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REVIEW ARTICLE

Organ Specific Tumor Markers: What's New?

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Abstract Tumor markers are molecules produced in the body in response to cancer. An ideal tumor marker should have high sensitivity and specificity, should be cheap, and should be easily detected in body fluids. Identification of novel markers is important and it is expected that with the advent of newer technologies, more reliable markers will be discovered. This review discusses the currently available tumor markers for different malignancies.

Keywords Immunohistochemical markers · Proteomic markers · Molecular markers

Introduction

Tumor markers are molecules produced by tumor cells or other cells of the body in response to cancer or certain benign conditions. Most tumor markers are secreted into blood and may be estimated in blood, but they may also be measured in urine, tissues etc. Tumor markers may be used for diagnosis, staging, and prognosis of cancer; they may also be used for monitoring treatment response as well as to check for cancer recurrence. There are a large number of tumor markers which are used for different types of cancers; many tumor markers may also be elevated in more than one type of cancer. A summary of the traditional tumor markers is given in Table 1.

Recent years have witnessed the emergence of a large number of tumor markers. Earlier there were two major tools for estimating tumor markers; Enzyme-Linked Immuno Sorbent Assay (ELISA) and Radioimmunoassay (RIA) [1]. Immunohistochemical markers (Estrogen and progesterone receptors, ER, and PR), molecular tools (TMPRSS2: ERG fusion genes, gene expression profiles) as well as proteomic tools are now employed to quantify cancer markers. Some of these markers have been accepted for use in clinical practice (e.g., ER and PR, gene expression profiling in breast cancer). Many more are likely to be introduced into the market in the near future [2].

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Classification of Tumor Markers

There are different ways of classifying cancer markers [1]. One traditionally accepted way of classification is into

1. Oncofetal antigens (CEA, AFP)
2. Glycoprotein antigens or carbohydrate antigens (CA 125, CA 19.9, CA 15-3)
3. Enzymes (PSA, ALP, NSE)
4. Hormone receptors (ER, PR)
5. Hormones (β-hCG, calcitonin)
6. Other biomolecules (VMA, 5HIAA).

Tumor markers may also be classified based on

1. Biochemical structure
2. Function
3. Combination of biochemical structure and function, and
4. Discovery of oncofetal antigens.

Why New Tumor Markers are Needed

An ideal tumor marker should have high sensitivity and specificity [3]. However, in practice the sensitivity and specificity of individual markers may vary widely. Table 2

Table 1 Traditionally used tumor markers in different types of cancers

Type of cancer	First line markers	Second line markers
Kidney cancer	Nil	Carbohydrate antigen 50 (CA 50), mucin-like cancer associated antigen (MCA)
Bladder cancer	Tissue polypeptide antigen (TPA), CA 19.9	Nil
Head & neck cancer	Nil	Squamous cell carcinoma antigen (SCC), tissue polypeptide antigen (TPA)
Lung cancer (Small cell cancer)	Neuron specific enolase (NSE)	Nil
Lung cancer (Epidermoid cancer)	Cytokeratin fragment 21.1 (Cyfra21.1)	Nil
Lung cancer (Adenocarcinoma)	Carcinoembryonic antigen (CEA)	Nil
Ovarian cancer (Choriocarcinoma)	Alpha fetoprotein (AFP), β human chorionic gonadotropin (β-hCG)	Nil
Ovarian cancer (Serous cancer)	CA 125	Nil
Ovarian cancer (Mucinous cancer)	CEA	Nil
Uterine cancer (Hydatidiform mole)	β-hCG	Nil
Uterine cancer (Squamous cell cancer)	SCC	Nil
Uterine cancer (Adenocarcinoma)	CEA	Nil
Gastric cancer	CA 19.9, CA 72.4	CEA
Esophageal cancer	Nil	SCC, TPA, CEA
Testicular cancer	AFP, β-hCG	Nil
Colorectal cancer	CEA	CA 19.9, TPA
Prostate cancer	Prostate specific antigen (PSA), prostatic acid phosphatase (PAP)	Nil
Pancreatic cancer	CA 19.9	CEA
Liver cancer	AFP	Ferritin
Melanoma	S-100	NSE

