Combined Carbon Dioxide Laser with Photodynamic Therapy for Nodular and Superficial Basal Cell Carcinoma

Almost Scarless Cure With Minimal Recurrence

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Background: Basal cell carcinomas (BCCs) are often seen by general practitioners, plastic surgeons, and dermatologists in the outpatient setting. Photodynamic therapy (PDT) and CO_2 laser when used as monotherapy have been successfully used to treat small BCC, with greatest success in the superficial histological subtype but have limitations compared to surgical excision due to a limited depth of penetration of PDT (2 mm absorption) limiting efficacy. We describe our experience of dual-modality treatment improving efficacy, cosmetic outcomes, and minimizing recurrence.

Methods: One hundred ten patients with a total of 177 lesions mainly on the head and neck were treated with combined therapy using an UltraPulse CO_2 laser and PDT using methyl aminolevulinate (METVIX) at the same sitting, with repeat PDT 1 week later. We evaluated recurrences, cosmetic outcomes, patient satisfaction, and costs.

Results: The mean age of patients was 67 years. The mean follow-up period was 32.2 months, with a range of 7.7 to 68.5 months. Eighty six lesions were followed up for more than 3 years. A total of 177 lesions were diagnosed and treated. Only biopsy-proven BCCs were included in this study. Histologically, 34 (19.2%) were superficial subtype, 50 (28.2%) nodular, 9 (5.08%) infiltrative, 7 (3.95%) morpheic, 3 (1.69%) mixed, and in 74 (41.8%) diagnosis was simply BCC. All lesions responded to treatment as assessed by clinical evaluation with regular follow-up. The total recurrence-free rate was 97.1%. In 88.1% lesions, a single cycle of treatment was required; 9.03% had 2 cycles and 0.56% underwent 3 cycles. In 3 of the patients, no data were available. Recurrences were noted in 5 (2.82%) cases. All recurrences were treated successfully, all but one using repeat laser-PDT. One patient underwent surgical excision. No significant complications were encountered, although mild hypopigmentation was occasionally seen and some discomfort is experienced with PDT.

Conclusions: Combined CO_2 laser and PDT have equivalent cure rates to surgery for BCCs—notably of the nodular subtype—these modalities acting synergistically. This strategy provides cure often with scarless outcomes as illustrated. Laser with PDT is most appropriate for patients who value excellent cosmetic outcomes and where avoidance of an invasive procedure is an important factor. In addition, this modality comes into its own for specific groups of patients, such as those on Warfarin or those with diffuse or multiple lesions.

Key Words: laser, CO_2, PDT, photodynamic therapy, BCC, basal carcinoma, MAL-PDT, ALA

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BACKGROUND

One of the difficulties in the management of basal cell carcinoma (BCC) is rationalizing the concept of "a cancer that isn't a cancer." Although these skin tumors are acknowledged as the leading cause of cancer in the western world,[1] both the medical profession and the lay public consider the notion of "cancer" as a disease which is commonly life-threatening and has the potential to metastasize. On both these counts, BCCs invariably fail to fulfill the perceived definition, and this leads many clinicians to use alternative terminology in discussions with patients—such as "rodent ulcer"—to avoid the use of the "c" word, which is unduly alarming and does not appropriately reflect the prognosis of most of these lesions. Although rare reports do exist of metastasis, and some lesions that have been neglected or are of certain histological subtypes in specific anatomical locations can be aggressive and occasionally fatal, this scenario is rare.[2] The morbidity associated with BCCs is therefore more commonly related to cosmetic deformity and functional compromise related to treatment itself—such as surgery including skin grafts and local flaps, rather than to mortality. Unlike melanoma and squamous carcinoma, the primary treatment for which is surgical excision, BCCs are treated using a large number of modalities [topical treatments, curettage, cryotherapy, radiotherapy, photodynamic therapy (PDT), laser, and surgery] under the care of surgeons, dermatologists, and clinical oncologists.[3,4] Most of these modalities can be considered "curative" depending on one's threshold for "cure" in recurrence rates of each modality, and each have their own pros and cons. The treatment options, evidence base, and outcomes of these have been published by the UK National Institute for Clinical Excellence and reviewed in other key papers.[5,6]

The most important outcome variables in the treatment of BCCs, therefore, are recurrence rates and cosmetic outcome. Because of the slow rate of growth of these lesions, and the generally favorable prognosis, topical treatments are commonly used for small and superficial lesions based on clinical diagnosis. This avoids the scarring associated with surgery, usually resulting in successful treatment, leaving surgery as the next alternative in case of recurrence or nonresolution. More invasive modalities tend to be used for larger lesions or those of an aggressive histological subtype.

