

**PROGNOSTIC SIGNIFICANCE OF EGFR, p53 AND E-CADHERIN
IN MUCOEPIDERMOID CANCER OF THE SALIVARY GLANDS
A Retrospective Case Series**

Jeanine HOYEK-GEBEILY¹, Edgard NEHMÉ¹, Georges AFTIMOS²
Claude SADER-GHORRA³, Zouka SARGI⁴, Amine HADDAD⁴

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ABSTRACT • OBJECTIVE : Evaluate the prognostic significance of EGFR, p53 and E-cadherin known, along with histopathologic criteria, in mucoepidermoid cancer (MEC) of the salivary glands.

MATERIALS & METHODS : Retrospective case series review between January 1994 and December 2002 of all patients with salivary glands mucoepidermoid cancer treated at one university hospital. Histopathology review and immunohistochemistry study for EGFR, p53 and E-cadherin was undertaken on formalin-fixed, paraffin embedded surgical specimens. Clinicopathological parameters were reviewed and survival analysis was conducted to study the prognostic significance of these factors.

SETTINGS : All patients were treated by the same multidisciplinary team which included three head and neck surgeons, one plastic surgeon, two medical oncologists and one radiation oncologist at Hôtel-Dieu de France, a tertiary care university hospital of Saint-Joseph University, Beirut-Lebanon.

RESULTS : Thirteen patients were treated for MEC during this period. The parotid gland was the most common site. Mean survival in this series was 61 ± 8 months (95% CI = 46-77 months). Positive lymph nodes status was a significant predictor of poor survival. EGFR and p53 were correlated to histological grade. EGFR tended also to be more elevated in major salivary gland tumors.

CONCLUSION : EGFR and p53 expressions were highly correlated to high histological grade, making them an interesting target for further investigation as prognostic factors in MEC.

INTRODUCTION

Mucoepidermoid carcinoma (MEC) is the most common malignant neoplasm of the salivary glands. Since its original classification in a "relatively favorable" group and a "high grade unfavorable" group, many grading schemes have been proposed. There is a large amount of evidence that currently accepted histological grading criteria correlate well with clinical behavior of these

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RÉSUMÉ • OBJECTIF : Evaluer l'influence pronostique de l'expression de l'EGFR et d'autres marqueurs tumoraux dans le cancer muco-épidermoïde (CME) des glandes salivaires.

MATÉRIEL & MÉTHODES : Revue rétrospective de tous les patients atteints de CME des glandes salivaires consultant à l'Hôtel-Dieu de France, centre tertiaire hospitalo-universitaire à Beyrouth, Liban, entre janvier 1994 et décembre 2002. Tous les patients ont été pris en charge par une équipe multidisciplinaire comportant trois chirurgiens ORL, un chirurgien plastique, deux oncologues et un radiothérapeute. Une étude immunohistochimique des facteurs p53, EGFR et E-cadhérine sur des spécimens chirurgicaux fixés au formol et incorporés dans la paraffine a été faite. Une analyse de survie a été ensuite menée pour évaluer l'influence de l'expression de ces marqueurs sur la survie.

RÉSULTATS : Treize patients ont été traités pour CME des glandes salivaires durant la période d'étude. La glande parotide a été la plus fréquemment atteinte. La survie moyenne a été de 61 ± 8 mois (IC à 95 % = 46-77 mois). La présence d'adénopathies s'est révélée être un facteur pronostique défavorable pour la survie. L'EGFR et la p53 ont été fortement corrélés au grade histologique. L'EGFR a de plus tendance à être plus élevé au niveau des glandes salivaires majeures.

CONCLUSION : La présence d'adénopathies a eu un impact pronostique défavorable significatif sur la survie. L'EGFR et la p53 sont fortement corrélés au grade histologique et semblent constituer une cible intéressante à explorer.

tumors [2]. Moreover, therapeutic decisions are based almost exclusively on histopathological criteria. More recently, several trials were conducted to define other reliable diagnostic and prognostic factors that could potentially influence therapeutic decisions.

