Factors Affecting Unfavourable Results from a Sinonasal Inverted Papilloma Surgery

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ABSTRACT

Objective: Sinonasal inverted papilloma (SNIP) is the most common nasal benign tumor, but locally invasive. The standard treatment is to identify origins of the tumor and total removal. Unfavourable results are finding postoperative residual or recurrent tumors. The aim of this study is to determine factors affecting postoperative residual or recurrent tumors and a rate of getting postoperative residual or recurrent tumors from SNIP surgeries.
Methods: A retrospective study in patients with SNIPs was conducted. Relationships between demographic data, tumor sites, tumor stages by Krouse classification, surgical approaches, surgeons' experience, using microdebrider assisted surgery, operative time, intraoperative blood loss, histopathology, Epstein Barr virus (EBV), human papillomavirus (HPV) infection, time to detect tumor after surgery and unfavourable results were evaluated. HPV and EBV were detected *by in situ hybridization*.
Results: 73 patients were included in this study. Unfavourable results were found in 27 patients (36.99%). 50% of patients received unfavourable results after postoperative duration of 115 months. 5 years of a disease-free survival rate was 64.3% (95% CI: 51.9% to 76.7%). The patients with external surgical approaches got worse results than those with endoscopic sinus surgery ($p = 0.01$, a hazard ratio of 3.88, 95% CI: 1.39 to 10.87). The patients operated without using microdebrider assisted surgery got worse results than those with using the device ($p < 0.001$, an adjusted hazard ratio of 5.09, 95% CI: 2.08 to 12.45). The patients with abnormal pathological changes (tissue dysplasia and malignant transformation) had worse results than those without changes ($p = 0.02$, an adjusted hazard ratio of 3.42, 95% CI: 1.24 to 9.38).
Conclusion: Non-endoscopic nasal surgery, non-using microdebrider assisted surgery, and abnormal pathological changes may be some of the causes of unfavourable results from SNIP surgeries. Long postsurgical surveillance should be done, because of 36.99% of patients received unfavourable results from SNIP surgeries.

Keywords: Sinonasal inverted papilloma; unfavourable results; relationship; sinus surgery (Siriraj Med J 2020; 72: 343-351)

INTRODUCTION

Sinonasal papillomas are nasal benign tumors developing from Schneiderian membranes, which are ectodermal remnants at boundary between nasal and sinus mucosa. They are classified into sinonasal inverted papilloma (SNIP), exophytic (fungiform) papilloma, and oncocytic (cylindrical cell) papilloma. The most common type of sinonasal papilloma is SNIP. SNIPs, which are found 0.2-1.5 cases per 100,000 populations[1,2], are the most common benign tumor of the nose and paranasal sinuses[13], but they are locally aggressive and usually recurrent. The tumors usually erode adjacent

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bones, extend to the orbit and intracranium. They have 5-15% risks of malignant transformation, and 5-15% risks of recurrence.[3-9] The main treatment is to identify all sites of tumor attachments, remove all tumors with affected mucosa, and drill out underlying bone in order to prevent tumor recurrence.[10] The standard treatment is an external approach with a medial maxillectomy via a lateral rhinotomy, or a midfacial degloving procedure.[11,41] Nowadays, an endoscopic surgery is usually performed, because it can reduce the morbidity of an external approach. An endoscope can help surgeons to visualize in the surgical field, even hidden sites such as an anterior wall of the maxillary sinus e.g., endoscopic Denker approach (anteromedial maxillectomy).[9,41] Therefore, some surgeons use an endoscope to assist an external approach to obtain complete tumor removal. A microdebrider is a powered rotary shaving device. It provides atraumatic dissection by resecting tissue precisely, minimizing unintended mucosal trauma. The using microdebrider assisted surgeries showed minimal bleeding, decreased surgical time, faster postoperative healing[19,22], and should reduce postoperative recurrences of SNIP surgeries. Postoperative recurrent rate of SNIP surgeries is lower in primary resections than secondary resections[10,12], so the patients with SNIPs should be operated as primary resections. Meta-analysis studies suggest HPV and EBV infection maybe potential causes of recurrence[2, 21,40], but no study in Thailand.

The risk factors affecting unfavourable results from SNIP surgeries, in literary reviews, are ages, genders, surgical approaches, tumor sites, tumor stages, histopathology, virus infection, and smoking[2,11-13]; however, they are still controversial. The purpose of this study is to determine the factors affecting postoperative residual or recurrent tumors and a rate of getting postoperative residual or recurrent tumors from SNIP surgeries.