Table 2 Sensitivity and specificity of important tumor markers [76]

Tumor marker	Primary cancer type	Sensitivity (%)	Other cancers	Non-cancerous conditions
CA 27.29	Breast	33 (early), 67 (late)	Colon, lungs, liver, stomach, pancreas, ovary, prostate	Breast, liver and kidney diseases, ovarian cyst
CEA	Colorectal	25 (early), 75 (late)	Breast, lung, stomach, pancreas, bladder, thyroid, head and neck, cervix, liver, lymphoma, melanoma	Cigarette smoking, peptic ulcer, inflammatory bowel disease, pancreatitis, cirrhosis, biliary obstruction, hypothyroidism,
CA 19.9	Pancreas	80–90	Colon, esophagus, liver	Pancreatitis, biliary diseases, cirrhosis
AFP	HCC, GCT	80 HCC	Stomach, pancreas, biliary	Cirrhosis, viral hepatitis, pregnancy
β-hCG	Non-seminomatous germ cell tumors, gestational trophoblastic tumors	85	Rarely GI cancers	Hypogonadal states, marijuana
CA 125	Ovarian	50 (early), 85 (late)	Endometrium, fallopian tube, breast, lug, esophagus, stomach, liver, pancreas	Menstruation, pregnancy, fibroids, ovarian cysts, pelvic inflammation, cirrhosis, ascites, pleural and pericardial effusion, endometriosis
PSA	Prostate	75	None	Prostatis, benign prostate hypertrophy, prostate trauma, after ejaculation

gives the sensitivity and specificity of some common markers. The drawbacks of available tumor markers [4] are

1. Early detection is difficult, since low levels are seen in normal individuals
2. Large volume of cancer needed for significant elevation above normal
3. Some people with cancer never get elevated levels
4. Elevated levels may be seen in non-cancerous conditions

There are a number of physiological and pathological factors which can affect results [4]; for example,

1. Renal failure, cholestasis—Increased levels of many markers even in non-cancerous conditions
2. Rheumatic diseases—CA 19.9 elevation
3. Drugs—e.g., anti androgens—PSA elevation
4. Rectal examination, trans uretheral manipulation—PAP, PSA elevation
5. Cigarette smoking—CEA elevation

To overcome these shortcomings of many of the traditional markers, there is a need for newer markers.

This review briefly describes the recent as well as other accepted markers in cancers of different organs like breast, ovary, pancreas, colorectum, lung, etc. As there are large number of markers reported [5–7], emphasis is on those markers which are approved by international cancer agencies for clinical use and other candidate markers, i.e., highly promising markers, not yet accepted widely. Focus will be on organ specific tumor markers.

Gynecological Cancers

Major gynecological malignancies are ovarian cancer, uterine cervical cancer, endometrial cancer, and trophoblastic tumors. Most of the tumor markers used are glycoproteins and they are detected using monoclonal antibodies. Tumor markers having good sensitivity and specificity, as well as those that can influence decisions between alternative plans for management are very useful [8]. Proteomic techniques are employed to detect new markers [9]. HPV and HSV viruses were detected in cervical cancer in South India [10]. Major gynecological cancer markers are summarized in Table 3.

CA-125

CA-125 was initially discovered in 1980s and it has been widely used in the diagnosis of epithelial ovarian cancer [11]. It may however also be elevated in a number of other inflammatory conditions including endometriosis, adenomyosis, pelvic inflammatory disease, menstruation, uterine fibroids, and benign cysts. It may also be elevated in cancers of endometrium, fallopian tube, pancreas, breast, colon, and lungs. CA-125 level is used to monitor the progress of ovarian cancer. Increase is a predictor of progression and rapid decrease is an indicator of favorable outcome. Rate of decrease is an independent prognostic factor. Along with clinical examination and trans-vaginal ultrasonography, it can be used for early detection of ovarian cancer.