Tumor markers are substances produced by tumor cells and help identifying them. Serologic tumor markers have been of little clinical interest in MEC and have deliberately been excluded in this study. Immunological

Departments of ¹Diagnostic and Oral Pathology, Faculty of Dental Medicine, Saint Joseph University (USJ), Beirut ; ²Histopathology, Faculty of Medicine, USJ ; ³Histopathology & ⁴ENT, CHU Hôtel-Dieu de France, Beirut, Lebanon.

Correspondance : Jeanine Hoyek-Gebeily, DDS, Faculty of Dental Medicine, St Joseph University, Beirut, Lebanon.

Phone : +961 3 699660

E-mail : jeanine_gebeily@hotmail.com

markers are more specific ; early studies show that EGFR (epidermal growth factor receptor) may play a therapeutic role in the future [16] ; it is a transmembranal proteic receptor with a tyrosine kinase activity which recognizes two ligands : EGF (epidermal growth factor) and TNF (tumor necrosing factor) ; high levels of EGFR have been associated with squamous cell carcinoma particularly in the aerodigestive tract where it has been associated with a higher rate of recurrence.

p53 protein is a tumor suppressor factor located on chromosome 17 and coded by the tumor suppressor gene ; it plays a major role in growth and regulation of normal cells and thus in inhibiting cancer cell formation.

Similarly, E-cadherin, an adhesion molecule, calcium dependent, plays an important role in cell growth and development. It may play a significant role in suppressing tumor development.

All three markers mentioned are known to have some relation to MEC of the salivary glands [3]. Data on the topic has shown conflicting results and no clear conclusions can be drawn [10, 16, 18].

MATERIALS AND METHODS

Patients

After approval of the study protocol by the ethics committee, the database of a tertiary university hospital – Hôtel-Dieu de France Hospital – was consulted for complete data retrieval. All patients having a mucoepidermoid cancer of the salivary glands at Hôtel-Dieu de France Hospital – between January 1994 and December 2002 were included. Charts were retrospectively reviewed up to the first diagnosis of malignancy and clinical and histological informations were collected for each case. All patients were treated by the same multi-disciplinary team which included three head and neck surgeons, one plastic surgeon, two medical oncologists and one radiation oncologist, according to a pre-established protocol of the Tumor Board at our institution.

Clinical information was retrieved from the medical records of the patients and data was gathered in order to complete the follow-up procedure for a complete survival analysis with no lost to follow-up. The following variables were studied : age at diagnosis, sex, tumor location, affected salivary glands, tumor size, histologi-

cal grade, presence of positive lymph nodes, presence of distant metastasis, tumor recurrence, disease free survival (DFS), and three tumor markers levels and distribution (p53, E-cadherin and EGFR).

Pathology and immunohistochemistry

Hematoxylin- and eosin-stained slides for all patients were reviewed and analyzed for histological grading, according to the criteria described by Auclair et al. [2] : a quantitative grading system based on a point score for each of the five histopathologic features was employed. Tumors with a point score of 0-4 were considered low grade, those with 5 or 6 where considered intermediate, and those with 7 or higher were considered high grade (Table I).

Then formalin-fixed, paraffin-embedded specimens available for all patients were cut, deparaffinized and rehydrated. Immunostaining for the markers was performed according to the manufacturer's instructions (EGFR : Biogenex®, p53 and E-cadherin : Novocastra®). Positive and negative controls were included with each group of sections for every marker. All stained slides were blindly reviewed by two experienced pathologists, without any knowledge of the clinical outcome. Range of expression of the studied markers • p53 (0 to 100) • E-cadherin (1 to 3) • EGFR (1 to 3), was determined as follows :

p53 was assessed by counting the numbers of positive nuclei in 400 cells in each tumor (Fig. 1).

E-cadherin and EGFR were graded on a score from 0 to 3 according to the score used in assessing c-erb-B2 as follow (Fig. 2 and 3) :

- 1.0 = No staining at all or membrane staining in less than 10 % of the tumor cells.
- 1+ = Faint/barely perceptible membrane staining in more than 10% of tumor cells. **The cells are only stained in part of their membrane.**
- 2+ = Weak to moderate staining of the entire membrane in more than 10% of tumor cells.
- 3+ = Strong membrane staining in more than 10% of the tumor cells.

