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Photodynamic Treatment of 206 Thin (≤ 1 mm) Basal Cell Carcinomas Using a Biphasic Activation Protocol: The Outcomes Over a 7-Year Period and the Rationale Behind the Treatment

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ABSTRACT

Background: Conventional photodynamic treatment (cPDT) of thin basal cell carcinomas (BCCs) has uncomfortably high rates of incomplete clearance. Incomplete clearance/recurrence rates for superficial BCCs are as high as 40% and even higher for tumours treated on the head and neck. Our experience has been that flushing is more pronounced on the head and neck during cPDT photoactivation. We postulated that haemoglobin, although delivering oxygen, may be acting as a competing chromophore.

Objectives: To determine whether a 2-phased photoactivation protocol, in which blood is removed before the second phase intense pulsed light (IPL) activation, improves clearance rates.

Methods: Retrospective observational study of 206 treatment-naïve BCCs ≤ 1 mm thickness treated over a 7-year period with a 2-phased photoactivation protocol ('biphasic PDT'). The first phase consists of conventional red-light activation (20−37 Jcm^{-2}). Second phase photoactivation uses IPL (30−45 Jcm^{-2}) delivered with sufficient mechanical pressure in the handpiece to blanch the skin.

Optical coherence tomography (OCT) has been used to aid in lesion diagnosis, to establish suitability of tumour for treatment and to improve verification of treatment outcomes.

Results: In the final group of 175 tumours, of which most were located on the head and neck and over 40% were nodular, there were only four incomplete treatments over a 2-year median follow-up period (up to 7 years). The few incomplete clearances were easily managed.

Conclusions: One or two biphasic photodynamic treatments are highly effective (98% clearance) in thin, treatment-naïve BCCs (≤ 1 mm in thickness) selected on clinical and OCT assessment.

Summary

What is already known about this topic?

- Conventional red-light photodynamic treatment of BCCs has uncomfortably high rates of incomplete clearance.
- Incomplete clearance rates of superficial BCCs are approximately 40% and are highest in the face and neck and in younger patients.
- The study was designed around a central hypothesis that haemoglobin, although delivering oxygen, which is essential for successful PDT, may be acting as a competing chromophore.

What does this study add?

- We present 7 years of data using PDT that incorporates a period of red-light activation immediately followed by intense-pulsed-light (IPL) delivered after removing blood ('biphasic-PDT').
- Adopting this protocol to thin, treatment-naïve BCCs (≤ 1 mm thickness), the data presented show a 98% clearance rate with a median 2-year follow-up.
- Most tumours were on the face and neck and 43% were nodular. Optical coherence tomography (OCT) has been used to validate treatment outcomes.

What are the clinical implications of this study?

- One or two biphasic photodynamic treatments are highly effective for treatment-naïve BCCs (≤ 1 mm thickness) including thin nodular and superficially infiltrating tumours on faces and noses.
- The few incomplete clearances were easily managed.
- Diagnosis and triage for biphasic treatments is undertaken by clinicians, and treatment can be undertaken by well-trained nurses.
- The results appear comparable with surgery in the treatment of such thin tumours.

1 | Introduction

Photodynamic therapy (PDT) is one of several modalities used in the treatment of basal cell carcinomas (BCC). Effective removal of thin BCCs can be achieved with little or no scarring but incomplete clearance is a problem using the conventional protocol (cPDT). The incomplete clearance/recurrence rate in Jansen et al.'s much cited 5-year follow-up study of superficial BCCs was approximately 40% [1]. The rate was even higher for lesions treated on the head & neck, and it was higher in younger patients.

Our observation is that flushing during red light photoactivation is more pronounced on the head and neck compared with other sites and have postulated that the increased blood flow, although delivering oxygen, also increases haemoglobin in the area which may be acting as a competing chromophore. Of additional concern is that during activation, there is conversion of oxyhaemoglobin to deoxyhaemoglobin [2] and that compared with oxyhaemoglobin, deoxyhaemoglobin is a sevenfold stronger absorber of the conventionally used 630 nm red light [3].

