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Evaluation of Diagnostic Utility of Serum Tumor Markers in Lung Cancer Patients at a North Indian Teaching Hospital

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ABSTRACT

Background: Accurate diagnosis of Lung cancer is solely dependent on biopsy and histopathology. Biopsy is invasive and often inconvenient due to issues like either site of lesion and accessibility or poor health condition of patient. Tumor markers have been used for evaluating patients' response to treatment and for prognostic purpose. Their role as independent diagnostic tool has not been established and is an area of continued research.
Aim: This study aims evaluate the relationship between tumor markers and histological types of carcinoma lung, and to determine whether these tumor markers together are useful for histological diagnosis of carcinoma lung. Methods: In this study, serum levels of eight tumor markers CEA, CA-125, NSE, CYFRA 21-1, Chromogranin-A, CA 19-9, AFP and β-hCG were analyzed in 18 normal subjects and 55 patients with histologically proven lung cancer. Results: The serum level of CEA and CYFRA 21-1 were significantly higher in non-small cell lung carcinoma (NSCLC) ($P < 0.05$), whereas the levels of NSE and Chromogranin-A were significantly higher in SCLC ($P < 0.05$). Among NSCLC, CEA was significantly elevated in 50% of adenocarcinoma cases. Conclusion: Combination of NSE, CYFRA 21-1, Chromogranin-A, and CEA can differentiate SCLC from NSCLC with high specificity in most patients with lung carcinoma, and NSCLC patients can be classified as adenocarcinoma or squamous carcinoma with limited sensitivity.

Keywords: tumor markers, lung cancer

INTRODUCTION

Lung cancer is one of the major causes of cancer related deaths worldwide. It is the most common incident cancer especially in men with 23 % total cancer related deaths globally. Early detection diagnosis and treatment is the cornerstone in successfully treating lung malignancies. Unfortunately, most of the cases of lung cancer remain asymptomatic and even radiologicaly indistinguishable from benign lesions in the early stages which accounts for higher mortality and reduced survival.

Lung cancer is broadly classified as Non-small cell Lung cancer (NSCLC) which comprises approximately 80-85% of all incident lung cancers and Small cell lung cancer (SCLC) which accounts for the rest. NSCL is further classified into three histological types: adenocarcinoma (AdCa), squamous cell carcinoma (SqCa), and large cell carcinoma (LcCa). SCLC accounts for 10–20% of all lung cancer patients but is the neoplasm with worst prognosis of the four histological types. SCLC shows greater response to treatment with chemotherapy and radiotherapy, whereas NSCLC responds well to surgical resection if detected early.[1,2] This makes histological diagnosis of lung cancer a prime necessity for therapeutic decision making and prognostic implications. Biopsy, either transthoracic, video-assisted thoracoscopy guided or transbronchial, is used widely for the histological diagnosis of lung cancer. Some authors recommend surgical resection in

cases of isolated single lung lesion for histopathology examination, where pre-test probability of malignancy is high on computed tomography (CT) scan and possibility of metastases has been ruled out using Positron emission tomography (PET).[3,4] However, besides being invasive and technically demanding, this is not always convenient, especially in patients with poor functional status. Besides, biopsies with limited tissue samples and different tissue areas may cause the wrong diagnosis. Therefore, a non invasion way for the histological diagnosis is required. The serum tumor markers may be a useful tool for this. A panel of tumor markers has been investigated for their value in lung cancer. Some markers have been found to be useful in diagnose lung cancer as well as in monitoring response to treatment. For example, Carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), and cytokeratin-19 fragments (CYFRA21-1) have been extensively studied in NSCLC.[5,6] In addition, Neuron-specific enolase (NSE) has also been studied in SCLC for therapy monitoring and for detection of prognosis.[7,8] It is possible that these tumor markers may be associated histological differentiation of lung cancer. However, the utility of tumor markers as a stand-alone modality in diagnosing lung cancer histologically is rarely reported. In this study, we analyzed the serum levels of eight tumor markers in suspected patients with lung cancer, evaluated the relationship between tumor markers and lung cancer histological types, and tried to determine whether the combination of these tumor markers was useful for histological diagnosis of lung cancer.

