The role of bronchial wash carcino-embryonic antigen assay in the diagnosis of non-small cell lung cancer

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بسم الله الرحمن الرحيم

"قالوا سبحانك لا علم لنا الا ما علمتنا انك انت العليم الحكيم"

صدق الله العلي العظيم

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Ali baay

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Abstract

Background

bronchogenic cancer one of the most common cancer in human & represent a diagnostic challenge as most of the available tests are either useful in the late stages or little bit invasive ,so the need for diagnostic test in the relatively early time & non-invasive is mandatory

Aim of the study

To assess the significance of bronchial CEA as a tumour marker for aiding the diagnosis of NSCLC & to see is there any difference between the serum & bronchial CEA &between tumour & non-tumour sides.

Patients & methods:

30 patients were involved in the study ,divided into 3 groups according to their diagnosis as cancer ,airway disease & Tuberculosis groups, assessment of their socio-demographic features ,clinical features CXR,CT scan & fibro-optic bronchoscopy were done & the CEA level were testes in the samples taken from serum, tumour & non-tumour sides

Result:

There was a statistically significant difference in the level of CEA in the bronchial wash of cancer patients group comparing to the serum of the same group & to the bronchial wash level in the other groups in favor of the cancer group patients, but no difference between the tumour & non tumour sides in the cancer group patients.

Conclusion

Bronchial wash CEA assay can be helpful in the diagnosis of NSCLC & can be take into consideration in the future work up

Introduction

Lung cancers have the highest incidence and mortality of all cancer worldwide. In 2008, 1.61 million new cases were registered , and 1.38 million deaths were due to lung cancer. The highest rates are in Europe and North America. In contrast to the reducing mortality rate in men, lung cancer mortality rates in women have been increasing over the recent years [1], [2]

There are two main variants of the disease, non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC).

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers. Histologically, NSCLC is divided into types as adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma. [1]

After the diagnosis had been made ,patients with NSCLC require a complete staging workup to assess the extent of disease, because staging has a major role in determining the choice of treatment[1]

Signs and symptoms

non-small cell lung cancer is often insidious, producing no symptoms until the disease is in late stage. Early recognition of symptoms may be beneficial to outcome. [2]

At time of initial diagnosis, 20% of patients have localized disease, 25% of patients have regional metastasis, and 55% of patients have remote spread[2]

Symptoms depend on the location of cancer.[2]

The most common signs and symptoms of lung cancer include the following:

- Cough
- Chest pain
- dyspnea
- coughing blood
- Wheezing
- Hoarseness of voice
- Recurring pulmonary infections
- Loss of Weight and appetite
- Fatigue

Metastatic signs and symptoms may include the following:

- Bone pain
- Spinal myelopathy
- Neurologic problems such as headache, weakness or numbness of limbs, dizziness, and fits[2]

Diagnosis

After history & physical examination , the chest x-ray is often the initial test to be performed.

Chest radiographs may show the following:

- Pulmonary nodule, mass, or infiltrate
- Mediastinal widening
- collapse
- Hilar lymph nodes enlargement
- Pleural effusion[1]

There are many methods of confirming the diagnosis which include the following:

1. Sputum cytology
2. Endoscopy of the bronchus
3. Transthoracic needle biopsy (CT- or fluoroscopy-guided)
4. Mediastinoscopy
5. Pleural fluid aspiration & analysis
6. Thoracoscopy[1]

Staging

A chest CT scan is the best for staging lung cancer. The TNM (tumor-node-metastasis) staging systems from the American Joint Committee for Cancer Staging and End Results Reporting are helpful for all lung carcinomas except small-cell lung cancer. [3]

The TNM takes into consideration the following information:

- **T** describes the size of the primary growth
- **N** describes the spread of cancer to the lymph nodes
- **M** indicates whether the cancer has distant spread

Primary tumor (T) involvement is as follows:

- Tx - Primary tumor cannot be assessed
- T0 - No evidence of tumor
- Tis - Carcinoma in situ
- T1, T2, T3, T4: size and/or extension of the primary tumor

Lymph node (N) involvement is as:

- Nx - Regional nodes cannot be assessed
- N0 - No regional node metastasis
- N1 - Metastasis in ipsilateral peribronchial and/or ipsilateral hilar nodes and intrapulmonary nodes, even involvement by direct extension
- N2 - Metastasis in same-side mediastinal and/or subcarinal node
- N3 - Metastasis in other-side mediastinal, contralateral hilar, ipsilateral or contralateral scalene node, or supraclavicular node

Metastatic (M) involvement is as follows:

- M0 - No metastasis
- M1 – remote metastasis[3]

Management

Surgery, chemotherapy, and radiation are treatment options for NSCLC. Because most lung cancers are difficult to be cured with currently available treatment modalities, the appropriate application of palliative care is an important part of the treatment of NSCLC. [4]

Surgery

Surgery is the treatment of choice for the early stages namely stage I and stage II NSCLC, which include the follows:

- Lobectomy
- Pneumonectomy
- Wedge resection of a lobe[1]

Chemotherapy

Approximately 80% of all patients with lung cancer are candidate for chemotherapy at some time during the course of their illness even sometime before surgery.

Multiple randomized, controlled trials and large meta-analyses all confirm the superiority of combination chemotherapy regimens for advanced NSCLC.

The American Society for Clinical Oncology (ASCO) recommend that first-line treatment for NSCLC is a platinum combination. In younger patients, with a good performance status or in the adjuvant setting, cisplatin is preferred, but in older patients or those with significant comorbidities, carboplatin may be substituted. [1]

Radiation

In the treatment of stage I and stage II NSCLC, radiation treatment alone is considered only when surgical intervention is not possible.[5] Radiation is a good option for lung cancer treatment among those who are not fit for surgery.[6] [7]

Do we need new diagnostic tools for NSCLC ?

There are important points:

1- In patients with NSCLC, some genetic and regulatory abnormalities have been considered vital for the cancer survival advantage. In this way, some researcher focus on the evaluation of a variety of tumor associated antigens (TAAs) for a better & early diagnosis. [8]

2- Lung cancer patients often do not exhibit specific symptoms, particularly in early stages. Therefore, the majority of lung cancer patients are diagnosed at late stage, which limit their benefitial treatment. recently, conventional diagnostic tests such as chest radiographs, computed tomography (CT) scans, and fiber optic bronchoscopy (FOB) are not sensitive enough for effective early diagnosis. Meanwhile, the benign pulmonary nodules and malignant cancer cannot be distinguished by imaging methods currently . [9] Whereas, the pathological and cytological detections needed to obtain tissue samples are invasive and difficult to redo. [10]

3- Endemic infectious lung disease may reduce accuracy of PET scanning for lung cancer

In a meta-analysis of 70 studies, it had been seen a high levels of heterogeneity in the accuracy of FDG-PET scanning for diagnosing lung nodules. Screening with FDG-PET with computed tomography was less specific in diagnosing malignancies in areas with endemic infectious lung disease compared with areas with non-endemic disease. A 16% lower average adjusted specificity was observed in endemic regions compared with non-endemic regions .[11]

Early diagnosis:

Detecting and treating cancer at its early stages, ideally during precancerous stages, could increase the 5-year survival rate by three- to four-fold with a potential for cure, but unfortunately, no screening tool has been shown to reduce disease-specific mortality rate as , from a population perspective, the ultimate measure of screening effectiveness is

'mortality reduction'− whether screening for the disease saves lives – which requires large randomized controlled trials, However, challenge appears from the low frequency of the disease in the population. Lung cancer occurs on an annual basis in less than 1% of heavily tobacco-exposed individuals, making it difficult to achieve a statistically powered study sample size.[12]

Another challenge is to define the most optimal high-risk group for screening and early diagnosis.

