellular level. PUVA has been shown to be highly effective in early CTCL (thin patches and plaques), with high levels of response rates and even complete clinical remissions (CCRs).[2] However, PUVA's effect on infiltrative thick lesions and tumors is controversial. Some studies assessing PUVA as monotherapy

demonstrated residual malignant infiltrates in the deep dermis after complete epidermal and superficial dermal clearance,[3] poor responses in erythrodermic patients,[4] and the inability to clear in SzS patients.[5] Another report showed significant and complete clearance of malignant infiltrates in over 40% of patients with tumors treated with PUVA as part of combination therapy with other agents.[6] Long-term remissions in early disease patients have been reported,[7] but, in general, maintenance therapy is required to sustain responses.

While PUVA has been clearly demonstrated to be effective in the treatment of CTCL, its efficiency is further improved and toxicity minimized by combining it with other therapies, such as retinoids and interferons (IFNs). Retinoids (acitretin and isotretinoin) and rexinoid (bexarotene) are photosensitizing agents and may reduce the total cumulative UVA dose needed to induce and sustain remission (RePUVA therapy).[8,9] In addition, bexarotene is an effective agent in the treatment of early and advanced disease with overall response rates of more than 50% in therapeutic doses.[10] Maintenance therapy with retinoids/rexinoids may prolong remissions. IFNs have been shown to be highly effective in the treatment of CTCL with response rates of up to 80% at higher doses, even in advanced disease.[11] IFNs may potentiate effects of PUVA and result in remission in previously refractive patients.[12] In addition, the use of both retinoids/rexinoids and IFNs is not immunosuppressive and does not result in increased cutaneous malignancies. Studies evaluating secondary cutaneous malignancies in CTCL patients after PUVA therapy are lacking; however, inferring from studies conducted with other patients treated with long-term PUVA or patients on long-term immunosuppressive therapies, the use of retinoids may be protective in CTCL patients from a skin carcinogenesis standpoint.[13]

Safety and Side-Effects

PUVA is a well established first-line therapy for selected patients with CTCL. However, it has several disadvantages and side-effects when compared with other skin directed therapies. The short-term side-effects of therapy are mostly associated with oral psoralen intake and include nausea, vomiting, inconsistent GI absorption, and consecutive variability in dosing. This in turn results in variable dosing of UVA that increases the potential for burning. Additionally, patients receiving PUVA treatment require periodic monitoring of hepatic function because PUVA is metabolized by the liver. This can become a serious problem, especially if patients are on other hepatotoxic drugs, such as retinoids and lipid lowering agents, among many others. As poly-pharmacy is common among elderly patients, additional oral medication may be perceived as a disadvantage in this context. In younger patients, the inconvenience of frequent (though brief) office visits may preclude some from using this modality.

A significant issue for PUVA is extended photosensitivity. Patients are advised to wear protective eyewear, avoid sunlight, apply sunscreens, and have regular full body dermatological assessments for skin cancer surveillance. Photosensitivity may be further increased by commonly used medications, such as antibiotics and diuretics; this underscores the need for thorough history taking before initiating PUVA therapy to ensure its safe administration and to avoid PUVA burns.

Skin cancers are significant long-term side-effects of PUVA therapy. Indirect evidence from psoriasis studies shows substantially increased risk for nonmelanoma skin cancers, most significantly dose dependent squamous cell carcinoma (SCC) and (potentially) melanoma.[1] The risk of skin cancers has not been systematically studied in CTCL patients, but may be higher than in psoriasis patients due to immunosuppression associated with the disease, which approaches 30%.[13] Some patients who develop leukoderma on long-term PUVA therapy have a very high rate of SCCs and require frequent monitoring (see Figure 1).

