

Extra-Laryngeal Recurrent Respiratory Papillomatosis: A 10-Year-Experience

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Background: Recurrent respiratory papillomatosis (RRP) is a common benign neoplasm affecting the larynx and upper respiratory tract. The patient has the potential to develop a fatal consequence and the disease itself is often difficult to treat because of its tendency to recur, spreading throughout the respiratory tract, and turn to malignancy.

Objective: To determine: (a) the incidence of extra-laryngeal involvement of respiratory papillomatosis, (b) treatment modalities and outcomes, (c) malignant change and (d) factors associated with the presence of extra-laryngeal involvement.

Material and Method: Medical records of extra-laryngeal papilloma patients between January 1998 and December 2007 at a tertiary hospital in Northeastern Thailand were retrospective reviewed. Demographic data, clinical findings, presenting symptoms, therapy, and outcomes were analyzed.

Results: Of the 53 patients diagnosed with RRP, eight had extra-laryngeal involvement (15.1%); four, three, and one of the trachea, trachea and lungs, and tracheostomy stoma, respectively. A common presenting symptom was hoarseness. Diffuse and lesions of the larynx were the most common characteristic in both extra-laryngeal (100%) and only-laryngeal (91%) groups. The respective extra-laryngeal spread develops within one year, 21 years, and 30 years in six cases (75%), one (12.5%), and one (12.5%), respectively. The respective improvement rate and curative rates of treatment were 25% and 37.5% for extra-laryngeal and 40.5% and 26.2% for only-laryngeal RRP. One patient died due to massive extra-laryngeal involvement of the lung and malignant change. Laser was used as treatment option in all cases. Increased use of KTP laser as additional treatment modality for extra-laryngeal RRP was observed. Tracheostomy had a significant association with the presence of extra-laryngeal involvement [p -value = 0.038, odds ratio 8.40 (1.32 to 53.40)].

Conclusion: RRP has a significant rate of extra-laryngeal spread with increased need of more optional treatment modalities. Tracheostomy is an important factor associated with the presence of extra-laryngeal spread. Malignant change should be taken into consideration as it can result in fatality.

Keywords: Recurrent, Respiratory, Laryngeal, Papillomatosis, Spread

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Recurrent respiratory papillomatosis (RRP) is the most common benign tumor seen by laryngologists⁽¹⁾. The most common involved site is the larynx. It is more commonly found in children than adults. Human papillomavirus (HPV) type 6 and 11 are believed to be a cause of this condition⁽²⁾. A national survey in the United States revealed that the respective incidence of respiratory papillomatosis in children vs. adults is 4.3 vs. 1.8 in 100,000⁽³⁾. Incidences of RRP per 100,000 children aged 0 to 14 years are 0.7 in Denmark, 0.1 in Japan and 2.8 in Thailand⁽⁴⁻⁶⁾. The prevalence of the disease is likely variable depending on the age of presentation, country, and socioeconomic status⁽⁷⁾.

RRP is a benign condition, difficult to treat due to its tendency to recur. It can pose a fatal risk as

the tumor can spread throughout the respiratory tract and obstruct the respiratory lumen, causing airway obstruction^(8,9). In 0.5% to 13% of the patients, the papillomas have been observed to change into squamous cell carcinoma⁽¹⁰⁻¹⁴⁾. Extra-laryngeal spread, especially to lung, making it difficult to treat due to its relative inaccessibility⁽¹⁵⁾. Prognosis has been reported poor, even fatal^(8,14). There are some proposed risk factors associated with extra-laryngeal spread such as presence of subglottic papilloma⁽¹⁵⁾, using jet ventilation as anesthetic technique⁽¹⁶⁾, young age, HPV type 11, and long duration of disease of more than 10 years⁽¹⁾. Regarding tracheostomy as a risk factor for extra-laryngeal spread, there were inconsistent reports^(3,8-10,15,17) with some studies showing that there was an association.

The main treatment modality is surgical removal. Carbon dioxide laser is the most commonly used tool⁽¹⁷⁻¹⁹⁾. There are adjunctive treatment modalities including interferon alpha, acyclovir,

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ribavirin, isotretinoin, indole-3-carbinol, photodynamic therapy, and other special surgical instruments such as KTP laser and powered instrument⁽²⁰⁾.

There are a few publications on this topic in Thailand^(4,6,21) with regard to incidence of extra-laryngeal RRP, treatment outcome, associated factors, and malignant change.

Our aims were to determine: (a) the incidence of extra-laryngeal involvement of this disease over the past 10 years, (b) treatment modalities and outcomes, (c) malignant change, and (d) factors associated with the presence of extra-laryngeal involvement. The results from the present study will help physicians know the nature of the disease and the outcome of treatment modalities. The present study can be used as baseline data for health policy planning and designing future clinical trials.

