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Medicine

"SERUM CEA AS A PREDICTIVE MARKER FOR DISTANT METASTASIS IN NON SMALL CELL LUNG CANCER"

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ABSTRACT Tumour marker (glycoprotein) are substances that are produced by cancer or by other cells (normal) of the body in response to cancer. No "universal" tumor marker that can detect any type of cancer has been found. More recently, patterns of gene expression and changes to DNA have also begun to be used as tumour markers. CEA has higher sensitivity for adeno carcinoma of lung and other adenocarcinoma jn advanced stages. A high preoperative serum CEA level is always associated with worst outcome in relation to post-operative survival, relapse or metastasis. Serum CEA level might be a useful predictor of survival for patients with early stage NSCLC.

KEYWORDS : Adenocarcinoma, CEA level, Lung cancer, NSCS, smoking , tumour marker

AIMS And Objective: To estimate serum CEA level newly diagnose non small cell lung cancer patient, To co-relate serum CEA level with the histology and stage of lung cancer, to compare serum CEA level between M0 and M1 stage of lung cancer

INTRODUCTION : Tumour marker are substances that are produced by cancer or by other cells (normal) of the body in response to cancer, however, they are produced at much higher levels in cancerous conditions[1,2]. These substances can be found in the blood, urine, stool, tumor tissue, or other tissues or bodily fluids of some patients with cancer[3,4]. Some tumor markers associated with only one type of cancer, some tumor marker are associated with two or more cancer types[5,6] and [7]. No "universal" tumor marker that can detect any type of cancer has been found. Sometimes, noncancerous conditions like Smoking[8] can cause increase the levels of certain tumor markers, in addition, not everyone tumor is associated with marker, The most commonly used markers circulating in the blood are neuron specific enolase (NSE), carcinoembryonic antigen (CEA), cytokeratin 19 fragments (CYFRA 21-1), squamous cell carcinoma antigen (SCC), cancer antigen CA 125 (CA 125) and tissue polypeptide antigen (TPA)[9,10,11]. before 1981 evaluating tumor marker in lung cancer not involving CEA as a tumor marker[12,13]. All histological types of lung cancer having elevated CEA but adenocarcinoma characteristically produce higher values than small, large or squamous cell carcinomas. More recently, patterns of gene expression and changes to DNA have also begun to be used as tumour markers[14,15].

Available (CEA) test measures the amount of this protein that may appear in the blood of some people who have certain kinds of cancers, antibodies to CEA are also commonly used in immunohistochemistry to identify cells expressing the glycoprotein in tissue samples[16,17], they are particularly associated with the adenocarcinomas, such as those arising in the colon, lung. It can therefore be used to distinguish between these and other similar cancers. For example between adenocarcinoma of the lung and mesothelioma[18]. CEA is normally produced in gastrointestinal tissue during foetal development, the production of CEA stops before birth, and it usually is not present in the blood of healthy adults. CEA are glycosyl phosphatidyl inositol (GPI) cell-surface-anchored glycoproteins of molecular weight of ~180 kD19. Globally, lung cancer attributes for about 13% of all new cancer cases and 19% of deaths related to cancer. In India, lung cancer comprises about 6.9% of all new cancer cases and 9.3% of all deaths related too cancer in both sexes. Lung cancers are generally divided into 2 main categories: Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC) [20, 21]. NSCLC accounts for approximately 85% of all lung cancers. NSCLC is divided further into Adenocarcinoma, Squamous cell carcinoma, and Large cell carcinoma with distinct histological and clinical characteristics[22,23].

Adenocarcinoma, arising from the bronchial mucosal glands, It is the subtype observed most commonly in persons who do not smoke[24]. It usually occurs in a peripheral location within the lung, in some cases at the site of pre-existing scars, wounds, or inflammation (i.e., a "scar carcinoma"). Bronchoalveolar carcinoma is a distinct subtype of adenocarcinoma, arises from type II pneumocytes and grows along alveolar septa[25], nearly 40 percent of those people newly diagnosed with lung cancer already have metastases to other parts of the body(common areas are the lymph nodes, liver, spine and pelvis, brain, and adrenal glands).

