Objective: To develop a practical staging system for predicting mortality of patients with recurrent squamous cell tumors of the oral cavity and oropharyngeal mucosa.

Design and Setting: An inception cohort at an academic medical center.

Patients: A total of 308 patients who had evidence of recurrent, persistent, or second primary tumors of the oral cavity and oropharynx between January 1, 1980, and December 31, 1991, of whom 162 (52.6%) met inclusion criteria.

Main Outcome Measure: One-year mortality.

Results: The median survival time was 10 months. In bivariate analysis, the TNM stage of the recurrent tumor, invasion of pharyngeal constrictors and the floor-of-mouth muscles, weight loss, local and systemic symptoms, and eating function had significant effects on mortality. Multivariable analysis (done by conjunctive consolidation and Cox regression) identified constrictor invasion, the TNM stage of the recurrence, and weight loss as having a substantial effect on mortality. A composite 4-stage system using these 3 variables demarcated 1-year survival rates of 88.2% (30/34), 71.9% (23/32), 32.6% (16/49), and 4.2% (2/47).

Conclusions: The TNM status of recurrent tumors predicts mortality, but constrictor muscle invasion and weight loss also have major prognostic importance. The consolidation of these variables into a composite staging system successfully stratifies patients with widely divergent mortality rates. Improved staging of recurrent head and neck tumors can lead to more effective decisions about the comparisons and merits of additional treatment.


INCE DENIOX and Schwartz1 introduced the TNM system of cancer classification in 1948, cancer staging organizations have regularly modified the corresponding strategies of prognostic analysis. These refinements—which have been directed toward improving the predictive ability of the models, promoting the practical application of staging systems, and establishing an international standard of classification—have the disadvantages of relying only on TNM-based measurements of the anatomical extensiveness of the tumor. The limitations of purely anatomical staging systems has been recently discussed,2,5 and the addition of clinical variables that reflect patients’ symptoms or comorbid status has markedly improved the accuracy of predictive models for primary tumors.3,7

An additional limitation of the TNM classification is that it has been used almost exclusively for primary tumors. Although the American Joint Committee on Cancer allows for a “re-treatment” classification of tumors appearing after a “disease-free interval,” the approach does not include patients with persistent disease. Furthermore, the primary surgical excision of an organ (eg, the larynx) may remove structures necessary for staging a recurrence. Without an established framework for assessing outcomes, anecdotal evidence is often used to select the treatment of recurrent head and neck tumors.

Survival after tumor recurrence has not been systematically studied despite its prevalence, morbidity, and cost. Although precise data are lacking, recurrent disease represents a substantial proportion of the tumors treated at tertiary care centers. Recurrent tumors, and their treatment, have potentially devastating effects on independence and social function by altering appearance and the ability to speak, swallow, chew, smell, and taste. The costs of caring for patients who
PATIENTS AND METHODS

STUDY POPULATION

The study was limited to patients being seen for the evaluation and treatment of “recurrent” squamous cell carcinoma in the mucosa of the oral cavity or oropharynx. We excluded patients with isolated cervical or distant metastases to ensure that the tumors originated from the oral cavity and oropharynx; isolated metastases could represent the spread of disease from other primary tumor sites.

Because such tumors may actually represent persistent tumors, truly recurrent tumors, or second primary tumors, the distinctions among them are defined in the “Classification of Data” subsection. To avoid confusion, however, the 3 types of tumors will be collectively called “second tumors” in the rest of this article.

The Yale Tumor Registry identified 621 patients with primary carcinoma of the oral cavity and oropharynx of squamous cell origin between January 1, 1980, and December 31, 1991. This time span was chosen to obtain a large number of patients and to allow subsequent second tumors to develop. Because tumors were not reliably classified in the tumor registry as primary or nonprimary, all available hospital, radiotherapy, and otolaryngology records were reviewed to find patients with second tumors of the oral cavity and oropharyngeal mucosa. Patients were considered to have a second tumor if, after treatment for cure of the primary tumor, evidence was found of tissue confirmation of a second tumor or the institution of additional oncological therapy. In patients with multiple “recurrences,” only the initial second tumor was considered.