MATERIALS & METHODS

This study was conducted in the Department of Pathology, Institute of Medical Sciences, Banaras Hindu University, Varanasifrom January 2017 to July 2018. Total 55 patients of all age group, diagnosed histopahologicaly as having lung carcinoma and 18 healthy controls were included in study after written informed consent was obtained from them. All cases have been taken from Department of Tuberculosis & Respiratory Diseases, Sir Sunderlal Hospital, Banaras Hindu University. The study was approved by Institutional Ethics Committee.

Inclusion Criteria: Patients with positive diagnosis of carcinoma of lung proven by histopathology examination.

Exclusion Criteria:

1. Metastases in the lung from a known primary.
2. Unproven histopathological diagnosis.
3. Patients not willing for diagnostic procedure or unwilling to participate.

Sample Collection:

From every clinically and radiologically suspected case of lung carcinoma, biopsy and four milliliter (ml) blood was taken in plain vial. Serum was stored at -20 °C and biopsy was processed accordingly.

Collection and processing of Lung Biopsy samples:

Lung biopsy samples were collected in 10% formalin and kept for fixation for 12-24 hours. All specimens were fixed in 10% buffered formalin and embedded in paraffin wax. Sections were then cut with different depth and thicknesses and stained with Haematoxylin and Eosin using standard procedure.

Histological diagnosis was made according to the 4th Edition of WHO Classification of Tumors of the Lung, Pleura, Thymus and Heart 2015.[9] Figures 1-3 show histology of Adenocarcinoma, squamous cell carcinoma and small cell carcinoma at 40x resolution.

