

HEAD AND NECK

The prognostic significance of E-cadherin expression in laryngeal squamous-cell carcinoma: a systematic review

Il significato prognostico dell'espressione di E-caderina nel carcinoma a cellule squamose della laringe: una revisione sistematica

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SUMMARY

The aim of this study was to systematically review publications that investigated the prognostic role of E-cadherin immunostaining in patients affected by laryngeal squamous cell carcinoma. An appropriate string was run on PubMed to retrieve articles dealing with this topic. A double cross-check was performed on citations and full-text articles by two authors independently to analyse all manuscripts and perform a comprehensive quality assessment. Among 89 abstracts identified, 13 articles were included. These studies reported on 1,121 patients with histologically confirmed diagnosis of laryngeal squamous cell carcinoma. Overall, there were 10 studies that showed a significant correlation between E-cadherin immunohistochemical expression and at least one of the clinical and histopathological parameters considered by the authors. In particular E-cadherin expression was significantly associated with N stage (five studies), grading (four studies) and disease-free survival/disease-specific survival (six studies). In conclusion, the findings of our review appear similar to the results published by other authors on the putative role of E-cadherin in progression of malignancy. In fact, for laryngeal squamous cell carcinoma it seems that lower levels of E-cadherin correlate with increased tumoural aggressiveness and worse prognosis. Nevertheless, further high-quality prospective studies should be carried out to clarify if E-cadherin expression may be considered as an independent prognostic factor for patients affected by laryngeal cancer.

KEY WORDS: Laryngeal squamous carcinoma • Immunohistochemistry • E-cadherin • Prognostic factors

RIASSUNTO

L'obiettivo di questo studio è stato di revisionare in modo sistematico gli articoli che indagavano il ruolo prognostico dell'espressione immunoistochimica di E-caderina nei pazienti affetti da carcinoma laringeo a cellule squamose. Una stringa di parole chiave è stata utilizzata per trovare su PubMed gli articoli pubblicati riguardo a questo argomento. Una doppia scansione incrociata è stata poi eseguita da due degli autori sulle citazioni e sui testi degli articoli per analizzare tutti i lavori e ottenere una piena verifica della qualità di ricerca. Su un totale di 89 articoli identificati sono stati inclusi 13 studi. Questi studi riportavano 1.121 pazienti con diagnosi confermata di carcinoma laringeo a cellule squamose. Complessivamente 10 studi hanno mostrato una correlazione significativa tra l'espressione immunoistochimica di E-caderina con almeno uno dei parametri clinico-patologici presi in esame dagli autori. In particolare l'espressione di E-caderina è risultata statisticamente connessa allo stadio linfonodale (cinque studi), al grading istologico (quattro studi), alla sopravvivenza libera da malattia (sei studi). In conclusione i dati osservati nella nostra revisione appaiono simili ai risultati pubblicati da altri autori riguardo il possibile ruolo di E-caderina nella progressione di varie neoplasie maligne. Infatti anche per il carcinoma a cellule squamose della laringe sembra che livelli più bassi di E-caderina siano correlati ad un aumento dell'aggressività tumorale e ad un peggioramento della prognosi finale. Tuttavia ulteriori studi prospettici di alta qualità dovrebbero essere compiuti per poter considerare l'espressione di E-caderina come un fattore indipendente di prognosi nei pazienti affetti da carcinoma laringeo a cellule squamose.

PAROLE CHIAVE: Carcinoma laringeo a cellule squamose • Immunoistochimica • E-caderina • Fattori prognostici

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Introduction

Head and neck squamous cell carcinoma (SCC) is the sixth most common type of cancer in the world, accounting for more than 540,000 new cases and 271,000 mortalities each year. Laryngeal SCC represents the second most common malignancy of the head and neck region in adults accounting for about 1.5% of all cancers ¹.

Known prognostic factors for survival and prognosis in laryngeal SCC are histopathological grading, involved subsite and tumour stage according to the TNM classification. Of these, the TNM system is the most sufficient, but its weakness in terms of prognostic accuracy is well recognised and patients with identical clinicopathologic features can show different clinical course or response to the same therapy ².

For subjects affected by laryngeal SCC, poor survival can be mainly attributed to the high frequency of local recurrence. In fact, the presence of lymph node metastases represents the most important adverse independent prognostic factor in this malignancy and decreases overall survival by more than 50% if extracapsular expansion exists ³.

