

# The Effect of 595 nm Pulsed Dye Laser on Superficial and Nodular Basal Cell Carcinomas

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**Background and Objective:** Basal cell carcinomas (BCCs) have supporting vasculature that could serve as a target for 595 nm pulsed dye laser (PDL). The objective of this study was to determine the effect of repeated PDL treatments on BCCs of superficial and nodular subtypes and of varying diameters.

**Study Design/Materials and Methods:** Twenty biopsy-proven BCCs received four 595 nm PDL treatments at 2-week intervals. The tumor and 4 mm of peripheral skin were treated using a set of previously optimized laser parameters: one pass, 15 J/cm<sup>2</sup> energy, 3 ms pulse length, no cooling, and 7 mm spot size with 10% overlap. The treated area was excised and evaluated histologically for residual tumor. Histologic response rates of the PDL treated BCCs were compared with that of non-PDL treated, matched control tumors.

**Results:** Nearly all BCCs <1.5 cm in diameter (n = 12) showed complete response to four PDL treatments (91.7%; n = 11/12) versus 16.7% of controls (n = 2/12, *P*-value = 0.0003). BCCs ≥1.5 cm in diameter (n = 8) showed a complete response rate of 25% (n = 2/8) versus 0% of controls (n = 0/8, *P*-value = 0.2). Mean clinical tumor diameter of the complete responders was 1.1 cm (n = 13) versus 2.2 cm (n = 7) for incomplete responders (*P*-value = 0.005). Tumor histologic types among the complete responders included superficial, nodular, micronodular, and keratinizing. Incompletely responding BCCs showed a significant reduction in tumor burden after PDL treatment, with residual histologic tumor burden ranging from <1% to 29% of the original clinical tumor diameter, compared to 13–68% residual tumor burden for the corresponding controls (*P*-value = 0.05).

**Conclusions:** PDL is an effective means of reducing tumor burden in patients with large BCCs and may be an alternative therapy in BCCs <1.5 cm in diameter. *Lasers Surg. Med.* 41:417–422, 2009. © 2009 Wiley-Liss, Inc.

**Key words:** pulsed dye laser; non-melanoma skin cancer; angiogenesis

## INTRODUCTION

Basal cell carcinomas (BCCs) are the most common skin cancer in the United States, with close to 1 million new cases diagnosed annually [1]. Because patients can have multiple BCCs, and some cannot tolerate multiple surgeries or the inflammation associated with topical immunomodulators, various non-surgical regimens, such as lasers, are being evaluated as possible treatment options.

BCCs are often clinically described as having telangiectasias [1]. Indeed, BCCs have been shown to utilize a specialized tumor-associated microvasculature for growth [2]. BCCs contain a basket-like capillary plexus interwoven throughout the tumor bed, with many abnormal blood vessels with luminal diameters of 20 μm and greater [3]. By specifically targeting the tumor vasculature, BCC tumor burden may be decreased or even eliminated with less damage to the surrounding skin structures.

Various types of lasers are used in oncology to debulk tumors, using both selective and ablative methods [4–8]. Pulsed dye laser (PDL) has been used to selectively target tumor vasculature with success in treating glottal dysplasia and squamous cell carcinoma in situ using 585 nm PDL [4,8]. Depending on fluence, 595 nm PDL can penetrate skin to thicknesses ranging from 0.75 to 1.25 mm. This range of dermal penetration encompasses the depth of the vasculature that supports most BCC [9]. Ectatic dermal blood vessels treated with 595 nm PDL can undergo selective photothermolysis with minimal damage to the surrounding tissue structures.

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Two previous studies have examined the use of PDL with BCCs. Allison et al. [10] used a single treatment of 585 nm PDL on seven BCCs, which resulted in histologic clearance of only one tumor. In superficial BCCs, using five treatments with 595 nm PDL, Campolmi et al. [11,12] demonstrated in two separate studies that 16 of 20 tumors showed no clinical recurrences at a minimum follow-up of 1 year. We designed a study to include repeated PDL treatments on multiple BCC subtypes based on optimized parameters from a previous study, which demonstrated 100% histologic tumor clearance with one treatment (correspondence with Silapunt et al.). Given that a skin biopsy can induce inflammation and tumor regression [13], we also included an analysis of control matched tumors that underwent biopsy and excision alone. We also performed complete excision of the tumors at the end of the study to determine histologic presence or absence of BCC after treatment.