Material and Method

Study design and setting

We retrospectively reviewed patients with RRP recorded in our hospital database in either electronic or paper form. Data spanning 10 years between January 1, 1998 and December 31, 2007 were requested from Division of Medical Records. Srinagarind Hospital is a university hospital located in the northeastern region of Thailand. The hospital provides tertiary care.

Case definition

RRP was determined by microscopic examination. It is characterized by multiple branching mucosal projections comprising a hyperplastic squamous epithelium overlying thin fibrovascular cores with basal and parabasal cell hyperplasia with nuclei perpendicular to the basement membrane. There is slight flattening at the surface with focal parakeratosis. There are mitotic figures and koilocytosis (i.e., wrinkled, hyperchromatic nuclei surrounded by a cleared halo in cells with a well-defined cell border). Patients with pathologic or microscopic confirmation of laryngeal papilloma retrieved from larynx, trachea, and lower airway were included in the present study. Patients with overall follow-up less than one year were excluded. Extra-laryngeal involvement was defined by papilloma discovered at trachea, bronchus or lung.

“Not improved” was defined as there was the same or bigger size of papilloma at the final follow-up time.

“Improved” was defined as papilloma was decreased in any magnitude of size.

“Cured” was defined as no papilloma detected on the last follow-up time and no need for treatment for at least one year.

Data collection

Data (including duration of symptoms, clinical presentation, clinical signs, diagnoses, and treatment) were extracted to our case record forms from the hospital registry, for out- and in-patients records.

Statistical analysis

The categorical variables were presented as frequencies and percentages. The associations between categorical variables were tested by odds ratio with 95% confidence interval and Fisher’s exact test using SPSS statistics 15.0 software. A *p*-value of less than 0.05 was considered as statistically significant.

Ethics approval

The present study reviewed and approved by the Ethic Committee for Human Research, Khon Kaen University (HE 511020).

Results

Among the 53 RRP patients, eight had extra-laryngeal spread (15.1%); of these respective four, three, and one the papillomas were seeding in the trachea (7.5%), bronchus and lung parenchyma (5.7%) and tracheal stoma (1.9%).

Demographics, symptoms, and characteristic of disease are shown as Table 1.

All of the extra-RRP patients underwent CO₂ laser removal. Adjunct therapy included cup forceps removal, KTP laser removal, and interferon injection. The first two options were more likely to be performed in the extra-laryngeal group. The treatment outcomes for the present study period were not significantly different in both groups (Table 2).

For cases that were cured, the mean surgical treatment was 3.4 times per year in their first year of treatment and 4.5 times per year during overall time period.

There was a significant association between tracheostomy and the presence of extra-laryngeal involvement of RRP (Table 3).

Duration between onset of diseases and time until extra-laryngeal spread ranged from 1 to 30 years. The respective spreads developed within 1 year, 21 years, and 30 years in six cases (75%), one (12.5%), and one (12.5%), respectively.

Table 1. Demographics, symptoms, and characteristic of disease

	Extra-laryngeal involvement (n = 8)	Only laryngeal involvement (n = 45)	Odds ratio (95% CI)	p-value*
Demographics				
Age (year), median (range)	5 (1 to 77)	15 (1 to 65)	NC	NC
Sex: female, n (%)	3 (37.5)	24 (53.3)	0.53 (0.11 to 2.47)	0.467
Symptoms, n (%)				
Hoarseness	4 (50.0)	29 (64.4)	NC	NC
Dyspnea	1 (12.5)	4 (8.9)	NC	NC
Hoarseness and dyspnea	1 (12.5)	12 (26.7)	NC	NC
Characteristic of disease, n (%)				
Diffuse	8 (100)	41 (91.1)	NA	1.000
Subglottic extension	0 (0.0)	12 (26.7)	NA	0.175

CI = confidence interval; NA = not available; NC = no comparison

* Fisher's exact test, significant value <0.05

Table 2. Treatment modalities and outcomes

	Extra-laryngeal involvement (n = 8)	Only laryngeal involvement (n = 45)	Odds ratio (95% CI)	p-value*
Treatment modalities, n (%)				
CO ₂ laser	8 (100)	45 (100)	NA	NA
Cup forceps removal	7 (87.5)	18 (40.0)	10.50 (1.19 to 92.74)	0.020
KTP laser	4 (50.0)	4 (8.9)	10.25 (1.83 to 57.51)	0.013
Interferon	1 (12.5)	0 (0.0)	NA	0.151
Tracheostomy	3 (37.5)	3 (6.7)	8.40 (1.32 to 53.40)	0.038
Intubation	0 (0.0)	7 (15.6)	NA	0.577
Outcomes, n (%)				
Not improved	2 (25.0)	15 (33.3)	1.20 (0.25 to 5.71)	1.000
Improved	2 (25.0)	18 (40.0)	NC	NC
Cured	3 (37.5)	12 (26.7)	1.65 (0.34 to 7.98)	0.673
Died caused by disease	1 (12.5)	0 (0.0)	NA	0.151