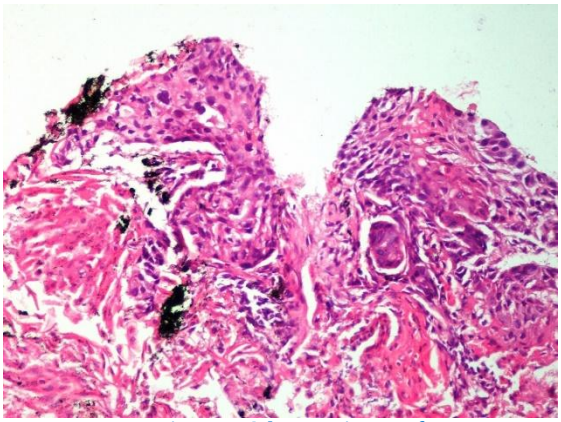

Figure 1: Adenocarcinoma of Lung

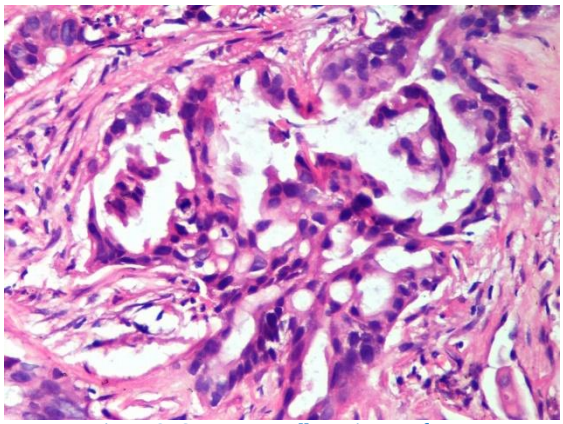

Figure 2: Squamous cell carcinomaof Lung

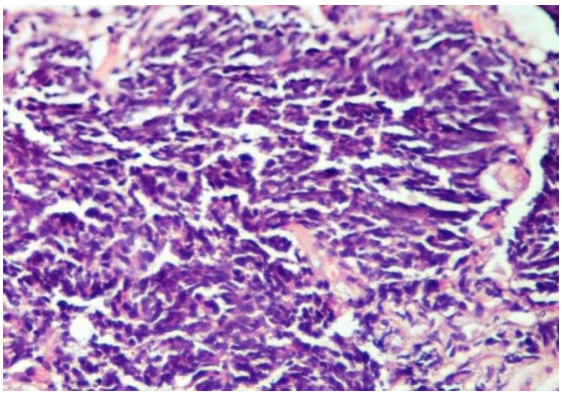

Figure 3: Small cell carcinoma of Lung

Collection of blood sample for Tumor marker study

4 ml of venous blood was withdrawn from the patients in plain vial and was allowed to clot for half an hour. After clotting, the tube was centrifuged at 1500-2000 rpm. After separation of serum, the serum was stored at – 20 degree Celsius until the performance of the test. 8 tests were included : Carcinoembryonic Antigen (CEA), Ovarian Cancer Antigen (CA-125), Pancreatic/Gut Cancer Antigen 19-9 (Ca 19-9), Chromogranin-A, Cyfra 21-1, Neuron-Specific Enolase (Nse), Alpha-Fetoprotein (Afp), β-Human Chorionic Gonadotropin (β-Hcg)

Results were statistically analysed using IBM SPSS software version 17.

RESULTS

This was an observational case control study. Baseline characters of study group are shown in table 1.

Table 1: Group Characteristics

Total Subjects	(N=73)	Cases (N=55)			Controls (N=18)
		NSCLC (n=45)		SCLC (n=10)	
		AdCa (n=24)	SqCa (n=21)		
Male	50	18	17	5	10
Female	23	6	4	5	8
Mean Age (years)	55.22±14.92	56.66±16.24			50.8±14.4
Smokers	46	40			6
Non Smokers	27	15			12

Out of 73 patients under study, 55 patients were of histopathologically proven lung carcinomas (75.3%) which were further subdivided histologically into SCLC (18.18%) and NSCLC (81.82%). Most common histological subtype of NSCLC was Adenocarcinoma (43.6%) followed by Squamous Cell Carcinoma (38.2%). Besides this 18 healthy controls were also taken.

Males were more commonly affected (72.7%) by lung carcinoma than females (27.3%) with male to female ration of 2.6 : 1, but no significant differences were found in the two group (younger vs. older) of male and female (P = 0.372).

Table 2: Histology according to gender.

Histology	Male N (%)	Female N (%)	Total N (%)	P- value
Adenocarcinoma	18(45.0%)	6(40.0%)	24(43.6%)	0.184
Squamous Cell Carcinoma	17(42.5%)	4(26.7%)	21(38.2%)	
Small Cell Carcinoma	5(12.5.0%)	5(33.3%)	10(18.2%)	
Total	40(100.0%)	15(100.0%)	55(100.0%)	

Adenocarcinomas 45% were males versus 40% females while in Squamous cell carcinoma 42.5% ere males versus 26.7% females. In Small Cell Lung Carcinoma, females were more affected (33.33%). Histological subtypes' distribution in males and females was statistically insignificant. See table 2.

Lung carcinoma in smokers (72.7%) is 3 folds that of non-smokers (27.3%). Hence there is significant relationship between smoking status and occurrence of bronchogenic carcinoma (P value = 0.006)

Table 3: Histology in smokers and in non-smokers.

Histology	Smoking Absent N%	Smoking Present N%	P-value
Adenocarcinoma	10(41.66%)	14(58.33%)	0.102
Squamous Cell Carcinoma	3(14.3%)	18(85.7%)	
Small Cell Carcinoma	2(20.0%)	8(80.0%)	
Total	15(27.3%)	40(72.7%)	

It was found that in Squamous cell carcinoma and small cell carcinoma, history of smoking was present in 85.7% and 80.0% respectively, while in adenocarcinoma only 58.3% patients were smoker. See table 3.

Table 4: Serum tumor marker in cases and controls.

