**Toxicities and early outcomes in a phase 1 trial of photodynamic therapy for premalignant and early stage head and neck tumors**

Peter H. Ahn a,*, Harry Quon a, b, Bert W. O’Malley c, Gregory Weinstein c, Ara Chalian c, Kelly Malloy c, d, Joshua H. Atkins e, Thomas Sollecito f, Martin Greenberg g, Sally McNulty a, Alexander Lin a, Timothy C. Zhu a, Jarod C. Finlay a, Keith Cengel a, Virginia Livolsi g, Michael Feldman g, Rosemarie Mick h, and Theresa M. Busch a

a Department of Radiation Oncology, University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104, United States

b Department of Radiation Oncology, Johns Hopkins University, 401 N. Broadway, Baltimore, MA 21231, United States

c Department of Otolaryngology-Head and Neck Surgery, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, United States

d Department of Otolaryngology, University of Michigan, 1500 E. Medical Center Dr, Ann Arbor, MI 48109, United States

e Department of Anesthesiology, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, United States

f Department of Oral Medicine, University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104, United States

i Department of Oral Medicine, University of Pennsylvania, 3400 Civic Center Blvd, Philadelphia, PA 19104, United States

g Department of Pathology, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, United States

h Department of Biostatistics and Epidemiology, University of Pennsylvania, 423 Guardian Drive, Philadelphia, PA 19104, United States

**SUMMARY**

**Objectives**—Management of early superficial lesions in the head and neck remains complex. We performed a phase 1 trial for high-grade premalignant and early superficial lesions of the head and neck using photodynamic therapy (PDT) with Levulan (ALA).

**Materials and methods**—Thirty-five subjects with high grade dysplasia, carcinoma in situ, or microinvasive (≤0.5 mm depth) squamous cell carcinoma were enrolled. Cohorts of 3–6 patients were given escalating intraoperative light doses of 50–200 J/cm² 4–6 h after oral administration of...
60 mg/kg ALA. Light at 629–635 nm was delivered in a continuous (unfractionated) or fractionated (two-part) schema.

**Results**—PDT was delivered to 30/35 subjects, with 29 evaluable. There was one death possibly due to the treatment. The regimen was otherwise tolerable, with a 52% rate of grade 3 mucositis which healed within several weeks. Other toxicities were generally grade 1 or 2, including odynophagia (one grade 4), voice alteration (one grade 3), and photosensitivity reactions. One patient developed grade 5 sepsis. With a median follow-up of 42 months, 10 patients (34%) developed local recurrence; 4 of these received 50 J/cm² and two each received 100, 150, and 200 J/cm². Ten (34%) patients developed recurrence adjacent to the treated field. There was a 69% complete response rate at 3 months.

**Conclusions**—ALA-PDT is well tolerated. Maximum Tolerated Dose appears to be higher than the highest dose used in this study. Longer followup is required to analyze effect of light dose on local recurrence. High marginal recurrence rates suggest use of larger treatment fields.

**Keywords**
Photodynamic therapy; Levulan; Head and neck cancer; Severe dysplasia; Carcinoma in situ; ALA; PDT; Aminolevulinic acid; Protoporphyrin IX

**Introduction**
Photodynamic therapy (PDT) uses a photosensitizing agent and light to kill cells, involving delivery of a photosensitizer or photosensitizer precursor followed by illumination at a specific wavelength of light. The appeal of PDT in oncology has been that photosensitizers such as Photofrin are retained in tumor tissues for longer periods compared to normal tissue. The selectivity of photosensitizer for diseased tissue, as well as the ability to target the light directly to diseased areas, has prompted interest in studying PDT as an organ-preserving treatment for premalignant and malignant conditions. Clinical reports of PDT in the treatment of malignancies include head and neck cancers [1], lung cancer [2,3], mesothelioma [4], esophageal [5], brain [6], breast [7,8], bladder [9,10], and prostate cancers [11].

Early superficial lesions in the oral cavity, larynx and pharynx are ideal PDT targets because head and neck anatomy often offers direct access for the laser. Depth of penetration of the laser light ranges from a few millimeters up to 20 mm depending on wavelength [12]. In a report of his experience and literature review, Biel showed an 89% complete response rate in patients with carcinoma in situ or early stage head and neck cancers treated with PDT and Photofrin as photosensitizer [13]. Preclinical reports of Photofrin for head and neck cancer have indicated possible benefit to two-part fractionated light delivery for tumor control [14]. PDT offers an attractive function-preserving alternative for patients in circumstances in which surgical resection can be cosmetically and functionally debilitating.

