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REVIEW ARTICLE

Erythroplasia of Queyrat treated by laser and light modalities: a systematic review

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Abstract Erythroplasia of Queyrat (EOQ) is a squamous cell carcinoma in situ most commonly located on the glans penis or prepuce. EOQ accounts for roughly 10 % of all penile malignancies and may lead to invasive squamous cell carcinoma. Standard therapy includes local excision, partial or total penectomy, cryotherapy, and topical cytotoxic agents. Treatment of EOQ has proven to be challenging due to low response rates and recurrence. In addition, radical procedures can significantly affect sexual function and quality of life. Alternative laser treatments and photodynamic therapy (PDT) offer promising results for treating EOQ. A systemic review of the literature was performed for articles discussing laser and light therapy for EOQ. Among the patients treated with the CO_2 laser, 81.4 % of cases had complete remission after one session of treatment. Patients treated with PDT presented with more variable results, where 62.5 % of those treated with methyl aminolevulinate photodynamic therapy (MAL-PDT) achieved complete remission. Aminolevulinic acid (ALA-PDT) treatment showed a similar rate of remission at 58.3 %. One study utilized the Nd:YAG laser, which resulted in a recurrence of the lesion in four of the five patients treated. Of the methods reviewed, the CO_2 laser offered the most promising results with a cosmetically excellent prognosis. Further studies with larger power and longer follow-up times are needed to determine the optimal treatment regimen for this penile malignancy.

Keywords Erythroplasia of Queyrat · Squamous cell carcinoma in situ · Penile carcinoma in situ · Laser therapy · Phototherapy

Introduction

Erythroplasia of Queyrat (EOQ), also known as Bowen's disease of the glans penis, is squamous cell carcinoma (SCC) in situ of the glans and prepuce of the penis. An estimated 10 % of all penile neoplasms are believed to be EOQ [1, 2]. The disease characteristically presents as a solitary or multiple nonhealing, well-defined lesion with a velvety red appearance. Redness, crusting, bleeding, pain, scaling, ulceration, and discharge may also be present [3]. EOQ may progress to invasive squamous cell carcinoma (SCC), with a reported incidence of 10 to 33 % [4]. Progression can be accompanied by development of ulceration and/or papillary manifestation [3, 5].

Standard therapeutic approaches include local excision, Mohs surgery, and partial or total penectomy. Of these surgical approaches, Mohs surgery produces the most cosmetically and functionally favorable outcomes. However, these invasive procedures have the potential to cause adverse psychosocial effects and worsen the quality of life. Other nonsurgical modalities include isotretinoin, 5-fluorouracil cream, imiquimod cream, cryotherapy, and cidofovir [6–9]. Treatment with topical cytotoxic agents is often not favored due to the necessity for extended administration [10]. Furthermore, the use of topicals is still controversial due to the variable effectiveness and limited long-term data, accentuating the need for alternate therapeutic options [7, 11–16].

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Laser therapy offers a promising route for the treatment of EOQ. The carbon dioxide (CO_2) laser is a viable option for the treatment of EOQ, effectively vaporizing affected areas, followed by the removal of the heat-separated tissue. The CO_2 laser is potentially advantageous due to its precisely controlled thermal damage, with minimal effects on tissue surrounding the target area. [17] The neodymium-doped yttrium aluminum garnet (Nd:YAG) laser, which penetrates the skin to cause coagulation at a depth of 3–10 mm, has also been shown to effectively treat EOQ lesions [18–21]. Additionally, photodynamic therapy (PDT) has also been used to treat basal cell carcinomas, SCC, and other skin cancers. Use of a photosensitizer, such as 5-aminolevulinic acid (ALA) or 5-methylaminolevulinic acid (MAL), causes an accumulation of protoporphyrin IX in tumor cells, which is subsequently activated by visible light. [22] Moreover, PDT causes selective destruction of abnormal cells with promising outcomes [23]. The present study seeks to systematically search and review the published literature to discuss the available treatment options of EOQ, with a primary focus on lasers and photodynamic light therapy. Considering the low number of published cases treated with laser and PDT modalities, this study seeks to comprehensively review the available reports and discuss which modalities may be the most promising for EOQ treatment.