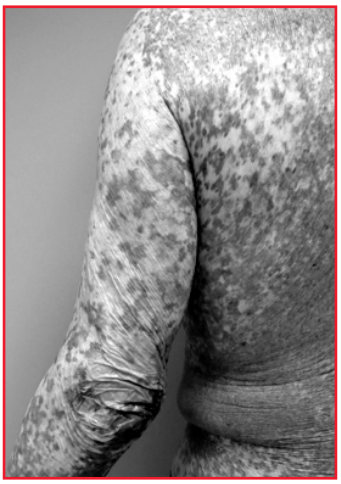

Figure 1a

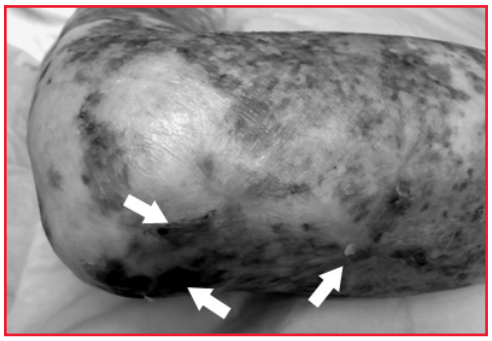

Figure 1b

Figure 1: Elderly African-American man with more than a 20-year history of PUVA therapy for MF, who developed leukoderma (a), and numerous SCCs on his arm (b).

ECP

Due to valid concerns with the safety and side-effects of PUVA, as well as with its limitation in the treatment of predominantly early disease, an attempt was made to improve its safety profile while extending its efficacy. It was hypothesized that if patients' leukopheresed blood were exposed extracorporeally to UVA in the presence of a photosensitizing agent (8-MOP), the benefits of the therapy might be extended to a more advanced patient population with a circulating malignant clone in their peripheral blood.

At the same time, the side-effects associated with skin UV irradiation would be eliminated. In 1987, a new medical device (UVAR® Instrument, Therakos) was approved by the US FDA for the treatment of CTCL.[14]

This is a leukopheresis-based procedure in which the patient's whole blood is processed extracorporeally: the white blood cells (WBC) are separated from the red blood cells (RBC) by centrifugation, exposed to UVA light, and then returned to the patient (hence the name "extracorporeal photopheresis" or ECP). Initially, induction of photosensitivity of WBCs was achieved by oral administration of 8-MOP prior to therapy. However, the oral route of administration is associated with the same side-effects discussed above for PUVA (i.e., nausea, vomiting, diarrhea, inconsistent blood levels of 8-MOP and photosensitivity). To avoid these, the procedure was further modified to use liquid psoralen (methoxsalen) at a concentration of 340ng/mL (Uvadex®, Therakos) added directly into the treatment bag after collection of the buffy coat by leukopheresis. Similar to the initial procedure, the WBCs are then exposed to ultraviolet A light in a photoactivation chamber. This is a clear plastic plate with a 1mm thin zigzagging pathway that allows for greater surface area of the WBC exposure to the UVA during their recirculation through the plate. The UVA lamps on both sides of the plate achieve cell exposure energy up to 2J/cm^2 of UVA, which is enough energy to induce apoptosis of all cells in the chamber.[15]

The RBCs and plasma are returned to the patient after each collection cycle and WBCs are returned to the patient at the end of the overall treatment. Each treatment lasts about 3 hours, depending on the technical aspects of the procedure. Usually, the therapy is administered for 2 days in a row, once per month, though other (accelerated) regimens have been used under certain circumstances. For patients sustaining clinical remission, the treatment interval may be slowly increased to two treatments every 6-8 weeks. If no evidence of active disease is present, the treatment may be discontinued with established close clinical follow-up.

Efficacy

Treatment of MF and SzS with ECP was thoroughly analyzed through a meta-analysis of 19 studies reporting the use of ECP as a monotherapy (5 studies), or as part of combination therapy (14 studies) in more than 400 patients.[16] The authors report that the combined overall response rate (OR) for all stages of CTCL was 55.7% (244 out of 438), with 17.6% (77 out of 438) achieving a complete response (CR). Analysis of data where ECP was used as a monotherapy revealed similar results with 55.5% OR and 14.8% CR.[16] Similarly, for erythrodermic disease (T4) the OR was 57.6% and CR was 15.3%. Notably, combined analysis of responses to ECP by SzS patients revealed an OR of 42.9% and CR of 9.5% (see Table 1).

