Regional Recurrence of Squamous Cell Carcinoma of the Nasal Cavity

A Systematic Review and Meta-analysis

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Objective: To demonstrate whether the regional recurrence (RR) of squamous cell carcinoma (SCC) of the nasal cavity is higher than previously suspected.

Data Sources: Original articles, including a previously published series from our institution, were identified from systematic searches of the MEDLINE database.

Study Selection: Studies that analyzed tumors other than SCC or tumors from sites other than the nasal cavity were excluded. Studies that did not report an RR were also excluded.

Data Extraction: Studies identified by the literature search were reviewed by a single reviewer (W.C.S.), and studies not excluded were reviewed for data extraction by 2 reviewers (W.C.S. and M.Y.C.).

Data Synthesis: From the 23 studies reviewed, the average weighted percentage RR for SCC of the nasal cavity was 18.1% (95% confidence interval, 13.4%-22.8%).

Conclusions: Currently, few authors advocate elective treatment of the neck in patients with high-risk SCC of the nasal cavity. The results of this systematic review and meta-analysis demonstrate that the RR of this entity may be higher than previously suspected. Because many studies included other histopathologies or analyzed recurrence data from tumors of multiple subsites, a true RR for SCC of the nasal cavity has not been firmly established. Now that a uniform staging system exists for nasal cavity cancers, better prospective analysis of these tumors will be available. The authors suggest that the risk of RR of certain high-risk SCCs of the nasal cavity to the lymph nodes, including the perifacial and upper cervical lymphatics, may approach the frequently cited 20% risk suggestive of consideration for elective regional therapy.

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Cancer of the nasal cavity is difficult to study because of its low occurrence rate, its presentation in various subsites of the nose, and the existence of multiple tumor histopathologies. These cancers represent 0.5% of all malignant neoplasms, 3% of head and neck cancers, and 30% of all malignant neoplasms of the nose and paranasal sinuses. Bhattacharyya reviewed the Surveillance, Epidemiology, and End Results database and demonstrated that approximately 50% of all cancers of the nasal cavity are squamous cell carcinoma (SCC). This figure is consistent with other reports of the pathologic examination of this tumor. Tumors such as adenocarcinoma, melanoma, and adenoid cystic carcinoma constitute the remaining 50% and, in many reviews of nasal cancer, all histopathologies are analyzed together. Treatment options for nasal cavity cancer include surgery, radiation therapy, or a combination of the two, and a recent large analysis reported 5-year survival and local control rates of 40% and 59%, respectively.

A historical lack of a unified staging system has hindered efforts to compare and contrast disease progression and treatment protocols for malignant neoplasms of the nasal cavity. Recently, cancer of the nasal cavity has been added to the American Joint Committee on Cancer staging system (released for use in January 2003). Under the section for tumors of the paranasal sinuses, nasal cavity and ethmoid sinus tumors are classified separately. The nasal cavity is further divided into 4 subsites: septum, floor, lateral walls, and vestibule. The ethmoid sinus is divided into 2 subsites: right and left. To date, no reports have been published that use this new staging system.

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In 2000, Fornelli et al published a review of 32 patients with SCC of the nasal cavity was 18.1% (95% confidence interval, 13.4%-22.8%).
cavity and reported a 5-year disease-free survival of 42% and a 5-year overall survival of 50%. Primary treatment among their 32 patients included surgery (n=15), external beam radiation (n=9), and a combination of surgery with postoperative irradiation (n=8). In that study, despite the fact that all patients presented without neck disease (stage N0), 13 of the 32 patients (41%) developed regional recurrence (RR) and most of the patients with RR (11 [85%]) died of disease. Six patients in that study elected to undergo prophylactic irradiation (PI) of the cervical lymph nodes and never developed RR. In contrast, 50% of those who did not undergo elective treatment of the neck (13 patients) developed RR of their cancer.8

This 50% RR described by Fornelli et al is higher than the typical 10% to 20% reported in the literature. Because of this discrepancy in rates of RR, the authors of this article set out to conduct a systematic review of the literature that would identify primary SCC of the nasal cavity and the reported RR of these tumors. This report presents the findings from a meta-analysis of the RR and survival for SCC of the nasal cavity.