Our primary objective was to determine if the activation effect can be enhanced by removing blood. We devised a protocol so that activating light is delivered in two phases: The first phase involves conventional red-light activation, and in the second phase, performed immediately following red-light, light is delivered once blood has been squeezed out of the tumour site. This is achieved with an intense pulsed light (IPL) device with mechanical pressure to the handpiece.

IPL consists of high irradiance polychromatic light where the spectral output can be restricted to above a certain wavelength using select 'cut-off filters'. The power density and pulse-width of the emission can also be controlled. IPL is conventionally used for selective thermolysis of pigment or blood. This generally requires pulse-widths below 30 ms. Such photothermal effects are undesirable in our study. To keep the photodynamic effect 'pure', our aim was to deliver light, but not to introduce photothermal effects. In our protocol, the pulse-width we used well exceeds the duration used for thermolysis of pigment or blood.

We refer to this 2-phased activation protocol as 'biphasic PDT' (bPDT). Our early results looked promising, and the method and preliminary results were published in 2020 [4]. Optical coherence tomography (OCT) was used as an aid in diagnosis and for monitoring outcomes in that series.

OCT imaging used to identify incomplete clearance of BCC following noninvasive treatment has been shown to be highly sensitive. Wolswijk et al. [5] demonstrated in 2023 that following treatment of 100 superficial tumours with imiquimod, PDT or 5-fluorouracil cream, there were 20 recurrences confirmed by histology. Clinical & dermatoscopic examination (CDE) detected 12 of these, but the addition of OCT detected all 20. In another study involving 58 BCCs treated by curettage and/or cPDT, Hussain et al. [6] demonstrated twice as many incomplete clearances with OCT + CDE than with CDE alone, and in another of their studies, they detected 29% more incomplete clearances with the addition of OCT at 3 months following treatment of BCCs with cPDT [7].

At our centre, bPDT has become standard practice for photodynamic treatment of BCC. Our decision to offer photodynamic treatment of BCC is determined by clinical, dermatoscopic and OCT characteristics of tumour. OCT has also been used as an aid in verifying treatment outcomes.

2 | Materials and Methods

This is an observational retrospective analysis of PDT for BCC outcomes at a single practice.

Data has been extracted pertaining to all biphasic treatments of previously untreated BCCs of up to and including 1 mm histological or OCT depth, that have been performed since OCT was installed at our centre (VivoSight Multi-beam Swept-Source Frequency Domain OCT, Michelson Diagnostics; specifications: class 1 eye safe; resolution < 7.5 μm lateral, < 5 μm axial; depth of focus, 1.0 mm; scan area, 6×6 mm^2). This period spans February 2018 to July 2024. Outcome data has been collected up to and including December 2024. Data retrieval was straightforward as all bPDT treatments are colour-coded in the practice's medical software.

Some tumours have maximum depths ascertained by both OCT and histology. Where there is disparity between OCT and histological depth, then the deeper of the two has been used. Where the OCT image quality is compromised making depth measurement less precise, for example, due to overlying scale, crusting, ulceration or blood, then the histological depth has been used.

All 206 tumours have been assessed by OCT before treatment, and 174 of 181 (96%) of those presenting for follow-up have included OCT assessment. There were short periods in 2020 and 2022 when the OCT device was out of service. This has affected the follow-up of seven lesions for which only CDE was undertaken.

Our practice is in outer metropolitan Sydney, Australia and draws patients from suburban areas as well as from rural areas. Our OCT facility is one of only two in the state of New South Wales.

Treatment involves standard lesion preparation with gentle use of a blunt curette to remove any overlying scale and aiming not to draw blood. Methyl-aminolevulinate (MAL) cream (Metvix) is then applied under an occlusive dressing for 3 h.