Use of ECP in early stages of CTCL is controversial. There are some reports of significant efficacy of ECP in stage IB patients with wide-spread skin disease, where response rates of 64% OR and 28% CR were cited.[16] Recently, a clinical trial was initiated to definitively address the use of ECP in early MF with minimal blood involvement.

The mechanism of action of ECP is not known. However, because only a small fraction of lymphocytes (up to 5%) is undergoing the process, the effects are thought to be better explained by induced immune responses resulting from the procedure. Several different mechanisms have been proposed to play a role, including dendritic cell activation, and loading by apoptotic lymphocytes as a result of UVA induced apoptosis.[17] The usual time to response may approach 6 months and an appropriate therapeutic trial is necessary before the therapy may be considered ineffective.

Safety and Side-Effects

The current ECP procedure using direct administration of psoralen into the photopheresis bag, bypassing oral administration, has significantly improved its safety profile. This technique can be safely administered in broad age groups from children (over 40kg) to the extremely elderly. The procedure has been performed safely by highly trained

Procedure	*TNM Stage*	*Treatment Duration*	*Response Rate*	*Response Duration*	*Safety*
PUVA	T1 – T3, Stages IA - IIB	2 months - indefinite	54%-65% (CR in early disease)	Variable, may be long-term	Nausea, vomiting, photosensitivity, acute burns, chronic photodamage, melanoma, non-melanoma skin cancers, inconvenience
ECP	T4, Stages III – IVA (? IB)	~ 6 months - indefinite	All stages: 56 % OR, 18% CR; T4: 58% OR, 15% CR; SzS: 43% OR, 10% CR	Not well defined	Fluid shifts and hypotension (especially in heart failure), need for peripheral or central access, high risk of infection with indwelling catheter, anemia, pain (needle stick), inconvenience

Table 1: Overall comparison between two photochemotherapeutic procedures (PUVA and ECP) including indications for treatment and responses to therapy.

photopheresis personnel in children under 40kg. However, technical treatment modifications are required. The procedure is contraindicated in patients with serious comorbid conditions where fluid shifts may not be well tolerated, including severe heart, liver or kidney failure.

Anemia with low hematocrit or conditions that may change the color or density of blood (such as extreme hypertriglyceridemia) may interfere with the proper collection of the WBC due to incorrect triggering of the light sensor separating these fractions during centrifugation of the blood. This is especially important for patients on concurrent retinoids or rexinoid (bexarotene).

Venous access may be a rate limiting step for some patients, because peripheral access is the preferred way of therapy delivery. Central catheters have been used in patients whose access was problematic, but this route should be carefully considered due to a high risk of sepsis from indwelling catheters and an even higher risk of infection in erythrodermic patients. Ports may also be used for treatment delivery, with variable success, and may be safer in these patients.

Side-effects of the procedure include pain associated with needle insertion; inconvenience of the procedure itself; hypotension (rare); anemia due to incomplete return of the RBC after the procedure; low grade fevers (very rare); and temporary increase in erythroderma.

Conclusion

Therapy for MF and SzS is based on the clinical stage of the patients. In early or localized patch stage MF (Stage IA-IIA), PUVA treatment alone or in combination with other skin-directed therapies may result in long-term clinical remission. In order to achieve and maintain clinical remission and to improve quality of life, systemic therapy may be necessary in more advanced disease. Combination therapies, including IFN plus PUVA, and bexarotene with PUVA may be more effective than PUVA alone for treatment of the recalcitrant disease.

