COLLECTIVE REVIEW

THE CLINICAL USEFULNESS AND LIMITATIONS OF TUMOR MARKERS

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DURING THE PAST TWENTY YEARS, tumor markers have been the focus of extensive research. Since the discovery of α-fetoprotein (AFP) and carcinoembryonic antigen (CEA) in the 1960s, numerous markers of human malignant lesions have been proposed for detecting, localizing and monitoring the response of the tumor to therapy. In this review, tumor marker is defined as a blood-borne substance found in excessive quantity or under abnormal conditions in patients with cancer. Tumor-associated antigens of the cell surface and intracellular proteins that are specific to malignant cells are not discussed.

A variety of circulating substances are classified as tumor markers. Current tumor markers include oncofetal antigens, placental proteins, hormones, enzymes, catecholamine metabolites and other molecular species (Table I). Classically, tumor markers are synthesized by malignant cells and released into the bloodstream; however, markers may be produced by host tissues in response to direct invasion or metabolic changes induced by the tumor.

Many theoretical applications exist for tumor markers in clinical medicine. Clinically important uses of these markers include early detection of the tumor, differentiating benign from malignant conditions, evaluating the extent of the disease, monitoring the response of the tumor to therapy and predicting the recurrence of the tumor. Various tumor markers have been used with variable success to accomplish these goals; however, no ideal tumor marker currently exists to satisfy all clinical applications with adequate sensitivity and specificity. This review critically analyzes the clinical usefulness and limitations of currently available tumor markers.

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CARCINOEMBRYONIC ANTIGEN

CEA is a complex glycoprotein with a molecular weight of approximately 180,000 daltons (1). This antigen was first discovered in patients with adenocarcinoma of the colon in 1965 (2). CEA represents a heterogeneous group of molecular species that consist of single polypeptide chains with varying carbohydrate components. The ratio of protein to carbohydrate varies from 1:1 to 1:5 in CEA molecules from different tumors (1, 3). CEA is metabolized primarily by the liver with a circulating half-life that ranges from one to eight days (4). Hepatic diseases, including extrahepatic biliary obstruction, intrahepatic cholestasis and hepatocellular disease, may impede clearance rates and increase serum concentrations of CEA (5, 6).

Normally, CEA is present in the fetal intestine, pancreas and liver during the first two trimesters of gestation (7). Since the development of a sensitive radioimmunoassay for this marker, CEA or CEA-like substances have been detected in a variety of non-neoplastic, nonfetal tissues. Normal colonic mucosa and pleural and lactating mammary tissue bind to anti-CEA antiserum (8, 9); however, the quantity of CEA or CEA-like molecules expressed in these tissues is much less than that observed in malignant tumors.

The normal range of concentrations of CEA, as determined by radioimmunoassay, is from zero to 2.5 to 3.0 nanograms per milliliter (10). Elevated serum levels of CEA may be found in a variety of benign and malignant conditions other than carcinoma of the colon. Benign conditions that cause elevated levels of CEA include cigarette smoking, bronchitis, emphysema, gastritis, gastric ulcer,

hepatic disease, pancreatitis, polyps of the colon and rectum, diverticulitis, Crohn's disease, benign prostatic hypertrophy and renal disease (11–13). In patients with no known carcinoma, increased levels of CEA have been detected in 13 per cent of heavy cigarette smokers, 15 to 20 per cent of patients with pancreatitis or polyps of the colon and rectum and 10 to 50 per cent of patients with inflammatory intestinal disease (14, 15). Approximately 50 per cent of patients with severe hepatocellular disease or biliary obstruction have significant elevations of serum levels of CEA secondary to impaired clearance (14, 16). In these benign conditions, elevated levels of CEA are usually transient and moderate in magnitude with rare instances of levels of CEA above 10 nanograms per milliliter.