A balance must be made where the likelihood of developing lung cancer outweighs the harms that can see from false-positive findings, which could create complications and unnecessary costs and anxiety associated with other diagnostic tests. [12]

The patients with the highest risk for the development of lung cancers:

- survivors of previous lung cancers .[12]

-patients with history of Tobacco use which is the major risk factor for primary lung cancer. [1]

-The subgroups of patients with airflow obstruction, chronic bronchitis or chronic obstructive pulmonary disease (COPD), which only occurs in approximately 25% of smokers, has a significantly high incidence of lung cancer, compared with smokers with similar smoking histories but with no airflow obstruction. [13] Chronic bronchitis is most commonly accompanied by airflow obstruction and, like airflow obstruction, is a marker for increased chance of lung cancer.[14] This association was substantially stronger for squamous cell carcinomas than for adenocarcinomas.[14]

The New Era diagnostic tools:

Advance Bronchoscopy:

CT scans are good at detecting small peripheral lesions, especially adenocarcinoma. However, CT scans are not good for detecting pre-invasive lesions and early lung cancer in the central airways, specifically small-cell lung cancer (SCLC) and the early stages of squamous cell carcinoma, which comprise 17–29% of all lung cancers.[15] Centrally located preinvasive and very early stages bronchial malignancies (e.g., severe dysplasia and CIS) are occult to the CT scans. Thus, the main challenge is to detect pre-invasive or early invasive disease. [16,17]

White light bronchoscopy (WLB) is insufficient to detect such lesions; therefore autofluorescence bronchoscopy (AFB) was made to overcome this limitation. AFB is now the gold standard test for detecting pre-invasive lesions. [18] some studies show that adding AFB to WLB

increases the sensitivity from 9 to 65% and 4 to 100% for moderate-to-severe dysplasia and CIS, respectively, However, AFB still hasn't been adopted in most of the clinics [18,19].

Within the past few years, a new bronchoscope, the narrow-band imaging bronchoscope (NBI), is under study to detect bronchial dysplasia and CIS. While AFB uses blue light (390–440 nm wavelength), the NBI uses two bandwidths of light: 390–445 nm (blue) light that is absorbed by superficial capillaries and 530–550 nm (green) light that is absorbed by blood vessels below the mucosal capillaries. These narrow wavelengths decrease the scattering of light and enable bright visualization of blood vessels.[20,21]

-Optical coherence tomography (OCT)

an optical imaging method that can give microscopic resolution for visualizing cellular and extracellular structures at and below a tissue surface.[22] OCT is similar to ultrasound imaging, but uses light rather than acoustical waves. In ultrasound, the imaging is accomplished by measuring the delay time (echo delay) for an incident ultrasonic pulse to be reflected back from structures within tissue. Some papers reported that quantitative measurement of the epithelial thickness showed that invasive carcinoma was significantly different than CIS and dysplasia was significantly different than metaplasia or hyperplasia .[23]

OCT appears to have great potential for detection of early lung cancer and precancerous lesions.

The autofluorescence endoscopy-guided OCT imaging of bronchial pathology is technically feasible. [24]

Confocal fluorescence microscopy

a new technique that procedures microscopic imaging of a living tissue and that enables *in vivo* microscopic examination of the airways and alveolar structure. Similar to autofluorescence bronchoscopy, the device utilizes a blue laser. The tiny probe is integrated into the working channel of a bronchoscope into the distal airway and alveoli. The magnification and resolution of the images is such that alveolar structures and intra-alveolar cells can be clearly visible.[25]

Molecular Screening:

Advances in molecular biology have led to new clues in lung cancer biology. Blood, sputum, bronchoalveolar lavage, bronchoscopic brushing or biopsies, and exhaled breath are sources for the identification and finding of various molecular abnormalities. [26]

Blood (Serum/Plasma) Analyses

Different genetic defects are observed in serum and/or plasma by evaluating circulating DNA, promoter hypermethylation, microsatellite instability, loss of heterozygosity (LOH), tumor-associated antibodies, proteomic profiles, circulating mRNAs and microRNAs (miRNAs). [27]

Sputum Analyses

In addition to the usual cytology assessment, different molecular biomarkers (chromosomal aneusomy, promoter hypermethylation, tumor-associated antigens) have been examined in sputum. [28]

Bronchoscopy Samples

The finding of molecular defects in bronchoscopy samples (bronchoalveolar lavage [BAL], bronchoscopic brushings and bronchial biopsies), although more invasive than blood and sputum analyses, can significantly raise the sensitivity of a detection test if compared with classical cytological evaluations. [28]

Loss of Heterozygosity: evaluating 80 BAL's from patients with lung cancer and control, *it was* .showed that the detection of LOH in four of eight loci diagnose cancer with a sensitivity and specificity of 73.9 and 76.5%, respectively. When combining the results of this molecular test with cytological examination, the sensitivity reached 82.6%.[29]

Tumor-associated Antigens: HnRNP A2/B1 antigen has also been found in BAL. in general, detection of hnRNP A2/B1 in BAL containing metaplastic or cancer cells predicts the presence of a neoplasm with a sensitivity and specificity of 96 and 82%, respectively.[30]

Chromosomal Aneusomy :Cytological and FISH methods utilizing LAVysion probes ,The sensitivities of cytology, FISH, or the combination of both, were 44, 49 and 61%, respectively, in brushing and 51, 71 and 75%, respectivtely, in BAL. [31] The combination of all these methods was significantly more effective than cytology by itself .[31,32] Another study showed the benefit of an additional FISH test performed on specimens diagnosed as non-cancer, atypical or suspicious by cytology, mainly for peripheral lung lesions.[33]

Gene Expression Analyses Another approach to find biomarkers for the early detection of lung cancer consists of using high-throughput techniques to study the molecular biology of bronchial epithelium and thus determine the molecular signatures that enable us to discriminate high-grade preinvasive lesions and/or invasive carcinoma from benign bronchial epithelium. [34]

Exhaled Breath Analysis of Volatile Organic Compounds

Exhaled breath analysis links specific volatile organic compounds (VOCs) to medical diseases , but has not yet been adopted for cancer diagnosis and screening.[35] The principle behind this research is that cancer-related metabolism is reflected in the circulation from the beginning of the disease.[36] These changes are manifested as a measurable changes(increase or decrease) in the levels of certain VOCs in the breath via air exchange in the lung, thus producing a unique 'smell' signature[35,36]

Tumour markers & bronchogenic carcinoma

Tumour markers are products found in tumour cells or body fluids. They are made by the tumour, or the host in response to the presence of the tumour and can be beneficial in differentiating tumour from normal tissue or determine the presence of a tumour . [37]

Classification of tumour markers: There are two main forms of tumour markers; Tumour associated antigens or cellular tumour markers, and humoral tumour markers which are detected in body fluids . [37]

Tuomer markers can be classified depending on the structure or biological function of the molecule: [38]

