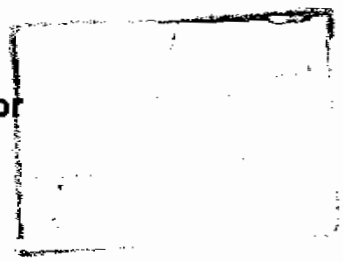
MOLECULAR MARKERS OF MALIGNANT NEOPLASMS OF ESTABLISHED CLINICAL VALUE AND DIFFERENT LABORATORY METHODS FOR THEIR ESTIMATION

Essay

Submitted in partial fulfillment for
Master Degree in
CLINICAL PATHOLOGY



By

SHEREEN MOHAMED FAHIM GHEITH
(M.B., B.Ch.)

Supervised By

PROF. DR. LAILA ABD EL AALA EL-SHAWARBY
Professor of Clinical Pathology
Faculty of Medicine, Ain Shams University

PROF. DR. AMANI IBRAHIM SALEH
Professor of Clinical Pathology
Faculty of Medicine, Ain Shams University

DR. HALA AHMED TALKHAN
Lecturer of Clinical Pathology
Faculty of Medicine, Ain Shams University

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بسم الله الرحمن الرحيم

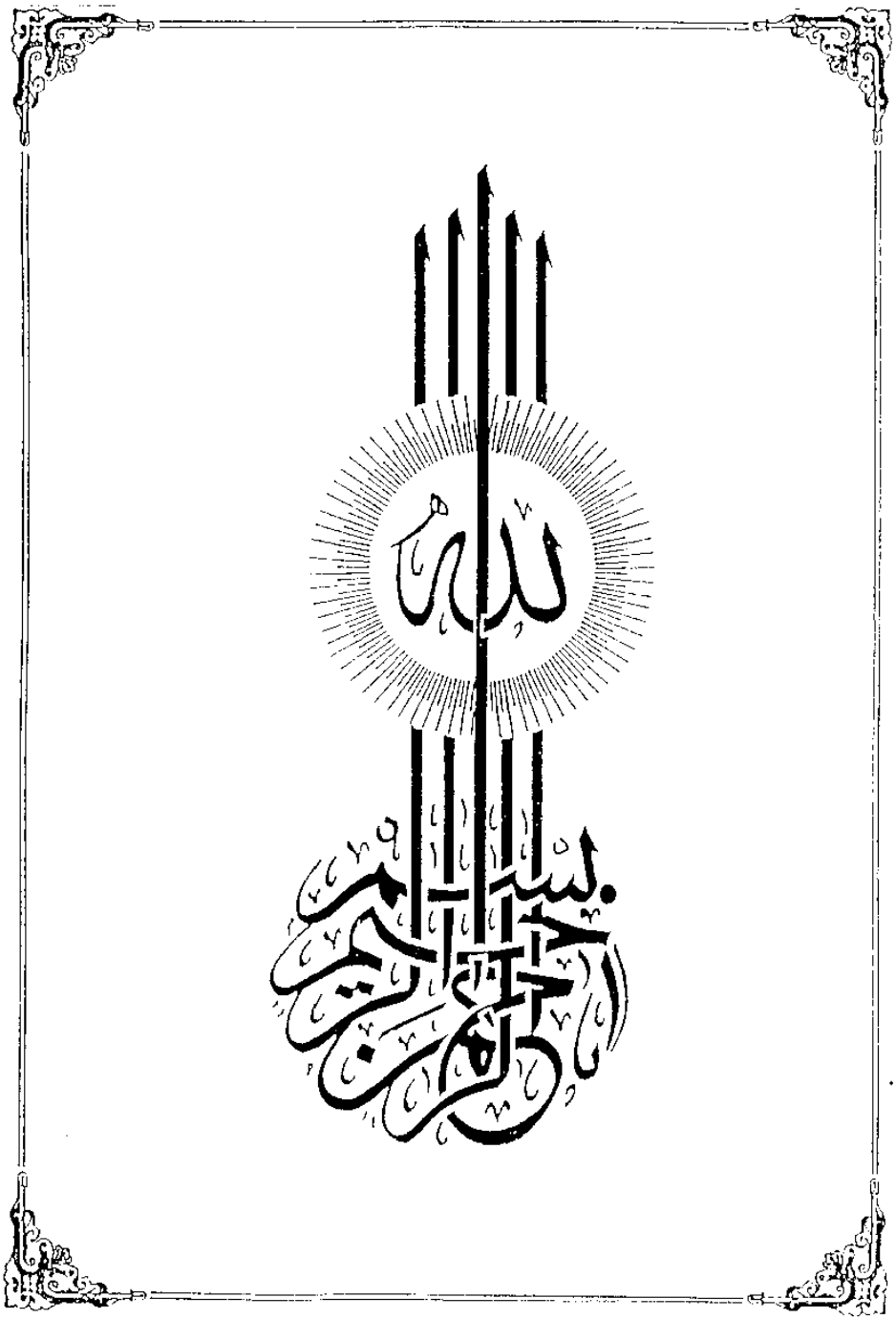
اقرأ باسم ربك الذي خلق

خلق الإنسان من علق

اقرأ وربك الأكرم الذي علم بالقلم

علم الإنسان ما لم يعلم

العلق ١-٥



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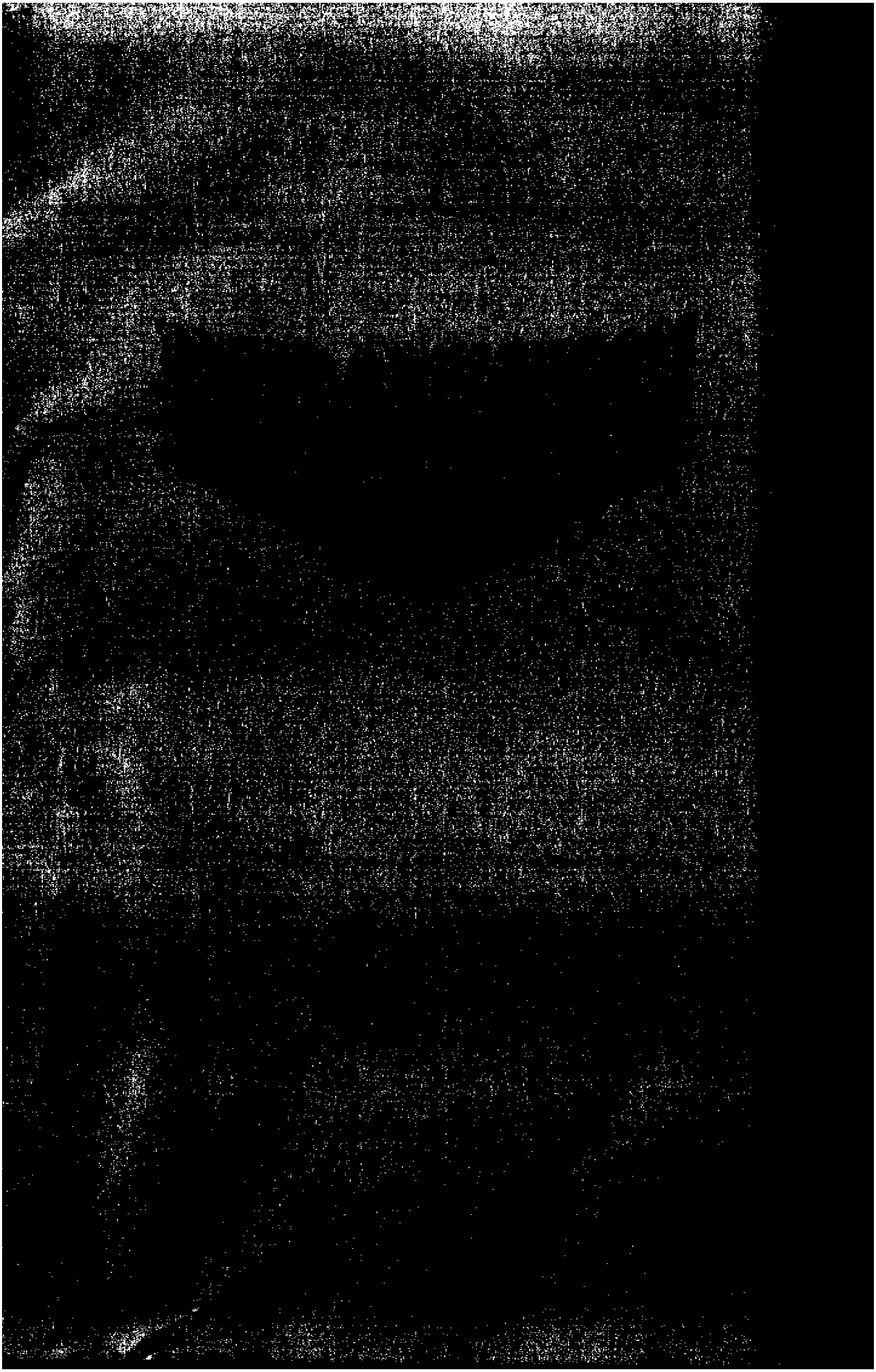
ABBREVIATIONS

