TUMOR MARKERS AND THEIR CLINICAL APPLICATIONS

Essay

Submitted in Partial Fulfilment of
The Master Degree in *General Surgery*

By

NAYEF MOTTASEM BARGHOUTY
M.B., B.Ch.

Supervised by

Prof. Dr. ABO BAKR AL SEDEEK MOSTAFA SALAMA
Prof. of General Surgery
Ain Shams University

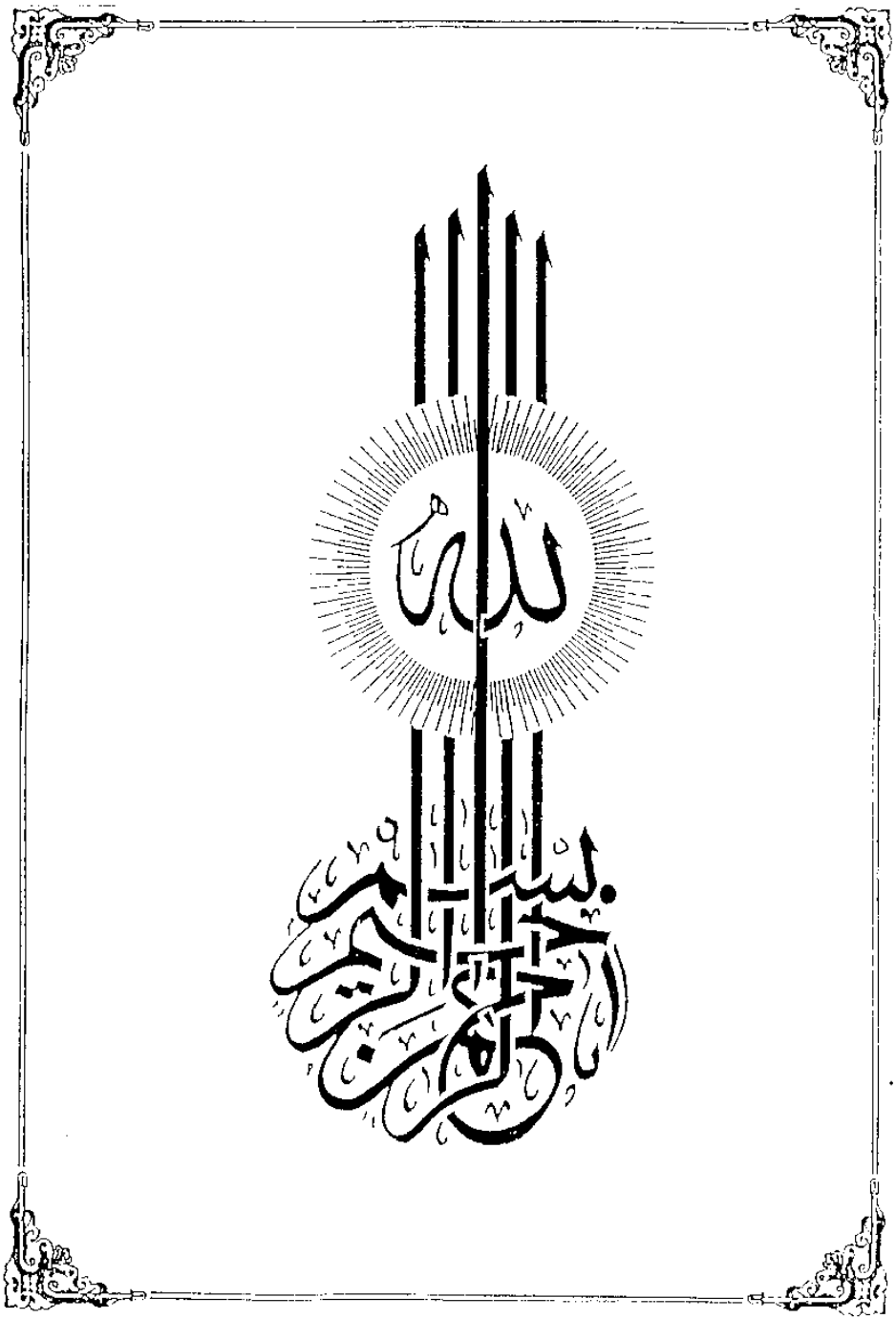
Faculty of Medicine
Ain Shams University
Cairo

