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REVIEW

PDT experience in Brazil: A regional profile

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Summary The success of PDT and its establishment into the existent hall of therapeutic modalities depends on the collection of reported experiences from around the world. In that sense, it is important to report approaches taken by different countries and what their views are on the future of PDT. Following this idea, we present our clinical experience in photodynamic therapy (PDT) in Brazil, as well as the experimental advances coming up in parallel with clinical implementation. This report is a consequence of pioneering work in a collaborative program involving the Physics Institute in São Carlos, São Paulo State (SP), Brazil, the Medical School of the University of São Paulo, Ribeirão Preto, SP, Brazil and the Cancer Hospital Amaral Carvalho, Jaú, SP, Brazil. This collaborative program, begun in 1997, with the first patient treated in 1999, has treated over 400 patients by late 2004. About 80% of lesions were located in the head and neck or skin, but experience is being built in esophagus, bladder, gynecology, and cutaneous recurrence of breast cancer, among others. The overall results have shown to be compatible with previously reported data. Modifications, whose goal is to improve patient benefit and optimize results, are being implemented as we gain experience. In parallel with the clinical development, several laboratories have started studying experimental whose purpose is to analyze the clinical results and to contribute to the worldwide effort to bring PDT to the forefront of therapies offered to patients. We present the overall results of our 5 years experience as well as the whole implementation process.

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Introduction

Photodynamic therapy (PDT) is a very powerful modality of cancer treatment with an interesting history. As pointed out in a recent review by Allison et al. [1] covering more than 100 years of the use of light as a tool for therapeutic purposes in North America, PDT is the final result of many observations accumulated over decades of photomedicine. The beauty of PDT is its simplicity. Activating the photochemical properties of substances called photosensitizers results in a cytotoxic and vasculotoxic chain of events of their photoproducts. For ''ideal'' PDT, a patient with a malignant tumor would be given a photosensitizer, which must be nontoxic in clinically useful doses. The photosensitizer should ideally concentrate more in malignant than in normal tissue, and therefore promote a high tumor to normal tissue photosensitizer concentration ratio. After delivering the drug to the target, a reliable light source illuminates the tissue activating the photochemical reaction that will result in the tumor death. Here, selectivity helps to prevent kill of normal tissue, an important concept for healing. There are many mechanisms for the development of cytotoxicity, the most important is the production of molecular singlet oxygen. Singlet oxygen is a very reactive chemical species that oxidizes most biological substrates. In this way, photosensitizers are the intermediate agent that allow transference of light energy into the tissue and promote destruction through a chemical reaction. There are many available photosensitizers in the market. They all have specific clinical utility and drawbacks [2].

The important concept is that the principles of PDT work very well in practice, although, we still have not yet optimized its clinical application. There appears to be missing links, which are important to allow us to take maximum advantage of the technique and to have more predictable results. We believe these details are holding PDT back from becoming a worldwide therapeutic modality. Much of the research work presently going on in our group is to focus attention to these details to transform PDT into a more acceptable therapy.

In Brazil, not long ago, clinical PDT was an unknown modality of treatment [3]. Only a few research scientists worked in this field. The efforts to make PDT clinically available have modified this scenario. Today, PDT in Brazil has passed through the stage of being unknown to the stage of admiration. There remains, however, much resistance against PDT, not because of risks, but because of the missing knowledge gap that demonstrates the advantages of PDT over traditionally employed techniques. Mang, in a recent article [4] highlighted an important issue, which is prevalent in Brazil. PDT is a technique presently in a stage where health professionals demonstrate a lot of interest and patients are getting familiar with the concepts. However, the applications are still restricted to a few hospitals and clinics, and currently this therapy is offered to patients whose stage of disease goes well beyond what traditional PDT techniques can control. Further, as PDT is a technique that combines drug and light source, the absence of one ingredient makes the initiation of a program impossible. Because the light sources are expensive and they require specialized skills, only large centers are currently routinely offering PDT. These programs are expanding in size and location due to progressively better results.

In this article, we describe the route that Brazilian professionals have taken to start a PDT program, results, difficulties, government issues and our present efforts to decrease the barriers that prevent spread of PDT in Brazil.

The route for PDT implementation in Brazil

First, it is important to note that for an emerging economy like Brazil, the importance of PDT is based on the simplicity of the technique when compared to conventional chemotherapy and radiotherapy. Radiation therapy facilities are rare

outside large cities, as is use of chemotherapy. PDT potentially can offer improved oncological therapy to the millions of Brazilians living in the countryside. Currently, 160 million people inhabit Brazil. The two most well known cities, São Paulo (20 million habitants) and Rio de Janeiro (8 million habitants) have world-class hospitals and medical care. Several other large cities also have excellent levels of oncological services. These hospitals and medical schools offer state of the art cancer care through surgical, medical and radiation oncology services. The same cannot be said for millions living in smaller cities and the countryside. Most patients have to travel long distances for treatment and this overloads the facilities of the big city hospitals. A number of well-equipped private clinics for cancer and other therapies exist but these are available to a relatively small group of wealthy or privately insured individuals. An obvious example is the outstanding plastic surgery centers that currently exist in the country.