Photodynamic therapy and CO_2 laser have both been successfully used as monotherapy to treat BCCs,[7–16] with greatest success in the superficial histological subtype. These modalities when used alone have a number of limitations when compared to surgical excision, in particular the limited depth of penetration of PDT (2 mm), which potentially limits the efficacy of treatment of thicker BCCs such as those of the common nodular subtype. Isolated CO_2 laser ablation is associated with dermal scarring. We have previously published our preliminary experience of combination therapy using both modalities simultaneously to demonstrate the initial safety and efficacy in 12 patients with up to 1 year of follow-up.[17] Subsequent to this preliminary study, we introduced dual-modality

therapy for BCCs into routine practice in our unit after approval by the hospital trust as a recognized treatment. We now describe our definitive experience in treating 177 lesions in a large series, some extending beyond 5 years of follow-up. These patients were offered laser-PDT or surgery based on current evidence and underwent informed consent based on our preliminary published experience. Exclusion criteria are listed as follows:

ulcerated lesions,
radio-recurrent lesions,
lesions abutting the ocular mucosa, and
lesions with squamous differentiation.

METHODS

Laser-PDT Technique

We use an UltraPulse CO_2 Laser (Lumenis, UK) set at 150 mJ, 10 Hz, with a 2-mm collimated beam to vaporize the BCCs, while maintaining a bloodless field with no eschar. The CO_2 laser is unique in its ability to provide pinpoint accuracy in surgical ablation to a depth of 200 μm per pass of the laser while providing a bloodless field which is critical to the feasibility of subsequently undertaking PDT at the same sitting. This is also an advantage when treating patients on aspirin or warfarin. The first pass of the laser ablates a 3-mm rim of normal epidermis around the tumor to facilitate penetration of the methyl aminolevulinate into tumor not visible on the surface.

Photodynamic therapy was carried out by application of the photosensitizing agent methyl aminolevulinate (METVIX) [Galderma] covered with an occlusive dressing for 3 hours and then typically illuminated with the Aktilite 16 LED lamp at 631 nm, 37 J/cm^2 for 7 minutes 24 seconds. Photodynamic therapy was alternatively activated using Intense Pulsed Light (IPL)—(Energist Ultra Variable Pulsed Light System; Energist, Swansea, UK) 80 J cm^{-2}, double pulsed at 40 J cm^{-2}, pulse train of 15 impulses each with a duration of 5 milliseconds using a 610 to 950-nm filtered hand piece. A dressing with topical neomycin ointment (Polyfax), to continue for 5 days is applied. Photodynamic therapy is repeated as per manufacturer's instructions 1 week later for all patients. Follow-up is undertaken at 6 weeks, 3 months, and 6 months, but often ongoing with patients with numerous lesions and elastotic skin. Figure 1 illustrates the treatment algorithm for laser-PDT. Of note, 3 of 5 patients with recurrence refused surgery and opted for repeat laser-PDT instead of surgery despite this algorithm. We include a table of basic costs (Fig. 2).

No accurate record-keeping of size of lesions was available that would have strengthened our study.

We also noted any poor cosmetic outcomes due to hypopigmentation, which is a rare but recognized feature of PDT, as well as any other notable problems. To assess for recurrence at follow-up, the treated areas were compared with pretreatment and any previous posttreatment photographs. The areas were then assessed clinically for changes in size, shape, pigmentation, or for any evidence of telangiectasia, ulceration, or nodularity.

In practical terms, the advantage of combination therapy lies in the vaporization of the elevated nodular component of the BCC, to produce a bloodless field at epidermal level, which is ready for application of the photosensitizer. With removal of this raised component, the depth of penetration of the PDT is likely to be enhanced, potentially allowing greater efficacy of treatment.