β-Human Chorionic Gonadotropin

β-Human chorionic gonadotropin is elevated in fetal tissues and a variety of gynecological cancers. Urinary gonadotropin fragment (which is the core β fragment excreted in urine) and lipid-associated sialic acid levels are elevated in up to 60% of patients with endometrial cancer. Tumors showing elevated β-hCG levels include choriocarcinoma of the uterus, embryonal carcinomas, polyembryomas, mixed cell tumors, and, rarely, dysgerminomas. Along with human placental lactogen (hPL), it is a useful marker for trophoblastic disease (partial and complete hydatidiform moles, gestational choriocarcinoma etc.) [12].

Table 3 Gynecological cancer markers

Important gynecological markers are
Alpha fetoprotein (AFP)
β Human chorionic gonadotropin (β-hCG)
Cancer antigen (CA-125)
Carbohydrate antigen 19-9
Carcino embryonic antigen (CEA)
Estradiol
Ferritin
Human telomerase reverse transcriptase (hTERT)
Inhibin
Mullerian inhibitory substance (MIS)
Topoisomerase II
Urinary gonadotropin fragment
Other emerging markers are
Cyclin E
HE4
Insulin like growth factor binding protein-3
Interleukin 8
Lysophosphatidic acid
Macrophage colony stimulating factor
Mesothelin
Osteopontin
OVX1
Tumor associated trypsin inhibitor
Vascular endothelial growth factor (VEGF)

Alpha Fetoprotein

Along with β-hCG, AFP (alpha fetoprotein) is used in the management of non-seminomatous germ cell tumors [13]. Persistent elevation of AFP and β-hCG indicates worse prognosis. In patients with extragonadal disease or metastasis at the time of diagnosis, AFP values in excess of 10,000 ng/ml or β-hCG levels above 50,000 mIU/ml is a poor prognostic sign. Similarly staged patients with lower AFP and β-hCG levels have a very high cure rate. AFP and β-hCG together is also used in evaluation of poorly differentiated metastatic cancers.

Carbohydrate Antigen 19-9

Elevated in 35% of patients with endometrial cancer. It is mainly used in follow-up evaluation of borderline ovarian tumors. It is not specific for ovarian cancer [11].

Cancer Antigen 27-29

Elevated in cancers of colon, stomach, kidney, lung, ovary, pancreas, uterus, and liver. However, it is also elevated in first-trimester pregnancy, endometriosis, ovarian cysts, benign breast disease, kidney disease, and liver disease [14].

Human Telomerase Reverse Transcriptase

Human telomerase reverse transcriptase (hTERT) is used as a biomarker in ovarian and uterine cancers. It could probably have a role in the early diagnosis of cervical cancer and cervical intra-epithelial neoplasia (CIN). Upregulation of hTERT may be a pathogenic mechanism in CIN [15].

Inhibin

It reaches a peak in the follicular phase of menstrual cycle and it is not detected in serum in post-menopausal women. It can be used for the diagnosis of primary and recurrent granulosa cell tumors and mucious ovarian epithelial tumors [16]. There are two forms inhibin A and B; both are elevated in these tumors. Free alpha sub-unit of inhibin can also be measured [17].

Estradiol

It is also used in granulosa cell tumors, but is not sensitive enough; about 30% of tumors do not produce estradiol. It can be used to detect recurrence [12].

Mullerian Inhibitory Substance (MIS)

Like inhibin it is undetectable in serum in post-menopausal women. It is highly specific for ovarian granulosa cell tumors [18].

Topoisomerase II

It is a promising marker for advanced epithelial ovarian cancers [19].

