Correlation of \( p53 \) and the Proto-Oncogene \( eIF4E \) in Larynx Cancers: Prognostic Implications

Cherie-Ann O. Nathan,\(^2\) Kenneth Sanders, Fleurette W. Abreo, Raja Nassar, and Jonathan Glass

Departments of Otolaryngology/Head and Neck Surgery [C-A. O. N., K. S.] and Pathology [F. W. A.], and the Feist-Weiller Cancer Center [C-A. O. N., J. G.], Louisiana State University Health Sciences Center and Veterans Administration Medical Center [C-A. O. N., J. G.], Shreveport, Louisiana 71130, and Department of Mathematics and Statistics, Louisiana Tech University, Ruston, Louisiana [R. N.]

ABSTRACT

\( p53 \) abnormalities constitute the most frequent genetic alterations identified in larynx cancers. \( p53 \) overexpression in histologically “tumor-free" surgical margins correlates with a high recurrence rate. However, only 50–60% of tumors overexpress \( p53 \). The tumor marker \( eIF4E \) is overexpressed in 100% of larynx cancers, and overexpression of \( eIF4E \) in histologically “tumor-free" margins predicts a significantly higher recurrence. We undertook this study to correlate the expression of \( p53 \) and \( eIF4E \) in the tumors and surgical margins of squamous cell cancers of the larynx and to determine their prognostic value. A retrospective analysis was performed on 54 patients who underwent surgery for squamous cell cancers of the larynx. Patient and tumor characteristics were reviewed, and the time to recurrence was noted. Paraffin-embedded sections from the tumors and surgical margins were immunostained with antibodies to \( eIF4E \) and \( p53 \), and a qualitative analysis was performed. All 54 patients (100%) overexpressed \( eIF4E \) in the primary tumor, whereas 25 of 53 patients (47%) were \( p53 \) positive. Thirty-two of the 54 patients (59%) had \( eIF4E \)-positive margins. All 6 of 53 patients (11%) with \( p53 \)-positive margins also overexpressed \( eIF4E \) in the margins. There was a significant correlation between \( p53 \) and \( eIF4E \) being positive in the margins (Spearman’s correlation coefficient, \( P = 0.03 \)). Twenty-one of the 25 patients (84%) that recurrent, including the 6 patients with \( p53 \)-positive margins, had \( eIF4E \)-positive margins. Hence, although the univariate analysis showed that nodal status and both \( eIF4E \) and \( p53 \) expression in the margins were significant predictors of recurrence (\( P < 0.05 \)), in the multivariate analyses only nodal status (and both \( eIF4E \) and \( p53 \)) were significant predictors of recurrence. Kaplan-Meier analysis demonstrated that the disease-free intervals for \( eIF4E \)-positive margins were significantly shorter than \( eIF4E \)-negative margins (\( P = 0.0007 \)). There was no additional effect to the combination of positive \( p53 \) and \( eIF4E \) margins (\( P = 0.21 \)). The overexpression of \( eIF4E \) in the margins appears to be a more sensitive indicator of recurrence and may be an earlier event in the process of tumorigenesis than \( p53 \).

INTRODUCTION

The process of tumorigenesis involves multiple molecular events involving both activation of proto-oncogene products that stimulate growth and inactivation of tumor suppressor genes, the products of which normally inhibit cell proliferation. As the process of carcinogenesis is better understood, molecular markers are playing an increasingly important role in the management of cancers in general and of head and neck carcinomas in particular. The proto-oncogene \( eIF4E \) is overexpressed in 100% of tumors of the breast, head and neck, and colon (1–3). In previous studies, overexpression of \( eIF4E \) in >5% of the basal cell layer of histologically tumor-free surgical margins of HNSCC\(^2\) patients predicted a significantly increased risk of recurrence (4). Mutations and overexpression of the tumor suppressor gene \( p53 \) are found in 40–60% of HNSCCs (5–7). A high correlation has been found between tumor recurrence and \( p53 \) mutations identified in the histologically “tumor-free" surgical margins (8). These findings indicate the limitations of microscopic histological diagnosis and the potential for molecular markers to guide clinicians in the management of head and neck cancer.

