Photodiagnosis and Photodynamic Therapy 28 (2019) 136–141

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Topical 5-aminolevulinic acid photodynamic therapy for laryngeal papillomatosistosis treatment

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ARTICLE INFO

Keywords:
Laryngeal papillomatosis
Recurrence
Photodynamic therapy
Human papillomavirus
Viral infection

ABSTRACT

Background: To explore the therapeutic effect of topical 5-Aminolevulinic Acid photodynamic therapy (ALA-PDT) on laryngeal papillomatosis (LP) treatment.
Methods: 13 patients with LP underwent topical ALA-PDT after tumor resection (CO_2laser or/and microdebrider resection). All patients were irradiated 3–4 times. After ALA-PDT treatment, the laryngoscopic examination was performed every 1–2 months to observe the therapeutic effect.
Results: All 13 patients were followed up for more than 1 year. Eleven cases (84.6%) showed no recurrence; two cases (15.4%) had relapses. One child developed III° inspiratory dyspnea caused by laryngeal mucosal edema and need endotracheal intubation again. Four patients had adhesion of the anterior commissure of the vocal cord. The detection rate of HPV infections was 76.9% and two patients had multiple HPV subtype co-infection.
Conclusions: The preliminary effect of topical ALA-PDT significantly reduces recurrence and improves the cure rate of LP. Further research on this treatment is still required.

1. Introduction

Laryngeal papillomatosis is a common benign tumor of the larynx frequently found in children. Approximately 80% of all cases occur in children under 7 years old, a large proportion of whom are under 5 years old [1,2]. Because laryngeal papillomatosis is characterized by its multiplicity, high recurrence, rapid growth, and frequent laryngeal obstruction, it seriously affects the physical and mental health of patients [3,4]. Human papillomavirus (HPV) infection is closely associated with the pathogenesis of laryngeal papillomatosis [5,6]. The most common infection pathway of laryngeal papillomatosis among children is mother-infant transmission, i.e., fetuses contract the viral infection via an HPV-infected birth canal. The disease is observable after several months to several years of viral latency. Laryngeal papillomatosis in children often manifests as hoarseness and dyspnea. However, because children cannot cooperate with a laryngeal cavity examination, the diagnosis and treatment are often delayed. By the time of disease detection, the scope of the laryngeal papillomatosis lesion has already become significant [4]. In adults, laryngeal papillomatosis mostly manifests as hoarseness.

Currently, laryngeal papillomatosis is treated using methods such as; CO_2 laser; microdebridement; argon plasma coagulation, cryotherapy, and electronic cauterization et al; and postoperative adjuvant drug treatments such as interferon and cidofovir et al [7,8]. However, the recurrence rate after one operation remains as high as 90% and most patients require repeated operations, which plaguing both them and their doctors [2]. In 1992, Abramson et al. [9] used photodynamic therapy (PDT) by intravenous drug administration to treat laryngeal papillomatosis and achieved a positive therapeutic result. However, the phototoxic and delayed reactions of PDT (e.g., serious skin damage due to the fact that the skin can absorb and retain hematoporphyrin and natural light exposure) greatly hindered the promotion of this therapy. In the 1990s, 5-aminolevulinic acid (5-ALA) used as a topical PDT treatment of HPV-infected mucosal diseases (e.g., condyloma acuminatum) [10], which eliminated the phototoxic and delayed reactions caused by the intravenous use of photosensitizers. In 2014, Zhou et al.

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https://doi.org/10.1016/j.pdpdt.2019.08.021
Received 10 May 2019; Received in revised form 6 August 2019; Accepted 16 August 2019
Available online 17 August 2019
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Table 1
Patient characteristics and outcomes.

