Expression of p53 and Bcl-xL as Predictive Markers for Larynx Preservation in Advanced Laryngeal Cancer

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**Objective:** To assess tumor markers in advanced laryngeal cancer.

**Design:** Marker expression and clinical outcome.

**Patients:** Pretreatment tumor biopsy specimens were analyzed from patients enrolled in the Department of Veterans Affairs Laryngeal Cancer Study.

**Main Outcome Measures:** Expression of p53 (OMIM TP53) and Bcl-xL (OMIM 600039) in pretreatment biopsy specimens was assessed for correlation with chemotherapy response, laryngeal preservation, and survival.

**Results:** Higher rates of larynx preservation were observed in patients whose tumors expressed p53 vs those that did not (80% [36 of 45 patients] vs 59% [24 of 41 patients], \( P = .03 \)). Higher rates of larynx preservation were also observed in patients whose tumors expressed low levels of Bcl-xL vs high levels of Bcl-xL (90% [18 of 20 patients] vs 60% [30 of 50 patients], \( P = .02 \)). Patients were categorized into 3 risk groups (low, intermediate, and high) based on their tumor p53 and Bcl-xL expression status. Patients whose tumors had the high-risk biomarker profile (low p53 expression and high Bcl-xL expression) were less likely to preserve their larynx than patients whose tumors had the intermediate-risk biomarker profile (high p53 expression and low or high Bcl-xL expression) or the low-risk biomarker profile (low p53 expression and low Bcl-xL expression). The larynx preservation rates were 100% (10 of 10 patients), 77% (26 of 34 patients), and 54% (7 of 13 patients) for the low-risk, intermediate-risk, and high-risk groups, respectively (\( P = .04 \), Fisher exact test).

**Conclusion:** Tumor expression of p53 and Bcl-xL is a strong predictor of successful larynx preservation in patients treated with induction chemotherapy and followed by radiation therapy in responding tumors.


Advances in chemotherapy, radiotherapy, and surgical techniques have improved the outlook of patients with advanced larynx cancer, enabling larynx preservation and improved quality of life. Up to this point, we have been unable to predict which tumors are likely to respond to chemotherapy and radiotherapy and which tumors will be resistant and persist. To better understand the biologic response to chemotherapy and radiotherapy, analysis of the phenotype of tumor cells by genetic and proteomic approaches has been under way for the past several years. Studies in the literature have examined the prognostic significance of various biomarkers, including cell cycle regulators, members of the proapoptotic family, angiogenesis markers, and proliferation markers in head and neck squamous cell cancer. Results have been mixed, reflecting the multitude of factors that contribute to the complex tumor biologic function, as well as the heterogeneity of head and neck cancers for site, stage, prognosis, and biologic characteristics.

The p53 protein has a central role in pathways responsible for maintaining cellular integrity. The p53 network is activated when cells are damaged or stressed. On activation, p53 can lead to cell cycle arrest and DNA repair, or it can cause programmed cell death. Wild-type p53 protein binds to DNA and regulates the expression of various target genes, including p21 (OMIM 116899) (CDKN1A also called cipl, waf1) and GADD45 (OMIM 126335), leading to blockade of cell cycle progression and initiation of repair. Similarly, p53-mediated transactivation of the BAX (OMIM 600040), NOXA (OMIM 604958), and PUMA (OMIM 605854) genes promotes cell death by apoptosis. Approximately 50% of head and neck tumors have
a p53 (OMIM 191170) mutation. The p53 protein is a molecular determinant regulating the response to chemotherapy. It was previously shown that head and neck tumor cell lines with mutant p53 were more sensitive to cisplatin than wild-type p53 lines. Others have shown p53 mutations to be associated with poor response to chemotherapy.12

Bcl-xL is a member of the antiapoptotic Bcl-2 protein family.13-15 Bcl-xL binds proapoptotic proteins such as Bak, Bad, and Bim via the BH3 domain and prevents these proteins from initiating apoptosis at the mitochondrial membrane.15,16 It was previously reported that Bcl-xL is overexpressed in 75% of head and neck squamous cell carcinomas.17 Overexpression of antiapoptotic proteins such as Bcl-2 and Bcl-xL is frequently associated with chemotherapy and radiotherapy resistance.13,18 Therefore, antiapoptotic proteins such as Bcl-xL and Bcl-2, in conjunction with p53, might be important components of response to cisplatin therapy.

