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COPPER TO ZINC RATIO IN EARLY, LOCO-REGIONALLY ADVANCED AND METASTATIC LUNG CANCER

1. Aalameen Sherwani 2. Mohd Ashif Khan 3. Mohsin Khan

1,2 Department of Translational & Clinical Research, Jamia Hamdard New Delhi (INDIA)

3. Department of Radiotherapy, Jawaharlal Nehru Medical College Amu Aligarh

Corresponding Author : Mohd Ashif Khan**Abstract:**

Lung cancer is one of the major public health burden amongst cancers as it is currently the most frequently diagnosed major cancer amongst men and 2nd most common overall in the world (estimated 2.21 million new cases in 2020) and the most common cause of cancer mortality worldwide (1.8 million deaths in 2020). In India also it is concerning with ranked 4th overall (2nd in males) amongst all cancers in terms of new cases with the incidence of 5.5% while 5 year prevalence was 5.86 per 1 lakh population. Further, lung cancer caused 66,279 no. of death, compromising of 7.8 percent of all cancer related deaths in India according to GLOBOCAN, March 2021 (8) It was a comparative study between these two groups that compared Serum Copper, Serum Zinc and Copper to Zinc ratio. Apart from these, observations were also made on the basis of age, gender and smoking and dietary habits of patients. Amongst our subjects, most patients were of the age group 50-70 years in both early and advanced cases with mean age of 56.41 in early group and 56.71 in advanced group. Most were males with only 3 females in early arm and 1 in advanced. All the 20 patients were vegetarian and smokers. The trend of Cu, Zn and Cu:Zn ratio was more or less same as most of the earlier studies i.e. lower values of serum Cu and Cu:Zn ratio in early lung cancer patients than advanced group while serum zinc level were more in patients of early lung cancer than advanced but the difference between two groups was not found to be significant. In early lung cancer pts, mean S. Cu value was found to be lower (i.e 148.00 ug/dL) than advanced cancer patients (i.e 166.61 ug/dL) with p value 0.234. Mean serum Zinc level in early cancer cases was higher (i.e 134.21 ug/dl) than advanced group (i.e 129.91 ug/dl) with the p value 0.631. Finally, Copper to Zinc ratio was observed which was found to be better indicator of early and advanced lung cancer cases than individual elements as its p value was 0.061 with mean Cu:Zn ratio in early arm was 1.11 while higher in advanced group i.e 1.29. Overall, the difference in levels of S. Copper, S. Zinc and Copper to Zinc ratio early and advanced lung cancer patients was not found to be significant.

Keywords: Copper-Zinc ratio, lung cancer, early detection.**INTRODUCTION**

Cancer is a major burden of disease worldwide. Each year, tens of millions of people are diagnosed with cancer around the world, and more than half of the patients eventually die from it. In many countries, cancer ranks the second most common cause of death following cardiovascular diseases. World Health Organization (WHO) defines lung cancer as tumors arising from the respiratory epithelium (bronchi, bronchioles, and alveoli).

Lung cancer is particularly troubling due to some of the major reasons. One, large number of its incidence and prevalence. Currently worldwide, amongst all major cancers, lung

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cancer is the most commonly diagnosed one in men and 2nd most common overall with

2.21 million new cases found in 2020 and also it caused maximum no. of cancer deaths last year i.e. 1.8 million deaths in 2020 (1) According to GLOBOCAN 2020, in India lung cancer was ranked 4th overall (2nd in males) amongst all cancers in terms of new cases with the incidence of 5.5% while 5 year prevalence was 5.86 per 1 lakh population. Further, lung cancer caused 66,279 no. of death, compromising of 7.8 percent of all cancer related deaths in India.(2) Peak incidence occurs between ages 55 and 65 years. Incidence is decreasing in men and increasing in women. (3) The prevalence of lung cancer in India appears to be on rise. Globally, as there is decline in smoking habits, it is also reflected by decrease in death rate due to lung cancer (4).

