E-Cadherin and Syndecan-1 Expression in Patients With Advanced Non-small Cell Lung Cancer Treated With Chemoradiotherapy

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Abstract. Background/Aim: The aim of the study was to investigate whether E-cadherin and syndecan-1 are molecular markers of advanced non-small cell lung cancer (NSCLC). Patients and Methods: The expression of E-cadherin and syndecan-1 (SDC1) was examined immunohistochemically on tissue specimens of 64 patients, with stage III disease at presentation. The obtained expression data were correlated with clinical parameters. Results: Negative expression of SDC1 was correlated with squamous histology (p=0.002). E-cadherin positive expression was significantly associated with increased 2-year overall survival (OS) rate (p=0.032). In the multivariate Cox analysis, performance status 0-1 was an independent predictor of OS (p=0.001) and disease-free survival (DFS) (p=0.001). E-cadherin expression was an independent predictor of OS (p=0.007) and DFS (p=0.029). Conclusion: E-cadherin might be a prognostic factor for OS and DFS in advanced stage NSCLC patients. Further investigations are needed for the establishment of E-cadherin and syndecan-1 as molecular markers, affecting treatment response and survival.

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ligands on the cell surface. Additionally, Syndecan-1 may act either as an inhibitor or a promoter of tumor progression, depending on the concertation of the signaling molecules between the cell surface and the extracellular matrix (13-15). It is also considered a co-receptor in signaling pathways, interacting with fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), and epidermal growth factor receptor (EGFR), affecting cell to cell interactions, altering signal transduction (16, 17), playing a role in cell proliferation, adhesion, migration, and angiogenesis (13, 18). SDC1 is highly expressed in epithelial malignancies, while it is reduced during malignant transformation of various epithelia, leading to mesenchymal characteristics and loss of the epithelial phenotype. Loss of SDC1 expression may be the hallmark step to EMT (19).

The aim of this study was to investigate the expression of E-cadherin and SDC1 in advanced stage NSCLC patients treated with chemoradiotherapy. The relationship of these molecules with other clinicopathologic factors of the disease was also examined.

Patients and Methods

Study design and patient population. Sixty-four (64) patients with inoperable advanced stage NSCLC were retroactively evaluated. Data were collected regarding host (age, sex, smoking history), tumor (T and N classification, histological grade and type) and treatment regimen (chemotherapy, radiotherapy). The disease was staged according to the 2017 American Joint Committee on Cancer (AJCC) staging classification. Histological typing was based on WHO classification. All patients had adequate medical records obtained during a meticulous follow up.

Ethical approval (Study number: 1322, School of Medicine, University of Ioannina, Greece) was obtained from the local ethics committee of the University Hospital of Ioannina. All patients were informed about the nature of the study and signed an informed consent. Formalin-fixed paraffin embedded tissue specimens were available.

Radiation therapy (RT) was performed using three-dimensional (3D) conformal techniques, with 6 MV photons, including primary tumor and lymph nodes. The mean biologically equivalent dose delivered to the planning target volume (PTV) was 60 Gy. The prescribed dose encompassed at least 95% of the PTV. No more than 20% of any PTV would receive >110% of its prescribed dose, while no more than 1% of any PTV would receive <95% of the desired dose. Cisplatin-based chemotherapy was administered either concurrently or sequentially to RT.

Immunohistochemistry. Immunostaining with monoclonal antibodies against E-cadherin (CM170B, Biocare Medical, CA, USA) and SDC1 (CD138) (clone DL-101, Santa Cruz, Dallas, TX, USA) was performed on formalin-fixed, paraffin-embedded tissue sections using the EnVision System (DAKO Corp). All tumor specimens were obtained before therapy. Duplicates of 1 mm diameter cores from the tumor center and noncancerous margin (2 punches, designated as tumor and corresponding normal tissue, respectively) were included in each sample, along with controls, to ensure reproducibility and homogenous staining.

Tumor specimens were reviewed by two pathologists (I.I. & D.S) blinded to any clinical information. The expression of E-cadherin, and SDC1 was evaluated by a semiquantitative method, in epithelial (cytoplasmic) and stroma components.

E-cadherin expression. Staining for E-cadherin was graded by comparing it to the staining intensity of the positive control core specimen and the percentage of tumor positive cells stained; grade 0 (no expression or minimal expression with less than 10-25 % of tumor cells stained), grade 1 (26-50% positive cells) and grade 3 (51-75% positive cells) and grade 4 (>75% positive cells). Scores of 0-3 indicated a negative expression, i.e., impaired expression; and ≥3 indicated a positive expression, i.e., preserved expression. The above scoring criteria were described by Mahler-Araujo et al., 2008 (20). Preserved expression implies that the cells preserve their morphology representing less aggressive tumors.

