

Factors affecting recurrence of sinonasal inverted papilloma

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Received: 29 April 2012 / Accepted: 26 September 2012 / Published online: 12 October 2012
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Abstract The aim is to study clinical characteristics and recurrence rates for sinonasal inverted papilloma (NIP), to evaluate relevant factors for its recurrence, and to compare the curative rates of different surgical approaches. The Krouse classification for the 156 follow-up cases of the patients with NIP was as following: 26 cases in T1, 33 cases in T2, 94 cases in T3, and 3 cases in T4. A total number of 99 cases of endoscopic sinus surgery were included, of which 26 cases of lateral rhinotomy approach were combined with Caldwell Luc approach, and 31 cases of nasal endoscopy combined with traditional surgery, with average postoperative follow-up of 3–11 years. Of the 156 studied patients with NIP, male:female = 1.69:1, age varied from 18 to 77 years, with average of 56 years, 19 cases showed postoperative recurrence, of which 8 cases developed to be squamous cell carcinoma. Among these 8 cases, 3 patients showed no recurrence after treatment in 5 years, and the other 5 patients died in 3–2 years period. Tumor recurrence rates for different surgical approach are: 9.09 % for endoscopic surgical group, 23.08 % for traditional surgical group, and 12.12 % for combined surgical group; tumor malignancy rates for different surgical approach are: 2.02 % for endoscopic surgical group,

11.54 % traditional surgical group, and 9.09 % for combined group, and Chi-square test showed that the differences in recurrence and malignancy rates for NIP patients with different surgical treatments were not statistically significant ($P > 0.05$). Recurrence rates for different stages are: T1 at 3.85 %, T2 at 12.12 %, T3 at 14.89 %, and T4 at 0.00 %, and the differences in the recurrence rates for different stages were not statistically significant ($P > 0.05$) by Chi-square test. There are clear clinical features for NIP, and the recurrence is related to the thoroughness of the first time surgical removal of lesions and is less relevant with Krouse classification stage and surgical approaches.

Keywords Inverted papilloma · Clinical · Surgical approach · Effects · Recurrence

Introduction

Sinonasal inverted papilloma (NIP) is the most common benign lesion (incidence is from 0.6 to 1.5 per 10^5 population [1]) that occurs in the nasal cavity and paranasal sinuses characterized by high recurrence rate (up to 78 % [2]) and malignant transformation potential (the malignancy rate is between 5 and 15 % [3]). Surgery is the preferred treatment for inverted papilloma. Traditional external approaches were mainly used in the past, while endoscopic sinus surgical technique has become a popular approach for NIP treatment nowadays; the major challenge for such treatment is the high postoperative recurrence rate. This report summarized our findings in terms of the clinical characteristics of NIP, the postoperative recurrence rate as well as the factors affecting the recurrence rate retrospective to the cases (156 cases in total) in our hospital from January 1998 to January 2008. The effectiveness of

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different surgical approaches was also evaluated aiming to provide references for future surgical treatment.

Materials and methods

A total of 193 cases of NIP were collected from January 1998 to January 2008 with full clinical information and clear pathology diagnosis (retreatment cases were not included). The average duration of follow-up for these patients was 3 years and the longest was 11 years. Among these 193 cases, 37 cases missed the follow-up ($37/193 = 19.17\%$). This study retrospectively analyzed the 156 cases which had complete follow-up data.

Averaging and Chi-square tests were used for statistical analysis using SPSS 13, where $P < 0.05$ indicated the statistical significance.