First-phase photoactivation aims at $37\,Jcm^{-2}$ of red light (Aktilite), around 500 s. The dose (duration) is reduced to around $20\,Jcm^{-2}$ (300 s) if flushing becomes marked or if pain becomes an issue. Second-phase activation, performed immediately after the first-phase, consists of $30-45\,Jcm^{-2}$ IPL using a cut-off filter in the 515−560 nm range (Sciton BBL). The technique is that the IPL is delivered with enough mechanical pressure to the handpiece to squeeze out blood, so the skin appears blanched. To achieve uniform blanching, the IPL is delivered through one of three smaller crystal adaptors ('finesse adaptors') that fit over the full-sized crystal in the handpiece. These come in sizes of 15 mm × 15 mm (square), 11 mm (round) and 7 mm (round).

The pulse-width is set to a duration that far exceeds conventional thermolytic settings. We have found that durations ≥ 100 ms have little or no damaging photothermal effects on Fitzpatrick types 1−3 skin using the above filters and power settings.

In our original protocol, $2 \times 15\,Jcm^{-2}$ passes ($30\,Jcm^{-2}$) IPL are undertaken (immediately following Aktilite) for the first treatment. A second treatment, which is our standard for tumours not confined to epidermis, is undertaken using $3 \times 15\ Jcm^{-2}$ passes ($45\,Jcm^{-2}$) following Aktilite. We aim so the second treatment is performed 1−3 weeks after the first.

In mid-2022, we changed the protocol so that for tumours < 1.2 cm diameter, and OCT showed that the tumour was no more than 0.4 mm maximal depth, only one treatment was performed. This consists of $20-37\,Jcm^{-2}$ Aktilite (dose steered by pain tolerance) followed by $3 \times 15\,Jcm^{-2}$ ($45\,Jcm^{-2}$) of IPL.

Patients are requested to return 3−6 months after their final treatment session for clinical and OCT assessment of the site. Following this assessment, they are asked to return 12 months later for another assessment, but since mid-2022, we discontinued the second follow-up assessment for patients where BCC was an isolated, one-off finding of skin cancer and it was a lower risk subtype at a lower risk site. For these patients, we have encouraged another assessment at our clinic, only for any

TABLE 1 | Details of incomplete clearances including further management and follow-up.

Age/sex	Site	Type/depth	Interval between treatment and when residual tumour was identified	Clinically evident	Treatment & follow-up
1. 51 F	Cheek	Nodular, 0.8 mm.	8 months (at first follow-up visit)	No. OCT: Solitary superficial focus, 2 mm × 0.7 mm.	Curettage & cautery. Clear on OCT 3 years later
2. 76 F	Cheek	Nodular, 0.9 mm.	5 years (lost to follow-up. Not seen until 5 years later)	Yes. Ulcerated tumour.	Excised, primary closure.
3. 47 F	Forehead	Nodular, 1 mm.	4 months (at first follow-up visit)	No. OCT: Solitary focus of tumour 0.3 mm × 0.3 mm at 0.5 mm depth.	Liquid nitrogen. Clear on OCT 6 months later.
4. 62 F	Ankle	Superficial, 0.35 mm.	6 months (OCT out of service)	Yes. Small focus of scaling at peripheral edge. Not confirmed by OCT or histology.	Liquid nitrogen. Not seen since liquid nitrogen treatment.

change or concern they may have at the treatment site. This change in protocol was on account of the promising results we had observed during the first 4 years. For follow-up appointments, patients are reminded with a text 3 business days earlier. If there is no response to the text or if the appointment is declined, patients are telephoned to arrange an alternative time.

Our clinical follow-up period in this cohort is lengthened on account of many patients electing to return for general checks and for concerns about other lesions. Previously treated sites are always assessed at subsequent visits.

3 | Results

Included in our series were 206 treated tumours from 140 patients. Eleven patients representing 25 tumours failed to attend for follow-up assessment. For six tumours, clearance was determined by CDE alone without OCT. These have been excluded from the final analysis. One tumour was determined incompletely cleared on CDE at a time when the OCT device was out of service. This case has been included in the results because in the analysis, CDE is enough to consider incomplete removal whereas OCT is considered necessary to certify complete removal.

In the final group, there are 125 patients representing 175 tumours.

