RESEARCH ARTICLE

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Predictive and Prognostic Significance of Serum Neuron-Specific Enolase in Patients with Metastatic Non-Small Cell Lung Cancer Receiving Gefitinib: A Prospective Study from South Egypt Cancer Institute

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Abstract

Background: Lung cancer remains the most lethal cancer in the world. Several predictive and prognostic biomarkers for non-small cell lung cancer (NSCLC) have emerged. Serum neuron-specific enolase (NSE) has been found to be elevated in up to 70% of patients with NSCLC. Prior retrospective studies have demonstrated conflicting results regarding the predictive and prognostic significance of baseline serum NSE in patients with metastatic NSCLC harboring epidermal growth factor receptor (EGFR) mutations who received tyrosine kinase inhibitors (TKIs). Our study aimed to evaluate the predictive and prognostic roles of pre-treatment serum NSE in patients with metastatic EGFR-mutated NSCLC planned to receive gefitinib therapy. **Methods:** In this prospective cohort study, we enrolled patients with known metastatic EGFR-mutated lung adenocarcinoma who presented at the Medical Oncology and Hematological Malignancies Department, South Egypt Cancer Institute (SECI), Assiut University; during the period from January 1st, 2021 to December 31st, 2022; and were planned to receive gefitinib therapy. Pre-treatment serum NSE was measured. The cut-off date of our study was July 31st, 2024. Association of baseline serum NSE level with therapy response and survival outcomes was analysed. **Result:** Forty eligible patients were enrolled. The median baseline serum NSE level was 9.0 ng/ml (range 6.0 – 15.3). Patients with high pre-treatment serum NSE level (higher than median level) were associated with significantly higher T and N clinical stages versus those with normal level (equal or less than median level). Regarding response rates, disease control rates (DCR) were significantly higher among those with normal serum NSE; whereas objective response rates (ORR) were similar in both groups. In terms of survival outcomes, high pre-treatment serum NSE was associated with worse progression-free survival (PFS) and overall survival (OS) outcomes. **Conclusion:** Baseline serum NSE is an independent poor predictive and prognostic factor for patients with metastatic EGFR-mutated NSCLC receiving gefitinib therapy.

Keywords: non-small cell lung cancer- neuron-specific enolase- gefitinib- epidermal growth factor receptor- prognosis

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Introduction

Globally, lung cancer ranks as the second most common cancer in both men (after prostate cancer) and women (after breast cancer). Furthermore, it is the leading cause of cancer-related deaths in both sexes with an estimated 2.2 million newly diagnosed cases and 1.8 million deaths worldwide in 2020 [1]. In Egypt, local cancer registries consider lung cancer the fifth most common cancer in both sexes representing about 5 % of all newly diagnosed cancer cases in 2022. Also, it is the fourth leading cause of cancer mortality with nearly 6,800 deaths in 2022 which constitutes about 7% of overall cancer mortality in Egypt [2].

Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases; with adenocarcinoma being the most frequent histologic subtype seen worldwide [3]. About 55% of NSCLC cases have metastatic disease at presentation which has an extremely poor prognosis (only 7% relative survival rate at 5 years) [4, 5].

The epidermal growth factor receptor (EGFR) is a trans-membrane protein that is a receptor for members of the epidermal growth factor family (EGF family) of extracellular protein ligands [6]. Activating epidermal growth factor receptor (EGFR) mutations have been identified in 10 – 60% of lung adenocarcinomas [7]. The majority of EGFR mutations results in activation of the tyrosine kinase domain, which is associated with

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sensitivity to the small-molecule EGFR tyrosine kinase inhibitors (TKIs); such as erlotinib, gefitinib, afatinib, osimertinib, and dacomitinib [8].

Neuron-specific enolase (NSE) is a neuro- and neuroendocrine-specific isoenzyme of enolase. It is considered a useful tumor marker for tumors of neural and neuroendocrine origin, such as neuroblastoma, neuroendocrine tumors and small cell lung cancer (SCLC). In addition, serum NSE was found to be elevated in up to 70% of patients with NSCLC [9]. Previous studies did not get concordant results concerning the relation between the pre-treatment serum NSE levels and both therapy response and survival outcomes in patients with metastatic EGFR-mutated NSCLC receiving gefitinib [10-15].

The aim of this study is to evaluate the predictive and prognostic significance of baseline serum NSE level in patients with metastatic EGFR-mutated NSCLC planned to receive gefitinib therapy.

