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Original scientific paper

Relationship of E-cadherin with Cervical Lymph Node Metastasis in Laryngeal Cancer

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A B S T R A C T

E-cadherin, a 120 kDa transmembrane protein, plays an important role in malignant progression and tumour differentiation. The loss or reduction in E-cadherin expression has been found in several tumours including laryngeal squamous cell carcinoma. The present study aimed to investigate the prognostic implications of changes in expression of the E-cadherin in laryngeal carcinoma. E-cadherin expression was determined by immunohistochemistry in paraffin- embedded tissue specimens from 80 patients. A staining score was given based on the percentage of cells stained (0–100%). E-cadherin expression varied greatly among tissue samples from 2 to 72 (median 25). Using the median expression of E-cadherin as a cut- off, 41 (51.3%) tumours were classified in the »low E-cadherin« group and the rest, 39 (48.7%) tumours, consisted the »high E-cadherin« group. We found significant differences in the staining scores of E-cadherin between those tumours with and without nodal metastases (p=0.025) and advanced clinical stage (TNM stage III and IV) (p=0.014). The results of a stepwise logistic regression analysis showed that E-cadherin staining score and the location of primary tumour were independent predictors of nodal metastases. The immunohistochemical determination of E-cadherin expression may be useful instrument to characterise the metastatic potential of carcinomas. Larger studies are needed to confirm the role of E-cadherin expression in predicting the behavior of laryngeal squamous cell carcinomas.

***Key words**: laryngeal cancer, cell adhesion molecule, E-cadherin, immunohistochemistry*

Introduction

Laryngeal carcinoma represents 2.4% of new cancer diagnoses annually in men[1]. The majority of these tumours are squamous carcinoma (more than 90%) ranging from poorly to well differentiated. The presence of lymph node metastasis is the most important prognostic factor in patients with laryngeal carcinoma and determines the treatment. The detection of lymph node metastasis is still difficult at the time of diagnosis. Physical examination, ultra-sound, magnetic resonance imaging or computed tomography are mainly based on the size of the lymph nodes and detect the late macroscopic nodal metastases, but microscopic ones evade recognition. Data from literature indicate that 4–40% of patients with laryngeal carcinoma and clinically negative neck lymph nodes have indeed occult metastases[2,3]. That's why it is very important to find markers that could predict the metastatic behavior of the primary tumour.

The development of human cancer is multiple steps processes that induce tumour invasiveness and metastasis. It has long been known that cell–cell adhesion is commonly reduced in human cancers. Cell adhesion molecules mediate cell-cell and cell-matrix interactions. Adhesion molecules consist of five major families: integrins, cadherins, immunoglobulin gene superfamily (IgSF), selectins and CD44. Cadherins are a group of calcium-depended adhesion molecules. They have an extracellular domain (N-terminal) and a cytoplasmic tail (C-terminal) which interacts with the cytoskeletal proteins via intracellular proteins termed catenins (α, β, γ) forming the E-cadherin-catenin complex[4]. There are four cadherin

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subclasses: epithelial cadherin (E-cadherin), placental cadherin (P-cadherin), neural cadherin (N- cadherin) and liver cell adhesion molecule (L-CAM)[5,6]. E-cadherin is expressed in all adult human epithelial tissues. It is a 120 kD peptide assigned to chromosome 16q22. Downregulation of E-cadherin reduces cell-cell adhesion and gap junction-mediated communication[7]. Several immunocytochemical studies have shown that reduced expression of E-cadherin is associated with invasive growth patterns, poor differentiation, metastases, and aggressive behavior of carcinomas.

The clinical significance of altered expression of E-cadherin remains controversial in laryngeal carcinoma. The present study aimed to investigate the prognostic implications of changes in expression of the E-cadherin in laryngeal carcinoma.

