Predictive Factors for Neoplasia and Malignancy in a Neck Mass

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Objective: To determine clinical factors that are able to predict the likelihood of neoplasia and malignancy of cervical masses.

Design: Retrospective review of case series. Data were collected for age, sex, a history of alcohol and tobacco use, mass location, number, bilaterality, size, and duration. Logistic regression was performed to determine which clinical variables were significant in a prediction model for neoplasia and malignancy in a cervical mass.

Setting: An academic general otolaryngology practice.

Results: Review of 160 open neck biopsies yielded 95 complete cases for regression analysis. Thirty cases of neoplasia (31.6%) and 12 cases of malignancy (12.6%) were noted. For the prediction of neoplasia, logistic regression analysis identified patient age, duration, and size of the mass to be statistically significant. The overall model for neoplasia had positive and negative predictive values of 63.6% and 78.1%, respectively, and an overall accuracy of 74.7%. For the prediction of malignancy, only age was found to be significant. The model for malignancy failed to show any classification utility beyond that of clinical judgment.

Conclusions: On the basis of clinical factors, a logistic regression model can distinguish patients who have a low chance for neoplasia in a neck mass, and thereby help avoid unnecessary biopsy. It is not as useful in selecting patients for early biopsy. The strict prediction of malignancy on the basis of clinical variables alone is difficult.


Otolaryngologists are frequently consulted to evaluate, and often perform biopsies of, masses within the neck. The patient may come to the otolaryngologist with a new-onset neck mass and no previous evaluation or may have had extensive evaluation including systemic workup and imaging studies. Regardless, the otolaryngologist is usually expected to finalize the diagnosis and establish the treatment plan. Making the final diagnosis often requires tissue for cytological or histological examination. Fine needle aspiration (FNA) has assumed a central role in the evaluation of neck masses, approaching 96% accuracy in the diagnosis of squamous cell carcinoma (SCCA) metastatic to the neck. However, when FNA does not yield a diagnosis of SCCA or other cytologically typical malignant neoplasm, histological diagnosis with formal excision of the mass is often required. This results in the excision of a substantial number of benign or “reactive” nodes and neck masses in an effort to exclude neoplasia or malignancy. Therefore, a retrospective analysis of open neck biopsies was conducted to determine potential preoperative factors that might predict the benign or neoplastic nature of a neck mass. These factors might then be used to select appropriate patients for observation vs open biopsy.

RESULTS

A total of 160 cases were identified for review for the 4-year period from January 1, 1994, through December 31, 1997. On review, 44 cases were excluded because of a history of previous or synchronous head and neck malignant neoplasm, or incorrect diagnosis. Twenty-one of the remaining 116 cases were excluded because of missing entries among independent variables. The remaining 95 complete cases underwent regression analysis. Descriptive clinical information for the series is summarized in Table 1. On final pathology, 65 lesions (68.4%) were reactive or nonneoplastic, and 30 lesions (31.6%) were neoplastic. Of the neoplasms, 18 (18.9%) were benign, and the
PATIENTS AND METHODS

A retrospective series of patients who underwent excision of a neck mass, isolated cervical lymphadenectomy, or open neck biopsy was identified by searching the procedural database of an academic general otolaryngology practice during a 4-year period. The study protocol was approved by the Committee on Clinical Investigations. The medical records, pathology reports, and radiological studies were reviewed and a database was constructed. Information regarding age, sex, smoking history, alcohol use, duration, location, bilateral- ity, number of masses, size of the neck mass, the FNA results, and final pathology results were tabulated. Size was recorded as the greatest clinical dimension of the largest (when more than one mass was present) neck mass. The location of the mass was classified as anterior triangle (regions II and VI), posterior triangle (region V), or submandibular region (region I). The characteristics of the mass were based on physical examination. Information from radiological studies was not included because of variabilities in their utilization and in the types of studies ordered. Thyroid and parotid lesions were excluded. Patients with a history of malignant neoplasm of the head and neck, or with inadequate documentation of the initial appearance, operation, or pathological results, were excluded from the analysis. The data were then examined with the SPSS statistical package (SPSS Inc, Chicago, Ill). Logistic regression was performed to determine the ability of the independent clinical variables to predict the outcome variables of whether the cervical mass was (1) neoplastic or not and (2) malignant or benign. The variables listed in Table 1 were included in the regression analysis primarily because of their clinical relevance, even if their univariate statistical significance was limited.2 The regression analysis was performed with forward stepwise conditional inclusion of independent variables in the model, with entry and exit criteria for predictor variables set at $P = .05$.2 The results of the review, descriptive statistics, and the regression analysis model are presented.