On the basis of the primary laryngeal subsite involved, for subjects with a clinically negative neck (cN0) there are two main strategies, which include elective neck dissection and “watchful waiting”. Currently, the National Cancer Comprehensive Network’s practice guidelines recommend to perform elective neck dissection for clinical N0 supraglottic SCC ⁴. However, personalised management of the cN0 neck, especially in patients with early laryngeal SCC would benefit greatly from staging techniques that increase the accuracy of assessment of nodal disease.

For these reasons, clinical staging should be supplemented by other factors that would increase our knowledge about the biologic behaviour of this tumour, and biological markers capable of distinguishing patients with good prognosis from those with poor prognosis are thus required ⁵.

An important step in the process of tumour metastases is the detachment of malignant cells from their original site. In normal epithelial tissues, cell-cell adhesion is mediated by a large number of cell adhesion molecules ⁶. Cadherins are a family of transmembrane glycoproteins with a highly conserved cytoplasmic tail, which interacts with the cytoskeleton via the intracellular proteins a, b and g catenins. The cadherin family contains several members, depending on their tissue distribution, including E-cadherin, which forms the key functional component of adherens junctions between epithelial cells ⁷. E-cadherin is

involved not only in cell adhesion and morphogenesis, but also in cellular signal transduction. In a variety of epithelial neoplasms, loss or reduction of E-cadherin expression has been associated with advanced stages of tumour growth, increased metastatic potential, shortened disease-free period and lowered overall survival, with a concomitant poor prognosis ⁸⁻¹².

The aim of our review was to systematically summarise published studies investigating the significance of E-cadherin immunohistochemical (IHC) expression in patients affected by laryngeal SCC.

Materials and methods

Search methods for identification of studies

In September 2017, a computerised MEDLINE search was performed from the start of the database until the end of September 2017 using the PubMed service of the US National Library of Medicine by running the following search string:

(“Cadherins”[Mesh] OR “Cadherin Related Proteins”[Mesh]) AND (“Larynx”[Mesh] OR “Laryngeal Neoplasms”[Mesh])

Reference lists from relevant articles were hand searched for further studies.

The initial search returned a total of 89 results. Abstracts and titles obtained were screened independently by two of the authors (FMG and MR), who subsequently met to discuss disagreements on citation inclusion.

Inclusion criteria for citations were:

- cohorts of patients with histological confirmed diagnosis of laryngeal SCC.

Exclusion criteria for citations were:

- analysis including samples of patients with histologically confirmed diagnosis of laryngeal basaloid SCC;
- articles concerning different markers than E-cadherin;
- data obtained from in vitro experiments;
- languages other than English.

Of the 89 articles, 15 met the initial inclusion criteria according to both authors (FMG and MR). These were obtained and reviewed in detail by the same two authors, who met and discussed disagreements on article inclusion. Inclusion criteria for full text articles and single patients identified were:

- sufficient and accurate description of IHC staining;
- sufficient and accurate description of statistical analysis.

Exclusion criteria were:

- analysis performed on specimens of patients with history of previous head and neck radiotherapy;

- analysis including samples of patients affected by SCC of other organs than larynx;
- analysis including duplicate data.

A total of three studies were excluded. The first was ruled out because of insufficient data while other two studies were excluded respectively for the presence of duplicate data (one study) and the inclusion of subjects affected by hypopharynx SCC (one study). A further manual check was performed on the references included in the articles and one additional study was identified that met the inclusion criteria. The final number of articles included in the present review was identified, and the main information was extracted and summarised.

Results

After an initial check, full-text retrieval and manual cross-checking of references included in the articles, 13 studies, comprising a total of 1,121 subjects, clearly met the inclusion criteria and were chosen for analysis (Fig. 1).

The main characteristics of the selected studies are summarised in Tables I, II.

All studies had a retrospective cohort design. The average length of follow-up was reported in six studies, with a mean of 40.3 months and ranging from 24 to 60 months.

Overall, the number of patients included in each study varied from 37 to 289.

The vast majority of patients (n = 467) had a glottic cancer, while supraglottic localisation was described in 445 subjects. A transglottic tumour was described in 66 cases and only 31 patients presented with subglottic localisation. Two studies did not report the specific subsite.