Looking at official data from the Brazilian government (National Institute of Cancer), cancer is the second major cause of death in Brazil. There are close to 400,000 new cases of cancer every year distributed among men and women. For both sexes, non-melanoma skin cancer is by far the commonest type of cancer affecting the Brazilian population. Coincidentally, this is a type of cancer well suited to be treated with PDT. This fact alone could justify the effort to have PDT as a regular modality of treatment available for the Brazilian population. This fact is reinforced when we compare new cancer cases every year to the treatments available within the current hospital infrastructure.

The clinical experience of PDT in Brazil [5], started with a collaborative effort between the Physics Institute of São Carlos—University of São Paulo, São Carlos, SP and Amaral Carvalho Hospital, Jaú, SP, and a later cooperation with the School of Medicine, University of São Paulo, Ribeirão Preto, SP. This group established international collaborations, first with T. Mang and R. Allison from the Buffalo General Hospital PDT Center in 1998 and later with D. Stranadko and V. Sokolov from Moscow—Russia in 2001. These international collaborations provided the training to start clinical applications. The Brazilian team visited these institutions for extended periods and observed multiple PDT treatments as well as undertook intensive didactic lectures. Based on these observations and on published international experience a clinical protocol was elaborated and approved by the Ethics Committee for Research in Medicine, University of São Paulo, followed by the approval of the Federal Committee for Research in Medicine, a Brazilian government entity, which oversees research in medicine at the national level. The idea was to demonstrate, in the first stage, the potential of the technique and to generate enough experience and excitement to show the Brazilian medical professionals the possibilities offered by PDT. At this initial stage the main multidisciplinary team consisted of a group of physicians (G. Cestari Filho Jr., J.C. Berto, A. Javaroni and J.O. Souza Júnior), nurses (M. Silva and V.S. Bonilha) and physicists (V.S. Bagnato and L.G. Marcassa). Initially, only patients with malignant skin lesions were involved in the protocol and as the group acquired experience, other tumors were included. All patients underwent multidisciplinary clinical assessment for their eligibility to receive PDT. We avoided patients with severe liver or other GI complications. During the evolution of this implementation, many devices to facilitate the light application were developed and we have also learned how to share responsibilities among the members of the team. After this initial stage, the group grew by incorporating other professionals as well as institutions. A larger multidisciplinary team was established and the Medical School of the University of São Paulo, Ribeirão Preto, SP was incorporated in 2002. At the same time experimental in vivo and in vitro studies started to take place in these institutions [6,7]. Particularly, the biochemistry department of the Chemistry Institute, São Carlos, SP [8]. Today, we have four hospitals performing clinical PDT at any time, and several specialized clinics are now joining the initiative.

PDT has received favorable recommendation from the Brazilian Federal Medical Council, to allow for nationwide approval of the technique. Brazilian companies have developed a laser and a LED (Light Emitting Diode) source for PDT applications. We are now expanding PDT applications for non-oncological applications, such as condiloma by HPV with great success.

Facilities and the multidiciplinary needs for PDT

PDT is a technique with multidisciplinary needs (Fig. 1). In Brazil, we have initiated PDT using a multidisciplinary approach. In general, PDT patients are initially seen by the physician, nurse and a physicist to assess their potential for PDT. Critically important are our nurses. The nurses, not only participate in the PDT procedures, but they are the closest contact for patients. Patients normally come to PDT mostly by their own initiative

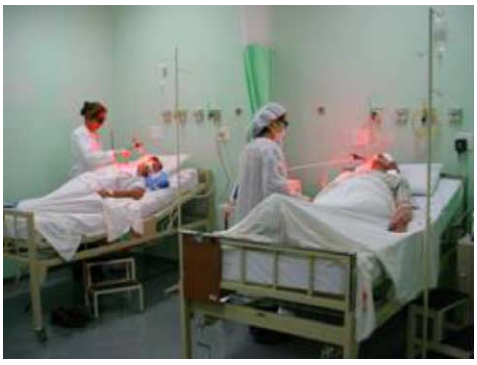

Figure 1 PDT facility at the Cancer Hospital Amaral Carvalho, Jaú, São Paulo. A dye laser pumped by an Argon ion laser allow us to couple light into optical fibers and treat two patients simultaneously or to treat two lesions in one patient. The system is normally operated by the physicist and fibers can be delivered even to the surgical room of the hospital. This is a reliable tunable system which is not dedicated to a single drug.

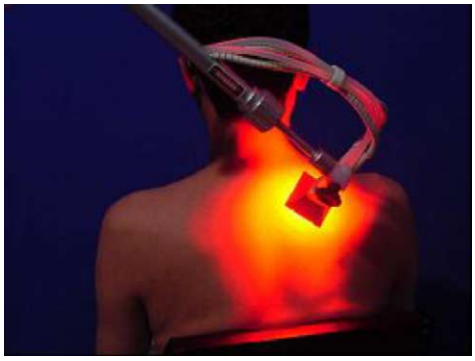

Figure 2 A Brazilian developed LED device allows illumination of large areas with typical light intensities of 150 mW/cm^2. This device is been commercialized by MM-Optics, São Carlos, São Paulo. The use of LED devices is interesting because of the narrow emission band compared to other non-laser light sources and its low cost.

and they have many questions. In conjunction with the physician, nurses spend additional time to assist the patient and answer questions. A well-prepared nurse is a critical component of the PDT program in Brazil. Table 1 shows the role of different professionals in our PDT team.