remaining 12 lesions (12.6%) were malignant. The relative proportions are displayed in Figure 1. The frequencies of neoplastic and malignant lesions in each location are depicted in Figure 2. Univariate statistics for the influence of the independent variables on the pathological outcomes of the neck mass are also given in Table 1. The final pathology results for the biopsy specimens are presented in Table 2. Results of FNA were available for 53 (55.8%) of the cases and suggested a neoplastic process in 21 (39.6%) of 53 cases.

The logistic regression model for the prediction of neoplasia was constructed with the 7 variables indicated in Table 1. The variable bilaterality was omitted because of a zero cell (no patients with bilateral neck masses had either a neoplastic or a malignant mass). With respect to the prediction of neoplasia, the logistic regression analysis identified patient age, duration, and size of the mass to be statistically significant predictors of neoplasia, along with the presence of a constant ($P < .05$ for significance of log-log rank improvement). The probability equation was determined to be as follows: probability (neoplasia) = $1/(1 + e ^{-z})$, where $z = -3.79 + 0.0347 \times \text{age in years} + 0.0072 \times \text{duration in weeks} + 0.405 \times \text{size in centimeters}$. The estimated odds ratios for the predictors age, duration, and size were an increase in odds of 1.42 (95% confidence interval [CI], 1.05-1.90) for each 10-year increase in age, 1.08 (95% CI, 0.99-1.17) for each 10-week increase in duration, and 1.50 (95% CI, 1.11-2.02) for each centimeter increase in size. The other independent variables (sex, a history of smoking, location, and number of masses) were not found to be statistically significant in predicting neoplasia. In addition, an interaction term for size and duration was not found to be significant. The accuracy, positive predictive value, and negative predictive value of the model for neoplasia are listed in Table 3 for a probability cutpoint of 0.5 (ie, lesions whose predicted probabilities are greater than 0.5 are classified as neoplastic). Adoption of a lower probability cutpoint of 0.25 (ie, lesions whose predicted probabilities of neoplasia are greater than 0.25 are classified as neoplastic) resulted in improvement in classification with respect to the model sensitivity, at the expense of specificity and overall accuracy (Table 4).

Logistic regression analysis for malignancy of the neck mass found only patient age and a constant to be significant ($P < .05$ for significance of log-log rank model improvement). The probability equation was as follows:

### Table 1. Descriptive Statistics for Independent Variables

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Finding</th>
<th>Univariate Significance* for Neoplasia</th>
<th>Univariate Significance* for Malignant Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (30.5)</td>
<td>.38</td>
<td>.82</td>
</tr>
<tr>
<td>Female</td>
<td>66 (69.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smoked‡</td>
<td>29 (30.5)</td>
<td>.58</td>
<td>.66</td>
</tr>
<tr>
<td>Never smoked</td>
<td>66 (69.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking at time of biopsy</td>
<td>16 (16.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy alcohol use</td>
<td>4 (4.2)</td>
<td>.14</td>
<td>.76</td>
</tr>
<tr>
<td>Location†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regions II-IV and VI</td>
<td>52 (54.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region V</td>
<td>10 (10.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region I</td>
<td>33 (34.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral masses</td>
<td>14 (14.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For categorical variables, significance corresponds to significance of Pearson χ² statistics; for continuous variables, to significance of Student’s t test.
†Variable analyzed in the regression model.

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probability (malignancy) = 1/(1 + e^{-z}), where z = −4.38 + 0.0510 \times \text{(age in years)}.

The estimated odds ratio increased by 1.66 (95% CI, 1.15-2.41) times for each 10-year increase in age. The other independent variables (sex, a history of smoking, size, location, duration, and number of masses) were not found to be statistically significant in predicting malignancy of the mass. The accuracy, positive predictive value, and negative predictive value of the prediction model for malignancy are demonstrated in Table 5. A clinically useful lower probability cutpoint could not be established for the outcome of malignancy.

