Association of Krouse Classification for Sinonasal Inverted Papilloma With Recurrence
A Systematic Review and Meta-analysis

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IMPORTANCE The risk factors for the recurrence of sinonasal inverted papilloma are still unclear.

OBJECTIVE To investigate the potential association between the Krouse classification and the recurrence rates of sinonasal inverted papilloma.

DATA SOURCES The EMBASE and MEDLINE databases were searched for the period January 1, 1964, through September 30, 2016, using the following search strategy: (paranasal sinuses [Medical Subject Headings (MeSH) terms] OR sinonasal [all fields]) AND (inverted papilloma [MeSH terms] OR (inverted [all fields] AND papilloma [all fields]).

STUDY SELECTION The inclusion criteria were (1) studies including sinonasal inverted papilloma only and no other forms of papillomas, such as oncocytic papilloma; (2) minimum follow-up of 1 year after the surgery; and (3) clear report of cases (recurrence) and controls according to the Krouse classification system or deducible from the full-text article. Literature search was performed by 2 reviewers. Of the 625 articles retrieved in the literature, 97 full-text articles were reviewed. Observational cohort studies or randomized controlled trials were included, and the following variables were extracted from full-text articles: authors of the study, publication year, follow-up data, and number of cases (recurrence) and controls (no recurrence) in each of the 4 stages of the Krouse classification system.

DATA EXTRACTION AND SYNTHESIS The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed. Odds ratios (ORs) and 95% CIs were estimated, and data of included studies were pooled using a random-effects model.

MAIN OUTCOMES AND MEASURES The main outcome was recurrence after surgical removal of sinonasal inverted papilloma according to each stage of the Krouse classification system.

RESULTS Thirteen studies comprising 1787 patients were analyzed. A significant increased risk of recurrence (51%) was highlighted for Krouse stage T3 disease when compared with stage T2 (pooled OR, 1.51; 95% CI, 1.09-2.09). No significant difference in risk of recurrence was found between Krouse stages T1 and T2 disease (pooled OR, 1.14; 95% CI, 0.63-2.04) or between stages T3 and T4 (pooled OR, 1.27; 95% CI, 0.72-2.26).

CONCLUSIONS AND RELEVANCE Inverted papillomas classified as stage T3 according to the Krouse classification system presented a 51% higher likelihood of recurrence. Head and neck surgeons must be aware of this higher likelihood of recurrence when planning and performing surgery for sinonasal inverted papilloma.
In this systematic review and meta-analysis of 13 studies comprising 1787 unique patients with sinonasal inverted papillomas, stage T3 disease was at significantly higher risk of recurrence when compared with stage T2. No differences in recurrence rates were found between stages T1 and T2 disease or between stages T3 and T4.

**Key Points**

**Question** Is the Krouse classification for sinonasal inverted papilloma associated with recurrence?

**Findings** In this systematic review and meta-analysis of 13 studies comprising 1787 unique patients with sinonasal inverted papillomas, stage T3 disease was at significantly higher risk of recurrence when compared with stage T2. No differences in recurrence rates were found between stages T1 and T2 disease or between stages T3 and T4.

**Meaning** Head and neck surgeons must be aware of this higher likelihood of recurrence for stage T3 when planning and performing the surgery for an inverted papilloma.

**Statistical Analysis**

The outcome of this meta-analysis was recurrence after surgery. Because the Krouse classification system is subdivided into 4 stages, 3 primary analyses were performed: (1) recurrence rate after surgery for stage T2 disease when compared with stage T1, (2) recurrence rate for stage T3 disease when compared with stage T2, and (3) recurrence rate for stage T4 disease when compared with stage T3. Hence, we evaluated the likelihood of presenting a recurrence for participants classified in a Krouse stage in comparison with the immediately lower stage. We performed the 3 analyses and not global testing followed by pairwise analyses to avoid multiple comparisons. We estimated the odds ratio (OR) and 95% CI for each study and used a random-effects model to pool estimates for each of the 3 analyses. The I² statistic was used to assess for potential heterogeneity between studies, and a value of 50% or greater was considered to identify high heterogeneity. We performed an influence analysis in which pooled estimates were calculated to omit one study at a time. All statistical analyses were performed with R software, version 3.1.3 (R Foundation for Statistical Computing). The meta and metafor packages were used for the meta-analysis.