Results

General situation

The 156 patients with NIP were composed of 98 males and 58 females, which put the ratio for male to female at 1.69 to 1; age varied from 19 to 77 years, with average of 56 years; the surgical approach can be divided as: 99 cases of endoscopic sinus surgery, 26 cases of traditional surgery, and 31 cases of endoscopic and traditional combined approach surgery. In these cases, 19 cases had postoperative recurrence, which represented the recurrence rate of 12.18% ($19/156$), and the earliest recurrence occurred at 1 month after surgery, the latest was 10 years postoperation. In the 156 cases, there were 8 cases of malignancy, representing ratio of 5.13% ($8/156$), 3 of them got malignancy before they visited our hospital, while the other 5 patients had either one or two nasal sinus surgeries for their NIP, and the malignancy occurred 2–6 years after surgery; all of them were confirmed as squamous cell cancer in pathology. Surgery and postoperative radiotherapy were performed for all the patients with malignancy, no recurrence was observed for 3 patients in 5 years, and other 5 patients died in 3 months to 2 years.

Site of lesion

In terms of the site of lesion, 43 cases originated from the maxillary sinus, 31 cases originated from sinus and nasal complex of ethmoid sinus, 8 cases from frontal sinuses, and 4 cases from sphenoid sinus, 66 cases involved nasal cavity and multiple sinus, with most of them in the area including nasal cavity, maxillary sinus and ethmoid sinus, of which

10 cases involving bilateral nasal cavity and paranasal sinuses, and 4 cases originated from nasal septum.

Krouse classification stand [4] for NIP was issued at 2000. T1 stage tumor is limited to nasal cavity, without invasion beyond the area of the sinus and nasal cavity, there is no malignancy in T1 tumor; T2 tumor is located in sinus and nasal complex of ethmoid sinus, while may involve the inside portion of maxillary sinus and nasal cavity. There is no malignancy in T2 tumor; T3 tumor is located outside, under, upper, front or back of maxillary sinus, sphenoid sinus and/or ethmoidal sinus, which may involve the inside of maxillary sinus, and ethmoidal sinus or nasal cavity, there is no malignancy in T3 tumor; T4 tumor period involves the areas beyond nasal cavity or sinus, such as orbit, intracalvarium, and pterion; T4 tumor shows malignancy.

We applied Krouse classification standard for 156 cases in this report, the result is as such: 26 cases at stage T1, 33 cases at stage T2, 94 cases at stage T3, and 3 cases at T4. Chi-square test was used to analyze the recurrence in different stages of NIP, the results showed that P value was greater than 0.05, which indicated that the difference of recurrence rates in different Krouse stages was not statistically significant.

Operation methods and curative effects

All surgery was performed under general anesthesia, including 99 cases of endoscopic sinus surgery, 26 cases with lateral rhinotomy approach, and some patients using lateral rhinotomy approach combined with Caldwell Luc surgical technique and 31 cases of nasal endoscopy approach combined with traditional surgery. Traditional surgical technique consists mainly of Caldwell Luc surgical approach, lateral rhinotomy approach, and mid-face lift surgery, etc. The combined technique refers to the joint surgical operation using both the traditional surgical technique and the endoscopic sinus surgery. The recurrence and malignancy for NIP patients in different stages treated by the three approaches were presented (Tables 1, 2).

In endoscopic surgery group, the recurrence rate was at 9.09% (9 cases out of 99), of which 6 cases got recurrence once, one case each for 3, 4, and 6 times recurrences, and

Table 1 NIP recurrence for different surgical approach

Surgical group	Number of cases	Rate of recurrence
Endoscopic surgical group	99	9.09 % (9/99)
Traditional surgical group	26	23.08 % (6/26)
Combined surgical group	31	12.90 % (4/31)

Statistical comparison for recurrence rate for different surgical approach for NIP: $\chi^2 = 3.73$ ($P > 0.05$)

Table 2 NIP recurrence for different Krouse stage

Krouse stage	Number of cases	Rate of recurrence
T1	26	3.85 % (1/26)
T2	33	12.12 % (4/33)
T3	94	14.89 % (14/94)
T4	3	–
Combined surgical group	31	12.90 % (4/31)

Statistical comparison for recurrence rate for different Krouse stages for NIP: $\chi^2 = 2.74$ ($P > 0.05$)

there were 2 cases for malignancy (2.02 %, 2/99). One patient received postoperative radiotherapy due to its active hyperplasia and had malignancy 3 years later, the other had malignancy 4 years later after the NIP surgery.