Patient	Age	Sex	Tumor site	No. of operations before PDT	Interval Time of Operations before PDT (d)	No. of PDT	follow-up time after PDT (m)	Recurrence after PDT	Recurrence site	Recurrence time after PDT (d)	No. of operations after PDT	HPV subtype
1	3	M	bVF, LV, EP, PS, HP, TO	5	60	3	45	Yes	bVF, LV, EP, PS	95	5	11
2	30	M	bVF, lLV, TR, SP	4	41	4	40	No		0	0	11
3	2	M	bVF, bLV, bFVF	5	50	4	39	No		0	0	11, 56, 66
4	32	M	bVF, bLV, TR	1	80	3	38	Yes	lLV	750	1	–
5	8	F	bVF, LV, TR	10	240	3	27	No		0	0	6
6	3	F	bVF, bLV	1	90	3	26	No		0	0	11
7	3	F	bVF, lLV, lFVF	2	30	2	16	No		0	0	6
8	4	M	bVF, bLV, EP	0	0	3	16	No		0	0	11
9	3	M	bVF, bLV, EP, TR	0	0	3	15	No		0	0	59
10	28	M	bVF, bLV, SG	3	120	2	13	No		0	0	6
11	4	M	bVF, bLV	0	0	3	13	No		0	0	–
12	1	M	bVF, bLV, EP	4	28	4	12	No		0	0	6, 52
13	41	M	bVF, bLV, SG	2	20	3	12	No		0	0	–

b: Bilateral; l: Left; r: Right; VF: Vocal fold; LV: Laryngeal ventricle; EP: Epiglottis; PS: Pyriform sinus; HP: Hard palate; TO: Tonsil; FVF: False vocal fold; SG: Subglottic; TR: Trachea; SP: Soft palate.

reported three cases of topical drug administration for the PDT treatment of recurrent laryngeal papillomatosis in children that achieved satisfactory results [11]. In February 2015, we also began to perform this research; the preliminary results are reported below.

2. Materials and methods

2.1. Subjects

Between February 2015 and February 2018, 13 patients with laryngeal papillomatosis underwent CO_2 laser resection (or CO_2 laser resection combined with microdebrider resection) as well as PDT with topical drug administration to treat laryngeal papillomatosis at our department. The sample comprised ten males and three females. Nine pediatric patients were between 1 and 8 years old, and four adult patients were between 28 and 41 years old. Three patients were first treated at our department, and the other patients received 1–10 previous treatments either at our hospital or other hospitals, for an average of 3.7 surgeries (Table 1). No patients underwent tracheotomy. The main symptoms were various degrees of hoarseness and dyspnea. Papillary masses were visible in the vocal cord or in the laryngeal cavity on physical examination. The study was approved by the Ethics Committee of Sun Yat-Sen Memorial Hospital. All patients or guardians were informed of the risks and advantages of the ALA-PDT treatment and agreed to receive ALA-PDT treatment.

3. Methods

3.1. Surgical removal of the tumor

The operation was performed under general anesthesia. With the assistance of a microscope, pedestal laryngoscope, and laryngeal endoscope, a CO_2 laser was used to remove the visible tumor. For lesions not readily exposed (e.g., those on the laryngeal surface of the epiglottis, infraglottic lesions, intratracheal lesions, and lesions on the back of the soft palate), a microdebrider was used to remove the tumor under a laryngeal endoscope or nasal endoscope.

3.2. PDT

(1) Treatment process. Five bottles of 5-ALA (118 mg/bottle, Shanghai Fudan-Zhangjiang Bio-Pharmaceutical Co., Ltd.) were used. Before use, 0.5 ml of injection water was added to one bottle of 5-ALA to create a 20% concentration solution in the dark. Five pieces of medical cotton pads with an attached string were used to absorb the drug solution, which were then attached to the entire laryngeal cavity including the infraglottic portion, glottic portion, and supraglottic portion. Attention was paid to the irregular cavities, including the epiglottic vallecular, laryngeal ventricle, anterior commissure, posterior commissure, infraglottic portion, and pyriform fossa. The medical cotton pads were replaced with new pads once every 35–40 min, for a total of five times in 3–3.5 h (Fig. 1).

(2) After the pads were removed, a photodynamic laser machine (FD-400-A, Wuhan Lingyun Co., Ltd., China) was used for PDT. A single optic fiber was used, the spot area was approximately 2 cm^2, the output wavelength was 635 nm, the laser energy was 200–280 mW, and the energy density was 80–120 J/cm^2 (Fig. 2). The light was first placed on the glottic portion and irradiated for 20 min. Then, it was placed on the supraglottic portion and irradiated for 20 min. If a lesion was found under the tracheal intubation or in the infraglottic portion, then the irradiation was performed under high-frequency ventilation, or intermittent irradiation was performed when the tracheal intubation was removed after the oxygen reserve was increased for 10–15 min, and the patient's blood oxygen was maintained above 90% during the operation. If the blood oxygen was less than 90%, repeat endotracheal intubation is needed