1- Enzymes: Alkaline phosphatase ,Prostatic acid phosphatase, Prostate specific antigen (PSA)
2- Hormones : ACTH, Calcitonin , Growth hormone ,HCG & Prolactin
3- Proteins: Immunoglobulins ,β2-Microglobulin & C- peptide
4- Ferritin
5- Oncofetal proteins : α- fetoprotein, CEA, Squamous cell carcinoma antigen (SCC) & Tissue polypeptide antigen (TPA)
6- Carbohydrate epitopes: CA 125, CA15.3 & CA19.9

Clinical uses of tumour markers:

Tumour markers can be useful for determining risk of cancer, screen for early cancer, establish diagnosis, estimate prognosis, predict that a specific therapy will work, or monitor for disease recurrence or progression . [39]

The sensitivity and specificity of tumour markers determine the clinical benefits of markers for each of these test. The ideal tumour marker would be highly specific for a particular cancer and highly sensitive for the required application . [39]

Screening: The principle of screening involves testing of apparently healthy individuals to detect early or occult disease. Screening for cancer is useful if the malignancy is prevalent and there are effective therapeutic interventions for early stage. [40]

the majority of the tumour markers have inadequate specificity and sensitivity profiles for effective use in cancer screening especially in populations with low prevalence for the particular cancer . In spite of this, researches show that tumour markers are increasingly used to screen for cancer in the clinical setting. [39,40]

Primary diagnosis: Ideally, a tumour marker needs to be 100% sensitive and 100% specific to be useful for definitive diagnosis of cancer.

Apart from Human Chorionic Gonadotropin (HCG) in choricarcinoma, few other markers are ideal for this application and so not recommended for this use . [40]

Prognosis: The tumour burden at the time of presentation is one of the determinants of prognosis in tumour. If a tumour marker concentration is related to the tumour size then it may be beneficial for prognostication.

HCG and AFP is used for prognosis in patients with testicular teratoma, while PSA has prognostic value in prostate cancer . [41]

Treatment monitoring detection of relapse: The most effective clinical use of tumour markers is in determining management efficacy and testing tumour recurrence . This application requires serial testing of a sensitive tumour marker, starting before any intervention is applied. The analytical aspects of the tumour marker are vital in interpreting concentrations of tumour markers in this application. The same analytical technique should be used in serial marker testing and any change in analytical methodology communicated to clinicians to enable proper interpretation of results . [40]

The treatment response may be judged depending on the marker as: [41]

(i) No change - tumour marker does not drop to less than 50% of the pre-treatment concentration;

(ii) Improvement - tumour marker drop to less than 50% of pre-treatment concentration;

(iii) Response – tumour marker drops to less than 10% of pre-treatment concentration;

(iii) Complete response – tumour marker drops to non-malignancy reference values.

The degree of decrease that indicates significant change may however differ depending on the specific tumour marker. [41]

Biochemical relapse may precede radiological or clinical relapse by many months to years . [40]

Factors which affect serum concentrations of tumor markers[42]

False positive results

- presence of inflammatory processes

-benign liver diseases and consequential disturbances in metabolism and excretion (AFP, TPA, CEA, CA 19-9, CA 15-3);

- disturbances of renal function (beta-2-microglobulin, calcitonin, PSA, CEA, CA 19-9, CA 15-3);

- extensive tumor necrosis;

- as a sequels of diagnostic and therapeutic procedures (digitorectal examination, mamography, surgery, radio and chemotherapy);

- as a consequence of many physiological conditions (pregnancy - ßHCG, CA 125, CA 15-3, MCA, AFP, menstrual cycle - CA 125).

False negative results

-complete absence of production (e.g. CA 19-9 in Le(a-b-) persons)

- inadequate expression of a certain antigenic determinant(or production in only some of tumor cells)

- inadequate blood circulation in the tumor

-formation of immune complexes with autoantibodies

- rapid degradation and clearance of antigens

Carcinoembyronic antigen (CEA):

It was first described in 1965 by Gold and Freedman, was characterized as a glycoprotein of 200 KD. [42]

It is normally produced in fetal life, but the production of CEA stops before birth. Therefore, it is not usually seen in the blood of healthy adults, although levels may increase in heavy smokers. [42]

CEA is encoded by the cea gene which is a member of the immunoglobulin super family. The human CEA gene family is clustered on chromosome 19q. In humans, the carcinoembryonic antigen family consists of 29 genes; of these, 18 are expressed, with 7 belonging to the CEA subgroup and 11 to the pregnancy-specific glycoprotein subgroup.

CEA is a substance normally found in a fetus so also referred to as an "oncofetal antigen" because of its similarity to fetal tissue. [42]

CEA is most usually tested in blood. It can also be measured in body fluids and in biopsy tissue. [42]

Although CEA was first identified in colon cancer, an abnormal CEA blood level is not specific for colon cancer nor for tumour in general, Elevated CEA levels are found in multiple of organs cancers other than colonic cancer , including pancreatic, gastric, lung, ovaries and breast cancers. [42]

It is also seen in benign conditions including cirrhosis, inflammatory bowel disease, peptic ulcer disease, obstructive jaundice, renal failure ,

chronic lung disease, and pancreatitis. The CEA was found to be elevated in up to 19 percent of smokers and in 3 percent of a healthy control persons. [42]

As a screening test, the CEA is also not enough . Since cancer prevalence in a healthy population is low, an elevated CEA has an unacceptably low positive predictive value, with too much false positives. [40]

The CEA has been suggested as having prognostic value for patients with colon tumour. Preoperative CEA values have been positively correlated with stage and negatively correlated with disease free survival. [41]

Although not adequately for screening a healthy population, CEA has been used to monitor recurrence. Early data suggested that CEA predated clinical relapse by several months. Subsequently, several investigators have examined intensive, serial CEA monitoring as an indicator for second look surgery in the hope that relapse could be detected at a time when surgical resection for cure was still possible. Determinations of CEA should be done frequently: at least every 3 months and if possible every 1 month to 2 months. Elevations above baseline should be verified rapidly to exclude laboratory error. [42]

The CEA is often positive in malignancies other than colonic. In cancer of the breast, lung, pancreas, stomach, and ovary the CEA may be high and can be used to follow the progress of disease or response to treatment. [41]

Carcinoembryonic antigen (CEA) in NSCLC:

Screening and diagnosis. CEA concentrations are particularly high in adenocarcinoma and large cell lung cancer, but the elevated concentrations also found in various benign pathologies and other malignancies limit its use in screening and limit its diagnostic use. However, CEA may be helpful in the differential diagnosis of non-small cell lung cancer, preferably in combination with CYFRA 21-1 . [43]

Prognosis and monitoring. CEA may provide prognostic information in NSCLC, particularly in adenocarcinoma of the lung . [43] Further it may have a role in monitoring therapy in advanced stages and detecting recurrent disease of non-small cell adenocarcinoma . [43]

Analytical concerns: mild higher CEA levels may be observed in smokers[38]

Smoking & CEA

Smoking is a world health problem. More than one billion people (men, 1 billion women, 250 million) smoke in the world resulting in 4.2 million annual deaths. In addition to premature aging, it causes varieties diseases including cancer.[12] Tobacco smoke contains over 4800 different

chemicals out of which 69 are carcinogens, and several are tumour promoters or cocarcinogens. [38]

The cancers related to smoking are cancers of lung, oral cavity, pharynx, larynx, oesophagus, pancreas, urinary bladder, and renal pelvis. There is also strong evidence for a causal association between cigarette smoking and cancers of the nasal cavities and nasal sinuses, oesophagus (adenocarcinoma), stomach, liver, kidney (renal-cell carcinoma), uterine cervix and myeloid leukaemia. [44]