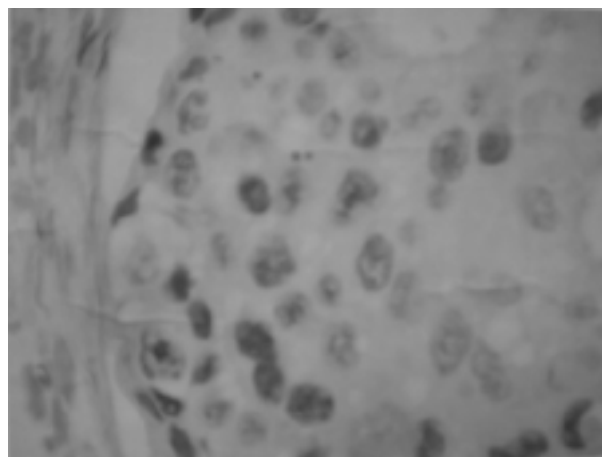


FIGURE 1. p53 expression

TABLE I
GRADING PARAMETERS AND POINT VALUES

PARAMETER	Point value
INTRACYSTIC COMPONENT < 20%	+ 2
NEURAL INVASION PRESENT	+ 2
NECROSIS PRESENT	+ 3
MITOSIS (4 or more per 10 HPF*)	+ 3
ANAPLASIA PRESENT	+ 4

*HPF: high power fields

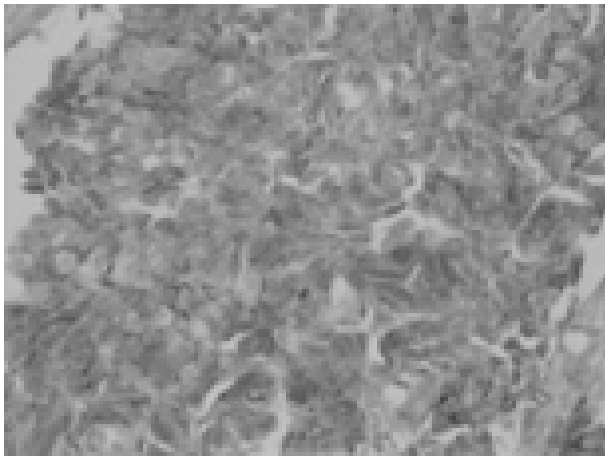


FIGURE 2. E-cadherin expression

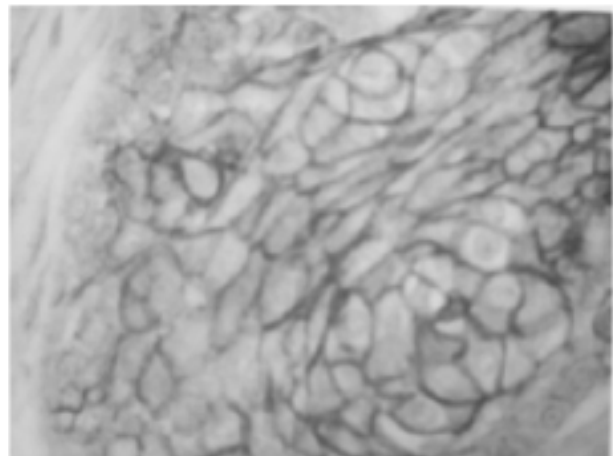


FIGURE 3. EGFR expression

Statistical analysis

Survival curves were calculated using Kaplan Meier Method (Fig. 4). Logrank test was used to test significance for qualitative factors. Univariate Cox proportional hazards models were adjusted for ordinal and semi-quantitative factors. The resulting univariate Odds Ratio (OR) is an estimation of the multiplicative risk ratio for each increment of the studied factor along with its 95% confidence interval. Univariate non parametric correlations between histological grade and tumor markers were done by Spearman's rho. The non parametric Mann Whitney U-test was used to compare tumor markers' levels between minor and major salivary glands. All statistical tests were two sided. A p value less than .05 is considered significant. All computations were done using SPSS v13 software (Chicago, Illinois). Results are expressed as percentage, mean \pm standard deviation (SD), range (minimum, maximum) median and 95% confidence intervals (CI).