Overall, the tolerance of the procedure was excellent. Mild discomfort is a feature of PDT for any nature, and we have initially overcome this with the use of electric fans, local anesthesia, water sprays, "Jellyperm" pads, and diversion techniques during treatment. A long-acting local anesthetic for the CO_2 laser ablation part of the procedure will still be effective at the time of PDT activation, and has now all but eliminated the painful component of PDT activation. Bupivacaine with epinephrine is a good choice which lasts long and maintains an optimum bloodless field.

RESULTS

Response and Recurrence Rates

Of the 110 patients, 37 patients were men and 73 women. The mean age was 67 years. The mean follow-up period was 32.2 months,

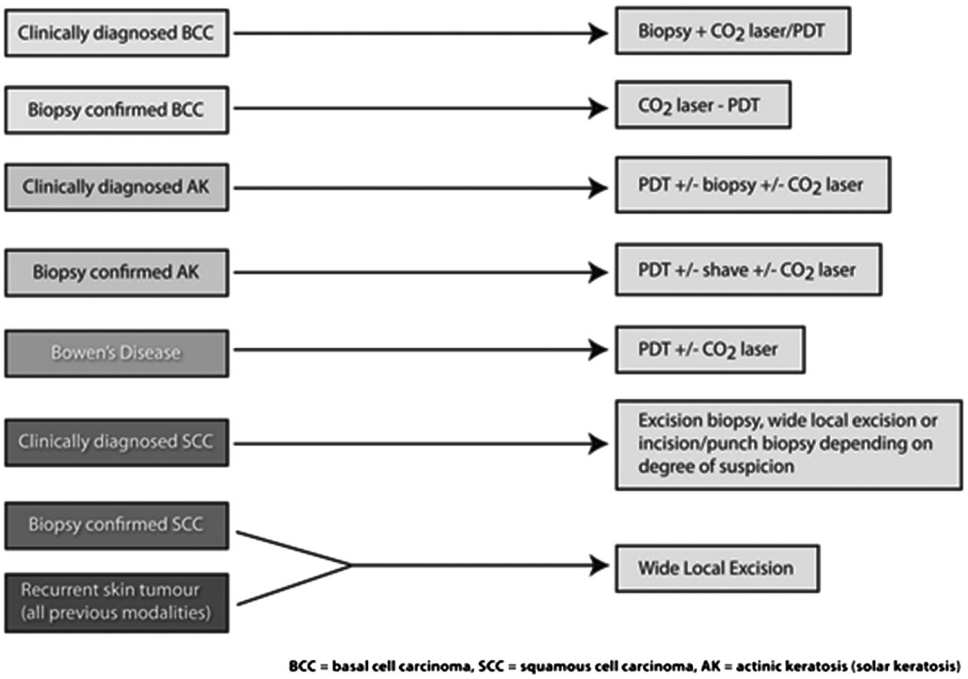

FIGURE 1. Treatment algorithm for laser-PDT.

DRUGS		
Metvix (methyl aminolevulinate 160 g /g) 2 G	at 0.3 G =	£36.66
1% Xylocaine & Adrenaline	1	£0.54
0.9% Sodium chloride	1 ampoule (10 ml)	£0.11
Polyfax ointment 20 g	1	£4.58
Geliperm 100 x 100 x 3.3 mm	1	£2.39
HSDU		
Wound care pack	1	£0.33
Anaesthetising pack	1	£0.35
DRESSINGS		
Interpose lite 5 x 7.5 cm	1	£0.05
Tegaderm 6 cm x 7 cm	1	£0.21
Miscellaneous		
Monoject Syringe 2 ml	1	£0.02
Monoject needle 21 G x 1.5" (Green)	1	£0.01
Sterican needle 17 g x 1.5"	1	£0.07
Disposable scalpel	1	£0.22
HISTOLOGY		
Histology of sample	1	proposed cost £70.00
STAFFING		
CNS	at 30 min =	£8.75
Support	at 45 min =	£5.48
TOTAL for 2-cycles of treatment with biopsy:		**EST £144**

FIGURE 2. Basic (non-infrastructural) costings and materials for laser + PDT treatment of 1 lesion.

with a range of 7.7 to 68.5 months. Eighty-six lesions were followed up for more than 3 years. A total of 177 lesions were diagnosed and treated. Only biopsy-proven BCCs were included in this study.