The reduction of these 621 patients to the eligible inception cohort of 162 patients is shown in Table 1. No evidence of further disease was found in 280 patients, some of whom had only palliative treatment of the primary tumor. Of the remaining 341 patients, 21 had been misclassified (eg, nonsquamous histologic features or nonoral tumors), and 12 had synchronous primary tumors of the oral cavity and oropharynx.

From the remaining 308 patients (49.6% of the original group) who had evidence of recurrent disease, 146 patients were excluded from this analysis. They comprised 53 patients with isolated regional cervical disease and 10 patients with distant metastases (in whom treatment would not be directed at the oral mucosa), 5 patients with metachronous nonoral head and neck tumors (eg, hypopharynx and larynx) that occurred before the second oral cavity or oropharyngeal tumor, and 28 patients in whom metachronous lesions developed without second oral tumors. An additional 50 patients were excluded because of inadequate records that lacked information about treatment of the primary and second tumor; TNM data, examination findings, and symptom history for the second tumor; or follow-up survival data.

The remaining 162 patients (52.6% of patients with recurrent disease) formed the inception cohort that was analyzed with second tumors of the oral cavity and oropharyngeal mucosa. This study was approved by the Yale Human Investigation Committee (protocol 8398).

DATA COLLECTION

Data from medical records and from available radiotherapy and otolaryngology records at the Yale New Haven Hospital, New Haven, Conn, were extracted onto a standardized form by data extractors unaware of survival outcome.

“Zero time” for survival analysis was the day therapy for the second tumor was initiated. In 8 patients for whom a definite decision was made to withhold treatment, the date of the decision was designated as zero time. The collected presero-time data included the stage, histologic description, and treatment of the primary tumor. Zero-time data included findings of the head and neck examination that were related to the second tumor; smoking and drinking history; symptom history; functional status; comorbidity; and pertinent histopathologic, laboratory test, and imaging results. Postzero-time data included details about the treatment and survival outcomes of the second tumor.

CLASSIFICATION OF DATA

Management of Data

The general methods of extraction and classification of archival data for patients with cancer have been discussed previously.9,10,13 Additional specifications are detailed below.

To ensure the scientific reproducibility of the extracted data, the following steps were taken:

- Criteria delineating the values of each variable were made explicit and kept in a coding handbook for reference during data extraction.
- Discrepancies about clinical variables in the medical record were addressed with the following conventions: symptoms or findings were recorded as present if noted by at least 1 member of the medical or nursing staff. When dimensional data (eg, the amount of weight loss or tumor diameter) were discrepant, the largest number was recorded.
- In addition, 10% of the cases were re-reviewed by a second otolaryngologist (E.M.W.). The χ2 statistic was used to assess the degree of agreement with the primary reviewer (B.Y.).

Designation of Treatment

Dosages and modalities of treatment were recorded for surgical therapy, chemotherapy, external-beam radiotherapy, and brachytherapy. Treatment was deemed palliative if the documented intent was limited to comfort measures or the relief of pain. In the absence of such documentation, treatment was presumed to be “curative.”

Treatment was designated as targeting either the original or the second tumor. The target was the original primary tumor if it was explicitly included in the pretreatment strategy. For example, if the treatment plan for a primary tumor included both external-beam radiotherapy and brachytherapy, then both treatments were associated with the primary tumor. If, however, the original treatment plan included only external-beam radiotherapy and persistent tumor was treated with brachytherapy, then brachytherapy was associated with the second tumor.