Materials and Methods

Patients

A total of 80 patients were included in the present study, 40 of them with glottic and 40 with supraglottic tumour. All patients were treated for laryngeal squamous cell carcinomas (SCCs) at the Clinic of Otorhinolaryngology and Maxillofacial Surgery of the Clinical center of Montenegro in Podgorica from 2001 to 2008. Both groups, glottic and supraglottic, consisted of 20 patients with early (TNM stage I and II) and 20 patients with advanced (TNM stage III and IV) cancer. The clinical information, including sex, age, histologic grade, primary tumour (T) classification, nodal (N) status, TNM stage, and oncological outcome, were obtained retrospectively from clinical records. Pathological staging was determined according to the 6th TNM Classification of malignant tumours of the International Union against Cancer[8]. Patients with second primaries or who had received primary radiotherapy and/or chemotherapy were not considered. All selected patients underwent primary partial (58 cases) or total laryngectomy (22 cases) as primary treatment. Neck dissection was also performed in 29 cases. In the analysis of clinical data we have defined poor oncological outcome as recurrence of disease or occurrence of metastasis after treatment. Disease-free survival was calculated from the period of treatment completion until the date of tumour relapse. Mean follow-up time (calculated in months from treatment completion to the last otolaryngological control) was 28.4 months (median 27 months, range 6–60 months). Clinicopathologic characteristics of the selected patients are shown in Table 1. The study was approved by the Center for science and researchs of the hospital. We did not need additional informed consent to use the specimens in this study because only archived material was used.

TABLE 1
CLINICOPATHOLOGIC CHARACTERISTICS OF 80 PATIENTS WITH LARYNGEAL SQUAMOUS CELL CARCINOMA

	No. of patients	%
All	80	100
Gender		
Male	61	76.2
Female	19	23.8
Age		
≤65 years	60	75
>65 years	20	25
Primary tumour site		
Glottic	40	50
Supraglottic	40	50
T stadium		
T1	19	23.7
T2	35	43.7
T3	23	28.8
T4	3	3.8
N stadium		
N0	61	76.2
N1	12	15.0
N2	7	8.8
Stage		
Stage I	19	23.8
Stage II	21	26.2
Stage III	32	40.0
Stage IV	8	10.0
Histological grade (HG)		
HG I	34	42.5
HG II	45	56.3
HG III	1	1.2
Loco-regional recurrence		
L-R rec. no	60	75
L-R rec. yes	20	25

Immunohistochemistry

Eighty specimens of formalin- fixed, paraffin- embedded tissue blocks were cut into 3-mm sections by a microtome. All included samples originated from complete resection material. The slides were then dewaxed, hydrated, and washed with TRISbuffered saline (TBS). This process was followed by microwave treatment for 20 min in citrate buffer (pH=6.0) to retrieve the antigens present. After blocking endogenous peroxidase activity in water with 0.3% H_20_2 for 30 min, tissue sections were incubated with anti- E-cadherin antibody (Clone NCH-38 diluted 1:50, DAKO, Denmark) for 30 min and mouse antigen was applied for 30 min. Immunodetection was performed with the Envision system, DAKO Autostainer, model VL1. Diaminobezidine (DAB) was used as a chromogen for 10 min. The slides were then counterstained with hematoxylin. Appropriate positive and negative controls were included in all reactions.

Evaluation of E-cadherin expression

The slides were viewed randomly, without clinical data, by one of the authors. The staining was predominantly membranous with some cytoplasmatic staining. A staining score was given based on the percentage of cells stained (0–100%). All stained cells were considered positive regardless of the intensity of the staining. For the purposes of this study, we classified the patients as low expressers (E-cadherin expression below the median of the staining scores) and high expressers (E-cadherin expression above the median).

Statistical analysis

The correlation between the clinicopathologic parameters and the expressions of E-cadherin were evaluated using chi-square (χ^2) test and Kruskal-Wallis test. The role of each possible prognostic factor (univariante analysis) and the joint effect of all these factors (multivariante analysis) was explored using the multivaniate logistic regression analysis. A p value less than 0.05 was considered to be significant in all statistical analyses. p values in the range $0.10>p\geq0.05$ were considered as indicating a statistical trend. All statistical analyses were conducted with SPSS 13.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA).

Results

Expression of E-cadherin was evaluated in 80 patients, from which 61 (76.2%) were males and 19 (23.8%) females. The mean age of the patients were 59.3±9.23 years, ranging from 37 to 81 years. Median age was 58 years. There were 40 (50%) cases with glottic and 40 (50%) cases with supraglottic tumour. The tumour stages were T1 to T4, N0-N2, M0. Forty patients had early cancer (Stage I or II) and 40 had advanced cancer (Stage III or IV). Twenty of 80 patients developed loco-regional malignancy recurrence (7 local recurrences, 13 recurrences to neck lymph nodes).

