

Characteristics of Recurrent Respiratory Papillomatosis and Impact Factors of Surgical Intervals

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Abstract

Objectives: Part I analyzes the clinical characteristics of JO-RRP and AO-RRP. Part II explores the influencing factors of surgical intervals. **Methods:** Part I: Clinical features were analyzed in 168 RRP patients (59 JO-RRP and 109 AO-RRP) diagnosed and treated in our hospital. Part II: The correlation of interoperative time with onset age, gender, Derkay anatomical score or surgical methods were analyzed in JO-RRP patients. **Results:** The interoperative time between operations in the JO-RRP group was 116.3 ± 75.9 days, and in the AO-RRP group was 169.1 ± 141.7 days ($p < 0.05$). In the JO-RRP group, the CO2 laser treatment interval (186.2 ± 140.1 days) was significantly longer than that of the microdebrider group (124.7 ± 114.5 days) ($p = 0.011$). **Conclusions:** 1. JO-RRP patients had higher Derkay score, higher surgical frequency and shorter surgical interval. 2. The surgical intervals lengthened with age and shortened with higher Derkay scores. CO2 laser surgery has the longest interoperative time.

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Results: The interoperative time between operations in the JO-RRP group was 116.3 ± 75.9 days, and in the AO-RRP group was 169.1 ± 141.7 days ($p < 0.05$). In the JO-RRP group, the CO2 laser treatment interval (186.2 ± 140.1 days) was significantly longer than that of the microdebrider group (124.7 ± 114.5 days) ($p = 0.011$).

Conclusions:

1. JO-RRP patients had higher Derkay score, higher surgical frequency and shorter surgical interval.
2. The surgical intervals lengthened with age and shortened with higher Derkay scores. CO2 laser surgery has the longest interoperative time.

Key words: recurrent respiratory papillomatosis, clinical characteristic, surgery, surgical interval, impact factor.

Level of Evidence: Level 3

Key Points:

1. The onset age of RRP showed a bimodal distribution (2-6 and 26-30 years old).
2. Men are more likely to develop AO-RRP.
3. JO-RRP patients had higher Derkey score, higher surgical frequency and shorter surgical interval. AO-RRP showed a higher proportion of dysplasia (72.4%) and the risk of cancer (2.8%).
4. The surgical intervals lengthened with age and shortened with higher Derkey scores.
5. Microdebrider is most commonly used, and CO2 laser surgery has the longest surgical interval for JO-RRP patients.

Introduction

Recurrent respiratory papillomatosis (RRP) is a benign tumor that occurs in the respiratory tract^[1]. At present, patients are usually divided into juvenile-onset recurrent respiratory papillomatosis (JO-RRP) and adult-onset recurrent respiratory papillomatosis (AO-RRP) according to whether they are over 18 years old, and RRP has a higher incidence in children and men^[2-4]. However, a third peak of incidence around 64 years was discovered by cross-sectional study^[5]. In general, JO-RRP grows rapidly, and the lesions are often multifocal, and they are prone to recurrence after surgery^[6]. Patients with AO-RRP are mostly localized, relatively slow-growing, and according to the available evidence, about 1-7% of cases will develop into squamous cell carcinoma^[7-10]. Pulmonary involvement occurs in approximately 3.3% of patients with juvenile laryngeal papilloma, and papilloma formation in the lungs and airways can lead to fatal obstructive pneumonia. In 16% of patients with lung involvement, it may progress to pulmonary malignancy^[11].

Previous research found that endotracheal intubation aggravated distal spread, and the longer the tube carrying time, the longer the disease time, affecting the remission rate and mortality of patients^[12, 13]. A study in Argentina of 82 patients with RRP under 16 years of age comparing the characteristics of RRP patients with or without extralaryngeal spread found that age younger than 5 years or history of tracheostomy at the time of diagnosis of RRP were factors associated with extralaryngeal spread, and the occurrence of extralaryngeal spread was also associated with HPV subtype 11 infection^[14].