Second, lung cancer is one of the most preventable of all the major malignancies. Most (but not all) lung cancers are associated with a well-known carcinogen—Cigarette Smoke. 80% of lung cancers occur in active smokers or those who stopped recently. There is a nearly linear correlation between the frequency of lung cancer and pack-years of cigarette smoking. The risk of cancer is lower among person who quit smoking than among those who continue smoking. Other than tobacco smoke, second hand smoke, environmental exposures, industrial exposure, radiation etc are some of the major risk factors. Considering the risk factors of lung cancer which mainly are modifiable risk factors, the onset of lung cancer can be prevented to a great extent. Given the undeniable link between cigarette smoking and lung cancer (and other tobacco related illnesses), smoking cessation must be promoted. Smoking cessation, even well into middle age, can minimize an individual's subsequent risk for lung cancer.

Third, that by the time it is noticed/presented, disease is already progressed a lot. When diagnosed, of over half of all patients with lung cancer presentation is either locally advanced or metastatic disease. Presentation includes chronic cough with or without haemoptysis in a current or former smoker with chronic obstructive pulmonary disease (COPD) age 40 years or older, persistent pneumonia etc. A loco-regionally advanced lung cancer is the one where the presentation is either due to extension of tumor cells beyond the site of origin that is lung to the nearby structures with direct continuity /extension or due to compression of neighbouring areas by the large tumor mass. Metastatic lung cancer begins in the lungs and spreads to other areas in no direct contact from the primary tumor i.e via mode of spread like hematogenous or lymphatic.

Fourth, it's high disease attributable deaths make it an important public health issue. Lung cancer have high morbidity and mortality with much decrease in quality of life and less survival. At the time of diagnosis, only 20% of pts have localized disease. Overall 5-year survival is 30% for males and 50% for females with localized disease and 5% for pts with advanced disease.

Moreover, like other cancers, with early identification, better response to treatment, greater and improved probability of survival and less morbidity, as well as less expensive treatment would be the outcomes of lung cancer as well. Diagnosing early is also especially important in lung cancer because smoking cessation can even be beneficial in individuals with an established diagnosis of cancer, as it is associated with improved survival, fewer side effects from therapy, and an overall improvement in quality of life. Moreover, smoking can alter the metabolism of many chemotherapy drugs, potentially adversely altering the toxicities and therapeutic benefits

of the agents. Consequently, it is important to promote smoking cessation even when diagnosis is established. In lung cancer, clinical outcome is related to the stage at diagnosis, and hence, it is generally assumed that early detection of occult tumors will lead to improved survival.

Therefore, in search of tests with good sensitivity, which are less invasive, cheaper, correlate with disease activity and indicates the diagnosis and prognosis of the disease, the biological role of trace metals especially copper and zinc, in different physiologic and pathologic conditions including various malignancy like lung carcinoma has been extensively investigated in recent years. Trace elements play an important role in the process of normal growth and differentiation of various tissues in humans. In addition, the requirement of trace elements is very essential for sustenance of tumour cell proliferation and is hence considered to be of significant importance (5).

Studies have shown that as the disease progresses, the serum copper level and copper/zinc ratio rises with the concomitant decrease of the corresponding serum zinc level. These trends are reversed in cases where the disease is in remission. In Lung cancer patients, Cu and Cu/Zn were higher and Zn was lower in advanced tumors than early ones and it becomes progressively higher with advancing stage of lung malignancy. Both the serum copper level and the copper/zinc ratio were strongly correlated to histopathological changes, clinical stage, and prognosis of Cancer (6). The ratio of copper to zinc is clinically more important than the concentration of either of these trace metals. More than the concentration of Zn or Cu in blood serum, it is important to have the balance between them. If the balance is changed several organic systems can be affected. Different diseases can be prevented when supplements are taken, and different drugs affect Cu and Zn concentrations what can cause the onset of different diseases (7). They are also considered to have a great diagnostic value in determining the local invasion of LC, tumor spread, postoperative survival and as screening test in the high-risk patients for LC. Additionally, determination of serum Cu/Zn ratio is simple, inexpensive, and noninvasive, and may have an important role in at least screening and early suspicion of lung cancer, if not in confirmation of the diagnosis. Thus, our study was also an effort to know that whether these trace elements and their ratio have any relation with the stage of lung cancer (.e early and advanced) and thus a role in prediction and prognosis of disease.