It had been mathematically proved that the exposure duration to tobacco smoke is much more vital than the daily number of cigarettes, so quitting as early as possible remains the most powerful factor in decreasing the cancer risk. [44]

Pipe and cigar smoking can also cause lung cancer, although the risk is not as high as with cigarette smoking". [45]
Heavy smoking over many years might also raise blood CEA levels. [38]

Most of the studies done so far are on cigarettes and pipe smokers, effect of hookah smoking on CEA levels has not been studied in detail although hookah/shisha is now considered as an extremely important world health problem. [45]

The aims of the study

1- To assess the significance of bronchial CEA as a tumour marker for aiding the diagnosis of NSCLC
2- To see is there any difference between the serum & bronchial CEA in the diagnosis of NSCLC
3- To correlated the bronchial CEA level in tumour & non-tumour sides with the diagnostic significance
4- To correlate the serum & bronchial CEA with multiple patients variables

Patients & methods

A case control study include 30 patients 15 male & 15 female, age ranging from 41-70 years

This study was conducted in Al-imamaeen al-khademmayn medical city / respiratory unit from Dec. 2013 to Sept. 2014

For all included patients:

- verbal consents were taken from patient to participate in the study

- concentrated history & physical exam were done to them.

-Chest X Ray were done for all patients

-for all patients chest CT(16 chest CT with contrast & 14 HRCT of chest) were done .

-3 ml of blood were aspirated from a peripheral vein & were sent to CAE assay

-Fibro-optic bronchoscopy were done to all patients for the following clinical indications:

-17 cases suspected to have cancer clinically or radiologically
- 8 cases suspected to have TB clinically or radiologically

- 5 cases suspected to have pulmonary lesion due to abnormal CXR

Under local anesthesia a FOB (storze machine) were done with full visualization to the whole major segments of both lung were done.

For patients with endobronchial mass, 10 ml of sterile normal saline was injected through the side-tube of the scope directly on the mass & re-aspirated completely (10ml) with brush were taken from the lesion & another sample obtained by the same maneuver taken from the other side basal segment of lower lobe in a new container , the samples labeled as Lt. & Rt. In each test tube

For patients with no mass ,10 ml of sterile normal saline were injected a above into the basal segment of the lower lobes & re-aspirated as above & collected in Lt. & Rt. Test tube

The bronchial samples were divided into plain test tubes & sent for :

- Fluid for AFB smear
- Fluid for gene Xpert
- Fluid for TB culture
- Fluid for cytology
- Fluid for CEA

Exclusion criteria:

1- Any patients with uncertain diagnosis
2- Any patients with any cancers rather than NSCLC
3- Any patients with liver or GI diseases
4- Any patients with hemolytic ,icteric or lipemic serum as it interfere with the test result

After we receive the results, the patients were divided into 3 groups:

1- Patient with NSCLC :10 patients all were diagnosed as NSCLC by 2 pathologists, 5 the diagnosis based on +ve cytology in bronchial wash,3 +ve brush & 2 by percutaneous CT guided FNA
2- Patients with airway diseases: 11 patients with COPD & bronchiectasis diagnosed by PFT & HRCT
3- Patients with inflammatory parenchymal respiratory diseases namely pulmonary TB: 9 patients diagnosed as TB by +ve AFB smear in bronchial wash in 6 patients,2 patients +ve gene Xpert in wash & 1 +ve culture of the wash

CEA measurement methods:

By using the VIDAS CEA(CEAS) kit(made by biomerieux company/Marcy- France) which is intended for use on the VIDAS

instrument as an automated assay for the quantitative measurement of CEA in human serum & body fluid using the enzyme linked fluorescent assay ELFA technique

Statistical Data Analysis

Statistical analysis was carried out using SPSS version 17. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Independent samples t-test was used to compare means between two groups. ANOVA test was used to compare means among three groups or more. Fisher-exact test was used to find the association between categorical variables. Paired t-test was used to compare means for paired of readings. Wilcoxon signed ranks test was used for paired readings when differences between those paired readings were none normally distributed. Pearson correlation coefficient (r) was used to find relationship between two continuous variables. A *p*-value of ≤ 0.05 was considered as significant.

Variant/group	cancer			Airway			TB			total
Gender	male		female	Male		female	male		female	30
	5		5	6		5	4		5	
age	40-59		>60	40-59		>60	40-59		>60	30
	5		5	4		7	5		4	
smoking	smoker	ex	non	smoker	ex	non	smoker	ex	non	30
	6	0	4	3	2	6	4	0	5	
Co-morbidity	yes	no		yes	no		yes	no		30
	2	8		4	7		2	7		
Mode of presentation	SOB	cough	Hem.	SOB	cough	Hem.	SOB	cough	Hem.	30
	2	7	1	1	6	4	2	4	3	
CXR	mass	Inf.	Eff.	mass	Inf	Eff.	mass	Inf	Eff	30
	10	0	1	0	10	1	0	10	1	
CT	mass	Inf.	Eff.	mass	Inf	Eff.	mass	Inf.	Eff	30
	10	0	1	0	10	1	0	10	1	
site	Bilat.	Rt.	Lt.	Bilat.	Rt	Lt.	Bilat	Rt.	Lt.	30
	1	6	3	5	3	3	7	2	0	
FOB	Nor.	mass	Con	nor	mass	con	nor	mass	con	30
	0	10	0	1	0	10	4	0	5	
Duration In months	<6	7-18	>19	<6	7-18	>19	<6	7-18	>19	30
	9	1	0	4	3	4	7	2	0	
total	10			11			9			30

Table 1 :all patients socio-demographical features

RESULTS

Mean Differences of Age by Type of Disease

There were no significant differences between means of age for the three study groups.

Variable	Type of disease	N	Mean ± SD	F-test	P-value
Age (years)	CA	10	62.5 ± 6.57	1.392	0.266
	TB	9	56.33 ± 8.51		
	COPD	11	60.18 ± 8.96		

Table 2: The mean differences of age by type of disease

*p value ≤ 0.05 was significant

Association between Gender and Type of Disease

There was no significant association between gender and type of disease groups.

Table 3 : Association between gender and type of disease.

Characteristic	Type of disease			P-value
	CA (%)	TB (%)	COPD (%)	
Gender				
Male	4 (40.0)	4 (44.4)	6 (54.5)	0.899
Female	6 (60.0)	5 (55.6)	5 (45.5)	

*p value ≤ 0.05 was significant
Fisher – exact test

So the all three groups are matched in age & gender with no statistically significant differences.

Part I

The Distribution of CA Patients group by Socio-Demographic Characteristics

1- Age:

Table 4: Mean ± SD and range of age of CA patients

Variable	Mean ±SD	Range
Age (years)	62.5 ± 6.57	55-70

2- **Gender**:

Figure 1 shows the distribution of CA patients according to gender. About (60%) of them were female.

