Evaluation of Diagnostic Value and Sensitivity of Tumor Markers

Essay

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بِسْمِ اللّهِ الرّحمَنِ الرّحيمِ

[...رَبِّ أَوزِعنِي أَن أَشكُرَ نِعمَتَكَ
الَّتِي أَنعَمْتَ عَلَيَّ و عَلى والِدَيَّ
و أَنْ أَعْمَلَ صَالِحاً تَرْضَاهُ و أَدْخِلْنِي
بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ]

صدق الله العظيم

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Saba Abdallah Abdelhamed

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List of Abbreviations

ACTH	: Adrenocorticotropic hormone
AFP	: Alpha-fetoprotein
AFP-MRNA	: Alpha-fetoprotein messenger ribonucleic acid
AFU	: Alpha-1fucosidase
ALF	: Alpha albumin
AP	: Alkaline phosphatase
ASCO	: American society of clinical oncology
BC	: Bladder cancer
BCG	: Bacillus-Calmette-Guerin
BCM	: Breast cancer mucin
BHCG	: Beta human chorionic gonadotrophin
BLAP	: Biliary alkaline phosphatase
BM	: Bone marrow
BPH	: Benign prostatic hyperplasia
BTA	: Bladder tumor antigen
CA15-3	: Cancer antigen 15-3
CCA	: Cholangiocarcinoma
CCA-CA	: Cholangiocarcinoma- associated carbohydrate antigen
CEA	: Carcinoembryonic antigen
CK	: Cytokeratins
CRC	: Colorectal cancer
CTC	: Circulating tumor cell
DCIA	: Ductal carcinoma in situ
DCP	: Descarboxy prothrombin
DFS	: Disease free survival
TGF	: Tissue growth factor
DNA	: Deoxy ribonucleic acid
DTCs	: Dissaminated tumor cells
ECM	: Extracellular matrix
EGFR	: Epidermal growth factor receptor

List of Abbreviations *(Cont...)*

EGTM	: European group on tumor marker
ELISA	: Enzyme linked immunoassay
EMA	: Epithelial membrane antigen
EOC	: Epithelial ovarian cancer
ER	: Estrogen receptor
ERCP	: Endoscopic retrograde cholangio-pancreatography
EUS	: Endoscopic ultrasound
FDA	: Food and drug administrations
FGF	: Fibroblast growth factor
FISH	: Fluorescence in situ hyberdization
FNA	: Fine needle aspiration
FNBA	: Fine needle biopsy aspiration
FOBT	: Fecal occult blood test
FOLH1	: Folate hydrolase 1
FQ-PCR	: Fluorescent quantitative PCR
GFAP	: Glial fibrillary acidic protein
GGT	: Gamma glutamyl transferase
GOLPH2	: Golgi phosphoprotein 2
GPC3	: Glypican 3
HCC	: Hepatocellular carcinoma
HK2	: Human kallikrein 2
HRB	: Horseradish peroxidase
HPLC	: High performance liquid chromatography
hTEP1	: human telomerase-associated protein 1
hTERC	: human telomerase RNA component
hTERT	: Human Telomerase Reverse Transcriptase
HuCC	: Human Cholangiocarcinoma cell
ICMA	: Immunochemiluminometric assay
IDC	: Intraductal carcinoma
IGF	: Insulin- like growth factor
IHC	: Immunohistochemistry

List of Abbreviations *(Cont...)*

IL	: Interleukin
IQPCR	: Immuno quantitative polymerase chain reaction
ITC	: Isolated tumor cell
LCA	: Lens culinaris lectin agglutinin
LDH	: Lactate dehydrogenase
MCA	: Mucin like carcinoma associated antigen
MEIA	: Microparticle enzyme immune assay
MS	: Mass spectrometry
MSIA	: Mass spectrometry immune assay
MUC	: Mucin
NACB	: National academy of clinical biochemistry
NSE	: Neuron specific enolase
NMIBC	: None muscle invasive bladder cancer
NMP22	: Nuclear matrix protein 22
nRT-PCR	: Nasted real time polymerase chain reaction
NSCLC	: None small lung cancer
OP	: Opisthochis viverrini
OS	: Overall survival
PAI1	: Plasminogen activator inhibitor 1
PALP	: Placental alkaline phosphatase
PAP	: Prostate acid phosphatase
PARP	: Poly –ADP ribose polymerase
PC	: Prostate cancer
PEM	: Polymophic epithelial membrane
PGF	: Placental growth factor
PR	: Progestrone receptor
PSA	: Prostate-specific antigen
PSAD	: Prostate specific antigen denisity
PSA-DT	: Prostate specific antigen doubling time
PSC	: Primary sclerosing cholangitis
PSM	: Prostate specific membrsne
PSMA	: Prostate specific membrane antigen
RCAS1	: Receptor binding cancer antigen expressed in siso cells

List of Abbreviations *(Cont...)*

RIA	: Radio-immunoassay
RNA	: Ribonucleic acid
RSs	: Recurrence score
RT-PCR	: Real time polymerase chain reaction
RTQPCR	: Real time quantitative PCR
SF	: Scatter factor
SV 40	: Simian vacuolating virus 40
SFLc	: Serum free light chain
STM	: Serum tumor marker
Tg	: Thyroglobulin
TGF-B	: Transforming growth factor beta
TIMP-1	: Tissue inhibitor of metalloproteinase type 1
TIS	: Tumor in situ
TPA	: Tissue polypeptide antigen
TSGF	: Tumor specific growth factor
UC	: Ulcerative colitis
IUCC	: International unit against cancer
uPA	: Urokinase plasminogen activator
VEGF	: Vascular endothelial growth factor
VMA	: Vanyillylmandelic acid