A variety of epithelial carcinomas produce CEA in addition to adenocarcinoma of the colon and rectum. Such tumors include carcinoma of the pancreas, lung, breast, stomach, thyroid gland and female reproductive tract (8, 17, 18). Of these noncolonic carcinomas, levels of CEA are most commonly elevated in carcinoma of the pancreas (65 to 90 per cent) and lung (52 to 77 per cent) (17, 19). Approximately one-half of the patients with carcinoma of the breast, stomach and thyroid gland demonstrate increased serum concentrations of CEA (19). Twenty-five to 40 per cent of patients with malignant lesions of the female reproductive tract, including carcinoma of the cervix uteri, endometrium and ovary, have elevated levels of CEA (8, 18).

CEA has been most extensively investigated in patients with carcinoma of the colon and rectum. The role of CEA in screening for malignant disease, predicting prognosis and monitoring the response of the tumor to therapy has been studied. The CEA assay is neither specific nor sensitive enough to be used to screen patients for malignant conditions. In 1976, the level of CEA was determined in 2,372 asymptomatic Australian patients. Of 73 who were found to have elevated levels of CEA, only nine were diagnosed with carcinoma. In seven of those nine, malignant disease was diagnosed before determining serum concentration of CEA. Thus, in only two of 2,372 (0.001 per cent) asymptomatic patients did detection of an elevated level of CEA lead to an earlier diagnosis of malignant disease. Furthermore, carcinoma was found in 25 of 2,372 patients (1.0 per cent) with normal levels of CEA.

Results of subsequent studies have demonstrated that the production of CEA by early, localized tumors is too low for testing of levels of CEA to be a useful screening tool. Levels of CEA are elevated in a minority of patients with localized malignant lesions originating in the colon (20 to 40 per cent), breast (15 per cent) and lung (45 per cent) (12, 19, 21). Thus, CEA is not useful for purposes of screening in asymptomatic patients or for detection of disease in patients with early stage malignant lesions.

In patients with carcinoma of the colon and rectum, elevation of CEA levels does not correlate with tumor differentiation and stage of disease. In general, patients with well differentiated carcinoma of the colon often have significant elevation of CEA levels; in contrast, patients with poorly differentiated tumors typically have normal levels of CEA (22). Immunohistologic techniques demonstrate a similar difference in staining for CEA within tumor tissue between well differentiated and anaplastic malignant lesions (23). Results of numerous studies have shown a positive correlation between the incidence of elevation of CEA level and stage of carcinoma of the colon and rectum. In 1972, levels of CEA were analyzed in 88 patients with carcinoma of the colon and rectum (24). Significant elevations of CEA occurred in 44.8, 75.8, 60.0 and 100.0 per cent of patients with Dukes' A, B, C and D stages, respectively. In 1978, preoperative levels of CEA were reported in 358 patients with carcinoma of the colon and rectum (25). In patients with primary carcinoma, above normal levels of CEA were found in 27.5, 45.1, 74.6 and 83.8 per cent of patients with Dukes' A, B, C and D tumors, respectively. One hundred and twenty-five of 155 patients (80.6 per cent) with local or distant recurrence had significantly elevated serum levels of CEA.

The magnitude of the elevation of levels of CEA correlates with stage of disease to a lesser extent. In 1983, mean levels of CEA of 7.8, 30.3, 58.1 and 134.3 nanograms per milliliter were reported in patients with stages A, B, C and D, respectively (26). Additional reports have demonstrated the greatest level of CEA in patients with hepatic metastases (19, 25). Tremendous variability exists, however, between individual patients depending upon both tumor-specific and host-specific factors.

The measurement of the level of CEA is most useful in predicting prognosis and monitoring response to therapy in patients with carcinoma of the colon and rectum. Results from numerous studies have demonstrated a positive correlation between the preoperative level of CEA and the risk of recurrence after surgical resection of car-

cinoma of the colon and rectum. In 1979, a reported 25 per cent recurrence rate in patients with carcinoma of the colon and rectum with normal preoperative levels of CEA was compared with a 50 per cent recurrence rate in patients with similar stage but with elevated levels of CEA (19). In 1978, the importance of preoperative concentration of CEA, independent of Dukes' stage of disease, was clearly demonstrated (25). In 55 patients with Dukes' B lesions, recurrent disease developed within 30 months in 22 per cent of patients with normal levels of CEA compared with 56 per cent of patients with elevated preoperative levels of CEA. Similar findings were reported in patients with Dukes' C; 59 and 85 per cent of patients with normal and elevated levels of CEA, respectively, recurred within 39 months of surgical resection.