Second Tumor Type (Recurrent vs Persistent vs Second Primary)

The distinction among recurrent, persistent, and second primary tumors has not been well defined. For example, when
an undetectable focus of tumor persists, the subsequent clinical reappearance of the tumor may be deemed a persistence (as it truly is) or a recurrence (as it may appear). For this study, we used the following criteria to classify second tumors:

- **Persistent** tumors showed continued evidence of the original tumor in the form of symptoms or morphologic features (physical examination, histopathologic description, and computed tomographic reports). Tumors also were classified as persistent, regardless of symptoms or morphologic features, if the second tumor was diagnosed within 3 months after therapy was completed for the original tumor.

- **In recurrent** tumors, the symptoms and morphologic evidence of the original tumor had been absent for at least 3 months.

- **In second primary** tumors, the lesion involved a different oral site.

### Designation of Symptoms

For a formal classification of symptoms, those associated with the second tumor had to be distinguished from those associated with primary tumor treatment or coexisting disease. We attributed the symptoms to the second tumor if they were consistent with the manifestations of the cancer rather than with the antineoplastic treatment or comorbidity. For example, a patient with prior radiotherapy who presented with xerostomia and oral bleeding would have the xerostomia attributed to treatment and the bleeding attributed to tumor.

Both localized and systemic symptoms were catalogued. Local symptoms included oral pain, otalgia, oral bleeding, dysphagia, and odynophagia. Systemic symptoms included fatigue and anorexia. Weight loss, which might have been evidence of either local or systemic problems, was analyzed separately.

### Assessment of Physical Findings

The TNM components were recorded when available for the primary tumor and the second tumor. As with symptoms, specific physical findings were considered present when noted by at least 1 provider. We also catalogued the presence of trismus, tumor fixation, cranial nerve paralysis, and skin involvement.

### Social Factors

The highest sustained exposure to tobacco and alcohol was recorded. Although we had planned to quantify exposure to these risk factors after the occurrence of the primary tumor, such information was documented too infrequently to allow a meaningful analysis.

### Functional Status

Patients’ functional status for activities of daily living, such as bathing, toileting, and dressing, was classified as dependent, partly dependent, or independent. Functional eating status was also dichotomized according to a regular solid diet, a soft or liquid diet, and the requirement for tube feedings.

### Prognostic Comorbidity

Comorbid illness was classified according to the index of Charlson et al. The original oral cavity or oropharyngeal cancer was not considered to be a comorbid condition.

### Histopathologic, Laboratory Test, and Imaging Results

When available, the grades of the primary and second tumor were noted. In the absence of an official pathology report, the highest reported grade (ie, most anaplastic) was used. Reports for complete blood cell counts, electrolyte values, liver function studies, blood gas analyses, and radiological studies were recorded at zero time. When repeated results were available, the results nearest to zero time but still preceding the institution of therapy were selected.

### Muscular Invasion

The authors’ clinical experience had suggested that a poor prognosis was heralded by second tumors invading pharyngeal constrictors or the floor of mouth musculature. Tumor invasion of these muscle boundaries was assessed from the findings of the physical examination and magnetic resonance imaging or computed tomographic reports. Only contiguous invasion of these muscles from mucosal lesions was included. Involvement by cervical metastases or tumorous fistula tracts through these muscles was not included. Finally, findings such as trismus (which may have implied pterygoid involvement) were not adequate to designate muscle invasion, unless supported by morphologic evidence.

### Follow-up and Outcome

Available records and Yale Tumor Registry data were used to determine the status of a patient (alive or dead) and the most recent date of follow-up.

### Therapeutic “Nil Hypothesis”

To identify prognostic factors and create a staging system for secondary tumors at zero time, all patient outcomes (mortality) were first analyzed, regardless of the subsequent treatment. This strategy assumes a therapeutic nil hypothesis, which is a tentative clinical assumption that postzero-time treatment has no effect on the clinical course. The assumption allows the staging system to be developed for all patients, regardless of therapy; the effects of treatment can be explored later for patients in similar prognostic stages.