TABLE 1. Patient Satisfaction Questionnaire

1. How important was it for you to be treated quickly after your diagnosis of skin cancer?
2. How would you rate the waiting time for treatment with (a) Surgery (b) Laser?
3. How would you rate the anxiety caused with (a) Surgery (b) Laser?
4. Rate the pain of each treatment (a) Surgery (b) Laser.
5. Rate the scar left by each treatment (a) Surgery (b) Laser.
6. How disruptive was each treatment to your life (a) Surgery (b) Laser?
7. Can you rate your overall experience of treatment (a) Surgery (b) Laser?

Histologically, 34 (19.2%) lesions were superficial subtype, 50 (28.2%) nodular, 9 (5.08%) infiltrative, 7 (3.95%) morpheic, 3 (1.69%) mixed, and in 74 (41.8%) diagnosis was simply BCC. All lesions responded to treatment as assessed by clinical evaluation with regular follow-up. The total recurrence-free rate was 97.1%. In 88.1% lesions, a single cycle of treatment was required; 9.03% had 2 cycles and 0.56% underwent 3 cycles. In 3 of the patients, no data were available. Recurrences were noted in 5 (2.82%) cases. All recurrences but one were treated using repeat laser-PDT, 1 patient underwent surgical excision. No significant complications were encountered, although mild hypopigmentation was occasionally seen in less than 5% of patients. Of the morpheic subtype of lesion, 2 of 7 recurred.

Patient-Related Outcomes

We were interested to compare laser-PDT with surgical treatment from a patient perspective and as an audit tool to improve our

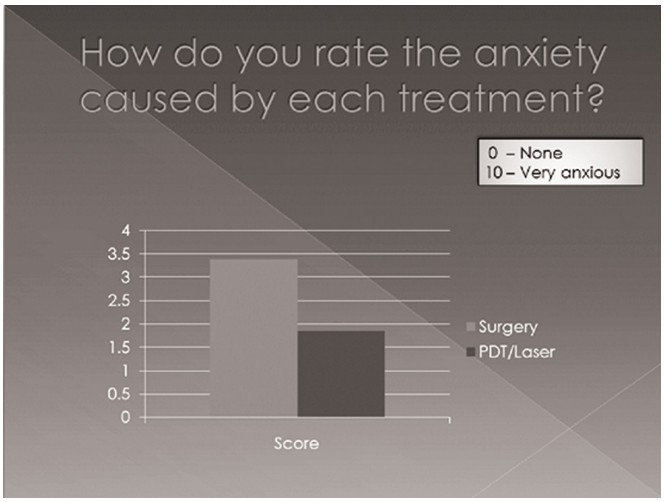

FIGURE 3. Patient-reported outcome surgery versus laser-PDT—anxiety levels.

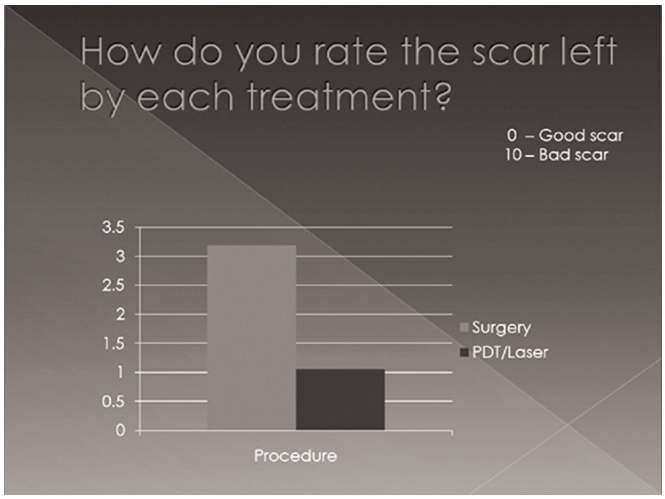

FIGURE 5 . Patient-reported outcome surgery versus laser-PDT—cosmetic outcome/scar.

practice. Thirty-three patients were found to have had previous excisional surgery for BCCs. A 7-part audit questionnaire was designed (Table 1) to compare the patients' experience of surgery with laser-PDT, answers all being on an analog scale of 0 to 10 (Figs. 3–7). Patients were all contacted by telephone and asked to complete the questionnaire verbally with 20 responses. Statistical analysis of results was performed using SPSS v15.0. A paired *t* test was used to compare results from the patient satisfaction part of the study, with confidence intervals set to 95%.