Determining biomarkers that predict treatment response and identifying low- and high-risk groups will help us select appropriate treatment options for patients and limit unnecessary patient morbidity due to ineffective treatment approaches. In addition, identification of mechanisms of treatment resistance will allow development of novel treatment approaches tailored to tumor biologic function. In this study, we sought to determine the predictive and prognostic significance of selected biomarkers in tumors from patients with advanced laryngeal carcinoma enrolled in the Department of Veterans Affairs Laryngeal Cancer Study.19 We evaluated pretreatment biopsy specimens from stage III and IV larynx cancer treated in the chemotherapy arm of the study. Constructing tissue microarrays with triplicate tumor and adjacent normal specimens, we determined the concordance between whole sections and tissue microarray immunostaining. We investigated whether expression of biomarkers was predictive of chemotherapy response, laryngeal preservation, and survival.

DEPARTMENT OF VETERANS AFFAIRS LARYNGEAL CANCER STUDY

Pretreatment paraffin-embedded tumor specimens were obtained from patients enrolled in a randomized study20 of stage III or IV larynx cancer. The study compared conventional surgery and radiotherapy vs induction chemotherapy (using 3 cycles of cisplatin and fluorouracil) followed by radiotherapy in response to ineffective treatment approaches. In addition, identification of mechanisms of treatment resistance will allow development of novel treatment approaches tailored to tumor biologic function. In this study, we sought to determine the predictive and prognostic significance of selected biomarkers in tumors from patients with advanced laryngeal carcinoma enrolled in the Department of Veterans Affairs Laryngeal Cancer Study.19 We evaluated pretreatment biopsy specimens from stage III and IV larynx cancer treated in the chemotherapy arm of the study. Constructing tissue microarrays with triplicate tumor and adjacent normal specimens, we determined the concordance between whole sections and tissue microarray immunostaining. We investigated whether expression of biomarkers was predictive of chemotherapy response, laryngeal preservation, and survival.

IMMUNOHISTOCHEMISTRY

The tissue microarrays were stained for p53 (Ab-6, clone DO-1; Lab Vision, Fremont, California) and for Bcl-xL (Ab-2, clone 7D9; Lab Vision). For whole sections, p53 and Bcl-xL staining was performed as described previously.3,17 Slides were deparaffinized and rehydrated. Antigen retrieval was performed by heating the slides to 92°C for 20 minutes in antigen retrieval buffer (DAKO, Carpinteria, California). The slides were allowed to cool for 20 minutes at room temperature, were rinsed in phosphate-buffered saline, and were incubated with peroxidase block (DAKO) for 5 minutes at room temperature. Nonspecific binding sites were blocked with 1.5% horse serum (Vector Laboratories, Burlingame, California) in a phosphate-buffered saline solution for 30 minutes. The slides were incubated with primary antibody (p53 [1:100] and Bcl-xL [1:100]) diluted in blocking buffer for 1 hour, were washed in a phosphate-buffered saline solution, and were incubated with biotinylated antimouse IgG (ABC Kit, Vector Laboratories) for 30 minutes; they were then washed again and incubated with avidin-biotin–conjugated peroxidase for 30 minutes, all at room temperature. Color was developed with diaminobenzidine tetrahydrochloride (Sigma-Aldrich Inc, St Louis, Missouri). The slides were counterstained with hematoxylin-eosin, dehydrated, and mounted with coverslips. Affinity-purified mouse IgG2a (Sigma-Aldrich Inc) was used as a negative control.

IMMUNOHISTOCHEMICAL INTERPRETATION

All slides were read independently by 2 pathologists (K.G.C. and N.D.) who were blinded to the clinical outcomes of the patients. Each core was evaluated for the percentage of tumor cells stained on a scale of 1 to 4, with 1 representing less than 5% staining; 2, 5% to 20% staining; 3, 21% to 50% staining; and 4, 51% to 100% staining.

STATISTICAL ANALYSIS

Associations between molecular biomarkers and categorical clinical outcomes were examined using χ² test or Fisher exact test wherever appropriate. For p53 immunostaining, staining proportion scores were averaged, and values less than 2 (representing <5% tumor cell staining) were considered low expression. For Bcl-xL immunostaining, scores were averaged, and values less than 3 (representing <21% tumor cell staining) were considered low expression. For combined marker analysis, the patients were grouped into 3 biomarker group categories based on their tumor p53 and Bcl-xL expression status and on prior laboratory findings that showed a difference in cisplatin sensitivity of cultured head and neck squamous cell carcinoma cell lines based on p53 and Bcl-xL expression.20 The high-risk biomarker group was composed of patients whose tumors expressed low levels of p53 staining (<5% stain proportion) and high levels Bcl-xL staining (>20% stain proportion). The low-risk biomarker group consisted of patients whose tumors expressed low levels of both p53 and Bcl-xL staining (<5% stain proportion for p53 and <21% stain proportion for Bcl-xL). The remainder of the patients were categorized in the intermediate-risk biomarker group (high p53 expression and low or high Bcl-xL expression). Time to event analyses for survival and larynx preser-
vation were based on Kaplan-Meier methods. In all cases, 2-sided $\alpha = .05$ was considered statistically significant. Associations of the results obtained with whole sections and with tissue microarray sections were evaluated using McNemar test for paired data.

