# Prognostic Significance of Serum Human Epididymis Protein 4 Level in Patients with Locally Advanced Non-Small Cell Lung Cancer who Underwent Definitive Chemo-Radiotherapy

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**ABSTRACT**

We aimed to investigate the prognostic significance of serum human epididymis protein 4 (HE4) level in patients with locally advanced non-small cell lung cancer (LA-NSCLC) who underwent definitive chemo-radiotherapy (CRT). A hundred seventeen patients with the diagnosis of LA- NSCLC were enrolled. The serum concentrations of HE4 were measured at the beginning of CRT, at the end of CRT, and 3 months after the completion of CRT. The median follow-up period was 21.7 months (range, 5.4-39.8 months). The mean serum HE4 levels prior to CRT, at the end of the CRT, and 3rd month after the completion of CRT were 159.2, 130.2, and 127.5, respectively (p= 0.023). The median progression free survival (PFS) was 15.4 months. One, and two-year PFS rates were 58.1%, and 22.2%, respectively. One, and two- year expected survival rates were 81.2%, and 62%, respectively. In multivariate analysis, stage (p= 0.002), HE4 levels after 3 months of CRT (p= 0.037) were predictive of OS. Stage IIIC patients had 10.2 times likely to death when compared to stage IIIA patients (95%CI: 2.3-45.7; p= 0.037). The increase of 1 HE4 levels after 3 months of CRT increased the mortality rate 1.002 (95%CI: 1.000-1.0004; p= 0.037). In multivariate analysis stage was predictive of PFS. When compared to stage IIIA patients, stage IIIC patients have 2.5 times risk for progression (95% CI: 1.2-5.2; p= 0.014). Our findings suggested that serum HE4 may be an important prognostic biomarker for LA-NSCLC patients. This issue warrants further prospective studies with more patient populations.

**Keywords:** Non-small cell lung cancer, Locally advanced, oncurrent chemo-radiotherapy, Human epididymis protein 4

## INTRODUCTION

Lung cancer still remains the most common cancer, and the most common cause of the cancer-related death worldwide.[1] Non-small cell lung cancer (NSCLC) represents approximately 80-85% of all lung cancer, and approximately two thirds of NSCLC cases were diagnosed at either locally advanced, or metastatic stages.[2] Several clinical and prognostic factors, including tumor stage, age, sex, histopathologic subtype, and cellular differentiation for lung cancer have been proposed; however, these biomarkers are not sufficient for accurately predicting the prognosis of NSCLC.[3] There has been still a need of a novel biomarker for predicting the prognosis, and treatment response in NSCLC.

Human epididymis protein 4 (HE4) is a secretory protein encoded by the Whey-Acidic Four-Disulfide Core domain protein 2 (WFDC2) gene, which is located on chromosome 20.[4,5] WFDC2 is a member of the protease inhibitor family with immune protective effects and is a promising novel cancer biomarker.[5]

HE4 was first identified in the epithelium of the distal epididymis and originally predicted to be a protease inhibitor involved in sperm maturation; however, widespread expression of HE4 has since been demonstrated in variety of normal human tissues including epithelia of the respiratory and reproductive tracts of both genders.[5-8]

HE4 has been approved by Food and Drug Administration (FDA) as a novel serum biomarkers for early diagnosis and monitoring of ovarian cancer.[9,10] To date, overexpression of HE4 has been demonstrated in a range of malignant neoplasms, particularly of gynecological and pulmonary origin.[11,12] Moreover HE4 expression has been shown to be associated with disease severity and shorter overall survival in a variety of tumors.[13-15] In the currents study, we aimed to investigate the prognostic significance of serum HE4 level in patients with locally advanced non-small cell lung cancer (LA-NSCLC) who underwent definitive chemoradiotherapy (CRT).

## MATERIALS AND METHODS

### *Patient Selection and Treatment Protocol*

Serum samples were collected from 117 patients between June 2017, and January 2020 from two different university hospitals. Tumor stage was determined according to the seventh edition of the American Joint Committee on Cancer (AJCC) TNM staging system classification system. Patients were eligible for the current study were as follows: (1) histologically or cytologically documented stage III (IIIA, IIIB, or IIIC) NSCLC, (2) the patients had no previous history of other cancers, CT, or RT (3) age ≥ 18 years, (4) Karnofsky performance score ≥ 70, (5) the patients had normal liver function tests, renal function tests, hematological parameters, and pulmonary function to receive CRT. Pathologic staging was characterized according to the seventh edition of the American Joint Committee on Cancer TNM staging system. Blood samples were collected from all patients at the time of diagnosis, at the end of the CRT, and 3 months after the completion of CRT.