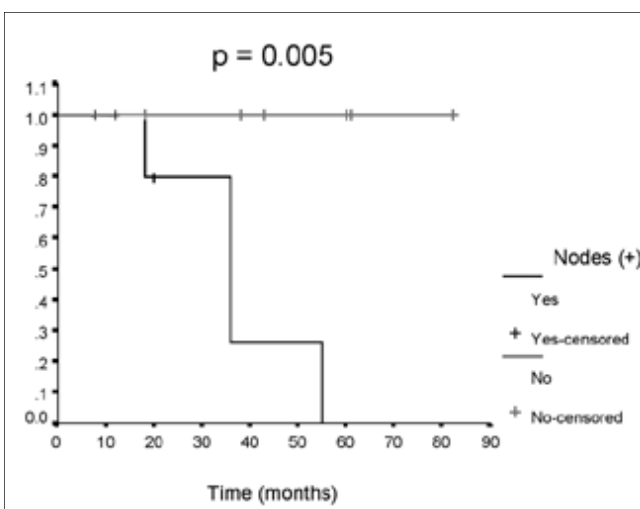


FIGURE 4. Cumulative survival of the 13 patients according to the status of lymph nodes (positive versus negative) using Kaplan-Meier method.

RESULTS

Descriptive study of the series

Thirteen patients fulfilled the inclusion criteria ; these were 7 men and 6 women, with a mean age 44.2 ± 21.1 years (14-80 years, median 44 years). Tumor's primary sites were distributed as follows : 9 parotid (69%), 1 sub mandibular, 2 palate and 1 sublingual). Mean maximal pathologic diameter of these lesions was 2.8 ± 3.7 cm with a median diameter 1.8 cm (1-14 cm). On follow-up, recurrence occurred in 5 cases after surgical excision (38.5%). Seven patients had nodal metastasis at the time of diagnosis (53.8%). Three patients developed metastasis (23.1%) and 4 patients died of the disease (DOD) during the follow-up period (30.8%). Only two cases had intermediate histological grade whereas the other 11 were distributed evenly in low and high grades.

Individual characteristics, tumor markers' levels and global survival of this series are shown in Table II. Survival rate reaches $90.1\% \pm 8.7\%$ at 6 months, decreases drastically to $68.2\% \pm 15.4\%$ at 12 months down to $51.1\% \pm 18.7\%$ at 55 months. Mean survival in this series was 61 ± 8 months (95% CI = 46-77 months). For p53, 75% of the cases had an expression as weak. E-cadherin was highly positive (3+) in 60% of the cases and EGFR was positive (2 to 3+) in 75% of the series.

Prognostic factors

Qualitative factors were studied in univariate analysis to assess their impact on survival. For example, 1 death occurred in men and 3 deaths occurred in women groups during follow-up. Mean survival in women was 73 ± 7 months (95% CI = 59-87 months), and mean survival in men was 39 ± 7 months (95% CI = 25-53 months). The observed difference in survival did not reach statistical significance ($p = 0.091$). Factors appearing to significantly alter late survival include positive lymph nodes ($p = 0.005$), the other factor being near significant, namely histological grade ($p = 0.110$) and less significantly parotid localization ($p = 0.132$). Figure 1 depicts

TABLE II
GLOBAL SURVIVAL RATE OF THE CURRENT SERIES

PATIENT	Gender	Age	Location	LOFU (Months)	Death	Survival ± SD	p53	E-Cadherin	EGFR	Histologic grade
1	M	58	Parotid	8	No	100%	50	3	2	High
2	M	65	Parotid	12	No	100%	0	1	2	High
3	M	67	Sublingual	18	Yes	90.9% ± 8.7%	0	3	1	High
4	M	18	Parotid	18	No	90.9% ± 8.7%	5	3	3	Intermediate
5	F	27	Parotid	20	No	90.9% ± 8.7%	0	3	1	Low
6	M	80	Parotid	36	Yes	68.2% ± 15.4%	3	3	3	High
7	M	60	Parotid	36	Yes	68.2% ± 15.4%	0	3	3	High
8	F	25	Palatine	38	No	68.2% ± 15.4%	0	2	1	Low
9	F	14	Palatine	43	No	68.2% ± 15.4%	0	2	2	Low
10	F	52	Parotid	55	Yes	51.1% ± 18.7%	10	2	2	High
11	M	44	Parotid	60	No	51.1% ± 18.7%	0	2	2	Low
12	F	30	Parotid	61	No	51.1% ± 18.7%	0	2	2	Low
13	F	34	Sub mandibular	82	No	51.1% ± 18.7%	0	3	2	Intermediate