Materials and Methods

This current study is a prospective cohort one conducted on patients with known metastatic EGFR-mutated lung adenocarcinoma who presented at the Medical Oncology and Hematological Malignancies Department, South Egypt Cancer Institute (SECI), Assiut University; during the period from January 1st, 2021 to December 31st, 2022; and were planned to receive gefitinib therapy to evaluate the relation of pre-treatment serum NSE level to the prognosis, and response to gefitinib therapy.

The inclusion eligibility criteria included patients with histopathologically confirmed diagnosis of lung adenocarcinoma harboring EGFR mutations and planned to receive anti-EGFR TKI therapy with gefitinib. All patients were at least 18 years old; and had Eastern Cooperative Oncology Group (ECOG) performance status score of 0 – 2 [16]. They all had clinical stage IV (metastatic) disease; and were treatment-naïve, or had received only one prior line of chemotherapy.

Patients with other synchronous primary cancers; those who had previously received anti-EGFR TKI therapy, or ≥2 previous lines of chemotherapy; and those who refused to be enrolled in the study, or withdrew their written consent during the study were excluded.

Serum NSE was measured for all patients before starting treatment with gefitinib using enzyme-linked immunosorbent assay (ELISA) technique. Serum NSE levels less than or equal median have been referred to as ''Normal serum NSE''; whereas levels higher than median have been considered as "High serum NSE". The patients were stratified into two main groups according to their baseline serum NSE level (normal versus high serum NSE).

All patients received gefitinib at the standard approved dose of 250 mg orally once a day. Treatment was continued until disease progression, unacceptable toxicity, or study cut-off date. Therapy-related adverse events were evaluated and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 5.0) system [17]. Patients were assessed clinically and radiologically every 3 months during the course of gefitinib therapy. Response to therapy was evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [18].

Primary endpoints were objective response rate (ORR), disease control rate (DCR), and progression free survival (PFS). The secondary endpoints were overall survival (OS), and safety profile. ORR is defined as the proportion of patients that achieved complete response (CR) or partial response (PR) to therapy; whereas DCR describes the proportion of patients that achieved CR, PR, or stable disease (SD) to therapy [19]. PFS is defined as the time from start of treatment until tumor progression, death, or last follow-up; whichever comes first; whereas OS is defined as the time from start of treatment until death, or last follow-up; whichever comes first [20]. Patients with missed follow-up or who are still alive at the time of study cut-off have been censored.

For statistical analysis, Statistical Package for the Social Sciences (SPSS) version 26.0 was used. Categorical variables were presented as frequency and percentage; and compared using the chi-square test or Fisher's exact test when appropriate. Continuous variables were reported as mean ± standard deviation (SD) if normally distributed; or median and range if not normally distributed. These variables were compared with the use of parametric Student's t-test or non-parametric Mann-Whitney U test. Survival curves were estimated with the Kaplan-Meier method and compared using the log-rank test to analyze the progression-free survival (PFS) and overall survival (OS) rate of the patients. For multivariate analysis, the adjusted hazard ratios (HRs) and corresponding 95% CI for PFS and OS were estimated with the Cox proportional hazard regression model. P-value (two-sided) of less than 0.05 has been considered statistically significant. The cut-off date of our study was July 31st, 2024.

Results

During the period of two years (from January 1st, 2021 to December 31st, 2022), 206 patients with NSCLC were assessed. Of those, 77 patients had metastatic lung adenocarcinoma with activating EGFR gene mutations. Thirty seven patients were excluded (29 received erlotinib; 4 received osimertinib; 2 refused therapy; and 2 died before assessment). Finally, 40 patients were subjected to final analysis (the normal serum NSE group: 23 patients; and the high serum NSE group: 17 patients).

Baseline characteristics

The mean age of our patients was 57.4 years; with about 65% of them aged less than 65 years. Eighteen (45%) patients were males. The median body mass index (BMI) was 27.6 kg/m2 (range; 21.4 – 34); with approximately 62.5% of patients being overweight (BMI 25.0 – 29.9), or obese (BMI ≥30). Twenty-seven patients (67.5%) had ECOG performance status score of 0 to 1. About 40% of the enrolled patients had a history of smoking. Thirteen patients (32.5%) had multi-comorbidities {defined as the presence of 2 or more long-term health conditions} [21].