MATERIAL & METHOD

Study Details :

This study, was conducted in a tertiary care hospital i.e Jawaharlal Nehru Medical College and Hospital at Aligarh, U.P on 20 patients of lung cancer between January to June, 2021. In the department of Radiotherapy, 56 patients were enrolled and finally included 20 patients, 10 cases of each early and advanced (included loco regionally & metastatic lung cancer). Amongst our subjects, most patients were of the age group 50-70 years in both early and advanced cases with mean age of 56.41 in early group and 56.71 in advanced group. Most were males with only 3 females in early arm and 1 in advanced. This was a cross sectional type of observational study that compared Serum Copper, Serum Zinc and Copper to Zinc ratio between these two groups. Apart from these, observations were also made on the basis of age, gender and smoking and dietary habits of patients.

The study protocol was approved by the Ethics Commission of J.N Medical College and Hospital A.M.U Aligarh (approval No. 311/2021), and the study was conducted in accordance

with the principles expressed in the Declaration of Helsinki. All participants provided written consent to take part in the research.

Baseline Workup :

Patients who presented with chief complaints suggestive of lung cancer were further evaluated with their consent. History was taken which included detailed history of present illness of main complaints with associated & other complaints, history of comorbidities & other chronic illnesses with their medications, past history of any illness/medications/radiations, occupational history, socioeconomic history, family history of similar or related illness, appetite & diet habits, addictions with detailed history of smoking habits etc. Then patients were examined for built and nutrition, general head to toe findings and systemic examination of respiratory, cardiovascular, abdominal, renal and nervous system with more focus towards respiratory system. Then patients were investigated which included routine blood tests like hemogram, RFT, LFT, ABG etc, pulmonary function tests, histopathological test for confirmatory diagnosis & type of lung cancer, radiological investigations like Chest X rays & CT scan for extent & staging of lung cancer and serum biomarkers were also done for some patients.

Then on the basis of staging patients were divided into two groups: 1.Early Stage 2. Advanced Stage (further stages) patients and each group included 10 patients. Further, especially for our study purpose serum copper and serum zinc level were evaluated of every patients in these two groups, followed by application of mathematics and statistics for Serum Copper: Zinc ratio, mean values, standard deviation, p value and finally the comparison between two groups were done that whether the difference of S.copper, S.zinc and their ratio is significant or not.

Inclusion Criteria :

Patients diagnosed with early or advanced metastatic lung cancer.

Confirmation of diagnosis on histological and cytological examination.

Either male or female.

Patients willing to participate in the study and capable of giving informed consent.

Exclusion criteria:

History of head injury, Patient had evidence of uncontrolled clinical diseases, including diabetes, blood pressure, asthmatic diseases or other chronic inflammatory conditions. Patients having thyroid dysfunction. Patients having neuropsychiatric disorders. On any psychotropic medications. Habit of any substance of abuse and using any concurrent medication like donepezil, rivastigmine, galantamine, memantine and other cholinergic drugs. Patient using anti inflammatory drugs. Alcoholics. Incompetent for interview.

Enrolment

All the patients fulfilling the eligibility criteria were explained the nature of the study, proposed intervention with possible adverse effects and treatment sequelae. Written informed consent was obtained from those voluntarily willing to participate in the study.

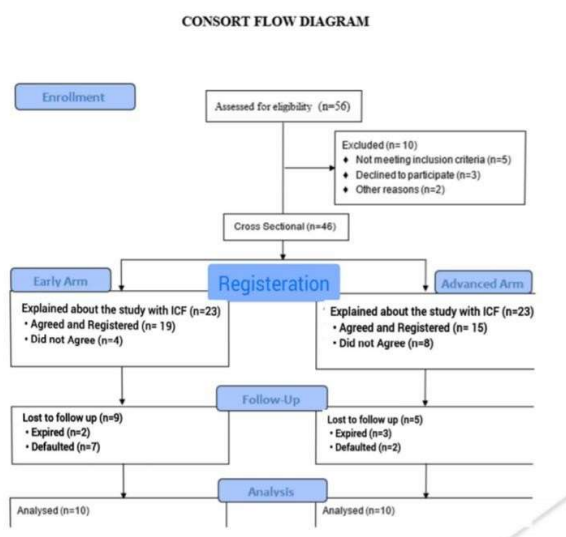
Blood Sample Collection :

5-10 ml of blood samples from lung cancer patients of early and advanced group were collected in appropriate vials after overnight fasting. This was sent to pathology lab for analysis. For determination of serum copper and zinc level, photometry technique was used.