LOFU : length of follow-up SD : standard deviation F : female M : male

for example survival plots according to lymph nodes status (positive or negative) showing a worse prognosis in patients with positive lymph nodes.

Each of quantitative and ordinal factors was assessed separately to elucidate their prognostic impact on survival. The resulting univariate odds ratio (OR) is an estimation of the multiplicative risk ratio for each increment of the studied factor along with its 95% confidence interval. Table III summarizes these data along with their statistical significance. Among these, only one factor proved to be near significant : histological grade (treated as ordinal variable) with a p value of 0.064. That is, for each increment of one unit in histological grade, risk of death is multiplied by 1.30 (95% CI = .99-1.70).

Relation between tumor markers and tumor localization

Tumor markers' levels were compared between minor and major salivary glands. Among all assessed factors, EGFR was statistically near significantly more elevated in major salivary glands (p = 0.063).

TABLE III

QUANTITATIVE FACTORS' IMPACT ON SURVIVAL AS DETERMINED BY UNIVARIATE COX REGRESSION

FACTOR	p	OR	IC 95%
Lesion size	.255	13.75	.15 - 1255.40
Age	.235	1.03	.98 - 1.09
Histological grade	.064	1.30	.99 - 1.70
p53	.164	1.16	.94 - 1.44
E-cadherin	.165	5.12	.51 - 51.32
EGFR	.110	2.11	.82 - 7.10

OR : odds ratio CI : confidence interval

Relation between tumor markers and histologic grade

Among all the factors studied, EGFR and p53 were the only factors being positively and almost statistically correlated to histological grade (p = 0.052 and 0.056 respectively by Spearman's statistics). That is EGFR, p53 and histological grade vary in the same directions.

DISCUSSION

Most of the 13 cases of mucoepidermoid cancer in this series occurred in the major salivary glands, predominantly the parotid gland, as opposed to the minor salivary glands with palatine propensity. This pattern is concordant with that of Brandwein et al. [1], showing a similar distribution in 48 cases of MEC of the salivary glands. Moreover, Goode et al. [4] found, in 234 cases of MEC of the salivary glands, that parotid gland was the most frequent localization (84%). In his series, recurrence rate was 9%, distant metastases were present in 5% of the cases and mortality was 11% with a follow-up of 156 months. Results of our series show a higher recurrence rate, more frequent metastases and a higher late mortality as well as a higher rate of patients with positive nodes at the time of diagnosis. Overall, global survival of our series decreases drastically at 12 months, reaching 51% at 82 months.

Among factors influencing survival, gender was found nearly statistically significant, with a worse prognosis for men who have a mean survival half that of women. Positive lymph nodes and histological grade were significantly or near significantly associated to a worse prognosis, all reducing survival by nearly half. Negative prognostic value of positive lymph nodes was also depicted by Pires et al. [3]. Conversely, in our series, age

at diagnosis, recurrence, tumor size and parotid localization did not influence survival. Similarly, Goode et al. [4] have established that most cases of MEC of the major salivary glands have low histological grade with good prognosis following superficial or total parotidectomy, with roughly no correlation with tumor size. Moreover, patients with high grade tumors and lesion size less than 3 cm had good prognosis following aggressive treatment, that is, no recurrence or local recurrence.