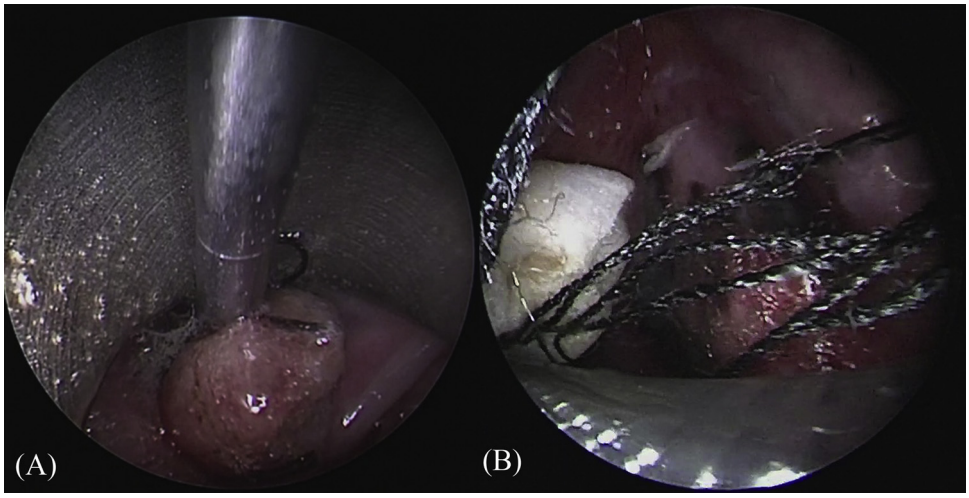

Fig. 1. Topical 5-ALA administration: Five pieces of medical cotton pads with an attached string were used to absorb the drug solution and attached to the entire laryngeal cavity including the glottic portion, supraglottic portion(A) and Subglottic portion(B).

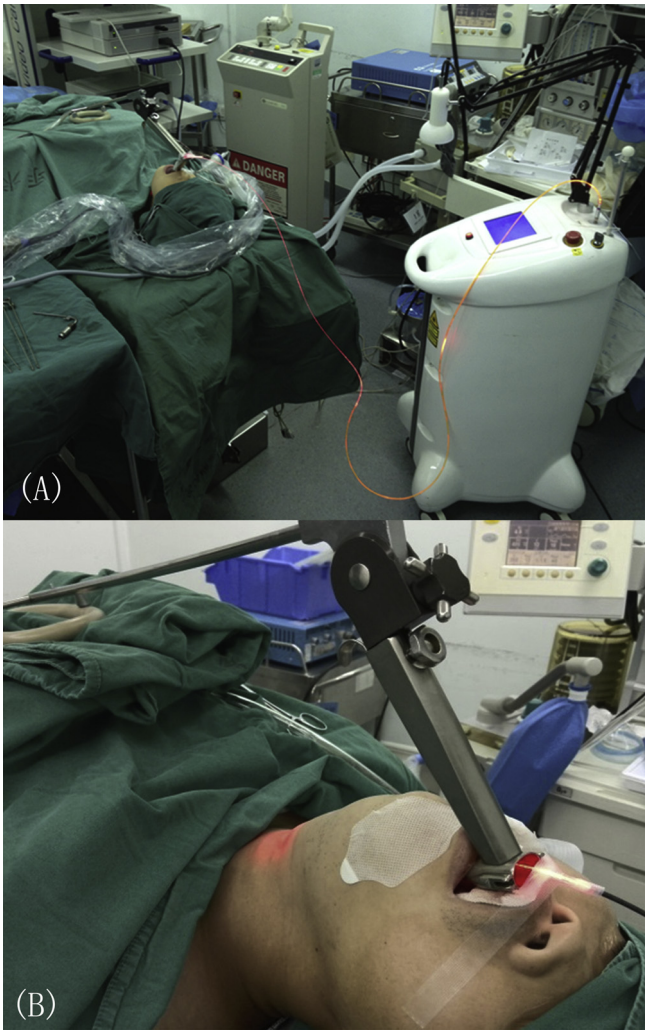

Fig. 2. Optic fiber irradiation through laryngoscope insertion into the laryngeal cavity. A: Outside scene of PDT; B: optic fiber fixed in the laryngoscope during irradiation.