One of the main problems in PDT is the availability of light sources and fibers. While those components are available in the international market, their prices are prohibitive to many clinics that want to try PDT first before starting to build a whole program. Originally, in conjunction with the Physics Institute, we built at the Amaral Carvalho Hospital, a fully equipped room with an Argon pumped dye laser, a small monocromator for wavelength measurements and two 2.0 Watts diode laser operating at 630 nm. More recently, a LED-based device developed in a collaborative program between the university and the private sector has been developed and used with great success for PDT of large skin lesions. Except for the Argon pumped dye laser, the devices are user friendly and do not demand a specialist to assist in their operation. The dye laser system is a very good device, with variability in power and wavelength, but it must be operated by a specialist. Since complicated instruments create additional difficulties for the implementation of the technique, it is not a good idea to have them during the start-up phase. In the Medical School in Ribeirão Preto, the newly opened PDT facility operates with a dedicated diode laser and a commercially available LED device from MM-Optics, São Carlos, SP, Brazil. For experimental research, a great deal of instrumentation composed of devices for preclinical studies, measuring scattered light, measuring mitochondria activity (respiratory cycle), among others have been developed or purchased. Fig. 2 shows the LED device used in three different laboratories. Fibers and power meters have been developed by the university and tested by many researchers participating in this program.

Table 1 Multidisciplinary PDT team: the staff and their role.

BIOCHEMIST	Cell culture studies (toxicity); Degradation	PHYSICIST	Light Source delivery; Dosimetry; Absorption; Fluorescence
CHEMIST	Synthesis; Absorption of light; Reaction; Degradation; Photosensitizers	NURSE	Drug administration; Follow-up; Side Effects; Care during application; Patient Instruction
BIOLOGIST	Cell culture studies (toxicity); Degradation	PHARMACIST	Drug preparation (topical, systemic) Drug preservation
PHYSICIAN/DENTIST	Patient; Lesion; Diagnosis; Application; Evaluation; Follow-up		

Description of treated lesions and overall results

We have been using PDT for both curative and palliative purposes. Table 2 summarizes the results. We discuss the treatment in detail below.

As an overall procedure, each case is discussed and the physician, nurse and physicist consider potential benefits and consequences of therapy. Dosimetry has always been a topic of discussion and most of our research is now focused on this subject. The use of non-laser light sources as well as the use of topical photosensitizer also have been introduced during this experimental phase of implementation.

Over 400 patients were selected to receive PDT treatments following a protocol approved by the Ethics Committee for Research in Medicine. The main criterion for patient selection was contraindication for conventional treatment such as surgery and radiotherapy. In the case of surgery, this was due to the patient's poor overall condition or those who failed surgery. In the case of radiation, it was due to tumor location in which PDT might be less morbid or for patients who failed radiotherapy. To select patients for PDT application, we initially preferentially considered skin lesions with easy light access and little possibility for complications. After acquired experience with PDT in skin lesions, more complicated cases were considered and included in the protocol. The photosensitizer was a hematoporphyrin derivative Photogem® (Moscow, Russia) for all cases of systemic injection and aminolevuleic acid (ALA) for topical applications of non-invasive skin basal cell carcinoma lesions. In the case of injection, 1.5—2.5 mg/kg was injected 24—48 h prior to light irradiation. For the case of ALA, a cream containing 20—25% of the photosensitizer was prepared and a drug—light interval of 4—6 h employed. We have used two different systems for light irradiation: a dye laser pumped by an argon ion laser (Coherent, USA) and a LED-based device. In the laser case, we operated with Kyton Red at 630 nm wavelength. The light was coupled

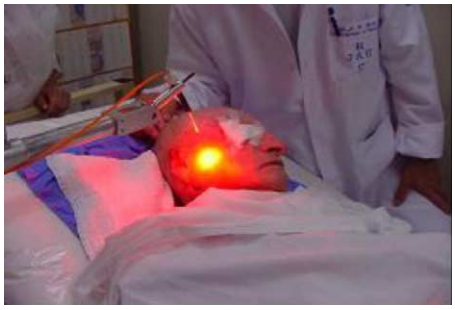

Figure 3 Typical application in a BCC in the head and neck. The spot size is controlled considering the beam divergence at the end of the fiber. In many cases, black paper or aluminized fabric protection is applied to the normal areas to avoid unnecessary illumination (patient under care of Dr. G. Cestari).

to a fiber and a power as high as 2.0 Watts could be delivered. The light spot was expanded according to the area of the lesion. Intensities were kept between 100 and 400 mW/cm^2. Doses varied from 150 to 300 J/cm^2 depending on the case, localization of the tumor, extension, amount of injected photosensitizer among other variables. For the LED-based device, the total emitted power was fixed at 3 W in an area of about 20 cm^2 resulting in a fixed intensity of about 150 mW/cm^2. In this case, the illumination of the lesion was done by blocking with black paper or aluminized fabric the adjacent normal tissue. The illuminated area included a margin conventionally considered in surgery. Since the majority of patients were of advanced age, we had patients inhaling oxygen during PDT to keep the oxygen saturation at the 98% level (Fig. 3).