CI = confidence interval; NA = not available; NC = no comparison

* Fisher's exact test, significant value <0.05

Table 3. Course of the diseases and outcomes for extra-laryngeal involvement RRP

No.	Sex	Age of onset (year)	Duration* (year)	Lesions	Tracheostomy retention time (year)	Treatment	Malignant change	Outcomes
1	M	1	1	Trachea, lungs	3 (since 1 year of age)	CO ₂ laser, cup forceps removal, KTP laser	Metastasis to C-spine	Died at 4 years of age
2	M	1	21	Trachea, lungs	17 (since 5 years of age)	CO ₂ laser, cup forceps removal, KTP laser	-	Not improved
3	M	10	1	Trachea, lungs	-	CO ₂ laser, cup forceps removal, KTP laser, interferon	-	Not improved
4	F	4	1	Trachea	-	CO ₂ laser, KTP laser	-	Improved
5	F	55	0	Trachea	-	CO ₂ laser, cup forceps removal	-	Improved
6	M	6	2 weeks	Trachea	-	CO ₂ laser, cup forceps removal	-	Cured
7	F	77	0	Trachea	-	CO ₂ laser, cup forceps removal	-	Cured
8	M	4	30	Tracheal stoma	30 (since 4 years of age)	CO ₂ laser, cup forceps removal	-	Cured

RRP = recurrent respiratory papillomatosis; M = male; F = female

* Duration between onset of disease and time until extra-laryngeal spread

Among the 53 RRP patients, two died; the one of the extra-laryngeal group died from pulmonary involvement and malignant change, while the one of only-laryngeal group died from a disease not associated with the papilloma (Table 2, 3). The malignant change rate in our study was 1.9% (1/53).

Discussion

Although RRP is a benign neoplasm, it is still discouraging for physicians dealing with this condition because of its high recurrence rate and a significant morbidity and mortality.

The most common symptom found was hoarseness. The papillomas were characteristically diffuse rather than localized. The duration of symptoms before seeing the physician ranged between 1 and 12 months. The signs and symptoms were similar between the extra-laryngeal-spreading and only-laryngeal group, which means that we cannot diagnose this disease with extra-laryngeal extension relying on the signs and symptoms alone. The most common site of lesions in both groups was the true vocal cord, which is consistent with previous studies⁽²⁾.

An average number of 3 to 4 admissions per year were needed for treatment. The duration of follow-up and treatment should be individualized, depending on the severity of symptoms. The mainstay of the treatment for laryngeal papilloma is the CO₂ laser. In the present study, special laser with flexible light cable (KTP laser) tended to be an adjunctive treatment modality used more in extra-laryngeal group than in only laryngeal group to access distal airway effectively.

Treatment outcome in only-laryngeal RRP and extra-laryngeal RRP were not different in our study. This result could not be a conclusion because we just observed the outcome in a limited time, in the long-term recurring disease, the outcome had not been occurred. In addition, the starting points of diseases were different. A limitation of this study is that it is a retrospective study. However, presence of extra-laryngeal involvement should be considered as a potential problem.

According to some studies, a frustrating problem in dealing with RRP is that its extra-laryngeal spread to lower airway and its potential malignant transformation usually results in treatment failure or even death^(8,9,14). The rate of extra-laryngeal involvement in the present study is 15.1% (8/53), comparable to previous reports (5% to 50%)^(8,15,20,22,23). Trachea was the most frequent site of extra-laryngeal spread⁽¹⁶⁾