**COMMENT**

Determining the neoplastic or benign nature of a cervical mass remains a complex and sometimes nebulous problem for the otolaryngologist. Several heuristics are often used in the evaluation and management of the neck mass. These include consideration of the patient’s risk factors for malignancy, the size and duration of the mass, as well as associated systemic and local symptoms. Use of these criteria to determine which neck masses require biopsy is often difficult. For example, one might elect to observe a neck mass, with the thinking that if it
does not enlarge, it is not likely to be malignant. However, a mass that persists, rather than regresses, is probably more likely to be neoplastic than simply infectious or reactive. This has led others to recommend various clinical criteria necessitating biopsy. Few will take issue with planned biopsy (and endoscopy) for a large neck mass that has been present for more than 6 weeks in a patient with a heavy smoking history. However, when these classic risk factors are not present, the management is debatable. Developing a model that would aid in predicting the likelihoods of neoplasia and malignancy could then be used to select patients for observation vs open biopsy. This would then hopefully spare appropriate patients an unnecessary biopsy, and hasten the biopsy and histological diagnosis in patients likely to have neoplasia.

The overall rates of neoplasia (31.6%) and malignancy (12.6%) in this series were somewhat lower than expected, given the largely adult population. Other studies have noted neoplasia and malignancy rates of 53% to 80% for neck masses in adults when thyroid disease is excluded. In contrast, in a descriptive series of 288 patients with neck masses, 37.9% were found to have cervical adenopathy. Some of this discrepancy likely stems from the fact that we routinely use FNA early in the diagnosis of cervical masses, especially in the adult population. The accuracy of the FNA in diagnosing SCCA tends to limit cases requiring open biopsy, given that cases with a positive FNA for SCCA will undergo panendoscopy and planned neck dissection, rather than excisional biopsy of the mass. Therefore, a selection bias away from malignancy is encountered. Consequently, these results are best interpreted in the setting of a patient with a previous FNA that was negative for SCCA in whom the regression model was then applied. Lymphoma accounted for 10 of the 12 malignant specimens, or 10.5% of the final diagnoses. This is not surprising given that 58% of patients with non-Hodgkin lymphoma and 70% of patients with Hodgkin lymphoma may initially have cervical adenopathy. Despite these biases, these results are in keeping with those in the literature and may be taken as a fairly representative sampling.

Fine needle aspiration was used in 55.8% of the reported cases. Our utilization is actually much higher for cervical masses when those that do not result in open biopsy are included. Those patients without FNA tended to be younger, have no risk factors, and have a history most compatible with a branchial cleft cyst or thyroglossal duct cyst. The correlation of FNA with final diagnosis was fair, as the overall FNA rate of neoplasia was 39.6% compared with the final diagnosis rate of 31.6%. In adults, however, FNA should be routinely used, given its low morbidity and high level of accuracy, especially in diagnosing metastatic SCCA of the head and neck.

The logistic regression model identified several of the intuitive variables that are clinically useful for predicting a higher likelihood of neoplasia among neck masses: increasing patient age, larger size, and longer duration. Interestingly, a history of smoking and location were not found to be predictive. These results generally correlate with the findings of Tsai et al, who also found larger size and advanced age to be predictive of malignancy. They did not find duration to be helpful, but did find supraclavicular location, number of masses, tenderness, and fixation to be statistically significant. Each of their variables was also positively correlated with malignant outcome. Their probability equation for malignancy then included a cumbersome 8 terms. They found a somewhat protective effect for bilaterality of the masses in their analysis as well. Some difficulties with comparison occur because of the composition of their series, as they had several cases of metastatic SCCA diagnosed by open biopsy, and their outcome variable was malignancy rather than neoplasia. Though the number of posterior triangle lesions was small, this region had the highest rate of malignancy (Figure 2). While others have found malignancy relatively more common in the posterior triangle, the regression model did not find location to be a statistically significant predictor of neoplasia or malignancy.