The only case that showed normal skin damage due to the systemic photosensitization was a hair stylist that kept working with the hair dryer. The fingertips showed some skin pealing which was completely controlled after she discontinued use of the hair dryer. After this observation, every patient was informed to not use this kind of device as well as all the other considerations of protection from sun and other bright light exposure. The skin hyperphotosensitivity was expected for the first two to

Table 2 Overall results for the PDT treatments.

Region	CR (100%) (%)	PR (>OR = 50%) (%)	Number of lesions
Skin	66	34	1050
Oral	45.5	54.5	84
Larynx	—	100	25
Nasopharynx	100	—	12
Eye inner canthus	90	10	28

Included are only patients for which follow-up data was available (CR, complete response; PR, partial response with 50% or more of volume tumor reduction).

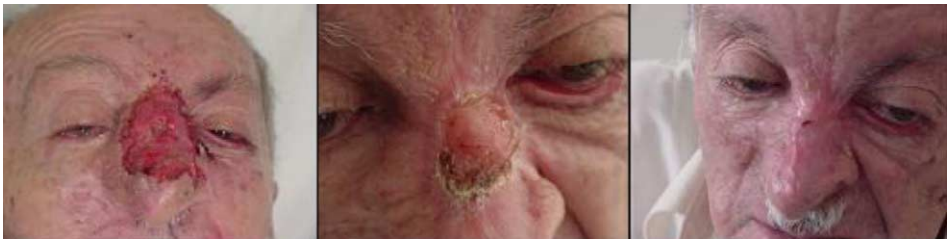

Figure 4 Example of a BCC treated with PDT. Here, we have the initial aspect of the lesion, 30 days and 12 months after treatment. This patient is being followed for over 30 months without recurrence. He had a long history of previously unsuccessful treatments (Patient under care of Dr. G. Cestari).

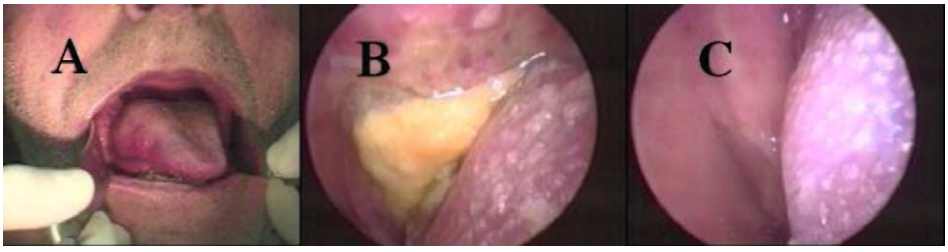

Figure 5 Example of SCC of the oral cavity. (A) Initial lesion, (B) 7 days after PDT where the tumor appears as a complete necrosis and (C) after 30 days with complete recovery of the mucosa.

four weeks but all patients were informed to avoid sunlight exposure for at least four weeks and also to perform a simple test exposing a small area of the hand. In the absence of any skin reaction the patient could abandon sunlight exposure precautions. Our patient population did not have difficulties following these instructions.

Oral cavity

Virtually, all treated patients had failed previous surgery. We have used 1.5 mg/kg of Photogem® for all cases, and illumination followed 24—36 h after photosensitizer administration. For oral cavity, we normally deliver no more than 200 J/cm^2 following previous published work [9]. In the case of direct illumination, the lesion was divided in a central spot and as many as needed peripherical spots. In the case of tumor more than 0.6 cm thick, an interstitial probe was used illuminating the tumor with cylindrical symmetry. The interstitial dose has to be carefully delivered, keeping to a 200 J/cm^2 average. We directly inserted the diffuser into the tissue. First, a 2 mm needle was introduced, creating a path for the introduction of a transparent quartz tube, 2.5 mm in diameter with one end closed. Finally, the fiber with the cylindrical diffuser was introduced within the tube. The use of a transparent tube seems important for the type of diffuser we use because of possible carbonizing action at the surface. In fact, in cases where the 1—2 cm long diffuser was employed with light power as high as 1.5 W, contact with blood or other pigmented tissue has produced enough light absorption to promote carbonization after several minutes of exposure. In those cases, destruction of the diffuser and damage to the tissue has been observed and most importantly, the PDT treatment was very inefficient. All tumors treated in the oral cavity were squamous cell carcinoma (SCC). All had shown significant response to PDT almost immediately after treatment. Normally, there is a rapid color change during the treatment, as result of severe vascular damage. In the cases of palate lesions, post-PDT swelling was not as intense as for floor of the mouth lesions. In three cases, the induced swelling was significant so a planned tracheostomy was performed. We observed significant clinical response in all oral lesions. For one patient with oral melanoma, the first PDT application showed very poor results. Positive response was obtained only with a combination of debulking surgery and PDT. Figs. 4—7 show many of the typical results. In a future report, we will present in detail our cases of oral cavity PDT.