E-cadherin expression was associated with the cell membrane and varied greatly among tissue samples from 2 to 72 (median 25). The mean expression of E-cadherin in considered study group was 28.86 (standard deviation [SD]=19.14). Using the median expression of E-cadherin as a cut- off, 41 (51.3%) tumours were classified in the »low E-cadherin« group (Figure 1) and the rest, 39 (48.7%) tumours, consisted the »high E-cadherin« group (Figure 2). The correlation of E-cadherin expression with clinicopathologic parameters is summarized in Table 2.

The expression of E-cadherin was not associated with age, sex, the primary tumour's location and differentiation grade. There were significant differences in the staining scores of E-cadherin between those tumours with and without nodal metastases (p=0.025) and advanced clinical stage (TNM stage III and IV) (p= 0.014). The differences in expression of E-cadherin between cases presented with tumour recurrence and the cases without recurrence were near statistically significant

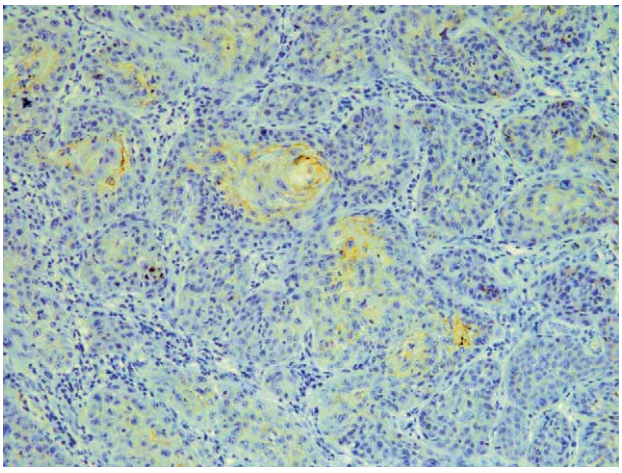

Fig. 1. Low expression of E-cadherin in laryngeal squamous cell carcinoma (Original magnification x100).

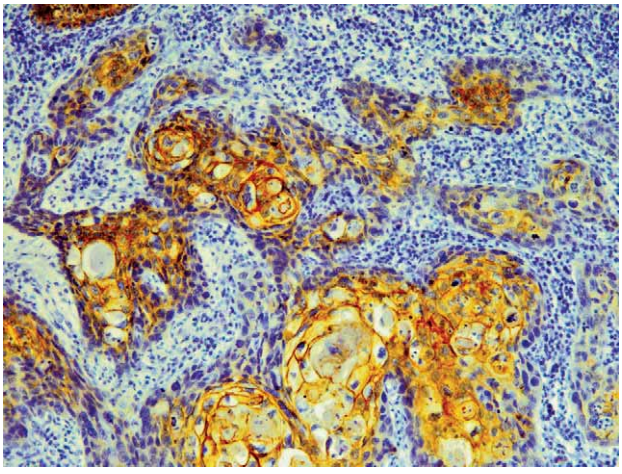

Fig. 2. High expression of E-cadherin in laryngeal squamous cell carcinoma (Original magnification x100).

(p=0.053). The expression of E-cadherin in advanced T3-T4 tumours was lower than in T1- T2 tumours but result is near statistically significant (p=0.079).

The results of a stepwise logistic regression analysis showed that E-cadherin staining score and the location of primary tumour were independent predictors of nodal metastases (Table 3). Patients with higher risk had lower expression of E-cadherin and supraglottic location of tumour.