RRP is still mainly based on surgical treatment, the most commonly used is microdebrider^[15], CO2 laser^[16] or 532nm Potassium-Titanyl-Phosphate laser (KTP laser)^[17-24]. However, surgery does not seem to completely prevent the recurrence of the disease, and the efficacy of a variety of existing adjuvant treatments is not clear, and some patients often require repeated surgery. The correlation between age of onset, lesion size, surgical mode and interval between operations has not been fully studied. In the current studies, the lack of uniform evaluation criteria for the description of lesion size hinders the systematic analysis of various studies.

Materials and methods

All subjects in this study were from cases diagnosed with RRP and underwent surgery in our hospital between January 2016 and December 2021, and eligible case demographic information, treatment-related information and postoperative follow-up data were collected. We have followed STROBE Statement (stroke-statement.org) as the reporting guideline.

The inclusion and exclusion criteria are as follows: Part I inclusion criteria: (1) cases with a preliminary preoperative diagnosis of "laryngeal mass" or "RRP" or "benign laryngeal tumor"; (2) Have a complete laryngoscopy report within one month before surgery, or check the extent of lesions during surgery and have detailed records; (3) the patient consents to surgical treatment; (4) Postoperative specimens were sent for examination, and pathology report RRP. Exclusion criteria: (1) postoperative loss to follow-up; (2) Those who have not operated again after surgery and cannot calculate the interval between operations; (3) History of surgery or radiotherapy for other pharyngeal and laryngeal diseases during the course of RRP.

Part II Based on the first part of the study, obtain information about each operation of JO-RRP patients, and treat each operation as a surgical case, and screen eligible surgical cases among the study subjects included in the first part according to the following criteria as the study subjects of the second part. Inclusion

criteria: Only a single surgical modality, such as a microdebrider or CO2 laser or KTP laser, was used intra-operatively. Exclusion criteria: (1) Use in combination with adjuvant therapy; (2) Postoperative pathology suggests malignant RRP transformation; (3) Previous history of tracheostomy surgery; (4) Papilloma lung involvement. The study was approved by the Ethics Committee of our institution.

Collect medical records of all included cases and record the following information: demographic information, including sex, age at first diagnosis (age at first diagnosis), age at onset (age at each onset); Clinical manifestations of the first episode: dysphonia, dyspnea, laryngeal obstruction division, dysphagia, Derkey score^[25] calculated according to the site and size of the first lesion; Information related to surgical treatment: including operation time, operation method, operation interval (days), postoperative pathology report.

In the second part, the patients are treated with surgery, which is performed by senior doctors in the Department of Nose and Throat of our hospital. According to the surgical method, the surgical cases included in the study were divided into three groups, namely microdebrider group, CO2 laser group and KTP laser group. Since in the second part, each patient undergoes at least two surgeries, and each procedure may be different, each patient who undergoes surgery will be treated as one surgical case, that is, each surgery will be analyzed as a study subject. The demographic information, surgical records and postoperative follow-up information of patients in the three treatment groups were collected, and the operation interval (days) of the three treatment groups was counted.

Statistics are performed using IBM SPSS Statistics²⁶. Continuous normal data are described by means \pm standard deviation, and the difference is tested by independent sample T. Categorical data are represented using n(%), and differences between groups are represented using chi-square tests or Fisher analysis. The chi-square goodness-of-fit test was used to compare the proportion of dichotomous variables such as sex proportion and whether dysplasia was present. The correlation between two continuous variables was analyzed using linear correlation (the closer the absolute value of r to 1, the stronger the correlation, <0.3 very weak correlation, 0.3-0.5 weak correlation, 0.5-0.7 medium correlation, >0.7 strong correlation). Graph visualization in GraphPadPrism. $P < 0.05$ is statistically significant.