In traditional surgery group, the recurrence rate was 23.08 % (6 cases out of 26), of which 4 cases got recurrence once, 2 cases got recurrence twice; 3 cases had malignancy (11.54 %, 3/26), where one patient had squamous cell carcinoma malignancy in part of tissues before visiting our hospital and the other two patients had malignancy 3 and 7 years later, respectively.

In combined approach surgery group, the recurrence rate was 12.12 % (4 cases out of 33), of which 2 cases got recurrence once, 1 case got recurrence twice, and 1 case got recurrence 4 times; 3 cases had malignancy (9.09 %, 3/33), of which 2 patients had surgery treatment due to nasal polyps in other hospital before their visit to our hospital and were confirmed as partial squamous cell carcinoma malignancy, and the other patient got malignancy 3 years later after the surgery.

Those recurrences and malignancies in nasal endoscopic surgery group, traditional surgery group, and the combined approach surgery group were analyzed with Chi-square test, P value was greater than 0.05, indicating that the differences for recurrence rate and malignancy rates in different approaches were not statistically significant; the recurrence for the patients in different stages was also analyzed with Chi-square test, P value was greater than 0.05, which indicated no statistically significant differences in recurrence rates for different Krouse stages.

Discussion

The relationship between the lesion site and the recurrence of NIP

Lesion site is significantly related to recurrence. NIP could involve multiple portions of the nasal cavity or sinus, mostly in the lateral wall of the nasal cavity and middle nasal meatus, especially in ethmoid, the open of maxillary

sinuses and near the medial wall of the maxillary sinus, occasionally in the frontal sinus, sphenoid sinus, nasal septum, and inferior nasal Concha, and few was in intracranial, orbital or pterygopalatine fossa after the bone was damaged. The NIP in nasal septum was rare, in this study, only 4 cases were in this situation. And almost all the NIP was unilateral, and bilateral case was rare, here, 10 cases (6.41 %, 10/156) involved bilateral nasal cavity and paranasal sinuses. In the 156 cases, 43 cases originated at maxillary sinus, 31 cases originated at ostiomeatal complex (OMC) and ethmoid sinus, since it was difficult to distinguish the two sites, the two sites were considered as one category. In addition, there were 8 cases for frontal sinuses, 4 for sphenoid sinus and 66 cases involving both nasal cavity and paranasal sinuses, which was difficult to identify their primary site of tumor. The recurrent rate at different lesion sites was analyzed by the Chi-square test, and the results suggested that the difference was statistically significant. Results from frontal sinus usually has high relapse rate because it is difficult to remove those tumors completely. The nasal endoscopic sinus surgery alone cannot remove the tumors completely as the maxillary sinus base wall significantly is lower than the nasal floor or angulus anteromedialis. In order to remove such tumors completely, the nasal endoscopic sinus surgery must be carried out in conjunction with the Caldwell Luc approach.

The residual base of tumor was considered as the main sites for recurrence, so the base and adjacent mucosa and periosteum should be removed together, that is, the normal mucosa and periosteum around the tumor in the scope of at least 5 mm should be removed completely, which suggested a clear safety boundary. Most of the recurrent sites for NIP were at original sites, especially those at maxillary and ethmoid sinus sites, or recurrent in entirely different sites. In this study, among the 19 patients with recurrence, 7 cases showed recurrence at the original sites, and other 9 cases at different sites. Such phenomenon is relevant to the “multi center origin” of NIP [5], which was one reason for high recurrence for NIP.