**Additional Analyses**

Risk of publication bias was evaluated using funnel plots, which show the estimate of the influence of each study against its SE. A Harbord test was used to assess any potential asymmetry in funnel plots. Because adding new studies to the existing evidence could lead to new conclusions, evaluating the contribution of a new study to the results is important. Thus, we used extended funnel plots to assess this potential impact. Extended funnel plots provide...
Figure 1. Flowchart of the Study Selection

| Articles identified in EMBASE and MEDLINE | 1283 |
| Articles retrieved after duplicates removed | 625 |
| Articles screened | 625 |
| Articles excluded after title and abstract screening | 528 |
| Full-text articles assessed for eligibility | 97 |
| Full-text articles excluded | 84 |
| Insufficient follow-up | 48 |
| Insufficient data | 36 |
| Articles included in qualitative and quantitative meta-analysis | 13 |

Results

Study Selection
As presented in Figure 1, the literature search retrieved 625 articles after duplicate publications were removed, and 97 full-text articles were assessed after irrelevant reports were excluded. We reviewed the bibliography of these articles, but no additional article was included. Overall, 13 articles complied with the inclusion criteria and were therefore included in the meta-analysis.3,6,7,15-24

Study Characteristics
The 13 included studies comprised 1787 unique patients. Characteristics of studies are summarized in the Table along with the total number of patients and the number of patients with disease at each Krouse stage. The minimum follow-up time was between 12 and 36 months, and the maximum follow-up time ranged from 3.5 to 16 years (although this time was not specified in 8 studies). Overall, 196 patients (11.0%) presented with a SIP classified as stage T1, 695 (38.9%) as stage T2, 800 (44.8%) as stage T3, and 96 (5.4%) as stage T4. There were 13 cases of recurrence for stage T1, 75 for stage T2, 124 for stage T3, and 17 for stage T4. In stage T4, carcinomas were diagnosed in 2% to 7% of patients depending on the study considered. Overall, carcinomas were present in 68 patients (3.8%).

Meta-analysis Results
Results of the meta-analysis are presented in Figure 2. No significant difference in risk of recurrence was found between stages T1 and T2 disease as presented in Figure 2A, with a pooled OR of 1.14 (95% CI, 0.63-2.04). A significantly increased risk of recurrence was highlighted for Krouse stage T3 disease compared with stage T2, with a pooled OR of 1.51 (95% CI, 1.09-2.09; Figure 2B). Finally, no significant difference in risk of recurrence was found for Krouse stage T4 disease compared with stage T3, with a pooled OR of 1.27 (95% CI, 0.72-2.26; Figure 2C). In all of these analyses, no between-studies heterogeneity was found ($I^2 = 0\%$).

Influence Analysis
As presented in eFigure 1 in the Supplement, the pooled OR and 95% CI would not have changed by omitting the studies one at a time. For comparison of stages T1 and T2 disease and stages T3 and T4, omitting the studies one at a time did not change the pooled estimate because no significant results were found. For comparison of stages T2 and T3 disease, the pooled estimate stayed significant regardless of the omitted study.

Publication Bias
Publication bias was investigated using funnel plots (Figure 3). Visual inspection of funnel plots did not reveal any obvious asymmetry for any of the 3 analyses. In addition, results of the Harbord test were not significant in all cases, showing no significant publication bias (stage T1 vs stage T2 disease, $P = .16$; stage T2 vs stage T3, $P = .14$; and stage T3 vs stage T4, $P = .64$).

Extended Funnel Plot
We carried out additional analyses using extended funnel plots to assess the potential influence of new studies on the results of our meta-analysis. For the 3 analyses, it appears unlikely that a new study would change our results (eFigure 2 in the Supplement). A new study added to the current evidence would not influence the absence of difference in recurrence rate between stages T1 and T2 disease and between stages T3 and T4 as well as the significant difference in recurrence rate between stages T2 and T3 disease.

Discussion
A 51% increased risk of recurrence for SIP classified as T3 disease was observed when compared with stage T2. However, no significant difference in risk of recurrence was found between stages T1 and T2 disease or between stages T3 and T4. Contradictory results have been reported regarding the ability of the Krouse classification system to estimate recurrence. Some studies highlighted an association between recurrence and the Krouse classification,6 but some others did not.3 Only 1 study attempted to evaluate the risk of recurrence according to the Krouse classification system and found no significant difference in recurrence rate at each stage of the classification.6 However, that study was a secondary analysis of a meta-analysis; thus, Kim and Kwon retrieved only 4
Another drawback of stage T4 is that it includes carcinoma largely differs and the risk or recurrence is likely different sites included in stage T3 do not represent the same difficulty in achieving a complete removal. For instance, a tumor involving the lateral part of the frontal sinus is more challenging to remove than a tumor limited to the medial part of the posterior wall of the maxillary sinus. Several studies reported an association between the involvement of the frontal sinus and the recurrence rate. These different locations included in the same stage (T3) may result in varying recurrence rates; thus, stage T3 likely gathers tumors with a different prognosis.