(50%), which is comparable to ours (37.5%). There are factors believed to be associated with this spread such as presence of subglottic papilloma, prolonged tracheostomy, several numbers of treatments, long duration of disease courses, and using jet ventilation as anesthetic technique^(8,15,16,23). However, these associations are controversial. For example, some studies^(8,10,15) supported the association between tracheostomy and extra-laryngeal spread but not for others^(3,9,17). The present study showed that there was a statistically significant association between tracheostomy and extra-laryngeal involvement of RRP. There were studies^(15,23) suggesting the association between subglottic extensions and extra-laryngeal spread. However, no significant association regarding this factor was discovered in the present study. The duration between onset of disease and the time until pulmonary spread was reported as 6 to 16 years⁽¹⁰⁾. We found the long duration of 21 years in one case and a rather short duration of one year in other case. First case with 21-year-duration also had a tracheostomy for 17 years. This combination may be responsible for pulmonary spread. In the second case with 1-year-duration, early spread might be from the severity of the disease itself, which was finally proved to be a malignancy. Silver et al⁽¹⁶⁾ reported that a common thread in RRP with extra-laryngeal spread was anesthetic technique with jet ventilation, which was used in almost all our cases. However, we could not evaluate this factor in our study. The rate of tracheostomy in our study was 11.3% (6/53), while others reported relatively wide range of 2% to 84%^(9,15,19,23). Orji et al⁽⁹⁾ reported about high rate of tracheostomy in children (84%) with low incidence of extra-laryngeal spread in RPP (4%). He explained that low incidence may be due to short duration of tracheostomy retention (3.5±3.2 months) while a high incidence^(15,23) (50% to 58%) was associated with long duration retention (30 to 34 months). Incidence of extra-laryngeal spread due to tracheostomy in the present study was 50% (3/6), which is the same rate as that of Cole et al⁽²³⁾ (6/12). Our tracheostomy retention time of extra-laryngeal involvement patients were 24, 204, and 360 months, respectively. All of these cases were referred from other hospitals and tracheostomy had been performed already. This long-term tracheostomy retention may explain our 15.1% rate of extra-laryngeal spread, although it is within the 5% to 50% range^(8,15,22,23). Pulmonary spread did not occur frequently but caused significant morbidity and mortality. Its rate was 5.7% (3/53) in our study,

the same rate as prior studies (1.8% to 16%)(^{8,10,14}). The rate of malignant transformation in the present study was 1.9% (1/53) within the range of other reports(¹⁰⁻¹⁴) (0.5% to 13%). Characteristics of RRP patients with malignant change was identified from previous studies(^{10,22}), it may relate to HPV type 11 infection(²¹), development of RRP since childhood, and long course of disease. Gélinas et al(¹⁴) reviewed malignant change and reported that the average interval between the diagnosis of RRP and that of malignancy was 19 years (4 to 45 years), but in 31.3% of cases, malignancy was diagnosed at the same time as those of RRP. Although the mean age of the majority of patients at development of malignancy in RRP patients with pulmonary spread was 34.0±7.6 years(¹⁰), carcinoma can develop at a younger age(²⁴) (6 years of age). In the present study, we observed a RRP patient who developed malignancy at young age with a rather short interval (3 years) from diagnosis of RRP to malignancy change. This case was diagnosed with RRP and a tracheostomy was performed at one year of age and then referred to our institute. After a 1-year-follow-up, extra-laryngeal spread to trachea and lung were observed. He was lost to follow-up and came back again two years later with more diffuse lung involvement. His sputum was positive for malignancy and there was cervical spine diffuse metastatic involvement and he died at the age of 4.

The treatment of this disease is a major challenge for physicians, as there is no curative treatment modality despite extensive researches in the past 20 years(⁷). Therefore, the treatment is still palliative. Education for patients and their parents should include the need for close follow-up. To elucidate the length of tracheostomy retention time that will affect the presence of extra-laryngeal spread, further study should be conducted.

Conclusion

RRP has a significant rate of extra-laryngeal spread with increased need of more optional treatment modalities. There is a significant association between tracheostomy and the presence of extra-laryngeal spread. Tracheostomy should be managed with caution especially for long-term retention. Malignant change should be taken into consideration as it can result in mortality.

What is already known on this topic?

There are a few published reports about this disease (RRP) in Thailand, especially clinical researches. Incidence of extra-laryngeal spread as well

as malignant change has not been reported. Although there are some reports from abroad, their context may be different than ours. In addition, some risk factors are still controversial due to different clinical settings (tracheostomy vs. extra-laryngeal spread)(^{4,5,21}).

What this study adds?

This study adds information about extra-laryngeal spread of RRP including incidence, some clinical information, malignancy change, and clinical factors associated with extra-laryngeal involvement. This report added up more information to the limited knowledge of this condition and stimulate further studies.

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Potential conflicts of interest

None.