The relationship between different stages and the recurrence of NIP

Our study showed there is no correlation between the Krouse staging and NIP recurrence. There was no uniformed clinical classification for NIP at present. Krouse classification standard in 2000 was most commonly used. In this study, according to this standard, there were 26 cases of stage T1, 33 cases of stage T2, 94 cases of stage T3, and 3 cases of stage T4. Mirza [6] reported that the recurrence rates for patients in T3 and T4 stages were higher than those in T1 and T2 stages; however, in our 156 follow-up cases, the recurrence rate was 3.85 % for T1,

12.12 % for T2, 14.89 % for T3, and all the patients in T4 stage showed tumor malignance. By statistical analysis, the *P* value was greater than 0.05, which suggested that the difference of recurrence rates in different Krouse stages was not statistically significant. Although in clinic it seemed that the recurrence rate for the patients in T3 stage was higher, the statistical data cannot support the correlation between the Krouse staging and NIP recurrence; for the patients in T3 and T4 stages, due to the larger tumor range, we usually used joint approach to resect tumors more completely; meanwhile, postoperative radiotherapy was used for the patients in T3 stage who had partial active hyperplasia to reduce recurrence.

The difference between surgical treatment and the recurrence of NIP

Surgical treatment is not related to the recurrence. Surgical excision was the preferred treatment for NIP, the traditional surgical approaches, such as Caldwell Luc surgery, lateral incision of nose, nasal cavity lateral resection, and mid-face lift surgery could provide a larger operation vision, thus aiding in the treatment for large tumors, but such approaches often had bad naked eye resolution and coarser treatment for lesion site, leaving noticeable facial scars. Nasal endoscopy had the advantage of higher resolution, which is especially important for smaller tumor treatment. Moreover, it could provide clear surgical vision to help accurately locate the site of tumors. In this study, 26 cases underwent traditional surgery treatment, with most of them displaying large tumor. Majority of such cases were also carried out in the early years of this study and Caldwell Luc and lateral rhinotomy approaches were used. The slightly higher recurrence rate (at 23.08 % for traditional surgery) may be due to the unclear safety boundary.

For the NIP patients in T1 and T2 stages, nasal endoscopic sinus surgery could achieve very good results. For the 31 patients with NIP in ostiomeatal complex and ethmoid sinus, since their original lesion sites were clear, the safety boundaries for mucosa should be at least 5 mm surrounding the tumor to cut off the mucosa and the periosteum. For the 43 patients with NIP in maxillary sinus, the regular lesion sites were around the maxillary sinus, using the telescopes of 0°, 45°, and 70° to make most of maxillary sinus visible, and then using electric cutting device, the tumors were completely cut off. For the eight cases with tumor basal in maxillary sinus, where the tumor was also hard to be cut off, the combined approach surgery of frontal sinus incision and endoscopic sinus was used. We avoided Lothrop surgery due to the fact that sphenoidal septum was the best barrier to prevent tumor invasion and spreading. For four patients with sphenoid sinus, the back-end of Concha nasalis media was removed to enlarge the

aperture of sphenoidal sinus for postoperative observation, and then made total excision of lesion of mucosa in sphenoid sinus; meanwhile, we paid attention to the connection between tumors and the inner surface of the sphenoid sinus and cautiously avoided any damages to the corresponding anatomical structure. For the patients in T3 or T4 stage who had a wider range of tumors, combined approach surgery approach was used, especially for the patients in T4, because the wide range of lesions was beyond nasal sinus range and endoscopic sinus surgery could not clear all the lesions, the surgical plan was designed based on the lesions situation, such as external approach or cranial nasal combined approach, to completely get rid of lesions [7]. The first surgery should identify the relationship between onset position of tumor and the surrounding tissue; specify the tumor boundary to ensure the 5 mm safety boundary and have a complete resection for all the tumor-related organs and mucosa.