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Introduction

A tumor marker is defined, as substance produced by tumor cells, or by other cells of the body, in response to cancer or certain benign conditions. These substances can be found in various body fluids or tissue specimens. Different tumor markers are found in different types of cancer, and levels of the same tumor marker can be altered in more than one type of cancer. In addition, tumor marker levels are not altered in all people with all cancer, especially in early stages. Scientists have not found tumor markers for all types of cancers. They are alone not sufficient for diagnosis, and are combined with biopsy to give a better picture of the clinical relevance of the cancer, or just merely to help diagnose it properly ***(Shaiquel et al., 2012).***

Clinical uses of tumor markers can be broadly classified into 4 groups: screening and early detection, diagnostic confirmation, prognosis and prediction of therapeutic response and monitoring disease and recurrence ***(Sharma, 2009).***

Classification scheme for tumor markers as follow: oncofetal antigens as Alpha-Fetoprotein (AFP), hormones as Catecholamines, glycoproteins as Cancer antigen 125 (CA 125), tumor associated viral antigen as Simian vacuolating virus 40 (SV 40), tumor associated proteins markers as immunoglobulins, ultra structural as desmin and components as filament component ***(Sharma, 2009).***

There are progressive attempts to improve the sensitivity and/or specificity of tumor markers have led to combination of tumor markers with other procedures (e.g., combination of CA 125 with ultra sonography for early detection of ovarian malignancy) ***(Sturgeon et al., 2008).***

Tumor markers can't be construed as primary modalities for the diagnosis of cancer, mainly because of the lake of sufficiently high specificity and sensitivity. However, since the prevalence of disease is likely to be higher in diagnostic situations, tumor markers in conjunction with other diagnostic modalities are helpful in differentiating between benign and malignant diseases, (e.g., CA 125 at levels more than 95 IU/ml, especially in postmenopausal woman with adnexal mass on radiological imaging, is virtually confirmatory of ovarian malignancy ***(Sharma, 2009).***

Tumor markers can be detected by either: Chemiluminesces, immunological detection usually relies on monoclonal antibodies that specifically bind to epitopes on tumor markers and are in turn tagged for identification with dyes in immunohistochemistry (IHC) which is the most used technique today, radioactive tags in radioimmuno assay (RIA), enzymes in enzyme linked immune-sorbent assay (ELISA), flow cytometry can analyze the presence and percentage of antibody tagged cells, genetic analysis and proteomic ***(WU, 2007).***

Aim of the Work

To throw a light on evaluation of diagnostic value and sensitivity of tumor markers and their laboratory assessment.

A tumor marker can be defined as substance present in, or produced by, a tumor itself or produced by host in response to a tumor that can be used to differentiate a tumor from normal tissue or to determine the presence of a tumor based on measurements in blood or secretions. Mostly tumor markers are proteins. These markers may be detected within exfoliated or distributed cells or as circulating agents within peripheral blood or plasma. Other biological specimens, typically bodily fluids (e.g.: Urine, saliva, sputum, cerebrospinal fluid, or effusions) may also contain tumor markers ***(Babu et al., 2012).***

A- An ideal tumor marker theoretically should have the following criteria:

- It should be highly sensitive and should have low false negatives.
- It should be highly specific and should have low false positive.
- It should have high positive and negative predictive value.
- 100% accuracy in differentiating between healthy individuals and tumor patients.
- It should be able to differentiate between neoplastic and non-neoplastic disease and show positive correlation with tumor volume and extent.
- It should predict early recurrence and have prognostic value.
- It should be clinically sensitive i.e., detectable at early stage of tumor.
- Its levels should be preceding the neoplastic process, so that it should be useful for screening early cancer.
- It should be either a universal marker for all types of malignancies or specific to one type of malignancy.

- It should be easily assayable and be able to indicate all changes in cancer patients receiving treatment.
- Should not be very costly.

(Malati, 2007)

B-Classifications of tumor markers:

(1) Epithelial markers

- Cytokeratins (CK)
- Epithelial membrane antigen (EMA)
- Oncofetal antigens
    a. Alpha-fetoprotein (AFP)
    b. Carcinoembryonic antigen (CEA)
- Desmoplakin

(2) Muscle antigens

- Desmin
- Actin
- Myoglobin
- Myosin

(3) Vascular antigen

- Cluster Of Differentiationmolecule (CD 34)
- CD 31

(4) Neural antigens

- Neuron specific enolase (NSE)
- Glial fibrillary acidic protein (GFAP)
- Synaptophysin
- Nerve growth factor receptor

(5) Prognostic Markers as AFP, PSA, and CA125

(6) Cell adhesion molecules

- Cadherins
- Integrins
- Selectins

(7) Proliferation markers

- Proliferating Cell Nuclear Antigen (PCNA)
- Ki67

(8) Enzymes and isoenzymes

- Prostatic acid phosphatase (PAP)
- Prostate Specific Antigen (PSA)
- Placental Alkaline Phosphatase (PALP)
- Lysozyme

(9) Protein

- Ferritin
- Glycoprotein
- Beta protein
- Immuno globulins

(10) Hormone receptors

- Estrogen receptor (ER)
- Progesterone receptor (PR)

(Babu et al., 2012).