1987

بسم الله الرحمن الرحيم

وما اوتيتم من العلم إلا قليلا

سورة الإسراء (آية ٨٥)



ACKNOWLEDGMENT

I would like to express my faithful gratitude for the help and the continuous supervision offered by Prof. Dr. Abo Bakr Al Sedeek Mostafa Salama, Prof. of General Surgery, Ain Shams University.

I am also grateful to Prof. Dr. Ali Khalifa, Prof of Biochemistry, Ain Shams University, for his assistance and advice in collecting the material of this essay.

I would like to record my sincere gratitude to my senior staff and colleagues.

Contents

INTRODUCTION

INTRODUCTION

Cancer cells synthesize a wide variety of biochemical products that can be detected in body fluids. The clinical implications of this phenomenon are quite obvious. At the present time our limited ability to detect small tumor masses represents one of the most formidable barriers to progress in cancer treatment. Existing therapies could be applied much more efficiently if only there were better methods of cancer detection. The search for unique molecular alterations associated with malignant transformation has been pursued for decades however studies utilizing highly sensitive analytical methods have shown that most of the tumor specific biological markers or biomarkers are also produced at some stage in normal embryogenesis *(Coggin et al., 1974)*.

These same substances can be detected at low levels in certain cancer-free subjects as well as in patients with non malignant diseases.

Tumor biomarkers are defined as any substance present in a body fluid which reflect either quantitatively or qualitatively the presence of malignant disease.

Most of the clinically useful tumor markers have been shown to be synthesized by cancer cells eg: peptide hormones and oncofetal antigen. However certain tumor markers such as hydroxyproline represent products that are derived from destruction of normal tissues. In addition recent studies have suggested that the presence of cancer may result in synthesis of marker substances by adjacent normal tissues or by distant organs *(Kessel et al., 1977)*.

Factors Affecting the Level of Tumor Markers

Multiple biological factors may influence the level of a particular tumor marker in any body fluid.

1. Number of tumor cells present and the kinetics of cancer cell proliferation and death.

2. Proportion of tumor cells synthesizing the marker and the synthetic rate per cell. Only certain cells within a tumor may make a marker and production may vary with the phase in the cell cycle and with the stage of differentiation of the cell.

3. Location of the marker within the tumor cell and the mechanism for release from cells and entry into circulation. Some tumor markers are cell-membrane constituents or secretory products and may be shed or released from viable cells. Other markers may be intracellular constituents which would only be released when tumor cells lose viability. Some tumor markers released from solid tumors might only enter the circulation in appreciable quantities after invasion of blood vessels, with such markers, levels in the region of the tumor or in directly contiguous body fluids or excretions might be much higher than in the circulation , and testing on these might be more useful then testing serum.

4. The half-life of the marker in the circulation can also vary considerably depending on the size and nature of the substance and the rate of marker catabolism and excretion by the host and the specific interactions between cancer cells and normal tissues *(Tormey et al., 1980)* (Fig 1).

Characteristics of Ideal Tumor Marker

1. It should be produced by the tumor cell and be readily detectable in body fluids.
2. It should not be present in health or in benign diseases.
3. It should be present frequently enough and early enough in the development of a malignancy to be used in screening for that cancer.
4. The quantity of a tumor marker should directly reflect the bulk of malignancy, and be detectable even when there is no clinical evidence of tumor.
5. Finally the level of the ideal marker should correlate with the results of anticancer therapy.

No marker described to date meets all of these criteria *(Bates et al., 1985)*.