Nasopharynx

We treated four patients with carcinoma of the nasopharynx with great success. The administrated dose of Photogem® was 1.5 mg/kg followed by illumination 24 h after. PDT was offered to patients who had failed previous treatment and had persis-

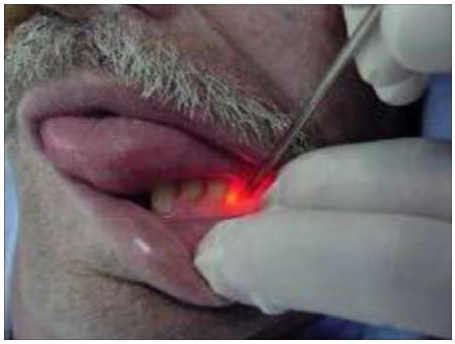

Figure 6 In this case the fiber with a cylindrical diffuser is used inside a quartz transparent tube introduced into the tumor. The calculation of the illumination time in these cases has to be done with care to guarantee good illumination throughout the whole lesion.

tent local disease. All PDT-treated lesions showed complete clinical response. One of the patients was free of the local tumor treated until the time of her death, 12 months later from metastases in the lungs. The other patients are still free of disease, the longest at 48 months follow-up. Two of the patients received two applications of PDT at an interval of 6 months. The results show that PDT may well be an appropriate form of treatment for this tumor site as a first option in selected patients.

Skin

Tumors of the skin exhibit many advantages compared to others sites when treated with PDT [10]. They are normally very accessible, allowing a good plan of illumination. This is an important guarantee for a well-performed PDT treatment because the whole tumor needs to receive light dose above threshold for a good outcome. Skin tumors are relatively flat and superficial presenting a clear surface for illumination. The level of scattered light outside the field of illumination allows for estimations for the overall light penetration, even with naked eye exam. We have found that the treatment success may be predicted by the reaction of the tissue following the illumination. After a few weeks, the necrosis of the tumor and the recovery of the surrounding tissue can be clearly observed. The scab at the tumor site and healing tissue surrounding it after treatment can be directly observed by the patient and the involved professionals, working as a real time feedback for on going procedures. During the healing process, the treatment margins often reveal if there is still tumor left behind, as well as the aspect of the selectivity of the treatment. Pain during treatment can be easily controlled with conventional analgesics. The illumination can be performed using fixed supports that hold the fibers, and the team composed of the physician and nurse always verify that the patient does not move during treatment. The fiber support can always be repositioned if the patient moves. An important point concerning skin diseases in Brazil is the fact that they are mostly BCC or Bowen's (rarely SCC) and these types of tumor take time to metastasize, giving the physicians the chance to observe one treatment for results and if indicated take action or modify the next treatment to ensure the best chance to cure the disease. We have observed that it is better to wait for the scab to fall off by itself. Rarely, in the case of extended lesions, one may think to remove the scab after a few months, to evaluate grafting, if necessary. In our series, many extensive lesions have been treated with good results by PDT alone. In extensive cases, a well-planned program for multiple treatments is usually necessary. In these cases, treating first, heavily the tumor border and then the remaining central part is our treatment approach. In the case of multiple BCC or widespread Bowen's disease, we think PDT shows clear advantages over surgery in terms of cosmesis and easy of therapy.

Skin lesions receive a higher light dose compared to mucosa. We deliver 250—300 J/cm^2 in all skin lesions. Patients in this group receive from 1.5 to

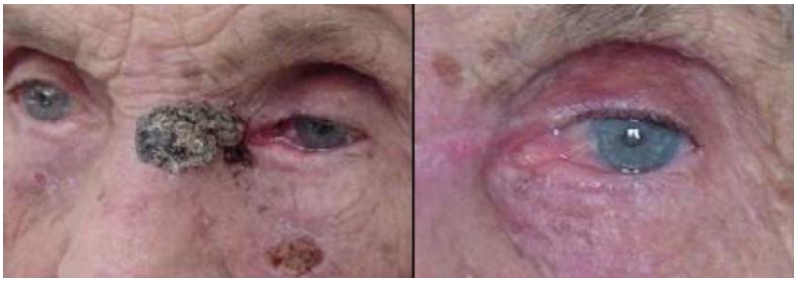

Figure 7 Tumor of the inner canthus of the eye. Treated lesions show 100% elimination with a single application. Special care with eye protection has to be considered in these cases (patient under care of Drs. G. Cestari and J. Berto).

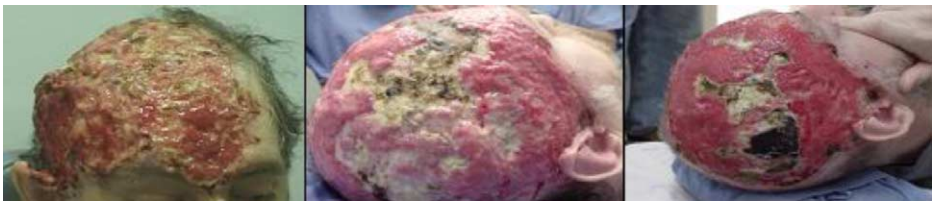

Figure 8 Extended skin cancers have been treated for curative or palliative intent. A treatment plan is necessary to perform a multi-course application. In this example, the left picture refers to the initial therapy, the middle refers to clinical appearance after 30 days of the second PDT course and the right after 60 days of the third PDT course.