### ANALYSIS OF DATA

Data from extraction forms were transferred to computer code with double-entry verification. Bivariate statistical analyses, including χ² test, χ² test for linear trend, and analysis of variance, were performed with a commercially available software system (Statistical Analysis Software, version 6.10, SAS Institute Inc, Cary, NC). The k statistic was used to assess interobserver variability. Weighted values for k (categorical-distance model) were applied when contingency tables were larger than 2 × 2. Multivariable analyses included proportional hazards regression (Statistical Analysis Software) and conjunctive consolidation. The latter technique was used to combine prognostically important variables into a practical staging system to predict mortality.
need sophisticated testing, undergo complex procedures, and sustain high complication rates may be considerable.

Amid this uncertainty, our objectives were to identify patient- and tumor-related factors that affect survival among patients with recurrent tumors of the oral cavity and oropharyngeal mucosa; to develop a common prognostic staging system for recurrent oral cavity and oropharyngeal tumors in patients with a diverse treatment history and residual anatomy; and to make the system sufficiently practical for use by physicians.

**RESULTS**

The inception cohort of 162 patients contained 104 men and 58 women; 140 patients were white, 18 were African American, 3 were Latino, and 1 was Asian. The median age (range) was 63 (25-100) years. Although the mean survival was 1.8 years, the skewed distribution of survival times suggests that the median survival, which was 0.8 years, is a more accurate reflection of typical survival.

Table 2 shows bivariate analyses of 1-year survival rates according to baseline variables. Age, sex, and comorbidity did not have a statistically significant effect on 1-year survival. The type of treatment of the primary tumor also lacked a statistically significant influence on survival, although there was a favorable trend (unadjusted for other factors) for surgical treatment. In addition, persistent tumors had lower 1-year survival rates than recurrent or second primary tumors. Clinical variables such as weight loss, the presence of systemic symptoms (fatigue and anorexia), and eating function also had a strong effect on mortality. For example, patients who had lost 20% or more of their weight had a 1-year survival rate of 17%, compared with a 1-year survival rate of 70% in those without weight loss.

Morphologic variables such as invasion of the pharyngeal constrictors or floor-of-mouth musculature and the TNM status also had strong predictive value. The 1-year survival rate was 57% in patients without muscle invasion but only 5% in those with invasion. Patients in TNM stage I (for the second tumors) had 1-year survival rates of 80%, but those in stage IV had rates of 21%. Because stage IV tumors had significantly worse survival in the presence of metastatic disease, however, we modified the TNM scheme to reflect this finding (Table 2). In our modification, patients with stage IV tumor without metastases are combined with patients with stage III disease to form stage III’. Patients with stage IV disease with metastases form stage IV’, with a 1-year survival rate of 0%. Stages I and II are unaffected by these modifications.
The dramatic effect of muscle invasion within shown in Table 3. One-Year Survival Rates for the Conjunction of Morphologic Variables.

<table>
<thead>
<tr>
<th>Modified TNM†</th>
<th>No Muscle Invasion</th>
<th>Muscle Invasion Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>28/35 (80.0)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>13/17 (76.5)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>28/63 (44.4)</td>
<td>2/34 (5.9)</td>
</tr>
<tr>
<td>IV</td>
<td>0/7 (0.0)</td>
<td>0/6 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>69/122 (56.6)</td>
<td>2/40 (5.0)</td>
</tr>
</tbody>
</table>

*The numerator denotes the number of patients alive at 1 year; denominator, the number of patients in each category. The 1-year survival rate is enclosed in parentheses. The shading indicates how cells are consolidated into composite morphology stages α, β, and γ. Ellipses indicate this category is not applicable.

†Modified TNM stages I and II are identical to TNM stages I and II. See text for distinctions between modified stages III and IV and TNM stages III and IV.