Due to their lack of specificity of organ and tumour that tumour markers cannot be used for screening of lung cancer in asymptomatic patients or in patients at high risk of malignancy, *CEA* is higher than 10 m g/L it is highly likely that the histology will indicate either adeno carcinoma or large cell lung cancer, high tumour marker concentrations reflect advanced tumour stage. However, low or mildly increased marker concentrations never exclude any kind of tumour disease or progression of disease however; the serum levels are raised in some types of cancer, which means that it can be used as a tumor marker in clinical tests. Serum levels can also be elevated in non cancers condition like heavy smokers. Approximately 40% of patients with lung adenocarcinoma show increased CEA level.[26], [27]Moreover; CEA is used to evaluate the prognosis and treatment effect of NSCLC and to determine recurrence, particularly in lung adenocarcinoma. For patients with NSCLC, high CEA level suggests a poor prognosis and high risk of cerebral metastasis.[28]

METHODS

The study was conducted in the department of the respiratory medicine, sardar patel medical collage Bikaner (Rajasthan) in 100 randomly selected case of lung malignancy (excluding small cell lung cancer) provide either by Bronchial washing, Bronchial brushing, Endobronchial biopsy and other related procedures

INCLUSION CRITERIA AND EXLUSION CRITERA

Patient willing for participation in the study between the ages of 12 years to 80 years. Patients diagnosed as Non-Small cell lung cancer by biopsy (bronchoscopic) or FNAC. Patients are exclude from study,age <12 years and >80 years, Non cooperative patients, Patients have platelets<50,000/mm, hemodynamically unstable and intractable cough patients, previously diagnosed cases of lung cancer and on chemotherapy or radiotherapy, no patients has been diagnosed as Small cell lung cancer therefore small cell cancer not include in study, major psychiatric illness, patients having cardiac instability & other serious co morbid illnesses.

RESULTS

TABLE 1 GENDER DISTRIBUTION

Gender	No. of Cases	Percentage
Male	87	87.0
Female	13	13.0
Total	100	100

According to above table, out of 100 patients 87% were males and 13% were females. Male to female ratio was 6.7:1.

TABLE 2 AGE GROUP DISTRIBUTION (Years.)

Age Group	No. of Cases	Percentage
<40	3	3.0
40-49	4	4.0
50-59	**31**	**31.0**
60-69	**56**	**56.0**
>70	6	6.0
Total	100	100

Majority of cases belonged to age group 60-69 years (56%) followed by 50-59 years (31%). Mean age was 60±8.8 years.

TABLE 3 DISTRIBUTION OF CASES ACCORDING TO SMOKING HABIT AND GENDER

Smoking Habit	Gender				Total	
	Male		Female			
	No.	%	No.	%	No.	%
Smoker	81	93	2	15	83	83
Non Smoker	6	7	11	85	17	17
Total	87	100	13	100	100	100

According to above table, majority of cases were smokers (83%), while 17% of cases were non smokers. Most of the female patients were non smokers i.e. 11 out of 13 (85%).

TABLE 4 SPECTRUM OF SYMPTOMS

Symptoms	No. of Cases	Percentage
Cough	94	94.0
Expectoration	68	68.0
Hemoptysis	32	32.0
Chest Pain	54	54.0
Dyspnea	48	48.0
HOV	10	10.0
Dysphagia	2	2.0
Anorexia	30	30.0
Weight Loss	18	18.0
SVC Syndrome	12	12.0
CNS Symptoms	4	4.0

HOV- Hoarseness of Voice

Commonest symptoms were cough (94%), followed by chest pain (54%), dyspnea (48%), hemoptysis (32%), anorexia (30%).