Among the analysed articles, 10 reported at least one significant correlation between E-cadherin IHC expression and the clinical or histopathological parameters evaluated. A significant correlation was found for N stage (5/13), grading (4/13), disease-free survival/disease-specific survival (6/13) and overall survival (3/13). Three studies failed to find any significant correlations.

Discussion

At present, it still appears difficult to forecast the exact prognosis for the clinical course of laryngeal SCC with established clinical parameters such as TNM classification and histopathological grading ². TNM classification represents the most powerful parameter, but is criticised as an unreliable prognostic indicator for the head and neck region due to unfavourable clinical outcomes, especially for small tumours ¹³. Moreover, analysing the clinical behaviour of laryngeal SCC, it must always take account of the

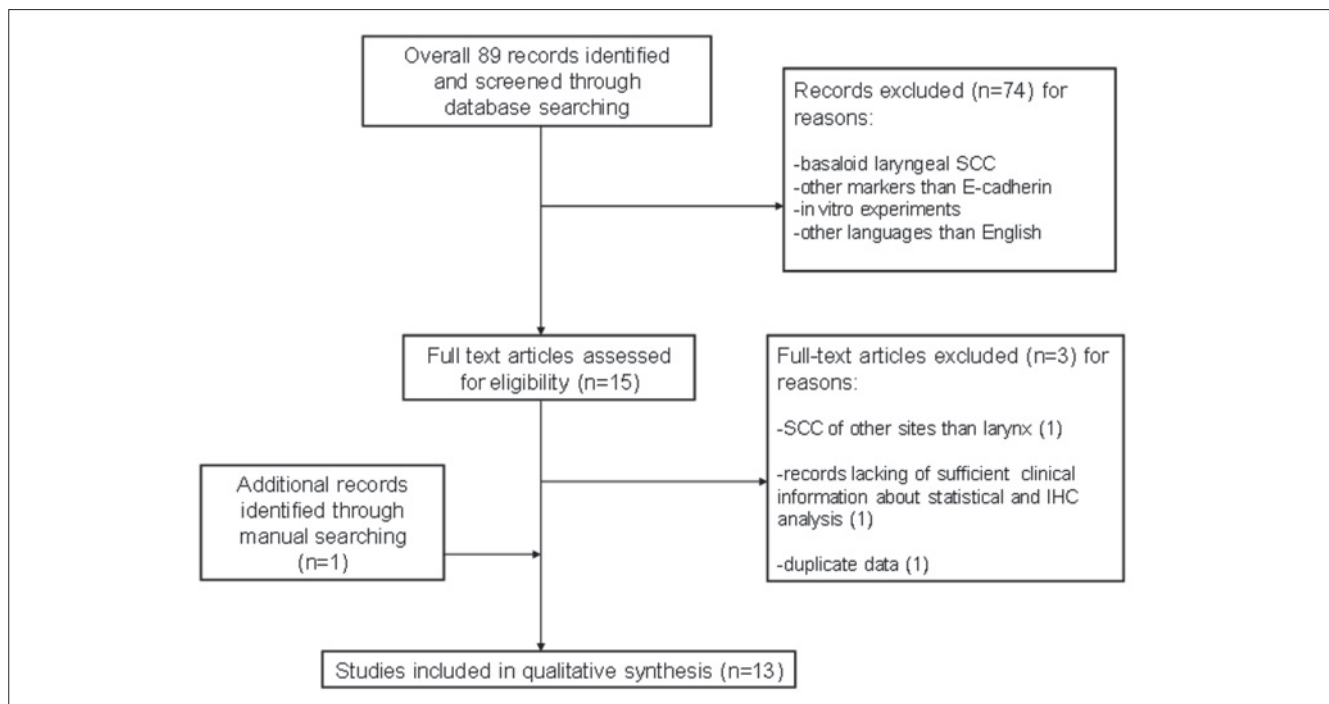


Fig. 1. Flowchart demonstrating study selection.

Table I. Main characteristics of the studies analysed with correlations between clinical-histopathological parameters and expression.