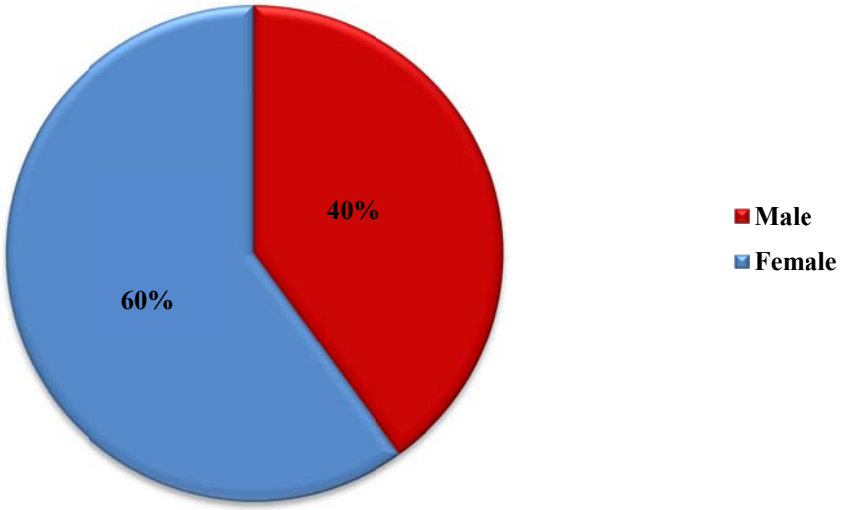

Figure 1: Distribution of CA patients according to gender

3- **Clinical Presentation**

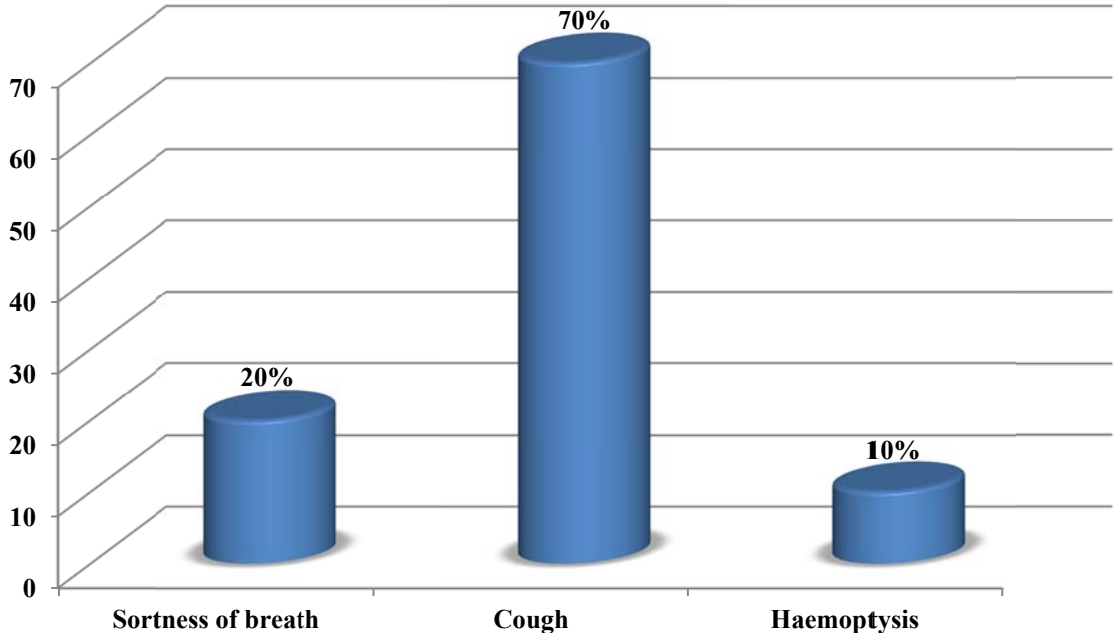

Figure 2 shows the distribution of CA patients according to presentation.

Majority (70%) of them presented with cough.

Figure 2: Distribution of CA patients according to presentation

4- Smoking Habit

Figure 3 shows the distribution of CA patients according to smoking habit. Majority (60%) of them were smokers.

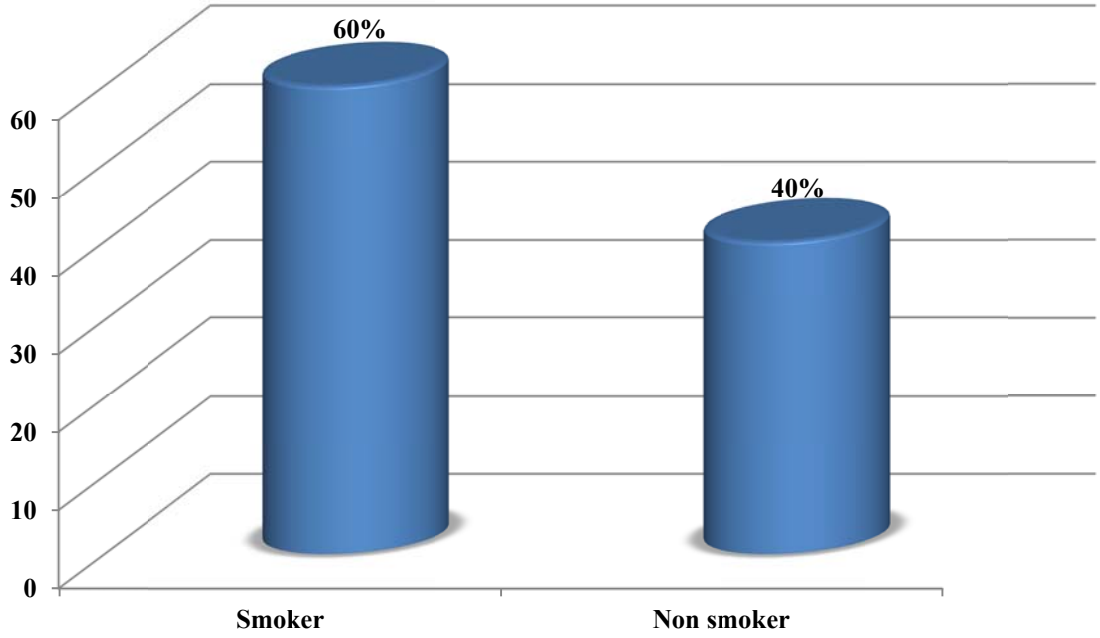

Figure 3: Distribution of CA patients according to smoking habit

5- Co-morbidity

Figure 4 shows the distribution of CA patients according to co-morbidity.

Majority (80%) of them presented with absence of co-morbid diseases.