### *HE4 measurement*

Blood samples were collected in serum separator tubes and were centrifuged at 1500 g for 10 minutes (Beckmann Allegra x-15 Centrifuge). Serum samples were stored at –80$^0$C. HE4 levels were measured by chemiluminescent microparticle immunoassay (CMIA) using the Architect I2000 (Abbott Diagnostics, Abbott Park, IL, USA). This assay is a two-step immunoassay for the quantitative determination of HE4 antigen in serum. This assay use anti-HE4-coated paramagnetic microparticles. After binding serum HE4 by microparticles, acridinium-labeled anti-HE4 congugate is added after following washing steps trigger solutions are addet to mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of HE4 antigen in the sample and the RLUs detected by the ARCHITECT i2000 system optics. The cut-off limit for serum HE4 was considered 70 pmol/L. The intra- and inter-assay coefficients of variations were less than 4% for the range of 50-1100 pmol/l. This kit's low limits of detection is less than 15 pmol/l and functional sensitivity is 20 pmol/L.[16]

### *Follow-up*

After completion of treatment, all patients were followed by treating physician and a medical oncologists. The blood sample analyses and chest tomography were made at periodically, and additional radiological imaging was also performed when necessary. The follow-up period was every 3 months for the first two years, every 6 months between 2nd and 5th years, and annually thereafter. Treatment responses were evaluated according to 1 Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria.[17]

This study was approved by ethical committee of Selcuk University Medical Faculty (Approval number: 2017/341).

### Statistical Analysis

All statistical analyses were performed using SPSS 22 (IBM Inc., Armonk, NY, USA). The primary outcomes of interest were overall survival (OS) and progression free survival (PFS). Time to death or progression was calculated as the period from date of diagnosis to date of death or first clinical or imaging evidence of disease recurrence. The $\chi^2$ test or student's t-test were used to analyze the differences in clinical and pathological factors. Univariate comparisons in survival analysis were performed via the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model, using covariates with a p-value less than 0.10 based on univariate analysis. Sensitivity and specificity for HE4 levels were calculated accord-

**Table 1.** Patient, tumor, and treatment characteristics for the entire cohort

| Characteristics | Patients (%) n= 117 |
|---|---|
| Gender | |
| Female | 20 (17.1) |
| Male | 97 (82.9) |
| Histology | |
| Adenocarcinoma | 47 (40.2) |
| SCC | 38 (35.5) |
| Large cell carcinoma | 11 (9.4) |
| Other | 21 (17.9) |
| Stage | |
| IIIA | 41 (35.0) |
| IIIB | 38 (32.5) |
| IIIC | 38 (32.5) |
| Weight Loss | |
| None | 66 (56.4) |
| < 5% | 23 (19.7) |
| 5-10% | 17 (14.5) |
| >10% | 11 (9.4) |
| Co-morbidities | |
| Absent | 58 (49.6) |
| COPD | 9 (7.7) |
| DM | 7 (6.0) |
| HT | 23 (19.7) |
| CAD | 15 (12.8) |
| CVD | 5 (4.3) |
| RT technique | |
| 3D-CRT | 95 (81.2) |
| IMRT | 22 (18.8) |

*Abbreviations: SCC: Squamous cell cancer; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; CAD; coronary artery disease; CVD: cerebrovascular disease; 3D-CRT: 3-dimensional conformal radiotherapy; IMRT: intensity modulated radiotherapy.*

ing to optimal cut off point. All p-values less than 0.05 were considered statistically significant.

## RESULTS

### *Patient Characteristics*

Between June 2017, and January 2020, 117 patients with the diagnosis of LA- NSCLC were enrolled. The patient and tumor and treatment characteristics are summarized in Table 1. The median age of the patients was 62 years (range, 28-80 years). All the patients were diagnosed histopathologically, and there were 47 (40.2%) with adenocarcinoma, and 38 (35.5%) squamous cell carcinoma histology. According to AJCC staging system, 41 (35%), 38 (32.5%), and 38 (32.5%), patients had stage IIIA, IIIB, and IIIC diseases, respectively.