TABLE 5 LOCATION OF THE MASS LESION

Mass Location	No. of Cases	Percentage
Central	83	83.0
Peripheral	17	17.0
Total	100	100

Majority of the patient in this study had central lesions (83%) on radiology, while 17% patients had peripheral lesions, 93% of patients were diagnosed by Fiber-Optic Bronchoscopy while the rest 7% by USG guided FNAC

TABLE 6 HISTOPATHOLOGY OF CASES

Histology	No. of Cases	Percentage
Squamous Cell Carcinoma	76	76.0
Adeno Carcinoma	22	22.0
Undifferentiated Carcinoma	2	2.0
Total	100	100.0

Out of 100 patients, 76% had Squamous cell carcinoma, Adeno carcinoma was seen in 22% and ,Undifferentiated carcinoma was seen in 2% cases.

Table 7 Histological Yield in Different Age Groups

Histological Yields	Age Group										Total	
	<40		40-49		50-59		60-69		>70			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Squamous Cell Carcinoma	1	33.3	1	25.0	22	73.3	48	84.2	4	66.7	76	76.0
Adeno Carcinoma	2	66.7	3	75.0	8	26.7	7	12.3	2	33.3	22	22.0
Undifferentiated Carcinoma	0	-	0	-	0	-	2	3.5	0	-	2	2.0
Total	3	100	4	100	30	100	57	100	6	100	100	100

Out of 100 patients, 76% had Squamous cell carcinoma and they were more prevalent in the age group 60-69 years (63%) with mean age of about 61.47±8.83 years. Adeno carcinoma was seen in 22% and they were more prevalent in 50-59 years (36.4%) with mean age of about 55.91±9.17 years. Undifferentiated carcinoma was seen in 2% and all of them were seen in 60-69 years (100%) with mean age of about 63.5±8.26 years.

Table 8 Histological Yield According to Gender

Histological Yield	Gender				Total	
	Male		Female			
	No.	%	No.	%	No.	%
Squamous Cell Carcinoma	69	79.3	7	53.8	76	76.0
Adeno Carcinoma	16	18.4	6	46.2	22	22.0
Undifferentiated Carcinoma	2	2.3	0	-	2	2.0
Total	87	100	13	100	100	100

Among 87 males, 69 had Squamous cell carcinoma, 16 had Adeno carcinoma and 2 had undifferentiated carcinoma.Among 13 females, 7 had Squamous cell carcinoma and 6 had Adeno carcinoma.

Table 9 Histological Yield According to Smoking Habit

Histological Yield	Smoking habit				Total	
	Smoker		Non smoker			
	No.	%	No.	%	No.	%
Squamous Cell Carcinoma	66	79.5	10	58.8	76	76.0
Adeno Carcinoma	15	18.1	7	41.2	22	22.0
Undifferentiated Carcinoma	2	2.4	0	0	2	2,0
Total	83	100	17	100	100	100

Out of 83 smokers, 66 had Squamous cell carcinoma, 15 had Adeno carcinoma and 2 had undifferentiated carcinoma. Out of 17 non smokers, 10 had Squamous cell carcinoma and 7 had Adeno carcinoma.

Table 10 Histological Yield According to Location of Mass Lesion

Histological Yield	Location of Mass				Total	
	Central		Peripheral			
	No.	%	No.	%	No.	%
Squamous Cell Carcinoma	70	84.3	6	35.3	76	76.0
Adeno Carcinoma	13	15.7	9	52.9	22	22.0
Undifferentiated Carcinoma	0	0	2	11.8	2	2.0
Total	83	100	17	100	100	100

Among the central mass lesion, majority had Squamous cell carcinoma i.e. 70 cases (84.3%), 13 had Adeno carcinoma (15.7%). Among the peripheral mass lesions, majority had Adeno carcinoma i.e. 9 cases (52.9%), 6 had Squamous cell carcinoma (35.3%) and 2 had Undifferentiated carcinoma (11.8%).This shows that central lesions are more common in squamous cell carcinoma and peripheral lesions are more common in adeno carcinoma.

