VOLUME - 10, ISSUE - 04, APRIL- 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Pulmonary Medicine

# A CROSS SECTIONAL STUDY FOR EVALUATION OF CARCINOEMBRYONIC ANTIGEN IN THE DIAGNOSIS OF NON-SMALL CELL LUNG CANCER, AT INSTITUTE OF RESPIRATORY DISEASES, SAWAI MAN SINGH MEDICAL COLLEGE, JAIPUR

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| **Dr. Jitendra Kumar Bairwa*** | MD,Department of Respiratory Medicine, Swai Man Singh Medical College. *Corresponding Author |
| **Dr. Rajendra Prasad** | MD, Department of Respiratory Medicine, Swai Man Singh Medical College. |
| **Dr. Narendra Khippal** | MD Senior Professor, Department of Respiratory Medicine, Swai Man Singh Medical College |
| **Dr. Chand Bhandari** | MD Senior Professor , Department of Respiratory Medicine, Swai Man Singh Medical College. |

**ABSTRACT** Currently, clinical diagnosis of lung cancer mainly relies on imaging modalities such as chest X-ray or low dose computed tomography (CT) scans. A non-invasive test with high specificity for distinguishing the indolent disease from lung cancer patients is highly demanded. A biomarker with high sensitivity and specificity for diagnosis at an early stage of the disease is significant for better survival.Serum CEA levels were observed to be significantly higher in NSCLC patients with worse prognosis and poorer survival rates. A cross-sectional study was conducted at theIRD, SMS Medical College, Jaipur involving 55 patients with newly diagnosed and histopathologically confirmed cases of NSCLC during one year period.The study population underwent clinical history and physical examination, routine blood investigations, chest radiography and CECT Chest.Serum CEA levels were recorded at the time of diagnosis of NSCLC & after completion of 6th chemotherapy and were correlated with RECIST criteria. In our study majority of the patients were middle aged, male,smokers. Most common histopathology was squamous cell carcinoma followed by adenocarcinoma. At the time of diagnosis, 50.91% patients had a raised serum CEA level (>10 ng/mL) most of whom hadadenocarcinoma with an advanced stage.Similarly, raised serum CEA level after 6th CT cycle was found to be significantly higher in patients with adenocarcinoma. After completion of 6th CT cycle, response was evaluated by RECIST criteria. Progression of disease was found to be significantly associated with adenocarcinoma. In our study, serum CEA levels were raised mainly in adenocarcinoma and associated with progression of the disease. So, serum CEA levels could be used clinically for diagnosis of NSCLC and also for monitoring for lung cancer during chemotherapy, radiotherapy, and surgery.

**KEYWORDS :** NSCLC (Non Small Cell Lung Cancer), CEA (Carcinoembryonic Antigen), RECIST (Response And Evaluation Criteria In Solitary Tumours), CT (chemotherapy)

## (I) INTRODUCTION

Worldwide, lung cancer is the most common cancer among men in terms of both incidence and mortality, and among women it has the third highest incidence, and is second after breast cancer in mortality.[1]The two main subtypes of lung cancer are small-cell lung carcinoma (SCC) and Non-small-cell lung carcinoma (NSCLC), which accounts for 15% and 85% respectively.[2]Most of NSCLC cases are locally advanced (stage III) or metastatic (stage IV) at the time of presentation.[3] Because of unfavorable prognosis of lung cancer, early diagnosis plays an important role in increasing the survival rate.

Currently, clinical diagnosis of carcinoma mainly relies on chest X-ray, low dose computerized tomography (CT) scans, and other imaging technology.[4]The high-false positive rates, harmful effects of radiation and cost may limit the diagnostic accuracy and utility in screening.[5]Therefore a non-invasive test with high specificity for distinguishing the indolent disease from lung cancer patients is highly demanded.[4,5]

There is no effective biomarker for early diagnosis of NSCLC. The available serum tests are minimally invasive and most desirable testing matrix in biomarker evaluations. Carcinoembryonic antigen (CEA) and cytokeratin (CYFRA21) are commonly investigated serum/plasma carcinoma protein biomarkers.[4,5]CEA is a cell adhesion glycoprotein expressed in gastrointestinal tissues at very low levels in healthy individuals. The serum CEA levels were observed significantly higher in NSCLC patients with worse prognosis and poorer survival rates.[4]

A biomarker with high sensitivity and specificity for diagnosis at an early stage of the disease is significant for better survival. There are limited studies available which describe the role of biomarkers in early detection of NSCLC. The aim of this study is to investigate the potential diagnostic and prognostic role of serum CEA levels in NSCLC.