AFP	=	Alpha fetoprotein.
ALT	=	Alanine aminotransferase.
APUD	=	Amine precursor uptake and decarboxylation.
APL	=	Acute promyelocytic leukemia.
Alpha-TGF	=	Alpha transformig growth factor.
AST	=	Aspartate aminotransferase.
BBT	=	Basal body temperature.
CA	=	Carbohydrate antigen.
CEA	=	Carcinoembryonic antigen.
CGRP	=	Calcitonin gene related peptide.
CT	=	Calcitonin.
Ct.Pr	=	Calcitonin precursor.
DRE	=	Digital rectal examination.
EGF	=	Epidermal growth factor.
EGF-R	=	Epidermal growth factor-receptor.
ELISA	=	Enzyme linked immunosorbent assay.
FC	=	Flow cytometry.
GGT	=	Gamma glutamyl transferase.
GnRh	=	Gonadotrophic relasing hormone.
GO	=	Ground stage.
HCC	=	Hepatocellular carcinoma.
HCG	=	Human Chorionic gonadotropin.

IA	=	Image analysis.
IRMA	=	Immunoradiometric assay.
Le	=	Lewis antigen.
MCA	=	Mucin like carcinogenic antigen.
MEN	=	Multiple endocrine neoplasia.
MRI	=	Magnetic resonance imaging.
mRNA	=	Messanger ribonucleic acid.
NSE	=	Neuron specific enolase.
PCR	=	Polymerase chain reaction.
POA	=	Pancreatic oncofetal antigen.
PSA	=	Prostate specific antigen.
RCC	=	Renal cell carcinoma.
RIA	=	Radioimmunoassay.
SCCL	=	Small cell carcinoma of the lung.
S-Th	=	Serine alpha 1-0 serine thereonin.
TPA	=	Tissue polypeptide antigen.
TRU	=	Transrectal ultrasonography.
TAG_{72}	=	Tumor associated glycoprotein.