Table 11 Frequency Based on Staging of Lung Cancer

Staging	No. of Cases	Percentage
Stage II	13	13.0
Stage III	25	25.0
Stage IV	**62**	**62.0**
Total	100	100

Out of 100 patients, 62% were diagnosed in stage IV, 25% in stage III and 13% in stage II.

TABLE 12 FREQUENCY OF SPECTRUM OF METASTASES

Metastasis	No. of Cases	Percentage
Pleural	36	36.0
Pulmonary	18	18.0
Liver	30	30.0
Adrenal	14	14.0
Bone	15	15.0
Brain	4	4.0
Multiple	46	46.0

Above table shows that majority of patients had pleural metastasis (36%), followed by liver (30%), pulmonary (18%), bone (15%), adrenal (14%) and brain (4%).46% of patients had multiple metastases.

TABLE 13 COMPARING GENDER AND SERUM CEA

Gender	Serum CEA				Total	
	≤5.0 ng/mL		>5.0 ng/mL			
	No	%	No	%	No	%
Male	31	86.11	56	87.5	87	87
Female	5	13.899	8	12.5	13	13
Total	36	100	64	100	100	100
Mean	3.26		34.93			
S.D.	1.22		20.11			

p=0.9545 (Not significant) (Unpaired t test)

In the present study, mean serum CEA levels in males were 14.12±30.56 ng/mL and in females were 13.51±16.21 ng/mL and this was not significant (p>0.05).

Table 14 COMPARING SMOKING HSBIT AND SERUM CEA

Smoking habit	Serum CEA(ng/ml)	
	Mean	S.D
Smoker	14.66	29.03
Non Smoker	11.2	16.78

P value =0.458
p>0.05 (Not Significant) (Unpaired t test)

In the present study, mean serum CEA level among smokers were 14.66±29.03 ng/ml and among non smoker were 11.02±16.78ng/ml and this was not significant

TABLE 15 COMPARING HPE AND SERUM CEA LEVELS

HPE	Serum CEA (ng/mL)	
	Mean	S.D.
Adeno Carcinoma	45.81	30.77
Squamous Cell Carcinoma	5.07	2.01

p value = 0.0012
p < 0.01 (Significant) (Unpaired t test)

In the present study, mean serum CEA levels in the Adeno carcinoma group was 45.81±30.77 ng/mL and in the Squamous cell carcinoma group was 5.07±2.01 ng/mL and this was statistically significant (p<0.01).

TABLE 16 ADENO CARCINOMA, SMOKING AND SERUM CEA

Adeno Carcinoma	Serum CEA (ng/mL)	
	Mean	S.D.
Smoker	57.17	58.08
Non Smoker	21.44	16.96

p value = 0.042
p < 0.05 (Significant) (Unpaired t test)

Among the Adeno carcinoma patients, the mean serum CEA levels among smokers were 57.17±58.08 ng/mL and that of non smokers were 21.44±16.96 ng/mL and this was statistically significant (p<0.05).

TABLE 19 SQUAMOUS CELL CARCINOMA, SMOKING AND SERUM CEA

Squamous Cell Carcinoma	Serum CEA (ng/mL)	
	Mean	S.D.
Smoker	5.27	1.98
Non Smoker	3.73	1.72

p value = 0.0239 p < 0.05 (Significant) (Unpaired t test)

Among the Squamous cell carcinoma patients, the mean serum CEA levels among smokers were 5.27±1.98 ng/mL and that of non smokers were 3.73±1.72 ng/mL and this was statistically significant (p<0.05)

TABLE 20 COMPARING STAGING OF NSCC AND SERUM CEA

Stage of NSCC	Serum CEA (ng/mL)	
	Mean	S.D.
II	2.35	1.78
III	5.89	4.55
IV	20.13	35.92

p value = 0.0327

p < 0.05 (Significant) (ANNOVA single factor test)
In the present study, there was significant difference between staging of lung cancer and serum CEA levels (p<0.05). Mean serum CEA levels in stage II was 2.45±1.78 ng/mL and in stage III was 5.89±4.55 ng/mL and in stage IV was 20.13±35.92 ng/mL.