ECP is a first-choice treatment of erythrodermic CTCL.[18] Similarly, the combination of ECP with other treatment modalities, including low-dose bexarotene, interferon, and total and localized skin electron beam have been shown to be superior to monotherapy. Though the mechanism of action of ECP is not completely understood, immunological factors are thought to play a role. As such, some argue that immunosuppressive agents (such as prednisone and chemotherapeutic agents) should be avoided during therapy. Investigations into the mechanism of action of ECP and potential combination therapies are ongoing.

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Use of Cutaneous Lasers and Light Sources: Appropriate Training and Delegation

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ABSTRACT

In recent years, there has been increasing concern among physicians, patient advocacy groups, and media watchdogs that laser, light, and cosmetic surgery are being practiced by poorly trained professionals, with resulting preventable injuries to patients. In response, several professional organizations have developed guidelines for the delegation of laser services to nonphysician providers. These guidelines delineate appropriate qualifications for delegating physicians and nonphysician providers, and also describe the circumstances and settings in which delegation is appropriate.

Key Words: *Laser, Cosmetic Surgery, Pulsed Light, Guidelines*

Historical Overview

As early as 8-10 years ago, reports documented the increasing tension between dermatologists and electrologists over the training required to perform laser hair removal, with dermatologists advocating for supervision by licensed physicians who are on-site. Some states that do not require licensing for electrologists to administer laser treatments, such as Texas, were of particular concern.[1,2] Yet concurrently, data showed that "properly trained" nurses had no greater risk than physicians of inducing undesirable outcomes, such as pigmentation change and blistering after laser hair removal with the long-pulsed alexandrite laser.[3] Recent studies suggest that a proportionately greater number of complications are arising from dermatologic care delivered by physician extenders. Nearly 53% of 488 dermatologists surveyed in Texas in 2004[4] reported seeing a greater number of complications associated with delegation to nonphysicians. Of those surveyed, 33% asserted that they knew of such complications arising in the absence of a supervising physician on-site during treatment delivery. This confirmed earlier results of a survey of 2,400 members of the American Society for Dermatologic Surgery (ASDS) in 2001, which ascribed the preponderance of post-treatment patient complications to "nonphysician operators," including cosmetic technicians, estheticians, and workers in medical/dental offices who performed procedures for which they were not appropriately trained, or who were inadequately supervised.[5] Further studies under the auspices of the ASDS are ongoing. A growing body of evidence suggests that nonphysician provision of laser services and insufficient physician supervision of extenders may be jeopardizing patients, unnecessarily raising complication rates, and leaving dermatologists vulnerable to public censure and legal liability.[6,7]

Training for Provision of Laser Services: Formal Guidelines and State Regulation

Several professional physician groups have attempted to delineate appropriate training standards for those using lasers on patients. Such standards have typically been embedded in larger position papers on the scope of practice or laser use. Moreover, given that even the physician leadership can differ on exactly how training standards should be implemented, these guidelines tend to be firm in tone, but vague in terms of specific benchmarks for competency.

American Academy of Dermatology

On February 22, 2004, the Board of Directors of the American Academy of Dermatology (AAD) approved a Position Statement on the Use of Lasers, Pulsed Light, Radiofrequency, and Medical Microwave Devices.[8] This one-page document notes that physicians using the aforementioned devices must be trained in relevant "physics, safety, and surgical techniques." Regarding physician and nonphysician roles during delegation of laser procedures, the following precautions should be observed:

A physician who delegates such procedures should be fully qualified by residency training and preceptorship or appropriate course work prior to delegating procedure to licensed or certified nonphysician office personnel and should directly supervise the procedures. The supervising physician shall be physically present on-site, immediately available, and able to respond promptly to any questions or problem that may occur while the procedure is being performed.

Any nonphysician office personnel employed and designated by a physician to perform a procedure must be under the direct supervision of the physician. For each procedure performed, the nonphysician office personnel must have appropriate documented training and education in the physics, safety, and surgical techniques of each system, be properly licensed in their state if required, and be adequately insured for that procedure. The nonphysician office personnel should also be appropriately trained by the delegating physician in cutaneous medicine.

