

## Excision Repair Cross Complementation Group 1 Immunohistochemical Expression Predicts Objective Response and Cancer-Specific Survival in Patients Treated by Cisplatin-Based Induction Chemotherapy for Locally Advanced Head and Neck Squamous Cell Carcinoma

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**Abstract** **Purpose:** To assess the correlation of excision repair cross complementation group 1 (ERCC1) immunohistochemical expression with objective tumor response and cancer-specific survival in patients with locally advanced head and neck squamous cell carcinoma treated with cisplatin-based induction chemotherapy. **Experimental Design:** The initial cohort was composed of 107 patients who were treated from 1992 to 1996 by an induction chemotherapy regimen for locally advanced head and neck squamous cell carcinoma. *p53* mutations had previously been studied. Pretherapeutic biopsy samples from 96 patients with a known tumor response were available. Two independent observers blinded to clinical annotations evaluated ERCC1 immunohistochemical expression. **Results:** Of 96 patients, 68 (71%; 95% confidence interval, 61-79%) had tumors that expressed ERCC1 intensively and diffusely. Using the logistic regression method, the 28 (29%) patients with tumors expressing ERCC1 at lower levels had a 4-fold greater odds of benefiting from an objective response to chemotherapy (odds ratio, 4.3; 95% confidence interval, 1.4-13.4; *P* = 0.01) compared with the group of 68 patients with high ERCC1 expression. ERCC1 and *p53* status, but not their interaction, were independent predictors of tumor response. In a Cox proportional hazard model adjusted on age, TNM stage, tumor differentiation, and tumor localization, ERCC1 low expression was associated with a lower risk of cancer death (risk ratio, 0.42; 95% confidence interval, 0.20-0.90; *P* = 0.04) whereas *p53* status had no prognostic value. **Conclusion:** Our results suggest that those patients characterized by low ERCC1 expression are more likely to benefit from cisplatin induction chemotherapy compared with patients with high ERCC1 expression.

Nucleotide excision repair plays a central role among DNA repair pathways and has been associated with resistance to platinum-based chemotherapy (1). The excision repair cross complementation group 1 (ERCC1) enzyme plays a rate-limiting role in the nucleotide excision repair pathway which recognizes and removes cisplatin-induced DNA adducts (2-4). ERCC1 is also an important factor in DNA interstrand cross-

link repair as well as in recombination processes (5-7). Several *in vitro* studies have linked platinum resistance to ERCC1 mRNA expression in ovarian, cervical, testicular, bladder, and non-small-cell lung cancer cell lines (8). The relation between ERCC1 mRNA expression and resistance to platinum compounds has been further corroborated by small clinical retrospective studies in patients with advanced-stage gastric, ovarian, colorectal, esophageal, and non-small-cell lung cancers (8-18). Recently, we established that ERCC1 immunohistochemical expression was predictive of the survival benefit of cisplatin-based adjuvant chemotherapy in a large randomized trial in patients with surgically resected non-small-cell lung cancer (19).

During the 1980s, it was discovered that the administration of chemotherapy before surgery (induction chemotherapy) could dramatically shrink head and neck squamous cell carcinomas (20). This observation led to the concept that chemotherapy-responsive tumors could be subsequently treated with radiotherapy alone, allowing organ preservation. Although therapeutic options for locally advanced head and neck squamous cell carcinoma have now evolved to include concurrent chemotherapy and radiotherapy (21, 22), the study of previous induction chemotherapy protocols may still

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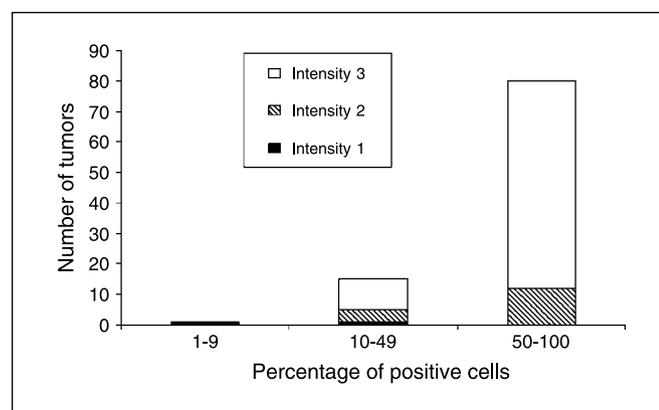
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**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

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**Fig. 1.** Distribution of percentage and intensity of ERCC1 immunostains in 96 patients.

provide useful information about which biological tumor characteristics can predict tumor responsiveness.