SDC1 expression. A semi-quantitative immunoreactive scoring system (IRS) was used for the evaluation of the expression of SDC1 (CD138). Membranous or cytoplasmic staining in cancer cells was considered as a positive result. The staining intensity was visually scored (0, no stain; 1, weak; 2, moderate; 3, strong) and the proportion of positive stained cells of the stromal component were assigned as 0, no stain; 1, 1-25%; 2, 26-50%; 3, >50%) (21). For

| Characteristics | No of cases | % |
|-----------------|-------------|---|
| Age (years), median (range) | 69 (49-84) | 94/6 |
| Gender (male/female) | 60/4 | |
| WHO/ECOG PS | | |
| PS 0 | 17 | 27 |
| PS 1 | 33 | 52 |
| PS 2 | 14 | 22 |
| Smoking status | | |
| Smokers | 55 | 86 |
| Never smokers | 9 | 14 |
| Histology | | |
| Squamous | 42 | 66 |
| Adenocarcinoma | 12 | 19 |
| Undifferentiated | 10 | 16 |
| Grade | | |
| G1 | 5 | 8 |
| G2 | 34 | 53 |
| G3 | 25 | 39 |
| Stage | | |
| IIIA | 53 | 83 |
| IIIB | 11 | 17 |
| Chemotherapy | | |
| Yes | 42 | 66 |
| No | 22 | 34 |
| Time of chemotherapy | | |
| Sequential | 6 | 9 |
| Concurrent | 36 | 56 |
| Radiotherapy | | |
| Yes | 64 | 100 |
| No | 0 | 0 |

Table 1. Patients and treatment characteristics (n=64).
the statistical analysis, the level of expression was classified into two groups, considered negative when the score was 0-5, and positive when the score was >6.

**Statistical analysis.** The relationship of SDC1 and E-cadherin expression with clinicopathological parameters of the patients was assessed using Chi-square and Fisher’s exact tests. Spearman’s rank correlation was used to analyze the correlations between E-cadherin and SDC1 expression. Study endpoints included overall survival (OS), disease-free survival (DFS), time to locoregional recurrence (LC) and time to distant metastasis (DM).

OS was defined as the time from diagnosis to death from any cause or the last follow up. DFS was defined as time to events including death or disease progression at local, regional or distant sites. The date of progression was defined as the date of radiological or histological confirmation if available, whichever occurred first. LC was defined as the time to documented recurrence in the lung or regional mediastinum lymphadenopathy. DM was defined as the time to documented recurrence in distant sites outside the locoregional sites of disease. Actuarial values of the endpoints were evaluated by the Kaplan–Meier survival analysis and log-rank tests.

Cox univariate analysis was used to determine the prognostic significance of variables, and Cox multivariable analysis was applied to identify independent prognostic factors for NSCLC patients. Cox regression analysis was used for univariate and multivariate analysis and parameters were compared with log-rank tests. p-Values of <0.05 were considered statistically significant; all p-values were two-tailed. All time-related outcomes were calculated from the day of diagnosis. Statistical calculations were performed using SPSS version 21.0 for Windows (IBM, Chicago, IL, USA).
Results

Demographics. A total of 64 patients with inoperable stage III NSCLC were included in the study. The median age at diagnosis was 69 years (range=49-84 years). Patient, disease and treatment characteristics are listed in Table I. The median follow-up of patients was 15 months (range=5-44 months).

Relationship between expression of E-cadherin, Syndecan-1 and clinical characteristics of the patients. E-cadherin expression had no statistically significant correlation with any of the clinical or treatment factors. However, male gender, smoking, grade 2 and grade 3 tumors, metastatic patients and squamous cell histology, had mainly negative E-cadherin expression.

Regarding syndecan-1, there was a statistically significant correlation between the negative expression of the molecule and squamous pathology (p=0.002). A statistical correlation between the positive expression of syndecan-1 and negative expression E-cadherin was also found (R=0.024, p=0.045).

Relationship between expression of E-cadherin, syndecan-1 and patient survival. Positive expression of E-cadherin was significantly associated with increased 2-year OS rate (43.8% vs. 17.4%, p=0.032), (Figure 1a), whereas syndecan-1 expression was not significantly associated with survival rates (30.3% vs. 20.7%, p=0.655), (Figure 1b). Although the result was not statistically significant, there was an indication that 2-year DFS rate could be correlated with the positive E-cadherin expression (30% vs. 16.6%, p=0.051), (Figure 2a), while there was no statistically significant correlation between 2-year DFS rate and the expression of syndecan-1 (33.3% vs. 11.1%, p=0.143), (Figure 2b).

Univariate analysis was performed to examine the impact of various factors on OS and DFS. Performance status (PS) was a significant predictor of OS [Hazard ratio (HR)=2.851, 95% confidence interval (CI)=1.835-4.430, p=0.001] and DFS (HR=0.566, 95%CI=1.762-3.897, p=0.002). A statistically significant difference in OS was observed, favoring the patients with E-cadherin expression (HR=1.824, 95%CI=1.018-3.266.