## (II) MATERIALS & METHODS

A cross-sectional study was conducted at the Institute of Respiratory Diseases, SMS Medical College, Jaipur, after taking written informed consent, a total of 55 patients with newly diagnosed and histopathologically confirmed cases of NSCLC were selected during a one yearperiod. Patients who had no prior history of chemotherapy or radiotherapy and with normal hepatic and renal function tests were included in our study. Patients with a previous or concomitant history of cancer other than NSCLC and those with other diseases known to be associatedwith raised serum CEA levels were excluded from our study.

The study population was subjected to clinical history and physical examination, blood counts, routine biochemistry, CEA levels, chest radiography and CT Chest. CT brain, abdomen and bone scans were performed as and when necessary. Fortissue diagnosis,samples were obtained by one of the modalitiesamongst fiberoptic bronchoscopy, CT guided FNAC/biopsy, pleural biopsy, USG guided biopsy and sent to pathology lab for histopathological examination. After histopathological or cytopathological confirmation, patients were stratified into different stages according to the 8th TNM staging for Lung Cancer.Blood samples for serum CEA were collected within 4 weeks from the first biopsy-proven lung cancer diagnosis and prior to radiotherapy or chemotherapy or before surgical removal of cancer.After pre-chemotherapy

evaluation all patients were treated with optimum chemotherapy regimens. All patients were assessed for tumor response according to RECIST criteria after the end of 6th cycle of chemotherapy.Response was defined as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according RECIST criteria.Serum CEA levels were recorded at the time of diagnosis of NSCLC and after the completion of 6th cycles of chemotherapy and correlated with progression or regression of NSCLC.

In our study, outcome variables were comparison of the CEA levels before and after designated chemotherapy &comparison of tumor size (assessed by RECIST criteria) before and after the chemotherapy.

The comparison of the variables which were quantitative in nature was performed using ANOVA and paired t test was used for comparison between pre and post chemotherapy. The comparison of the variables which were qualitative in nature was performed using Chi-Square test/Fisher's exact test.

## (III) RESULTS

Baseline characteristics of the patients are shown in the table [Table 1]

In the present study, majority of the patients (45.45%) were in the age group of 61-70 years followed by 32.73% patientsin 51-60 years age group and 14.55% patients in>70 years age group. Age group was <=50 years in only 4 out of 55 patients (7.27%).Themean value of age (years) of study subjects was 61.69±8.9.In our study 90.91% of patients were males and 9.09% of patients were females. While 94.55% of patients were smokers, only 3 out of 55 patients (5.45%) were non-smokers.

The majority of patients were diagnosed by fiberoptic bronchoscopy (67.27%). While squamous cell carcinoma was diagnosed in majority (58.18%) of NSCLC patients, adenocarcinoma was diagnosed in 30.91%, unspecified NSCLC in 9.09% and large cell carcinomain only 1 out of 55 (1.82%) patients.

In our study, 56.36% & 25.45% of male patients were diagnosed as squamous cell carcinoma and adenocarcinoma, respectively. Approximately 50.9% of patients were in Stage III & 49.9% in stage IV lung cancer.

**Table 1 - Demographic profile of patients**

| Patient characteristics | Total number (n = 55) |
|---|---|
| Age (mean) | 61.69±8.9 |
| **Sex** | |
| Male | 50 (90.91%) |
| Female | 5 (9.09%) |
| Smoking Status | |
| Chronic active smoker | 26(47.27%) |
| Ex- Smoker | 26(47.27%) |
| Non Smoker | 3(5.45%) |
| Histology | |
| Adenocarcinoma | 17(30.91) |
| Squamous cell carcinoma | 32(58.91) |
| Unspecified carcinoma | 1(1.82%) |
| Large cell carcinoma | 5(9.09%) |
| Tumour stage | |
| Stage III | 28 (50.9) |
| StageIV | 27(49.1) |
| ECOG performance status | |
| 1 | 17(30.91) |
| 2 | 29(52.73%) |
| 3 | 9(16.36%) |
| Haemoglobin (gm/dl) (mean + SD) | 11.9±1.67 |
| Total Leukocyte Count (/mm$^3$) | 10.47±3.7 |
| Weight (kg) | 51.84±9.39 |
| Body mass index (kg/m$^2$) | |
| <18.5 | 31(56.36%) |
| 18.5 to 24.99 | 24(43.64%) |