Other recent markers in ovarian cancer include lysophosphatidic acid (a lipid found to be elevated in serum and ascites fluid), mesothelin, HE4, osteopontin, vascular endothelial growth factor (VEGF), and interleukin 8, macrophage colony stimulating factor, and different kallikreins. These markers though promising are yet to be approved in actual clinical scenario [20].

Breast Cancer

There are many accepted tumor markers used in breast cancer [21, 22]. Tumor markers used in screening, treatment, and surveillance of breast cancer are CA 15-3 [23], CA 27.29 [14], carcinoembryonic antigen (CEA) [24], estrogen-receptor (ER) [25, 26], progesterone receptor (PR) [25], human epidermal growth factor receptor 2 (HER2) [27], urokinase plasminogen activator (uPA) [28], plasminogen activator inhibitor 1 (PAI-1) [28], and certain multiparameter assays for gene expression (Mammoprint, Onco Type DX etc.) [29]. Certain markers like DNA ploidy by flow cytometry [30], p53 [31], cathepsin D [32], cyclin E [33], proteomics [34], detection of bone marrow micrometastases [35], and circulating tumor cells (CTCs) [36] are considered, but no evidence is available which would recommend them for routine clinical use. Breast cancer markers are summarized in Table 4.

BRCA1/2 gene mutations have been described in familial breast cancer patients. Our own research has identified mutations in BRCA1 and BRCA2 genes including a high incidence of 185delAG mutation in BRCA1 gene [38–40]. We have studied the role of ErbB2 (HER2) and associated clinicopathological parameters in the Indian population and found that ErbB2 is overexpressed in 43.2% of subjects [41].

Estrogen and progesterone receptors

Estrogen-receptor and PR should be measured on every primary invasive breast cancer and may be measured on metastatic lesions if the results would affect treatment planning. Steroid hormone receptor status should be used to identify patients most likely to benefit from endocrine

Table 4 Breast cancer markers

Commonly employed markers are
CA 15-3
CA 27.29
CEA
Estrogen and progesterone receptors (ER, PR)
HER2
uPA
PAI-1
Multi-parametric gene expression assays
Other potential markers are
DNA ploidy (Flow cytometry)
p53
Cathepsin D
Cyclin E
Proteomic markers
CTC
Bone marrow micrometastasis
Ki-67
P27
P21
Thymidine kinase
Topoisomerase II

therapies. In patients with ductal carcinoma in situ (DCIS) who are candidates for hormonal therapy, data are insufficient to recommend routinely measuring ER and PR. In both premenopausal and post-menopausal patients, steroid hormone receptor status should be used to identify patients most likely to benefit from endocrine forms of therapy in both the early breast cancer and metastatic disease settings. In patients with DCIS who are candidates for hormonal therapy, data are insufficient to recommend routine measurement of ER and PR for therapy recommendations [25, 26].

HER-2/neu

To guide selection of trastuzumab (herceptin) in the adjuvant or metastatic setting, HER2 expression or amplification should be evaluated in every primary invasive breast cancer, either at the time of diagnosis or at the time of recurrence [27]. HER2 may be useful to predict response to specific chemotherapeutic agents. Based on level II evidence, overexpression of HER2 (3+ by protein or > 2.0 fluorescent in situ hybridization [FISH] ratio by gene amplification) identifies patients who may benefit more from anthracycline-based adjuvant therapy. HER-2/neu levels are overexpressed in about 15–40% of breast cancers. It indicates highly aggressive tumors but they are responsive to trastuzumab. Tumors which are HER-2/neu negative will not respond to trastuzumab therapy.