Methods

A systematic search of the National Library of Medicine's PubMed Database was performed on February 15th, 2016 to find articles published between January 1st, 1980 and February 2016) that related to EOQ and all of the alternative terms that could specify an equivalent diagnosis of EOQ, such as in situ squamous carcinoma of the glans/prepuce. We defined EOQ as SCC in situ or Bowen's disease occurring on the penile mucocutaneous epithelium. The following search terms were used: "erythroplasia of Queyrat," "penile intraepithelial neoplasia," and "(intraepithelial neoplasia OR Bowen's disease OR in situ squamous cell carcinoma OR Carcinoma in situ) WITH/AND (glans or prepuce or urethra or meatus)." The search results were also cross-referenced with the SCOPUS database. Articles not written in English and performed on animal subjects were excluded. Articles discussing light or laser therapy for the treatment of EOQ were included for further review. If an article did not have an abstract, the entire manuscript was analyzed for content and then included or excluded based on the relevance of the information. Only articles with cases that had a biopsy performed for histological confirmation of EOQ were included. Studies that failed to distinguish EOQ patients from other cohorts within the same group with a different diagnosis were excluded. Initial search returned 2051 articles. After screening of titles and abstracts, 20 articles remained as potential candidates for inclusion and were reviewed in full-text version. Further exclusion upon full-text review due to studies not providing relevant data resulted in a final total of 18 articles to be included in this review.

Results

Laser therapy

Eight studies that used laser modalities in the treatment of EOQ were included [17, 21, 24–29], comprising a total of 34 patients (Table 1). A total of 27 patients were treated with CO_2 laser, and 7 patients were treated with Nd:YAG lasers. Three studies consisted of multiple patients, with the remainder being single case reports. These studies administered laser treatment in either superpulsed wave ($N = 3$) or continuous wave ($N = 5$) mode with fluence ranging from 3 to 15 W. After the initial laser administration, a single layer of tissue was removed and additional pulses of laser were applied in three studies [17, 26, 28]. All studies used the CO_2 laser as first-line therapy except one case [26], in which the patient received Mohs' micrographic surgery and developed a recurrent lesion 4 years later.

The number of treatment sessions ranged from 1 to 3, with the majority of patients achieving complete remission ($N = 33$, 97.1 %, 33/34), determined at follow-up between 6 weeks to 40 months after therapy. In one study [21], recurrence of EOQ after laser therapy resulted in five patients (5/19, 26.3 %). Of these, one patient was treated with the Nd:YAG laser earlier in the study, whereas the four remaining patients were treated with CO_2 laser therapy. One other study [28] that utilized CO_2 laser therapy reported the recurrence of the treated lesion in one of the eight patients (12.5 %) treated. Repeated treatment resulted in complete remission. The remaining studies ($N = 6$) discussing CO_2 laser therapy achieved complete remission in all patients ($N = 7$).

Of the patients treated with CO_2 therapy, five (19 %) patients relapsed, with four of those undergoing a second session of CO_2 laser and achieving CR. The remaining patient who was initially treated with a CO_2 laser returned with an infiltrating penile carcinoma that was subsequently treated with partial penile amputation when examined at 6-year follow-up [21]. Ninety-six percent (26/27) of patients treated with the CO_2 laser experienced CR. In contrast, 14 % ($N = 1$) experienced relapse when treated with the Nd:YAG laser ($N = 1$) [21, 28]. These patients continued laser treatment with the same laser used as the initial treatment. All patients treated with Nd:YAG laser experienced CR.

The administered CO_2 laser therapy was reportedly well tolerated. Some pain or slight burning sensation during the treatment was reported in two studies [25, 26]. Otherwise,