In 1981, the over-all survival time was correlated with preoperative levels of CEA in 563 patients with carcinoma of the colon and rectum (27). Significantly shorter survival time was found in patients with levels of CEA >4 nanograms per milliliter compared with patients with levels <4 nanograms per milliliter. In patients with levels of CEA >10 nanograms per milliliter, survival time was further decreased. In a subsequent report by the same group, the over-all survival time of patients with carcinoma of the colon and rectum who were free of metastases was significantly reduced among those patients with preoperative levels of CEA >5 nanograms per milliliter (28). In patients with distant metastases, the level of CEA was unrelated to survival time. Thus, the preoperative level of CEA is associated with risk of recurrence after surgical resection and with the over-all survival time in certain groups of patients with carcinoma of the colon and rectum.

The serial measurement of CEA is an important monitor of clinical response to antineoplastic therapy. After complete surgical resection of carcinoma of the colon and rectum, elevated levels of CEA should rapidly return to normal. Typically, levels of CEA become normal within several weeks after complete surgical resection. In 1981, the National Institute of Health Consensus Conference stated that normal levels of CEA should be observed within six weeks of curative resection (13). Persistently elevated or progressively rising levels of CEA after surgical treatment usually indicate incomplete surgical resection (29, 30). A similar correlation between levels of CEA and response to radiation therapy and chemotherapy has been demonstrated (31–33); however, the time required for normalization of levels of CEA after effective therapy is increased with these treatment methods.

TABLE I.—TUMOR MARKERS

Oncofetal antigens	Enzymes
Carcinoembryonic antigen	Acid phosphatase
Alpha-fetoprotein	Bone alkaline phosphatase
Placental proteins	Catecholamine metabolites
Human chorionic gonadotropin	Miscellaneous
Human placental lactogen	Polyamines
Placental alkaline phosphatase, Regan isoenzyme	Acute phase proteins
	Immunoglobulins
Hormones	
Calcitonin	
Adrenocorticotropic hormone	
Antidiuretic hormone	

The most important use of serial measurements of CEA is to detect recurrent or metastatic carcinoma of the colon and rectum after an interval of complete clinical remission. In patients with recurrent disease, significant elevation of levels of CEA has been shown to precede clinical and roentgenologic detection of disease by two to 18 months (34). Second-look laparotomies have been advocated based solely upon rising levels of CEA in an attempt to cure patients with an early stage of recurrence. The current studies are not randomized, however, and, therefore, the effect of CEA directed second-look laparotomy upon the survival time of patients remains unclear.

Numerous studies have reported results of second-look surgical procedures based upon rising levels of CEA after a period of clinical remission. In 1978, second-look laparotomies were performed in 40 patients with rising levels of CEA (35). Twenty-two patients were analyzed retrospectively and 18 patients were studied prospectively. Of these 40 patients, 36 were found to have metastatic disease and 19 underwent curative resection. Of the 22 patients retrospectively studied, four remained alive with no evidence of disease for ≥three years. In 1978, findings from a series of 14 patients who underwent second-look laparotomies based upon rising levels of CEA were reported (36). All 14 of the patients had metastatic disease and curative resection was performed in seven. Four were alive with no evidence of disease from one to three years after curative resection. In 1980, recurrent disease was found in 15 of 16 patients who underwent second-look laparotomies (37). Curative resection was performed in only four in this study. In 1981, recurrence was found in 33 of 37 patients who underwent laparotomies that were performed for rising levels of CEA (38). Complete resection of recurrent disease was performed in 16 of 37 instances.