Immunohistochemistry Based Markers

Immunohistochemistry based markers of proliferation are new tests. Present data are insufficient to recommend measuring markers of proliferation to assign patients to prognostic groups. These include Ki67, cyclin D, cyclin E, p27, p21, thymidine kinase, and topoisomerase II [37].

uPA and PAI-1

Urokinase plasminogen activator and PAI-1 as markers for breast cancer are recent introductions to laboratory medicine [28]. In patients with newly diagnosed, node-negative breast cancer, uPA and PAI-1 measured by ELISA on 300 mg or more of fresh or frozen breast cancer tissue may be used to determine prognosis. Especially in hormone receptor—positive women who will receive adjuvant endocrine therapy, low levels of both markers are associated with a sufficiently low risk for recurrence that chemotherapy will only confer minimal additional benefit. Compared with observation alone, cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)-based adjuvant chemotherapy offers substantial benefit in patients with high-risk for recurrence, based on high levels of uPA and PAI-1.

Cyclin E

Cyclin E fragments as markers for breast cancer are also new [33]. Currently available data are insufficient to recommend use of whole-length or fragment measurements of cyclin E to manage patients with breast cancer.

Proteomic Analysis

Proteomic analysis for breast cancer is also a new development; present data are insufficient to support use of proteomic patterns to manage breast cancer [34].

Multiparameter Analysis of Gene Expression

Multiparameter analysis of gene expression for breast cancer is new [29]. The Onco *type* DX assay (Genomic Health Inc, Redwood City, CA) can be used to predict the risk for recurrence in newly diagnosed patients with node-negative, ER-positive breast cancer who are treated with tamoxifen. Onco *type* DX may help identify patients who should most benefit from adjuvant tamoxifen and who may not require adjuvant chemotherapy. Patients with high

recurrence scores seem to benefit relatively more from adjuvant chemotherapy with CMF than from tamoxifen.

Bone Marrow Micrometastases

Bone marrow micrometastases as markers for breast cancer are a new topic to the guidelines [35]. Currently available evidence is insufficient to recommend evaluation of bone marrow micrometastases for management of patients with breast cancer.

CTC Assays

Circulating tumor cell (CTC) assays as a marker for breast cancer is also a new topic to the guidelines [36]. CTCs should not be used to diagnose breast cancer or to guide any treatment decisions in patients with breast cancer. Cell Search Assay test (Veridex, Warren, New Jersey) for CTC is not recommended in patients with metastatic breast cancer.

Male Testicular Germ Cell Tumors

Germ cell tumors (GCTs) constitute 90–95% of all primary testicular tumors and are divided into the categories of seminoma and nonseminoma, the latter comprises all tumors that are not pure seminoma. Male testicular GCTs are one of the few malignancies for which specific biochemical tumor markers have been identified that are simple to measure in serum and useful in the diagnosis and management of the disease. The prognostic utility of serum tumor markers in GCTs is reflected by the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system, which includes a separate category to account for the elevation of three markers: alpha fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH) [42, 43].

Among the other markers in GCTs are gamma-glutamyltranspeptidase (GGT), an enzyme found primarily in the liver and is most commonly used as a marker of disease of the liver, biliary system, and pancreas. Up to one-third of patients with seminomas also have elevated serum GGT. Placental-like alkaline phosphatase (PLAP) is often elevated in patients with seminomas, but increased PLAP concentrations are also associated with a number of other malignancies, as well as smoking. The lack of sensitivity and specificity for these and other investigated substances limit their clinical utility. Germ cell tumor markers are given in Table 5.

Table 5 Germ cell tumors

Commonly employed markers are
AFP
hCG
LDH
Other markers are
GGT
PLAP

Prostate Cancer

Prostate specific antigen (PSA) is the most useful marker in prostate cancer [44]. PSA doubling time is used to assess risk as well as a guide treatment decisions. However PSA has many limitations. Prostatic acid phosphatase (PAP) is very useful in monitoring recurrence. Molecular markers such as *HER2* amplification [45], expression of the proto-oncogene *BCL-2*, [46] and the *TMPRSS2-ERG* fusion gene [47] remain to be validated and are not currently recommended for routine testing in the NCCN Guidelines. Table 6 gives the prostate cancer markers.