Eighty-one are female (65%) accounting for 105 tumours. Forty-four patients are male (35%) with 70 tumours. Forty-four tumours (25%) have histopathology and the remainder have been included on clinical and OCT diagnosis. The median maximum tumour depth was 0.5 mm. Seventy-four tumours (42%) were nodular or of more aggressive subtypes. This included 12 tumours with infiltrating features. One hundred and six tumours (61%) were located on the face or neck, of which 61 were nodular and/or had infiltrating features.

There were 43 tumours on noses (25%) of which 28 were nodular and/or had infiltrating features.

During a median follow-up period of 2 years (up to 6 years, 10 months), we identified four incomplete clearances. This represents a 98% clearance rate across a mixed clinical material including head, neck and nose.

Two of the cases we have identified as incomplete clearances were not evident on CDE but were evident on OCT assessment. All four incomplete clearances have been easily managed. The details are included in Table 1.

For the subgroup of BCCs treated since mid-2022 (< 1.2 cm diameter, and ≤ 0.4 mm OCT depth) where only one biphasic treatment was performed, there were 50 treated tumours in 38 patients. 21/50 were located on head and neck sites. There have been no incomplete clearances in this group, and the median follow-up period is 12 months. Baseline characteristics of this subgroup compared to the two-treatment group are presented in Table 2.

The IPL phase of treatment was very well tolerated. Typical feedback from patients was that the most uncomfortable part of treatment was pain during the conventional red-light phase of activation. No patient required local anaesthesia.

Post treatment, crusting lasting 3–4 days was not uncommon and was managed with application of bland emollients. This was more frequently observed on noses. Infection requiring antibiotics was not encountered in any patient. Erythema extending beyond the treatment site and lasting days, sometimes weeks was not infrequent. At times, this required some reassurance.

4 | Discussion

The high clearance rate using this protocol is very different to our previous experience of the cPDT protocol for which our experience was similar to the Jansen study [1]. At our practice we used cPDT for BCCs from 2005 but discontinued in 2007 due to concerningly high incomplete clearance rates.

Our experience of OCT for detecting incomplete clearance is similar to the previous reports [5–7]. In this cohort of thin BCCs there have been no tumours that have recurred following OCT validation of clearance from 3 months.

TABLE 2 | Baseline characteristics of the 1 treatment subgroup compared with characteristics for those who had 2 treatments (note that patients with multiple tumours can appear in both groups).

	1 Biphasic treatment	2 Biphasic treatments
Number		
Of tumours	50	125
Of patients	38	97
Age range	32–89	26–94
(average age)	(58)	(57)
Sex	63% female, 37% male	61% female, 39% male
Site		
Head & neck	42% (21)	68% (85)
Trunk	36% (18)	21% (26)
Upper limbs	18% (9)	4% (5)
Lower limbs	4% (2)	7% (9)
BCC subtype		
Superficial	98% (49)	42% (52)
Nodular	2% (1)	49% (61)
Infiltrating	Nil	10% (12)
Median maximum tumour depth (mm)	0.3	0.6
Median follow-up period	12 months	2 years