Cancer arises via a multi-step process. In certain cell types such as hematopoietic cells, a single genetic event that blocks differentiation may be sufficient for clonal expansion (9). In contrast, in cancers of epithelial origin such as in HNSCC, genetic events involving multiple genes appear to be necessary for clonal expansion, frequently with the loss of a tumor suppressor gene in conjunction with activation of one or more oncogenes contributing to tumorigenesis (10). Multiple pathways for tumor development are possible, and the presence or absence of a particular genetic change might be reflected in the carcinogenic phenotype. The opportunity for this type of analysis is possible in HNSCCs, where overexpression of the proto-oncogene \( eIF4E \) occurs in all cases, but aberrations of the tumor suppressor gene \( p53 \) occurs at a lower frequency. In this study, we explored in HNSCC whether \( eIF4E \) and \( p53 \) overexpression in histologically negative tumor resection margins are correlated and determined whether there is an added recurrence risk when both markers are overexpressed in the margins.

MATERIALS AND METHODS

Patients and Tumor Material. Fifty-four patients with SCCs of the larynx treated between 1988 and 1995 at Louisiana State University Medical Center, Shreveport, and the Veterans Administration Hospital were studied retrospectively. The selection criteria for this study included patients that underwent surgical resection for SCC of the larynx with curative intent and had received no prior treatment and for whom tissue blocks were available of the tumor and surgical margins. Standard adjuvant therapy consisting of postoperative radiotherapy was used for advanced stage disease. If any surgical margins on the final pathology report were positive for cancer, the patient was excluded from the study. Some patients had been analyzed previously for overexpression of \( eIF4E \) alone (11). Medical charts were reviewed for the following factors: age, race, sex, tumor size, node status, stage, site, histological grade of the tumor, postoperative radiation therapy, disease-free interval, and recurrence. The clinical characteristics are summarized in Table 1. Groups A and B refer to patients with \( eIF4E \) and -positive margins, respectively, and groups C and D refer to those with \( p53 \) and -positive margins, respectively.

Formalin-fixed, paraffin-embedded tissue blocks from the primary tumors and all of the mucosal surgical margins were obtained from all 54 patients. However, only 53 of 54 patients’ materials were available for \( p53 \) assessment. One slide from each block was stained with H&E and reviewed by the study pathologist, who was unaware of the clinical details. All tumor slides revealed malignant cells, and all surgical margins showed no evidence of carcinoma. Two additional sections, 5-µm thick, were mounted on polylysine-coated slides (Fisher Scientific, Pittsburgh, PA) for immunohistochemical analysis. Normal epithelium from a non smoker with Zenker’s diverticulum was used as a control. Negative controls with omission of the antiserum from the primary incubation were included.

Immunohistochemical Staining. Immunohistochemical staining for \( eIF4E \) was performed with a polyclonal antibody to \( eIF4E \) (1). Immunostaining for \( p53 \) was carried out by the avidin-biotin-peroxidase enzyme complex with a
monoclonal anti-p53 antibody as described by Biogenex (clone DO7; Biogenex, Inc., San Ramon, CA). This has been shown to react with both wild-type and mutant forms of the p53 protein. The details of the staining and subjective scoring have been described earlier (11). In the tumor, positive p53 staining was the presence of an unequivocal brown stain in the nucleus of 10% or more of tumor cells, whereas positive eIF4E stain was the presence of reddish brown perinuclear staining in 10% or more of the tumor cells. The 10% cutoff value was chosen based on a strong correlation between mutations in the p53 gene and the accumulation of p53 protein in 10% or more of tumor cell nuclei (12). The mucosal margins were considered positive if similar staining was seen in >5% of the basal cell layer. This cutoff was selected from results of previous studies using immunohistochemical analysis with eIF4E antibody (4, 11). The scoring was performed by two of the authors, who were unaware of the clinical details.