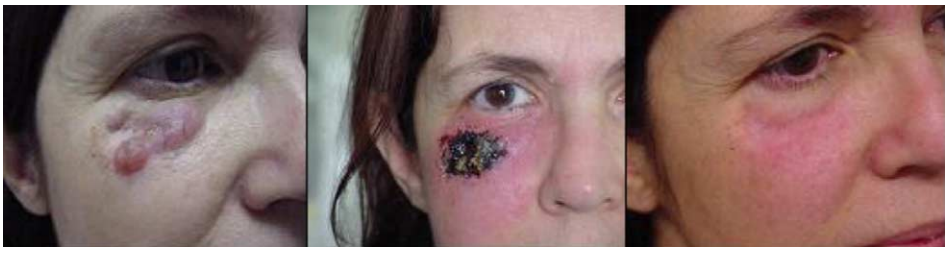

Figure 9 This patient did not want surgery as she was afraid of the aesthetic result. The following sequence can be observed: initial lesion, 15 days after and 1 year after PDT treatment.

2.5 mg/kg of Photogem® or ALA cream with a 20% concentration. The sensitizer choice followed our protocol. The topical cream was only indicated for the most superficial lesions.

The majority of cases were basal cell carcinoma (BCC) and in a few cases we have other rarer types. Three cases of melanoma were included, with one of the cases being an advanced stage. For the melanoma cases, we had one partial response (70% elimination of the lesion) but no response in the other two cases.

For the BCC cases, treatment varied according to the geometry of the lesion and the specific location. In general, we have used aluminized fabric to protect the areas that we do not want to illuminate.

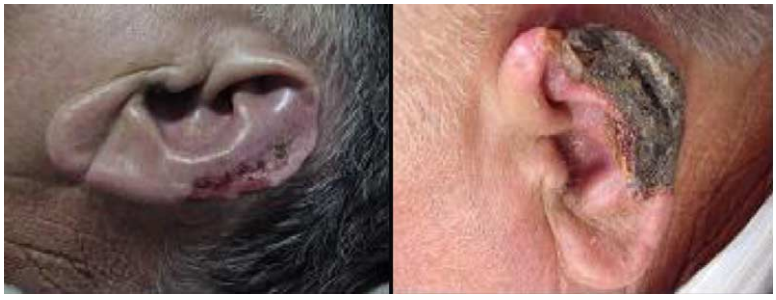

Figure 10 Cancer lesions in the ear. The pictures show the evolution at 2 and 6 months follow-up.

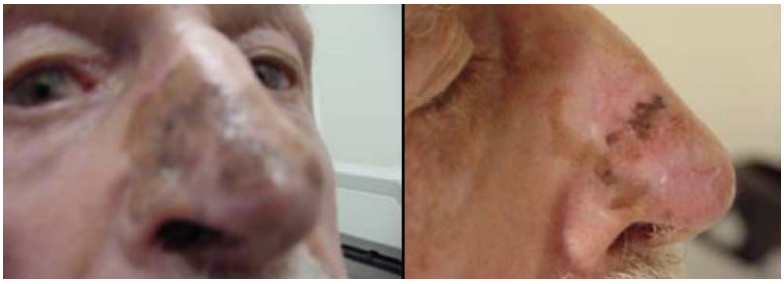

Figure 11 This is a melanoma case where we achieved a partial response after 2 months of PDT treatment. Present on going research may come up with a better protocol to treat melanoma using PDT.

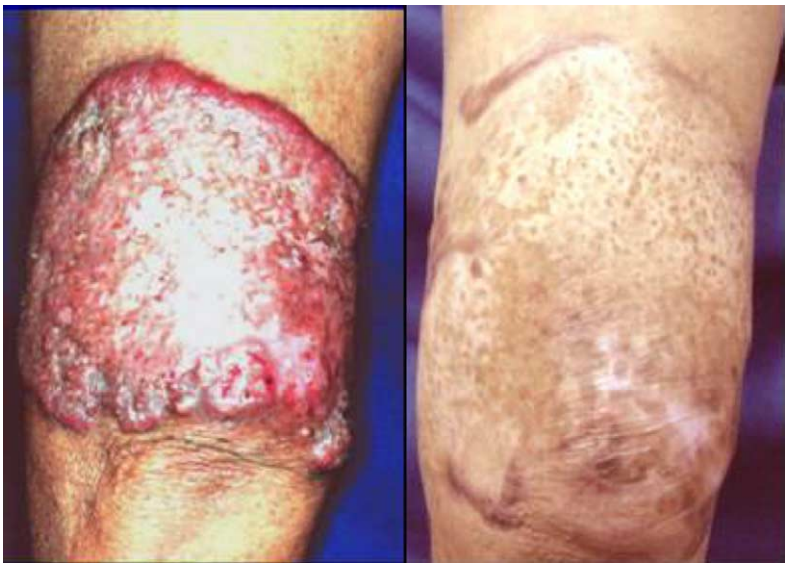

Figure 12 This lesion was not indicated for surgical removal due to its size and anatomical site (elbow). This *keratoacanthoma cuminatum* was treated twice by Dr C. S. Souza with a satisfactory final result.

There are many additional applications of PDT for non-cancer skin diseases like psoriasis and keratosis. We have started to treat these but with lower light doses.

One particular type of lesion that has shown good response to PDT is lesion at the inner canthus of the eye. For these cases, a special spoon-shaped device has been developed to be put in the inner part of the eyelid to protect the eye during illumination. Fig. 7 shows a typical result for an inner canthus of the eye patient with complete response and good cosmetic results. We have had 90% elimination of inner canthus eye lesions with only a single application of PDT. The recovery takes about 4 months.

Figs. 8—12 are good examples of PDT results in our PDT program.