As regards presenting symptoms, 24 patients had

persistent cough; 24 patients had difficulty of breathing; 11 patients presented with hemoptysis; 9 patients presented with chest pain; whereas 11 patients presented with symptoms of metastases. Concerning tumor site, 19 patients (47.5%) had tumors in the right lung; and 21 patients (52.5%) had tumors in the left lung.

Based on the 8th edition of the primary tumor, lymph nodes, and distant metastasis (TNM) staging system of NSCLC [22], 16 patients (40%) had T1/2 disease; whereas 24 patients (60%) had T3/4 disease. Twelve patients (30%) had N0/1 disease; in contrast to 28 patients (70%) who presented with N2/3 disease. Referring to M stage, only 9 patients (22.5 %) had M1a/1b disease; while the other 31 patients (77.5%) presented with M1c disease.

Regarding sites of metastases and number of metastatic organs, 17 patients (42.5%) had metastases in only one organ; compared with 23 patients (57.5%) who had metastases in two or more organs. Synchronous oligometastases {defined as a maximum of 5 metastases in less than or equal 3 organs} [23] were present in only 7 patients (17.5%); in contrast to the remaining 23 patients (82.5%) who presented with synchronous polymetastatic disease.

Pointing to tumor pathologic characteristics, 25 patients (62.5%) had tumors of grade 1 or 2; whereas 15 patients (37.5%) had grade 3 tumors. Necrosis was absent or rare in 21 patients (52.5%); and extensive in 19 patients (47.5%). Hemorrhage was evident in pathological examination of 22 cases (55%). High mitotic index was found in 21 cases (52.5); in contrast to low mitotic index in 19 cases (47.5%).

Twenty-nine patients (72.5%) had EGFR exon 19 deletion; whereas 11 patients (27.5%) had EGFR exon 21 L858R activating mutation. As regards pre-treatment serum NSE, the mean level (± SD) was 9.28 ng/mL (± 2.22); whereas the median level was 9.0 ng/mL with a range from 6.0 to 15.3 ng/mL.

Fifteen cases (37.5%) had received first-line chemotherapy before starting Gefitinib therapy. Of these cases, 9 patients received Gemcitabine plus Platinum agent (Cisplatin or Carboplatin) regimen; whereas 6 patients received paclitaxel plus platinum agent regimen. As regards response to prior first-line chemotherapy at first assessment, 10 cases of the 15 patients achieved partial response (PR), or stationary disease (SD); in contrast to the remaining 5 cases who developed progressive disease (PD) at their first assessment.

Correlation between NSE level and other clinico-pathological characteristics

The clinico-pathological characteristics of the two groups of patients (normal versus high baseline serum NSE level) were similar except for T and N clinical stages which were significantly higher in the high serum NSE group (p= 0.003 for T stage; p= 0.041 for N stage) (Table 1).

Response rates

According to the RECIST 1.1, the outcomes of gefitinib therapy among the enrolled patients in this study were CR: 0.0% (0/40); PR: 37.5% (15/40); SD: 52.5% (21/40); PD: 10% (4/40); ORR: 37.5% (15/40); DCR: 90% (36/40). No statistically significant association was found between pre-treatment serum NSE and ORR of Gefitinib therapy (p= 0.187) whereas normal pre-treatment serum NSE was associated with statistically significant higher DCR with gefitinib therapy (p= 0.026).

Survival outcomes

Concerning PFS, the median PFS was 17.4 months (95% CI: 12.6 – 22.1) for all patients; 38.8 months (95% CI: 14.1 – 63.5) among those in the normal serum NSE group; and 13.5 months (95% CI: 7.3 – 19.7) in those with high serum NSE level (p= 0.005) (Figure 1).

Regarding OS, the median OS was 31.0 months (95% CI: 19.5 – 42.5) for all patients; 41.7 months (95% CI:

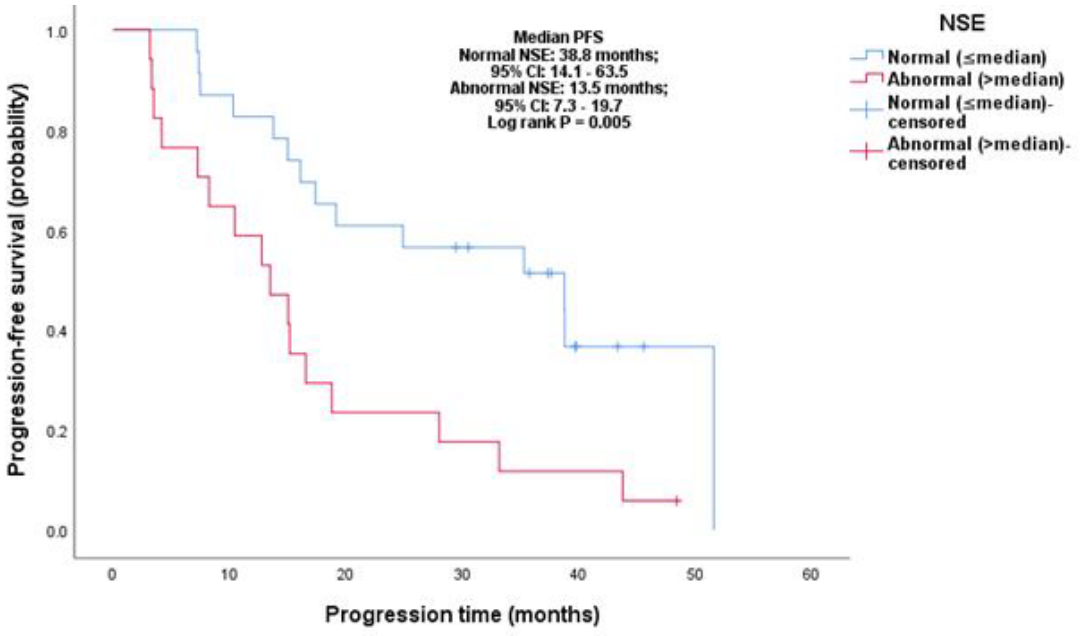

Figure 1. Kaplan-Meier Curve Showing Relation between Serum NSE and PFS

Table 1. Correlation between Serum NSE and Patient Characteristics

Characteristic	Normal serum NSE [n= 23]		High serum NSE [n= 17]		P-value
	Number	Percentage	Number	Percentage	
Age					
<65 years [n= 26]	16	69.6	10	58.8	0.481
≥65 years [n= 14]	7	30.4	7	41.2	
Sex					
Male [n= 18]	10	43.5	8	47.1	0.822
Female [n= 22]	13	56.5	9	52.9	
BMI					
Underweight/ Normal Weight [n= 15]	7	30.4	8	47.1	0.283
Overweight/Obese[n= 25]	16	69.6	9	52.9	
PS (ECOG)					
0-1 [n= 27]	15	65.2	12	70.6	0.72
2 [n= 13]	8	34.8	5	29.4	
Smoking status					
Never [n= 24]	16	69.6	8	47.1	0.151
Ever [n= 16]	7	30.4	9	52.9	
Multi-comorbidity					
No [n= 27]	16	69.6	11	64.7	0.746
Yes [n= 13]	7	30.4	6	35.3	
Site					
Right lung [n= 19]	11	47.8	8	47.1	0.962
Left lung [n= 21]	12	52.2	9	52.9	
Stage					
T stage					
T1/2 [n= 16]	14	60.9	2	11.8	0.003
T3/4 [n= 24]	9	39.1	15	88.2	
N stage					
N0/1 [n= 12]	10	43.5	2	11.8	0.041
N2/3 [n= 28]	13	56.5	15	88.2	
M stage					
M1a/1b [n= 9]	8	34.8	1	5.9	0.054
M1c [n= 31]	15	65.2	16	94.1	
Number of metastatic organs					
1 organ [n= 17]	11	47.8	6	35.3	0.428
≥2 organs [n= 23]	12	52.2	9	64.7	
Type of metastases					
Oligometastases [n= 7]	4	17.4	3	17.6	0.987
Polymetastases [n= 33]	19	82.6	14	82.4	
EGFR mutation genotyping					
Exon 19 deletion [n= 29]	15	65.2	14	82.4	0.297
Exon 21 L858R mutation [n= 11]	8	34.8	3	17.6	
Pathology report					
Grade					
Grade 1/2 [n= 24]	15	65.2	9	52.9	0.433
Grade 3 [n= 16]	8	34.8	8	47.1	
Necrosis					
Absent/Rare [n= 21]	13	56.5	8	47.1	0.554
Extensive [n= 19]	10	43.5	9	52.9	

Abbreviations: NSE, neuron-specific enolase; BMI, body mass index; PS, performance status; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PR, partial response; SD, stationary disease; PD, progressive disease.