### *Treatment Outcomes*

The median follow-up period was 21.7 months (range, 5.4-39.8 months). The mean serum HE4 levels prior to CRT, at the end of the CRT, and 3rd month after the completion of CRT were 159.2, 130.2, and 127.5, respectively (p= 0.023) (Figure 1). The median progression free survival (PFS) was 15.4 months. One, and two-year PFS rates were 58.1%, and 22.2%, respectively. The median overall survival times have not been reached yet. One, and two- year expected survival rates were 81.2%, and 62%, respectively. In multivariate analysis, stage (p= 0.002), HE4 levels after 3 months of CRT (p= 0.037) were predictive of OS (Table 2). Stage IIIC patients had 10.2 times likely to death when compared to stage IIIA patients (95%CI: 2.3-45.7; p= 0.037). The increase of 1 HE4 levels after 3 months of CRT increased the mortality rate 1.002 (95%CI: 1.000-1.0004; p= 0.037). In multivariate analysis stage was predictive of PFS. When compared to stage IIIA patients, stage IIIC patients have 2.5 times risk for progression (95%CI: 1.2-5.2; p= 0.014).

### *Toxicity*

Treatment-related toxicities were summarized in Table 3. None of the patient's experienced severe adverse events that necessitated the cessation of RT. Grade 2 leukopenia, thrombocytopenia, and anemia were encountered in 4.3%, 11.1%, and 4.3% of the patients, respectively. The most common radiation-related non-hematological toxicity was esophagitis, and grade 2 and grade 3 esophagitis were seen in 38.5%, and 5.1% of the patients, respectively.

## DISCUSSION

Currently, medicine is in an era of personalized medicine and targeted therapy, which may be a new promise to patients with LA-NSCLC. Therefore it is critical to identify novel biomarkers that can improve the treatment results in the near future. HE4, originally discovered by Kirchhoff in the human distal epididymal epithelial cells, is located

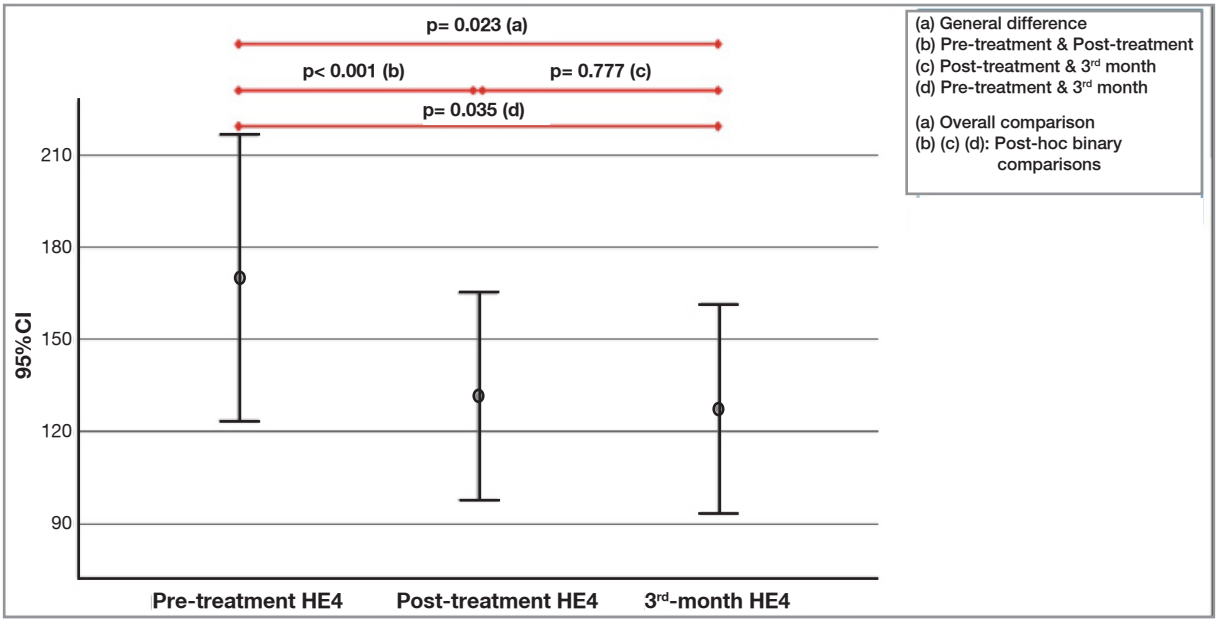


**Figure 1.** Post-hoc pairwise comparisons

on chromosome 20 at 20q12-13 and contains five exons and four introns.[7,8,18] It contains a gene encoding protein domains that have homology with whey acidic protein, by which the product encoded is mainly protease inhibitor.[18] As a member of the protease inhibitor family, it has an inhibitory effect on cell proliferation. It has been reported that HE4 is a novel biomarker of serous, and endometrioid ovarian carcinoma.[19] Moreover HE4 serum levels of ovarian cancer patients may be a useful marker for tumor progression.[20] However, the association of serum HE4 levels and other types of cancer remained to be unsolved. The studies were inconclusive because of small sample sizes and inconsistencies in results. The goal of the current study was to evaluate the prognostic significance of serum HE4 levels in patients with LA-NSCLC who underwent definitive CRT, and our findings showed that HE4 levels after 3 months of CRT were predictive of OS.