Thus, second-look laparotomy, based solely upon elevated levels of CEA, detects recurrent or metastatic disease in 90 per cent of patients. Curative resection is performed in approximately one-half of these patients; however, only 25 per cent of patients who undergo laparotomy survive long term free of disease. Additional prospective, randomized trials are required to determine the effect of second-look laparotomy based solely upon rising levels of CEA on both disease-free and over-all survival time.

α-FETOPROTEIN

AFP is an oncofetal protein that was first discovered in 1963 in the serum of mice with hepatoma (39). AFP is a single polypeptide chain with a molecular weight of about 70,000 daltons (40). Approximately 4 per cent of this molecule consists of carbohydrate with only minor variations in the sialic acid content originating from different sources (41). AFP is measured either by radioimmunoassay, which is sensitive to 5 nanograms per milliliter, or agar-gel diffusion, which detects concentrations greater than 3,000 nanograms per milliliter (42,43). In normal adults, levels of AFP range from 1 to 25 nanograms per milliliter (44). The circulating half-life of AFP is from 3.5 to 6.0 days (41).

AFP is normally produced during fetal development by the liver, yolk sac and gastrointestinal epithelium (45). AFP is the major serum protein in the fetus and reaches its highest concentration in the 12th to 15th week of gestation (44, 45). In adults without malignant disease, elevations of serum levels of AFP occur during the second and third trimesters of pregnancy and in patients with benign hepatic disease (46, 47). Increased levels of AFP are particularly common in patients with hepatocellular disease, such as cirrhosis, acute and chronic hepatitis and hepatic necrosis, in contrast to patients with cholestatic disease (46-48). As many as two-thirds of patients with acute viral hepatitis may demonstrate increased serum levels of AFP during the recovery phase of hepatocellular regeneration (48, 49).

In 1964, elevated levels of AFP were first demonstrated in patients with hepatoma (50). Increased levels of AFP were found in approximately 70 per cent of patients with hepatoma in the United States and Europe and almost 90 per cent of patients with hepatoma in Africa and the Orient (51). Seventy-five per cent of patients with germ cell tumors, particularly teratocarcinoma of the testis and embryonal cell carcinoma, demonstrate increased serum levels of AFP (44). Levels of AFP are less commonly elevated in patients with carcinoma of the pancreas (23 per cent), stomach (18 per cent), lung (7 per cent) and colon (5 per cent) (44, 52).

AFP has not proved useful as a screening test for hepatoma even in the high risk populations of Africa and the Far East. Several large screening studies have been performed using the agar-gel diffusion method for assaying AFP. In a study of 9,000 people in Africa, serial measurements of AFP were performed during a two year period (53). Hepatoma developed in nine patients in this series with only six demonstrating elevated levels of AFP. The tumor was completely resected in only one patient. Results from a second study of more than 340,000 people in China found hepatoma in 129 of 147 patients (87.7 per cent) with elevated levels of AFP (54). Although more than one-half of those with hepatoma were asymptomatic at the time of screening, symptoms developed in all within one to three months. Therefore, screening of high risk populations does not allow detection of hepatoma early enough to improve patient survival time.

In patients with hepatoma, the incidence of elevation of levels of AFP correlates with tumor burden. In 1971, levels of AFP were analyzed in 120 patients with hepatoma; elevations of AFP were reported to be more common among patients with larger, more anaplastic tumors (55). In 1972, similar results were reported in patients with hepatoma; all of the patients with tumors larger than 5 kilograms in weight demonstrated increased levels of AFP compared with only 50 per cent of those with tumors weighing less than 2 kilograms (56). No correlation exists between the level of AFP and survival time in patients with hepatoma (55–57).