Using Photofrin as photosensitizer in PDT is associated with an extended period of skin sensitivity to light, lasting up to 6–8 weeks after drug administration, which is a deterrent for ambulatory patients with early stage disease. One Photofrin alternative is 5-aminolevulinic acid or ALA (Levulan®, DUSA Pharmaceuticals, Inc.), a natural precursor in the heme
biosynthetic pathway. ALA can be administered orally or topically, leading to the endogenous production and accumulation of protoporphyrin IX (PpIX). PpIX is activated at the same light wavelength as Photofrin (630 nm). Compared to the 6–8 week photosensitivity with Photofrin, ALA-induced PpIX skin photosensitivity persists for 24–48 h after administration. ALA-mediated PDT has been used in animal studies for esophageal [15], brain [16,17], and prostate cancer [18]. Orally administered ALA has been evaluated clinically for high grade dysplasias and superficial cancers of the esophagus. A series of 5 patients of high-grade dysplasia with Barrett's esophagus were treated, without toxicities or recurrences [19]. A series of 66 patients treated for high-grade intraepithelial neoplasia (31) or early adenocarcinoma (35) demonstrated no major complications [20]. With median 37 month follow-up, disease free survival was 89% for high-grade intraepithelial neoplasia and 68% for mucosal cancer. Oral ALA has been reported for a total 14 patients with high-grade dysplasia or microinvasive cancer of the head and neck. The above studies identify a dose of 60 mg/kg of oral ALA as safe in PDT for superficial epithelial lesions.

Due to the favorable absorption and clearance profiles of PpIX, we conducted a phase 1 trial of orally administered ALA with escalating doses of PDT light for head and neck lesions. The trial included patients with severe dysplasia, carcinoma in situ, or microinvasive carcinoma of the head and neck, dividing treatment into fractionated and non-fractionated cohorts. The primary purpose was assessing the safety and maximum tolerated PDT light dose with orally administered ALA. Due to limited data on efficacy of ALA-mediated PDT in this population, the secondary purpose was preliminarily assessing efficacy of ALA-PDT in this population.

**Methods**

Patients were eligible if they had high-grade dysplasia, carcinoma in situ, or invasive squamous cell carcinoma of the head and neck with depth of invasion ≤1.5 mm on surgical biopsy or resection specimen as read by a dedicated pathologist. Patients with intact disease or disease present at the resection margin were eligible, as long as the PDT procedure was within 4 months of pathologic diagnosis. All subjects were treated in accordance with protocols approved by the Institutional Review Board at the University of Pennsylvania. Pretreatment evaluation included a complete history and physical examination, informed consent, fiber-optic nasopharyngolaryngoscopy with digital photographs, routine laboratory examination, and tissue diagnosis by the Department of Pathology.

ALA was administered as an oral dose of 60 mg/kg dissolved in 50 ml water 4–6 h prior to light delivery. After oral administration of ALA, subjects remained in clinic with light precautions. Vital signs were assessed before, immediately after ALA administration, every 15 min for the first two hours, and then hourly until the procedure.

Activating light generated using a Ceralas Series GaAlAs diode laser (Biolitec Inc., Vienna) was applied 4–6 h after ALA administration. Study subjects were treated with a total fluence of 50, 100, 150 and 200 J/cm² using red light (629–635 nm). Light was delivered using either a microlens (MedLight SA, Ecublens, Switzerland) or with a balloon diffusing fiber (MedLight SA, Ecublens, Switzerland) depending on tumor location and shape.
microlens provided a collimated circular laser beam covering a superficial circular area in accessible areas, and was used for most patients. For 9 patients, a microlens could not adequately cover a cylindrically-shaped lesion. In these cases, a cylindrical diffusing fiber with a chosen active length (2, 3, 4, 5 cm) was placed within a balloon catheter. The balloon was inflated by saline to keep it in contact with the treated area. The light doses were measured using an isotropic detector located in-situ at the treated surface for all patients. As a result, the light dose was always correctly quantified regardless of applicator geometry. A fluence rate of 100 mW/cm$^2$ was delivered to the target, measured by a calibrated isotropic detector positioned on the tissue surface. At each light dose, separate patient cohorts were treated with continuous (unfractionated) or fractionated (two-part) illumination. Fractionation involved delivery of 20% of fluence, a 90–180 s break, then resumption to full fluence.