The goal of this study was to examine whether ERCC1 immunohistochemical expression predicted objective tumor response and cancer-specific survival in a cohort of patients who had been treated in the 1990s with a regimen of cisplatin-based induction chemotherapy for locally advanced head and neck squamous cell carcinoma.

## Materials and Methods

**Patients and treatment plan.** The study was composed 96 patients with locally advanced head and neck squamous cell carcinoma, who had been treated in the Service d'Oto-Rhino-Laryngologie et de Chirurgie de la Face et Cou (Hôpital Tenon, Paris, France) from 1992 to 1996. These 96 patients were part of a larger cohort including 107 patients who had been studied for *p53* mutations (23). From the initial cohort, paraffin-embedded tumor material was missing in nine cases. Two additional cases were excluded because of unavailable data about tumor response, yielding 96 patients. A comparison between the 96 patients included in this study and the 11 excluded patients showed that there was no significant difference in their main characteristics including gender, TNM stage, tumor localization, tumor differentiation, response rate, *p53* mutation rate, duration of follow-up, and number of cancer-specific deaths (Supplementary Table S1). The median age was lower ( $P = 0.04$ ) for included patients (60 years; interquartile range, 52-65 years) as compared with excluded patients (52 years; interquartile range, 48-58 years).

Eligible patients were predominantly men (86 of 96; 90%). According to the American Joint Committee on Cancer staging (24), the tumors were classified as T<sub>1</sub> and T<sub>2</sub> (18 patients) or T<sub>3</sub> and T<sub>4</sub> (78 patients), and nodal involvement was classified as N<sub>0</sub> (46 patients), N<sub>1</sub> (13 patients), N<sub>2</sub> (22 patients), or N<sub>3</sub> (15 patients). The primary tumor site was the oral cavity (3 patients), the oropharynx (35 patients), the larynx (36 patients), and the hypopharynx (22 patients).

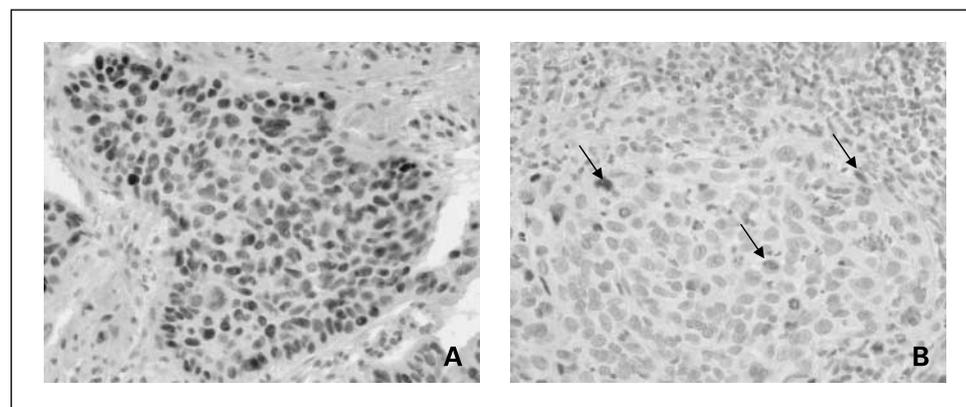
All induction regimens consisted of cycles combining cisplatin (20 mg/m<sup>2</sup>/d) and fluorouracil (1,000 mg/m<sup>2</sup>/d) for 4 days. Chemotherapy was discontinued in patients who did not respond after two cycles. Two patients had only 1 cycle, whereas 22 patients had 2 cycles and 72 patients had 3 cycles. An objective response was defined by tumor shrinkage of >50% of initial tumor size according to WHO criteria (25). Responders were treated by radiotherapy at the same institution. Patients with recurrent or metastatic disease during follow-up had additional radiotherapy (10 cases) and/or chemotherapy (28 cases) with various compounds including cisplatin, 5-fluorouracil, methotrexate, bleomycin, ifosfamide, and mitomycin C.