## MATERIALS AND METHODS

IRB approval #1985 was obtained from the Boston Veteran's Affairs Research and Development Office prior to patient recruitment. Twelve male patients with 21 biopsy-proven BCCs on the trunk and extremities were recruited from the general and surgical dermatology clinics at the Boston Veteran's Affairs Hospital in Jamaica Plains, MA. Morpheaform, infiltrative, and recurrent BCCs were excluded from this study. Twenty historical control BCCs treated with biopsy and excision at the Boston VA between 2003 and 2008 were also chosen: these non-PDL treated tumors were matched for clinical diameter, histologic subtype, and location (trunk vs. extremity.) We were unable to obtain a matched control for the largest tumor in the study (tumor 21, measuring 7 cm in diameter).

All 21 tumors received four consecutive PDL treatments at minimum 2-week intervals. At the first visit, the selected treatment area and 4 mm of normal skin were assessed, demarcated, and photographed. A Tegaderm template was created for each individual treatment site. Removal of the scale crust with hydrogen peroxide revealed healthy underlying skin. At each laser visit, the same demarcated tumor site was treated with the 595 nm PDL (VBeam Perfecta, Candela Corporation) at the following parameters: one pass at energy of 15 J/cm<sup>2</sup>, pulse length of 3 ms, no dynamic cooling mode, 7 mm spot size with 10% overlapping between the pulses. These parameters demonstrated complete histologic clearance of BCCs after one treatment in a previous study.

At least 2 weeks after the final laser treatment, the BCC and the 4 mm margins of skin treated with PDL were surgically removed as a disk excision. The resultant tissue corners were removed, and the wound was repaired with a complex linear closure.

The excised skin tissue was processed in the Boston VA Department of Pathology. The excisional tissue specimens were sectioned and processed according to routine practice, with complete examination of the specimen on hematoxylin and eosin (H&E) stains. The tumors were cut as a breadloaf completely into ~2 mm sections, and each section was cut at

4 μm sections onto glass slides. We examined at least 4–5 H&E stained slides for each tumor after PDL treatment and excision. Complete response was defined as no histologic evidence of BCC after standard sectioning of the tumor. Incomplete response is defined as any residual histologic evidence of BCC in the excised tissue. For the eight incomplete responding BCCs, residual tumor burden of all PDL treated and control tumors were measured on the H&E stained excision slides using ocular microscopy. The percentage of residual tumor burden was calculated by the ratio of the histological measurement of the maximal remaining tumor after PDL treatment to the maximum clinical diameter measured prior to PDL treatment. For the seven PDL treated tumors with matched controls, the percent residual tumor burden was compared to the residual tumor burden of their control tumors, using a paired *t*-test to assess for a statistically significant difference between the two groups. Odds ratios and Mantel–Haenszel calculations were performed to determine the significance of the complete response rates for only the 20 PDL treated tumors with matched control tumors. (Note: tumor 21 was excluded from the odds ratio data analysis because a matched control was unable to be obtained.) For statistical analysis, all odds ratios, Mantel–Haenszel calculations, and students/paired *t*-tests were calculated using STAT-SAK software, v2.63.

## RESULTS

The 21 tumors enrolled in the study varied in clinical characteristics (Tables 1 and 2). Clinical tumor diameters ranged from 0.5 to 7 cm. Nineteen tumors were located on the trunk, and two tumors were located on the extremities. The histological tumor subtypes included: superficial (9), nodular (2), superficial and nodular (8), nodular and micronodular (1), and superficial, nodular, and micronodular (1). Figure 1 shows the clinical and histologic images of tumor 8, a nodular BCC treated with PDL.

Of the 21 treated BCCs, 20 had matched controls and were included in the following odds ratio analysis. The histologic examination of excisions from 13 of 20 tumors treated four times with PDL showed complete response (65%) compared to 2 of 20 controls (10%), (OR = 16.7, *P*-value = 0.0004). The characteristics of the control tumors' maximum diameters were similar to those of the 20 treated tumors (control tumors: 0.6–3.2 cm, mean 1.5 cm, median 1.2 cm; vs. PDL treated tumors: 0.5–4 cm, mean 1.5 cm, median 1.3 cm). Histologically, the re-excision specimens were notable for the absence of scarring or post-inflammatory pigmentation. No significant dermal fibrosis, vascular ectasia, inflammation, or pigment laden macrophages were observed. Prominent vascularity and erythrocyte extravasation was noted in the reticular dermis, which correlated with known laser induced dermal changes.