(Fig. 3). Regarding the dorsal part of the soft palate, an optic fiber was placed to the tumor area under the guidance of a nasal endoscope, and a 20-min irradiation was performed. For oral and oropharynx lesions, an opener was used to open the mouth, and external irradiation was used to irradiate for 20 min.

(3) Treatment cycle: After approximately 25 d, the irradiation was repeated. If tumors were found before irradiation, the tumors were removed first, and the irradiation was performed second. If no visible tumor was detected during the last treatment, then one or two extra photodynamic treatments were recommended. All patients were irradiated three to four times. After treatment, a laryngoscopic examination was recommended to perform every 1–2 months. If the lesion did not recur for more than 1 year, then examinations were performed every 6 months. If recurrence was present, then the physician communicated with the patient or their family members about various treatment methods, including resection alone or irradiation following resection.

4. Results

All 13 patients were followed up for more than 1 year (six were followed up for 2 years). Eleven cases (84.6%) showed no recurrence; two cases (15.4%) had relapses. One patient was an adult, the relapse occurred about 25 months after the operation, and the recurrent tumors were located in the laryngeal ventricle. The patient underwent CO_2 laser resection and continued to be followed up. No recurrence was observed 13 months later. The other patient was a child who experienced relapse 3 months after the operation. The recurrent tumors were located at the bilateral vocal cords, laryngeal ventricle, epiglottis, and pyriform fossa, and the scope was smaller than before. The guardian of the patient refused to continue with PDT, and the tumors were regularly removed at our hospital and other hospitals (Table 1) (Figs. 4 and 5).

One 2-year-old patient developed III° inspiratory dyspnea 8 h after the first operation likely caused by laryngeal mucosal edema. Endotracheal intubation was performed again, and the patient was sent to the intensive care unit (ICU) for treatment and sent back to general ward while the condition improved 4 d later. Four patients had adhesion of the anterior commissure of vocal cord.

Following the operation, the tumor samples of all of the patients were subjected to HPV detection and typing. Ten HPV infections were detected. The detection rate was 76.9%. Two patients had multiple HPV subtype co-infection (Table 1).

5. Discussion

Laryngeal papillomatosistosis (LP) is a disease that presents in both juvenile (JLP) and adult patients (ALP), which mainly affects the larynx

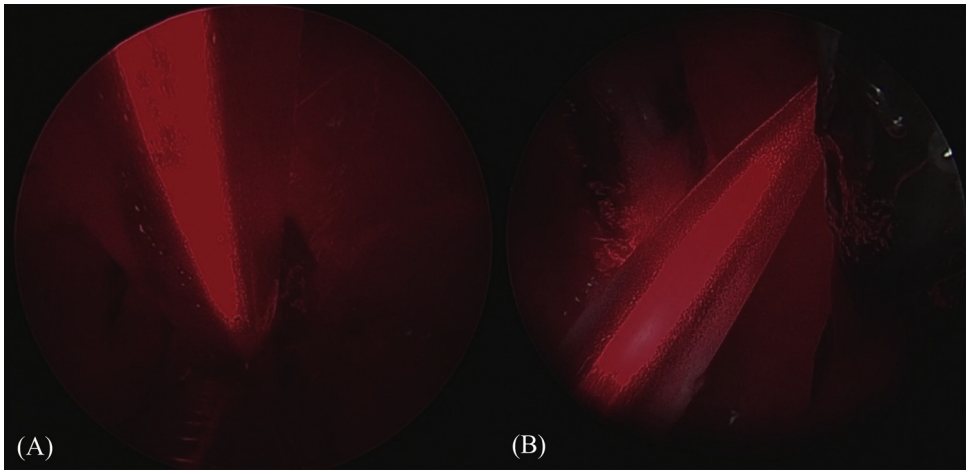

Fig. 3. Inside scene of PDT A: First placed on the glottic portion and irradiated for 20 min; B: Intermittent irradiation on subglottic portion with tracheal intubation removed.