## RESULTS

### p53 AND Bcl-xL IMMUNOSTAINING

Nuclear p53 expression was scored in 86 evaluable pretreatment biopsy specimens from patients in the chemotherapy arm of the study. p53 Expression was observed in 52% (45 of 86 patients) of the tumor specimens. Bcl-xL expression was evaluated in 70 pretreatment tumor specimens. Bcl-xL staining was localized in the cytoplasm of tumor cells. Some staining was also observed in the stromal lymphocytes and surface epithelium, but only tumor cell staining was scored. High Bcl-xL expression was observed in 71% (50 of 70 patients) of the tumor specimens.

### CORRELATION OF p53 IMMUNOSTAINING IN WHOLE SECTIONS AND TISSUE MICROARRAY CORES

There is concern that tissue microarrays may not adequately represent the marker expression in a tumor compared with what can be assessed using whole sections. We compared p53 staining averages between whole tissue sections and tissue microarray sections. Sixty-eight subjects had paired pretreatment whole tissue and tissue microarray p53 results. There was no statistically significant difference between the mean p53 staining using whole section immunostaining compared with tissue microarray immunostaining ($P = .27$, paired t test). Similarly, a comparison of the data using p53 staining averages classified as high or low showed disagreement in only 11 subjects. Using McNemar test for paired data, the difference in classification was not statistically significant ($P = .23$), and the $\kappa$ statistic tells us that the agreement was significantly better than chance alone ($P < .001$). In sum, the p53 immunostaining results were highly correlated and were not statistically different between whole sections and tissue microarray samples. These data support the use of tissue microarrays for biomarker identification in pretreatment biopsy samples.

### CORRELATION OF p53 IMMUNOSTAINING AND CLINICAL OUTCOME AMONG PATIENTS IN THE CHEMOTHERAPY ARM

Higher rates of larynx preservation were observed in patients whose tumors expressed p53 vs those whose tumors did not (80% [36 of 45 patients] vs 59% [24 of 41 patients], $P = .03$). After 2 cycles of induction chemotherapy, patients with tumors expressing high p53 staining had a similar rate of response (partial or complete) compared with patients with tumors expressing low p53 staining (86% [38 of 44 patients] vs 78% [29 of 37 patients], $P = .38$). The relative risk of laryngectomy among patients with low p53 expression in their tumors was 2.10 times that of patients with high p53 expression in their tumors ($P = .04$). Furthermore, patients with high p53 expression tumors had a clinically impressive and statistically significantly longer larynx preservation time than those with low p53 expression tumors ($P = .02$) (Figure 1). There was no difference in overall survival ($P = .70$) or disease-free survival ($P = .98$) among patients according to pretreatment p53 immunostaining results (Figure 2).

### CORRELATION OF Bcl-xL IMMUNOSTAINING AND CLINICAL OUTCOME MEASURES

Patients whose tumors expressed low Bcl-xL staining had a statistically significantly higher rate of larynx preservation and longer laryngeal preservation than patients whose tumors expressed high Bcl-xL staining ($P = .02$) (Figure 3). In fact, 18 of 20 patients (90%) whose tumors expressed low Bcl-xL staining preserved their larynx.
ynx compared with 30 of 50 patients (60%) whose tumors expressed high Bcl-xL staining \( (P=.02) \). Patients were 50% more likely to preserve their larynx if their tumors expressed low Bcl-xL staining. There was no statistically significant difference in overall \( (P=.55) \) or disease-free \( (P=.73) \) survival according to Bcl-xL expression \( \text{(Figure 4)} \). We also explored the relationship between larynx preservation and survival of patients in the chemotherapy arm of the study and found that larynx preservation and survival were unrelated. This is thought to be because of the therapeutic effectiveness of early salvage surgery that was planned for all patients in the trial who had nonresponding tumors.