AFP is useful to monitor tumor response to therapy and to predict clinical relapse in patients with hepatoma. Levels of AFP precipitously fall to normal after complete surgical resection (44, 58). Persistent elevation or gradual increase after initial decline of serum levels of AFP indicates persistent or recurrent disease, respectively (58, 59). Although chemotherapy has limited efficacy in this disease, it was reported, in 1974, that a 50 per cent reduction in the levels of AFP after chemotherapy indicates effective tumor response (58). Thus, AFP is most valuable for monitoring tumor response to therapy and predicting relapse in the individual patient.

Elevations of levels of AFP occur in 75 per cent of patients with teratocarcinoma of the testis and embryonal cell carcinoma (51, 60). Human

chorionic gonadotropin (HCG) is a second marker that is frequently elevated in patients with nonseminomatous germ cell tumors (51, 61). Although levels of AFP are not elevated in patients with pure seminoma, levels of HCG may be increased in 50 per cent of patients with an advanced stage of seminoma (62, 63). Results of immunohistochemical studies indicate that AFP and HCG are produced by embryonal cells and syncytiotrophoblastic cells, respectively (61).

The incidence of elevation of levels of AFP and HCG correlates with the stage of disease in patients with nonseminomatous germ cell tumors. In 1981, levels of AFP and HCG were analyzed in 78 patients with nonseminomatous carcinoma of the testis (64). Elevation of the level of the tumor marker occurred in 18, 58 and 87 per cent of patients with Stage I, II and III disease, respectively. Because the incidence of marker levels is low in early stage disease, AFP and HCG are less useful in screening for carcinoma of the testis.

In general, pretreatment levels of AFP and HCG were inversely related to prognosis in patients with advanced stage of disease. In 1984, elevation of the marker and response to chemotherapy alone or combined chemotherapy and surgical treatment were analyzed in 103 patients with bulky Stage II or III nonseminomatous germ cell tumors (65). Complete remission occurred in 92 per cent of patients with normal levels of markers, 37 per cent of patients with the level of one marker elevated and 39 per cent of patients with levels of both markers elevated. Survival time was projected in 69 patients with metastatic teratoma based upon initial levels of tumor markers and similar results were found (66). Survival rates of 96 and 56 per cent were reported in patients with normal levels and elevated levels of AFP and HCG, respectively. In 1983, levels of the markers and prognosis in patients with metastatic germ cell tumors of the testis were retrospectively studied (67). By multivariate analysis, levels of HCG but not AFP were predictive of response to antineoplastic therapy and survival time.

Serial measurements of AFP and HCG are particularly valuable in monitoring the response of carcinoma of the testis to therapy. After surgical resection or complete response to chemotherapy, elevated levels of tumor markers fell to the normal range (64, 68). In 1977, recurrence of tumor in 24 patients with carcinoma of the testis was reported after orchiectomy or lymph nodal dissection (69). In 16 of 24 patients, levels of AFP or HCG were elevated prior to clinical detection of recurrent disease. Similar results were found with elevated levels of tumor markers preceding clinical or roentgenologic detection of disease by five or more months (70). Although elevated levels of HCG or AFP are invariably associated with recurrence of tumor, normal levels of these markers may occur despite tumor progression (71, 72). In 1981, normal levels of markers were reported in six of 30 patients with known metastases for a false-negative rate of 20 per cent (73). Negative tumor markers were reported in 12 of 22 patients (54 per cent) with surgically proved residual carcinoma (74). Thus, serial monitoring of levels of AFP and HCG is an important, early indicator of recurrence of tumor when levels of the markers are elevated. Normal levels of these markers cannot reliably exclude recurrent disease.

HUMAN CHORIONIC GONADOTROPIN

HCG is a glycoprotein hormone with a molecular weight of 45,000 daltons (60). This hormone is composed of two polypeptide chains. The α-subunit is common to several glycoprotein hormones secreted by the anterior pituitary. The β-chain is unique and confers structural and functional identity to these hormones (75). The antigenic individuality conferred by the β-chain provides the basis for radioimmunoassay of this hormone (76); however, some homology exists between the β-subunits of HCG and human luteinizing hormone (HLH) and may cause immunologic cross-reactivity between these two hormones. A falsely elevated level of HCG is particularly common among patients who previously had undergone orchiectomies with extremely high levels of HLH (77, 78). Suppression of the hormone prior to determining concentration of HCG reduces the incidence of false-positive results in these patients (79). The circulating half-life of HCG is 12 to 20 hours (60).