Statistical Analysis

Null Hypothesis (H0): There is no significant difference between the analyzed groups
Alternative Hypothesis (H1): There is a significant difference between the analyzed groups
Descriptive characteristics including frequency, percentage, mean, standard deviation values are calculated for each variable. Testing of hypothesis was performed separately for discrete and continuous variables. For discrete variables, chi square and Fisher's exact test were implemented. For continuous variables, t test was applied after confirming that the variables follow normal distribution.

The level of significance was set at 5%. If the p value is less than 0.05 then the null hypothesis is rejected and it is concluded that there is a significant difference between the tested groups. If the p value is greater than 0.05 then it is concluded that there is no significant difference between the groups and that the variables are same.



OBSERVATIONS & RESULTS

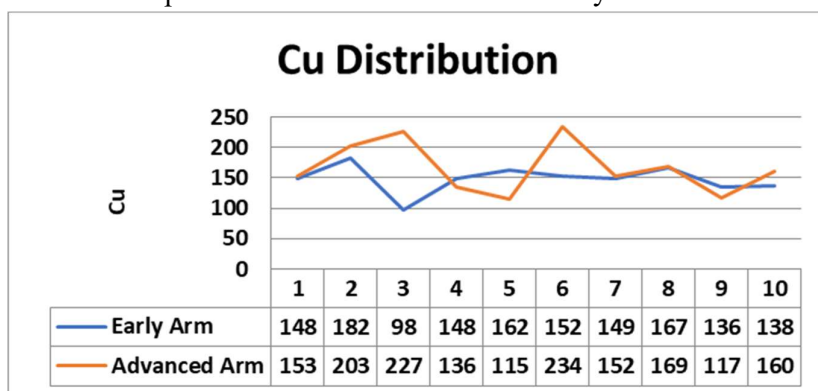
COMPARISON OF CU

Table showing comparison of Cu in early and the advance arm

Group	N	Mean	Standard Deviation	p value
Early	10	148.00	22.29	0.234

Advanced (included locoregionally & metastatic)	10	166.61	42.19	
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Graphs show Cu distribution in the early and the advanced arm

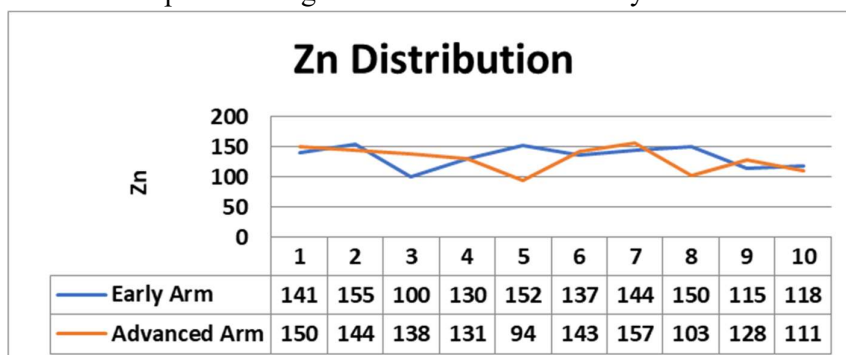


COMPARISON OF ZINC

Table showing comparison of Zn in early and the advanced arm

Group	N	Mean	Standard Deviation	p value
Early	10	134.21	18.16	0.631
Advanced(included locoregionally & metastatic)	10	129.91	20.95	