**Immunostaining for ERCC1.** A standard immunohistochemistry protocol was used. Briefly, after epitope retrieval in citrate buffer (10 mmol/L, pH 6.0; heated for 30 min in a water bath), slides were incubated at a 1:300 dilution for 60 min with a monoclonal ERCC1 mouse antibody (clone 8F1, NeoMarkers) that was raised against the full-length human ERCC1 protein. Antibody binding was detected by means of an ABC kit with NovaRED as the substrate (Vectastain Elite, Vector Laboratories) and Mayer's hematoxylin as the counterstain. Sections of normal tonsil tissues were included as external positive controls and endothelial cells or fibroblasts surrounding the tumor area served as internal positive controls.

**Microscopic analysis.** Two investigators (A.H.L. and J.H.), who were blinded to clinical data, independently evaluated ERCC1 staining under the light microscope at  $\times 200$  and  $\times 400$  magnifications. Tumor nuclear staining intensity was graded on a scale of 0 to 3 using adjacent nonmalignant cells as a reference (intensity 2). The percentage of positive tumor nuclei was evaluated and a proportion score was attributed (0 if 0%; 0.1 if 1-9%; 0.5 if 10-49%; 1.0 if  $\geq 50\%$ ) as previously described (26, 27). This proportion score was then multiplied by the staining intensity of nuclei to obtain a final semiquantitative H-score (26, 27).

**Sequencing of the *p53* gene.** All tumors had been analyzed by direct sequencing of all coding exons of the *p53* gene (23).

**Statistical analysis.** To compare groups, we used the Mann-Whitney *U* test for continuous variables and the Fisher exact test for discrete variables. Odds ratios and *P* values for predictors of tumor response were determined using the logistic regression method in univariate and multivariate analyses. Survival rates were estimated using the Kaplan-Meier method. Analysis of contributing factors to cancer-specific death was done using Cox models adjusted for known prognostic factors including age, tumor location, TNM stage, and tumor differentiation. All comparisons were two tailed.  $P < 0.05$  was considered significant.



**Fig. 2.** Representative examples of ERCC1 immunostains. *A*, H-score 3: strong and diffuse staining. *B*, H-score <3: moderate staining in few tumor cells (arrows). Original magnification,  $\times 400$ .

**Table 1.** Baseline characteristics of patients and tumors according to immunohistochemical ERCC1 expression levels

	Low ERCC1 H-score <3 (n = 28)	High ERCC1 H-score 3 (n = 68)	P
Age-years			
Median	62	59	0.15
Interquartile range	52-67	51-64	
Gender			
Female	3	7	1.00
Male	25	61	
T stage			
T <sub>1</sub> -T <sub>2</sub>	7	11	0.39
T <sub>3</sub> -T <sub>4</sub>	21	57	
N stage			
N <sub>0</sub> -N <sub>1</sub>	17	42	1.00
N <sub>2</sub> -N <sub>3</sub>	11	26	
Tumor differentiation			
Poor	9	6	0.03
Moderate	7	22	
Good	12	40	
Tumor localization			
Oral cavity	1	2	0.13
Oropharynx	13	22	
Larynx	12	24	
Hypopharynx	2	20	
p53 gene			
Wild-type	15	47	0.17
Mutated	13	21	

**Results**

**Immunohistochemical data.** The distribution of percentages and intensities of ERCC1 staining is shown in Fig. 1. The median H-score was equal to the maximum possible score (H-score 3) as 68 (71%) tumors expressed ERCC1 at that level. A score less than the median (H-score <3) was therefore used to identify low ERCC1 expression in 28 tumors. Representative examples of tumors expressing ERCC1 at low or high levels are shown in Fig. 2.

**ERCC1 staining and baseline characteristics of patients and tumors.** Table 1 shows baseline characteristics of patients and tumors according to ERCC1 expression. Tumors expressing ERCC1 at lower levels were less differentiated than those expressing the protein at high levels (P = 0.03). There was no difference for any other characteristics including age, gender, TNM stage, and tumor localization.

The p53 gene was mutated in 34 cases (Supplementary Table S2). There was no significant difference in the mutation rate between tumors with high ERCC1 levels (21 of 68; 31%) and those with low ERCC1 levels (13 of 28; 46%).

**ERCC1 staining and objective response to chemotherapy.** Among 28 patients with tumors expressing ERCC1 at low levels, 22 (79%) had an objective response, as compared with 38 of 68 (56%) patients with tumors expressing ERCC1 at high levels (P = 0.04).