The model for neoplasia possesses some clinical utility, although it is limited. For the present series, the model’s sensitivity of 46.7% for neoplasia was poor, but its specificity for neoplasia of 87.7% was good. If the probability cutoffpoint is lowered to 0.25, the sensitivity improves to 70.0%, with a necessary drop in specificity to 63.1% (Tables 3 and 4). This cutoffpoint decrease results in the reclassification of more lesions as neoplastic, thereby allowing fewer truly neoplastic lesions to be overlooked. However, this also subjects an additional 16 patients to an unnecessary biopsy. A clinically useful model should both select patients for early biopsy and identify patients who could safely avoid surgery. The former corresponds to a high positive predictive value, and the latter to a high negative predictive value. The model’s negative predictive value (at the cutoffpoint of 0.5) of 78.1% implies that if the model were used to predict neoplasia and therefore stratify patients for biopsy vs observation, the otolaryngologist would miss approximately 22 cases of true neoplasia among 100 patients who avoided biopsy. This translates into substantial cost savings but also misses a large number of patients with neoplasia. In addition, with an incidence of neoplasia of 31.6%, a surgeon who elected to withhold biopsy for all patients would be correct 68.4% of the time. Lowering the classification cutoffpoint to 0.25 does somewhat improve the negative predictive value (Tables 3 and 4) at the expense of overall accuracy. The positive predictive value of 63.6% suggests that the model is not as useful in selecting patients for early biopsy, and lowering the cutoffpoint further worsens this statistic to 46.7%. Thus, the model alone should not be used in the absence of continued follow-up and clinical judgment. The model may, however, be helpful in counseling patients regarding their risk of neoplasia in a specific clinical setting.

The modeling of the malignant outcome was not successful. Although the logistic regression model found age to be positively correlated with malignancy, the final model did not predict any lesions to be malignant, resulting in a sensitivity of 0.0%. The overall accuracy was...
87.4%, but this model is not clinically useful since it does not add anything beyond clinical judgment. When the probability cutpoint was lowered to 0.25, no useful improvement in the classification of malignancy occurred.

The model for neoplasia may be used to determine the estimated probability of neoplasia in a neck mass given the clinical variables of age, size, and duration. Alternatively, the odds ratios can be computed. The data for neoplasia indicate that a 60-year-old patient has an increase in odds of (1.415)\(^4\), or 4.0 times over a similar patient’s odds at the age of 20 years. Similarly, a 4-cm lesion will be (1.499)\(^3\), or 3.7 times, as likely to be neoplastic as a 1-cm mass. Finally, a mass that remains present even after 30 weeks will have an increased odds ratio of (1.075)\(^3\), or 1.24 times. Duration was the most weakly correlated independent variable, as indicated by the relatively low odds ratio and the 95% CIs. When the predictors of age, size, and duration are taken together, the odds ratios multiply, and the potential for neoplasia increases rapidly. This strongly reinforces the appropriateness of prompt biopsy of masses larger than 4 cm in patients older than 40 years that have been present for extended periods. Using the model for neoplasia is probably more clinically appropriate than a model only for malignancy, since most neoplastic (and all malignant) masses should undergo biopsy.

These results must be interpreted with some caution because of the retrospective nature of the study and potential selection biases. In almost all cases, patients with neck masses and risk factors for SCCA receive FNA and formal endoscopy before open neck biopsy. This selects for the elimination of SCCA cases (ie, malignant cases) from this analysis, as evidenced by the incidence of only 1 patient with a final diagnosis of SCCA after open biopsy. Therefore, these data are best applied to patients who have no evidence of SCCA on FNA and upper endoscopy, or in whom the likelihood of SCCA is very low. A second selection bias also exists toward malignancy, since all of these cases ultimately underwent biopsy. Cases that require biopsy are more likely to be malignant, since neck masses that were observed and subsequently regressed would have never been included in this series. These biases may be assessed further by examining the rates of malignancy for cases that had an initial FNA (20.8% malignancy on final pathology report) and those that did not (2.4%). This is probably because FNA was more likely to be used when the clinician suspected malignancy, and therefore the presence of an FNA before biopsy is a marker for malignancy. To some extent, the model developed might perform better on all cases as they are initially evaluated, because of these selection biases. A prospective analysis of neck masses seen by the otolaryngologist is under way to better answer these questions.

Increasing patient age and size and duration of a neck mass render the mass more likely to be neoplastic. Duration is the least powerful predictor. Sex, location, a history of smoking, and the number of masses do not have a statistically significant bearing on the likelihood of malignancy.

Although a regression model may be fairly accurate in predicting neoplasia for neck masses, it cannot replace clinical judgment. Consideration of the clinical situation and vigilant follow-up remain essential. In the prediction of the malignant nature of a neck mass, increasing age renders a higher probability of malignancy. However, the prediction model is no better than clinical judgment.

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REFERENCES