Table 1. Continued

Characteristic	Normal serum NSE [n= 23]		High serum NSE [n= 17]		P-value
	Number	Percentage	Number	Percentage	
Hemorrhage					
Absent [n= 18]	12	52.2	6	35.3	0.289
Present [n= 22]	11	47.8	11	64.7	
Mitotic index					
Low [n= 19]	12	52.2	7	41.2	0.491
High [n= 21]	11	47.8	11	58.8	
Previous chemotherapy					
No [n= 25]	15	65.2	10	58.8	0.68
Yes [n= 15]	8	34.8	7	41.2	
Response to chemotherapy at first assessment					
PR/SD [n= 10]	6 of 8	75	4 of 7	57.1	0.608
PD [n= 5]	2 of 8	25	3 of 7	42.9	

Abbreviations: NSE, neuron-specific enolase; BMI, body mass index; PS, performance status; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PR, partial response; SD, stationary disease; PD, progressive disease.

Table 2. Univariate/Multivariate Analysis of PFS

Covariate	Univariate (for unadjusted HRs)			Multivariate (for adjusted HRs)		
	HR	95% CI	P-value	HR	95% CI	P-value
Serum NSE	2.8	1.33 – 5.88	0.007	3.03	1.37 – 6.73	0.006
Grade	2.3	1.07 – 4.92	0.032	0.46	0.15 – 1.38	0.166
Necrosis	2.85	1.30 – 6.25	0.009	0.91	0.22 – 3.70	0.893
Hemorrhage	2.84	1.27 – 6.35	0.011	1	0.32 – 3.12	0.994
Mitotic index	3.68	1.61 – 8.41	0.002	7.42	1.47 – 37.48	0.015

Abbreviations: PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; NSE, neuron-specific enolase.

28.2 – 55.1) for those with normal serum NSE level; 25.4 months (95% CI: 15.1 – 35.6) among those with high serum NSE level (p= 0.019) (Figure 2).

Moreover, multivariate analysis using the Cox proportional hazards regression model confirmed that pre-treatment serum NSE levels are significant independent predictive factors for PFS (HR= 3.03; 95% CI: 1.37 – 6.73; p= 0.006) {Table 2}; and OS (HR= 2.37; 95% CI: 1.03 – 5.44; p= 0.041) (Table 3).

Discussion

To the best of our knowledge, this study is the first one in Africa and the Middle East that specifically investigated