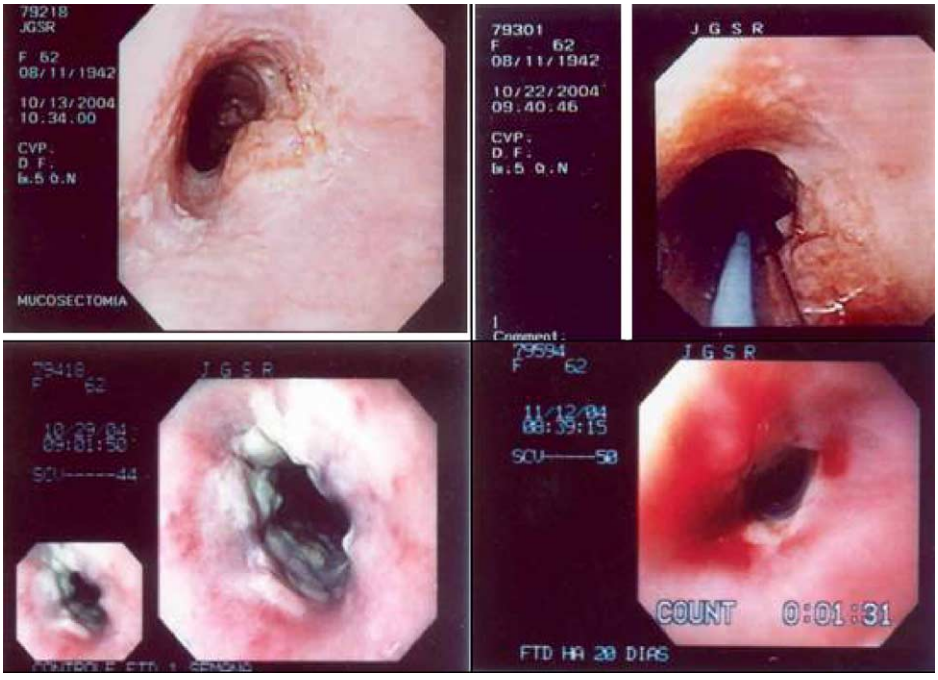

Figure 13 Detail of an application of esophagus cancer where the linear diffuser fiber is positioned inside a transparent gastro-sound tube.

Esophagus and bladder

A total of 7 patients with SCC in the esophagus were treated with PDT. We have used cylindrical diffusers and doses that varied from 100 to 250 J/cm^2. Patients received 1.5 mg/kg of Photogem® and illumination within 24—36 h. We have observed tumor elimination in 4 of the 7 patients. The superficial lesions show a good response to PDT. For patients with already advanced stage disease, the treatment only promotes a better quality of life by opening the esophagus. In one patient, a combination of transparent stent and periodic application of PDT held the disease in the esophagus for over a year. Chest pain was reported by all patients and a mild to moderate stenosis was observed in all patients. In some of the patients, mechanical dilation was necessary and successful. We have developed a specific way to illuminate the tumor and to prevent patient discomfort during the whole endoscopic procedure. This consists of using a transparent endogastric tube with the fiber in it. We will describe this procedure in detail in a coming report. At the present time, a clinical trial involving PDT and ultrasonic depth evaluation of the lesions is being carried out. Fig. 13 shows one of the treated esophagus by Dr. Modena from the Medical School of Ribeirão Preto and Fig. 14 shows a patient from Hospital Amaral Carvalho during a PDT esophagus procedure through a transparent endogastric tube.

The patients treated with PDT in the bladder, had multiple superficial lesions and they were treated by a cystoscopic procedure. In one of the patients, the tumor was first resected with an electronic cutter, followed by PDT. Besides a strong cystitis, all patients show complete elimination of lesions within a 36 months period.

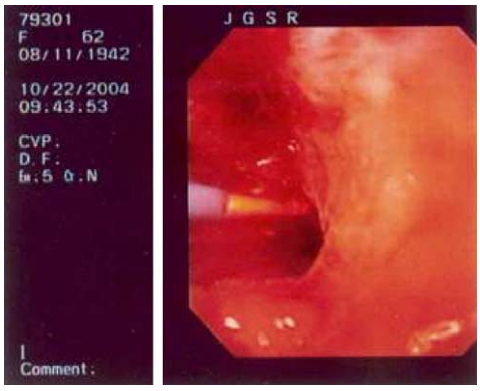

Figure 14 Patient under esophagus PDT treatment. The use of a fiber inside a transparent endogastric tube of large diameter allow us to obtain more comfortable therapy.