MATERIALS AND METHODS

A retrospective study was conducted on patients, selected from 289 cases of SNIP surgeries, at Siriraj Hospital between January 2004 and December 2012. All patients, presenting as primary SNIPs, are more than 18 years old, postoperative tumor surveillance to December 2019. Exclusion criteria included partial or incomplete resection, revision surgery, and incomplete patient data. Demographic data, tumor sites, tumor stages by Krouse classification[14], surgical approaches, surgeons' experience, using microdebrider assisted surgery, operative time, intraoperative blood loss, histopathology, EBV, HPV infection, and a date of finding postoperative tumors were evaluated. The criteria of unfavourable result are finding postoperative residual or recurrent tumor by nasal endoscopic examination and pathological confirmation. The recurrent cases were defined as finding postoperative tumor after postoperative duration of 3 months. A total of 73 patients were selected in this study (Fig 1).

Hematoxylin and eosin-stained pathological slides were reviewed, and the diagnosis was confirmed by one pathologist (T.P.). Paraffin-embedded tissue blocks were selected for tissue microarray. The tissue microarray sections were hybridized separately with a target probe of Ventana Inform HPV II Family® 6 Probes, for low-risk HPV genotypes 6,11, then Ventana Inform HPV III Family® 16 Probes, for high-risk HPV genotypes 16, 18, 31, 33, 35 45, 51, 52, 56, 58, 66, and Epstein Barr virus encoding RNA (EBER).

This study protocol was approved by the Institutional Review Board Committee of the Siriraj Hospital. The sample size calculation was based on the study of Busquets et al.[8], found 15 % of postoperative SNIP recurrences. Sixty-one patients were required to get 95% confidence level with a type I error at 0.05.

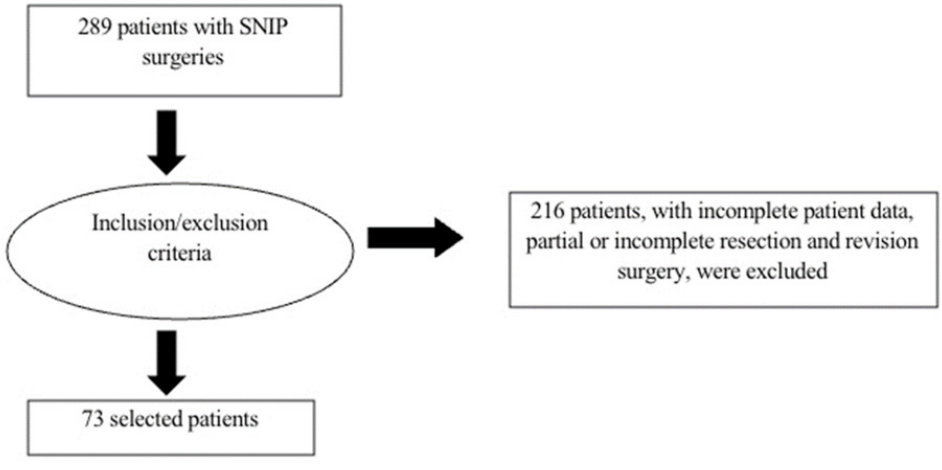

Fig 1. Flowchart of this study

Statistical analysis

The data was presented as numbers and percentages. If quantitative variables were normally distributed, the results were expressed as mean values and standard deviation, otherwise as median. A difference between two groups was analyzed by using t-test, or Mann-Whitney U test. Qualitative data are reported as counts and frequencies, and differences between two groups were analyzed by using Pearson Chi-Square test or Fisher's exact test, and receiver operating characteristic (ROC) curve. Cox regression was used to analyze the association of factors of unfavorable results. Kaplan-Meier curve and log rank test were used to analyze a disease-free survival. A p value of 0.05 was considered as a statistical significance. All calculation was performed by using SPSS, PASW statistics for windows, version 18.0.

RESULTS

General data

The age of the 73 patients ranged from 24 to 87 years, with a mean of 54.90 ± 13.27 years. There were 37 males and 36 females. The most common presenting symptom was nasal obstruction (71.60%). Other presenting symptoms were rhinorrhea/postnasal drip (11.24%), epistaxis (6.51%), smell dysfunction (2.96%), facial pain (2.96%), headache (1.78%), blocked ear (1.18%), toothache (1.18%), and oropharyngeal pain (0.49%).