Table 21 COMPARING "M" STAGING AND SERUM CEA

M Staging	Serum CEA (ng/ml)	
	Mean	S.D.
M0	4.71	4.14
M1	20.01	35.92

P value =0.0018
P<0.01(Significant) (Unpaired t test)

When serum CEA level were compared between stage M0 and M1, there was a significant difference between the two stages (p<0.01) with mean serum CEA level in M0 was 4.71±4.14ng/ml and that M1 was 20.10±35.92ng/ml

TABLE 22 COMPARING "M" STAGING, ADENO CARCINOMAAND SERUM CEA

Adeno Carcinoma	Serum CEA (ng/mL)	
	Mean	S.D.
M 0	13.07	3.13
M 1	58.08	55.60

p value = 0.0064

p < 0.01 (Significant) (Unpaired t test)
Among Adeno carcinoma patients, mean serum CEA levels in stage M0 was 13.07±3.13 ng/mL and in stage M1 was 58.08±55.60 ng/mL and this was statistically significant (p<0.01).

TABLE 23 COMPARING"M" STAGING, SQUAMOUS CELL CARCINOMAAND SERUM CEA

Squamous Cell Carcinoma	Serum CEA (ng/mL)	
	Mean	S.D.
M 0	3.19	1.29
M 1	6.52	1.0

p < 0.001 (Significant) (Unpaired t test)

Among the Squamous cell carcinoma patients, mean serum CEA levels in stage M0 was 3.19±1.29 ng/mL and in stage M1 was 6.52±1.0 ng/mL and this was statistically significant (p<0.001).

Discussion:
Serum CEA is one among the tumour markers used largely as a

prognostic factor in evaluating the response to lung cancer treatment29. Increased serum CEA levels following chemo or radiotherapy or surgery suggest presence of occult metastasis30, distant metastasis or relapse of the disease. Out of 100 cases 87 were males and 13 were female with male to female ratio of about 6.7:1. Majority of proved cases of lung cancer in the study were >50yrs (93%) with mean age of 60±8.8 years and ranging from 21-78 years. other studies like (Hyde was 60years, Jindal et al was 53.3 years, U Ahmet et al was 60.5 years, A Oscar et al was 60.7 years). majority of the male patients were smokers (93%) and majority of females were non smokers (85%). Most of them were chronic smokers. Various other(Jindal et al, Gupta et al) studies over the years have very well established that smoking is one of the commonest aetiologies of lung cancer and majority of them start smoking early and continued for longer periods. In the present study we observed that cough (94%), chest pain (54%), dyspnoea (48%) and recurrent hemoptysis (32%) were the main respiratory symptoms. 83% of patients had central lesions and 17% had peripheral lesions in radiology. Ninety three patients were diagnosed by FOB and rest 7 by USG guided FNAC, among all Squamous cell carcinoma was the commonest type with 76% of cases. It was more common in smokers (79.5%) and was relatively more common in males (79.35) than in females (50.8%), majority of patients were diagnosed at stage IV (62%) compared to stage III (25%) and stage II (13%). Among the stage IV group, majority of patients had pleural metastases (36), followed by liver (30), pulmonary (18) and 36 patients had multiple metastases. Liver was the most common site of distant metastasis (30%), followed by bone (15%). This is supported by fact that smoking is largely a habit of males in this part of country and Squamous cell carcinoma is more common among smokers[31],[32,33].