To date, data concerning prognostic significance of tumor markers in MEC of the salivary glands are inconclusive [5-6]. For example, in 15 cases of MEC of the submandibular glands, Alves et al. [7] found that Ki67 expression was 47.7% and was related to bad prognosis, a fact not confirmed by other studies [8-11]. In other examples, Cardoso et al. [12] and Frankenthaler et al. [13] linked PCNA expression to histological grade while Pires et al. [3] found it had no impact on survival. In the series of Perez et al. [14] composed mainly of 21 children and adolescents, expression of p53, PCNA, Ki67, C-erb-2 and Bcl-2 was not correlated to prognosis, a finding similar to the series of Kernohan et al. [15] concerning specifically C-erb-2. This correlation of Ki67, C-erb-2 and PCNA to survival was not addressed in our series which focused only on p53, EGFR and E-cadherin.

In the present series, 75% of the cases had an expression of p53 as weak as 5 points on a 100-scale, E-cadherin 3+ in roughly half of the cases and EGFR 2 to 3+ in 75% of the cases. Weak to moderate loss of expression of E-cadherin has been related to malignant tumors subtype including mucoepidermoid low-grade of the salivary glands [16-17], and moderate to extreme loss or alternative cytoplasmic non-functional expression of E-cadherin were observed in cases of high-grade carcinomas [16]. These findings suggest an association of E-cadherin expression with histological grade of MEC, which could not be confirmed in this series.

EGFR tends to be more elevated in major salivary glands tumors. EGFR expression tends to correlate with histological grade, both varying in the same direction, a finding corroborated by Kiyoshima et al. [10]. Gibbons et al. [18] found also a higher expression of EGFR in MEC cytoplasm and membrane. Moreover, knowing that histological grade has a near significant effect on survival as demonstrated from Cox regression, the combination EGFR-Histological grade would bear a more significant prognostic value.

p53 did not seem to have a significant impact on survival in our series. Yin et al. [11], in their series of MEC of the minor salivary, found a similar impact of p53, Bcl-2, TUNEL (a marker of apoptosis) and Ki67 on survival. p53 was almost correlated with histological grade in this series, corroborating the results of Kiyoshima [10].

The retrospective character of our series portends an inherent bias. Another limitation is that of the independence of predictors, that is, if the effects observed for each factor are independent of those of the other factors.

The answer cannot be found in this series because of the small sample size.

Despite the small number of cases in this retrospective study, there seems to be a clear trend for EGFR and p53 markers to correlate with histological grade. Further studies are required to assess the real prognostic significance of these tumor markers.

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مفهوم انذار 35p و EGFR و E-CADHERIN في سرطان بشراني مخاطي للغدد اللعابية. دراسة مجموعة استرجاعية.

موجز: الموضوع – تقييم الاثر الانذاري لمفهوم EGFR للغدد اللعابية.

المرضى والطرق – سيرة استرجاعية لكل المصابين بسرطان بشراني مخاطي للغدد اللعابية الذين استشاروا مستشفى اوتيل ديو الاستشفائي التابع لجامعة القديس يوسف في بيروت – لبنان من كانون الثاني (يناير) ١٩٩٤ لغاية كانون الاول (ديسمبر) ٢٠٠٢. اهتم بكل المرضى مجموعة اختصاصيين شملت ٣ جراحين في امراض الاذن والانف والحنجرة وجراح تجميل واختصاصيين (٢) بالامراض السرطانية واختصاصي بالمعالجة الاشعاعية. دراسة مناعية نسجية كيميائية للعوامل p53 و EGFR و E-CADHERIN على الانموذج الجراحي المثبت بالفرمول ومدمج بالبرافين. دراسة حياة المرضى لاحقا تمت لتقييم تاثير الواسم على الحياة.

النتائج – ١٣ مصابا بسرطان بشراني مخاطي عولجوا خلال دراسة الموضوع. الغدة النكفية كانت الاكثر اصابة. متوسط الحياة لهذه المجموعة ٦١ ± ٨ شهور (فترة ثقة ٩٥% = ٤٦ – ٧٧ شهرا). كان وجود عقد مريضة من الاسباب السيئة للانذار.

نسبة للحياة EGFR و p53 متعلقة بالدرجة النسجية EGFR وكان اتجاهه الى المستوى الاعلى للعقد اللعابية الهامة **الخلاصة –** وجود العقد المريضة يشير الى الانذار السيء نسبة للحياة. EGFR و p53 متعلق بالدرجة النسجية وتشكل هدفا هاما للبحث في هذا الموضوع.