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เนื้องอกปาปิลโลมาของทางเดินหายใจที่กระจายออกนอกกล่องเสียง: ประสบการณ์ 10 ปี

นัฏธิกร ไกรสรทองศรี, สุรพล ชี้อตรง, ภัทรวุฒิ วัฒนศัพท์, ภาธร ภิรมย์ไชย

ภูมิหลัง: เนื้องอกปาปิลโลมาของทางเดินหายใจ (*recurrent respiratory papillomatosis (RRP)*) เป็นเนื้องอกชนิดไม่ร้ายแรงที่พบบ่อยที่สุดของทางเดินหายใจและมักพบที่กล่องเสียง โรคนี้เป็นปัญหาต่อการรักษาเนื่องจากเป็นกลับซ้ำได้บ่อย สามารถกระจายออกนอกกล่องเสียง (*extra-laryngeal spread*) และเปลี่ยนแปลงเป็นเนื้องอกชนิดร้าย (*malignant transformation*) ได้ซึ่งทำให้ผลการรักษาแย่งลง หรือ ถึงแก่ชีวิตได้

วัตถุประสงค์: เพื่อศึกษา 1) อุบัติการณ์การกระจายออกนอกกล่องเสียงของโรค 2) การรักษาและผลการรักษา 3) การกลายเป็นเนื้อร้าย และ 4) ปัจจัยสัมพันธ์กับการกระจายออกนอกกล่องเสียง

วัสดุและวิธีการ: การศึกษาเชิงพรรณนาค้นย้อนหลัง โดยทบทวนบันทึกเวชระเบียนทางการแพทย์ของผู้ป่วยเนื้องอกปาปิลโลมาออกนอกกล่องเสียง ในระหว่าง พ.ศ. 2541 ถึง พ.ศ. 2550 ที่โรงพยาบาลตติยภูมิ ในภาคตะวันออกเฉียงเหนือ ประเทศไทย วิเคราะห์ผลจากข้อมูลด้านประชากร ลักษณะทางคลินิก อาการแสดง การรักษา และผลการรักษา

ผลการศึกษา: จากผู้ป่วยทั้งหมดที่เป็นเนื้องอกปาปิลโลมาของกล่องเสียง จำนวน 53 ราย พบว่ามี 8 ราย (15.1%) ที่เนื้องอกกระจายออกนอกกล่องเสียง โดยพบที่หลอดลม 4 ราย หลอดลมและปอด 3 ราย และบริเวณปากแผลเจาะคอ 1 ราย อาการที่พบบ่อยส่วนใหญ่ คือ อาการเสียงแหบ ลักษณะที่ตรวจพบของเนื้องอกที่บริเวณกล่องเสียงทั้งกลุ่มที่เนื้องอกจำกัดอยู่เฉพาะกล่องเสียง และกลุ่มที่เนื้องอกกระจายออกนอกกล่องเสียง พบเป็นลักษณะกระจายทั่วไป (*diffuse lesion*) (100% vs. 91%) ระยะเวลาจากที่เป็นโรคจนถึงเมื่อมีการกระจายออกนอกกล่องเสียง คือ 1 ปี (6 ราย: 75%), 21 ปี (1 ราย: 12.5%), 30 ปี (1 ราย: 12.55%) ผู้ป่วยทั้งหมดได้รับการรักษาหลักโดยวิธีการใช้คาร์บอนไดออกไซด์ เลเซอร์ และพบว่าในผู้ป่วยที่เนื้องอกกระจายออกนอกกล่องเสียง ต้องใช้เลเซอร์พิเศษ (*KTP*) เป็นการรักษาเสริมเพิ่มมากขึ้น ผลการรักษาดีขึ้น 25%, หาย 37.5% ในกลุ่มผู้ป่วยที่เนื้องอกกระจายออกนอกกล่องเสียง และดีขึ้น 40.5%, หาย 26.2% ในกลุ่มที่เนื้องอกจำกัดในกล่องเสียง พบผู้เสียชีวิต 1 ราย เนื่องจากเนื้องอกกระจายไปที่ปอดและกลายเป็นเนื้อร้าย พบความสัมพันธ์ระหว่างการใส่ท่อเจาะคอช่วยหายใจ และการกระจายของเนื้องอกนอกกล่องเสียงอย่างมีนัยสำคัญ [(*p-value* 0.038, *odds ratio* 8.40 (1.32-53.40)]

สรุป: พบว่ามีอุบัติการณ์ของการกระจายของเนื้องอกปาปิลโลมาออกนอกกล่องเสียงอยู่ในระดับที่ไม่ควรละเลย ซึ่งการรักษามักต้องการวิธีการรักษาเสริมเพิ่มเติมมากขึ้น พบว่าการเจาะคอใส่ท่อหายใจมีความสัมพันธ์กับการพบการกระจายออกนอกกล่องเสียง การกลายเป็นเนื้อร้ายก็เป็นปัญหาที่ควรสนใจเพราะทำให้ผู้ป่วยถึงแก่ชีวิตได้