Patients preferred laser-PDT in all aspects except the pain from treatment which was worse with PDT activation (and has been subsequently resolved because of this audit). Our results were statistically highly significant in 2 specific areas despite the relatively small numbers, these being the cosmetic outcome of the scar ($P < 0.001$) and the anxiety related to treatment ($P < 0.001$) (Table 2), as well as the overall procedure. Further significant results included the waiting time and pain of the procedure.

No other evidence has been published to date with reference to the anxiety caused by PDT or the other accepted treatment modalities. The reason for patients being less anxious about PDT were unclear but could possibly be related to the absence of an operating room environment and the general factors associated with surgery such as bleeding, diathermy (sound and smell), and lying flat on an operating table. The pain experienced during treatment with PDT is a recognized drawback of the treatment. This small audit helped us to develop a long-acting local anesthesia strategy at the time of CO_2 ablation, eliminating the severe pain component of PDT.

DISCUSSION

Of all the numerous modalities that exist for the treatment of BCC, only surgery (standard surgery and Mohs micrographic surgery) provide histological confirmation of successful treatment. The basis for treatment of BCCs with the other commonly used modalities (cryotherapy, radiotherapy, topical therapies, curettage, PDT as monotherapy, and laser monotherapy) rely on the evidence base for successful treatment and recurrence rates. This study provides an evidence base for laser-PDT with 100% initial ablative response and recurrence rates of 2.7% with an average of 32 months follow-up.

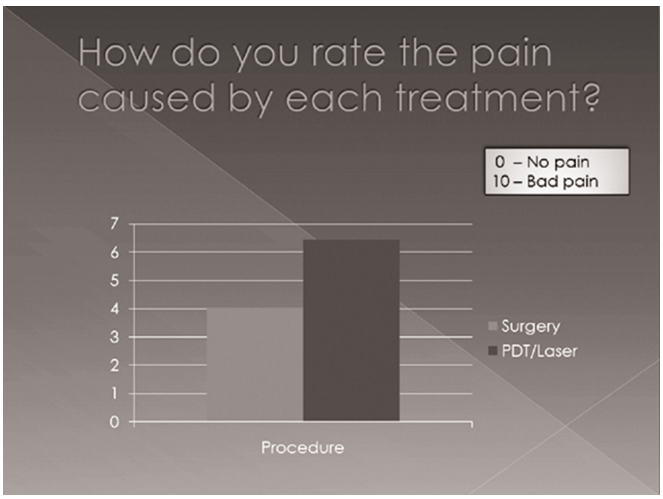

FIGURE 4 . Patient-reported outcome surgery versus laser-PDT—pain scores.

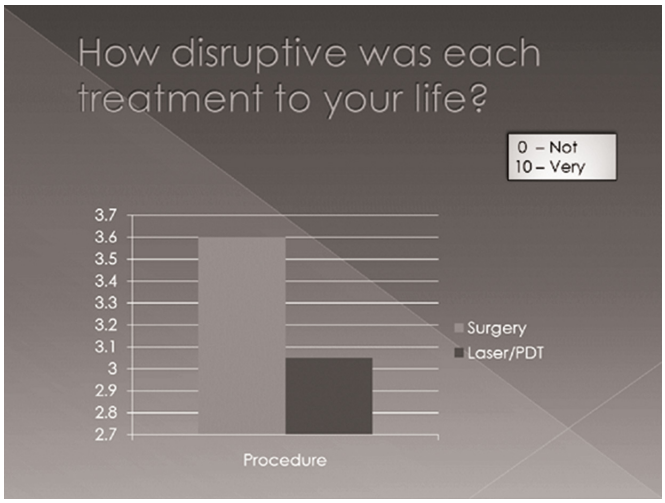

FIGURE 6. Patient-reported outcome surgery versus laser-PDT—disruption to life.