Breast

Our experience with PDT breast cancer has been restricted to a few cases of chest wall recurrence after total mastectomy. In those cases, the patients have extensive superficial lesions and they respond quite well to the treatment with an extensive area of necrosis. We have used a LED light device for those cases, and we now believe that 200—300 J/cm^2 of dose may be too high with a

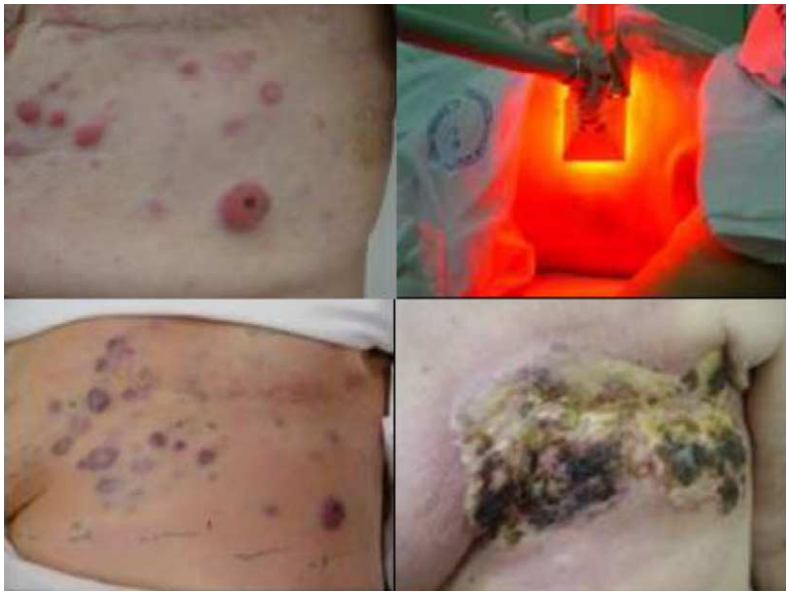

Figure 15 Treatment of a chest wall lesion using a LED device. The large illumination area of these devices allows a fast treatment with good overall result.

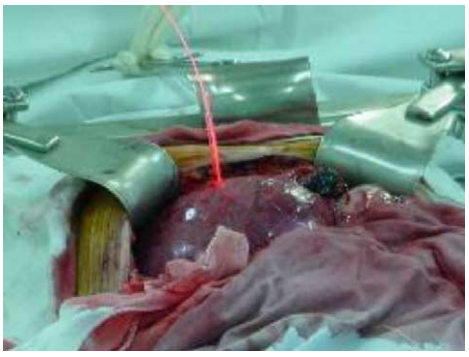

Figure 16 Application of interstitial PDT in a hepatocarcinoma patient. The application can be done with a single fiber in multiple points or with multiple fibers. The fiber has linear diffusers.

drug dose of 1.5 mg/kg and 24 h between injection and illumination. Dr. Cacilda Souza from the Medical School of Ribeirão Preto is carrying on PDT for a group of chest wall recurrence patients using a lower light dose, 100 J/cm^2 and a 48 h interval between drug administration and illumination. The level of necrosis in these cases is reduced and the patient has an easier post-treatment recovery.

Our experience with chest wall is just beginning and are following steps reported by Allison et al. [11] with lower drug dose. Chest wall patients normally present to us with external beam-irradiated tissue and PDT seems to act in a more severe fashion than in the non-irradiated tissue. This may explain the over necrosis observed in our patients. Fig. 15 shows a chest wall application using a LED device. A treatment with a large LED light field is faster than using laser microlenses making the treatment easier on the patient.

Other lesions

We have treated many other types of lesions, located in numerous anatomical sites such as penis, intestine, lung, and liver. In a few cases, the use of an interstitial fiber to promote tissue illumination has been used. Fig. 16 shows an interstitial use of fiber for PDT of a non-surgical case of hepatocarcinoma, where the application has the aim of tumor reduction only. We are now in a stage of spreading our results around the country to stimulate other groups to get involved with this technique. A trial of PDT for the papiloma virus has been carried out with a very positive early result. Our cases will be reported in detail in a separate article.

Laboratory work

Beside the clinical implementation of PDT, we have been involved in setting up a laboratory structure to carry out experiments in this field. Reviewing experimental research together with the clinical team results in a very nice combination because it creates the opportunity for clinical feedback. Our main concern has been to be able to work on a real time dosimetry concept where many different variables can be placed together and evaluated during treatment to optimize the final result. Our clinical experience has shown that PDT works but additional work must be done in dosimetry to improve it. Better use of available sensitizers is one of our goals. On the experimental front, we have three institutions involved: the Physics Institute in São Carlos has taken the duties to develop the necessary instrumentation as well as perform research in the field of photo-stability of photosensitizers, light propagation in biological medium and fluorescence detection of photosensitizers in vitro and in vivo. The pharmacokinetics of experimental models has also been included among activities carried out in the physics domain. The Chemistry Institute of São Carlos has taken the responsibility to work on biochemistry investigations of the photosensitizers used at the clinical level. Experiments to determine the cytotoxicity and photoproducts of the optically degraded photosensitizer as well as the photon effect on specific cell culture are their main activities. Finally, the School of Medicine in Ribeirão Preto is doing all the pre-clinical studies to determine the threshold dose, PDT action on mitochondria and the evaluation of new PDT devices.

The three institutions work closely together and share part of the facilities to generate the necessary synergism demanded by PDT.

Conclusions

In conclusion, we have implemented PDT in Brazil with great success. The initial resistance of physicians over the use of PDT has been overcome by good results and the country is experiencing a spread of this treatment with many new clinics and hospitals involved in PDT. The current results are satisfactory, but there is room for improvement. In particular, further application of our protocols and better understanding of the concept of PDT dosimetry are critical. We have observed that the collaborative ventures between researchers in different fields as well as the extrapolation of experimental models to the clinic produce considerable improvement in our results. We strongly believe that the

next generation of treatments will show enhancement over current results and are optimistic about PDT becoming a mainstream treatment choice.

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