Tumour marker	Controls N=18	Cases N=55	P value
CEA >5.0 ng/ml	1(5.5%)	16(29.0%)	0.040
Range	1-5.5	1-128	
Mean±SD	1.93±1.05	10.99±21.25	
Median	2.0	3.0	
95th Percentile	3.37	48	
CA125 >35.0 U/ml	2(11.11%)	15(27.27%)	0.159
Range	5-55	5-232	
Mean±SD	16.39±13.05	39.37±51.74	
Median	12.0	12.0	
95th Percentile	42.25	150.36	
NSE >13.0 µg/l	0(0%)	7(12.72%)	0.111
Range	1-12	1-160	
Mean±SD	3.33±2.99	11.85±27.42	
Median	2.5	3.0	
95th Percentile	9.45	77.6	
CYFRA21-1 >3.3 ng/ml	1(5.5%)	22(40.0%)	0.006
Range	0.5-3.5	0.5-70	
Mean±SD	1.16±0.75	7.87±14.17	
Median	1.0	2.5	
95th Percentile	2.22	33	
Chromogranin A >108.0ng/ml	0(0%)	3(5.45%)	0.111
Range	2-28	0.6-300	
Mean±SD	9.67±7.81	34.55±58.33	
Median	8.0	8.0	
95th Percentile	25.45	125.9	
CA19-9 >35.0 U/ml	0(0%)	6(10.9%)	0.144
Range	1-30	1-171	
Mean±SD	6.67±7.55	21.04±35.77	
Median	4.0	10.0	
95th Percentile	17.25	92.1	
βHCG >5.0 mIU/ml	2(11.11%)	8(14.5%)	0.713
Range	2-6	2-22	
Mean±SD	2.77±1.35	3.32±2.9	
Median	2.0	2.2	
95th Percentile	5.85	6.15	
AFP >8.5 ng/ml	2(11.11%)	12(21.8%)	0.317
Range	2-10	2-15	
Mean±SD	4.06±2.5	5.65±3.47	
Median	3.0	5.0	
95th Percentile	9.15	12.0	

All CEA, CA12-5, NSE, CYFRA 21-1, CA 19-9, Chromogranin A were increases in carcinoma lung cases as compared to controls.

CEA was raised in 29% patients as compared to controls while CA 12-5 was not significantly raised in carcinoma cases. NSE was raised in 12.72% of carcinoma cases but not detected in controls although not significant. Similarly CA 19-9, Chromogranin, β-HCG and AFP were not significantly raised in carcinoma lung cases as compared to controls. Only CEA and Cyfra21-1 were significantly elevated in lung carcinoma group, as compared to those in control group (p = 0.040& 0.006 respectively). (Table 4)

CEA (35.5% versus 10.0%) and CYFRA 21-1 (42.2% versus 30%) were significantly elevated in Non-small cell lung carcinoma (P 0.035 and P 0.018 respectively). Whereas NSE (40% versus 6.7%) and Chromogranin A (40% versus 6.7%) were significantly raised in Small cell lung carcinoma (P 0.001, P 0.001).

Table 5: Serum tumour marker in histological types of lung carcinoma.