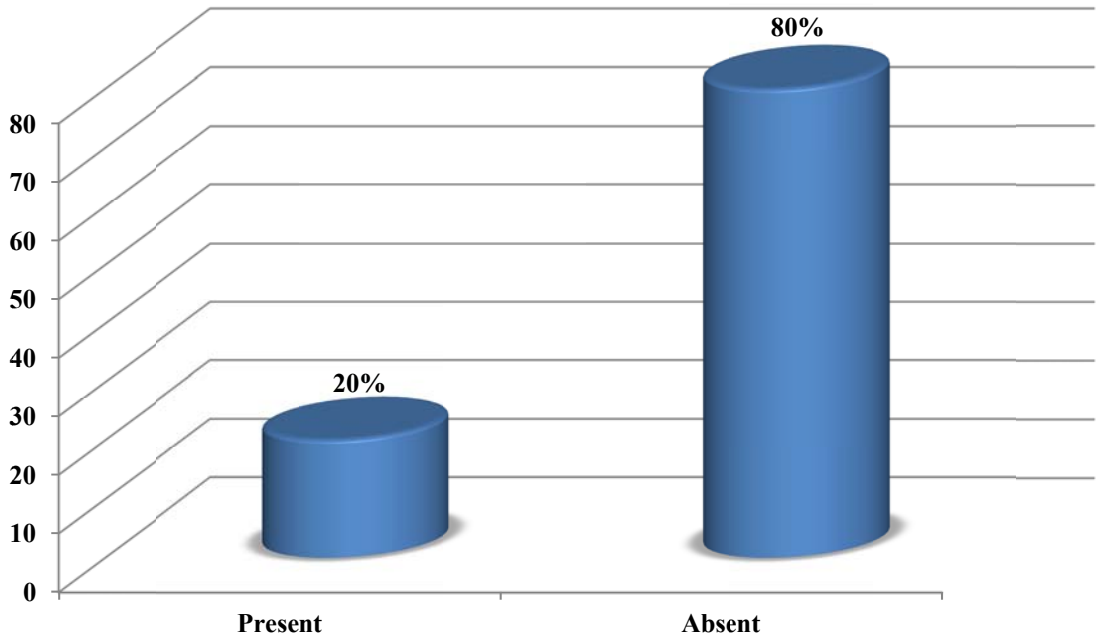

Figure 4: Distribution of CA patients according to co-morbidity

6- Duration of Disease

Figure 5 shows the distribution of CA patients according to duration of disease. Majority (50%) of them presented with less than 3 months duration.

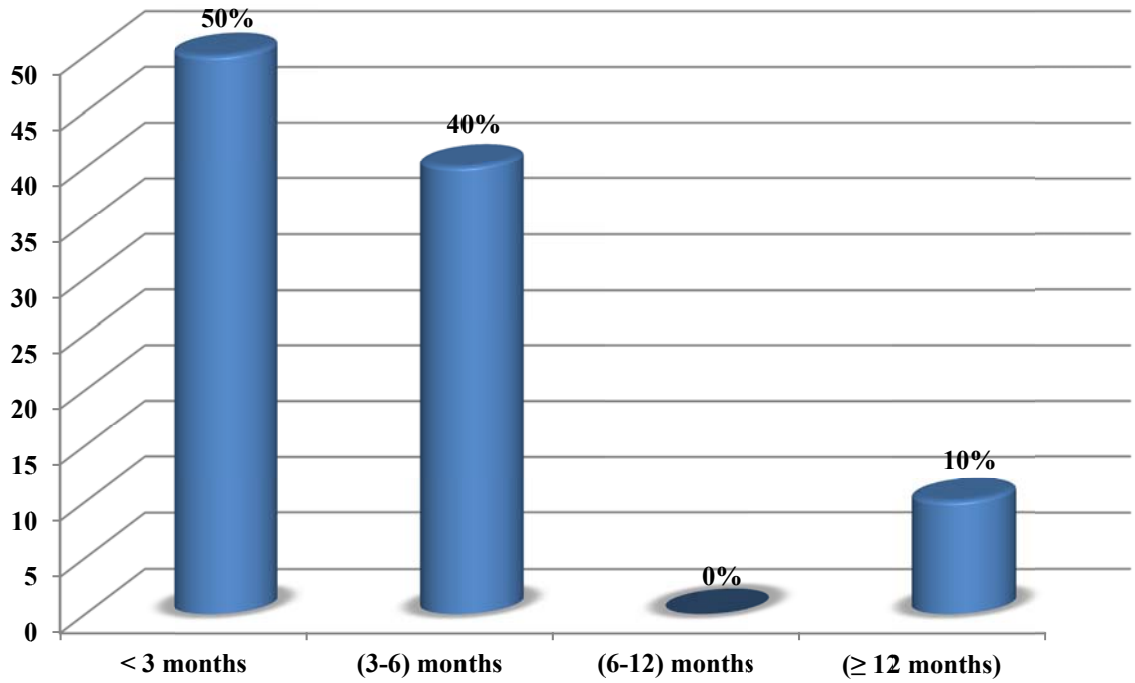

Figure 5: Distribution of CA patients according to duration of disease

7- Side of Lesion

Figure 6 shows the distribution of CA patients according to side of lesion.

Majority (60%) of them presented with lesion in right brachial tree.

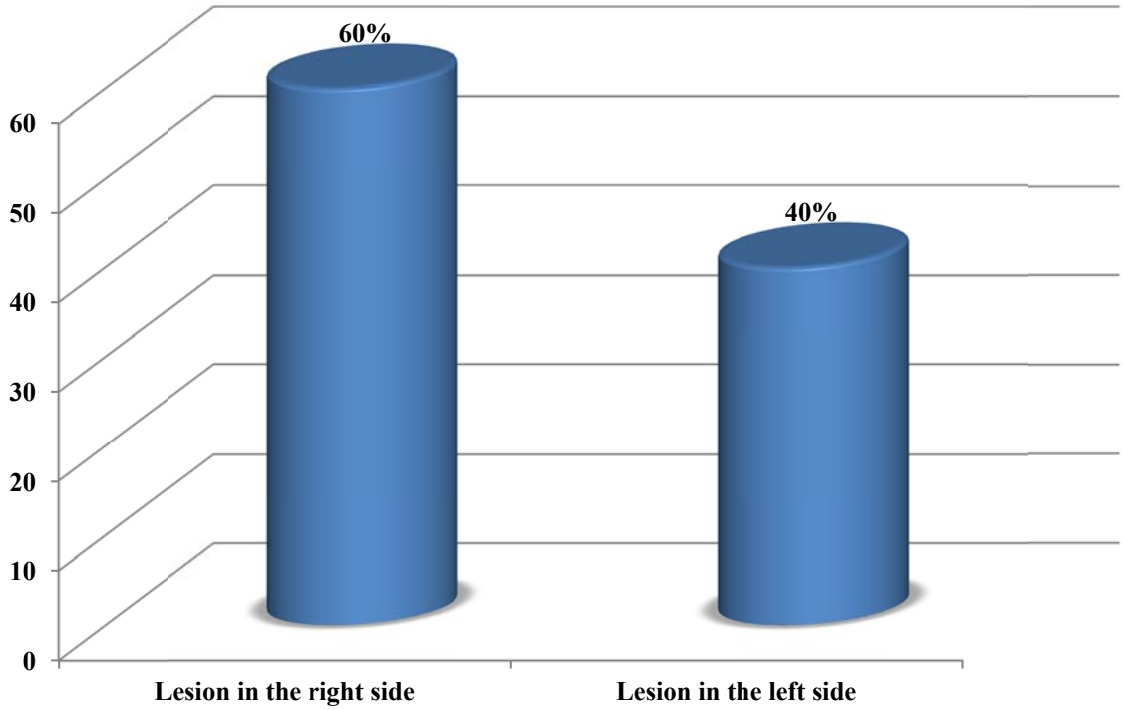

Figure 6: Distribution of CA patients according to side of lesion

8- Investigation Results

Table 2 shows the distribution of CA patients according to investigation results includes (X-ray, CT scan and bronchoscopy).

Table 5: Distribution of patients according to investigation results

Investigation	Frequency (%)
X-ray findings	
Mass	8 (80.0%)
Mass and effusion	1 (10.0%)
Mass and infiltrate	1 (10.0%)
Total	10 (100.0%)
CT findings	
Mass	9 (90.0%)
Mass and effusion	1 (10.4%)
Total	10 (100.0%)
Bronchoscopy findings	
Mass	10 (100.0%)
Total	10 (100.0%)

Part II CAE variant

Mean Differences of Serum CEA by Type of Disease

Table 6 shows mean differences of serum CEA (Ng/ml) by type of disease including (NSCLC , tuberculosis and airway diseases). There were no significant differences between means of serum CEA for study groups.