Almost all treatments were performed under general anesthesia. One patient with lower lip pathology was treated as an outpatient under local anesthesia to the submental nerve. All subjects were hospitalized overnight for observation. Biopsy specimens of diseased tissue were collected before PDT in order to establish eligibility, as well as after PDT in order to assess response (1 month in patients without a clinical response and at 3 months in all patients).

Post-treatment, all patients were instructed to avoid sunlight for 3 days. Toxicity endpoints were graded using the Cooperative Group Common Toxicity Criteria (CTCAE v.3.0). Patients were followed week 1, week 2–3, day 30, day 90, every 3 months for 24 months, and then annually. Dose-limiting toxicity (DLT) was defined by a grade 3 toxicity by 30 days after administration of PDT. Patients were taken off protocol if they underwent a recurrence, but followed off-protocol for further progression.

For purposes of statistical analysis of treatment response, patients were divided into groups receiving low (50 and 100 J/cm$^2$) and high PDT light dose (150 and 200 J/cm$^2$). Complete response at 3 months was evaluated with a planned biopsy at that timepoint. Kaplan Meier analysis with log-rank analysis of local recurrence-free survival was used to compare the low and high PDT light dose groups. For assessment of toxicity between the low and high dose groups, two-sided Fisher exact test was used to assess for statistical significance between the two groups.

**Results**

From November 2009 to October 2014, 35 subjects were enrolled. Two of the subjects were the same patient undergoing separate treatment for a second primary (1 subject) or recurrent disease (1 subject). One patient who tolerated initial treatment at 50 J/cm$^2$ without complication was treated for a second time 10 months later for a local recurrence at a higher dose (150 J/cm$^2$, fractionated). This patient who had history of liver transplant on immunosuppression underwent treatment and developed expected edema at the treatment site which quickly resolved but then developed pulmonary edema and sepsis of either pulmonary or urinary origin, and significant hypoxemia from a tension pneumothorax. It was determined that the pneumonia, sepsis and respiratory failure could possibly be related
to study treatment with the patient’s immunosuppression as a possible contributing factor. On autopsy, cause of death in relation to ALA and PDT could not be conclusively determined.

Five subjects could not be treated with PDT light after ALA administration, although 2 of these subjects subsequently underwent successful treatment with ALA-PDT. Since the events preventing light delivery occurred prior to the administration of the experimental aspect of this dose escalating protocol for PDT illumination, these patients were not considered to have experienced a DLT. One patient was found to have an elevated creatinine level after ALA administration and the procedure was aborted; this event was subsequently found not to represent artifact of ALA interaction with the Jaffe method for calculating creatinine instead of true renal failure [21]. This patient subsequently underwent PDT with ALA successfully. A second patient was found to have developed quick interval progression when examined in the operating room, making her a poor candidate for light; she underwent reresection and subsequently received PDT with ALA for high-grade dysplasia at the surgical margin. A third patient developed laryngeal edema in the operating room, subsequent to attempts at intubation and prior to delivery of PDT light. The cause of the edema was uncertain, but may have been related to prolonged light exposure from repeated attempts at intubation by a new anesthesiology trainee. The patient ultimately opted for resection. A fourth patient became profoundly hypotensive after administration of anesthetic in the operating room prior to delivery of PDT light but after the administration of ALA, and the procedure was aborted. A fifth patient developed transaminitis and became hypotensive after receiving ALA but prior to undergoing anesthesia, and could not receive PDT. Since hypotension is a known ALA side effect, especially in patients with cardiovascular comorbidities, care was taken to avoid enrollment of subjects with significant cardiovascular comorbidities [22]. Patients were regularly monitored for changes in blood pressure after administration ALA (every 15 min for 2 h) per protocol. Two patients were initially unable to undergo PDT illumination due to hypotension. Due to this hypotension effect, it became our policy to administer intravenous hydration in the 4–6 h between ALA and PDT administration at a rate of 100 mL per hour.

Of the 30 patients who received ALA and illumination, 7 received 50 J/cm² (3 non-fractionated and 4 fractionated), 6 received 100 J/cm² (3 non-fractionated and 3 fractionated), 9 received 150 J/cm² (6 non-fractionated and 3 fractionated), and 8 received 200 J/cm² (4 non-fractionated and 4 fractionated). One patient in the 150 J/cm² non-fractionated cohort developed a DLT, thus the protocol required enrollment of 6 patients under these illumination conditions (5 patients were evaluable due to the death). Therefore, a total of 29 patients were evaluable (Table 1). The median followup period of evaluable patients was 41.6 months (range, 3.2–59.4 months).