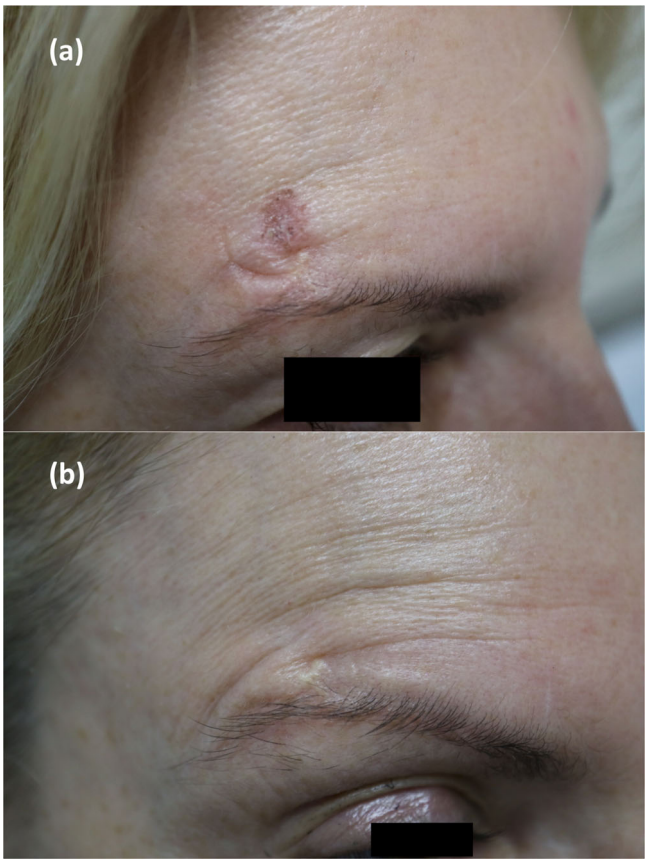

FIGURE 1 | 58-year-old lady. Punch biopsy showed nodular BCC 1 mm depth. (a) Note the flecks of pigment and that the scar at the inferior end of the tumour is pre-existing from childhood trauma. The arc-shaped indentation is a temporary artefact from the OCT stand-off headpiece. (b) Four months following biphasic photodynamic treatment. There is no evidence of residual tumour on OCT imaging. The scar from childhood is still visible, but there's no scar in the treatment area.

Photodynamic treatment of skin cancer involves three key components and the science behind the biphasic protocol is yet to be explored. For optimal PDT outcomes, there needs to be adequate delivery of activating light [8]; second, there needs to be adequate uptake of photosensitiser by tumour cells [9]; and third, this must be in the presence of adequate free oxygen in tissue [10].

Compared to cPDT, bPDT introduces changes in both the dose of light used and its method of delivery. A lower recurrence rate on account of an increased dose of red light has already been demonstrated by Todd et al. [11]. Following a single treatment in a mixed cohort of superficial BCCs and Bowen's Disease, they showed an incomplete clearance rate of 40% at 3 months follow-up assessment with a 75 Jcm^{-2} dose, compared to 50% for the 37 Jcm^{-2} group.

In the following discussion, we raise some hypotheses regarding movement of light and changes in free oxygen that may reconcile with the higher treatment efficacy of biphasic photoactivation. One hypothesis is that if additional activating light is delivered in a bloodless field, this will result in additional enhancement on account of deeper penetration of light and a marked increase of photon travel throughout tumour and peritumour stroma from scattering.

BCC tumour nests are translucent, so for those visible-light photons that cross the epidermis, more will reach thicker collagen fibres in the underlying tissue. Back-scatter and side-scatter will then occur so photons will arrive at tumour cells from all directions [12]. This will result in an increase in the photodynamic dose to parts of tumour that might otherwise have been shadowed by small opacities in the tumour environment such as melanin, keratin or blood. The presence of epidermal atrophy should increase this enhancement. A pigmented BCC we have treated using this protocol is presented in Figure 1.

Removal of haemoglobin will also allow passage of more potent activating wavelengths in the green to yellow spectrum (515–590 nm). Oxyhaemoglobin and deoxyhaemoglobin are strong absorbers of light in this spectrum [3]. Green and yellow light can be included in the IPL emission by selecting appropriate cut-off filters. Using a 560 nm cut-off filter, the emission will include yellow light as well as red (including the higher PpIX absorption peak at 575 nm). Use of a 515 nm cut-off filter will additionally include highly potent wavelengths in the green band including the high PpIX absorption peak that occurs at 539 nm.

Our posit that scattered light is of higher quality for photodynamic activation is supported by our experience treating endophytic nodular tumours where the tumour consists of multiple ovoid nests grouped within a basket of collagen at the side and deep margins. There were many of this type in our series. The OCT appearance can be likened to a 'bird's nest' structural framework and the collagen surrounds may cause a 'light trapping' effect. These types of tumours are common and easily recognised with OCT. Our experience has been that these tumours respond extremely well to bPDT particularly when they are pink or red (Figures 2 and 3).