Adeno carcinoma was found in 22% of cases in this study and found to be more prevalent in age group <60 years (mean age 55.91±9.4 years) and good number of them were non smokers (41.2%) and was more common in females (46.2%). Adeno carcinoma had brain metastases 3 out of the 4 patients, serum CEA levels in these (brain mets) patients were >60ng/ml. This shows brain metastasis is more common in Adeno carcinoma and it is associated with higher serum CEA levels32 (Similar results were found in Oscar et al,Malhotra et al and Jindal et al, Basu et al, U Ahmet et al, Shankar et al and Devkota et al. Age and gender does not affect the serum CEA level (Said AF et al, U Ahmet et al92) Among the Adeno carcinoma patients, the mean serum CEA levels among smokers were 57.17±58.08 ng/mL and that of non smokers were 21.44±16.96 ng/mL and this was statistically significant ($p<0.05$) and among the Squamous cell carcinoma patients, the mean serum CEA levels among smokers were 5.27±1.98 ng/mL and that of non smokers were 3.73±1.72 ng/mL and this was statistically significant ($p<0.05$)This discrepancy in our study was due to the fact that majority of the non-smokers had adenocarcinoma with high serum CEA levels34. In our study, when histopathology of lung cancer was compared with serum CEA levels, patients with adeno carcinoma had significantly higher serum CEA levels compared to squamous cell carcinoma (45.81 vs. 5.07 ng/ml)35,36 with p value <0.01. (studies that support our study are U Ahmet et al, P Icard et al, Said AF et al, PF Joseph et al, A Oscar et al and J Wang et al).Serum CEA levels are elevated in advanced stages of lung cancer with highest in stage IV (20.13±35.92 ng/ml) with $p<0.05$(study that support Said AF et al). In our study, when serum CEA levels were compared with M staging of Non Small cell lung cancer, there was a significant difference between stage M0 and M1 with mean values of 4.71 vs. 20.01 ng/ml ($p<0.01$). In case of adeno carcinoma, the statistical significance was $p<0.01$ and for squamous cell carcinoma $p<0.001$. Studies that also support U Ahmet et al and M Tomita et al. In case of adeno carcinoma, a cut-off value of 16ng/ml has sensitivity of 87.5% and specificity of 83.3%. In case of squamous cell carcinoma, cut off value of 5.76 ng/ml has sensitivity of 76.7% and specificity of 93.9% for predicting metastasis (using SPSS to test the sensitivity and specificity of serum CEA in predicting metastasis). In squamous cell carcinoma, S-CEA threshold of 6.4 ng/ ml, predictive sensitivity and specificity for distant metastases were 58.1% and 81.0% respectively. In adenocarcinoma, S-CEA threshold of 19ng/mL37,38, predictive sensitivity and specificity for distant metastases were 73.7 and 85.7% respectively.

Interpretation and conclusion: Tumor markers are substances that are produced by cancer or by other cells of the body in response to cancer or certain benign (noncancerous) conditions. Serum CEA cannot be used as a diagnostic marker or for screening purposes because of its less specificity. It is also elevated in other cancers like colorectal cancer, breast, gastric and ovarian cancers and also in non cancerous conditions like chronic bronchitis, colitis etc. Smoking also influences serum levels. CEA has higher sensitivity for adeno carcinoma of lung and advanced stages. Serum CEA has a greater prognostic significance in lung cancer. CEA has higher sensitivity for adeno carcinoma of lung and advanced stages. Serum CEA has a greater prognostic significance in lung cancer. A high preoperative serum CEA level is always associated with worst outcome in relation to post-operative survival, relapse or metastasis. A high serum CEA level in early stages of lung cancer should always raise a suspicion of occult metastasis and should be evaluated further with other diagnostic procedures like PET scan and also requires a close postoperative follow-up. Serum CEA level might be a useful predictor of survival for patients with early stage NSCLC, and that a persistently high CEA level after surgery is a particularly strong indicator of a very poor prognosis. Evaluation of serum CEA level is also useful for monitoring the response to postoperative chemotherapy and detecting whether there is cancer relapse.

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