HCG is normally secreted by placental tissue with highest circulating levels occurring at 60 days of gestation (80). Significant elevation of levels of HCG occurs only during pregnancy and in patients with trophoblastic neoplasms or nonseminomatous germ cell tumors (81). Normal serum levels of 1 nanogram per milliliter may be increased to 1,000,000 nanograms per milliliter in the presence of trophoblastic disease (81, 82). HCG may be secreted in small amounts by the testis, pituitary gland and gastrointestinal tract (75). Mildly elevated levels of HCG (<10 nanograms per milliliter) may occur in patients with

nontrophoblastic neoplasms and a variety of benign diseases, including peptic ulcer disease, inflammatory intestinal disease and cirrhosis (75, 82).

Essentially, 100 per cent of patients with trophoblastic tumors and 70 per cent of patients with nonseminomatous germ cell tumors demonstrate elevated levels of HCG (60, 75). The value of HCG in predicting prognosis and monitoring response to therapy in patients with nonseminomatous germ cell tumors has been previously discussed. In patients with trophoblastic disease, levels of HCG correlate with tumor burden, prognosis of patient and response to therapy.

HCG is an extremely sensitive monitor of viable trophoblastic cells. It has been estimated that HCG can be detected in the serum of patients with only 10^4 to 10^5 trophoblastic tumor cells (83, 84). This tumor marker exceeds, by several logarithms, the lower limit of clinical or roentgenologic detection of tumor cells (approximately 10^8 cells).

Numerous investigators have demonstrated that levels of HCG correlate with tumor burden and prognosis of the patient. In 1976, an association between pretreatment urinary excretion of HCG and survival time in patients with trophoblastic neoplasms was reported (85). In this study, death occurred in 10.5 per cent of patients with urinary excretions of HCG of 10^2 to 10^3 International units per day and 60.8 per cent of patients with urinary excretion of HCG $\geq 10^6$ International units per day. Pretreatment serum levels of HCG of >40,000 International milliunits are similarly associated with decreased survival time compared with lower serum levels of HCG (86).

HCG is an excellent marker for monitoring the response of trophoblastic disease to therapy. Since 10^4 to 10^5 tumor cells are necessary to produce detectable serum levels of HCG, chemotherapy must be continued beyond the point at which levels of HCG become undetectable (83). Occult metastases can be detected by an elevation of levels of HCG and appropriate therapy instituted before recurrence of tumor can be demonstrated by clinical or roentgenologic techniques. Finally, since HCG does not readily cross the blood and brain barrier, a ratio of cerebrospinal fluid to serum of >1:60 is suggestive of cerebral metastases (87).

CALCITONIN

Calcitonin (CT) is a peptide hormone composed of 32 amino acids with a molecular weight of 3,419 daltons (88). CT is a hypocalcemic factor secreted by the C cells of the thyroid gland. The serum half-life of CT is 12 minutes and normal levels are <0.1 nanogram per milliliter radioimmunoassay (89, 90).

Marked elevations of serum CT are observed in patients with medullary carcinoma of the thyroid (90, 91). Other neoplasms less frequently associated with increased levels of CT include small-cell carcinoma of the lung, carcinoma of the breast, carcinoid, hepatoma, renal cell carcinoma and Zollinger-Ellison syndrome (92–95). Elevated serum levels of CT have been reported in patients with benign diseases, including pancreatitis, hyperparathyroidism (primary and secondary), Paget's disease of bone and pulmonary disease (92, 96).

The primary clinical application of serum CT is to detect familial medullary carcinoma of the thyroid (MCT). In familial MCT, genetic transmission occurs in an autosomal dominant pattern (90). Although secretion of CT normally fluctuates in these patients, provocative tests, such as pentagastrin stimulation or calcium infusion, have greatly increased the sensitivity of this test to detect MCT (97).