Tumour marker	AdCa N=24	SqCa N=21	SCLC N=10	P value
CEA >5 ng/ml	12(50.0%)	3(14.28%)	1(10.0%)	0.011
Range	1-128	1-48	1-12	
Mean±SD	20.34±28.34	4.37±10.16	2.46±3.45	
Median	7.50	2.0	1.0	
95th Percentile	55 .65	8.0	7.86	
CA125 >35 U/ml	9(37.5%)	5(23.8%)	2(20.0%)	0.658
Range	8-232	5-126	8-82	
Mean±SD	54.33±65.65	29.83±38.96	23.50±24.14	
Median	18.50	10.0	12.0	
95th Percentile	182.2	108.0	66.7	
NSE >13 µg/l	1(4.16%)	2(9.52%)	4(40.0%)	0.014
Range	1-15	1-89	2-160	
Mean±SD	4.0±3.3	11.0±24.0	32.50±50.54	
Median	3.0	3.0	9.0	
95th Percentile	9.7	77.0	123.5	
CYFRA21-1 >3.3 ng/ml	7(29.16%)	12(57.14%)	3(30.0%)	0.125
Range	0.5-15	0.5-70	0.5-22	
Mean±SD	3.32±3.77	14.59±20.69	4.70±6.73	
Median	2.0	3.5	2.0	
95th Percentile	11.7	65.0	16.6	
Chromogranin A>108ng/ml	2(8.33%)	1(4.76%)	4(40.0%)	0.016
Range	1-135	0.6-300	0.8-213	
Mean±SD	31.12±40.80	27.98±65.77	56.58±76.66	
Median	9.5	6.0	2.0	
95th Percentile	110.2	90.0	172.0	
CA19-9 >35 U/ml	4(16.66%)	1(4.76%)	1(10.0%)	0.440
Range	1-171	1-170	1-38	
Mean±SD	27.25±41.9	17.33±35.81	13.90±11.41	
Median	13.0	9.0	10.50	
95th Percentile	117.95	30.0	34.4	
βHCG >5.0 mIU/ml	4(16.66%)	2(9.5%)	2(20.0%)	0.687
Range	2-22	2-6.5	2-6	
Mean±SD	3.6±4.1	2.85±1.57	3.8±1.4	
Median	2.0	2.3	3.75	
95th Percentile	6.39	6.0	5.7	
AFP >8.5 ng/ml	6(25.0%)	3(14.28%)	2(20.0%)	0.880
Range	2-15	2-12	2-12	
Mean±SD	6.08±3.7	5.83±3.19	5.3±3.56	
Median	5.5	5.0	4.5	
95th Percentile	12.0	10.0	11.1	

CEA was significantly elevated in 50% of Adenocarcinoma whereas in Small cell carcinoma and Squamous cell carcinoma only 10-14.28% had elevated values and this rise was statistically significant. NSE was raised in 40% cases of Small cell carcinoma as compared to Adenocarcinoma (4.16%) and Squamous cell carcinoma

(9.52%) and this was also statistically significant. Same was noticed in Chromogranin A, which was elevated in 40% of small cell carcinoma as compared to Adenocarcinoma (8.33%) and Squamous cell carcinoma (4.76%) and was statistically significant. AFP and β-HCG were mildly raised in Adenocarcinoma and Small cell carcinoma but statistically it was not significant (P 0.687 & P 0.880).See Table 5.

DISCUSSION

According to WHO classification Non-small cell lung carcinoma comprises 80–90% and Small cell lung carcinoma comprises 10-20% of lung cancer. In our study there were 45 patients (81.82%) with Non-small cell lung carcinoma and 10 patients (18.18%) with Small cell lung carcinoma. The distribution of histological subtypes of lung cancer has been changing over the last few decades. In past decades, Squamous cell carcinoma and Small cell lung carcinoma were the most frequent histological subtypes of lung cancer. However in previous large epidemiological studies, Adenocarcinoma has been reported as the most common histological subtype of lung cancer.[10,11] In contrast to this most of the Indian studies still report Squamous cell carcinoma as the commonest subtype.[12,13] In our study Adenocarcinoma was the commonest (43.6%) histological subtype followed by Squamous cell carcinoma (38.2%) and Small cell lung carcinoma (18.2%). Similar to this Malik et al in their study observed that Adenocarcinoma was the commonest histological subtype, accounting for 39% of all lung cancer cases in a subset of Indian population. [14] They proposed that if a careful independent pathological review is done, Adenocarcinoma may be the commonest histological subtype in other Indian studies as well.

So far in clinical practice tumor markers have been used to monitor treatment response in terms of reduction in levels circulating in blood. Significant decrease in circulating blood levels of a marker in response to a given chemotherapy or immunotherapy predicts sensitivity to that particular drug. But none of the markers have significant specificity alone in diagnosing a particular histological type of lung cancer. In this study, we tried to correlate between group of tumor markers and the histological subtypes of lung cancer.