Table II. Patient and treatment characteristics (n=64).

|                        | OS       | DFS       |
|------------------------|----------|-----------|
|                        | HR       | 95%CI     | p-Value | HR       | 95%CI     | p-Value |
| Gender (male vs. female) | 1.233    | 0.445-3.415 | 0.687   | 0.566    | 0.136-2.359 | 0.434   |
| Male vs. female         |          |           |         |          |           |         |
| Performance status (PS) | 2.851    | 1.835-4.430 | 0.001   | 2.634    | 1.762-3.897 | 0.002   |
| 0-1 vs. 2               |          |           |         |          |           |         |
| Smoking status          | 0.777    | 0.389-1.590 | 0.489   | 0.627    | 0.244-1.611 | 0.333   |
| Yes vs. No              |          |           |         |          |           |         |
| Histology               | 1.104    | 0.785-1.553 | 0.569   | 0.944    | 0.614-1.611 | 0.333   |
| Squamous vs. adeno vs. undifferentiated | | | | | | |
| Grade                   | 1.332    | 0.880-2.016 | 0.175   | 1.422    | 0.866-2.334 | 0.164   |
| G1 vs. G2 vs. G3        |          |           |         |          |           |         |
| Chemotherapy            | 1.702    | 0.998-2.898 | 0.051   | 1.959    | 1.037-3.702 | 0.038   |
| Yes vs. No              |          |           |         |          |           |         |
| E-cadherin expression   | 1.824    | 1.018-3.266 | 0.035   | 1.952    | 0.966-3.945 | 0.062   |
| Positive vs. Negative   |          |           |         |          |           |         |
| Syndecan-1 expression   | 0.897    | 0.546-1.476 | 0.670   | 0.664    | 0.349-1.187 | 0.158   |
| Positive vs. Negative   |          |           |         |          |           |         |

Table III. Multivariate analysis.

|                        | OS       | DFS       |
|------------------------|----------|-----------|
|                        | HR       | 95%CI     | p-Value | HR       | 95%CI     | p-Value |
| Performance status (PS) | 0.008    | 0.000-0.153 | 0.001   | 0.004    | 0.000-0.061 | 0.001   |
| 0-1 vs. 2               |          |           |         |          |           |         |
| E-cadherin expression   | 0.48     | 0.234-0.790 | 0.007   | 0.432    | 0.204-0.832 | 0.029   |
| Positive vs. Negative   |          |           |         |          |           |         |
thought to play a role in NSCLC, which may be associated with increased relapse and poor survival (25). Notably, our results highlight the complex role of the cell-adhesion system in carcinogenesis. Reduced expression of E-cadherin and increased expression of SDC1 may be correlated with dismal prognosis due to loss of epithelial morphology and cell to cell to matrix adhesion.

Regarding SDC1, few studies have investigated its expression in NCSLC, with conflicting results. In a study by Toyoshima et al., increased SDC1 levels did not correlate with OS (27), while in recent studies, reported strong expression of SDC1 in operable squamous cell lung carcinoma, correlated with low grade tumours and a favourable prognosis (19). Our results showed a statistically significant correlation between SDC1 expression and squamous histological type (p=0.002), mirroring findings from a prior study that evaluated the levels of the protein in the squamous cell subtype (19). Given the fact that SDC1 degradation is linked to the invasiveness of several cancers, to some extent, loss of SDC1 expression in NSCLC may be associated with high metastatic potential and more aggressive tumours (28, 29). Supporting the previous comment, in a recent study, the loss of SDC1 expression in patients with colorectal cancer was associated with aggressive behavior and poor outcome (30). Additionally, in some experimental studies, it has been shown that SDC1 expression is associated with the maintenance of epithelial morphology, and the inhibition of invasiveness in vitro (4, 14, 15, 31).

The most important limitation of the present study is its retrospective design. Nevertheless, although there was a comparatively small number of patients analyzed, patients were treated relatively consistently and data were collected during a meticulous follow-up.

In summary, to our knowledge, this study is the first to evaluate the expression of E-cadherin and SDC1 in NSCLC patients. E-cadherin might be a prognostic factor for OS and DFS in advanced stage NSCLC patients. Additionally, concerning histological subtypes, squamous cell cancer may express SDC1.

**Conflicts of Interest**

The Authors declare no conflicts of interest regarding this study.

**Authors’ Contributions**

E.B., P.T., D.M. conceived the idea, planned the experiments and shaped the research. S.M. and I.S. contributed to sample preparation. E.I and A.D. carried out the laboratory work. E.P., D.M. and P.G. took the lead to the statistics and analyzed the data. E.P. and P.G. took the lead in writing the manuscript. All Authors provided critical feedback and approved the final manuscript.
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