PDT is oxygen-dependent and short durations of IPL (of second-phase activation) will need to be met with abundant free oxygen in the target tissue. Oxygen is consumed during first-phase activation (red-light) which may result in an undesirable decrease in pO_2 and compromised IPL activation. We postulate, however, that this is not necessarily the case: During red-light activation, some oxygen will be photochemically consumed, but activation also results in a rise in temperature and hyperaemia [13]. Hyperaemia implies increased delivery of oxyhaemoglobin, and heat results in increased O_2 dissociation from haemoglobin [14]. A rise in pO_2 in nodular BCCs (> 2 mm thick) towards the end of a period of photoactivation was noted in one study [15], but there are no studies investigating changes in pO_2 for thinner BCCs or immediately following photoactivation. We postulate that there may be a higher tissue pO_2 following completion of the red-light phase though the degree may be site-dependent and lesion-dependent.

It is important to note that second phase (IPL) activation on its own is less likely to be successful on account of insufficient free oxygen. This may be corrected, though, if more passes are used and the interval between passes is extended. We have not explored this.

Our experience using the biphasic protocol is that reactions are often strong and targeted (Figure 4). This is very different to our experience using cPDT. Our inference is that mechanical

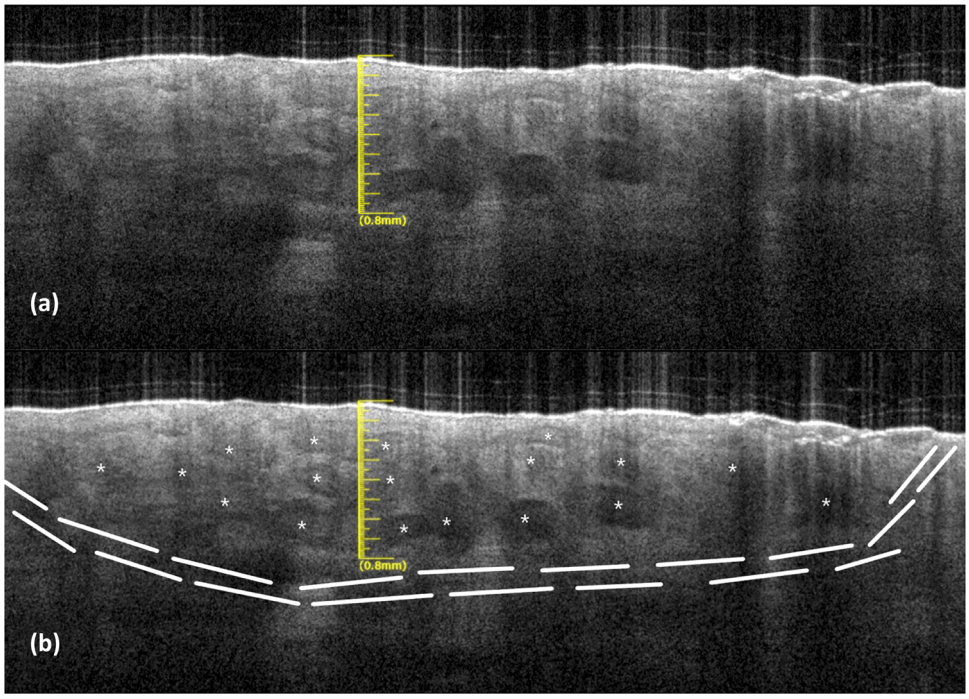

FIGURE 2 | (a) OCT image of endophytic nodular tumour on nasal sidewall. The depth is 0.8 mm. (b) The tumour nests are marked with asterisks, and dense surrounding collagen is marked with white lines, giving the appearance of a 'bird's nest'. This tumour also shows epidermal atrophy. The sketch is drawn by AJ.