In patients who underwent the procedure, toxicities were tolerable (Table 2). The most common toxicity was mucositis, which occurred in 86% of patients treated at 50 J/cm² and 100% of patients treated at the higher light doses. In all cases, mucositis was grade 3 or lower in severity, but patients who received higher doses of PDT light (150 and 200 J/cm²) had higher rates of grade ≥2 mucositis than those who received lower PDT light doses (50 and 100 J/cm²). This difference approached statistical significance (77% versus 100%
respectively for lower and higher doses, \( p = 0.078 \)). In all cases, the mucositis resolved by 30 days. No pain was reported by subjects treated with 50 J/cm\(^2\), but this increased to 33% of subjects reporting pain after treatment at 100 J/cm\(^2\), with 88% and 63% reporting pain after treatment at 150 and 200 J/cm\(^2\), respectively. Six patients reported grade 1, 7 patients reported grade 2, and 1 patient who was treated at 150 J/cm\(^2\) reported transient grade 3 pain. More patients who received lower doses of PDT light (50 and 100 J/cm\(^2\)) reported no or grade 1 pain compared to patients who received higher doses (150 and 200 J/cm\(^2\)) of PDT light (8% versus 44%, \( p = 0.044 \)). The manifestations of pain and mucositis almost universally resolved by the week 2 visit, with no pain or mucositis events representing a DLT.

Tongue swelling occurred in 14%, 17%, 38%, and 25% of patients treated at 50, 100, 150, and 200 J/cm\(^2\) respectively, which were all grade 2 or less and quickly resolved. Treatment resulted in one instance of grade 4 odynophagia and one instance of grade 3 voice alteration at a light dose of 50 J/cm\(^2\); another six cases of transient odynophagia or voice alteration that were all grade 1 or grade 2 occurred at higher light doses. Weight loss was minimal and no different between treatment groups, with one grade 1 and two grade 2 episodes of weight loss. Photosensitivity reactions of grade 2 or less occurred in 10 of 29 evaluable patients who received ALA and light. Rates of grade 2 or higher aspiration, infection, liver toxicities, and neuropathy were also not different among the light doses. We could not detect a difference in toxicities between the fractionated and continuous-light cohorts.

There is not yet enough follow-up to determine long-term dose response. At 3-months, complete response as determined by biopsy was obtained for 20/29 (69%) of patients. The 3-month complete response rate was 5/7 (71%) for the 50 J/cm\(^2\) cohort, 3/6 (50%) for the 100 J/cm\(^2\) cohort, 6/8 (75%) for the 150 J/cm\(^2\) cohort and 6/8 (75%) for the 200 J/cm\(^2\) cohort (\( p = 0.82 \)). One patient treated in the 100 J/cm\(^2\) non-fractionated arm experienced local failure at 1 month, and 5 months later was retreated in the 200 J/cm\(^2\) fractionated arm as primary retreatment; she has no evidence of disease 41 months after retreatment. There was no difference in local recurrence between the fractionated and non-fractionated groups (not shown, \( p = 0.82 \)).

Preliminarily, patterns of local recurrence appear more pronounced in lower dose arms that progressive decreases with higher PDT doses (Table 3). Local recurrences occurred at rates of 57%, 33%, 25% and 25% after PDT at 50, 100, 150, and 200 J/cm\(^2\), respectively. These findings are confounded by shorter follow-up for higher-dose arms with the lower light dose group having a 55 month median follow-up and the higher light dose group having a 30 month median follow-up, with the last 3 enrolled patients having been followed for 6 months. It is worthwhile to note that local recurrences occurred within a median 2.9 months after PDT administration (range [1.3, 19.0 months]) (Fig. 1). There was a 69% complete response rate for subjects treated with all fluences. No statistically significant difference was detected in local recurrence rates between the two low (50 and 100 J/cm\(^2\)) and two high (150 and 200 J/cm\(^2\)) light dose groups at this early juncture (\( p = 0.87 \)). The 6-month local recurrence-free rate for the 50 and 100 J/cm\(^2\) cohort was 59%, while the rate for the 150 and 200 J/cm\(^2\) cohort was 66%. In the 24 patients with oral cavity lesions, the 6-month local...
recurrence-free rate for the 50 and 100 J/cm² cohort was 45%, while the rate for the 150 and 200 J/cm² cohort was 61%.