In summary, the AAD document notes that the "Academy endorses the concept that use of properly trained

nonphysician office personnel under appropriate supervision allows certain procedures to be performed safely and effectively." The earlier exhortation that the supervising physician be present on-site is thus balanced by the concession that delegation of laser procedures to nonphysicians is inherently acceptable.

American Society of Laser Surgery and Medicine

The most extensive work in this area has been by the American Society of Laser Surgery and Medicine (ASLMS), which has incorporated the relevant guidelines established by the American National Standards Institute (ANSI) Z136.3 Standard Safe Use of Lasers in Healthcare Facilities.[9] Regarding operator qualification in the context of laser safety, ASLMS guidelines include the following clauses:

The laser will be operated only by those who have had training in laser theory, techniques of control, and operation of the laser(s) or IPL.

A program for laser safety training will be made available to ALL personnel working around the lasers. The Laser Safety Officer shall have discretion, according to ANSI standards, in delineating which personnel are required to undergo which levels of training. All of the training shall be documented and kept on file.

ASLMS also further clarifies training requirements in documents on office-based laser procedures[10] and nonphysician use of lasers.[11,12]

The ASLMS Principles for Nonphysician Laser Use,[11] and Educational Recommendations for Laser Use by Nonphysicians,[12] reproduced below, are slightly more specific:

Principles for Nonphysician Laser Use

Any physician who delegates a laser procedure to a nonphysician must be qualified to do the procedure themselves by virtue of having received appropriate training in laser physics, safety, laser surgical techniques, pre- and postoperative care, and be able to handle the resultant emergencies or sequelae.

Any nonlicensed medical professional employed by a physician to perform a laser procedure must have received appropriate documented training and education in the safe and effective use of each laser system, be a licensed medical professional in their state, and carry adequate malpractice insurance for that procedure.

A properly trained and licensed medical professional may carry out specifically designed laser procedures only under physician supervision and following written procedures and/or policies established by the specific site at which the laser procedure is performed.

Since the ultimate responsibility for performing any procedure lies with the physician, the supervising physician should be immediately available and shall be able to respond within five minutes to any untoward event that may occur. Ultimate responsibility lies with the supervising physician.

The guiding principle for all physicians is to practice ethical medicine with the highest possible standards to ensure the best interest and welfare of each patient is guaranteed. The ASLMS endorses the concept that use of properly trained and licensed medical professionals, under appropriate supervision, allows certain laser procedures to be performed safely and effectively.

Educational Recommendations for Laser Use by Nonphysicians

Individuals should be trained appropriately in laser physics, tissue interaction, laser safety, clinical application, and pre and post operative care of the laser patient. Prior to the initiation of any patient care activity the individual should have read and signed the facilities policies and procedures regarding the safe use of lasers.

Continuing education of all licensed medical professionals should be mandatory and be made available with reasonable frequency (including outside the office setting) to help ensure adequate performance. Specific credit hour requirements will be determined by the state, and/or individual facility.

A minimum of TEN procedures of precepted training should be required for each laser procedure and laser type to assess competency. Participation in all training programs, acquisition of new skills and number of hours spent in maintaining proficiency should be well documented.

After demonstrating competency to act alone, the designated licensed medical professional may perform limited laser treatments on specific patients as directed by the supervising physician.

American College of Surgeons

Among major specialties approved by the American Council on Graduate Medical Education (ACGME), surgery has been among the most active in promulgating outlines for laser training and use. This broad field is experienced at incorporating and regulating new operative technologies, but the breadth of laser use in surgery limits the specificity of the relevant parts of the American College of Surgeons' (ACS) Statement on Laser Surgery,13 revised in 2007 from the original statement published in 1991:

Surgery is performed for the purpose of structurally altering the human body by the incision or destruction of tissues and is a part of the practice of medicine. Surgery is also the diagnostic or therapeutic treatment of conditions or disease processes by any instruments causing localized alteration or transposition of live human tissue, which include lasers, ultrasound, ionizing radiation, scalpels, probes, and needles. All of these surgical procedures are invasive, including those that are performed with lasers, and the risks of any surgical intervention are not eliminated by using a light knife or laser in place of a metal knife or scalpel.