Results

Part I:

A total of 168 patients were enrolled, with a male-to-female ratio of 120:48 (male:female=2.5:1), the age of initiation was 0.5~85 years old, the average age was 29.8 years, and the overall age of initiation was bimodal distribution, and the peaks of the two age distributions were about 2~6 years old and 26~30 years old. According to whether the age of first episode was over 18 years old, the above patients were divided into JO-RRP patients and AO-RRP patients. There were 59 patients with JO-RRP, the male to female ratio was 34:25, male accounted for 56.36%, female accounted for 43.64%, and the age proportion was not statistically significant ($p=0.34$). The age was 7.6 \pm 5.0 years, of which a peak occurred at 2~6 years old, and patients in this age group accounted for 33.4% of all JO-RRP patients. There were 109 patients with AO-RRP, the male to female ratio was 86:23, 78.9% were males and 21.1% were females, and the age difference was statistically significant ($p < 0.01$). Age 41 \pm 16 years old, peak incidence in 26~30 years old.

Presenting symptoms

Of the 59 patients with JO-RRP at their first presentation, 53 (89.8%) had dysphonia, 39 (66.1%) had dyspnea, of which 20 had laryngeal obstruction I degree, 16 patients showed laryngeal obstruction II degree, 3 patients had laryngeal obstruction III degree, of which 1 patient was admitted to the emergency department and dyspnea was relieved immediately after RRP resection, and the other 2 (3.4%) patients had undergone tracheostomy in an external hospital at the time of admission. 15 (25.4%) patients had dysphagia.

Of the 109 adult RRP patients, 104 (95.4%) had dysphonia and 5 (4.6%) had dyspnea, of which 4 had laryngeal obstruction I degree and 1 had laryngeal obstruction II degree, all of which were relieved after RRP resection. 3 (2.8%) patients had dysphagia.

The basic information and clinical features of JO-RRP and AO-RRP cases in the first part are shown in Table 1.

Lesion distribution features

The Derkey score was 10 ± 5.9 in patients with JO-RRP and 6.5 ± 4.3 in patients with AO-RRP, and patients with JO-RRP had higher Derkey scores than patients with AO-RRP, and the difference between the two was statistically significant ($p=0.001$).

In the JO-RRP group, anatomical site involvement was the most common glottis, with 58 cases (98.3%) involving the glottis, followed by supraglottic and subglottic cases with 54 cases (91.5%) and 35 cases (59.3%), respectively. These patients underwent RRP resection and were transferred to Shanghai Pulmonary or Chest Hospital for further diagnosis and treatment. In AO-RRP patients, anatomical site involvement was also the most common glottis, 102 (93.6%) involved glottis, followed by supraglottic and subglottic 50 (45.9%) and 22 (20.2%), respectively, tracheal involvement in 1 case (0.1%), and no cases involving the lungs.

Surgical modalities

By the end of follow-up, 168 patients had undergone 682 surgeries. Of these patients, 117 (71.3%) had used only one surgical modality, 37 (22.6%) had used 2, and 10 (6.1%) had used three surgical modalities.

At the end of follow-up, 59 JO-RRP patients underwent a total of 267 surgeries, including 225 Microdebrider (81.5%), CO2 lasers 20 (7.2%), KTP lasers 20 (7.2%), and microlaryngeal forceps 2 (4%), all performed under general anesthesia. Of these patients, 40 (72.7%) had used only one surgical modality, 13 (23.6%) had used 2, and 2 (3.6%) had used three surgical modalities.

A total of 415 surgeries were performed in 109 patients with AO-RRP, including 54 Microdebrider (13%), 100 CO2 lasers (24.1%), 252 KTP lasers (60.7%), and 9 microlaryngeal forceps (2.2%). Among these patients, 77 (70.6%) used only one surgical method, 24 (22.0%) used 2 surgical methods, and 8 (7.3%) used three surgical methods.

Number of surgeries undergone

A total of 682 surgeries have been performed by 168 patients, ranging from 2~42 surgeries per patient, of which 56 (34.1%) patients have undergone more than 4 surgeries and 13 (7.9%) patients have undergone more than 10 surgeries. These patients underwent an average of 0.2~12 surgeries per year, of which 18 (11%) patients had an average of more than 4 surgeries per year.