In our study, eight common tumor markers used for cancer diagnosis were tested and analyzed. When tumor markers were compared amongst cases and controls, CEA was raised in 29% patients as compared to controls while CA 12-5 was not significantly raised in carcinoma cases. NSE was raised in 12.72% of carcinoma cases but not detected in controls although not significant. Similarly CA 19-9, Chromogranin, β-HCG and AFP were non-significantly (mildly) raised in carcinoma lung cases as compared to controls. Consistent with previous studies, [15-17] our study showed that the serum levels of CEA and CYFRA 21-1 in the lung cancer group were significantly higher than those in the control group (P = 0.04 & 0.006 respectively). This indicated a potential role for these tumor markers in lung cancer differential diagnosis.

When tumour markers were compared in Non-small cell lung carcinoma versus Small cell lung carcinoma, we found that CEA (35.5% versus 10.0%) and CYFRA 21-1 (42.2% versus 30%) were significantly elevated in Non-small cell lung carcinoma (P 0.035 and P 0.018 respectively). These results were in concurrence with the previous studies by Fang et al, 2018 [18] and Linjie et al, 2017. [17]

Whereas NSE (40% versus 6.7%) and Chromogranin A (40% versus 6.7%) were significantly raised in Small cell lung carcinoma (P 0.001, P 0.001). These results were similar to that of Wojcik et al. 2008,[19] Molina et al., 2009 [21] and Nisman et al., 2009.[20]

CEA was significantly elevated in 50% of Adenocarcinoma whereas in Small cell carcinoma and Squamous cell carcinoma

only 10–14.28% had elevated values and this rise was statistically significant (P 0.035), as in studies of Molina et al; 2009 [21] & Oremek et al., 2007.[22]

Higher mean serum level and high positive rate of CYFRA21-1 were found in Squamous cell carcinoma; however, these results were not statistically significant. NSE was raised in 40% cases of Small cell carcinoma as compared to Adenocarcinoma (4.16%) and Squamous cell carcinoma (9.52%) and this was also statistically significant. (P 0.001). These results are similar to that of Wojcik et al., 2008, Molina et al., 2009 and Nisman et al., 2009.[19-21] Similar thing was noticed in Chromogranin A, which was elevated in 40% of small cell carcinoma as compared to Adenocarcinoma (8.33%) and Squamous cell carcinoma (4.76%) and was statistically significant, similar to results of Giovanella et al [23] & Pujol et al.[24]

CA 19-9 was mildly elevated in 16.6% Adenocarcinoma cases, 10.0% Small cell carcinoma and 4.7% of squamous cell carcinoma patients but the difference was not significant (p>0.05).This in contrast with results of study by Niklinski et al.[23] which showed elevated CA 19-9 levels most frequently with adenocarcinoma, differing significantly from other subtypes.

AFP and β-HCG were mildly raised in adenocarcinoma and SCLC but statistically it was not significant (P 0.687 & P 0.880). In contrast Ishikura et al & Arnould et al[25-26] showed significantly raised AFP in Adenocarcinoma while raised levels of AFP in Squamous cell carcinoma. Such variations could be attributed to ethnic differences in study population. Smaller sample size in our case could also be a factor and further large scale study to evaluate this relationship could be undertaken.

CONCLUSION

We conclude that the combination of NSE, CYFRA 21-1, Chromogranin A and CEA can differentiate SCLC from NSCLC with a high specificity in most patients with lung cancer, and some NSCLC patients can be classified as adenocarcinoma or squamous carcinoma correctly. However individually, these markers still cannot replace the pathological diagnosis. Tumor markers could be useful for some suspected patients with lung cancer in whom the serum markers are the only choice that limited by their health situation, or as one of diagnostic tools in patients who has other clinical evidences indicating the histology.

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