Variable	Type of disease	N	Mean ± SD	F-test	P-value
Serum (CEA)	CA	10	2.95 ± 1.95	0.994	0.383
	TB	9	3.38 ± 1.96		
	Airway dis.	11	2.26± 1.51		

Table 6: The mean differences of serum CEA (Ng/ml) by type of disease difference

*p value ≤ 0.05 was significant

2- Mean Differences of CEA between Tumour and Non Tumour Sides among CA Patients

Table 7 shows mean differences of CEA between tumour and Non tumour sides among CA patients. There were no significant differences between means of CEA at tumor and Non tumor sides.

Table 7 : The mean differences of CEA between tumor and Non tumor sides

Variable	Categories	N	Mean	Paired t-test	df	P value
CEA (Ng/ml)	Tumor side	10	15.77	-0.549	9	0.596
	Non-tumor side	10	21.56			

*p value ≤ 0.05 was significant
**p value ≤ 0.01 was significant

as there is no difference in between the tumour & non tumour sites in all diseases groups so the mean of the both sides were measured & taken as bronchial CEA level

as the normal level of the CEA in the bronchial fluid is not equal to that of the serum & no accurate cut for the normal limit is set so trials for the cut level were conducted on 5,10,15 & 20 Ng/ml & show the significant differences stared from 15 Ng/ml .

V Association between Bronchial CEA and Type of Disease

Table 8 shows association between bronchial CEA and type of disease. There was significant association between bronchial CEA and type of disease.

Table 8 : Association between bronchial CEA and type of disease.

Characteristic	Type of disease			P-value
	CA (%)	TB (%)	COPD (%)	
Bronchial CEA (Ng/ml)				
≥15	6 (60.0)	0 (0.0)	5 (45.5)	
< 15	4 (40.0)	9 (100.0)	6 (54.5)	**0.016***

*p value ≤ 0.05 was significant
Fisher – exact test

Median Differences of CEA between Bronchial Wash and Serum among CA Patients

Table 9 shows median differences of CEA between bronchial wash and serum among CA patients. There were significant differences between medians of CEA at bronchial wash and serum.

Table 9 : The median differences of CEA between bronchial wash and serum

Variable	Categories	N	Median	Z	P value
CEA (Ng/ml)	bronchial wash	10	15.67	-2.701	**0.007***
	Serum	10	2.05		

Wilcoxon rank test.
*p value ≤ 0.05 was significant
**p value ≤ 0.01 was significant

Part III study variable:

The Correlation between Serum (Carcinoembyronic Antigen) and Age among CA Patients

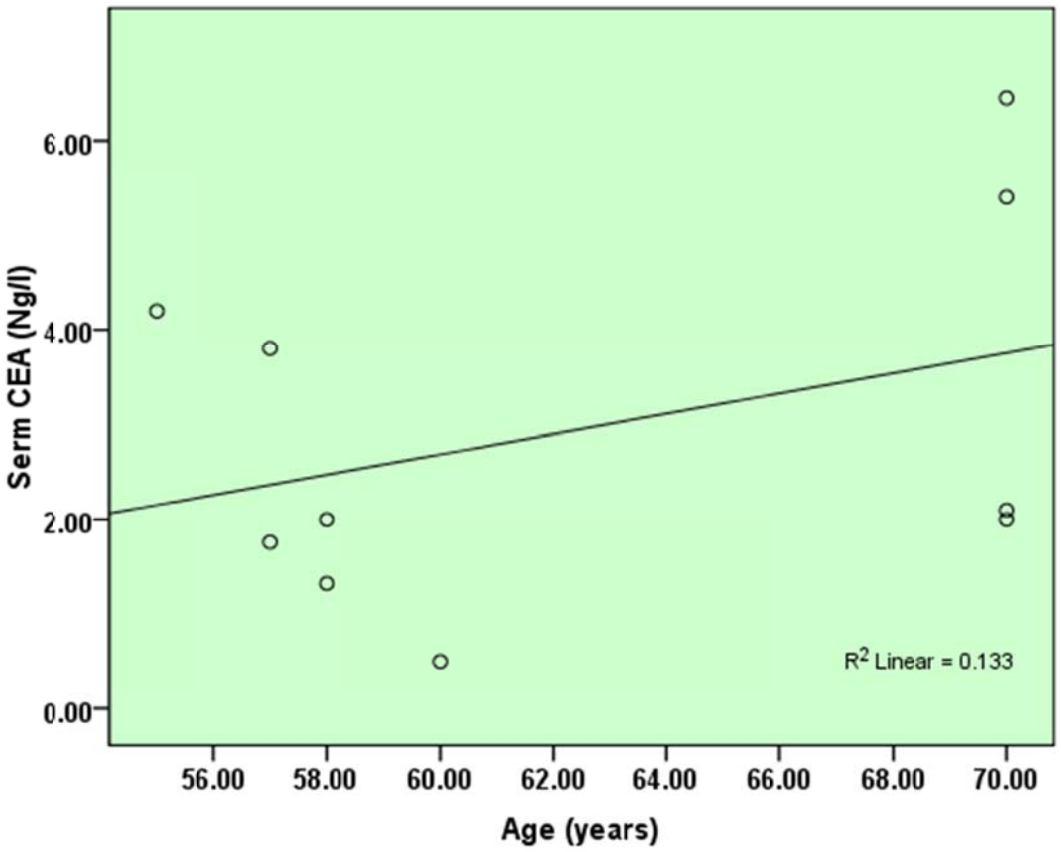

Figure 7: The correlation between Serum (Carcinoembyronic antigen) and age

Figure 7 shows the correlation between Serum (Carcinoembyronic antigen) and age among CA patients. There was no significant correlation between these two variables. (r =0.364, P = 0.3).

Mean Differences of Serum (CEA) by Study Variables among CA Patients

Table 10 shows mean differences of serum (CEA) by study variables including (gender, smoking habit, mode of presentation, duration of disease, side of lesion and co-morbidity) among CA patients. There were significant differences between means of serum (CEA) by smoking habit, while there were no significant differences between means of serum (CEA) for other study variables.

Table 10: The mean differences of serum (CEA) by study variables

Variable	Categories	N	Mean ± S.D	t-test	P value
Gender	Male	4	2.64 ± 1.86	-0.395	0.704
	Female	6	3.15 ± 2.10		
Smoking habit	Smoker	6	3.93 ± 1.84	2.489	**0.038***
	Non smoker	4	1.48 ± 0.73		
Mode of presentation	Cough	7	2.79 ± 2.22	- 0.391	0.706
	Other presentation	3	3.33 ± 1.17		
Duration of disease	< 3 month	5	2.92 ± 2.29	-0.048	0.963
	≥ 3 months	5	2.98 ± 1.73		
Side of lesion	Right	6	3.31 ± 2.3	0.717	0.494
	Left	4	2.40 ± 1.24		
Co-morbidity	Present	2	2.05 ± 0.07	-1.511	0.174
	Absent	8	3.17 ± 2.10		

*p value ≤ 0.05 was significant

The Association between bronchial CEA and Study Variables

Table 11 shows the association between bronchial CEA and study variables including (gender, smoking habit, mode of presentation, duration of disease, side of lesion and co-morbidity) among CA patients. There was no significant association between bronchial CEA and study variables.