Sixty-three patients had multiple tumor sites (86.30%). All SNIPs were unilateral sites, found 37 right-sided tumors, and 36 left-sided tumors. Tumors were located at lateral nasal wall (34.72%), maxillary sinus (23.83%), ethmoid sinus (19.17%), sphenoid sinus (5.70%), frontal sinus (7.25%), middle turbinate (4.66%), superior turbinate (2.07%), nasal septum (1.55%), and inferior turbinate (1.04%). Tumor stages by Krouse classification[14] revealed 4 groups as T1 (5.48%), 20 patients as T2 (27.40%), 47 patients as T3 (64.38%), and 2 patients as T4 (2.74%).

Endoscopic sinus surgeries were performed in 49 patients (67.12%). 6 patients (8.22%) underwent external surgical procedures and 18 patients (24.66%) were operated by combined approaches. Microdebriders were used in 28 of all cases (61.64%). SNIPs with tissue dysplasia without malignant change were found in 3 patients (4.11%). All of them were gotten postsurgical recurrences. Malignant transformations to squamous cell carcinoma occurred in 3 patients (4.11%). All of them were synchronous malignancy, no regional or distant metastasis, and recurrent tumors were found in 2 patients. All patients with malignant transformations were received postoperative radiation therapy, and 2 patients were received concurrent chemotherapy. A surgical margin was not free in one patient; however, all patients with malignant changes had survived.

Analysis of unfavorable results

The unfavourable results were found in 27 patients (36.99%) (7 residual cases, and 20 recurrent cases) and 50% of patients received unfavourable results after postoperative duration of 115 months. 5 years of a disease-free survival rate was 64.3% (95% CI: 51.9% to 76.7%). A mean time of unfavourable results was 30.23 months (ranging from 0.82 to 115.31 months).

Genders, ages, and onset of disease

An average age of the patients with unfavourable results was 50.82 years old, which is lower than a mean age of 57.30 years old in the successful group. There was a statistically significant difference between the two groups (p = 0.04). However, no relationship was found between genders, onset of disease and unfavourable results (p = 0.52, 0.27, respectively) (Table 1).

Tumor sites and stages

No statistical significances were found between each of the tumor sites (lateral nasal walls, ethmoid sinuses maxillary sinuses, sphenoid sinuses, frontal sinuses, superior turbinates, middle turbinates, inferior turbinates, and nasal septums), multiple tumor sites, tumor stages and unfavourable results (p = 0.19, 0.52, 0.61, 0.52, 0.61, 0.14, 0.28, 1.00, 0.55, 0.74, and 0.82, respectively) (Table 1).

Surgical approaches, intraoperative time, techniques, and blood loss

A significantly difference was found between three surgical approaches (p = 0.04) (Table 1). Both an endoscopic sinus surgery and an endoscopic assisted external surgical procedure offered better outcome than an external surgical procedure (p = 0.007, 0.04, respectively). However, no different in treatment outcome was found between the two groups using endoscope (p = 0.60). The patients with external surgical approaches had worse results than those with endoscopic sinus surgery (p = 0.01, a hazard ratio of 3.88, 95% CI: 1.39 to 10.87) (Fig 2).

No difference in surgical treatments was found between experienced and training surgeons (resident and/or fellow under supervision) (p = 0.45) and no relationships between intraoperative time, blood loss and unfavourable results were found (p = 0.16, 0.39, respectively) (Table 1).

Microdebrider is an assisted surgical device in nasal surgery and can be used for cutting and removing

TABLE 1. Factors affecting unfavourable results from SNIP surgeries in univariate analysis.

Factors	Successful treatments (n = 46)	Unfavorable treatments (n = 27)	*P*-value
Genders			0.52
Male	22	15	
Female	24	12	
Mean of ages (years)	57.30	50.82	**0.04*** **
Median of disease onset (months)	7.5 (3,12)	12 (3,24)	0.27
Tumor sites:			
Lateral nasal walls			0.19
No	2	4	
Yes	44	23	
Ethmoid sinuses			0.52
No	24	12	
Yes	22	15	
Maxillary sinuses			0.61
No	16	11	
Yes	30	16	
Sphenoid sinuses			0.52
No	40	22	
Yes	6	5	
Frontal sinuses			0.61
No	38	21	
Yes	8	6	
Superior turbinates			0.14
No	45	24	
Yes	1	3	
Middle turbinates			0.28
No	42	22	
Yes	4	5	
Inferior turbinates			1.00
No	45	26	
Yes	1	1	
Nasal septums			0.55
No	45	25	
Yes	1	2	
Multiple sites			0.74
No	7	3	
Yes	39	24	
Tumor stages			0.82
T1	3	1	
T2	12	8	
T3	30	17	
T4	1	1	