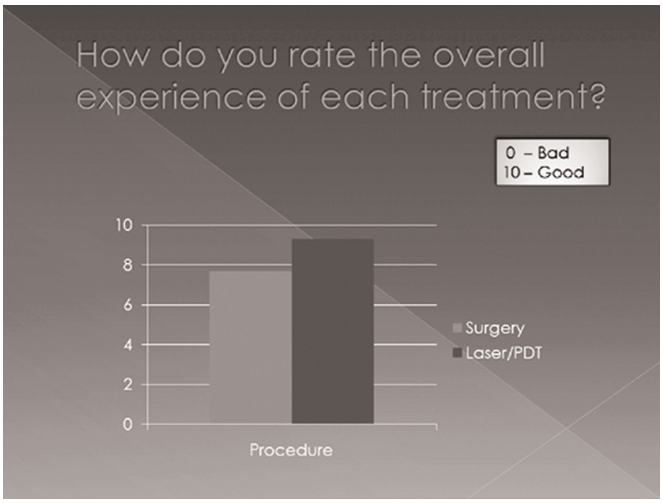

FIGURE 7. Patient-reported outcome surgery versus laser-PDT—overall experience.

FIGURE 8. Large nodular lower eyelid BCC treated with 1 cycle of laser-PDT with outcome at 12 months.

Our dual-therapy approach demonstrates synergism between the laser and PDT, probably by a much greater penetration of PDT in the absence of epidermis and after subtotal lesional ablation. This may extend the remit of these modalities to the treatment of larger lesions than were previously considered untreatable using laser or PDT alone. This large series, many with more than 5 years follow-up, provides a considerable weight of evidence to recommend this modality for oncological safety. As demonstrated in the figures, cosmetic outcomes are exceptional, usually without a visible scar, and laser-PDT is thus suited in particular for cosmetically sensitive areas or for patients for whom surgery is a less favorable option. Examples of patients having undergone treatment are illustrated in Figures 8–11, and these images are typical rather than exemplary. These dramatic results should provide incentive for future randomized clinical controlled trials. The advantages of laser-PDT can be seen when comparing the 2 different patients with almost identical lesions in Figure 11: one patient treated with laser-PDT and the other with flap reconstruction.

CO_2 laser monotherapy is a very versatile device in skin oncological practice, providing good visualization of a bloodless plane, short healing times, and excellent cosmetic outcomes.[8–10] UltraPulse techniques, as used in this study, reduce unwanted thermal damage extending outward from the ablation zone, thus improving healing and reducing scarring.

Photodynamic therapy as monotherapy for BCCs is effec tive in the treatment of BCCs with a better cosmetic result than conventional surgery. However, there is a trend for higher recurrence rates with this modality in all but superficial subtypes due to a limited depth of penetration.[7,8,13] Photodynamic therapy as monotherapy for nodular BCCs has therefore fallen out of favor. This evidence from large series of BCCs treated with PDT show a wide range of response rates from 34% to 100%, with inferior clearance rates in nodular compared with superficial subtypes. Methyl aminolevulinate (METVIX) PDT is proven for BCC, offering advantages over nonmethylated 5-ALA in improved skin penetration, and routine use of double PDT treatments (as used in our protocol) is recommended to improve treatment efficacy.[18]

This apparently synergistic treatment seems most appropriate for patients who value excellent cosmetic outcome over the inconvenience of making additional visits to the clinic, or where avoidance of an invasive procedure is an important factor. We would advocate this therapy following detailed consent from the patient (at which point we discuss our own recurrence rates). It is appropriate to treat lesions in certain anatomical areas, and those patients adverse to surgical intervention by their own choice or as advised by their clinician.

TABLE 2. Patient-Related Outcome Data

	Paired Differences							
				CI of Difference				
	Mean	SD	SE of Mean	Lower	Upper	*t*	*df*	Significance
Waiting times	0.95	1.5	0.336	0.25	1.65	2.83	19	0.11
Anxiety	1.55	1.54	0.344	0.83	2.27	4.51	19	0.001
Pain	−2.4	3	0.67	−3.8	0.997	−3.58	19	0.002
Scar outcome	2.15	1.57	0.35	1.42	2.88	6.15	19	0.001
Disruption	−0.55	1.73	0.387	1.36	0.26	−1.42	19	0.172
Overall	1.65	1.34	0.302	1.02	2.28	5.47	19	0.001

CI indicates confidence interval; *df*, degrees of freedom (n − 1).