Improved diagnostic accuracy has been reported by combining pentagastrin stimulation with selective catheterization of the inferior thyroid vein (98). Using this test, kindreds of patients with MEA-II syndrome (MCT with pheochromocytoma, parathyroid hyperplasia and mucocutaneous lesions) have been studied (97, 98). In 1975, elevated levels of CT were detected in four children of one relative with MEA-II syndrome after pentagastrin stimulation (98). All four of the children had normal thyroid glands upon physical examination and radionuclide scan. After total thyroidectomy, small foci of MCT were found in all four of the specimens.

Serial measurements of levels of CT are valuable in monitoring therapy in patients with MCT. Persistent or recurrent elevation of levels of CT after thyroidectomy typically indicates residual or recurrent disease (97, 99). Occasional instances of patients with elevated levels of CT for several years have been reported, however, with no clinically detectable recurrence (89). In patients with increased levels of CT, selective venous catheterization can be used to localize recurrent disease (98, 99). In malignant diseases other than MCT, levels of CT are not accurate in predicting recurrence of tumor or response to chemotherapy.

CATECHOLAMINE METABOLITES

The most commonly assayed catecholamine metabolites are vanillylmandelic acid (VMA) and homovanillic acid (HVA), which are metabolites of norepinephrine and dopamine, respectively. Urinary levels of these metabolites can be accurately measured from a single urine specimen (100). Gas chromatographic techniques are more accurate to detect these metabolites than colorimetric methods, which require avoidance of tea, coffee, fruit and vanilla from the diet for 72 hours before urinary sampling (100, 101). Catecholamine metabolites are most useful in diagnosing and monitoring patients with neuroblastoma (102).

Neuroblastoma is a malignant lesion of neural crest tissue, which most commonly occurs in children. Although it has been suggested that all of the neuroblastomas produce some catecholamine metabolites, elevated urinary levels of VMA or HVA are observed in 75 to 95 per cent of patients with this tumor (100, 101). In 1978, a positive correlation between pretreatment urinary levels of VMA and HVA and stage of disease was reported (103); however, the absolute levels of urinary catecholamine metabolites were not found to predict survival time independent of stage of disease. In contrast, in 1973, urinary levels of catecholamine metabolites were analyzed in 98 patients and results demonstrated decreased survival time in patients with higher excretion of HVA (104). Improved survival time was reported in patients with a ratio of urinary VMA to HVA of ≥ 1.5 (105).

Serial monitoring of urinary levels of catecholamine metabolites is extremely important after treatment for neuroblastoma. The failure of urinary excretion of catecholamine to normalize after initial therapy is associated with uniform mortality within two years (104). In this study, the two year survival rate of patients with normal urinary levels of catecholamine after treatment was 85 per cent. Subsequent recurrence of tumor is heralded by elevated urinary levels of catecholamines before clinical or roentgenologic signs in more than 90 per cent of instances (102, 105). Thus, urinary catecholamine metabolites are useful indicators of the extent of disease, prognosis and recurrence in patients with neuroblastoma.

PROSTATIC ACID PHOSPHATASE

Acid phosphatase was first proposed as a marker of advanced carcinoma of the prostate in 1938 (106). Acid phosphatase is normally found in greatest concentration in the prostate gland and its secretions. The acid phosphatases, however, are a group of enzymes that are also present, in lower concentrations, in bone, kidney, liver, spleen and intestine (107). Prostatic acid phosphatase (PAP) is a glycoprotein with a molecular weight of 100,000 daltons, which consists of two identical subunits. Several isoenzymes exist that differ in the carbohydrate portion of the molecule (107, 108).