Colorectal Cancer

Carcinoembryonic antigen is a longstanding marker of prognosis and recurrence. However it is nonspecific and can be elevated in numerous benign or malignant conditions. Thus, an elevation in CEA is not diagnostic. Nevertheless, approximately 80% of patients with metastatic disease demonstrate CEA elevation. In the NCCN Guidelines, measurement of CEA is recommended at baseline in all patients with a diagnosis of colorectal cancer and after completion of adjuvant therapy as surveillance for recurrence [48].

Mutations in *KRAS* gene in colorectal tumors were identified as predictive of non-response to the monoclonal antibodies cetuximab and panitumumab, targeting the epidermal growth factor receptor (EGFR). In the NCCN Guidelines for colon and rectal cancers, *KRAS* mutation analysis is now recommended in all patients with metastatic colorectal cancer upon diagnosis of stage IV disease

Table 6 Prostate cancer markers

Commonly employed markers are
PSA
PAP
Other markers are
HER-2
BCL-2
TMPRSS2-ERG fusion gene study

and before treatment with cetuximab or panitumumab is considered. Patients with tumors harboring a *KRAS* mutation should not be treated with either of these agents [49].

The NCCN Guidelines recently incorporated tumor *BRAF* V600E mutation analysis as an optional test for patients with newly diagnosed *KRAS*-nonmutated metastatic colorectal cancer to facilitate prediction of responsiveness to EGFR-targeted therapies. *BRAF* V600E mutation may be associated with poor prognosis, which may confound understanding about its value in predicting responsiveness to EGFR inhibitors. The current NCCN Guidelines acknowledge the inconsistencies in the current data surrounding *BRAF* V600E mutation as a predictive marker [49].

Microsatellite instability (MSI) reflects a deficiency in a mismatch repair protein (MMR) function, most commonly MLH1, MSH2, MSH6, and PMS2. MSI and MMR testing are both accepted for the diagnosis of Lynch syndrome (hereditary nonpolyposis colorectal cancer) in patients and families. The NCCN Guidelines, therefore, include a statement noting that such testing should be considered in all patients diagnosed with colorectal cancer before the age of 50 years [50].

HER2 overexpression, by immunohistochemistry or FISH, is detected in approximately 10–20% of patients who have gastroesophageal cancers. In hepatocellular carcinoma (HCC), the glycoprotein AFP is measurable from serum in approximately 70% of cases, although it is neither a sensitive nor a specific diagnostic test for HCC. Nevertheless, results of AFP testing can be useful in conjunction with other test results to guide management of patients for whom a diagnosis of HCC is suspected. Serum AFP measurement is recommended in the NCCN Guidelines as a screening tool for patients at risk for HCC, to aid in diagnosis in patients with a suspicious liver lesion, and for surveillance after surgery, locally ablative treatments, or transplant in patients with confirmed HCC [51]. Table 7 gives the common colorectal markers.

Pancreatic Cancer

The major useful tumor marker for pancreatic carcinoma is still carbohydrate antigen 19-9 (CA 19-9). CA 19-9 is a murine monoclonal antibody originally made against colorectal cancer cells. The CA 19-9 antigen is a sialylated oligosaccharide that is most commonly found on circulating mucins in cancer patients. It is also normally present within the cells of the biliary tract and can be elevated in acute or chronic biliary disease. Some 5–10% of patients lack the enzyme necessary to produce CA 19-9. In the absence of biliary obstruction, intrinsic liver disease or benign pancreatic disease, a CA 19-9 value greater than 100 U/mL is highly specific for malignancy, usually pancreatic [52].