Table 11 Association between bronchial CEA and study variables

Study variables	Bronchial CEA		P-value
	≥15 (%)	< 15 (%)	
Gender			
Male	2 (33.3)	2 (50.0)	1.000
Female	4 (66.7)	2 (50.0)	
Smoking habit			
Smoker	5 (83.3)	1 (25.0)	0.19
Non smoker	1 (16.7)	3 (75.0)	
Mode of presentation			
Cough	5 (83.3)	2 (50.0)	0.5
Other presentation	1 (16.7)	2 (50.0)	
Duration of disease			
< 3 months	3 (50.0)	2 (50.0)	1.000
≥ 3 months	3 (50.0)	2 (50.0)	
Side of lesion			
Right	5 (83.3)	1 (25.0)	0.19
Left	1 (16.7)	3 (75.0)	
Co-morbidity			
Present	1 (16.7)	1 (25.0)	1.000
Absent	5 (83.3)	3 (75.0)	

*p value ≤ 0.05 was significant, Fisher – exact test.

Discussion

By analyzing the cancer group patients characters , the age of all the patients are above 50 years as the disease commoner in elderly due to prolonged exposure time to the risk factors as smoking orenviromental or occupational hazzards. [1] [12]

Regarding the gender in the study is more in female 60% which is against the expected male predominance but this can be explained because of small sample size & the study include only the non-small cell bronchogenic cancer not all the types of bronchogenic cancer.[12]

The commonest mode of presentation is cough while the hemoptysis is the least common & the duration of the symptoms in the cancer group is shorter in relation to the airway diseases as the symptoms in the latter group is usually slowly progressive.

As expected the smoker are more in cancer patients than the non-smoker as the smoking is the most important risk factor for all the bronchogenic cancer types[12]

The site of the cancer is more common on the right side & that can be explain by the larger size of the right lung[12]

Regarding the carcino-embryonic antigen values:

There are no difference in between the bronchial wash level in tumour & non tumour sites which may indicate no benefit for the CEA level in the localization or there is some sort of contamination between the both side fluid in the lungs or can indicate micro-metastasis between the two sides make the CEA level about the same.

There is a statistically significant difference between the bronchial & serum CEA in the cancer group which mean the use of bronchial CEA may aid in diagnosis even when the serum level is normal which can be explain on the base of earlier stage, direct excretion of the antigen from the endobronchial growth or poor serum CEA reaction to endobronchial NSCLC.

The failure of finding a significant role of serum CEA assay in the diagnosis of bronchogenic cancer is consistent with most of the study that state a weak diagnostic benefits as comparing with the follow up ,response to treatment & disease recurrence.[1,2,42,43]

There is a significant difference between the diseases groups in bronchial CEA in favoring cancer group especially in patients with parenchymal (TB) disease group.

The level of statistical differences is increased with increasing the cut value of the CEA test as in 5ng/l with no significant difference to 20 ng/l as a very significant finding with the 15 ng /l (taken as the standard in this test) is the 1st level with statistical significance, this finding is against most of the paper that state the level of CEA in the serum is equal to that of the body fluid (except CSF) as pleural fluid or pancreatic cyst aspirate[46.47]

In Jin Hur etal study (reference No 48) they use the cytological fluid from a transthoracic pulmonary nodules aspirate to measure the CEA level they face the same problem of no defined normal valve for CE in the cytological fluid so they use 0.6 ng/ml which is much lower than our cut level of 15 ng/ml or even that of the pleural fluid =5 ng/ml, but really there is no published study about the use of such test in the bronchial wash as in our study.

Regarding the correlation of the CEA level with study variables:

There are no statistical differences among all the variables with the bronchial level while only the smoking affect the serum level meaning the effect of the smoking on the serum level (increase the serum level by the smoking without an accompanied diseases) is not seen in the bronchial CEA level which mean more specific for the diseases

The finding of higher serum level of CEA in smoker is go with all the papers that were mentioned in the introduction [38,44,45]

Conclusions

1- The bronchial CAE assay can be useful & adjuvant in the diagnosis of NSCLC & can add weight to the other diagnostic tools
2- The serum CEA test is not useful as bronchial CEA test in the diagnosis of NSCLC
3- There is no effect of smoking on the bronchial level of CEA as that seen in the serum CEA test ,as the later can be altered by smoking without other pulmonary diseases
4- There is no difference in the diagnostic significance of the bronchial CEA test level when the bronchial wash divided according to the sites of the tumor as both the tumor & non- tumor sides CEA levels show non-significant different results
5- There are no affection of the serum & bronchial CEA level with many socio-demographic variable for the patients which mean it is a test with accepted specificity.

Recommendations

1- A larger study is recommended to show the usefulness of the bronchial CEA not only in the diagnosis of NSCLC but also other types of bronchogenic cancer & other pulmonary diseases
2- More studies are needed to state the benefits of bronchial CEA test in the prognosis, follow up ,disease recurrence & response to treatment .
3- A use of bronchial CEA in the clinical practice for cases of bronchogenic cancer which is not confirmed by other diagnostic work up

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الخلاصة

الخلفية

السرطان قصبي المنشأ واحدة من أكثر أنواع السرطان شيوعا في النوع البشري وتمثل تحديا في التشخيص بسبب الاختبارات المتاحة هي إما تكون ذات شأن تشخيصي في المراحل المتأخرة أو قليلا تداخلية، وبالتالي فإن الحاجة إلى اختبار تشخيصي في مراحل مبكرة نسبيا صار إلزامية

الهدف من الدراسة

لتقييم أهميةCEA في السائل القصبي كعلامة الورم لمساعدة تشخيصNSCLC و لنرى هل هناك أي فرق بين المصل و CEAالشعب الهوائية وبين الورم وغير ورم الجانبين.

المرضى وطرق:

شارك ٣٠ مريضا في الدراسة، وتنقسم الى ٣ مجموعات وفقا لتشخيصهم كما السرطان وأمراض الشعب الهوائية ومجموعات السل، وتقييم الخصائص الاجتماعية والديموغرافية، وميزات السريريCXR ، والاشعة المقطعية وناظور القصبات الليفي البصري تم القيام به ومستوى CEA تم قياسه في العينات المأخوذة من مصل الدم والأورام وغير ورم الجانبين

النتيجة:

كان هناك فروق ذات دلالة إحصائية في مستوى CEA في السائل القصبي من مجموعة مرضى السرطان مقارنة مع المصل من نفس المجموعة وعلى مستوى السائل القصبي في المجموعات الأخرى لصالح مرضى مجموعة السرطان، ولكن لا فرق بين ورم وغير السرطانية الجانبين في مرضى مجموعة السرطان.

استنتاج

القصبي غسل CEA الفحص يمكن أن تكون مفيدة في تشخيص NSCLC ويمكن أن تأخذ

بعين الاعتبار في العمل في المستقبل.

دور فحص مستوى CEA في السائل القصبي في تشخيص سرطان الرئة ذي الخلايا غير الصغيرة

أطروحة

مقدمة إلى المجلس العلمي للطب الباطني كجزء من متطلبات نيل شهادة زمالة المجلس العراقي للاختصاصات الطبية في طب الامراض التنفسية

من قبل

الدكتور علي صالح بيعي

زميل المجلس العراقي للطب الباطني

اشراف الاستاذ

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الجامعة النهرين

2015