Graphs showing Zn distribution in the early and the advanced arm

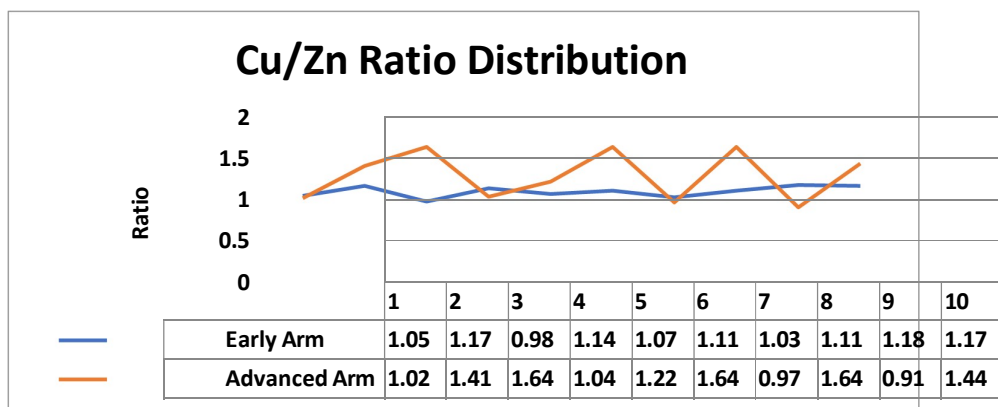


COMPARISON OF CU/ZN RATIO

Table showing comparison of Cu/Zn ratio in the early and the advanced arm

Group	N	Mean	Standard Deviation	p value
Early	10	1.11	0.07	0.061

Advanced (included locoregionally & metastatic)	10	1.29	0.29	
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EARLY ARM MASTERCHART

S. No.	CR No.	Gender	Age	Vegetarian Diet	Smoking Status	Cu	Zn	Cu/Zn	Histopathological Findings
1	27806/2021	Male	61	Yes	Yes	148	141	1.049645	S/o Metastatic poorly def CA
2	27835/2021	Male	68	Yes	Yes	182	155	1.174194	Metastatic Adeno CA
3	27837/2021	Male	40	Yes	Yes	98	100	0.98	Metastatic squamous CA
4	27880/2021	Male	54	Yes	Yes	148	130	1.138462	Metastatic adeno CA
5	27987/2021	Female	49	Yes	Yes	162	152	1.065789	Metastatic small cell neuroendocrine CA
6	27989/2021	Male	72	Yes	Yes	152	137	1.109489	S/o mod def adeno cell CA

7	28002/2021	Male	64	Yes	Yes	149	144	1.034722	S/o moderate ly diff adeno cell carcinoma lung
8	28110/2021	Female	52	Yes	Yes	167	150	1.113333	Squamous cell CA metastatic
9	28023/2021	Female	46	Yes	Yes	136	115	1.182609	S/o moderate def squamous cell CA
10	28056/2021	Male	58	Yes	Yes	138	118	1.169492	S/o positive for malignancy favouring metastatic squamous cell CA

ADVANCED ARM MASTERCHART

S.No	CR No.	Gender	Age	Vegetarian Diet	Smoking Status	Cu	Zn	Cu/Zn	Histopathological Findings
1	28053/2021	Male	66	Yes	Yes	153	150	1.02	Metastatic large cell neuroendocrine CA
2	28066/2021	Male	67	Yes	Yes	203	144	1.409722	Metastatic squamous cell CA

3	28097/2021	Male	75	Yes	Yes	227	138	1.644928	S/o moderately diff squamous cell carcinoma lung
4	28042/2021	Male	68	Yes	Yes	136	131	1.038168	S/o Positive for malignancy favouring metastatic adeno CA
5	27417/2021	Male	33	Yes	Yes	115	94	1.223404	S/o Metastatic poorly deff CA
6	28096/2021	Female	55	Yes	Yes	234	143	1.636364	S/o Metastatic adeno carcinoma
7	28030/2021	Male	50	Yes	Yes	152	157	0.968153	Metastatic squamous cell CA
8	27551/2021	Male	60	Yes	Yes	169	103	1.640777	S/o mod def squamous cell CA
9	27484/2021	Male	38	Yes	Yes	117	128	0.914063	S/o Positive for malignancy favouring adeno CA
10	28112/2021	Male	55	Yes	Yes	160	111	1.441441	Metastatic s cell CA squamou

RESULT

In early lung cancer patients, mean Serum Copper value was found to be lower (i.e 148.00 ug/dL) than advanced cancer patients (i.e 166.61 ug/dL) with p value 0.234. Mean serum Zinc level in early cancer cases was higher (i.e 134.21 ug/dl) than advanced group (i.e 129.91 ug/dl) with the p value 0.631. Finally, Copper to Zinc ratio was observed which was found to be better indicator of early and advanced lung cancer cases than individual elements as its p value was 0.061 with mean Cu:Zn ratio in early arm was 1.11 while higher in advanced group i.e 1.29. Overall, the difference in levels of Serum Copper, Serum Zinc and Copper to Zinc ratio early and advanced lung cancer patients was not found to be significant.