TABLE 1. Factors affecting unfavourable results from SNIP surgeries in univariate analysis. (continued)

Factors	Successful treatments (n = 46)	Unfavorable treatments (n = 27)	*P*-value
Surgical approaches			**0.04*** **
Endoscopic sinus surgery	34	15	
External surgical procedure	1	5	
Endoscopic assisted external surgical procedure	11	7	
Median of intraoperative time (minutes)	120 (90,150)	140 (100,180)	0.16
Median of intraoperative blood loss (ml)	225 (80,450)	300 (100,550)	0.39
Using microdebrider assisted surgery			**0.005*** **
Non-using	12	16	
Using	34	11	
Surgeons' experience			0.45
Experience	36	19	
Training	10	8	
Tissue dyplasia and malignant transformation			**0.05*** **
No dysplasia and malignant transformation	45	22	
Dysplasia and malignant transformation	1	5	
HPV infection			0.37
No HPV infection	46	26	
HPV infection	0	1	

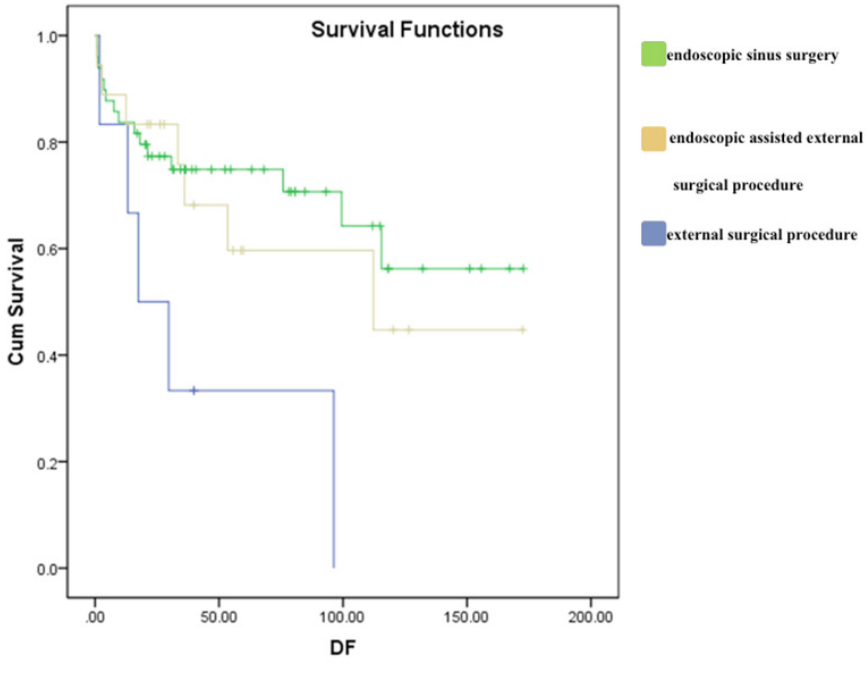

Fig 2. Disease free survival and surgical approaches

tissues, together. The patients with using microdebrider assisted surgery got better surgical outcomes than those without using the device (p =0.005) (Table 1).The patients operated without using microdebrider assisted surgery got worse results than those with using the device (p = 0.001, a hazard ratio of 4.51, 95% CI: 1.88 to 10.81, and p < 0.001, an adjusted hazard ratio of 5.09, 95% CI: 2.08 to 12.45, in multivariate backward cox regression analysis with abnormal pathological changes (tissue dysplasia and malignant transformation) (Fig 3).

Histopathology

The relationship was found between abnormal pathological changes (tissue dysplasia and malignant transformation) and unfavorable results (p = 0.05) (Table 1). The patients with the changes got worse unfavourable results than those with no pathological change (p = 0.05, a hazard ratio of 2.59, 95% CI: 0.97 to 6.90, and p = 0.02, an adjusted hazard ratio of 3.42, 95% CI: 1.24 to 9.38, in multivariate backward cox regression analysis with using microdebrider assisted surgery) (Fig 4).

Virus infection

Only one patient in the unfavourable group was positive for HPV type 6 by *in situ* hybridization and no EBV was detected in all patients. No relationship was found between HPV infection and unfavorable results (p = 0.37) (Table 1).