Table 1 Laser treatment of erythroplasia of Queyrat

Study	*N*	Mean age	Laser	Wave/mode	Specifications	Outcome	Mean follow-up (mo)	Adverse effects
Rosemberg & Fuller (1980) [24]	1	75	CO_2 laser	Superpulsed wave	100 pps, 3.8 W	CR	1.5	Slight burning sensation (24–48 h).
Rosemberg (1985) [25]	2	–	CO_2 laser	Continuous wave	3 W, 2.0 mm diameter	CR	38	–
Greenbaum et al. (1989) [26]	1	77	CO_2 laser	Continuous wave	5 W, 159 W/cm^{2a}	CR	16	Re-epithelialization at 14 days, cosmetically excellent, some pain.
Ross et al. (1998) [27]	1	74	CO_2 laser	Continuous, defocused mode	7 W continuous	CR	12	None reported. Re-epithelialization at 3 weeks.
Bezooijen et al. (2001) [21]	12	52[b]	CO_2 laser	Continuous wave	15 W, Repeated at 2–4 months ($N = 3$ out of 4 relapses)	Relapse in 33 % ($N = 4$). CR ($N = 11$).	32[b]	–
Bezooijen et al. (2001) [21]	7	52[b]	Nd:YAG laser	–	23–30 W	Relapse in 14 % CR ($N = 7$)	32[b]	–
Conejo et al. (2005) [28]	8	64	CO_2 laser	Superpulsed wave	10,600 nm, 5 W[a]	Relapse ($N = 1$, treated again with CR)	12	Re-epithelialization at 14–28 days, cosmetically excellent.
Losada et al. (2005) [17]	1	34	CO_2 laser	Continuous wave	(1 mm diameter, 5 W/cm^{2a} Repeated for remaining lesion.	CR	6	–
Yamaguchi et al. (2014) [29]	1	87	CO_2 laser	Superpulsed wave with surgical excision	10 W	CR	3	No major complications or pain.

CO_2 carbon dioxide, *CR* complete remission, *MMS* Mohs micrographic surgery, *Nd:YAG* neodymium-doped yttrium aluminum garnet, *pps* pulses per second

[a] Followed by the removal of a single tissue layer and additional laser pulses

[b] Reported data not separated by treatment modality

the use of this modality allowed complete re-epithelialization at 2–4 weeks and cosmetically excellent healing.

Photodynamic therapy

A total of ten studies consisting of 67 patients utilized PDT (Table 2) to treat EOQ [13, 23, 30–37]. Four studies used ALA as the photosensitizer, seven more recently published studies used MAL, and one study used both MAL and ALA. Regardless of the type of PDT, the photosensitizer was applied using an occlusive dressing for 3–5 h. Light therapy was generally administered using 570–670 nm of red light with MAL and 600–730 nm of light with ALA. One study [30] used white light at 400–700 nm after ALA photosensitization. Fluence of the light therapy administered varied dramatically, with fluences from ALA ranging from 50 to 125 J/cm^2 and those with MAL ranging from 35 to 75 J/cm^2, with the majority set at 37 J/cm^2 ($N = 5$). A greater number of studies reported the use of PDT as a first-line treatment option; however, four studies [13, 23, 30, 33] reported prior trials with other modalities, including topical 5-fluorouracil, circumcision, Mohs micrographic surgery, iridium wire brachytherapy, topical imiquimod, and CO_2 laser therapy.

The number of sessions varied dramatically among the studies, with a range from 1 to 10 sessions. Outcome similarly varied among studies, with an overall trend of complete remission in a large portion of the patients. In the earliest study [30], the use of ALA-PDT resulted in complete remission of one case of four presented. The remaining three cases had recurrent lesions after two sessions and were subsequently treated with CO_2 laser therapy. Two additional studies using ALA-PDT reported spread and progression of the lesion [31, 33]. One case [31] reported the development of invasive SCC at 4 months and was treated with partial penectomy. The other study [33] reported one case of the lesion spreading, with the remaining six patients in the study entering complete remission. Paoli et al. [32] administered ALA- or MAL-PDT to their patients, with two receiving both modalities. Complete