DISCUSSION

Cancer is a major burden of disease worldwide. Each year, tens of millions of people are diagnosed with cancer around the world, and more than half of the patients eventually die from it. In many countries, cancer ranks the second most common cause of death following cardiovascular diseases. World Health Organization (WHO) defines lung cancer as tumors arising from the respiratory epithelium (bronchi, bronchioles, and alveoli).

Lung cancer is particularly troubling due to some of the major reasons. One, large number of its incidence and prevalence. Currently worldwide, amongst all major cancers, lung cancer is the most commonly diagnosed one in men and 2nd most common overall with around

2.21 million new cases found in 2020 and also it caused maximum no. of cancer deaths last year i.e. 1.8 million deaths in 2020. According to GLOBOCAN 2020, in India lung cancer was ranked 4th overall (2nd in males) amongst all cancers in terms of new cases with the incidence of 5.5% while 5 year prevalence was 5.86 per 1 lakh population. Further, lung cancer caused 66,279 no. of death, comprising of 7.8 percent of all mortalities related to cancer. The prevalence of lung cancer in India appears to be on rise. Globally, as there is decline in smoking habits, it is also reflected by decrease in death rate due to lung cancer. Second, lung cancer is one of the most preventable of all the major malignancies. Most (but not all) lung cancers are associated with a well-known carcinogen—Cigarette Smoke. 80% of lung cancers occur in active smokers or those who stopped recently. There is a nearly linear correlation between the frequency of lung cancer and pack-years of cigarette smoking. The risk of cancer is lower among person

who quit smoking than among those who continue smoking. Other than tobacco smoke, second hand smoke, environmental exposures, industrial exposure, radiation etc are some of the major risk factors. Third, that by the time it is noticed/presented, disease is already progressed a lot. When diagnosed, of over half of all patients with lung cancer presentation is either locally advanced or metastatic disease. Fourth, lung cancer having high morbidity and mortality with much decrease in quality of life and less survival. At the time of diagnosis, only 20% of pts have localized disease. Overall 5-year survival is 30% for males and 50% for females with localized disease and 5% for pts with advanced disease.

Like other cancers, with early identification, better response to treatment, greater probability of survival and less morbidity, as well as less expensive treatment would be the outcomes of lung cancer as well. Detecting cancer early and avoiding delays in care will lead to significant improvements in the lives of cancer patients. Diagnosing early is also especially important in lung cancer because smoking cessation can even be beneficial in individuals with an established diagnosis of cancer, as it is associated with improved survival, fewer side effects from therapy, and an overall improvement in quality of life. Moreover, smoking can alter the metabolism of many chemotherapy drugs, potentially adversely altering the toxicities and therapeutic benefits of the agents. In lung cancer, clinical outcome is related to the stage at diagnosis, and hence, it is generally assumed that early detection of occult tumors will lead to improved survival.

In search of investigations and tests with good enough screening and diagnosing role, which are easy, less invasive, cheaper, correlate with disease activity and indicates the diagnosis and prognosis of the disease, the biological role of trace metals, in different physiologic and pathologic conditions including various malignancy like lung carcinoma has been extensively investigated in recent years. The determinations of Cu, Zn, and Cu/Zn are simple, noninvasive and inexpensive. Cu:Zn ratio are effective predictive indicators of lung cancer and may help evaluate the prognosis of patients. As the disease progresses, the serum copper level and copper/zinc ratio rises with the concomitant decrease of the corresponding serum zinc level. These trends are reversed in cases where the disease is in remission. In various studies, both the serum copper level and the copper/zinc ratio are strongly correlated to histopathological changes, clinical stage, and prognosis of Cancer. They also appear to have a great diagnostic value in determining the local invasion of lung cancer, tumor spread, postoperative survival and as a screening test in the high-risk patients for lung cancer. The ratio of copper to zinc is clinically more important than the concentration of either of these trace metals. More than the concentration of Zn or Cu in blood serum, it is important the balance between them. If the balance is changed several organic systems can be affected. Different diseases can be prevented when supplements are taken, and different drugs affect Cu and Zn concentrations what can cause the onset of different diseases.