JO-RRP patients underwent an average of 3.4 surgeries per year. 36 (61%) underwent more than 2 surgeries per year, and 14 (23.7%) underwent an average of more than 4 surgeries per year. The number of surgeries of these patients decreased with age, and patients aged 0~6, 6~12 and 12~18 years experienced an average of 4.3, 3.1 and 1.6 surgeries per year, respectively.

AO-RRP patients underwent an average of 1.8 surgeries per person per year, of which 36 (33%) underwent an average of no more than 1 surgery per year, 98 (90%) underwent an average of no more than 3 surgeries per year, and only 4 (3.7%) underwent an average of more than 4 surgeries per year. There was no significant difference in the number of surgeries experienced per year for patients of three different age groups.

The average number of surgeries per year for different age groups in the JO-RRP and AO-RRP groups is shown in Fig.1.

Interval between procedures

The interval between operations in the JO-RRP group and AO-RRP group was 116.3 ± 75.9 days, and the interval between operations in the AO-RRP group was 169.1 ± 141.7 days, and the interval between the operations of AO-RRP patients was longer, and the difference between the two was statistically significant ($p=0.045$).

Histopathological features

In the histopathology report of patients with JO-RRP, 9 cases (15.2%) of RRP with dysplasia were suggested, and no cases of RRP with carcinogenesis were found. Among AO-RRP patients, 79 cases (72.4%) were reported by postoperative histopathology with RRP with dysplasia, 3 cases (2.8%) were reported with RRP with carcinogenesis, and the cases with carcinogenesis were treated according to the principle of surgical treatment of malignant tumors. The difference between was statistically significant ($p < 0.01$).

Part II:

In patients with JO-RRP, the correlation between gender, age of onset, Derkay score, surgical method and surgical interval was analyzed to explore the influencing factors of surgical interval after surgical treatment of RRP.

A total of 55 patients with JO-RRP were included, with a male to female ratio of 31:24, an age of onset of 6.7+-4.3 years, a range of 0.5~17 years, and a total of 265 surgeries, including 225 times (84.9%) of microcutter, 20 times (7.5%) of CO2 laser, and 20 times (7.5%) of KTP laser, all of which were hospitalized under general anesthesia. The basic information of the cases and the number of surgeries are shown in Table 2.

Correlation between sex and time between operations

According to gender, there were two groups of men and women, 31 men and 24 women, the interval between operations in the male group was 231+-41.4 days, and the interval between the female group was 141.3+-30.1 days, and there was no significant difference ($P = 0.057$).

Correlation between age of onset and time between operations

The correlation between age of onset and interval between surgery was analyzed by linear correlation, and the results showed that the age of onset and interval between surgery were weakly correlated ($r = 0.28$, $p < 0.01$ +-+-. < 0.05). It can be seen that the interval between operations is positively correlated with the age of onset. Among them, there is a significant difference between patients of different ages in the JO-RRP group. The interval between operations in different age groups of JO-RRP is shown in fig.2.A.

Correlation between Derkay scores and time between operations

The correlation between Derkay score and surgical interval was analyzed by linear correlation, and the results showed that Derkay score had a weak correlation with surgical interval ($r = -0.29$, $p < 0.01$).

According to the Derkay score three-equal method, the patients were divided into three groups: 0~9 points, 10~18 points, and 19~27 points, and the interval between operations was 158.0+-119.2 days, 123.4+-118.6 days, 62.6+-48.7 days ($p < 0.01$).

The relationship between surgery interval and Derkay score is shown in fig.2.B.

Comparison of the time between operations for RRP with three surgical modalities

According to the surgical method, the surgical cases were divided into three treatment groups, namely microdebrider, CO2 laser and KTP laser group. The comparison of the operation intervals of the three surgical methods is shown in fig.2.C.

In the JO-RRP group, the interval between procedures for microdebrider was 124.7+-114.5 days, for CO2 laser group 186.2+-140.1 days, and for KTP laser group 139.2+-108.3 days.