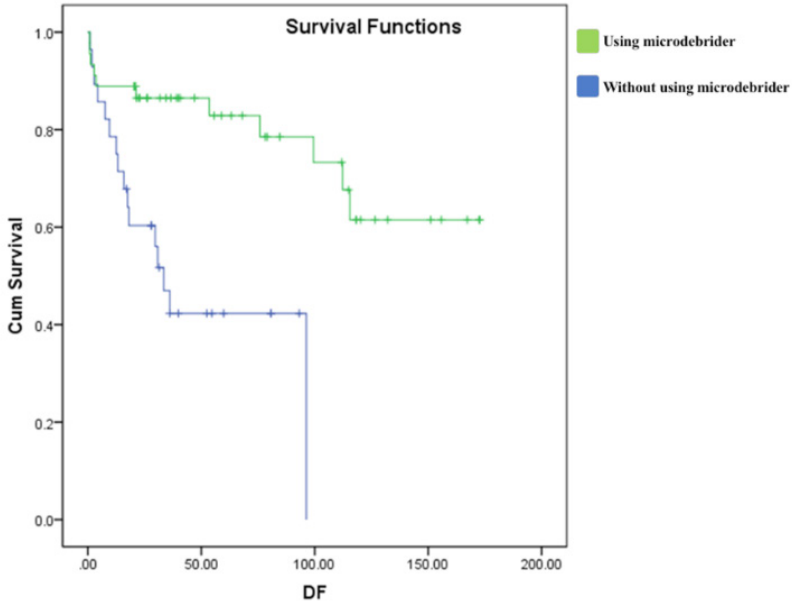

Fig 3. Disease free survival and using microdebrider assisted surgery

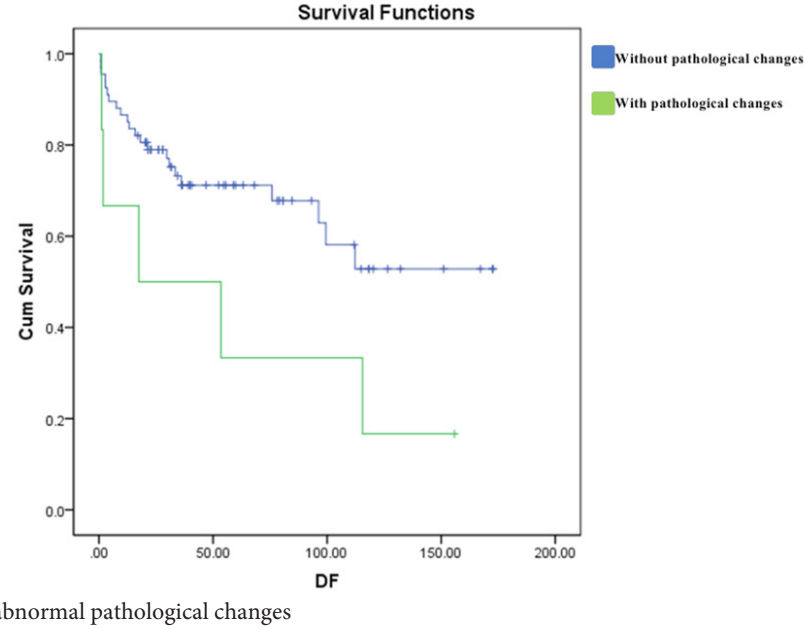

Fig 4. Disease free survival and abnormal pathological changes

DISCUSSION

Factors affecting unfavourable results from SNIP surgeries could be surgical approaches, using microdebrider assisted surgeries, and abnormal pathological changes.

An average age of the patients with unfavourable results was 50.82 years old, which is lower than a mean age of 57.30 years old in the successful group. The patients with unfavourable results of SNIP surgeries were younger than those with good results as other studies[20,36,39], because they might get more risks of exposure with chronic inflammatory conditions, such as chronic infection, smoking, pollution[15,16], which could induce normal tissues developing to SNIPs. However, it might be no clinical significance in surgical decisions between age groups.

The surgical approaches, which depended on surgeons' experience, tumor sites, were selected in each patient. The patients with external surgical approaches had a hazard ratio of 3.88 to get failed results. The groups of using endoscope had better outcomes, as other studies[8,9,18], because endoscope can help surgeons to visualize in all surgical fields, even hidden sites such as an anterior wall of maxillary sinus, a lateral wall of frontal sinus. Therefore, we should use endoscope to assist in SNIP surgeries, especially in high Krouse classification.