In our study, at the time of diagnosis, 50.91% patients had a raised serum CEA level (ng/mL) with themean valuebeing 51.56 ± 97.47. Raised Serum CEA levels at the time of diagnosis were significantly higher in Adenocarcinoma, Large cell carcinoma as compared to Squamous cell carcinoma and Unspecified NSCLC: (82.35%, 100% vs 31.25%, 60% respectively) (p value = 0.002). Mean values of serum CEA levels at the time of diagnosis was highest in adenocarcinoma (112.92 ± 151.5) followed by unspecified NSCLC (56.04 ± 61.33) and large cell carcinoma (55.25 ± 0) and lowest in squamous cell carcinoma (18.15 ± 31.57) (p value=0.011) [Table 2]

After completion of 6th CT cycle serum CEA level was normal in 50.91% and increased in 49.09% patients. Mean value of serum CEA level after 6th CT cycle (ng/mL) of study subjects was 72.33 ± 110.36.

Raised Serum CEA level after 6th CT cycle was significantly higher in adenocarcinoma andlarge cell carcinoma as compared to squamous cell carcinoma and unspecified NSCLC: (94.12%, 100% vs 21.88%, 60% respectively) (p value <0.0001). Mean values of serum CEA level after 6th CT cycle(ng/mL) was highest in adenocarcinoma (163.72 ± 140.35) followed by unspecified NSCLC(73.85 ± 99.2) and large cell carcinoma (32.8 ± 0) and lowest in squamous cell carcinoma (24.78 ± 53.07) (p value<0.0001).[Table 2]

The change in CEA levels between before and after chemotherapy were compared in patients with squamous cell carcinoma (increased in 59.38% while decreased in 40.62%), adenocarcinoma (increased in 82.35% while decreased in 17.65%) , Large cell carcinoma (decreased in all 100% patients) and Unspecified NSCLC (increased in 60% whiledecreased in 40%).

**Table 2 - Comparison of serum CEA levels between types of lung cancer**

| Serum CEA levels | Squamous cell carcinoma (n=32) | Adenocarcinoma (n=17) | Large cell carcinoma (n=1) | Unspecified NSCLC (n=5) | Total | P value | Test performed |
|---|---|---|---|---|---|---|---|
| **Serum CEA levels before chemotherapy(ng/mL)** | | | | | | | |
| Increased | 10 (31.25%) | 14 (82.35%) | 1 (100%) | 3 (60%) | 28 (50.91%) | 0.002 | Chi square test,12.804 |
| Normal | 22 (68.75%) | 3 (17.65%) | 0 (0%) | 2 (40%) | 27 (49.09%) | | |
| Mean ± SD | 18.15 ± 31.57 | 112.92 ± 151.5 | 55.25 ± 0 | 56.04 ± 61.33 | 51.56 ± 97.47 | 0.011 | ANOVA;F value=4.107 |
| Median(25th-75th percentile) | 5.75(3.108-11.775) | 100(15.6-145) | 55.25(55.25-55.25) | 40.12(1.51-100.2) | 10.23(3.77-71.5) | | |
| Range | 1.5-148 | 2.25-639.4 | 55.25-55.25 | 0.19-138.2 | 0.19-639.4 | | |
| **Serum CEA level after 6th CT cycle(ng/mL)** | | | | | | | |
| Increased | 7 (21.88%) | 16 (94.12%) | 1 (100%) | 3 (60%) | 27 (49.09%) | <.0001 | Chi square test,24.55 |
| Normal | 25 (78.13%) | 1 (5.88%) | 0 (0%) | 2 (40%) | 28 (50.91%) | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mean ± SD | 24.78 ± 53.07 | 163.72 ± 140.35 | 32.8 ± 0 | 73.85 ± 99.2 | 72.33 ± 110.36 | 0.0001 | ANOVA;F value=8.308 |
| Median(25th-75th percentile) | 6.01(3.46-9.302) | 180(29.2-205) | 32.8(32.8-32.8) | 35(3.5-88.26) | 10(5.175-101.2) | | |
| Range | 1.25-220 | 8.47-550 | 32.8-32.8 | 2.5-240 | 1.25-550 | | |
| p value | 0.379 | 0.147 | - | 0.447 | 0.075 | - | - |
| Tests performed | Paired t test;0.893 | Paired t test;1.525 | - | Paired t test;0.842 | Paired t test;1.815 | - | - |