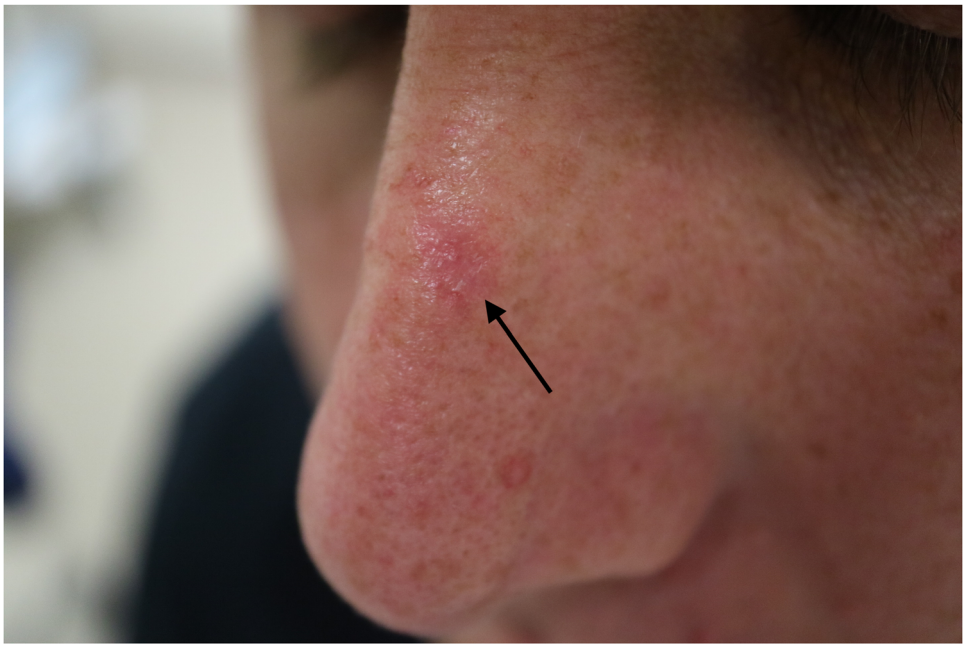

FIGURE 3 | This is the tumour represented in Figure 2.

pressure to remove blood will immediately remove haemoglobin, but it is not removing dissociated oxygen. This remains in tissue long enough to be utilised photodynamically.

The high proportion of tumours on the head and neck and the higher representation of women in our cohort deserve comment. Australian citizens have universal government-funded health insurance ('Medicare') that provides subsidies toward treatments which are undertaken outside of public hospitals. This includes treatment of skin cancer which includes surgery, curettage and cautery and cryosurgery, but it does not include photodynamic treatment. Consequently, the higher out-of-pocket expenses incurred with PDT make patients disinclined to consent to such treatment unless they perceive other benefits. This may include better aesthetic outcomes at cosmetically sensitive sites.

In addition, patients with facial BCCs have also seen us because of concerns over the costs of surgical treatment. In Australia,