The following tabulations displays important variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle invasion</td>
<td>0.76</td>
</tr>
<tr>
<td>TNM stage</td>
<td>0.84</td>
</tr>
<tr>
<td>Modified TNM stage</td>
<td>0.78</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0.68</td>
</tr>
<tr>
<td>Eating function</td>
<td>0.61</td>
</tr>
<tr>
<td>Charlson index, modified</td>
<td>0.56</td>
</tr>
</tbody>
</table>

The k values reflect the degree of interobserver agreement beyond what can be expected by chance. (By the criteria of Landis and Koch,21 “nearly perfect” agreement exists when k>0.8, and “significant” agreement occurs when k>0.6.)

Multivariable analyses were used to identify variables with the greatest independent predictive power. One analytic technique—conjointive consolidation—is a form of multivariable analysis that directly demonstrates the additive effect of individual variables and then consolidates pertinent variables into composite categories.

In the present study, this technique was applied first to combine the 2 morphologic variables—muscle invasion and modified TNM stage—in a conjunctive effect, shown in Table 3. (Note that this composite “morphologic variable” represents an intermediate stage in the analysis.) The dramatic effect of muscle invasion within modified stage III is evident (and would not be readily apparent with customary multivariable analysis).

The composite morphologic stages α, β, and γ were analyzed as the number of patients alive at 1 year vs the number of patients in each stage (with the 1-year survival rate [percentage] given in parentheses):

Table 5. Final Clinicomorphologic Staging System

<table>
<thead>
<tr>
<th>Stage Description</th>
<th>One-Year Survival *</th>
</tr>
</thead>
<tbody>
<tr>
<td>A ≤T2 N0 M0 and no weight loss</td>
<td>30/34 (88.2)</td>
</tr>
<tr>
<td>B ≤T2 N0 M0 and weight loss &lt;20% or &gt;T2 N0 M0 without metastases, muscle invasion, or weight loss</td>
<td>23/32 (71.9)</td>
</tr>
<tr>
<td>C ≤T2 N0 M0 and weight loss ≥20% or &gt;T2 N0 M0 without metastases, muscle invasion, but with weight loss</td>
<td>16/49 (32.6)</td>
</tr>
<tr>
<td>D Muscle invasion or metastases, regardless of weight loss</td>
<td>2/47 (4.2)</td>
</tr>
</tbody>
</table>

*The numerator denotes the number of patients alive at 1 year; denominator, the number of patients in each category. The 1-year survival rate is enclosed in parentheses.

Next, similar conjunctions were attempted for only the clinical variables. The prognostic value of weight loss alone, however, was not significantly improved when combined with other variables (data not shown), such as eating function, local symptoms, or systemic symptoms. Accordingly, as the final step in constructing the staging system, the clinical variable “weight loss” was combined with the composite “morphologic variable,” with the effects shown in Table 4. Each variable has a distinct and independent effect on mortality within categories of the other variable. For example, in any given morphologic stage (α, β, or γ), increasing weight loss produces a monotonic gradient on survival. Similarly, for all levels of weight loss, worsening morphologic stage worsens survival. This “double gradient”22 phenomenon indicates that both variables have independent effects on survival. These 2 variables were, therefore, consolidated to create the final, 4-stage, clinicomorphologic composite staging system, shown in Table 5.

Clinicomorphologic descriptions of the 4 composite stages are provided in Table 5 to save clinicians the intermediate step of separately determining the morphologic stage. To demonstrate that this composite staging system is able to differentiate between clinicomorphologic stages beyond 1 year, Kaplan-Meier survival was plotted for 3 years (Figure), and substantive separations were maintained.

In addition to the conjunctive consolidation, we also performed a traditional multivariable analysis with Cox (proportional hazards) regression. The results of this technique, which does not provide direct outcome rates for patients with selected characteristics, confirm the variables having the greatest effect on survival: the invasion of muscle boundaries, the modified TNM stage, and weight loss (Table 6).
To prepare a practical staging system that clinicians would find useful in the management of patients with “recurrent” oral cavity and oropharyngeal tumors, we have developed a 3-variable model that includes data on the TNM status, muscle invasion, and weight loss. Although the inclusion of other variables might have improved the predictive ability further, the minor improvements did not justify the added complexity.