**Table 2.** Prognostic factors for overall survival according to Cox-regression analysis

| | HR | 95,0% CI for HR | | p |
|---|---|---|---|---|
| | | Lower | Upper | |
| **Initial Model** | | | | |
| Stage (ref:IIIA) | | | | 0.002 |
| Stage IIIB | 2.9 | 0.6 | 14.8 | 0.21 |
| Stage IIIC | 10.6 | 2.3 | 47.8 | 0.002 |
| Pre-treatment HE4 | 1.0 | 1.0 | 1.0 | 0.67 |
| Post-treatment HE4 | 1.0 | 1.0 | 1.0 | 0.75 |
| 3rd months HE4 | 1.0 | 1.0 | 1.0 | 0.18 |
| **Final Model** | | | | |
| Stage (ref:IIIA) | | | | 0.002 |
| Stage IIIB | 3.0 | 0.6 | 15.1 | 0.19 |
| Stage IIIC | 10.2 | 2.3 | 45.7 | 0.002 |
| 3rd months HE4 | 1.002 | 1.000 | 1.004 | 0.037 |

High HE4 expression has shown to be associated with disease severity, and worse OS in a variety of tumors.[11-14] Considering HE4 expression was associated with the progression of lung cancer, the prognostic value of HE4 expression in lung cancer patients has been investigated in several published studies, however, the results remain controversial.[11-29] Table 4 shows the relevant published data on studies evaluating the prognostic significance of HE4 in patients with NSCLC. Lamy et al. investigated the association between serum HE4 levels, and overall survival in patients with stage I-IV NSCLC.[22] They found that serum HE4 levels were significantly higher in patients with advanced TNM stage and positive nodal status. Moreover they showed a positive correlation between the pre-treatment serum HE4 levels, and OS. Kumbasar et al. evaluated both the diagnostic performance and the post-resection progress of serum

**Table 3.** Treatment-related toxicities

| Toxicity | Frequency (%) |
|---|---|
| Hematological toxicities | |
| Leukopenia | |
| Absent | 49 (41.9) |
| Grade 1 | 63(53.8) |
| Grade 2 | 5 (4.3) |
| Grade 3 | 0 (0.0) |
| Thrombocytopenia | |
| Absent | 82 (70.1) |
| Grade 1 | 22 (18.8) |
| Grade 2 | 13 (11.1) |
| Grade 3 | 0 (0.0) |
| Anemia | |
| Absent | 72 (61.5) |
| Grade 1 | 40 (34.2) |
| Grade 2 | 5 (4.3) |
| Grade 3 | 0 (0.0) |
| Non-Hematological toxicities | |
| Nausea | |
| Absent | 91 (77.8) |
| Grade 1 | 23 (19.7) |
| Grade 2 | 3 (2.6) |
| Grade 3 | 0 (0.0) |
| Vomiting | |
| Absent | 94 (80.3) |
| Grade 1 | 23 (19.7) |
| Grade 2 | 0 (0.0) |
| Grade 3 | 0 (0.0) |
| Esophagitis | |
| Absent | 14 (12.0) |
| Grade 1 | 52 (44.4) |
| Grade 2 | 45 (38.5) |
| Grade 3 | 6 (5.1) |
| Fatigue | |
| Absent | 34 (29.1) |
| Present | 83 (70.9) |
| Pneumonia | |
| Absent | 11 (9.4) |
| Present | 106 (90.6) |

HE4 in patients with stage III-IV NSCLC.[29] Their data demonstrated that HE4 is a potential biomarker for the diagnosis of NSCLC with high sensitivity and specificity and could also be used to detect recurrences following resection. They showed that a significant decrease of serum HE4 levels at post-operative 1st month, particularly for stages III and IV. Lan et al examined the role of HE4 in the diagnosis and prognosis of patients with LA-NSCLC, who underwent concurrent CRT.[21] Their results demonstrated that higher serum HE4 levels were associated with poor response to CRT, and shorter OS. Moreover Jiang et al. studies the prognostic significance of serum HE4 levels in human NSCLC among a Chinese population.[23] They found that high HE4 expression was correlated with TNM stage, lymph node metastases, and distant metastases in NSCLC patients. Furthermore, HE4 expression was found to be an independent poor prognostic factor for 5-year OS. In our study we also demonstrated that high serum HE4 levels after 3rd months of CRT were associated with worse OS.