Statistical Analysis. The data on patient characteristics and surgical margins were analyzed statistically with SAS Version 6.07 (SAS Institute, Cary, NC). The major statistical end point of this study was time to recurrence calculated from surgery to the date of the first documented recurrence. Contingency tables and the $x^2$ test were used to evaluate the association of eIF4E and p53 in the surgical margins with race, sex, stage, lymph node status, histological grade, postoperative radiation, and eIF4E and p53 expression in the tumor and margins. A univariate analysis of the above clinical factors was performed using the Cox model to identify those variables significantly associated with prognosis. Risk ratios with a 95% CI were calculated. Cox multiple regression analysis was then performed using the backward selection, and the stepwise method with the variables that were significant at the 10% level in the univariate analysis. This multivariate analyses was performed to test for the simultaneous effect of two or more factors. Quantitative scoring of p53 and eIF4E expression did not appear to correlate with recurrence, and hence a qualitative analysis was performed. Event time distributions for recurrence were estimated by the Kaplan-Meier method and compared by the log-rank test to determine the individual and combined effects of eIF4E and p53 expression in the margins. Similar curves were performed to determine the effects of node status with eIF4E and p53 levels in the margins, because nodal status is a significant prognostic factor in HNSCC. These three variables were expressed as two categories, each negative or positive: “negative” representing N0 status and no overexpression of eIF4E and/or p53 in the margins and “positive” representing N1, N2, N3 nodal status and eIF4E and/or p53 overexpression in the margins. To simplify the analysis, all categories were collapsed into two groups, as listed in Table 1, groups A & B, except grade, which was analyzed as three categories. Age was considered a continuous variable. All nonrecurr- observations were considered censored in the Cox regression analysis.

RESULTS

Patient Characteristics. Fifty-four patients with SCC of the larynx were entered in the study. There were no statistically significant associations between eIF4E and p53 expression in the margins and sex, race, tumor stage, lymph node status, and degree of tumor differentiation, as seen in Table 1.

Immunohistochemical Analysis for eIF4E and p53. All 54 patients (100%) overexpressed eIF4E in the tumors, whereas 25 of the 53 patients (47%) had p53-positive tumors. In tumors overexpressing p53 and eIF4E, at least 40–100% of the cells stained positive for the markers well in excess of the 10% of tumor cells staining positive, chosen as the cutoff. eIF4E staining in the tumor cells was seen in at least 60–70% of tumor cells. Fig. 1 is an example of a SCC of the larynx immunostained with eIF4E (Fig. 1B) and p53 antibody (Fig. 1C). Fig. 1A is the H&E-stained section of the tumor. Thirty-two of the 54 patients (59%) had at least one eIF4E-positive margin, whereas only 6 patients (11%) had p53-positive margins. Of the 25 patients with p53-positive tumors, 15 (60%) patients had eIF4E-positive margins, whereas 6 (24%) patients had p53-positive margins. Fig. 1, E and F, is a histologically “tumor-free” margin (Fig. 1D; H&E) from a patient that was positive for eIF4E but not for p53. Fig. 1, H and I, are margins from a patient that is positive for both eIF4E and p53, respectively.

Table 2 shows a comparison of the distribution and average expression of eIF4E and p53 expression in the tumor according to four groups shown in Table 1. Again, there was no significant association between the expression of the markers in the tumor and the surgical margins. The correlation coefficient between p53 and eIF4E in the tumor was not significant (Spearman’s correlation, $P = 0.07$), unlike the margins that exhibited a significant correlation ($P = 0.03$).

eIF4E and p53 Expression and Treatment Outcome. The follow-up period ranged from 1 to 120 months. The overall median DFI was 25.5 months, with 25 of the 54 patients having recurrence of their tumor. Twenty-one of the 25 patients (84%) that recurred had eIF4E-positive margins, whereas 6 patients (24%) had p53-positive margins. All 6 of these patients also had eIF4E-positive margins. The primary end point of this study was DFI. Hence, the median DFI was 38.5 months for the eIF4E-negative margin group and 14.5 months for the eIF4E-positive margin group, respectively ($P = 0.0007$, log rank test). The median DFI was 27 months for the p53-negative margin group and 13.5 months for the p53-positive margin group ($P = 0.01$, log-rank test).

Univariate analysis showed that nodal status and eIF4E- and p53-positive margins were significantly associated with a poor prognosis (Table 3). However, the multivariate analyses using those factors that were significant at the 10% level in the univariate analysis indicated that only nodal status ($P = 0.0004$) and eIF4E in the margins ($P = 0.003$) were significant predictors of recurrence. The analysis showed an 8-fold risk of developing recurrence (2.5–24.4, 95% CI) for eIF4E-positive margin patients, with a 5-fold risk of recurrence (1.9–11.4, 95% CI) for positive nodes. Interestingly, p53 expression in the
surgical margins did not appear to have any additional effect on recurrence, presumably because all 6 patients with p53-positive margins were also positive for eIF4E. Fig. 2 shows the Kaplan-Meier analysis comparing time to recurrence for eIF4E and p53 positivity in the margins. There was a significant difference in time to recurrence between eIF4E-positive and -negative margins (Fig. 2A) and p53-positive and -negative margins (Fig. 2B). However, there was no further impact with the addition of p53 positivity to eIF4E-positive margins (Fig. 2C).