Complete response in RECIST criteria after 6th CT was significantly higher in unspecified NSCLC as compared to squamous cell carcinoma, adenocarcinoma and large cell carcinoma (20% vs 9.38%, 0%, 0%, respectively). Partial response in RECIST criteria after 6th CT was significantly higher in large cell carcinoma, squamous cell carcinoma and unspecified NSCLC as compared to adenocarcinoma (100%, 50%, 40% vs 23.53%, respectively) [Table 3]

The proportion of patients with stable disease were significantly higher in squamous cell carcinoma (25%) and adenocarcinoma (17.65%) patients whereas progression of disease was significantly higher in adenocarcinoma (58.82%) and unspecified NSCLC (40%) patients (p value = 0.046). Serum CEA levels were raised mainly in stage IV as compared to stage III.

In our study raised serum CEA levels at the time of diagnosis of NSCLC was mainly associated with Adenocarcinoma with advanced stage. After completion of 6th CT cycle response is evaluated by RECIST criteria and progression of disease was mainly found to be associated with adenocarcinoma.

**Table 3 -Comparison of RECIST criteria after 6th CT between type of lung cancer**

| RECIST criteria after 6th CT | Squamous cell carcinoma (n=32) | Adenocarcinoma (n=17) | Large cell carcinoma (n=1) | Unspecified NSCLC (n=5) | Total | P value | Test performed |
|---|---|---|---|---|---|---|---|
| Complete response | 3 (9.38%) | 0 (0%) | 0 (0%) | 1 (20%) | 4 (7.27%) | 0.046 | Chi square test, 14.097 |
| Partial response | 16 (50%) | 4 (23.53%) | 1 (100%) | 2 (40%) | 23 (41.82%) | | |
| Stable disease | 8 (25%) | 3 (17.65%) | 0 (0%) | 0 (0%) | 11 (20%) | | |
| Progression of disease | 5 (15.63%) | 10 (58.82%) | 0 (0%) | 2 (40%) | 17 (30.91%) | | |
| Total | 32 (100%) | 17 (100%) | 1 (100%) | 5 (100%) | 55 (100%) | | |

## (IV) DISCUSSION

Tumor markers are molecules present in blood or tissue that are produced by tumor cells or by the host in response to cancer whose detection or measurement is useful in screening high-risk population, diagnosis, prognosis and monitoring the disease in remission or after surgery, radiation, and chemotherapy.

The ideal marker for cancer is a "blood test" in which a positive result indicates patients with malignancy, one that would correlate with stage and response to treatment and that could be easily, and reproducibly measured.[6]Serum biomarkers could be used as a noninvasive, cost-effective way to differentiate lung carcinoma patients.

For NSCLC in particular, serum CEA levels have been widely reported to be correlated with advanced disease, early relapse, pathological upstaging, poor therapeutic response, and survival.[7]As it is a noninvasive test, it can be used for early diagnosis of lung cancer thereby improving the survival rate and prognosis in such patients. CEA levels can be used as potential predictor for the progression of disease during chemotherapy. Follow-up CEA levels can be helpful in detecting early cancer recurrence which might otherwise remain elusive by imaging studies.

In our study, CEA levels were raised in 50.91% of all NSCLC cases & normal CEA levels were seen in 49.09% of cases at the time of diagnosis (p value= 0.002) which was in contrast with the study by **Nikolaos Tsoukalas et al.**[8] who proposed that CEA levels were only raised in 30% of all NSCLC cases.**JianWang et al.**[9]found in their study that serum CEA levels were higher in lung cancer than in benign lung diseases, but is not accurate enough in differentiating lung cancer from them.**Rafael Molina et al.**[10]also detected raised serum CEA levels in a much higher proportion (61.9%) of NSCLC cases similar to our study.