GENERAL USES OF TUMOR MARKERS

GENERAL USES OF TUMOR MARKERS

I. The Use of Tumor Markers in Mass Screening of Normal Populations

Mass screening programs for the detection of cancer have had a broad appeal among health professionals and the general public. However much of this appeal is based upon two simple assumptions which lack adequate clinical validation. The first of these assumptions is that earlier detection of cancer will result in improved prognosis. Although this first assumption seems self evident, there is presently no compelling evidence to suggest that improved survival has resulted from detection programs for cervical cancer, breast cancer and other common malignancies *(Miller et al., 1976)*.

A second attractive assumption is that a blood test with high predictive value will ultimately be developed for widespread use in cancer screening. The problem here is that all blood tests currently in use for any disease are much less effective than we would expect them to be when they are employed as screening tools. This same problem is likely to be obtained for any mass cancer screening test.

The predictive value of a screening test is determined by the interaction of three important variables: The sensitivity of the test, the specificity of the test, the prevalence of the disease in the examined population. The term sensitivity is used to characterize the frequency of true positive results when the test is administered to patients who are known to have the disease. The term specificity is used to characterize the frequency of true negative results when the test is administered to individuals who are known to be free of the disease.

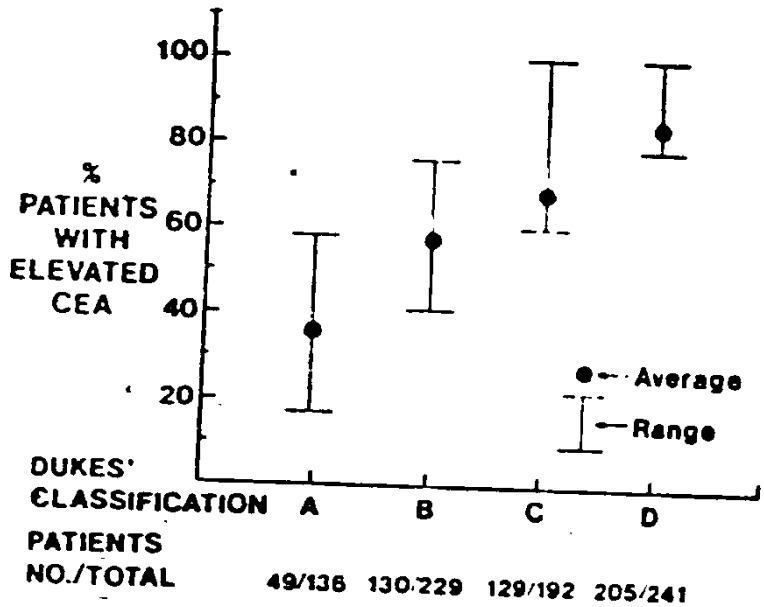
The ideal screening test would always yield positive results in any patient with disease (100 percent sensitivity) and negative results in any individual without the disease (100 percent specificity). However there is presently no practical screening test for cancer that meets these ideal standards.

Furthermore sensitivity is inversely linked with specificity. When a quantitative screening test is employed, the selection of a level at which the test is considered to be positive then becomes very important. Selection of a level that will provide very high sensitivity generally diminishes the degree of specificity, whereas the selection of a level that ensures maximum specificity tends to decrease the sensitivity. For example, *Hansen et al., 1974* used a value of more than 2.5 ng/ml as an abnormal for plasma carcinoembryonic antigen (CEA) test for colorectal carcinoma, which provided a sensitivity of 67 percent and a specificity of 90 percent. A definition of abnormal as more than 10 ng/ml increases the specificity to 99.9 percent but decreases the sensitivity to 6.4 percent.

Prevalence is probably the most important factor in determining the predictive value of a screening test. The term prevalence rate is used to characterize the number of patients per 100,000 population who have the disease and is roughly equal to the incidence of the disease times the duration of the disease. Even when a particular screening test demonstrates both high sensitivity and high specificity, prevalence has an important influence upon the predictive value of the test.