The American College of Surgeons believes that surgery using lasers, pulsed light, radiofrequency devices, or other means is part of the practice of medicine and constitutes standard forms of surgical intervention. It is subject to the same regulations that govern the performance of all surgical procedures, including those that are ablative or nonablative, regardless of site of service (that is, hospital, ambulatory surgery center, physician's office, or other locations). Patient safety and quality of care are paramount, and the College therefore believes that patients should

be assured that individuals who perform these types of surgery are licensed physicians (defined as doctors of medicine or osteopathy) who meet appropriate professional standards. This is evidenced by comprehensive surgical training and experience, including the management of complications, and the acquisition and maintenance of credentials in the appropriate surgical specialties (that is, board certification) and in the use of lasers, pulsed light, radiofrequency devices, or other similar techniques.

Individuals who perform laser surgery utilizing lasers, pulsed light, radiofrequency devices, or other techniques should meet the principles of the College in all respects, to include the avoidance of any misrepresentations to the public regarding unfounded advantages of the laser compared with traditional operative techniques. [13]

Furthermore, the ACS Statement on Issues to Be Considered Before New Surgical Technology is Applied to the Care of Patients, the subsection on "Is the individual proposing to perform the new procedure fully qualified to do so?" includes the following passage:

In order to determine and apply proper indications for a procedure and to select the appropriate patients for applications of the technology, comprehensive knowledge of the disease process and experience in management of patients with the disease is essential. Prompt recognition and management of complications can only be achieved when the individual or team member is fully qualified in all aspects of treatment of the disease.[14]

American Society for Dermatologic Surgery

Within dermatology, the American Society for Dermatologic Surgery (ASDS) has been most active in developing guidelines for the nonphysician practice of medicine, in particular, the use of lasers. This multi-pronged approach has included alerting state medical boards to the potential hazards to patients, publishing statistical data in the professional medical literature, making information easily available to patients on the Internet, and conducting a public relations campaign to apprise patients of the dangers inherent in receiving laser services from unqualified personnel.

At present, the ASDS guidelines assert that cosmetic procedures, including cutaneous laser procedures, be delivered only by MDs and DOs who have been adequately trained. A qualified physician may delegate some procedures to certified or licensed office personnel (e.g., RN, CMA, LPN, PA, NP) if, and only if, the delegated individuals are properly trained in the specific procedure and the physician remains physically on-site and available to respond in a timely manner to questions or problems that may arise.[15]

In recognition of the fact that laser hair removal procedures, in particular, are likely to be performed by nonphysicians, the ASDS provides, in the public portion of its web-site, a statement entitled *Don't Get Burned – What You Need to Know About Laser Hair Removal*,[16] which reads in part:

- *Do consult a qualified physician: Regulations for laser use have not kept up with the demand and consumers should be cautious of nonphysicians practicing these procedures in spas/salons. Only a physician who is board-certified in dermatology or another specialty with equivalent training and experience should perform this procedure or the physician can designate another trained technician to perform a procedure as long as he/she is under the direct (on-site) supervision of the physician.*
- *Do ask questions: What kind of lasers do they use? What kind of training or experience do they have? Can you speak with one of their clients? If the person performing the procedure can't answer these simple questions, you should walk away.*
- *Do ensure the physician has experience with different skin types: People of a darker complexion may experience unusual lightening of the skin if an incorrect laser is used at an inappropriate setting.*

State Medical Boards

State medical boards have taken notice of the media furor surrounding adverse events resulting from laser use by nonphysicians. The Louisiana State Board of Medical Examiners has begun to require that the use of medical lasers and chemical peeling procedures be under direct supervision by an on-site physician. Similarly, the New York State Board of Medicine has construed laser hair removal by lasers and intense pulsed light devices to constitute the practice of medicine, and hence to be permissible only when performed by a physician or under a physician's direct supervision. The Massachusetts legislature established a task force within the Board of Medicine to report back to the legislature by May, 2007 with draft standards or regulations on medi-spas.