Table 7 Colorectal cancer markers

Common markers are
CEA
KRAS mutations
BRAF V600E mutation
Microsatellite instability
HER-2 overexpression

Evaluation of CA 19-9 levels has been used as an adjunct to imaging studies for helping determine the resectability potential of pancreatic carcinoma. Fewer than 4% of patients with a CA 19-9 level of more than 300 U/ml have been found to have resectable tumors. CA 19-9 is least sensitive for small early-stage pancreatic carcinomas and has not proven to be effective for the early detection of pancreatic cancer or as a screening tool. An elevated CA 19-9 level is found in 0.2% of an asymptomatic population older than 40 years. 80% of these are false-positive results. If only symptomatic patients are studied, 4.3% have elevated CA 19-9 levels. Two-thirds of these results are false-positive. It however has growing importance in the staging and follow-up of patients with this disease. Patients presenting with low levels of CA 19-9 (<100 IU) are unlikely to have occult metastatic disease. A falling CA 19-9 seems to be a useful surrogate finding for clinical response to the therapy. If biliary obstruction is not present, a rising CA 19-9 suggests progressive disease. Preoperative CA 19-9 levels may be of prognostic value with high levels indicating poorer outcome and less chance of resectability. Preoperative values above 50 U/ml have been shown to be associated with higher chances of recurrence [52].

Carcinoembryonic antigen is a high molecular weight glycoprotein found normally in fetal tissues. It has commonly been used as a tumor marker in other gastrointestinal malignancies. Only 40–45% of patients with pancreatic carcinoma have elevations in CEA levels. Multiple other benign and malignant conditions can lead to elevated CEA levels; thus, CEA is not a sensitive or specific marker for pancreatic cancer [53].

Many other tumor markers have been studied in pancreatic cancer, but none has yet been shown to have general clinical utility in this disorder. As with all cancers, there is growing interest in molecular diagnosis using powerful techniques such as gene expression microarrays and proteomics. These novel tests are adding to our understanding of the basic defects causing pancreatic neoplasms and pathobiology. However, these are still research tools at present [54].

Lung Cancer

Several molecular diagnostic markers are of value in patients with non-small cell lung cancer (NSCLC). The most important of these, EGFR overexpression or mutation has been shown to positively predict response to erlotinib or gefitinib, which are EGFR-targeted tyrosine kinase inhibitors. The incidence of mutation or overexpression is influenced by ethnicity, and appears to be present in 30–40% of Asian patients vs. 10–15% of North American patients. NCCN Guidelines now recommend that *EGFR* mutation status be considered (by direct sequencing for mutation, gene copy number testing by FISH, or immunohistochemistry for protein overexpression) when selecting first line therapy for patients with metastatic or recurrent NSCLC, including patients with poor performance status [55, 56]. In addition there are a number of other traditional markers which are summarized in Table 1.

Head and Neck Cancers

HPV Screening

The NCCN Guidelines now recommend testing for HPV in patients with oropharyngeal cancers. The high-risk oncogenic HPV subtype HPV-16 is strongly associated with the development of oropharyngeal and tonsillar squamous cell carcinomas, independent of smoking and alcohol exposure; HPV-16 is associated with most head and neck tumors; other oncogenic HPV subtypes may also cause head and neck cancer (e.g., HPV-18, -31, -33, -35). Patients with HPV-related tumors appear to have significantly improved response rates and overall prognosis [57]. SCC and TPA are used as second line markers (See Table 1).

Thyroid Cancer

Serum thyroid-stimulating hormone (TSH) is a very sensitive measure for hyperthyroidism/hypothyroidism. A sensitive TSH assay is useful in the evaluation of solitary thyroid nodules. A low serum TSH value suggests an autonomously functioning nodule, which typically is benign. However, malignant disease cannot be ruled out on the basis of low or high TSH levels. Other thyroid function tests are usually not necessary in the initial workup [58].

Serum thyroglobulin measurements are not helpful diagnostically because they are elevated in most benign thyroid conditions. Serum thyroglobulin level is a tumor marker for papillary, follicular, and Hürthle cell thyroid cancers [58].

Thyroid-stimulating hormone, thyroglobulin, and anti-thyroglobulin antibody levels are measured postoperatively to guide decision-making regarding the use of radio-iodine, to adjust dosage of levothyroxine, and to monitor for recurrence [58].

