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Review

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Tumor markers: when, whom?

Artuner Varlıbaş, Aydın Çifci

Department of Internal Medicine, Faculty of Medicine, Kırıkkale University, Kırıkkale

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Corresponding Author: Artuner Varlıbaş, artunervarlibas@gmail.com

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ABSTRACT

Cancer is a leading health problem with its prevalence, clinical course and deaths all over the world. It is known that cancer is the second leading cause of death in Turkey after cardiovascular diseases. Therefore, intensive research is carried out on the early diagnosis and treatment of cancer. The most important of these are tumor markers that are still used in clinical practice. Based on this definition, it is theoretically possible to obtain information about the presence of the tumor and the character of the tumor by investigating tumor markers in body fluids. A tumor marker is a molecule that is present in the structure of the tumor cell, secreted by the tumor cell or produced in response to the tumor and can be measured or demonstrated in body fluids. However, its use is limited due to its low sensitivity and specificity to cancer type in the early period. Therefore, it is important to select the appropriate test at the appropriate time for the appropriate patient. In this review, general principles regarding the use of tumor markers were tried to be explained.

Keywords: Tumor markers, cancer, early diagnosis

INTRODUCTION

Each cell has its own unique molecules that it produces due to its structure or physiological function. With the measurement of these molecules from blood or body fluids, it is possible to obtain information about the presence and functionality of that cell or tissue. Basically, a tumor marker is a molecule that is present in the structure of a tumor cell, secreted by the tumor cell or produced in response to the tumor, and can be measured or demonstrated in body fluids. Based on this definition, it is theoretically possible to obtain information about the presence of the tumor and the character of the tumor by investigating tumor markers in body fluids.[1-3]

With its prevalence and difficulties in diagnosis and treatment, cancer is a challenging disease for clinicians and a popular field for researchers. Every day, new advances in cancer are announced and new techniques against cancer are discussed. Which molecule is the tumor marker and its place in cancer treatment is now indispensable for research and guidelines.[2-5]

Cancer is a leading health problem with its prevalence, clinical course and deaths all over the world. According to GLOBOCAN, there was an incidence of 19.3 million new cancer cases and almost 10.4 million cancer-related deaths worldwide in 2020. According to the records of the Ministry of Health of the Republic of Turkey, in 2017, approximately 180,000 people were diagnosed with cancer in our country, one in every five deaths was caused by cancer and the second most common cause of death in our country was cancer.[6,7]

AREAS OF USE AND PURPOSES OF TUMOR MARKERS

Tumor markers are used for various purposes in the clinical diagnosis and treatment phase. For our clinical purposes, a tumor marker should be detected in those with that disease, it should not be present in those who do not have that disease, it should be detected in the early and silent period of the disease, it should be specific to a particular organ or cancer type, it should provide information about its quantitative value and the size and metastases of the tumor, and it should act in correlation with cancer progression and regression. However, current tumor markers are far from these expectations. Tumor markers in routine use can be measured at high values in non-cancerous and benign conditions, result in normal results in the early stages, and cannot be detected in every patient with that cancer, even though it is defined as particular to a specific cancer. The mismatch between expectations and facts greatly restricts the use of tumor markers.[1,2,4,8]

Screening programs are applications such as examination, imaging, sample examinations for the early diagnosis and early treatment of a particular disease in the society. Diseases that frequently appear in the society, have an asymptomatic period in their course, are easy to treat or save lives when recognized early; diseases that are very difficult to treat or result in death when recognized late are candidates for screening programs. From this point of view, cancers are excellent candidates for screening programs. Cancer screening programs are carried out with various methods and the use of tumor markers for screening is a popular field of study. However, its use is limited due to its low sensitivity and specificity to cancer type in the early period.[1,3,8-11]

The low sensitivity and specificity of tumor markers limit their use for screening purposes as well as their use in diagnosis. Tumor markers have a limited and helpful role in diagnosing cancer today, and biopsy and histopathological examinations are still the priority for definitive diagnosis. They can help with whether a tumor in a particular organ is benign or malignant. They can guide the determination of histopathological diagnosis. They are frequently used in the diagnosis of metastatic cancers of unknown primary origin.[3,12,13]

One of the main elements in the planning of cancer treatment is prognosis. Although tumor stage, tumor size and metastasis are generally evaluated when determining the prognosis, tumor markers may contribute to the prognosis. One of the important problems in the follow-up of cancer treatment is the response to the treatment applied. Although radiological methods stand out in this regard, it is thought that tumor markers can be used. Recurrence and metastasis are another issue that should be followed up as well as the treatment response. Routine follow-up of tumor markers in post-treatment follow-up can alert the clinician about new metastasis and recurrence in patients.[3,4,14-16]

PROMINENT TUMOR MARKERS IN CLINICAL PRACTICE

Although new molecules are proposed as tumor marker candidates every day and new application potentials are attributed to them, tumor markers in routine use within the current guidelines and laboratory facilities are limited in number.