Authors	Year	No. of patients	pT stage				pN stage		Tumour subsites				Mean follow-up period (Mo.)
			T1	T2	T3	T4	N–	N+	Glottic	Supraglottic	Transglottic	Subglottic	
Rodrigo et al. ²³	2007	95	12	35	36	12	42	53	0	95	0	0	n/a
Zou et al. ³³	2010	150	n/a	n/a	n/a	n/a	83	67	122	16	0	12	49
Paksoy et al. ²⁵	2011	56	0	22	24	10	33	23	24	16	14	2	n/a
Li et al. ⁶	2012	64	8	14	32	10	28	36	36	21	0	7	60
Carico et al. ²⁹	2012	55 [*]	55	0	0	0	55	0	48	7	0	0	36
Akdeniz et al. ²⁶	2013	38	2	16	9	11	23	15	1	22	15	0	n/a
Ahmed et al. ²⁷	2014	75	n/a	n/a	n/a	n/a	51	24	n/a	n/a	n/a	n/a	40
Psyri et al. ³⁴	2014	289 ^{**}	n/a	n/a	n/a	n/a	243 [°]	45 [°]	125	135	23	6	n/a
Greco et al. ³⁰	2015	82	n/a	n/a	n/a	n/a	48	34	47	26	9	0	33
Ali Bayram et al. ³⁵	2015	60	0	8	36	16	30	30	0	60	0	0	n/a
Cappellesso et al. ²⁸	2015	37	1	8	23	5	16	21	n/a	n/a	n/a	n/a	n/a
Barutçu et al. ³⁶	2016	41	14	22	5	0	34	7	25	16	0	0	24
Qian et al. ³¹	2016	79	n/a	n/a	n/a	n/a	53	26	39	31	5	4	n/a

^{*}: 4 carcinoma in situ + 4 verrucoid carcinoma; [°]: one patient missing data; ^{**}: IHC analysis performed for 286 patients.

supraglottis subsite as it has a richer lymphatic supply. That consideration supports the published data showing a higher incidence of lymph node metastases and occult metastases for supraglottic SCC in comparison to glottic SCC⁶.

Currently, imaging techniques such as CT, MRI and ultrasound guided fine needle aspiration cytology are employed to assess the status of cervical lymph nodes. However, the limited sensitivity and specificity of CT and MRI in detection of lymph node metastases must be considered. For ultrasound-guided fine-needle aspiration cytology, although it can detect more than 80% lymph node metastases, there is still a risk of occult metastases¹⁴.

During the last years, many studies were planned with the aim to investigate the role played by different cellular biomarkers, which could help to potentiate our diagnostic and therapeutic capability. Indeed, the number of potentially useful biomarkers is large and many studies have been published on this topic. Therefore, in recent years several reviews were published that summarise the litera-

ture on specific cellular biomarkers and tumour progression in head and neck¹⁵⁻²⁰ and laryngeal SCC^{2,5,21-24}.

E-cadherin is expressed in the lower spinous and basal cell layer and is involved in the transduction of signals controlling various cellular events, including polarity, differentiation, growth and cell migration. E-cadherin provides intercellular adhesion of cancer cells and its suppression in the primary lesion plays a role as a trigger for liberalisation of cancer cells²⁵.

Regarding the role of E-cadherin in laryngeal SCC, there are some interesting results that could be extrapolated from the selection of the studies included herein. Akdeniz et al.²⁶, analysing the IHC expression of E-cadherin in tissue specimens of 38 patients with laryngeal SCC, noted that a lower level of E-cadherin protein expression correlated with poor differentiation of the tumour ($p < 0.05$) and a major risk of nodal metastases ($p = 0.045$). Ahmed et al.²⁷, in their cohort of 75 subjects, found a significant correlation between reduced E-cadherin expression and poor tumour differentiation ($p = 0.004$), lymph node

Table II. E-cadherin thresholds of positivity and correlations with clinical-histopathological parameters.