Table 2 Photodynamic therapy for erythroplasia of Queyrat

Study	*N*	Mean age	PDT	Wavelength (nm)	Fluence, courses	Outcome	Mean follow-up (range), months	Adverse effects
Stables et al. (1999) [30]	4	62.75 (49–75)	ALA	630 or 400–700	125 J/cm^2	CR at 6 months ($N=1$), recurrence after 2 sessions ($N=3$, subsequent CO_2 laser tx)	– (12–36)	Tingling/burning during tx. Mild swelling and discomfort with dysuria resolving at 2–5 days.
Varma et al. (2000) [31]	1	38	ALA	600–730	105 J/cm^2, ×3	Remaining erythema treated with 5-FU. Development of invasive SCC, treated with partial penectomy	4	Tolerable discomfort during tx.
Wang et al. (2008) [33]	7	–	ALA	–	80–100 J/cm^2, 60 mW/cm^2, ×2–7	CR ($N=6$). Spread of lesion ($N=1$)	12	Minimal scarring.
Paoli et al. (2006) [32]	7	68.4 (52–82)	ALA	600–730	50–80 J/cm^2, 35–80 mW/cm^2	CR ($N=3$), Recurrence ($N=2$), Incomplete c learance ($N=2$)	46.5 (35–58)	Pain and temporary superficial erosions. No scarring or deformities.
Paoli et al. (2006) [32]	2	52 (49–55)	ALA + MAL	600–730	50–80 J/cm^2, 35–80 mW/cm^2	Incomplete clearance ($N=1$), Recurrence ($N=1$)	65 (38–92)	Pain and temporary superficial erosions. No scarring or deformities.
Paoli et al. (2006) [32]	1	42	MAL	570–670	37 J/cm^2, 37 mW/cm^2	CR	9	Pain and temporary superficial erosions. No scarring or deformities.
Feldmeyer et al. (2011) [13]	11	69 (49–87)	MAL	570–670	75 J/cm^2	CR ($N=3$), partial remission ($N=4$). Tumor progression ($N=2$), alternative therapy required ($N=5$).	– (4–45)	Erythema / burning during tx. Temporary dysuria ($N=4$), hematoma ($N=1$), discontinuation of tx due to pain ($N=2$). None ($N=3$).
Lee & Ryman (2005) [23]	1	82	MAL	630	37 J/cm^2	CR at 9 weeks. Pt died due to unrelated cause at 18 weeks.	2.25	Mild swelling, redness, and pain subsiding at 5 days.
Fai et al. (2012) [34]	23	62.5 (36–82)	MAL	red light	37 J/cm^2, ×2 over 2 weeks.	CR ($N=19$). Persistent lesion ($N=3$).	18 (8–30)	Persistent local symptoms delaying 2nd session by 1 week ($N=7$). Pain, burning, erythema, edema, erosion/ulceration (N = 23). Blistering and dyschromia/hyperpigmentation ($N=4$).
Park et al. (2012) [35]	1	50	MAL	Red light,	37 J/cm^2 ×10 over 4 months.	Decrease in size, but developed into invasive SCC. Partial penectomy resulted in CR at 12 months.	12	Tolerable discomfort during tx.
Calzavara-Pinton et al. (2013) [37]	8	57.5 ± 14.1	MAL	635 ± 18	37 J/cm^2	CR ($N=5$)	9.5	Marked local reaction ($N=6$), moderate ($N=1$), no reaction ($N=1$). Marked pain or burning during tx ($N=3$).
Cinotti et al. (2014) [38]	1	65	MAL	578 (copper bromide laser)	35 J/cm^2, 400 ms, ×2 at 2 weeks	CR at 5 months, determined by confocal technique. Confirmed at 1 year follow-up by skin biopsy.	12	–

5-FU 5-fluorouracil, *ALA* aminolevulinic acid, *CO_2* carbon dioxide, *CR* complete remission, *MAL* methyl aminolevulinate, *MMS* Mohs micrographic surgery, *PDT* photodynamic therapy, *SCC* squamous cell carcinoma, *tx* treatment

remission was observed in four cases after two to eight sessions of therapy. Three patients developed recurrent EOQ, while three patients had incomplete clearance of the primary lesion after receiving only one treatment session.

Utilizing MAL-PDT seems to exhibit greater efficacy compared to using ALA monotherapy as a sensitizer. In one study [13], 3–11 patients entered complete remission. Of the remaining cases, four entered partial remission, two developed tumor progression, and five patients required alternative therapy. Fai et al. [34] reported 19 of 23 patients entered complete remission after weekly sessions over 2 weeks. In another study [36], five of eight patients entered complete remission after therapy. The remaining studies involving MAL-PDT were case reports. One case [37] of a 65-year-old who received two sessions of treatment was confirmed to be in complete remission at 1 year. Interestingly, one study [35] discussed a case highly refractory to MAL-PDT. A 50-year-old male presenting with EOQ was treated with ten sessions of MAL-PDT over 4 months. While a decrease in size was observed, the lesion developed into invasive SCC. Ultimately, partial penectomy resulted in complete remission confirmed at 12 months after treatment.