Practical Issues in Nonphysician Laser Practice: Financial Incentives, Patient Safety, and Adverse Events

From a practical standpoint, the dangers of inappropriate delegation of laser services or nonphysician practice of medicine include:

- impaired patient safety, such as
  - increased frequency of avoidable adverse events
  - failure to treat adverse events appropriately and in a timely manner;
- provision of unnecessary or inappropriate laser services
- over-treatment
- subordination of patient well-being to financial productivity of the practice.[17]

In the case of laser use in a spa, the financial incentives for delegation are further enhanced by the nature of the business model, which resembles a retail store rather than a medical practice, and to a greater extent than in a physician practice, service providers may be compensated on an incentive basis. There may be no physicians present at most

times, and there may even be a dearth of medical personnel. In many spas, services are provided by estheticians and nonmedical, nonphysician providers, who are not inculcated as are physicians and nurses in the need to ensure patient well-being.

Problems that have been commonly seen in unsupervised or nonphysician laser centers have been numerous and varied and include:

- burns associated with excessive treatment levels
- burns and post-treatment hyperpigmentation associated with treatment of tanned individuals
- scarring and hypopigmentation associated with excessive treatment, multiple passes, or cooling excess or failures
- delayed healing, erosions, and ulceration associated with untreated herpes simplex infection or impetigo
- configurate linear and round patterning of the skin associated with improper treatment resulting in tattooing with the laser handpiece
- corneal and retinal injury due to inadequate use of eye protection.

Some of these problems, like hyperpigmentation, will eventually resolve, but hypopigmentation and configurate scarring can be persistent and disfiguring. Rampant infection can result in functional loss, including permanent impairment of facial sensory structures.

The problem of impaired safety is exacerbated by the lack of general dermatologic training among nonphysician providers of laser services. In general, low-level and even some high-level nonphysician providers are trained mostly in the technique of laser service delivery, with lesser training in the management of adverse events, and little or no training in general cutaneous medicine. Adverse events, and especially unusual cases, may be recognized late by such providers, who may then treat them incorrectly. Especially when physician supervision is light, incorrect treatment may continue for some time, until the problem has worsened and permanent sequelae may be inevitable. It is a truism in cutaneous laser therapy that firing a laser handpiece may be the least important portion of the treatment; it is everything but the actual treatment, including patient selection, parameter selection, and recognition and management of undesirable outcomes, that requires judgment and training. In the spa environment or in a poorly supervised laser practice, the pressure to "convert" all consultations into treatments may result in poor patient selection, which in turn may dramatically increase the rate of adverse events.

Incentives for nonphysician providers to maximize revenue generation in a spa or thinly supervised setting can increase the risk of adverse events by:

- hurrying preoperative evaluation and laser treatment.
- encouraging the treatment of patients who may be poor laser candidates.

To the extent that nonphysician providers may have a skewed financial incentive structure, wherein they are more often rewarded for revenue generation than penalized for adverse events and patient dissatisfaction, the impetus to increase business may dominate. The result means greater risk for the patient, and for the ostensibly delegating but possibly off-site physician, who may have medico-legal responsibility for problems accruing from delegated services.

Beyond adverse events, such incentives may lead to unnecessary treatments motivated by the desire to increase financial yield by extending the number of sessions. Indeed, more revenue may be generated by systematically undertreating patients to ensure that they return for more visits. Subtherapeutic treatments may also reduce the risk of adverse events when laser treatments are delivered by minimally trained nonphysician providers. While undertreatment is unlikely to cause irrevocable physical injury, it is a form of fraud that wastes patients' time and money.