A systematic review of the literature was performed on November 18, 2005, in the following manner. First, the Ovid search engine was used to query the MEDLINE database. The terms nose.mp, squamous cell carcinoma.mp, and recurrence.mp were combined with AND searches, initially resulting in 79 articles. The titles and abstracts of the articles were carefully reviewed, and those that pertained to reconstruction, surgical technique, or general head and neck tumors were excluded. Case reports, reports on non-human studies, and non-English reports were also excluded.

Next, a similar search was performed using the PubMed search engine to query the MEDLINE database. The terms nasal cavity cancer and squamous cell carcinoma were applied, and the search initially produced 83 articles. The same exclusion criteria were applied.

The results from these 2 search strategies were combined to yield 44 unique papers that were then evaluated to identify studies that had measured the RR and the presence of lymph node metastases at presentation for patients with a diagnosis of SCC of the nasal cavity. References of the studies were reviewed for additional potentially relevant studies. Studies reporting data on nasal cancers other than SCC and studies reporting data on tumors outside the nasal cavity (eg, in the maxillary sinus) were also excluded, resulting in a total of 23 articles appropriate for this study.5,8-29 Studies identified by the literature search were reviewed by a single reviewer (W.C.S.), and studies not excluded were reviewed for data extraction by 2 reviewers (W.C.S. and M.Y.C.).

The pooled RR was calculated as the weighted average of RR from the individual studies that met the inclusion criteria. In addition, the pooled 5-year survival rate was calculated as the weighted average of data from the studies that reported survival rates. The weight for each calculation was the number of patients in the original study.

For studies that reported separate RR for patients who did and did not receive PI, we calculated the odds ratio of RR with PI. The statistical significance of each odds ratio was tested with the Fisher exact procedure.30

To estimate the relative risk of RR with PI, individual odds ratios were used in a meta-analysis conducted with the non-model-based Cochran-Mantel-Haenszel (CMH) and the model-based logistic regression approaches. These 2 approaches are often used in meta-analyses that involve binary outcomes (eg, recurrence vs nonrecurrence) because the approaches estimate the pooled odds ratio and test the homogeneity of effect from the individual studies.31 The logistic regression approach also allows inclusion of covariates in the model and does not restrict the sample size. In the CMH approach, the analysis created a 3-way contingency table stratified by study. The homogeneity of effect for the CMH approach was determined with the Breslow-Day test, and that for the logistic regression approach was determined with the Wald test. The FREQ procedure in SAS statistical software32 was used to estimate the RR, odds ratios, 95% confidence intervals (CIs), Fisher exact procedure, and CMH procedure. The LOGISTIC procedure in SAS32 was used for logistic regression. All statistical tests were 2-sided, with P < .05.

Our literature search identified 23 original studies5,8-29 published between 1974 and 2002 that reported on the treatment of SCC of the nasal cavity. The mean age of the 927 patients in these studies was 63.1 years and 73.4% were male. The mean patient follow-up period was 4.4 years (range, 2-11 years) (Table 2).
ies\textsuperscript{5,8,13-17,19,20} reported data separately for patients who did and did not receive PI. The odds ratios from 4 of these 5 studies was less than 1.0, which suggests that PI reduced the risk of RR; none of the odds ratios in these individual studies, however, was statistically significant at the \( P < .05 \) level (Table 3). The range of the odds ratios for these 5 studies was 0.08 (Fornelli et al\textsuperscript{8}) to 1.57 (Levandag and Pomp\textsuperscript{17}). In 4 of the 5 studies analyzed, however, no patient who received PI developed RR.\textsuperscript{5,8,13,18}

In the meta-analysis, both the CMH test and the logistic regression test were used to calculate a pooled odds ratio (Table 3). The CMH approach produced a pooled odds ratio of 0.18 (95% CI, 0.04-0.77; \( P = .009 \)). The Breslow-Day test for homogeneity of effect was not statistically significant (\( P = .08 \)), suggesting that the results of the individual studies were homogeneous. Using the logistic regression approach, the pooled odds ratio was 0.16 (95% CI, 0.03-0.72; \( P = .02 \)). The Wald test for homogeneity was statistically significant (\( P = .005 \)), suggesting that the results of the individual studies were not homogeneous.