An important clinical finding from this study is that the quantitative effect of constrictor and mylohyoid invasion on mortality approaches that of metastatic disease. Accordingly, muscle invasion warrants being considered for inclusion in second-tumor staging of laryngeal and hypopharyngeal tumors and possibly in primary tumors as well. In addition, modified TNM staging of second tumors had an independent, strong effect on mortality. Although the TNM modification may seem unnecessary, the substantial improvements in predictive ability justify this approach. Furthermore, even more substantial TNM modifications may be necessary to develop prognostic models for second tumors in other sites—eg, a laryngectomy removes the structures that are used in TNM staging of the larynx.

Clinical variables such as weight loss or alcohol abuse have been previously shown to have a strong prognostic effect on mortality but remain largely ignored in tumor staging. Given the heightened awareness of expensive testing in the managed care era, however, perhaps more attention should be given to measuring other relatively simple clinical variables, such as comorbidity, which are not only inexpensive but are also highly prognostic.

In our analyses, additional variables, such as albumin levels or primary TNM stage, had strong effects on mortality (data not shown). These were left out of the staging system, however, for 2 reasons. First, laboratory values vary by institution, and their inclusion might require potentially complicated conversion factors. Second, the primary TNM stage was not included because tertiary care centers occasionally do not have access to original tumor details. Therefore, our approach based staging only on second tumor variables that would be readily available from a routine history and careful examination at the time a second tumor was being evaluated.

Although multivariable adjustments in this study diminished the effect of a second tumor type on mortality, we suspect that a biological explanation may exist for what seems clinically intuitive: persistent tumors fare worse than recurrent tumors, which fare worse than second primary tumors. True distinctions between these patterns may await a molecular or cellular explanation, but the disparate clinical behaviors deserve prompt further investigation.

Although the results of our study confirmed a priori clinical suspicions regarding variables with substantial effect on mortality, our staging system requires formal validation with another data set. We, therefore, plan to validate this model on a second retrospective series of patients and use it to determine whether different treatments affect the outcome for second oral cavity and oropharyngeal tumors. In addition, because the breadth of data that can be collected from retrospective analyses is limited, we plan to prospectively validate this staging system.

The high incidence of second tumors, the accompanying morbidity and mortality, and the potential for disproportionate resource consumption suggest that systematic study is needed for second tumors. Accepted staging systems for second tumors would improve the identification of patients with consistently good (or poor) prognoses, such as those in our composite stage A (or D), with a more appropriate use of curative (or palliative) treatment. The clinical use of prognostic staging systems for second tumors would provide a means for comparing outcomes of therapy and for making informed decisions about the merits of additional treatment.

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Dr Yueh was a Robert Wood Johnson Clinical Scholar at Yale University School of Medicine, New Haven, Conn, during this research.

Table 6. Results of Cox Multivariable Regression

<table>
<thead>
<tr>
<th>Variable*</th>
<th>No. of Categories</th>
<th>Hazard Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified TNM stage</td>
<td>4</td>
<td>2.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Muscle invasion</td>
<td>2</td>
<td>2.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3</td>
<td>1.6</td>
<td>.001</td>
</tr>
<tr>
<td>Eating function</td>
<td>3</td>
<td>1.4</td>
<td>.12</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>2</td>
<td>1.4</td>
<td>.18</td>
</tr>
<tr>
<td>Type (persistent vs other)</td>
<td>2</td>
<td>1.1</td>
<td>.63</td>
</tr>
<tr>
<td>Location (oral cavity vs oropharynx)</td>
<td>2</td>
<td>1.1</td>
<td>.79</td>
</tr>
</tbody>
</table>

*Shaded variables are those with greatest impact on survival, confirming the results of the conjunctive consolidation.
REFERENCES