Conclusions

While current guidelines on appropriate cutaneous laser training and delegation are not detailed and comprehensive, some recommendations occur repeatedly in guidelines proposed by various national professional organizations. In particular, it is apparent that:

- optimal laser use occurs when a physician who is trained in a relevant specialty, with additional training for the specific laser to be used, directly performs laser services on an appropriately selected patient.
- laser training of nonphysician providers should be comprehensive and not limited to merely delivering a technical service, but should include theoretical and practical training, and should encompass an understanding of patient selection, adverse events, and appreciation of the limits of this training.
- even when nonphysician personnel are appropriately trained, delegation of laser use should occur in the context of adequate physician oversight under ideally direct, on-site supervision. In medicine, a quest for efficiency or revenue maximization by an individual or corporate entity can never supersede the responsibility to ensure patient safety.
- in medicine, a quest for efficiency or revenue maximization by an individual or corporate entity can never supersede the responsibility to ensure patient safety.

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Class	Name/Company	Approval Dates and Comments
Antibacterial Agent	**Retapamulin Ointment 1%** *Altabax®* GlaxoSmithKline	The US FDA approved this antibacterial in April 2007 for the topical treatment of impetigo due to susceptible strains of *Staphylococcus aureus* or *Streptococcus pyogenes*, the two most common types of bacteria implicated in this kind of infection. This product is the first in a new class of prescription topical antibacterials to be used twice daily for a 5 day period in patients ≥9 months.
Vaccine	**Quadrivalent Human Papillomavirus Recombinant Vaccine** *Gardasil®* Merck	The US FDA received a supplemental Biologics License Application in April 2007 for this cervical cancer vaccine. The updated labeling will include efficacy data showing some protection against additional HPV types responsible for >10% of cervical cancers. Efficacy data indicates protection against additional vaginal and vulvar cancers and data on immune memory. This vaccine is approved for use in girls and women ages 9-26 for the prevention of HPV types 16- and 18-related cervical cancers, cervical precancers (CIN 2/3 and AIS), vulvar precancers (VIN 2/3) and vaginal precancers (VaIN 2/3) and for the prevention of genital warts and low-grade cervical lesions (CIN 1) caused by HPV types 6, 11, 16 and 18.
Antihistamine	**Desloratadine** *AERIUS®/ AZOMYR®/ NEOCLARITYN®* Schering-Plough	The European Commission approved two new formulations of this antihistamine in April 2007: orodispersible tablets for the treatment of symptoms associated with allergic rhinitis and chronic idiopathic urticaria (CIU) in adults and children >6 years of age; and oral solution for the treatment of symptoms associated with allergic rhinitis and CIU in adults and children >1 year of age.

Drug News

Health Insurance Coverage for Laser System	PhotoMedex announced in March 2007 that the Blue Cross Blue Shield Association revised the portion of its National Reference Policy in the US to now include the PhotoMedex® XTRAC® Laser System's treatment for psoriasis. The policy now states that the XTRAC® Laser may be considered medically necessary for the treatment of mild-to-moderate psoriasis that is unresponsive to conservative treatment, and further states that the XTRAC® laser may be considered medically necessary for the treatment of moderate-to-severe psoriasis comprising less than 20% of body surface area.
Effects of Caffeine on Methotrexate	In an article recently published in the *International Journal of Dermatology**, Swanson and colleagues reported that, based on animal and human studies, the therapeutic benefit of methotrexate in the treatment of rheumatoid arthritis may be substantially reduced in patients who are concomitantly consuming caffeine. The authors further concluded that their results did not rule out an effect of caffeine in other inflammatory diseases treated with methotrexate. *Swanson DL, et al. *Int J Dermatol* 46(2):157-9 (2007 Feb).

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