**COMBINED BIOMARKER ANALYSIS**

Both p53 and Bcl-xL expression results were evaluable in 57 pretreatment biopsy specimens from patients enrolled in the chemotherapy arm of the study. Patients were grouped into 3 categories based on their tumor expression of p53 and Bcl-xL as described in the “Statistical Analysis” subsection of the “Methods” section. All patients \( (10 \text{ of } 10 \text{ [100%]}) \) with low p53 expression and low Bcl-xL expression in their pretreatment biopsy specimens preserved their larynx. In contrast, patients with tumors expressing low p53 staining and high Bcl-xL staining were 16 times more likely to have a laryngectomy. In this group, more than half \( (7 \text{ of } 13 \text{ [54%]}) \) underwent laryngectomy. Therefore, together these markers can define low-risk (low p53 expression and low Bcl-xL expression) and high-risk (low p53 expression and high Bcl-xL expression) biomarker groups. Those patients whose tumors expressed high p53 staining and low or high Bcl-xL staining constituted an intermediate-risk group in which 26 of 34 patients \( (77\%) \) had salvage surgery \( (P=.01, \text{test for trend}; P=.04, \text{Fisher exact test}) \). Logistic regression analysis showed that a patient was 4 times more likely to require a laryngectomy if the patient had an intermediate-risk biomarker profile compared with a low-risk biomarker profile. Similarly, a patient having a high-risk biomarker profile was 4 times more likely to undergo laryngectomy compared with a patient having an intermediate-risk profile. Time to laryngectomy was also statistically significantly shorter in the high-risk biomarker group compared with the other 2 biomarker groups \( (P=.03) \) \( \text{(Figure 5)} \). Chemotherapy response was higher in patients with a low-risk biomarker profile. All patients with tumors having a low-risk biomarker profile responded to chemotherapy (partial or complete response) compared with 82\% \( (27 \text{ of } 33 \text{ patients}) \) in the intermediate-risk biomarker group and 67\% \( (8 \text{ of } 12 \text{ patients}) \) in the high-risk biomarker group \( (P=.06, \text{test for trend}) \). The median survival of patients enrolled in the chemotherapy arm of the study whose tumors displayed the low-risk phenotype was 48 months, compared with 28 months for patients with the intermediate-risk phenotype and 22 months for patients with the high-risk phenotype \( (P=.57) \). Although there was no statistically
significant difference in disease-free survival among the groups \((P = .34)\), patients with a low-risk biomarker profile fared better than patients in the other 2 biomarker profile groups (Figure 6).

**COMMENT**

Squamous cell carcinoma of the head and neck demonstrates a high incidence of p53 suppressor gene alterations; consequently, the loss of p53 function has an important role in the pathogenesis and progression of these malignant neoplasms. Although many investigations have been performed to assess the role of p53, the results have been contradictory regarding the prevalence and the biologic and clinical effects on tumor behavior. This could be attributable to small sample sizes, mixed cohorts of tumors and patients, and differences in methodological approaches. In this study, pretreatment tumor biopsy specimens from patients enrolled in the Department of Veterans Affairs Laryngeal Cancer Study were analyzed for p53 and Bcl-xL expression. The major advantages of our patient group include the availability of reliable 10-year outcome data, uniform site (larynx) and uniform stage (stage III or IV) of tumors, and the randomization to induction chemotherapy plus radiotherapy given in a standardized protocol.

Data presented herein suggest that, in advanced laryngeal cancer, tumor expression of p53 defines a subset of patients with a high likelihood of larynx preservation. The present study expands on a previous study that showed an association of high p53 expression with larynx preservation, as well as a study indicating that low tumor expression of Bcl-xL, a protein that blocks apoptosis, is associated with larynx preservation in patients treated with induction chemotherapy followed by radiotherapy. Although high p53 expression and low Bcl-xL expression are each independently significantly associated with larynx preservation, we demonstrate in the present study that the interaction of Bcl-xL expression with p53 expression more accurately identifies those patients with the best and worst probabilities of larynx preservation. Using the markers together, we are able to define low-, intermediate-, and high-risk biomarker phenotypes. Specifically, combined low tumor expression of p53 and Bcl-xL is a stronger predictor of larynx preservation than high p53 expression irrespective of Bcl-xL status. This observation was initially unexpected given the association between overexpression of p53 and larynx preservation. The low-risk biomarker phenotype (10 of 57 patients [18%]) and the high-risk biomarker phenotype (13 of 57 patients [23%]) each represent a small but significant proportion of patients, whereas the intermediate-risk biomarker phenotype represents a much larger proportion of patients (34 of 57 patients [60%]). Therefore, the high rate of larynx preservation (26 of 34 patients [77%]) in the intermediate-risk biomarker group accounts for the statistically significant association between larynx preservation and p53 expression.