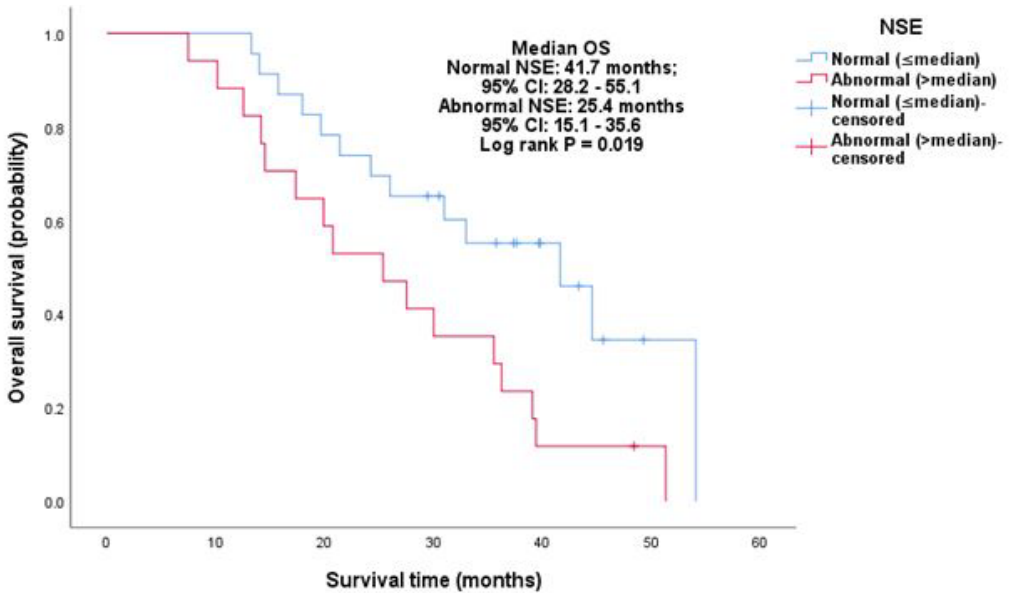

Figure 2. Kaplan-Meier Curve Showing Relation between Serum NSE and OS

Table 3. Univariate/Multivariate Analysis of OS

Covariate	Univariate (for unadjusted HRs)			Multivariate (for adjusted HRs)		
	HR	95% CI	P-value	HR	95% CI	P-value
Serum NSE	2.4	1.13 – 5.09	0.023	2.37	1.03 – 5.44	0.041
Grade	2.52	1.13 – 5.62	0.024	0.59	0.18 – 1.89	0.373
Necrosis	3.13	1.37 – 7.13	0.007	1.19	0.27 – 5.30	0.825
Hemorrhage	2.93	1.27 – 6.75	0.012	0.96	0.31 – 3.04	0.948
Mitotic index	4	1.64 – 9.75	0.002	4.85	0.88 – 26.71	0.07

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; NSE, neuron specific enolase.

the role of serum NSE in NSCLC. This prospective study enrolled 40 patients with metastatic EGFR-mutated lung adenocarcinoma planned to receive gefitinib therapy. Analysis of the relation between the clinico-pathologic criteria of the patients and their baseline serum NSE level demonstrated that those with high pre-treatment serum NSE level are associated with statistically significant higher T and N clinical stages. These findings are partially in agreement with the study by Yu D. et al., which stated that high serum NSE is associated with higher T clinical stage; but did not find any significant association between serum NSE level and N clinical stage [9]. This may be explained by the fact that NSE is an enzyme that has a major role in aerobic glycolysis which helps cells to proliferate quickly [24]; and hence high serum NSE concentrations are associated with higher T and N clinical stages.

Referring to treatment outcomes based on pre-treatment serum NSE level, this study declared that there is no statistically significant association between pre-treatment serum NSE level and ORR of Gefitinib therapy which is in concordance with the study by Yan P. et al., [25]. In addition, DCR of Gefitinib is significantly higher in patients with normal pre-treatment serum NSE level which was also concluded by Wang Y et al. [12]. Conversely, the above results are not in concordance with the study by Zhaio XM et al. [15]; which found that there is no significant difference in response to therapy with EGFR TKIs (including gefitinib) in patients with metastatic NSCLC based on the baseline serum NSE .

As regards survival outcomes, the median PFS of patients with high baseline serum NSE levels is approximately 25 months shorter than those with normal baseline levels. Also, the median OS of patients with high pre-treatment serum NSE levels is nearly 16 months shorter than those with normal pre-treatment levels. According to the above data, we demonstrated statistically significant improvement in both PFS, and OS among patients with normal pre-treatment serum NSE level. Moreover, multivariate cox regression analysis confirmed that baseline serum NSE level is an independent prognostic parameter for both PFS and OS of our study population. These findings are consistent with the studies by Yan P. et al.; Inomata M. et al.; Koung Jin Suh et al.; which all reported that pre-treatment serum NSE level has a statistically significant independent association with survival outcomes [25-27]. Contrary to our results, the study by Zhaio XM et al. [15]; which did not find significant differences in both PFS and OS outcomes based on the baseline serum NSE in patients with advanced NSCLC with EGFR-sensitive mutations who received gefitinib. Also, Fiala O et al. [14]; declared that high serum NSE is a strong independent predictive factor for short PFS of patients with NSCLC treated with EGFR-TKIs; whereas OS outcomes are similar in both groups of patients (normal versus high serum NSE) [14]. Our findings may be because NSE promotes rapid growth and proliferation of tumor cells which may contribute to the increased aggressiveness of tumors and their poor response to therapy [24]. In addition, NSCLC with high serum NSE may be associated with small cell component which is associated with poor prognosis [28].

Immunohistochemical (IHC) staining of the tumor specimens for NSE was not performed based on the evidence from the studies by Inomata M. et al., and by Tiseo et al., and other similar studies which concluded that there is no significant association between the plasma NSE levels and the findings of IHC [26, 29].

The relatively small sample size is one of the limitations of our study. In addition, it is dependent on a single institute experience. In the future, we recommend further studies on a larger scale with larger sample size including the experience of multiple institutions. Furthermore, analysis of the association between serum NSE and response to systemic therapies other than TKIs (e.g., anaplastic lymphoma kinase (ALK) inhibitors; and immune checkpoint inhibitors) may be considered.

In conclusion, this prospective study demonstrated that baseline serum NSE is an independent predictive and prognostic factor for patients with metastatic EGFR-mutated NSCLC receiving gefitinib therapy.