Complete response correlated with tumor diameter; the average diameter of complete responders was 1.1 cm, as compared to non-responders (2.2 cm) (*P*-value = 0.005). Response rates were analyzed for tumors stratified into

**TABLE 1. Basal Cell Carcinoma Response to Pulsed Dye Laser: Tumor Type, Tumor Size and Tissue Site**

Lesion	Histologic subtype	Tissue site	Clinical tumor size (cm)	BCC response (calculated % residual)
1	S	L medial abdomen	1.5 × 0.7	C
2	S	Mid-back	0.7 × 0.8	C
3	S	Mid-back	1.3 × 1.0	C
4	S	Upper back	1.2 × 0.8	C
5	S	L elbow	1.0 × 0.9	C
6	S	R superior shoulder	1.1 × 1.0	C
7	S	Midline upper back	1.2 × 0.9	C
8	N	L medial shoulder	0.9 × 0.7	C
9	N, K	R chest	1.1 × 0.7	C
10	S, N	L lateral shoulder	1.0 × 0.8	C
11	S, N, K	L clavicle	0.5 × 0.5	C
12	S, N, K	L lateral thigh	2.0 × 1.7	C
13	N, MN	Mid-back	0.5 × 0.6	C
14	S	R lower back	1.5 × 1.0	I (3%)
15	S	R lower abdomen	2.2 × 1.6	I (6%)
16	S, N, K	L lateral abdomen	1.7 × 1.0	I (21%)
17	S, N	L clavicle	2.2 × 1.1	I (7%)
18	S, N	L upper back	3.0 × 2.0	I (<1%)
19	S, N, K	R upper back	3.5 × 4.0	I (1%)
20	S, N	L upper chest	0.7 × 0.9	I (29%)
21	S, N, MN, K	L posterior shoulder	7.0 × 4.0	I (14%)

S, superficial; N, nodular; MN, micronodular; K, keratinizing; C, complete tumor response (no residual tumor); I, incomplete response (residual tumor).

small (<0.7 cm), medium (0.7–1.4 cm), and large BCCs (1.5 cm and greater). Compared to their controls, small and medium sized BCCs had a combined response rate of 91.7% (OR = 55.0, *P*-value = 0.0003). The 91.7% response rate of small and medium sized BCCs was also significantly different from the response rate of large BCCs (25%) (combined OR = 67.0, *P*-value = 0.0004; Fig. 2).

Complete response was also most often observed for superficial BCC (7/9 or 77%) as compared to other subtypes (6/12 or 50%) (Table 2). While a higher percentage of cases of superficial BCC showed complete response to therapy, the comparison to all other BCC subtype did not reach statistical significance. Nevertheless, most cases, regardless of subtype, showed complete response to PDL therapy. In an effort to assess the reduction of tumor bulk after PDL treatment, the pre-treatment maximum clinical diameters

of incompletely responding BCCs were compared to their corresponding post-treatment maximum diameters measured on histology, and their ratio was defined as “residual tumor burden” (Table 3). The residual tumor burden of all eight incomplete responders was reduced to <1–29% of their original burden prior to PDL treatment. The percentage residual tumor burden of seven of these incompletely cleared PDL treated tumors is also significantly less than of their respective control tumors (13–68%; *P*-value = 0.05.) These debulked tumors included two superficial BCCs, and six combinations of other subtypes, including nodular, micronodular, and keratinizing.

## DISCUSSION

In this pilot study, we demonstrated that PDL therapy may lead to complete tumor clearance in 91.7% of BCC

**TABLE 2. Pulsed Dye Laser Treated Basal Cell Carcinomas: Clinical Characteristics Based on Histologic Subtype**

Histologic subtype	Mean diameter (range) (cm)	# of tumors	# of complete responders	# of incomplete responders
Superficial	1.3	9	7	2
All other subtypes	2.7	12	6	6
Nodular	1.2	2	2	0
Superficial and nodular	1.8	8	3	5
Nodular and micronodular	0.6	1	1	0
Superficial, nodular, and micronodular	7	1	0	1