If we consider the case of the CEA test, since the history of its discovery, characterization and subsequent clinical application provides an excellent example of the problems associated with the development of any

Fig. 2: Correlation between the CEA titer and the stage of disease in patients with colorectal carcinoma.



(Tormey et al., 1980)

Modified Dukes classification of Colorectal Carcinoma

Stage	Substage	Spread
A	A1	Mucosa
	A2	Submucosa
	A3	Muscularis Propria
B	B1	Beyond Muscularis propria
	B2	Free serosa involved
C	C1	Local node metastases
	C2	Apical node metastases
D	D1	Local tumor remaining (histologic)
	D2	Distant metastases (clinical)

(Newland et al., 1981)

tumor biomarker as a screening test for cancer. In 1965, *Gold* and *Freedman* first reported that tumors derived from human gastrointestinal tract contained a substance (CEA) which was absent from normal gastrointestinal tissues but present in the fetal gastrointestinal tract. These same investigators subsequently developed a sensitive radio-immunoassay for CEA. Sera of 36 patients with colorectal cancer where tested and 35 were found to have detectable levels of CEA whereas none of the sera from normal individuals were positive *(Thomson et al., 1969)*. It has been demonstrated that CEA test is less frequently positive in patients with potentially curable disease (Dukes A, B and C) than in patients with advanced disease (Dukes D) *(Tormey et al., 1980)* (Fig. 2).

Although the CEA test was originally considered to be specific for colorectal cancer, it has now been shown to be positive in patients with many other malignant disorders including breast, lung, gynecological cancer *(Wang et al., 1975)*. Even more important in terms of any potential role as a clinical test for cancer detection and diagnosis, CEA has also been detected in a variety of non malignant conditions *(Hansen et al., 1974)* (Table 1).

How effective would be a mass screening program for colorectal cancer if the CEA test is employed as a screening instrument? We can derive a very good estimate using sensitivity data from Fig. (2) and specificity data from table (1) and the prevalence rate of colorectal cancer in general population. The overall sensitivity of CEA test for all stages of colorectal cancer is 67 percent. In nonsmoking healthy subject the specificity of CEA test is 97 percent, but a practical mass screening program would never be applied to such an ideal population. The smoking habit alone reduces the specificity of CEA test to 81 percent, and there are few nonmalignant diseases in which the specificity of the test is much higher than about 70 percent. The

prevalence rate of colorectal cancer in the population to be screened is the last figure we would need to know in order to estimate the effectiveness of the CEA as a screening test. If we assume that the screening program would be applied only to subjects over the age of 35 years then the prevalence rate would be 0.2 percent *(Prorock, 1976)*. The anticipated results of this screening program for colorectal cancer are given in table (2).

Only 200 subjects among the screened population of 100.00 would actually have colorectal cancer, and 134 of these subjects would be identified by means of a positive test. However an additional 9980 subjects without colorectal cancer would have a positive CEA test. This provides a ratio of 74 subjects with a false-positive test to every subjects with a true-positive test. The medical costs of applying additional diagnostic studies in every subject with positive test would be enormous. Not only would the bowel have to be examined but other organs would have to be evaluated as well, since elevated levels of CEA are also seen with cancers of many different organs. The lesson learned from considering CEA test as a model for cancer screening is simple. High sensitivity of a tumor marker is virtually meaningless by itself. Even if the sensitivity of CEA test in our example had been 100 percent the ratio of the false positive to the true positive would still have been an unacceptable 50 : 1. Specificity is certainly quite important in determining the predictive value of a screening test. However, the specificity of a tumor marker would have to be nearly 100 percent for a marker to yield a minimum false positive results when unselected populations are screened for an uncommon disease like colorectal cancer. The most important single factor in determining the predictive value of any screening test is the prevalence. This factor alone suggests that future cancer detection programs should be restricted to population that are selected as being at high risks for the disease *(Tormey et al., 1980)*.