In this trial, we did not find a statistically significant relationship between the markers and survival. We suspect that this is because prompt surgical treatment for nonresponders in larynx cancer is an effective therapeutic option; therefore, these patients do not have worse prognosis than those who respond to induction chemotherapy. Nevertheless, the survival curves begin to separate into 3 groups suggestive of a minor effect on survival. In a larger cohort, this minor effect might become more impressive.

The excellent larynx preservation observed in the low-risk biomarker group is consistent with results published about head and neck cancer cell lines demonstrating that tumor cells with low (wild-type) p53 expression and low Bcl-xL expression undergo apoptosis in response to cisplatin. Low expression of the apoptosis-blocking protein Bcl-xL in tumors should allow DNA damage-induced apoptosis when p53 is wild type. Most tumor cells with wild-type p53 do not express nuclear p53 because of the short half-life of this protein. Therefore, we conclude that the favorable outcome of patients whose tumors have low p53 expression and low Bcl-xL expression is likely because of induction of apoptosis by cisplatin. Tumor cells harboring mutant p53 should be unable to arrest and repair DNA damage induced by cisplatin. These tumor cells are also resistant to p53-dependent apoptosis and likely undergo cell death by mitotic catastrophe. In fact, patients whose tumors express high levels of p53 (intermediate-risk biomarker phenotype) have intermediate but reasonably favorable rates of larynx preservation. Finally, the most cisplatin-resistant phenotype in this model would be tumor cells with wild-type p53 and high levels of Bcl-xL. In fact, head and neck tumor cell lines selected for cisplatin resistance in vitro harbored both wild-type p53 and high levels of Bcl-xL. In the present study, low tumor expression of p53 combined with high tumor expression of Bcl-xL defines a patient subset with a low likelihood of larynx preservation. We are in the process of completing p53 mutation analysis in these specimens, but based on our data thus far, most of the tumors with low p53 expression have wild-type and presumably functional
p53. Although these p53 analyses should confirm the predictive models proposed herein, p53 expression by itself or combined with Bcl-xL expression is a potent predictive marker.

Further study is needed to determine if these models hold true in the setting of other treatment protocols with different induction regimens, concomitant treatment approaches using chemotherapy and radiotherapy, and other head and neck tumor sites such as the oropharynx. Work is under way to evaluate the predictive ability of these markers in a successful protocol in advanced laryngeal cancer recently completed at the University of Michigan, Ann Arbor.\textsuperscript{27} In addition, promising biomarker findings supporting the role of p53 and Bcl-xL expression in predicting outcome have been recently obtained in a clinical trial of patients with advanced oropharynx cancer.\textsuperscript{28} In this latter trial, additional factors such as human papillomavirus and expression of the epidermal growth factor receptor seem to have prognostic significance.

Our results also suggest that novel agents that target Bcl-xL in the setting of cells with wild-type p53 would be good candidates to overcome cisplatin resistance in larynx cancer. Our group has reported the use of a novel therapeutic agent, (−)-gossypol, which targets Bcl-xL in head and neck cancer models in vitro and in vivo.\textsuperscript{30} Others are developing agents that target the cell survival proteins in different cancers.\textsuperscript{31,32} Defining the molecular mechanisms responsible for tumor cell resistance to standard therapies and designing targeted therapy to overcome the resistant phenotype constitute the future of cancer therapy and may someday improve survival in these patients.

Submitted for Publication: February 9, 2007; final revision received June 27, 2007; accepted July 29, 2007.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by grant R01 CA83087 from the National Center Institute (Dr Bradford) and by Head and Neck Specialized Program of Research Excellence Grant P50 CA97248 and Cancer Center Support Grant P30 CA46592 from the University of Michigan.

Previous Presentations: This study was presented at the 2006 American Head and Neck Society Annual Meeting and Research Workshop on the Biology, Prevention and Treatment of Head and Neck Cancer; August 18, 2006; Chicago, Illinois.

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Financial Disclosure: None reported.

Funding/Support: This study was supported by grant R01 CA83087 from the National Center Institute (Dr Bradford) and by Head and Neck Specialized Program of Research Excellence Grant P50 CA97248 and Cancer Center Support Grant P30 CA46592 from the University of Michigan.

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Correction

Error in Byline. In the byline of the article titled “Keratinocyte Growth Factor and Autocrine Repair in Airway Epithelium,” which appeared in the April 2004 issue of the Archives (2004;130[4]:446-449), the sixth author’s last name should have been spelled Parashurama.