CONTENTS



INTRODUCTION

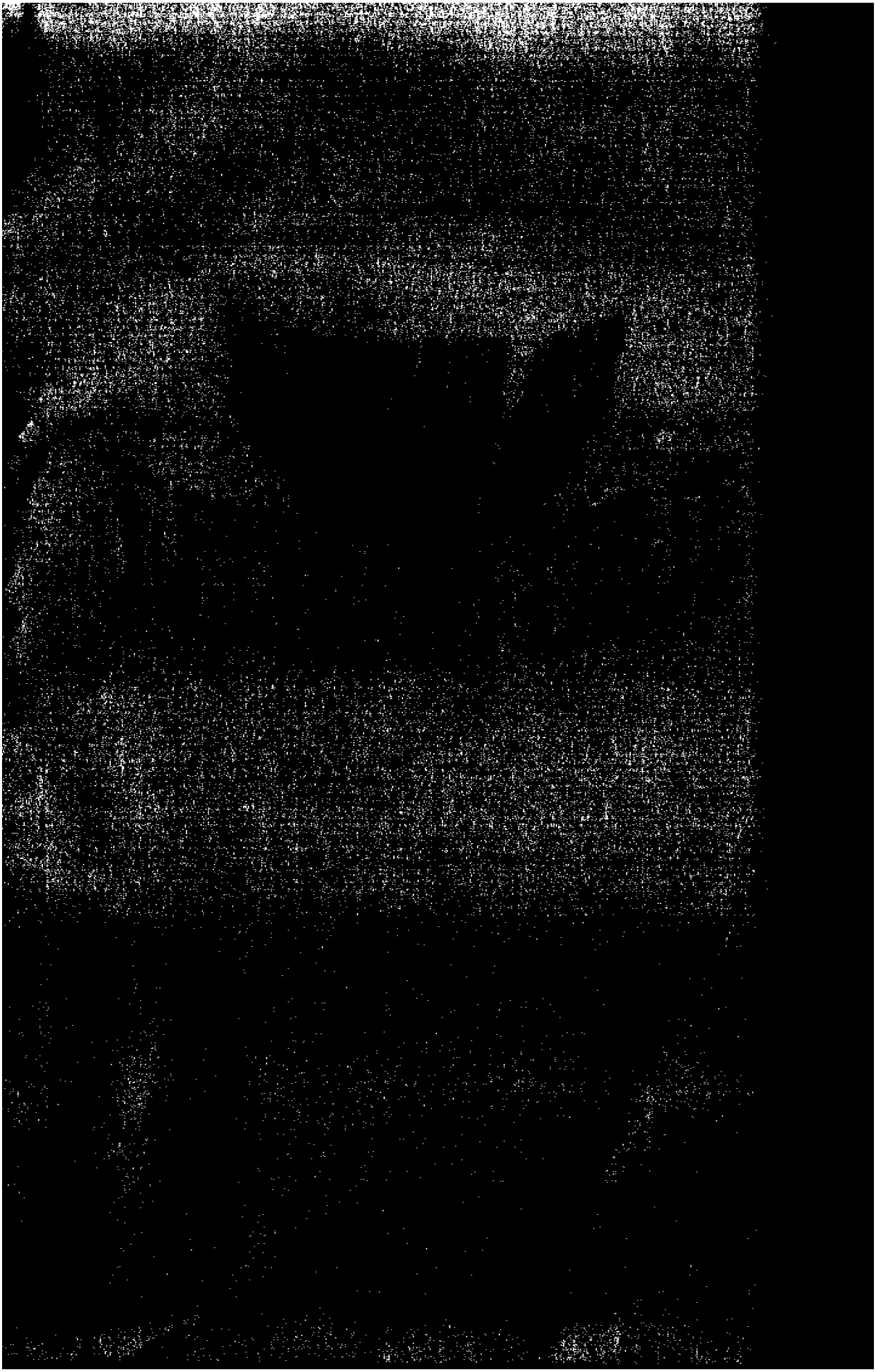
The term tumor marker designates a broad category of substances produced by malignant cells or benign cells in response to the presence of malignancy. Marker substances are classified as tumor associated or tumor specific.

Many new and useful tumor markers have been developed on the basis of monoclonal antibodies. They may serve to define, track and manipulate tumor cells.