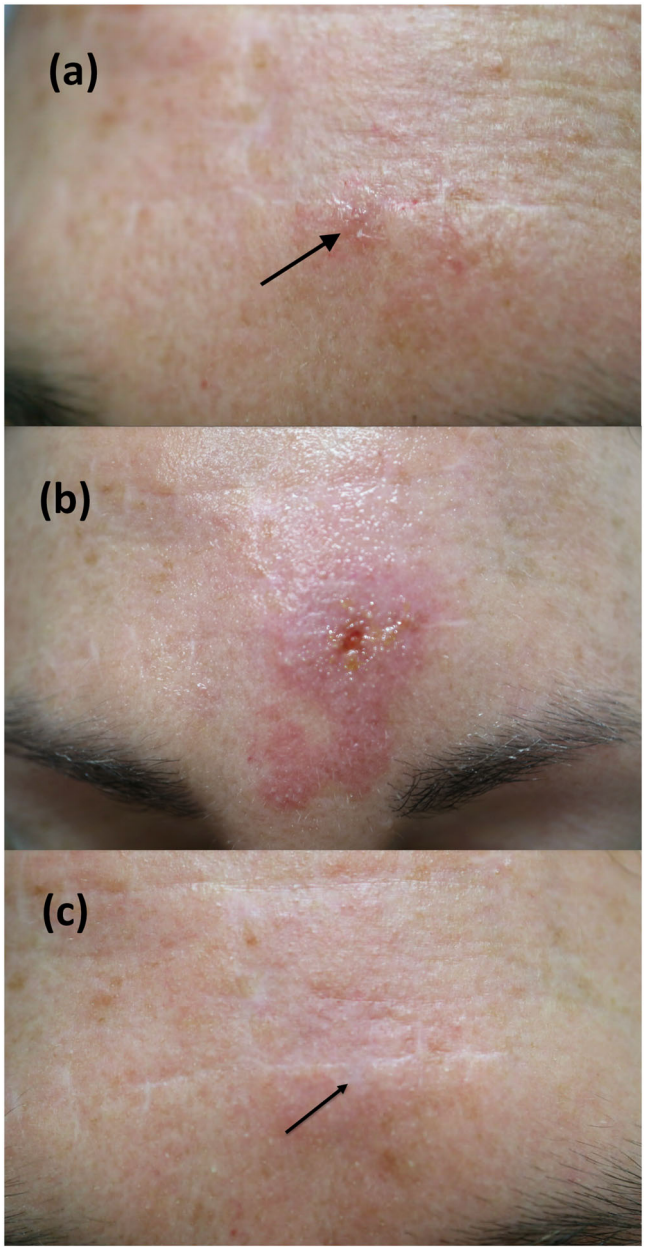

FIGURE 4 | (a) Forehead BCC. OCT showed a nodulo-infiltrative tumour 1.2 mm depth. (b) One day after first treatment showing 'targeted tumour necrosis' and a flare reaction. In this case, there is a defect corresponding to the tumour site. The flare settled within a few days. (c) Four months after second treatment. The treated BCC site is arrowed. OCT imaging showed no evidence of residual tumour. Note that this non-recurrent tumour is on one of the long arms of an H-plasty scar from a BCC excised 6 years earlier.

admission to privately run day surgery facilities is commonplace to access the removal of head and neck BCCs by plastic surgeons and by micrographic surgeons. Costs then become much more substantial and run into several thousands of dollars. Some patients seek less expensive alternatives when confronted with such costs.

This study has important nuances that need some elaboration: First, recurrent tumours and those previously treated have been excluded from this analysis. Second, although all non-recurrent BCCs ≤ 1 mm we have treated with bPDT have been included (February 2018 to July 2024), we have not treated tumours which are rich in collagen and appear white. These have been surgically removed and have proven to be morphoeic, sclerotic subtypes of BCC. We have assumed that penetration of light and/or photosensitiser will present severe issues for photodynamic treatment. Third, we have also steered away from treating prominent papular (exophytic) types of BCC which appear translucent and pale. From our early experience treating thicker lesions, we have noted that these less-vascular types are less responsive to bPDT. We speculate that a lack of oxygen may be a factor. Such tumours are generally well-marginated and easily removed by other means.

The strengths of this study are the large cohort, the long period of follow-up and that OCT has been used for monitoring. The limitations are that this is a one-centre study, that there is some heterogeneity in the methods used which comes from being a retrospective observational study, and that 11 of 140 patients (25 lesions) have been lost to follow-up. Most in this contingent have travelled from afar; some did not attend visits during the pandemic period; and we have a large Australian Defence Force personnel presence in our cohort of whom some have moved to different bases.

5 | Conclusion

One or two photodynamic treatments using a modified protocol which consists of a period of conventional treatment immediately followed by IPL (using a 560 or 515 nm cut-off filter) delivered with enough mechanical pressure to blanch the skin, was highly effective in a large group of thin, treatment-naïve BCCs (≤ 1 mm depth) chosen on clinical criteria and OCT assessment. This includes many nodular tumours on faces and noses. The few incomplete clearances encountered were easily managed.

Author Contributions

Robert Stephens: data curation, conceptualisation, writing – original draft preparation, graphical abstract. **Chris Anderson:** writing – draft preparation and editing, biophysical aspects discussion, supervision. **Rolf Saager:** writing – biophysical aspects discussion. **Antony Johnston:** figure preparation, graphical abstract, data compilation. **Dariush Adybeik:** data collection and data compilation.

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The authors have nothing to report.

Ethics Statement

All patients in this manuscript have given written informed consent for participation in the study and the use of their deidentified, anonymized, aggregated data and their case details (including photographs) for publication. Ethical approval: N/A. Retrospective observational study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data is available upon request due to privacy/ethical restrictions.

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