The beta unit of human chorionic gonadotropin, also known as B-hCG, is produced by the placenta and is in routine use as a pregnancy test. However, germ cell tumors can be pathologically detected in the presence of trophoblastic tumors. When used together with other tumor markers, it can give an idea in terms of histological diagnosis at the diagnosis stage and can be used in follow-up.[14,17]

Alpha-fetoprotein (AFP) is often used in the follow-up of chronic liver patients and in the diagnosis of hepatocellular cancer. Although it has low sensitivity in the early period, it is used for screening in people at risk (cirrhosis and chronic hepatitis patients). In addition, its quantitative value can provide information about prognosis and can be a guide for treatment planning. AFP can also be detected in stomach and germ cell tumors. Other causes of AFP elevation include hepatitis, cirrhosis, and pregnancy.[18-20]

Carcinoid tumors cause carcinoid syndrome with the mediators they secrete. Serotonin is the molecule primarily responsible for carcinoid syndrome and is very difficult to measure and interpret. For this reason, the measurement of 5-Hydroxyindoleacetic acid (5-HIAA), a breakdown product of serotonin, is very valuable in terms of diagnosis in the suspicion of carcinoid syndrome and can also be used in the follow-up of treatment. Apart from carcinoid syndrome, it can also be seen in lung cancer, pancreatic islet tumors and non-malignant diseases of the intestine.[18,21,22]

Carcinoembryonic antigen (CEA) is frequently detected in gastrointestinal tract (GI) cancers, primarily colorectal cancers. Apart from cancer, it can be seen in GI diseases such as gastritis, pancreatitis, pancreatitis, colitis. It can give high results in patients who smoke. Due to its low sensitivity and specificity, it is not used for screening purposes. CEA can provide valuable information on prognosis in colorectal cancers. Treatment planning can be followed up in terms of monitoring the treatment response and recurrences.[18]

The prominent tumor markers in breast cancer are CA 15-3 and CA 27.29. Tumor markers are prominent in breast cancer screening and diagnosis in examination and imaging, but are also used in monitoring, especially for metastasis and recurrence. CA 15.3 can cause adenocarcinomas of various organs and liver diseases, high levels of sarcoidosis and hypothyroidism.[18-21]

CA-125 is frequently detected in advanced ovarian cancers and is measured at normal values in half of the early-stage cases. In addition, it may increase in the presence of pelvic inflammatory disease (PID), endometriosis, hepatitis and non-ovarian cancers. Due to these limitations, although the use of CA-125 alone or together with ultrasonography for screening purposes has been studied, it has not been included in current guidelines. CA-125 is a valuable marker in monitoring whether ovarian masses known to be present are benign or malignant and treatment response.[18,19,21]

Although CA 19.9 has been associated with colorectal cancers, it is a tumor marker of pancreatic cancer with its frequent detection in pancreatic cancers. CA 19.9 can be detected in GI malignancies and used for follow-up.[18,22-24]

Prostate-specific antigen (PSA) is the most important marker of prostate cancer. Although PSA elevation raises the suspicion of cancer and the need for a biopsy, PSA is a prostate-specific molecule and can be high in many prostate-related conditions. These conditions can be pathological (benign prostatic hyperplasia (BPH), prostatitis), physiological (ejaculation), even medical interventions (rectal

Table. Intended use of tumor markers and other pathologies with high detection[4,5,9-13]

Organ/tumor	Tumor marker	Intended use	Other pathologies in which the marker can be detected
Liver	AFP	Screening, diagnosis, follow-up	Hepatitis, cirrhosis, pregnancy, other malignancies
Carcinoid tumor	5-HIAA	Diagnosis, follow-up	Pancreatic islet tumor, lung cancer, intestinal diseases
Colon and rectum	• CEA • CA-19.9	Follow-up	• GI malignancies, GI benign diseases, Thyroid medullary cancer • GI malignancies
Choriocarcinoma	B-hCG	Diagnosis, follow-up	Testicular cancer, trophoblastic tumor
Breast	CA-15.3	Follow-up	Liver diseases, sarcoidosis, hypothyroidism, other malignancies
Ovarian	CA-125	Diagnosis, follow-up	PIH, endometriosis, hepatitis, peritoneal irritation, other malignancies
Pancreas	CA-19.9	Follow-up	GI malignancies
Prostate	PSA	Screening, diagnosis, follow-up	BPH, prostatitis, iatrogenic interventions
Thyroid (well differentiated)	Thyroglobulin	Follow-up	Surgical and invasive interventions, benign diseases of the thyroid, pregnancy
Thyroid (medullary carcinoma)	Calcitonin	Follow-up	Liver and kidney malignancies

examination, cystoscopy and biopsy). It should be kept in mind that BPH is the most common cause of PSA elevation. Despite the difficulties in differential diagnosis, PSA is the first test evaluated in social screenings, in the diagnosis of prostate cancer and other benign prostate diseases, and in determining the need for biopsy. It can be monitored for response and recurrence.[25-27]

Thyroglobulin is specific to thyroid tissue and is involved in thyroid hormone metabolism. Thyroglobulin is used to evaluate the success of treatment of well-differentiated thyroid cancers after treatment and to investigate the presence of recurrence in follow-ups. Invasive procedures against the thyroid gland, inflammation of the thyroid gland and autoimmune diseases, disorders in iodine metabolism, pregnancy may cause an increase in thyroglobulin. Among thyroid cancers, medullary thyroid carcinoma is in a different position from other thyroid cancers due to its origin from parafollicular C cells, and calcitonin is used instead of thyroglobulin in its follow-up. Calcitonin may also be high in liver and kidney-related malignancies.[2-4,28,29]

CONCLUSION

There is a bias and expectation in society, and even in clinical routine, that tumor markers give a definitive view of whether a person has cancer. Clinicians, patients, and healthy people who are worried about cancer hope that there is a technique that works with a simple blood test and tells the patient if they have cancer, but that expectation is far from over right now.

- Tumor markers do not give precise information about whether a person has cancer.
- Tumor markers are more valuable in monitoring patients diagnosed with cancer than in cancer research in healthy people.
- A tumor marker can be detected in many different cancers.
- Even if it has been identified for a specific cancer, it may not be detectable in all patients with that cancer.
- Tumor markers may indicate non-cancerous diseases.
- Inappropriate use of tumor markers causes loss of resources and time, and may lead the patient to troublesome, dangerous or even fatal examination and research processes.
- Tumor markers should only be used in certain patients for specific purposes.

ETHICAL DECLARATIONS

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