The majority of patients receiving photodynamic therapy tolerated the treatment. Commonly reported adverse effects included temporary tingling, burning, pain, or other discomfort during and after the therapy ($N = 59$ patients). One study [13] did report the discontinuation of treatment in two patients due to intolerance of the therapy-associated pain. In another study [34], 7 of the 23 treated patients required the delay of the second session by 1 week due to persistent local symptoms. Additionally, temporary dysuria was reported in patients of two studies [13, 30]. Other adverse effects included mild swelling and redness with a small number of patients developing a hematoma, erosion/ulceration blistering, and dyschromia/hyperpigmentation.

Discussion and conclusion

Surgical excision by means of partial or total penectomy is currently regarded as the standard therapy for EOQ. Such radical procedures can significantly impact a person's quality of life and interfere with sexual function. Laser and light therapy offers a safe and effective alternative modality for treating EOQ. The use of the Nd:YAG laser was discussed in one study consisting of seven patients [21], with the recurrence of the lesion occurring in one patient. In comparison, the use of the CO_2 laser demonstrated greater efficacy. Of the 27 patients receiving CO_2 laser therapy in this review, only five incidents of relapse were reported [21, 28]. Treatment with the CO_2 laser was repeated in four of those patients, which resulted in complete remission. The effectiveness of the CO_2 laser with minimal adverse effects may be attributed to its ablative mechanism with only superficial penetration. Such qualities make this modality suitable and effective for the conservative treatment of EOQ with a cosmetically excellent prognosis and minimal effect on sexual function and quality of life. These two modalities were the only reported lasers used for EOQ therapy. Likely, their epidermal-specific ablative properties governed the selection of these lasers over others. The longer wavelengths, emitted by lasers such as the CO_2 and Nd:YAG, are absorbed by cellular water of the epidermis; this allows localized skin resurfacing and is ideal for epidermal lesion removal [38].

Photodynamic therapy, however, presented with more varied results. Of the 48 patients treated with MAL-PDT, only 30 (62.5 %) achieved complete remission. Treatment with ALA-PDT had a similarly low rate of complete remission, seen in 10 of the 21 cases (47.6 %). Of note, patients in four of the included studies on PDT received some form of previous treatment [13, 23, 30, 33]. This possibility of the study population skewed towards more aggressive malignancies may act as a factor confounding the reported efficacy of PDT. Comparatively, a review on the use of PDT with topical photosensitizers for cutaneous in situ SCC demonstrated 100 % clearance rates with recurrence rates from 0 to 52 % [39]. The higher recurrence coupled with the risk for metastatic disease of SCC is of concern for the currently available PDT technology for cutaneous SCC.

Of the two laser modalities presented in this review, the CO_2 laser therapy is the most promising method. Based on the data presented, a low recurrence rate is to be expected, and the most common side effects would be slight pain and/or discomfort during the administration of the therapy. Complete re-epithelialization would be expected in 2–4 weeks with an excellent cosmetic prognosis. However, the power of the included studies is small and patient follow-up was at most 1 year, with the exception of one study at 36–40 months [25]. Thus, larger prospective studies with longer follow-up are required.

To the authors' knowledge, this is the most comprehensive review discussing laser and light therapies in the treatment of EOQ, and the limitations must be discussed. The retrospective and literature review design of this study comes with inherent limitations such as publication bias. This has been addressed by the systematic search of two extensive databases (PubMed and SCOPUS). Additionally, this review attempts to comment on the efficacy of the different modalities in treating EOQ. However, due to the small number of reported cases and total patients ($N = 101$), the assessment of these modalities is limited in statistical power. Another factor to take into consideration is the short follow-up times after treatment (unweighted average, 13.4 months). Future larger powered studies investigating the efficacy of the CO_2 laser therapy is warranted to determine the optimal treatment regimen, including the number of treatment sessions required.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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