In our study, serum CEA levels before chemotherapy were significantly high in adenocarcinoma andlarge cell carcinoma as compared to squamous cell carcinoma and unspecified NSCLC (82.35%, 100% vs 31.25%, 60%, respectively) (p value = 0.002) which was similar to the study done by **Jian Wang et al.**[9] High CEA expression was detected more frequently in adenocarcinomas (72.2%) as compared to other NSCLCs(69.0%) than in squamous cell carcinomas (25.4%, P<0.001). CEA levels were minimally raised in squamous cell carcinoma.

**Molina et al.**[10]also found that CEA serum levels are more likely to be elevated in adenocarcinomas in comparison with the other subtypes of NSCLC.They also observed in their study that CEA values are more frequently raised in stage IV NSCLC as compared to earlier stages of NSCLC, with this difference being more apparent in adenocarcinomas than in squamous cell carcinomas.These findings are similar toour observations as described above.

Raised CEA levels are mainly associated with advanced stage lung cancer (IIIC, IVA, and IVB) which was similar to the study done by **Nikolaos Tsoukalas et al.**[8] who reported that CEA values are more frequently increased in stage IV NSCLC than in NSCLC of earlier stages. They also found in their study that serum CEA levels were significantly higher in adenocarcinomas than in squamous cell carcinomas.

After completion of the 6th CT cycle, serum CEA level were significantly higher in adenocarcinoma andlarge cell carcinoma as compared to squamous cell carcinoma and unspecified NSCLC (94.12%, 100% vs 21.88%, 60% respectively) (p value <0.0001). Mean values of serum CEA level after 6th CT cycle(ng/mL) were highest in adenocarcinoma (163.72 ± 140.35) followed by unspecified NSCLC(73.85 ± 99.2), large cell carcinoma(32.8 ± 0)and lowest in squamous cell carcinoma (24.78 ± 53.07) (p value<0.0001).

After completion of the 6th CT cycle, response was assessed by RECIST criteria. While Objective Response (OR, complete plus partial response) was seen in 45.82% of all NSCLC cases, stable disease in 20% and progression of disease seen in 30.91 % patients. Objective Response was significantly higher

in large cell carcinoma, squamous cell carcinoma and unspecified NSCLC as compared to adenocarcinoma (100%, 50%, 40% vs 23.53%, respectively). The proportion of patients with stable disease was significantly higher in squamous cell carcinoma (25%) and adenocarcinoma (17.65%) and the progression of disease was significantly higher in adenocarcinoma (58.82%) and unspecified NSCLC (40%) (p value = 0.046).

The potential prognostic role of CEA was addressed in the studies done by **Ozeki et al.**[11] **and Pollan et al.**[12] They found that patients with NSCLC and normal CEA serum levels have longer overall and disease-free survival than those with abnormal CEA serum levels. Interestingly, **Tomita et al.**[13] found that worse prognosis of patients with abnormal CEA values is only seen in adenocarcinomas and not in squamous cell carcinomas.

In our study,raised serum CEA level after 6th CT cycle was significantly higher in adenocarcinoma response and progression of disease was associated with Adenocarcinoma (58.82%). Our study confirms the results of other previous studies on CEA levels in NSCLC that raised serum CEA levels are associated poor survival.

Serum carcinoembryonic antigen (CEA) levels are a predictor of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) efficacy and are associated with epidermal growth factor receptor (EGFR) gene mutations. In all patients treated with optimum chemotherapy, the serum CEA levels increased with the progression of the disease.

So CEA levels can be used as a potential predictor for the progression of disease during chemotherapy and serial CEA levels on follow up can be helpful in detecting early cancer recurrence.

### (V) Conflict of interest

All authors declare that there is no conflict of interest in relation to this article.

### (VI) Acknowledgements

The authors would like to thank Dr. Narendra Khippal, Senior Professor, IRD and Dr. Chand Bhandari, Senior Professor, IRD for their invaluable contributions in this study.

### (VII) Source of funding

This study was funded by the Department of Respiratory Medicine, SMS Medical College, Jaipur.

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