Tumor markers may be detected in body fluids, tissue specimens or extracts (Mendelsohn, 1987).

The number of tumor markers used clinically has grown rapidly in recent years. The important aim of cancer research now is to find new methods that will improve the accuracy and sensitivity of cancer diagnosis, treatment and follow-up. Nowadays, genetic markers, i.e. amplification of oncogenes may serve as a prognostic marker in certain neoplasms. The development of molecular biology had provided new techniques for prospective molecular diagnosis.

The aim of this work is to write a review about the different types of tumor markers in clinical use, their classification and their clinical value in monitoring therapy and follow up of the patients.



TUMOR MARKERS

The researches of tumor markers started at the discovery of Bence Jones protein in 1848. Recently, several tumor markers using the methods of monoclonal antibodies have been invented. Usually tumor markers are measured in sera, so the early diagnosis of cancer by tumor markers are sometimes difficult. For the early diagnosis of cancer by tumor markers, inventions of new tumor markers, improvement of assay systems and materials and the combination of several tumor markers have been tried (Yoneshima et al., 1988).

The tumor marker is a substance which is produced or induced by tumor cells and is released into blood or other body fluids or expressed on the cell surface in large quantities by malignant cells than by the normal counterparts. Thus it represents a relative rather than an absolute marker of malignancy. It does not necessarily have to be tumor specific (Hiari, 1988). Tumor markers that are produced by tumor cells or stromal cells are said to be tumor derived or tumor specific while marker produced by non malignant cells as a result of disturbances by the tumor are said to be tumor associated. Tumor markers are determined

either by measuring their concentrations in body fluid or detection of the marker on the cell surface (Brikmayer and Kalvins, 1990).

Clinical applications of tumor markers:

Tumor markers are used for:

1) Detection:

Screening of asymptomatic population at risk before it is suspected clinically.

2) Diagnosis:

In distinguishing benign from malignant conditions in patients in early stages of cancer. It depends on the specificity of the tumor marker for that tumor.

3) Prognosis:

To be of value, the tumor concentration should correlate with tumor size or activity.

4) Monitoring:

Ascertain the patients response to therapy. Effective therapy results in corresponding fall in the plasma concentration of the tumor markers.

5) Follow-up:

For recurrence, most valuable function of tumor markers especially when a clinical evidence of recurrence is difficult to obtain. It is accompanied with progressive rise in marker concentration.

6) Staging:

for determining the extent of the disease. The concentration of the marker should be proportional to the extent of the disease.

7) Classification:

To clarify the optimum choice of therapy and predict the biological behavior of the tumor (Joss and Cerny, 1990).

None of the tests currently available is specific and sensitive enough to fulfill the criteria of a screening test in asymptomatic population. The interpretation of a single determination does not allow a definite conclusion. It should be stressed that a negative tumor marker result can not be used to exclude primary malignancies (Humphery, 1989). Combining different parameters can improve the diagnosis precision, but even when different parameters are combined, the results are not reliable enough to be used as

a screening test. They are used in conjunction with radiology and tissue biopsy and other data to establish the diagnosis of malignancy (Lahounsen et al., 1987).

Some markers are normally present in significant quantities in blood and are elevated in cancer. Although these markers can be highly sensitive they lack specificity (Waldmann and Herberman, 1982). The reason for their lack of specificity can reside in the antiserum used for determination of tumor markers. Some antisera may cross react with immunologic determinants on similar, but not identical components. On the other hand, abundance of identical components also associated with some non malignant disease due to increased production or release or decreased degradation of the tumor marker may also lead to inspecificity (Newman et al., 1974).

Continuous monitoring of a patient who was tumor marker positive, even after the concentration of that marker has stabilized, normalized or become undetectable following successful therapy is important for early detection of metastases (Phol, 1990). It is important to distinguish between the established role of a tumor marker and its potential role as suggested by recent research. Clinical