Elevated serum calcitonin levels are highly suggestive of MTC. Serum calcitonin measurement, which was once the mainstay in the diagnosis of FMTC, has been replaced by sensitive polymerase chain reaction (PCR) assays for germline mutations in the *RET* proto-oncogene [59]. These mutations are present in patients with MEN 2A, MEN 2B, and FMTC [60]. However, calcitonin and the more sensitive pentagastrin-stimulated calcitonin are used as tumor markers to monitor patients who have been treated for MTC. Because of the low incidence of MTC overall, testing of serum calcitonin is not a cost-effective screening tool in the primary workup of thyroid nodules. In patients with sporadic medullary thyroid carcinoma, as well as in those suspected to have a familial syndrome (such as multiple endocrine neoplasia type 2A), testing for *RET* proto-oncogene mutations is recommended to identify new kin at risk, and to determine the likelihood of other conditions (such as pheochromocytoma and parathyroid disease). Indices of prognosis, serum calcitonin and CEA levels, should be checked both at baseline and after surgery as surveillance for patients with medullary thyroid carcinoma. Postoperative calcitonin levels correlate with recurrence risk and survival.

Lymphomas/Leukemias

For chronic myeloid leukemia (CML), BCR–ABL gene testing can be done in blood and bone marrow [61]. The gene is used for diagnosis and follow-up. B-2-microglobulin (B2M) is elevated in chronic lymphocytic leukemia (CLL) and some lymphomas. B2M may also be elevated in multiple myeloma and some non-cancerous conditions like renal and hepatic diseases. Higher B2M signifies poor prognosis [62]. Abnormal karyotype was identified in more than 50% of all in South India [63].

There are about 80 different 'CD markers' present on the surface of lymphocytes which can be detected in lymphomas (Hodgkin's/Non-Hodgkin's) by immunohistochemistry and/or flow cytometry [64]. Totally there are about 30 different types of lymphomas and these CD markers serve as molecular signatures to diagnose each type. Additional molecular tests include kappa/lambda, cyclin D1, TCR gene rearrangements [65], antigen receptor gene rearrangements [66], cytogenetic/FISH panel etc.

Bladder Cancer

Bladder tumor antigen (BTA) and NMP22 are two tumor markers done for bladder cancer [67]. Urinary tumor markers are not recommended. The standard tests for diagnosis and follow-up are however cystoscopy and urine cytology. For advanced bladder cancer, CEA, CA 125, CA 19-9, and TPA are elevated and are used. These markers can be used for follow-up as well [67].

Melanoma

Potential markers for melanoma include TA-90, CEA-CAM, ICAM-1, osteopontin, MIA, GDF-15, TIMP-1, and S100B. Higher levels of these markers are found in metastatic melanoma [68].

Gastric Cancer

Tumor markers are less promising for gastric cancer. Available markers are CEA, CA 72-4, CA 19-9, and HER2 [69, 70]. These are not specific for stomach cancers. Defective IL-2 R gene expression is noted in gastric cancer [71].

Oral Cancer

Viruses like HSV, HPV, and HHV-6 are implicated in the pathogenesis of oral cancers [72]. p53 can be used as a tumor marker to detect oral cancer early [73]. Jackfruit lectin can be used in the differential diagnosis of premalignant and malignant lesions of oral cavity, based on the differences in nature and intensity of binding [74]. Chromosomal abnormalities are also noted in squamous cell carcinoma of oral cavity [75].

Summary

Recent years have seen the emergence of a whole new lot of biomarkers. These have been made possible due to the evolution of newer technologies like proteomics and molecular analysis. Many of these markers are very promising. The traditional markers used widely at present have many limitations. Many of these may be replaced by the newer markers in the future. One would hope that emerging techniques would lead to the identification of markers with high specificity and sensitivity and these in turn would allow the earlier diagnosis of cancer, and improved cancer care.

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