and trachea, and may lead to symptoms of dysphonia, obstruction of the upper airway, stridor and respiratory distress. JLP is a common tumor in the larynges of children that accounts for 80% of all childhood laryngeal tumors. Although this disease has a tendency to self-heal during puberty, pediatric patients must receive surgery to solve the breathing problems mentioned above. However, most patients relapse in the brief time after treatment in clinical practice, and dyspnea reoccurs in a short time. Several of pediatric patients must undergo surgery every month to relieve laryngeal obstructions, and some of them must undergo tracheotomies and wear tracheotomy tube over the long term to maintain an unobstructed respiratory tract [4]. Some pediatric patients with laryngeal papillomatosis die after all rescue measures are ineffectual due to the dyspnea caused by the extensive invasion of the tumors in the throat, trachea, and bronchus [3].

The etiology of Laryngeal papillomatosis is not fully understood. Currently, recurrent Laryngeal papillomatosis is associated with HPV infection. Luzar et al. [12] reported that the positive detection rate of type 6 and type 11 HPV in children with recurrent Laryngeal papillomatosis was 95.8%. Furthermore, they suggested that type 6 and type 11 HPV are the main pathogenic factors of recurrent laryngealpapillomatosis in children [13]. The HPV detection rate in this study was 76.9%. Moreover, in addition to the type 6 and type 11 infection, two patients presented with high-risk HPV subtype co-infection. Recurrence can occur when latent HPV is activated, when the HPV in the tumor contaminates other areas with blood flow, or when the virus is seeded in new wounds due to surgery. However, the current surgical tools commonly used in clinical practice (e.g., CO_2 laser, microdebridement and argon plasma coagulation) cannot solve the latency and seeding of HPV. Therefore, clinicians must search for methods to further reduce the recurrence rate of laryngeal papillomatosis.

In 1992, Abramson was the first to report the use of PDT to treat laryngeal papillomatosis [9]. Subsequently, Shikowitz et al. wrote a series of reports. A growth rate scoring system was used to assess the number and area of the lesions as well as the airway obstruction degree of the patients. The growth rate score decreased by approximately 50% after PDT on average, which was significantly better than the decrease associated with the traditional method [14]. However, the

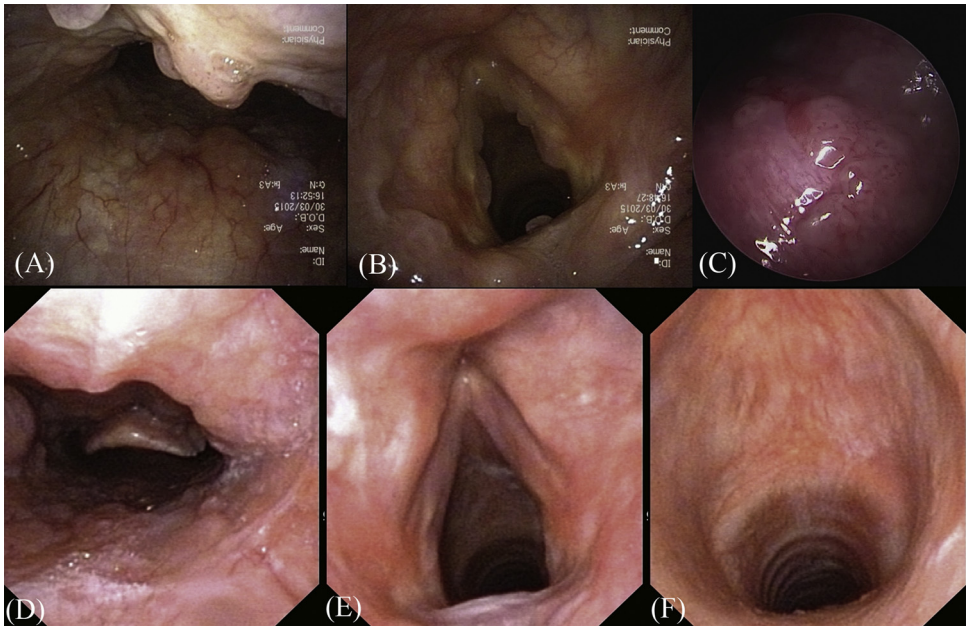

Fig. 4. The papillomatosistosis of Patient 2 was located in soft palate(A), bilateral vocal fold and left false vocal fold(B), and trachea(C), after the papillomatosistosis removing and 4 times ALA-PDT, there was no recurrence in soft palate(D), larynx(E) and trachear(F) in 40-month follow-up.