Combination of Nodal Status/p53 Margins/eIF4E in Margins. Because nodal status in larynx cancer is significantly associated with recurrence, a subset analysis was performed comparing eIF4E and p53 expression in the margins with the presence or absence of nodal metastasis. Fig. 3A shows that patients with eIF4E-positive margins significantly increased the probability of recurrence regardless of nodal status. A pairwise comparison of the curves show that recurrence in patients with node-negative, eIF4E-negative margins (curve A) was significantly different from patients with negative nodes and eIF4E-positive margins (C; \( P = 0.002 \)). Similarly, recurrences were less likely in patients with positive nodes and eIF4E-negative margins (B) than with positive nodes and margins (D; \( P = 0.0002 \)). Analysis for the influence of nodal positivity and p53 overexpression in the margins is shown in Fig. 3B. Margins that were p53 positive conferred a significantly worse DFI compared with patients with negative margins for node-negative disease (curve A versus C; \( P = 0.005 \)). However, p53-positive margins had no further effect on recurrence if...
significant (curve A versus majority of solid tumors require elevated levels of tumors was not a significant predictor of recurrence. It appears that the 54) of margins are consistent with previous results (4). Likewise, our findings of to the small sample size (8) or the discrepancies between immuno-expression of eIF4E a proto-oncogene, and p53, a tumor suppressor gene, have been demonstrated previously to have a significant impact on recurrence and hence on survival. Our findings of p53 overexpression in the primary tumor are similar to previous studies (13, 14). Presumably, the somewhat lower frequency of over-expression of p53 in the surgical margins in our series is attributable to the small sample size (8) or the discrepancies between immunohistochemistry and sequencing results (15). Likewise, our findings of eIF4E overexpression in 100% (54 of 54) of tumors and 59% (32 of 54) of margins are consistent with previous results (4).

In our series, overexpression of eIF4E and p53 in the primary tumors was not a significant predictor of recurrence. It appears that the majority of solid tumors require elevated levels of eIF4E for tumor progression. However, in HNSCC unlike breast cancer, once eIF4E is elevated in the tumor it ceases to be an important prognostic factor (4, 16). It may be that eIF4E plays an important role during the process of malignant transformation and not once invasion of the basement membrane has occurred. The prognostic role of p53 expression in tumors is still controversial. The lack of correlation between p53 expression and clinicopathological parameters originally reported by Field et al. (17) has been substantiated. In some studies, p53 has been shown to be a significant predictor of shorter survival, with p53 elevation associated with rapid tumor proliferation, highly malignant behavior, and earlier development of tumor recurrence and second primary tumors (18, 19). In patients treated with radiotherapy with curative intent, there was a significant reduced disease-free survival among patients whose tumors had mutation of p53 (20). In contrast, p53 overexpression was shown to correlate with increased survival in patients with squamous cell carcinoma of the tongue base (21). Overexpression of p53 predicts response to treatment with 74% of patients overexpressing p53 able to have larynx preservation versus 52.5% in the p53-negative group (22).

In our study, p53 and eIF4E expression in surgical margins were associated with an increase in recurrence rates. In earlier reports, p53 mutations and overexpression in surgical margins have predicted recurrence (8, 23). However, our multivariate analysis showed that only nodal status ($P = 0.0004$) and eIF4E in the margins ($P = 0.003$) were significant predictors of recurrence in larynx cancers. Although all six patients with p53-positive margins recurred, these six patients also had eIF4E-positive margins. Hence, when the simultaneous effect of both variables was tested, p53 overexpression was no longer significant. A similar conclusion was reached by Kaplan-Meier analysis comparing disease-free survival in patients with eIF4E-positive and p53-positive margins to patients with eIF4E-positive and p53-negative margins. It is possible that the small sample size could have masked a contribution of p53 overexpression in the margins. In our study of the 32 patients with eIF4E-positive margins, nodes were positive (curve B versus D; $P = 0.69$), although the presence of positive nodes alone, even in the p53-negative cases, was significant (curve A versus B; $P = 0.0008$).