Author Contribution Statement

All authors were involved in planning the research and study design. Material preparation and data collection were performed by A.H.M. Processing of NSE test and interpretation of results were done by D.A.M. Statistical analysis was conducted by S.M.K. The paper draft was written by A.Z.A and M.G.M. All authors reviewed and approved the final manuscript.

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Ethical approval statement

Concerning ethical considerations, an individual written consent was obtained from each patient participating in our study. This study was approved by the Institutional Ethical Committee of South Egypt Cancer Institute; and its Institutional Review Board (IRB) approval number is 558; on October 16th, 2020. The drugs were supplied either by treatment decisions at state expense, or by health insurance.

Availability of data

All data generated and analyzed during this study can be accessed through direct communication with the corresponding author and the agreement of all research team members.

Consent for publication

Informed consent for publication was obtained from all participants in the study.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

References

1. Filder-Benaoudia MM, Torre LA, Bray F, Ferlay J, Jemal A. Lung Cancer incidence in young women vs. young men: a systematic analysis in 40 countries. Int J Cancer. 2020;147(3):811-9. https://doi.org/10.1002/ijc.32809.
2. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, et al. Global Cancer Observatory: Cancer Today [Internet]. Lyon, France: International Agency for Research on Cancer; 2024 Feb 8.
Available from: https://gco.iarc.fr/today/en/dataviz/globe?mode=population.
3. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER Cancer Statistics Review, 1975-2017 [Internet]. Bethesda, MD: National Cancer Institute; 2020. Available from: https://seer.cancer.gov/csr/1975_2017/.
4. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. CHEST. 2017;151(1):193–203. https://doi.org/10.1016/j.chest.2016.10.010.
5. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer – major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):138-55. https://doi.org/10.3322/caac.21390.
6. Franklin WA, Veve R, Hirsch FR, Helfrich BA, Bunn PA. Epidermal growth factor receptor family in lung cancer and premalignancy. Semin Oncol. 2002;29(1):3–14. https://doi.org/10.1053/sonc.2002.31520.
7. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for Epidermal Growth Factor Receptor Mutations in Lung Cancer. N Engl J Med. 2009;361(10):958-67. https://doi.org/10.1056/NEJMoa0904554.
8. Riely G, Politi K, Miller V, Pao W. Update on epidermal growth factor receptor mutations in non-small cell lung cancer. Clin Cancer Res. 2006;12:7232-41. https://doi.org/10.1158/1078-0432.CCR-06-0658.
9. Yu D, Du K, Liu T, Chen G. Prognostic value of tumor markers, NSE, CA125 and SCC, in operable NSCLC Patients. Int J Mol Sci. 2013;14(6):11145-56. https://doi.org/10.3390/ijms140611145.
10. Broers JL, Carney DN, de Ley L, Vooijs GP, Ramaekers FC. Differential expression of intermediate filament proteins distinguishes classic from variant small-cell lung cancer cell lines. Proc Natl Acad Sci U S A. 2015;82(13):4409–13. https://doi.org/10.1073/pnas.82.13.4409.
11. Kimura H, Yamaguchi T, Nishino K, Nakagawa M, Yokota S, Nishikawa H, et al. Clinical significance of serum neuron-specific enolase in non-small cell lung cancer. Nihon Kokyuki Gakkai Zasshi. 1998;36(2):128-32.
12. Wang Y, Tang D, Sui A, Jiao W, Luo Y, Wang M, et al. Prognostic significance of NSE mRNA in advanced NSCLC treated with gefitinib. Clin Transl Oncol. 2013;15(5):384-90. https://doi.org/10.1007/s12094-012-0939-3.
13. Xu FZ, Zhang YB. Correlation analysis between serum neuron-specific enolase and the detection of gene mutations in lung adenocarcinoma. J Thorac Dis. 2021;13(2):552-61. https://doi.org/10.21037/jtd-20-1633.
14. Fiala O, Pesek M, Finek J, Benesova L, Minarik M, Bortlicek Z, et al. The Role of Neuron-specific Enolase (NSE) and Thimidine Kinase (TK) Levels in Prediction of Efficacy of EGFR-TKIs in Patients with Advanced-stage NSCLC. Anticancer Res. 2014 ;34(9):5193-98.
15. Zhaio XM, Zhao J, Xing KL, Sun S, Luo ZG, Wang HJ, et al. Prognostic and predictive value of serum carcinoembryonic antigen levels in advanced non-small cell lung cancer patients with epidermal growth factor receptor sensitive mutations and receiving tyrosine kinase inhibitors. Oncotarget. 2017;8(41):70865-73. https://doi.org/10.18632/oncotarget.20145.
16. Azam F, Latif M, Farooq A, Tirmazy S, AlShahrani S, Bashir S, et al. Performance Status Assessment by Using ECOG (Eastern Cooperative Oncology Group) Score for Cancer Patients by Oncology Healthcare Professionals. Case Rep Oncol. 2019;12(3):728-36. https://doi.org/10.1159/000503095.
17. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. Actas Dermosifiliogr. 2021;112(1):90-2. https://doi.org/10.1016/j.ad.2019.05.009.
18. Eisenhauer E, Therasse P, Bogaerts J, Schwartz L, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47. https://doi.org/10.1016/j.ejca.2008.10.026.
19. Nie RC, Chen FP, Yuan SQ, Luo YS, Chen S, Chen YM, et al. Evaluation of objective response, disease control and progression-free survival as surrogate end-points for overall survival in anti–programmed death-1 and anti–programmed death ligand 1 trials. Eur J Cancer. 2019;106:1-11. https://