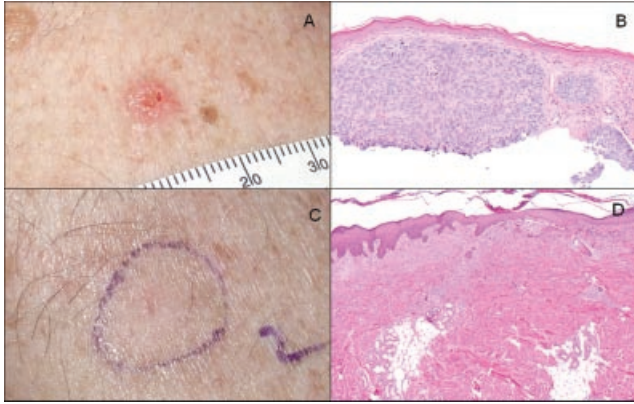


Fig. 1. Complete response: BCC before and after PDL treatment. **A:** Nodular 0.9 cm × 0.7 cm BCC present on the L medial shoulder. **B:** nodular BCC prior to PDL treatment (20× H&E stain, shave biopsy). **C:** Two weeks after the second PDL treatment, the tumor is clinically resolved. **D:** After four PDL treatments there was no histologic evidence of tumor in the excision specimen (4× H&E stain).

<1.5 cm in diameter. Multiple treatments of BCCs with PDL resulted in dramatically reduced tumor mass in all. Complete responders, independent of histologic subtype, were more likely to have smaller clinical diameters compared to non-responders. While the overall histologic response rate (65%) was less than the clinical response rate of Campolmi et al.'s 2005 study (80%), this difference may be due to our enrollment of patients with much larger tumors. Our histologic response rate for patients with small and medium sized tumors (91.7%) is more than the clinical response rates of Campolmi et al. where the treated tumors were all <1 cm in clinical diameter. In

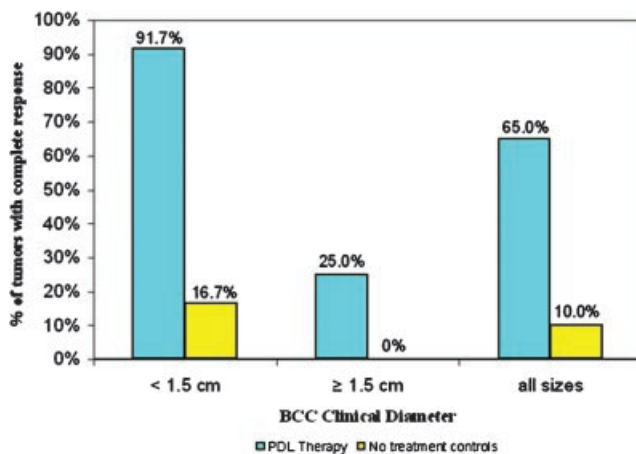


Fig. 2. Histologically confirmed clearance of basal cell carcinoma by 595 nm Pulsed Dye Laser: Comparison with no treatment: Blue, complete responders from PDL (PDL treated BCCs); Yellow, complete responders from no treatment (controls BCCs).

addition, Campolmi et al. 2008 [16] recently treated 20 superficial type BCCs with 595 nm PDL at equivalent laser parameter treatments as our study, and demonstrated an 80% complete response rate at 1 year clinical follow-up—this is similar to our 77% (7/9) histologic complete response rate for superficial BCCs treated with PDL. However, given this comparison is between histologic and clinical response rates, further studies should involve treatment of more complex BCC histologic subtypes with PDL followed by observation of long-term clinical observation (6 months to 1 year) combined with histologic evaluation.

We observed complete tumor responses in a variety of subtypes: 6 of 12 BCCs containing nodular and micronodular histologic subtype showed response to PDL. In addition, most incompletely responding tumors with a significant decrease in tumor burden after PDL treatment were not superficial tumors, but rather were combinations of other histologic subtypes including nodular, micronodular, and keratinizing. Therefore, PDL treatment may be considered not only for superficial type BCCs, but also potentially to treat nodular, micronodular, and combined histologic subtype BCCs.

Various reasons could exist as to why smaller BCCs respond more completely to PDL than larger BCCs. Clinically smaller BCCs and their associated vasculature may still be in a fragile, nascent phase of growth, and thus more susceptible to laser treatment. Five hundred ninety-five nanometers PDL dermal penetration depth is around 1 mm, which approximates the border of the papillary and the reticular dermis—these settings may be optimal for disrupting the amount of vasculature required for tumors of these sizes. As tumor diameter does not necessarily correlate with tumor depth, future studies may include the use of punch biopsies or ultrasound to assess for tumor depth prior to laser treatment.