Authors	E-cadherin assay	E-cadherin location	Cutoff level	Clinical and histopathological investigated parameters					
				T	N	Stage	Grade	DFS/DSS	OS
Rodrigo et al. ²³	IHC	C-M	Score	No	Yes	N/E	No	No	N/E
Zou et al. ³³	IHC	C	Score	Yes	Yes	N/E	Yes	Yes	N/E
Paksoy et al. ²⁵	IHC	n/a	> 75%	N/E	No	N/E	N/E	N/E	N/E
Li et al. ⁶	IHC	C-M	Score	N/E	Yes	N/E	N/E	Yes	Yes
Carico et al. ²⁹	IHC	M	Score	N/E	N/E	N/E	Yes	No	N/E
Akdeniz et al. ²⁶	IHC	C-M	Score	N/E	Yes	No	Yes	N/E	N/E
Ahmed et al. ²⁷	IHC	C-M	> 50%	N/E	Yes	Yes	Yes	Yes	N/E
Psyrrri et al. ³⁴	IHC	C-M	Score	No	No	No	No	Yes	No
Greco et al. ³⁰	IHC	C-M	> 50%	N/E	N/E	N/E	N/E	Yes	Yes
Ali Bayram et al. ³⁵	IHC	n/a	> 25%	No	No	No	No	N/E	N/E
Cappellesso et al. ²⁸	IHC	M	Score	N/E	No	N/E	N/E	Yes	N/E
Barutçu et al. ³⁶	IHC	n/a	> 50%	No	No	No	No	No	No
Qian et al. ³¹	IHC	C-M	> 20%	No	No	No	No	N/E	Yes

IHC: immunohistochemistry; M: membrane; C: cytoplasmic; DFS: disease free survival; DSS: disease specific survival; OS: overall survival; YES: significant correlation; NO: no significant correlation; n/e: not evaluated.

metastasis ($p = 0.006$), advanced T-stage ($p = 0.001$) and TNM stage ($p = 0.001$). Cappellesso et al.²⁸, in a cohort of 37 patients, observed a significant correlation ($p = 0.04$) between lower levels of E-cadherin and shorter disease-free survival (DFS), while there was no relation with nodal stage. Carico et al.²⁹ analysed a group of 55 patients affected by T1N0 laryngeal SCC. The authors did not find a significant relation between low E-cadherin levels and poorer DFS. However, a significant association was noted between scarce presence of E-cadherin and less differentiated tumour grade ($p = 0.006$). An interesting study was recently performed by Greco et al.³⁰ who analysed the relation between E-cadherin expression by IHC and survival rates in a cohort of 82 patients. The authors observed that patients whose tumours overexpressed both cytoplasmic and membranous E-cadherin experienced worse 3-year overall survival (OS). Similarly, patients whose tumours overexpressed cytoplasmic E-cadherin experienced significantly worse 3-year disease specific survival (DSS).

These results are surprising because overexpression of E-cadherin should result in the stabilisation of cadherin/catenin complexes. Li et al.⁶, analysing the specimens of 64 patients, found that reduced E-cadherin expression was significantly correlated with lymph node metastases ($p < 0.001$). Moreover, the Kaplan-Meier survival curves showed a significant correlation between E-cadherin expression and patient survival ($p < 0.05$). Indeed, the high expression group of patients presented higher OS and DFS rates.

Recently, Qian et al.³¹, in a cohort of 79 patients, found that a significant correlation ($p = 0.028$) was present between elevated E-cadherin expression by IHC and higher OS. Analysing the specimens of 95 subjects, Rodrigo et al.³² noted that decreased E-cadherin expression was correlated with the presence of nodal metastases ($p = 0.006$). In their cohort of 150 patients (mainly affected by supraglottic SCCs), Zou et al.³³ reported a significant association between E-cadherin immunostaining and T-stage

($p = 0.000$), cervical lymph node metastasis ($p = 0.000$) and histological grade ($p = 0.048$). A tendency for low E-cadherin expression to correlate with tumour recurrence was also found ($p = 0.000$), but at multivariate logistic regression analysis E-cadherin was not an independent predictor factor of DFS ($p = 0.063$). Psyrri et al.³⁴ conducted a study on a larger cohort of 286 patients. On the basis of their analysis, the authors concluded that patients whose tumours overexpressed both cytoplasmic and membranous E-cadherin experienced longer DFS compared to those whose tumours overexpressed only cytoplasmic E-cadherin ($p = 0.0106$). However, it must be noted that some authors failed to observe a significant relation between E-cadherin IHC expression with oncological features and survival^{25 35 36}.

Conclusions

On the basis of data collected in our review, the role of E-cadherin in laryngeal SCC progression remains still difficult to elucidate. An important relation seems to exist between reduction of cellular E-cadherin levels and development of nodal metastases with consequent worsening of prognosis. Nevertheless, many inconsistencies were present between the studies analysed, especially regarding the patient populations and IHC scoring system. Thus, in our opinion, new prospective studies with homogeneous cohorts of patients are required to draw definitive conclusions about this topic.

Conflict of interest statement

None declared.

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