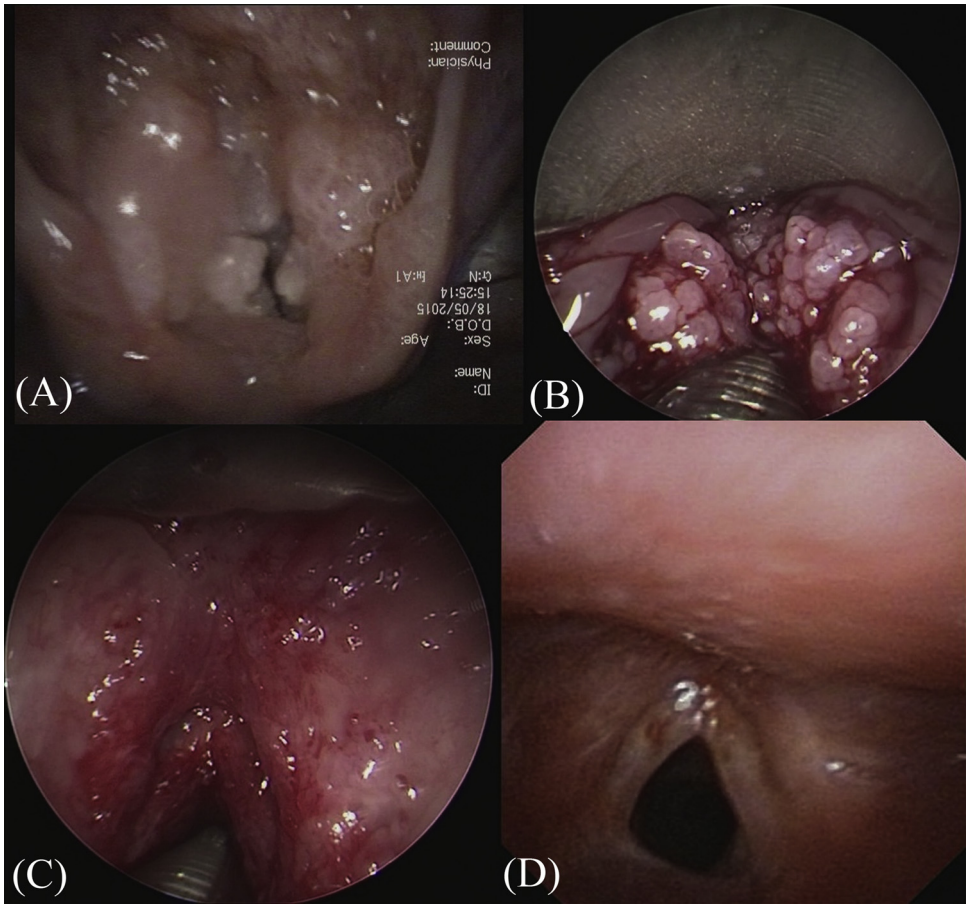

Fig. 5. the papillomatosistosis of Patient 3 was locate in bilateral vocal fold, laryngeal ventricle and false vocal fold(A, B), after the papillomatosistosis removing(C) and 4 times ALA-PDT, there was no recurrence in 39-month follow-up(D).

photosensitizer that was applied systemically engendered phototoxic and delayed reactions. For example, the human skin can absorb and retain hematoporphyrin, and natural light exposure can cause serious skin damage, which greatly hindered the promotion of this therapy.

Recently, with the advent of topical photosensitizers, PDT has been used to treat HPV infection-associated diseases, and it has achieved promising efficacy when treating condyloma acuminate, cervical canal HPV infection, anal and intraurethral papilloma, and skin verruca. In recurrent laryngeal papillomatosis, PDT may also alter the immune response and increase the reactivity to even low concentrations of viral proteins [15,16]. Current evidence regarding the efficacy of PDT in recurrent laryngeal papillomatosis is controversial [9,17,18].