doi.org/10.1016/j.ejca.2018.10.011.
20. Mariotto AB, Noone AM, Howlader N, Cho H, Keel GE, Garshell J, et al. Cancer survival: an overview of measures, uses, and interpretation. J Natl Cancer Inst Monogr. 2014;2014(49):145-86. https://doi.org/10.1093/jncimonographs/lgu024.
21. Harrison C, Fortin M, van den Akker M, Mair F, Calderon-Larranaga A, Boland F, et al. Comorbidity versus multimorbidity: Why it matters. J Comorb. 2021;11:2633556521993993. https://doi.org/10.1177/2633556521993993.
22. Lababede O, Meziane M. The Eighth Edition of TNM Staging of Lung Cancer: Reference Chart and Diagrams. Oncologist. 2018;23(7):844-48. https://doi.org/10.1634/theoncologist.2017-0659.
23. Dingemans AC, Hendriks LEL, Berghmans T, Levy A, Hasan B, Faivre-Finn C, et al. Definition of Synchronous Oligometastatic Non-Small Cell Lung Cancer-A Consensus Report. J Thorac Oncol. 2019;14(12):2109-19. https://doi.org/10.1016/j.jtho.2019.07.025.
24. Li S, Cao L, Wang X, Wang F, Wang L, Jiang R. Neuron-Specific Enolase Is an Independent Prognostic Factor in Resected Lung Adenocarcinoma Patients with Anaplastic Lymphoma Kinase Gene Rearrangements. Med Sci Monit. 2019;25:675-90. https://doi.org/10.12659/MSM.913054.
25. Yan P, Han Y, Tong A, Liu J, Wang X, Liu C. Prognostic value of neuron-specific enolase in patients with advanced and metastatic non-neuroendocrine non-small cell lung cancer. Biosci Rep. 2021;41(8):BSR20210866. https://doi.org/10.1042/BSR20210866.
26. Inomata M, Hayashi R, Yamamoto A, Tokui K, Taka C, Okazawa S, et al. Plasma neuron-specific enolase level as a prognostic marker in patients with non-small cell lung cancer receiving gefitinib. Mol Clin Oncol. 2015;3(4):802-6. https://doi.org/10.3892/mco.2015.568.
27. Suh KJ, Keam B, Kim M, Park YS, Kim TM, Jeon YK, et al. Serum Neuron-Specific Enolase Levels Predict the Efficacy of First-Line Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors in Patients With Non-Small Cell Lung Cancer Harboring EGFR Mutations. Clin Lung Cancer. 2016;17(4):245-52. https://doi.org/10.1016/j.cllc.2015.11.012.
28. Lin Q, Cai GP, Yang KY, Yang L, Chen CS, Li YP. Case report: small cell transformation and metastasis to the breast in a patient with lung adenocarcinoma following maintenance treatment with epidermal growth factor receptor tyrosine kinase inhibitors. BMC Cancer. 2016;16:593. https://doi.org/10.1186/s12885-016-2623-4.
29. Tiseo M, Ardizzoni A, Cafferata M, Loprevite M, Chiaramondia M, Filiberti R, et al. Predictive and prognostic significance of neuron-specific enolase (NSE) in non-small cell lung cancer. Anticancer Res. 2008;28(1):507-13.