The difference between CO2 laser and microcutter was statistically significant ($p = 0.011$). CO2 laser had a larger interval between operations than KTP laser, but there was no significant difference ($p > 0.05$). KTP laser had a larger interval between operations than microdebrider after treatment, but there was no significant difference ($p > 0.05$).

Discussion

The part I of the study found that age did have a bimodal distribution without a significant trimodal distribution. At the same time, the study further confirmed that there are significantly different clinical characteristics of the two types of patients with bimodal distribution, so this study still supports the generally accepted view that RRP patients are divided into JO-RRP or AO-RRP patients according to whether they are over 18 years old.

The recurrence trend in the JO-RRP group was significantly earlier than that in the AO-RRP group, and patients with JO-RRP usually had faster disease growth, were more likely to cause airway obstruction, and relapsed faster after treatment, which was consistent with the characteristics of RRP disease reported in the current literature. Bronchoscopy can directly visualize lesions of the lower respiratory tract while specimens are collected for histopathological examination^[26]. For all patients with RRP in this study, disease involves the most common site of glottis, followed by supraglottic, consistent with previously reported results^[27].

The part II of the study showed that the interval between operations was affected by the age of onset, Derkay score, and surgical method. There are studies found clinical features such as younger age and HPV-11 infection in patients are more dangerous^[28]. In our study, for JO-RRP, the interval between operations is related to the age of onset, Derkay score, and surgical modality, but not gender. The interval between surgeries increases with age, and the higher the Derkay score, the shorter the spacing between surgeries.

Microdebrider is the most commonly used surgical method, but its surgical interval is the shortest, and the interval between CO2 laser surgery is the longest. Microdebrider have a number of advantages that make them suitable for JO-RRP patients. It can quickly relieve airway obstruction, especially in patients with JO-RRP who have dyspnea due to large lesions. Respiratory papillomatosis involving the trachea is a challenging problem, and the selection of longer Microdebrider allows the cutting of lesions in the trachea^[29].

Unlike cold devices, CO2 lasers have a non-contact cutting function and hemostatic effect. A German multicenter study by Papispyrou^[15] on the status of treatment modalities for RRP found that CO2 laser treatment was the most common modality used alone or in combination with other treatment modalities. On the one hand, in the KTP laser surgery protocol, patients can avoid the risks of general anesthesia surgery, while saving a lot of time and energy required for hospitalization, and doctors also save time for general anesthesia waiting and preoperative preparation in local anesthesia surgery. The process is relatively convenient, which is very convenient for patients with repeated attacks to come to the doctor. On the other hand, patients who choose KTP laser surgery usually have mild disease, the lesion volume is not large and the scope is more limited, and the voice function of postoperative patients may recover faster, and patients experience better. For these reasons, KTP lasers are more accessible to patients.

This study has the following limitations. First, changes in voice function and swallowing function were not investigated pre- and post-operatively, as retrospective studies cannot collect complete case information, and studies in this area can be added in future prospective studies. Secondly, we observe whether there is recurrence through laryngoscopy, and formulate a surgical plan according to the patient's symptoms, but in fact, the time of the two may be somewhat different, and each patient's medical conditions lead to this time difference. Third, the power of the CO2 laser or KTP laser, or cutting depth may be one of the prognostic factors of this disease, which requires further experimental verification.

Conclusions

1. JO-RRP patients had higher Derkay score, higher surgical frequency and shorter surgical interval.
2. The surgical intervals lengthened with age and shortened with higher Derkay scores. CO2 laser surgery has the longest interoperative time.

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Fig.1.A.Average number of surgeries per year for different age groups in the JO-RRP group; B. Average number of surgeries per year for different age groups in the AO-RRP group.

Fig.2.A.Interval between operations at different ages in the JO-RRP group; B.Relationship between operation interval and Derkay score in the JO-RRP group; C.Comparison of the operation intervals of the three surgical methods in the JO-RRP group.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Conflict Of Interest The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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