In 2014, Zhou et al. [11] treated three patients with recurrent laryngeal papillomatosis using plasma surgery combined with ALA-PDT. Each patient received postoperative ALA-PDT treatment, and ALA-PDT was performed again 2 weeks and 6 weeks after surgery. No recurrence was observed after 3–12 months of follow-up. In 2016, Zhang et al. [19] treated three patients with recurrent laryngeal papillomatosis via CO_2 laser combined with PDT. Three PDT treatments were performed, and no recurrence was observed after 6–24 months of follow-up. They described PDT with a topical drug administration that achieved positive results. We also performed this technique since 2015. Currently, 13 patients have been followed up for more than 1 year: 11 patients have shown no recurrence, and the cure rate is 84.6%. One of the relapsed patients has an extensive multifocal case, although recurrence remains, the scope of the tumor is now smaller. The other relapsed patient only showed the recurrence of a small lesion on one side of the laryngeal ventricle approximately 25 months after the operation. After CO_2 laser resection was performed, the patient continued to receive 13 months of follow-up treatment, and no recurrence was observed.

The current results show that compared with the traditional "point-clearing" physiotherapies including laser and low-temperature plasma therapy, the unique "surface-clearing" mechanism of PDT acts on the entire laryngeal mucosa tissue, significantly improving surgical outcomes. However, drug concentration and irradiation time are based on the treatment of condyloma acuminate and the pharmacological results of 5-ALA regarding the current topical drug administration pathway for photodynamic intralaryngeal treatment. A more appropriate dose and irradiation time might need further study to treat laryngeal mucosal lesions and, in particular, those with an extensive scope. Because the laryngopharyngeal structure is complex and uneven, the light that shines on the surface of the mucosa, including the anterior commissure and laryngeal ventricle, can be reflected so that the light energy in the irradiated region is the superimposed energy after multiple reflections. Moreover, this light intensity is difficult to calculate. The structure can also block the irradiation of the laser and affect the efficacy of the treatment. The recurrence in the laryngeal ventricles of these patients might be related. In addition, obstruction due to an anesthesia cannula also affects drug introduction, the contact of the drug with the mucous membranes, and the irradiation of the laser. For the area that was affected by an anesthesia cannula, we conducted irradiation under high-frequency ventilation or intermittent irradiation when the tracheal intubation was removed after the oxygen reserve was increased. The procedure lasted 10–15 min, and patient blood oxygen level was maintained above 90% during the operation. This protocol mostly avoids the influence of anesthesia intubation on efficacy. If an anesthesia cannula with an optic fiber exists in the future, then the surgical safety of PDT for infraglottic and intratracheal tumors can be improved.

Four patients in this study presented with adhesion of the anterior

commissure, which might have been related to the multiple previous surgical history. In addition, the main adverse reactions of PDT include inflammatory reactions (97%), abnormal liver function (59%), pain (48%), and phototoxicity (34%) [20]. Most of the reactions were mild, and the patients recovered quickly. One patient had postoperative dyspnea, which was likely the edema of the airway mucosa, suggesting that patient breathing should be closely observed after PDT, and Glucocorticoid should be used during and after PDT to prevent the dyspnea caused by airway edema. Tracheal stenosis is a rare complication of PDT that might be related to the excessive use of photosensitizer or the excessive energy of irradiation [21].

The disadvantage of this treatment method is that the operative time is longer, especially the time of topical drug administration. Systemic use of ALA is quite safe and can reduce the operative time, such as photofrin and mTHPC have been used in the oral cavity, which can be taken by mouth in divided doses. Unfortunately, there was no experience of systemic use of ALA in our hospital, we will consider this method in the future if possible.

To date, there is insufficient evidence from high-quality, multicenter, randomized controlled trials to determine whether PDT alters the course of Laryngeal papillomatosis or provides an added benefit to surgery in patients with the disease. In addition, basic research also must be conducted to further determine the dose of PDT as well as the power and time of laser irradiation to prevent related complications.

6. Conclusions

This study preliminarily indicated that topical ALA-PDT is an effective treatment for laryngeal papillomatosis, which significantly reduces tumor recurrence, and further improves the cure rate. However, because there were no consensus exists concerning the treatment dosage, the power and time of irradiation, the frequency of treatment, or whether to combine this treatment with antiviral drugs, further investigation is required.

Funding

This study was supported by Natural Science Foundation of Guangdong Province, China (2018A030313691).

Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work.

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