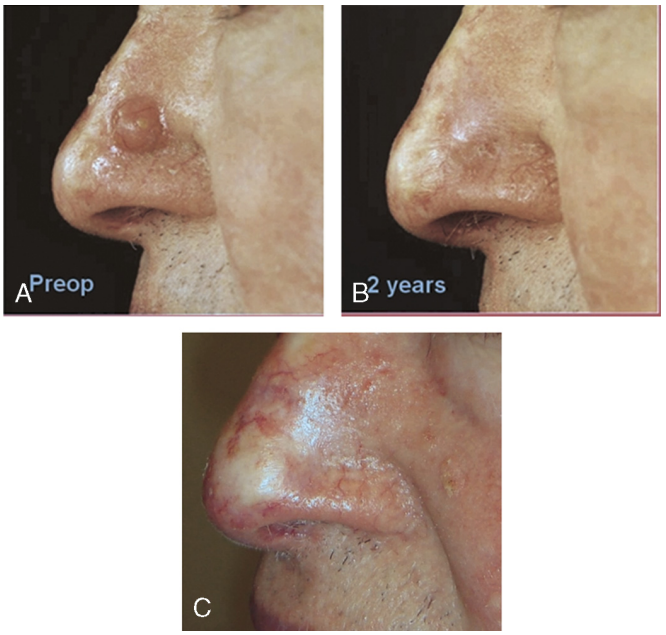

FIGURE 9. Young patient with nodular BCC—ideal candidate for this modality of treatment. Shown pretreatment and at 1 year.

FIGURE 11. Large nasal BCC pretreatment and at 1 year posttreatment and comparison with equivalent lesion a different patient treated with excision and flap reconstruction.

Photodynamic therapy and CO_2 laser treatments, in either single or multiple sessions, may or may not be cost effective depending on patient factors and individual unit facilities. For example, avoidance of admission of patients on warfarin for critical reasons to the ward for anticoagulation and multiple coagulation screens as a prelude to subsequent surgery would make laser-PDT a more favorable strategy. A table of costs is provided. However, combined laser-PDT may not be cost effective in all patients groups. Although 5-methyl-ALA remains relatively expensive, further studies with more cost-effective cheaper photoactivators may affect the cost effectiveness of dual-modality therapy. Nevertheless, the costs remain favorable compared to surgery.

In a modest audit of patient-related outcome measures and satisfaction, laser-PDT scored highly and was preferred to surgery in most measures. Patients found PDT-activation painful, which is a recognized problem with PDT, and we substituted a long-acting local anesthesia at the time of CO_2 ablation which has mitigated this problem.

We provide the clearest evidence so far that PDT and CO_2 laser act synergistically in the treatment of BCC, and in particular nodular BCC, setting the stage for future randomized clinical controlled trials comparing surgery with laser-PDT. We have demonstrated a safety track-record spanning 8 years with excellent clinical and cosmetic outcomes.

CONCLUSIONS

We suggest that combining CO_2 laser with PDT is an emerging frontline treatment for superficial and nodular BCCs, with minimal recurrence rates (<3%) and excellent cosmetic outcomes with medium and long-term follow-up of up to 8 years.

Morpheic lesions should not be treated with this modality as they have higher recurrence rates. CO_2 laser and PDT seem to play a synergistic role in the treatment of BCCs, and combined treatment has extended the remit of PDT to allow treatment of larger and nodular lesions, with the CO_2 laser being unique as an accurate, finely controlled and hemostatic ablative tool providing a wound bed receptive to PDT. Both the surgical team and the patients have been pleased with the results over many years. This treatment seems most appropriate for patients who value excellent cosmetic outcomes over the inconvenience of making additional visits to the clinic, or where avoidance of an invasive procedure is an important factor. It is of

FIGURE 10. A, B, C, Large nasal nodular BCC, (a) pretreatment and (b) at 2 years and (c) at 4 years after 2 treatment cycles.

potential benefit especially in cosmetically sensitive areas such as the face, areas prone to poor scarring such as the presternal area, in younger patients seeking excellent cosmesis, in patients for whom anesthesia may be problematic, in patients with numerous and frequently occurring lesions, or those taking anticoagulants (which do not need cessation, nor the patients hospital admission). This treatment modality complements surgery, not replaces it, in the armamentarium of a holistic surgeon or physician treating cutaneous malignancies and aiming for a scarless cure.

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