Our study, which was conducted in a tertiary care hospital i.e. Jawaharlal Nehru Medical College and Hospital at Aligarh, U.P was done on 20 patients of lung cancer, that included 10 cases of each early and advanced lung cancer. It was a comparative study between these two groups that compared Serum Copper, Serum Zinc and Copper to Zinc ratio. Apart from these, observations were also made on the basis of age, gender and smoking and dietary habits of patients. Amongst our subjects, most patients were of the age group 50-70 years in both early and advanced cases with mean age of 56.41 in early group and 56.71 in advanced group. Most were males with only 3 females in early arm and 1 in advanced. All the 20 patients were vegetarian and smokers. The trend of Cu, Zn and Cu:Zn ratio was more or less same as most of the earlier studies i.e. lower values of serum Cu and Cu:Zn ratio in early lung cancer patients than advanced group while serum zinc level were more in patients of early lung cancer than advanced but the difference between two groups was not found to be significant. In early lung cancer pts, mean Serum Copper value was found to be 148.00 ug/dL (with standard deviation of 22.29) while in advanced cancer patients mean value of Serum Copper was more

i.e. 166.61 ug/dL (with SD of 42.19) and the p value between the two came out to be 0.234. Serum Zinc level in early cancer cases had mean value of 134.21 ug/dl (with SD of 18.16) which was higher than that observed in advanced group i.e. 129.91 ug/dl (SD= 20.95) and the p value for this was calculated to be 0.631.

Finally, Copper to Zinc ratio was observed which was found to be better indicator of early and advanced lung cancer cases than individual elements as its p value was 0.061 with mean Cu:Zn ratio in early arm was 1.11 (SD= 0.07) while higher in advanced group i.e. 1.29 (SD=0.29). Overall, the difference in levels of Serum Copper, Serum Zinc and Copper to Zinc ratio early and advanced lung cancer patients was not found to be Significant.

This study had some limitations. The sample size of 20 participants was small for results to be generalized on larger population. Other, small duration of study and thus patients could not be adequately followed up and evaluated. Also, Cu and Zn levels in serum and the Cu:Zn ratio may have been affected owing to the pathological type, differentiated degree, sample type, occupational activities, dietary habits, geographical locations, sex, body mass index, age and other physiological and pathological conditions. Therefore, further studies to determine other influential factors and appropriate reference intervals are needed. Finally, because of current limitations in cellular

functional assays, the precise mechanism of the association of trace elements in lung cancer requires further investigation to determine the biological significance of these trace elements and their usefulness in the prevention, diagnosis, and prognosis of lung cancer. At last but not the least, patients were on treatment and that may had impact on results. Therefore, further studies are needed to address these limitations.

CONCLUSION

This study explore the relationship between lung cancer and serum Cu and Zn levels and the Cu:Zn ratio in the early and advance lung cancer patients. The Cu level and Cu:Zn ratio were found to be effective diagnostic indicators of lung cancer. Determining the Cu level and Cu:Zn ratio is a simple and inexpensive means to effectively predict the prognosis of patients with early and advance lung cancer patients. Furthermore, these findings are likely to be useful in future studies assessing trace element nutritional status and the prognosis of lung cancer and in helping to identify and protect the population of India at a greater risk of lung cancer.

We examined serum copper (Cu), serum zinc (Zn), and the serum copper/zinc ratio (Cu/Zn) in 20 patients. All of them were seen to have an abnormal shadow in the chest X-ray films, that is, 20 patients with lung cancer (LC). The mean of Cu in the early patients are 148.00 and in advanced patients are 166.61 and the mean of Zn in the early patients are 134.21 and in the advanced patients are 129.91 and the Cu Zn ratio mean in early patients are 1.11 and the advanced LC patients are 1.29 and the p value is 0.061.

There is no significant relation between early and the advance lung cancer patients.

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