The recurrence rate was the most important indicator for the evaluation of surgical treatment for NIP. Most researchers believed that the main cause of recurrence was incomplete resection of tumors, especially condition of resection of tumors at the first surgery was closely related to the tumor recurrence [8]. In this study, the shortest recurrence time was 1 month after surgery, which was mainly due to the skill of the surgeon and the incomplete resection of tumor, for this case, joint surgical approaches should be used for the complete resection of tumor, and for the other 2 cases, the recurrence occurred 6 months after the surgery, the diagnosis indicated that the recurrence was related to the unclear safety boundary during the surgery cleanup. For the 156 cases, the recurrence rate was 12.18 %, which was consistent with the literature, in which 9.0 % for nasal endoscopy, 23.0 % for traditional surgery, and 12.12 % for combined approach surgery. *P* value was greater than 0.05 by Chi-square test, which suggested that the recurrence rate difference for different surgery approaches was not statistically significant, and nasal endoscopy surgery was not better than traditional surgery statistically, so nasal endoscopy could not totally replace the traditional surgery approaches.

The relationship between other factors and the recurrence of NIP

It was observed in clinic that the onset probability of NIP gradually increased for nasal polyps patients as more recurrence of nasal polyps. In this study, 14 cases had nasal polyps before, in which 10 cases had undergone nasal polyps resection surgery multiple times in other hospital before they were confirmed as NIP, one of them had gone through six nasal polyps resection surgery in other hospital and was confirmed as NIP at last. The increase of the

recurrence of nasal polyps was a dangerous factor for the occurrence of NIP, so in clinical diagnosis, for those who had single side nasal polyps, especially those who had underwent multi-time nasal polyps removal surgery, it is recommended to take general histopathological examination after the removal of nasal polyps to reduce the recurrence rate and misdiagnosis rate. NIP was often associated with sinusitis and nasal polyps, which may be associated with the nasal cavity inflammation caused by the blockage for sinus mucosa by tumor.

The postoperative follow-up was an important measure to reduce the recurrence, follow-up examination should be carried out using nasal endoscopy, the purpose of short-term follow-up was to help epithelial and healing of the cavity, and the purpose of long-term follow-up was to keep the cavity epithelial and timely detect the recurrence or malignancy. In the recent 5 years, antiviral therapy was used for the patients with NIP surgery in our hospital, such as interferon injection, and rinsing nasal cavity with saline. The preliminary result is promising and the follow-up is still carrying on.

The malignancy of NIP

NIP had malignant trends, most of the malignance was squamous cell carcinoma, in which these two kinds of tumors often coexisted [9]. In this study, the malignancy rate was 5.13 %, and all of the 8 malignant cases were squamous cell carcinoma, whose working or living environment was specific carcinogenic factors free and also without any family history. 3 cases had partial malignancy before the first visiting and other 5 cases had malignancy 3 years (2 cases), 4 years (1 case), and 7 years (2 cases) after nasal sinus surgery, respectively. Malignant transformation associated with their biological characteristics, regardless the number of operation. Literature reported [10] that there was still no guarantee for free of tumor malignancy even with thorough removal of tumor. The patients with malignancy in this study group underwent radiotherapy after the surgery, only 3 cases experienced no recurrence during 5-year follow-up, and other 5 cases showed rapid progress, 3 cases died for intracranial metastases, 1 case died for lung metastasis, and 1 case died for nasal hemorrhage and systemic cachexia. Once tumor malignancy was confirmed, surgery and radiotherapy should be taken [11], the follow-up after surgery should be long-term even life-long, to realize early detection for early treatment. Malignancy should be considered when the following circumstances occurred: rapid growth or faster violations to adjacent tissues after the complete resection and nasal bleeding.

Besides surgical resection, radiotherapy is also an important means of treatment, for which there are still some disagreements. Gomez [12] suggested that radiotherapy could be used for those whose tumor cannot be completely resected, tumor recurrence multiple times, the inverted papilloma combined with malignancy, or who were not suitable for surgery. In the 19 recurrence cases, 3 cases had radiotherapy due to the active tumor proliferation, one of them had malignance 3 years after surgery, and the other 2 cases were without tumor recurrence and malignance during the 5 years of follow-up. Therefore, radiotherapy is currently used only as a secondary or palliative means.

Conflict of interest The authors have no conflicts of interest to declare. We have no financial relationship with the organization that sponsored the research.

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