Discussion

The presence of lymph node metastases is the single most adverse independent prognostic factor in head and neck SCCs[9]. The preoperative detection of lymph node metastases is crucial to the effective treatment of patients with laryngeal SCCs. Diagnostic imaging techniques have the fundamental limitation that the metastases need to have a minimal size of at least several

TABLE 2
THE CORRELATION OF E-CADHERIN EXPRESSION WITH CLINICOPATHOLOGIC PARAMETERS IN 80 PATIENTS WITH LARYNGEAL SQUAMOUS CELL CARCINOMA

Variables	Number of patients	E-cadherin expression[a]		
		Low	High	p value[b]
Sex				0.698
Male	61	32	29	
Female	19	9	10	
Age (years)				0.518
≤65 years	60	32	28	
>65 years	20	9	11	
Primary tumour site				0.263
Glottic	40	23	17	
Supraglottic	40	18	22	
T classification				0.079
T1 and T2	54	24	30	
T3 and T4	26	17	9	
N status				0.025
N0	61	27	34	
N+	19	14	5	
TNM stage				0.014
I and II	40	15	25	
III and IV	40	26	14	
Histologic grade				0.848
G1	34	17	17	
G2 and G3	46	24	22	
Loco-regional recurrence				0.053
L-R rec. no	20	14	6	
L-R rec. yes	60	27	33	

[a] Low E-cadherin expression below 25, High E-cadherin expression above 25; [b] χ^2-test

TABLE 3
RESULTS OF LOGISTIC REGRESSION MODEL ON LYMPH NODE METASTASES

Variable	Hazard ratio	95% Confidence interval	p value
Primary tumour site (Supragllotic/glottic)	11.31	2.01–63.65	0.006
E-cadherin score (Low/High)	6.49	1.68–25.00	0.007

millimeters to be detected. Even ultrasound with ultrasound- guided fine-needle aspiration biopsy identifies clinically occult metastases with a sensitivity of no more than 48 to 76%[10,11]. This means that small metastatic deposits will still be undetected, and uncertainty about the true lymph node status of the neck will remain.

The ability to identify molecular markers from a primary tumour biopsy sample that predict cervical lymph node metastases would enable the selection of patients at risk for lymph node metastasis. It is accepted that the suppression of cell- cell adhesiveness have an important role in facilitating the dissemination of tumour cells from the primary site and the establishment of metastasis[12]. Among the several families of adhesion molecules, E-cadherin has been suggested to play a role in the process of nodal metastasis in several cancers. E-cadherin mediates homophilic, calcium-dependent cell-cell adhesion, and its cytoplasmic portion binds to β-catenin, which connects the adhesion complex to the actin cytoskeleton. Downregulation of E-cadherin reduces cell-cell adhesion, gap--junction mediated communication, and prevents terminal differentiation of cells- thus maintaining the ability of continued proliferation[7]. The loss of E-cadherin expression in tumour tissue leading to more aggressive phenotype because neoplastic cells have higher tendency to spread to adjacent tissues and lymph nodes.

A reduced or absent expression or abnormal location of E-cadherin/catenin complex has been observed in several human carcinomas including gastric[13], bladder[14], prostate[15], lung[16], colon[17], breast[18]. In several studies have been reported that abnormal expression of E-cadherin correlated with clinicopathological characteristics of head and neck SCCs, such as lymph node metastases, and disease-free survival. In a group of 50 patients with head and neck SCCs Mattijssen et al. found relation between high levels of membrane- associated E-cadherin expression and favorable outcome[19]. Schipper at al. observed that E-cadherin expression decreased with loss of differentiation in primary carcinomas, and that lymph node metastases expressed a lower level of the protein, suggesting an important role of cadherin loss in the metastatic process[20]. Simionescu et al. studied 42 cases of oral SCCs with different sites (tongue, lips, palate, and gums) and investigated the imunoexpression of adhesion molecules[21]. The study indicated the decreasing degree of immunostaining for E-cadherin parallel with decreasing of oral SCCs differentiation grade. Franchi and colleagues observed that low expression of E-cadherin in laryngeal SCCs significantly correlated with the presence of occult nodal metastases[22]. Eriksen et al. suggest that the loss of adhesion – the loss of adherens junctions (E-cadherin) and hemidesmosomes (integrin) – predicts the risk of nodal metastases at the time of diagnosis[23]. However, a number of other studies have failed to show a relationship between E-cadherin expression and these clinicopathological variables[24]. Takes et al. have examined histological features and biological markers in 31 patients with laryngeal carcinomas[25]. From all the markers investigated immunohistochemically, E-cadherin was not relevant to prediction of lymph node metastasis. Liu et al. have studied the markers associated with tumour invasion and metastasis in 59 patients with laryngeal and hypopharyngeal SCCs with node metastases[26]. No relationship was found between immunolabeling of cancer cells for E-cadherin and the presence of lymph node metastasis.