Zhong et al., performed a meta-analysis in order to define the prognostic role of HE4 expression in lung cancer patients.[11] They analyzed a total 1412 patients from 8 different studies from different parts of the world. Interestingly, their results suggested that high serum HE4 level was a marker of poor prognosis in lung cancer patients, particularly in Asian patients with lung cancer. However there was no significant association between high HE4 expression and poor OS in Caucasian patients. These results indicated that the race was a significant source for conflicting results from different studies. From this perspective, best of our knowledge, the current study is the first one investigating the prognostic role of serum HE4 levels in Turkish lung cancer patients who underwent definitive CRT. Our results showed that high serum HE4 levels associated with worse OS.

In the current study, we investigated the prognostic role of HE4 in stage III NSCLC patients. OS in patients with high-HE4 after 3rd month of CRT was worse in the low-HE4 group. However we could not show any association between the OS and either pre-treatment or post-treatment HE4 levels. Additionally, we could not demonstrate a significant difference between the progression-free survival between and the serum high-HE4 levels. The reasons for this may be due to our small number of cases. However these results suggest that high serum HE4 levels may play a critical role in tumor progression in patients with NSCLC.

There are some limitations to our study that should be mentioned. First, the sample size of the current study was relatively small. Second the study was

**Table 4.** Published data on studies evaluating the prognostic significance of HE4 in patients with NSCLC

| First author/Year | N | Histology | Stage | HE4 testing method | Follow-up time (month) | Results/Comments |
|---|---|---|---|---|---|---|
| Yamashita, 2011 (13) | 137 | NSCLC | I-IV | IHC | 60 | HE4 serum levels are prognostic for OS |
| Lui, 2013 (24) | 169 | NSCLC | I-IV | ELISA | 36 | Serum HE4 may be used as a potential marker to differentiate lung cancer from pulmonary tuberculosis |
| Nagy, 2014 (26) | 98 | NSCLC/SCLC | I-IV | CMIA | 24 | Serum HE4 level is diagnostic for men lung cancer |
| Zhang, 2014 (28) | 191 | NSCLC/SCLC | I-IV | ELISA | 24-83 | HE4 serum levels are prognostic for OS |
| Lou, 2014 (25) | 153 | NSCLC/SCLC | IV | ELISA | N/A | HE4 is not prognostic |
| Jiang, 2014 (23) with | 100 | NSCLC | I-IV | ELISA | 60 | High HE4 expression was correlated TNM stage, lymph node metastases, distant metastases, and 5-year OS. |
| Lamy, 2015 (22) | 346 | NSCLC | I-IV | ELISA | 50 | Pre-treatment serum high HE4 level significantly correlated with shorter survival |
| Lan, 2016 (21) | 218 | NSCLC | III | ELISA | 0.3-57 | HE4 serum levels are associated with CRT response and OS |
| Kumbasar, 2017 (29) | 31 | NSCLC | III-IV | ELISA | N/A | HE4 is a potential biomarker for diagnosis of NSCLC, and could also be used to detect recurrences following resection |
| Current study CRT | 117 | NSCLC | III | ELISA | 5.4-39.8 | Stage, HE4 levels after 3 months of were predictive of OS |

*NSCLC: Non-small cell lung cancer; SCLC: small cell lung cancer; N/A: not available; ELISA: enzyme-linked immunosorbent assay; IHC: immunohistochemistry; CMIA: chemiluminescent micro-particle immunoassay; CRT: chemoradiotherapy; OS: Overall survival*

conducted at two different university hospitals in Turkey, which may limit the generalizability of the results to larger populations. Besides these limitations, the current study's strengths include the prospective design, and relatively longer follow-up duration. Furthermore, we selected only stage III NSCLC patients, and all patients underwent definitive CRT, therefore the study population was homogenous. As a result, the prognostic significance of HE4 in this subgroup of patients could have been clearly assessed.

In conclusion olarak başlayan paragraf: "In the current study, we demonstrated that demonstrated that, HE4 levels after 3 months of CRT were predictive of OS. The increase of 1 HE4 levels after 3 months of CRT increased the mortality rate 1.002. Therefore the high serum HE4 levels may be predictive for worse OS in patients with LA-NSCLC

***Funding:***
*This study supported by Turkish Oncology Group (TOG); Date: November, 16, 2018; Decision No: 2018-2.*

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