The patients operated without using microdebrider assisted surgery had an adjusted hazard ratio of 5.09 to get unfavourable results. The group with using microdebrider, which can cut together with tissue suction, got better results, because surgeon could see clearly operative field and got completely tumor removal.[8,19,22] Unfortunately, the device is a special instrument which is not included in the standard instruments in SNIP surgeries. According to our study, surgeons should use this device to get good outcomes in all cases of SNIP surgeries.

The study by Lisan et al.[2] found that the tumor attachment sites were related to tumor recurrences, especially in the frontal sinus, and in cases with multiple tumor origins. There were not found in our and others study[36,42], because of few patients included in some tumor sites. No relationship was found between Krouse classification, and unfavourable results as other studies[10,12-13,17,38-39], because of also few patients in T1 and T4.

Long intraoperative time and high intraoperative blood loss might be factors of poor surgical outcomes such as delayed wound healing, incomplete tumor removal, but no relationship between those and unfavourable results were found in our study. Experienced surgeons should be better in surgical outcomes than training surgeons. No difference in curative effects in surgical experience was found, because Siriraj Hospital is a tertiary care and an otolaryngological training center. Even though, patients were in training cases, our staffs had to supervise our training surgeons and completely examine those patients before finishing operations.

In this study, a statistical significance was found between the patients with abnormal pathological changes (tissue dysplasia and malignant transformation) and unfavourable results. The patients with that changes got an adjusted hazard ratio of 3.42 to get unfavourable results as previous studies that found features of atypia, enhanced hyperkeratosis, presence of squamous hyperplasia[12,42] may predispose to recurrence. Thus, we should pay more attention to those and frequently postoperative surveillance with the changes that could be a factor of tumor recurrences.

EBV was not detected in all patients as same as other studies[15] and could not be a factor of unfavorable results. One patient with an unfavourable result was positive for HPV type 6 by *in situ hybridization*. Our study is the first study of HPV in nasal tumors in Thailand, so there is no study in that for comparison. The HPV studies, which were found low HPV detection, in head neck tumors in Thailand[25-29], might be used as comparison. HPV was low detected in our study, which contrasted with previous studies[21-24] because HPV might rarely be found in these regions in Thailand, and Ventana Inform HPV Family® cannot detect all HPV types. Our negative results could be true negative, because Ventana Inform HPV Family® can be usually used in paraffin-embbed tissues as other studies and *in situ hybridization* can detect HPV as same as other molecular techniques.[30-35] The study by Holte et al.[36] found a decreasing ratio of HPV-positive SNIPs with advanced tumor stages as T3,4 of Krouse classification. The positive case in our study was in T2 of Krouse classification and other negative results were usually found in T3 of Krouse classification. Accordingly, HPV infection may not be a risk factor of unfavourable results in SINP surgeries in Thailand.

The unsuccessful treatment rate of 36.99%, in our study, was nearly the recurrent rate of 30.51% in the past study by Jareoncharsri et al.[37] and 37% in the other study in Thailand by Fooanant et al.[18] The recently meta-analysis study by Peng et al.[9] found the recurrence rate was 12.8%. In our study, the unsuccessful treatment rate was higher than that study, because our study included residual and recurrent tumors, was long terms postsurgical surveillance, and microdebrides were not used in all surgical cases. SNIPs in our country may tend to recur. The 115 months of 50 % finding postoperative tumor were suggested postoperative surveillance should be at least 10 years.

Malignant transformation (4.11%) was lower than other studies of 5 to 15 % of malignant transformation.[11-12,38] This finding may indicate that SNIPs in Thailand are non-violent, but frequently recurrent.

The drawback of this study is not included some factors, which might be factors of unfavourable results, such as smoking, pollution, revision surgery, sending an intraoperative tumor margin and few patients in some Krouse classification.

The prominence of this study is a retrospective study, which is no bias in surgical outcomes, and long postsurgical surveillance. From our and other studies in Thailand[18,37], SNIPs may tend to recur, low malignant changes and need long postsurgical surveillance. The future study should include a medical genetic study in patients with SNIPs and malignant changes, and a benefit of using microdebrider assisted surgery.

CONCLUSION

Non-endoscopic nasal surgery, non-using microdebrider assisted surgery, and abnormal pathological changes were possible risk factors of unfavourable results in SNIP surgeries. Because of the patients, with using nasal endoscopes and microdebriders assisted SNIP surgeries, gotten better surgical results, both devices should be the standard equipments in SNIP surgeries. The patients with abnormal pathological changes should be frequently surveilled, because they had a risk of postoperative recurrences. Long postsurgical surveillance should be done, because of 36.99% of patients received unfavourable results from SNIP surgeries.

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