Of the 29 patients, 7 (24%) underwent progression to invasive disease in the area of or adjacent to the treated field. This study was notable for the high rate of marginal recurrences, with rates of 25–63% depending on treatment cohort (Table 3). At 6 months, there was no difference in marginal recurrence with a marginal recurrence-free survival rate for the 50 and 100 J/cm² cohorts of 92% (95% confidence interval [54%, 99%]), and a rate for the 150 and 200 J/cm² cohorts of 55.9% (95% confidence interval [25%, 78%]). Marginal and out-of-field recurrences occurred within a median 2.7 months after PDT administration (range [1.2, 27.3 months]). While the 50 J/cm² group had no marginal recurrences but higher local failure rates (57% compared to 25–33% for the 100–200 J/cm² groups, Table 3), many of the patients in this cohort with local failures were lost to follow-up soon after their local recurrences and could not be assessed for subsequent marginal recurrence. A treatment field encompassing an extended area surrounding the visible boundaries of the lesion was used for treatment of the last 5 subjects. In patients in whom an extended treatment field was not used, 7/24 patients (29%) experienced a marginal recurrence at 6 months, compared to 0/5 patients who were treated with extended treatment fields.

**Discussion**

In this phase 1 series, we find that treatment of premalignant and early stage head and neck tumors with PDT is generally well tolerated. We found an expected rate of side effects, with pain and mucositis dependent on dose of the PDT light used. DLT was not reached in our cohort of patients. Ultimately, 2 patients could not be treated with ALA-PDT due to an effect of Levulan precipitating hypotensive episodes and/or transaminitis; this has prompted us to carefully select patients without significant cardiovascular history prior to offering PDT with ALA. One patient developed laryngeal edema, but this was consistent with a reaction to the light used for intubation for general anesthesia after ALA but prior to light administration. One patient with significant medical comorbidities developed sepsis and pulmonary edema, passing away in a manner that could possibly be related to his treatment.

Whether control at the local site is improved with higher doses of PDT light is uncertain in this interim analysis, and this study is not powered to make that determination. A confounding factor in an interim evaluation of efficacy is the mix of patients who received ALA-PDT definitively for unresected disease (18 patients) or for dysplasia, carcinoma in situ or microinvasive carcinoma at the margin of resected disease (11 patients), although the proportions of definitive versus adjuvant treatment was generally balanced amongst the PDT doses (Table 1). However, patients with moderate and high grade dysplasias present at the surgical margin in oral cavity cancers have been demonstrated to have a 51% rate of local recurrence [23], similar to progression rates expected for unresected high-grade dysplasias. We also found a significant rate of marginal recurrences when the local site is controlled. As we appreciated this phenomenon, we widened the PDT light field to account for field precancerization amid concerns that we were generally underestimating the area at risk for recurrence. Indeed, other studies have shown that areas previously thought to be tumor-free have precursor lesions with genetic changes predisposing for local or marginal recurrences.
Among the 5 patients who were treated with the larger fields, there have been no cases of marginal recurrence.

Several reports indicate that patients with early stage cancer or early recurrences in the head and neck, particularly the oral cavity and larynx, have excellent responses to PDT [25,26]. Biel et al. treated 48 patients with early head and neck squamous cell carcinomas using the photosensitizer Photofrin. Of those, 25 had carcinoma in situ (CIS) and T1 cancers, 17 of which were radiation therapy failures. There was a complete clinical and pathologic response in all patients and they remained without recurrence at a mean follow-up of 27 months. An additional 23 patients had early carcinomas (CIS, T1 and T2) of the oral cavity, nasal cavity and nasopharynx. After treatment, all patients achieved a complete response rate of 87% [27]. In a review of the literature, Biel noted a complete response rate of 85% (145/171) after a single PDT treatment with Photofrin in patients with CIS, T1 and T2 cancers of the oral cavity, larynx, and pharynx [28].

ALA has previously been used for head and neck lesions. Four patients were treated with ALA for head and neck squamous cell carcinoma, and the treatment was found to be tolerable [29]. Fan et al. used ALA with fractionated (two-part) light delivery to 100 or 200 J/cm² for 18 patients with moderate and high-grade dysplasia as well as invasive carcinoma of the head and neck. Of the 5 patients treated with high-grade dysplasia, there was a complete pathological response in 3 out of 4 evaluable patients. One out of 6 patients with invasive disease had complete pathologic response. This was felt to be due to limited depth of penetration of thick invasive lesions. There were no reports of issues with hypotension or permanent episodes of liver dysfunction in these series [30].