In presented study, we analyzed the clinicopathologic significance of E-cadherin expression among 80 patients with laryngeal SCCs. E-cadherin expression was an independent predictor of lymph node metastases. This is consistent with another study on laryngeal tumours[22,27], and with large studies in other histological types metastases[28–30]. This suggest that the immunohistochemical determination of E-cadherin expression gives us an instrument to characterise the metastatic potential of these carcinomas. That's why E-cadherin expression may play a role in the decision to treat a N0 neck with a neck dissection or with close follow-up. In our study lower expression of E-cadherin was significantly associated with advanced clinical stage (TNM stage III and IV). There was no significant correlation between the expression of E-cadherin and age, sex and primary location of tumour. Generally, E-cadherin expression was found to be high in well differentiated cancers, but reduced in undifferentiated cancers[19,20,22,31]. We found general, but not significant, decline in E-cadherin expression with increasing dedifferentiation of the tumour. This finding is in line with those of Rodrigo et al.[27]

Several explanations can be suggested for conflicting results reported in previous studies about clinical significance of altered expression of E-cadherin in the laryngeal SCCs[12]. The site and number of analysed cases, selection of tumours (stage, tumour grade), differences in surgical approach (extent of lymph node dissection), and differences in staining evaluation may individually or in combination be responsible. E-cadherin expression is not a static unchangeable characteristic. Also, the presence of an adhesion molecule shown immunohistochemically does not always suggest that this molecule is really active. Chromosomal aberrations and protein expression are different in some parts of the tumour compared with others, which is usually thought to be a result of clonal evolution.

Conclusion

Lower expression of E-cadherin in primary laryngeal squamous cell carcinomas correlated significantly with tumours with nodal metastases and with advanced TNM stage. Reduction of E-cadherin expression in these carcinomas was an independent predictor of lymph node metastases.

Results of the present study suggest that expression of E-cadherin may increase our ability in identifying patients with more aggressive disease who are at considerable risk for occult metastases and who may benefit from elective neck dissection. So it is very important to use markers studied on the biopsy material of the primary tumour that could predict the metastatic behavior. Since metastasis is a multistep process, one single marker is not enough, but a panel of several ones will be able to predict metastatic behavior of the tumours. Uniform standards are required to make the results of studies comparable. Larger studies are needed to confirm the role of E-cadherin expression in predicting the behavior of laryngeal squamous cell carcinomas.

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ODNOS EKSPRESIJE E-KADHERINA SA REGIONALNIM METASTAZAMA ZA KARCINOME LARINKSA

E-kadherin, a 120 kDa transmembranski protein, ima važnu ulogu u tumorskoj dediferencijaciji i malignoj progresiji. Smanjenje ili gubitak ekspresije E-kadherina je nađeno za više različitih tumora uključujući i karcinome larinksa. Cilj ovog istraživanja je da ispita prognostički značaj promjene u ekspresiji E- kadherina za karcinome larinksa. Ekspresija E-kadherina je analizirana imunohistohemijski kod 80 pacijenata. Rezultat imunohistohemijske ekspresije E-kadherina predstavljao je postotak obojenih ćelija (0–100%). Ekspresija E- kadherina u promatranom materijalu varirala je 2 do 72 (medijana 25). U odnosu na medijanu ekspresije ispitanici su podijeljeni u dvije grupe, 41 (51.3%) tumor je klasificiran kao »niska ekspresija E-kadherina«, a ostalih 39 (48.7%) pacijenata je činilo grupu »visoka ekspresija E-kadherina«. Značajno slabija ekspresija E-kadherina nađena je u pacijenata sa prisutnim regionalnim metastazama u vratu ($p=0.025$) i onih sa uznapredovalim stadijem bolesti (TNM stage III and IV) ($p=0.014$). Multivarijantnom logističkom regresijskom analizom dobili smo da su ekspresija E-kadherina i primarna lokalizacija tumora nezavisni prognostički parametri za prisustvo metastaza na vratu. Imunohistokemijsko određivanje ekspresije E- kadherina može biti vrlo korisno u procjeni metastaskog potencijala tumora ali ovo treba potvrditi dodatnim istraživanjima.