The results of the logistic regression analysis of tumor response are shown in Table 2. In univariate analysis, patients with low ERCC1 levels had an almost 3-fold greater odds of responding to chemotherapy compared with patients with high ERCC1 levels. Patients with p53 wild-type status had a slightly

greater than 3-fold odds of responding to chemotherapy as compared with patients with p53 mutation. Both variables could be entered in a multivariate model (goodness of fit, P = 0.0006 by  $\chi^2$  test). The adjusted odds ratios were >4 for both p53 wild-type and ERCC1 low expression. The interaction between ERCC1 and p53 gene status was not significant (P = 0.53) and was not used in the model.

**ERCC1 staining and cancer-specific death.** A total of 49 cancer-specific deaths (37 in the high ERCC1 group and 12 in the low ERCC1 group) had been recorded. The median survival time was shorter for those patients with high ERCC1 tumors (27.7 months) than for patients with low ERCC1 tumors (40.5 months), but the difference was not significant (P = 0.25 by the log-rank test; Kaplan-Meier curves available on request). Using a Cox model adjusted on the main prognostic factors including age, TNM stage, tumor location, and tumor differentiation, the hazard of cancer-specific death was lower in those patients with low ERCC1 tumors (adjusted hazard ratio, 0.42; 95% confidence interval, 0.20-0.90) as compared with patients with high ERCC1 tumors (overall model fit, P = 0.0005 by  $\chi^2$  test). Adjusted hazard ratios for each variable are shown in Table 3. Neither p53 status nor the interaction between ERCC1 expression and p53 status was prognostic in this model.

**Discussion**

In the current study, we evaluated ERCC1 expression by immunohistochemistry within the nuclei of tumor cells in patients with advanced head and neck squamous cell carcinoma treated by cisplatin-based induction chemotherapy. The assumption was that pretherapeutic ERCC1 protein levels within tumor cells were correlated with their DNA damage repair capacity. A less efficient DNA-repair capacity could affect the cell response to DNA damage and could thus render cancer cells more sensitive to cisplatin chemotherapy. We found that both

**Table 2.** Odds ratio and P value for ERCC1 expression, p53 status, T stage, and N stage using logistic regression analysis of objective response

	Odds ratio	95% Confidence interval		P
		Low	High	
Univariate analyses				
ERCC1 H-score				
<3	2.9	1.04	8.0	0.04
3	1			
p53 gene				
Wild-type	3.3	1.4	8.0	0.007
Mutated	1			
T stage				
T <sub>1</sub> -T <sub>2</sub>	1.7	0.6	5.3	0.35
T <sub>3</sub> -T <sub>4</sub>	1			
N stage				
N <sub>0</sub> -N <sub>1</sub>	1.5	0.6	3.5	0.36
N <sub>2</sub> -N <sub>3</sub>	1			
Multivariate analysis				
ERCC1 H-score				
<3	4.3	1.4	13.4	0.01
3	1			
p53 gene				
Wild-type	4.6	1.7	12.1	0.002
Mutated	1			

**Table 3.** Hazard ratios for cancer death in the Cox model adjusted on main prognostic factors in head and neck squamous cell carcinoma

	Adjusted hazard ratio	95% Confidence interval		P
		Low	High	
Age	0.96	0.93	0.99	0.02
T stage (T <sub>1</sub> -T <sub>2</sub> vs T <sub>3</sub> -T <sub>4</sub> )	0.76	0.34	1.69	0.50
N stage (N <sub>0</sub> -N <sub>1</sub> vs N <sub>2</sub> -N <sub>3</sub> )	0.41	0.22	0.76	0.004
M stage (M <sub>0</sub> vs M <sub>1</sub> )	0.18	0.08	0.42	0.0001
Tumor differentiation	0.73	0.46	1.15	0.17
Tumor localization	1.06	0.75	1.52	0.73
ERCC1 (H-score <3 vs 3)	0.42	0.20	0.90	0.03

tumor response rate and cancer-specific survival were inversely correlated to ERCC1 expression within tumor nuclei before treatment, which is consistent with our initial hypothesis.