We find PDT with ALA to be safe with generally tolerable side effects in our population of patients with high-grade dysplasia, carcinoma in situ, and early stage carcinomas of the head and neck. DLT was not reached in our study, and we would recommend that PDT-ALA be advanced to a phase II trial to determine efficacy, at our highest light dose of 200 J/cm².

Conclusions

We find that administration of photodynamic therapy with Levulan allows for shortened periods of light restriction, and is generally well tolerated. We find suggestion that the regimen is effective in terms of local control especially at higher light doses, when the alternative involves function-altering resection. There was an initially high rate of marginal recurrences, and larger treatment fields should be considered. More followup is required to estimate local control, especially when comparing the effectiveness of lower versus higher PDT light doses.

Acknowledgements

This work was funded by grant 5R01CA129554-03 from the National Institutes of Health United States. 5-aminolevulinic acid (Levulan®) was provided by DUSA Pharmaceuticals.
References


Fig. 1.
Local recurrence-free survival for all patients (n = 29).
Table 1

Patient characteristics.

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<td>6</td>
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<td>1</td>
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Table 2

Toxicities as a function of PDT light dose for patients treated with continuous (unfractionated) and fractionated (two-part) illumination.

<table>
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<tr>
<th>Toxicity</th>
<th>50 J/cm² (N = 7)</th>
<th>100 J/cm² (N = 6)</th>
<th>150 J/cm² (N = 8)</th>
<th>200 J/cm² (N = 8)</th>
<th>All patients treated (N = 29)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>a All Grades # (%)</td>
<td>Grade 3 # (%)</td>
<td>Grade 4 # (%)</td>
<td>Grade 3 # (%)</td>
<td>Grade 4 # (%)</td>
</tr>
<tr>
<td>Pain</td>
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<td>0</td>
<td>0</td>
<td>7 (88%)</td>
<td>1 (13%)</td>
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<tr>
<td>Mucositis</td>
<td>6 (86%)</td>
<td>3 (43%)</td>
<td>0</td>
<td>6 (100%)</td>
<td>2 (33%)</td>
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<td>Odynophagia</td>
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<td>2 (33%)</td>
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<td>Weight loss</td>
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<td>0</td>
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<td>1 (13%)</td>
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<tr>
<td>Photo-sensitivity</td>
<td>2 (29%)</td>
<td>0</td>
<td>0</td>
<td>3 (50%)</td>
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<td>Tongue swelling</td>
<td>1 (14%)</td>
<td>0</td>
<td>0</td>
<td>1 (17%)</td>
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</tr>
<tr>
<td>Voice alterations</td>
<td>1 (14%)</td>
<td>1 (14%)</td>
<td>0</td>
<td>3 (50%)</td>
<td>0</td>
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<tr>
<td>Abnormal liver function</td>
<td>5 (71%)</td>
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<td>0</td>
<td>4 (67%)</td>
<td>1 (17%)</td>
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*aGrade 1 to 4 included.*
Table 3
Recurrence rates as a function of PDT light dose and continuous (unfractionated) versus fractionated (two-part) illumination. Recurrences are separated into those that are local and those that are marginal.

<table>
<thead>
<tr>
<th>Dose Combined</th>
<th>Fractionated</th>
<th>Total number</th>
<th>Local recurrence (%)</th>
<th>Marginal recurrence (%)</th>
</tr>
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<tbody>
<tr>
<td>50</td>
<td>7</td>
<td>4 (57%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>2 (67%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>2 (50%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>6</td>
<td>2 (33%)</td>
<td>3 (50%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>1 (33%)</td>
<td>2 (67%)</td>
<td></td>
</tr>
<tr>
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<td>3</td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>8</td>
<td>2 (25%)</td>
<td>5 (63%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5</td>
<td>1 (20%)</td>
<td>3 (60%)</td>
<td></td>
</tr>
<tr>
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<td>1 (33%)</td>
<td>2 (67%)</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>8</td>
<td>2 (25%)</td>
<td>2 (25%)</td>
<td></td>
</tr>
<tr>
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<td>4</td>
<td>1 (25%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>1 (25%)</td>
<td>2 (50%)</td>
<td></td>
</tr>
</tbody>
</table>