**DISCUSSION**

In this study of laryngeal cancer, we wanted to correlate the prognostic value of eIF4E and p53 levels in the tumor and surgical margins. Overexpression of eIF4E, a proto-oncogene, and p53, a tumor suppressor gene, have been demonstrated previously to have a significant impact on recurrence and hence on survival. Our findings of p53 overexpression in the primary tumor are similar to previous studies (13, 14). Presumably, the somewhat lower frequency of over-expression of p53 in the surgical margins in our series is attributable to the small sample size (8) or the discrepancies between immunohistochemistry and sequencing results (15). Likewise, our findings of eIF4E overexpression in 100% (54 of 54) of tumors and 59% (32 of 54) of margins are consistent with previous results (4).

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18 patients had loco-regional recurrence, whereas only 3 had distant recurrence (Table 2). The effect of loco-regional recurrence on distant metastatic dissemination has been shown to be dependent events (24, 25).

Nodal metastasis is a known prognostic factor in HNSCC (26). Increased p53 expression in the primary tumors and positive nodes confers the worst prognosis (27). As we have shown previously, the combination of nodal metastasis with eIF4E-positive margins was significantly worse than nodal metastasis with eIF4E-negative margins (P = 0.0002). However, p53 overexpression in the margins did not worsen the prognosis for patients with nodal metastasis (P = 0.69).

There were 6 patients with p53-positive margins and 32 patients with eIF4E-positive margins. However, all patients with p53-positive margins also had eIF4E-positive margins. Hence, eIF4E overexpression is more prevalent than p53 and may suggest different routes to tumorigenesis. It is possible that eIF4E overexpression occurs earlier in the process of tumorigenesis than p53 expression, although the temporal relationship of these markers has not been elucidated. In previous studies, elevation of eIF4E appeared to be a relatively early event in the development of HNSCC tumors. The overexpression of eIF4E occurred in 44% of the preinvasive lesions of the head and neck displaying low-grade dysplasia (28). There are conflicting reports as to when in tumorigenesis p53 mutations appear. In HNSCC, p53 mutations have been reported as relatively late events in the genesis of head and neck cancers (6). In addition, p53 mutations are less common in preinvasive cancer than in invasive cancer (29). Thus, p53 mutations are not only less common events but also occur relatively late in tumor progression. However, other studies have shown that p53 was expressed in the early stages of malignant progression (30, 31). In this study, even in the 25 cases of p53-positive tumors, only 24% of the patients overexpressed p53 in the tumor margins, whereas 60% of these patients overexpressed eIF4E. Although the sequence of events in a multi-step process can only be compared in increasing grades of dysplasia, the data presented here and in earlier reports (28) suggest that early in this process eIF4E is elevated, providing the cell with a selective growth advantage. Interestingly, p53 expression in premalignant lesions was increased only in those specimens that exhibited detectable p53 expression in the tumors in the majority of cases (18, 30). We had similar findings because the expression of p53 in the margins was seen only in those cases that also expressed p53 in the primary tumor, although this could relate to the sensitivity of the assay.

The mechanisms by which eIF4E and p53 contribute to tumor progression are markedly different. Overexpression of eIF4E increases the translation of specific growth-promoting proteins, including cyclin D1, myc, ornithine decarboxylase, and proteins responsible for angiogenesis (basic fibroblast growth factor and vascular endothelial growth factor) and metastasis (V6 splice variant of CD 44 surface glycoprotein and collagenase type IV; Ref. 32). Mutations in p53 affect transcriptional control of gene control and dysregulate the cell cycle (13, 33). As a consequence, the biological role of p53 to protect cells from DNA damage is abrogated (34–36). In the clonal evolution model of tumor progression, a series of mutagenic events take place (37). The overexpression of p53 appears to occur later in this process and in turn may further contribute to enhanced genomic instability, resulting in tumor progression.

The prognosis of head and neck cancer has not changed in the past two decades. Markers are required to identify those patients who would benefit from adjuvant therapy. Because eIF4E is elevated in 100% of tumors and appears to be overexpressed earlier than p53, eIF4E overexpression in surgical margins appears to be the more sensitive marker for recurrence. In addition to its utility as a marker, eIF4E may be a suitable target for therapeutic intervention. In this regard, studies with antisense cDNA to eIF4E are contemplated in patients with eIF4E-positive margins who are at extremely high risk for recurrence (38).

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