**Table 3. Odds Ratios of RR for Patients Receiving PI of the Neck for SCC of the Nasal Cavity\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Source</th>
<th>Odds Ratio (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ang et al,\textsuperscript{5} 1992</td>
<td>0.20 (0.01-5.03)</td>
<td>.47\textsuperscript{b}</td>
</tr>
<tr>
<td>Chobe et al,\textsuperscript{18} 1988</td>
<td>0.11 (0.06-2.26)</td>
<td>.11\textsuperscript{b}</td>
</tr>
<tr>
<td>Fornelli et al,\textsuperscript{8} 2000</td>
<td>0.08 (0.00-1.51)</td>
<td>.06\textsuperscript{b}</td>
</tr>
<tr>
<td>Levandag and Pomp,\textsuperscript{17} 1990</td>
<td>1.57 (0.21-11.90)</td>
<td>&lt;.001\textsuperscript{b}</td>
</tr>
<tr>
<td>McCollough et al,\textsuperscript{15} 1993</td>
<td>0.58 (0.03-12.29)</td>
<td>&lt;.001\textsuperscript{b}</td>
</tr>
<tr>
<td>Pooled analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cochran-Mantel-Haenszel test</td>
<td>0.18 (0.04-0.77)</td>
<td>.009</td>
</tr>
<tr>
<td>Logistic regression</td>
<td>0.16 (0.03-0.72)</td>
<td>.02</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The studies listed reported separate RRs for patients receiving and not receiving PI of the neck for SCC of the nasal cavity.

The weighted average RR for SCC of the nasal cavity from the 23 studies was 18.1% (95% CI, 13.4%-22.8%; range, 0% [Schafer and Hill\textsuperscript{28}] to 50% [Fornelli et al\textsuperscript{8}]). The weighted 5-year disease-free survival for the 9 studies\textsuperscript{5,8,12,13,15-17,19,20} that reported this measure was 59.7% (95% CI, 58.2%-61.3%). The weighted 5-year overall survival for the 13 studies\textsuperscript{5,8,9,11-13,17,19,21} that reported this outcome was 62.7% (95% CI, 61.9%-63.5%).

Patients in 7 of the 23 studies were treated with PI of the regional lymphatics,\textsuperscript{5,8,11-15,17,19,21} but only 5 studi-
eral, most of the literature concerning head and neck cancer of the 2 approaches produced slightly different results. In general with either neck dissection or irradiation. In patients with these tumors are treated prophylactically with either neck dissection or irradiation. Tumors in regions such as the supraglottis are accepted to have a high rate of regional metastasis, and N0 necks in patients with these tumors are treated prophylactically with either neck dissection or irradiation. In conclusion, our meta-analysis yielded an 18.1% RR in patients with intranasal SCC. In addition, PI may decrease the incidence of RR. Although further study is needed, we suggest that patients with intranasal SCCs that demonstrate high-risk characteristics be considered for prophylactic treatment of the neck with either surgery or radiation therapy.

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References 5, 9, 10, 12, 13, 15-18, 22, 24-27, 29, 33-35.
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Author Contributions: Drs Scurry, Goldenberg, and Fedok had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Scurry, Goldenberg, Chee, Lengerich, and Fedok. Acquisition of data: Scurry, Chee, and Fedok. Analysis and interpretation of data: Scurry, Goldenberg, Lengerich, Liu, and Fedok. Drafting of the manuscript: Scurry, Goldenberg, Chee, Lengerich, and Fedok. Critical revision of the manuscript for important intellectual content: Scurry, Lengerich, Liu, and Fedok. Statistical analysis: Scurry, Lengerich, and Liu. Administrative, technical, and material support: Fedok.

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Additional Information: Dr Liu completed his work on this project while at the Division of Epidemiology, Department of Health Evaluation Sciences, Penn State University.

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