The eight incomplete responders demonstrated an estimated 71–99% reduction in tumor size after PDL. Even when incorporating a mean 20% shrinkage in tumor length associated with loss of elastic skin tension during excision [14], the residual estimate for the tumor most resistant to PDL in this study would not change significantly (tumor 20: 29% residual tumor vs. 35% residual tumor).

The largest tumor in this study (tumor 21), which was 7.0 cm × 4.0 cm prior to treatment and demonstrated an estimated 86% reduction in tumor burden after treatment, came from a patient with a history of large, recurrent BCCs, treated mainly with surgical excision requiring extensive grafting repair. While we only studied a few cases of larger BCCs, these results suggest that PDL may also be an effective method of selectively debulking very large BCCs in order to facilitate excision.

Photodynamic therapy (PDT) is another selective therapy that combines red light and topical photosensitizers, and has been accepted for treatment of BCC. A recent study of PDT on large BCCs > 5 cm in diameter demonstrated that one-third of tumors still recurred at 36-month follow-up [15]. Since many of the incompletely responding tumors in our study also showed some regression with PDL treatment, perhaps a combination of PDL

**TABLE 3. Analysis of Residual Tumor for Incompletely Responding Basal Cell Carcinomas**

Tumor	Clinical maximum diameter (cm)	Histologic measurement of maximal residual tumor (cm)	Estimated residual tumor (%)	Estimated residual tumor (controls) (%)
14	1.5	0.05	3	16
15	2.2	0.12	6	46
16	1.7	0.36	21	45
17	2.2	0.15	7	13
18	3	0.01	<1	68
19	3.5	0.05	1	31
20	0.9	0.26	29	0
21	7	0.95	14	N/A

Estimated residual tumor =  $100\% \times (\text{Histological measurement of maximal residual tumor/clinical maximum diameter})$ .

Lesion 21 is without a matched control tumor.

and PDT would be effective in treating large, recalcitrant BCCs.

The safety of lasers including non-tumor-specific tissue damage is important to consider. Given the fluences used in the study, one might be concerned about non-selective effects of PDL treatment resulting in ulceration or scarring. None of our patients experienced tumor ulceration after therapy. The most notable clinical reaction was purpura followed by a gray discoloration of the skin, occasionally with a slightly hemorrhagic scale crust. Removal of the scale crust with hydrogen peroxide revealed healthy underlying skin. At 2 weeks after treatment, all patients demonstrated complete healing clinically. The histology of the excised specimens also supports this lack of destructive changes, as none demonstrated evidence of scarring, tissue necrosis, or post-inflammatory pigmentation. This absence of tissue damage is in dramatic contrast to ablative methods such as CO<sub>2</sub> lasers [16] which result in immediate non-selective vaporization of the tissue and resultant scarring.

PDL is not likely to induce tumorigenesis because the absorption wavelength of 595 nm is located in the visible yellow light spectrum. One case report exists of BCC arising in a PDL and argon laser treated port wine stains; this patient also received childhood radiation treatment, which may be another etiology of BCC formation [17].

As a therapeutic option PDL may not be limited to superficial BCCs, because several histologic subtypes of BCC, including nodular, micronodular, and keratinizing types appear to be at least partially susceptible to PDL treatment. Future studies are needed to examine the recurrence rates of superficial and non-superficial BCCs after PDL treatment, to assess the efficacy of 595 nm PDL as a stand-alone treatment or in combination with other treatments, and to compare PDL treatment to other accepted therapies such as surgical excisions with appropriate margins, electrodesiccation and curettage, cryotherapy and imiquimod. In addition, variations in the laser parameters (multiple passes, pulse stacking, more percentage of overlapping pulses, variable pulse widths, varying fluences), or even types of lasers with deeper penetration may be evaluated for larger and more

vascularized tumors. Currently, dose-response studies are underway to examine the effect of varying PDL fluence on BCC tumor burden reduction. Finally, a larger study with more histologic subtypes would help to elucidate which subtypes besides superficial BCCs are most susceptible to PDL treatment.

In conclusion, 595 nm PDL has the potential to serve as an effective non-surgical, non-scarring treatment method for BCCs <1.5 cm in diameter and for superficial BCCs. The results from this smaller pilot study may support future large randomized, controlled clinical trials examining varying BCC histologic subtypes, different BCC treatment methods as controls, and more optimized PDL parameters.

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