Our study was based on the results from a well-documented cohort, in which *p53* gene status had been found predictive of tumor response (23). Although it was not possible to study all tumor samples for the original cohort, eligible cases that were included in our study did not significantly differ in most of their characteristics from cases that were not, including frequency of the *p53* mutation and response rates. Excluded patients were younger than included patients, but no correlation between age and tumor response has ever been documented in head and neck squamous cell carcinoma.

Evaluation of the immunohistochemical staining was based on a semiquantitative scale measuring the percentage of tumor cells stained and the intensity of staining that used as a reference the internal protein expression in nonmalignant cells adjacent to tumor cells. Because ERCC1 is ubiquitously expressed in nontumor cells, the internal reference method reduces the sample variability that can be affected by tissue fixation. The same scoring method was used as in the IALT-Bio study on non-small-cell lung cancer (19), and in both studies the cutoff value for ERCC1 levels was a priori defined as the median, which allowed the best possible assignment of the study population to the two subgroups of low and high ERCC1 expression.

Tumor shrinkage is induced by chemotherapy and, if confirmed by independent studies, ERCC1 expression can be considered as a predictor of tumor response to cisplatin-based chemotherapy. The meaning of the association between low ERCC1 and prognosis is less clear, however. First, it should be noted that the difference in prognosis between low and high expressers observed in our present report as well as in previously mentioned studies (8–18) could be due to intrinsic differences in tumor biology instead of being related to treatment. Second, whereas ERCC1 action is clearly crucial for nucleotide excision repair, it can also play a role in other DNA damage repair processes, notably recombination, which is involved in the repair of radiation-induced DNA double-strand breaks (5–7). Joshi et al. (11) have reported that *ERCC1*, *thymidylate synthase 1*, and *glutathione S-transferase  $\pi$*  mRNA high expression was associated with shorter survival of patients treated with trimodality therapy for esophageal cancer. Nix et al. (28) also reported that “normal” expression of both ERCC1 and XRCC1 was associated with radioresistance in laryngeal tumors. In the study population, responders to cisplatin-based chemotherapy were subsequently treated with

radiotherapy. We cannot exclude that the better prognosis in patients with low ERCC1 could be related to increased sensitivity to radiotherapy or to additional treatments during follow-up, or that *p53* status could have an effect in subgroups of patients in relationship with the use of particular compounds.

Moreover, our study harbors several limitations: only 29% (95% confidence interval, 21-39%) of tumors had ERCC1 levels lower than the median, which is in contrast with the high proportion of responders as well as the generally recognized sensitivity of head and neck squamous cell carcinoma to cisplatin-based chemotherapy. Indeed, 63% (95% confidence interval, 53-72%) of the patients in our study experienced an objective response; that is, apart from patients with low ERCC1 expression, many patients with high ERCC1 expression also benefited from cisplatin-based chemotherapy. The low sensitivity of the ERCC1 test (i.e., the low probability of reduced ERCC1 expression among responders) clearly limits its usefulness as a predictive tool for individual patients. Moreover, this remark implies that other molecular mechanisms lie in the complex pathway leading to tumor response. Indeed, the predictive value of ERCC1 was stronger when the variable was analyzed together with *p53* gene status. Interactions between ERCC1 and *p53* are complex, and few conclusions can be drawn about how these proteins can act together to explain the cell response to cisplatin. The most obvious scenario is that DNA damage signaling induces a cell growth arrest mediated by the *p53*-induced cyclin-dependent kinase inhibitor p21<sup>WAF</sup>, thus allowing DNA repair to proceed before replication. Whereas this scenario cannot be refuted, the lack of statistical association between ERCC1 protein expression and *p53* mutational status suggests that the actions of ERCC1 and *p53* are, at least in part, independent. In mouse models, *p53* levels are increased in *ERCC1*-deficient cells, but the absence of *p53* does not rescue the *ERCC1*-deficient phenotype (29).

In conclusion, the present study suggests that ERCC1-mediated repair of DNA damage contributes to the clinical outcome in patients treated with cisplatin-based induction chemotherapy for advanced head and neck squamous cell carcinoma. In this context, it is strongly recommended to include the collection of tissue or blood samples to assess tumor DNA repair capacity or surrogate markers, such as ERCC1 expression and DNA repair polymorphisms (30), in every prospective trial on induction chemotherapy. Whereas most trials on induction chemotherapy failed to reveal any survival benefit, the study of biomarkers involved in DNA damage repair could help to identify the subgroup of patients most likely to benefit from chemotherapy.

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