In addition, our results indicate that no difference in risk of recurrence exists whether the tumor is classified as stage T1 disease (involving only the nasal cavity) or stage T2 (involving the ethmoid sinus, the medial maxillary wall, or the ostiomeatal complex). Similarly, no difference in recurrence rate was found between stages T3 and T4 disease. Stage T4 gathers tumors extending beyond paranasal sinuses and tumors presenting with a synchronous carcinoma. However, stage T4 may be inappropriate and misleading. Synchronous carcinomas are included in stage T4 regardless of the extension of the tumor or whether it is limited to the nasal cavity or extended to the skull base, for instance. In these situations, the type of surgery largely differs and the risk or recurrence is likely different. Another drawback of stage T4 is that it includes carcinoma, regardless of the type of carcinoma. No differences exist between a focal in situ carcinoma (potentially representing an unexpected discovery on the postoperative histological analysis) and an invasive squamous cell carcinoma. If the diagnosis of a synchronous invasive squamous cell carcinoma is known before the surgery, it will influence the surgical procedure—an open approach is recommended by several authors. Other factors, such as drilling the underlying bone or human papillomavirus infection, are still debated as potential risk factors for recurrence. In addition, the diagnosis will lead to a postoperative irradiation therapy, whereas a simple surveillance is generally required for incidental findings of focal in situ carcinomas.

This meta-analysis focused on the Krouse classification system as a potential risk factor for recurrence. Obviously, other factors are associated with recurrence. For instance, in a recent meta-analysis, an endoscopic approach was associated with a 44% reduced risk of recurrence when compared with an open approach. Other factors, such as drilling the underlying bone or human papillomavirus infection, are still debated as potential risk factors for recurrence. Future systematic reviews and meta-analyses may be helpful to clarify the potential role of these factors on recurrence rate.

**Limitations**
Some limitations should be considered when interpreting our results. As with any meta-analysis, ours may be biased in part because of publication bias. Nevertheless, we assessed publication bias using funnel plots and the Harbord test, and none of our 3 analyses showed a significant small-study effect. In addition, adding results of future studies could modify our results. Thus, to explore for the potential impact of new studies, we used extended funnel plots. Inspecting these funnel plots revealed that an updated result of our meta-analysis would be unlikely to differ from the results presented here.

### Table. Characteristics of Included Patients and Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country of Study</th>
<th>Inclusion Years</th>
<th>Patients in Study, No.</th>
<th>Patients With a SIP According to Krouse Classification Stage, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarletta et al.</td>
<td>Italy</td>
<td>2014</td>
<td>110</td>
<td>8 45 56 1</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>South Korea</td>
<td>2012</td>
<td>578</td>
<td>42 240 272 24</td>
</tr>
<tr>
<td>Lombardi et al.</td>
<td>Italy</td>
<td>2011</td>
<td>212</td>
<td>16 78 104 14</td>
</tr>
<tr>
<td>Gras-Cabrerizo et al.</td>
<td>Spain</td>
<td>2010</td>
<td>79</td>
<td>8 31 35 5</td>
</tr>
<tr>
<td>Durdu et al.</td>
<td>Turkey</td>
<td>2009</td>
<td>56</td>
<td>6 16 25 9</td>
</tr>
<tr>
<td>Mackie et al.</td>
<td>France</td>
<td>2004</td>
<td>55</td>
<td>8 26 18 3</td>
</tr>
<tr>
<td>Woodworth et al.</td>
<td>United States</td>
<td>2007</td>
<td>114</td>
<td>12 33 53 16</td>
</tr>
<tr>
<td>Minovi et al.</td>
<td>Germany</td>
<td>2006</td>
<td>87</td>
<td>11 37 37 2</td>
</tr>
<tr>
<td>Wolfe et al.</td>
<td>United States</td>
<td>2004</td>
<td>50</td>
<td>8 12 25 5</td>
</tr>
<tr>
<td>Pasquini et al.</td>
<td>Italy</td>
<td>2004</td>
<td>86</td>
<td>9 55 17 5</td>
</tr>
<tr>
<td>Xiao-Ting et al.</td>
<td>China</td>
<td>2003</td>
<td>156</td>
<td>26 33 94 3</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>South Korea</td>
<td>2008</td>
<td>136</td>
<td>23 71 41 1</td>
</tr>
<tr>
<td>Sautter et al.</td>
<td>United States</td>
<td>2007</td>
<td>68</td>
<td>19 18 23 8</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>1787</td>
<td>196 695 800 96</td>
</tr>
</tbody>
</table>

Abbreviation: SIP, sinonasal inverted papilloma.
Our findings could have clinical implications for the management of SIP. Head and neck surgeons must be aware that SIP classified as Krouse stage T3 is at higher risk of recurrence than SIP classified as stage T2. This result must be considered when planning the surgery. In addition, surgeons must be even more thorough in removing such tumors given that several
authors suggest that recurrence is largely due to an incomplete initial removal.\textsuperscript{3,15,30,31} Hence, for tumors classified as stage T3 especially, given that they present a higher risk of recurrence, evaluating the association of some surgical techniques with lowered recurrence rate, such as drilling the underlying bone as suggested by some authors, is important.\textsuperscript{15,19,27}

Conclusions

This systematic review and meta-analysis revealed a 51% increased risk of recurrence for SIP classified as Krouse stage T3 disease when compared with stage T2, but no differences in
recurrence rate were found between stages T1 and T2 disease or between stages T3 and T4. Head and neck surgeons must be aware of this higher likelihood of recurrence for stage T3 when planning and performing SIP surgery.