Levels of PAP are elevated in a variety of benign conditions, such as osteoporosis, hypoparathyroidism, hyperthyroidism, prostatic surgical treatment, catheterization of the urinary tract and benign prostatic hypertrophy (109, 110). In addition to carcinoma of the prostate, other malignant diseases with elevated levels of acid phosphatase include multiple myeloma, osteogenic sarcoma and bony metastases (110, 111). Acid phosphatase is not useful as a screening tool for early detection of carcinoma of the prostate primarily because of the high prevalence of benign prostatic hypertrophy in the general population.

Levels of PAP can be measured by biochemical or immunologic methods. Radioimmunoassay is much more sensitive than chemical determination and, in general, the level of PAP correlates with the stage of disease (112). In 1980, significantly

TABLE II.—POTENTIAL TUMOR MARKERS

Tumor markers	*Malignant disease*
CA 19-9	Carcinoma of the colon and rectum*, pancreas and stomach
CA 125	Carcinoma of the ovaries*, carcinoma of the pancreas (nonmucinous types), lung and gastrointestinal tract
Pancreatic oncofetal antigen	Carcinoma of the pancreas
Prostate-specific antigen	Carcinoma of the prostate
Neuron-specific enolase	Neuroendocrine tumors
Galactosyltransferase isoenzyme II	Carcinoma of the colon*, pancreas and stomach
Lipid-bound sialic acid	Lymphoma, leukemia, carcinoma of the ovaries, melanoma, carcinoma of the lung, sarcoma, carcinoma of the colon
5'-Nucleotidase	Hepatic metastases
gamma-glutamyltranspeptidase	Hepatic metastases
Aryl sulfatase B	Carcinoma of the colon
Bombesin	Small-cell carcinoma of the lung
Neurophysin	Small-cell carcinoma of the lung
Pregnancy-specific B_1-glycoprotein, SP-1	Trophoblastic tumors
Alpha$_2$-pregnancy-associated globulin	Carcinomas of the female reproductive tract
Tennessee antigen	Gastrointestinal tumors, sarcomas, leukemia

*Indicates predominant malignant disease associated with specific tumor marker.

elevated levels of PAP in 12, 32, 47 and 86 per cent of patients with stages A, B, C and D of carcinoma of the prostate, respectively, were reported. Using biochemical assays of enzyme function, levels of acid phosphatase are elevated in only 50 to 80 per cent of patients with carcinoma of the prostate (114). Levels of acid phosphatase in the bone marrow have been determined in an effort to improve the diagnostic accuracy of this marker in patients with metastatic disease (115); however, the role of levels of acid phosphatase obtained by aspiration of bone marrow remains controversial.

Acid phosphatase may be of value in monitoring response to therapy. In one study, a direct correlation was observed between reduced levels of serum acid phosphatase and a 50 per cent reduction in the mass of the tumor after therapy (116). Thus, PAP has definite limitations as a tumor marker for carcinoma of the prostate. Other markers, such as prostate-specific antigen, are currently being investigated in an effort to identify more sensitive and specific indicators of carcinoma of the prostate. Preliminary results indicate that levels of prostate-specific antigen correlate with stage and response of tumor to therapy (117).

ADRENOCORTICOTROPIC HORMONE

Adrenocorticotropic hormone (ACTH) is the most frequently observed ectopic hormone produced by neoplasms. In 1928, the first instance of ectopic production of ACTH in a patient with small-cell carcinoma of the lung was reported (118). Ectopic production of ACTH has been subsequently associated with other malignant diseases, including adenocarcinoma and squamous cell carcinoma of the lung, carcinoid, pancreatic islet cell tumors, carcinoma of the breast, carcinoma of the colon, pheochromoctyoma, thymoma, medullary carcinoma of the thyroid gland and carcinoma of the ovaries (119-121). Elevated levels of ACTH have been observed in numerous benign conditions, including chronic obstructive pulmonary disease, obesity, hypertension and diabetes mellitus (122, 123).

Carcinoma of the lung, particularly small-cell carcinoma, is the most common cause of ectopic production of ACTH (124); however, most carcinomas of the lung secrete "big" ACTH, a prohormone with 3 to 5 per cent of the biologic activity of native ACTH (125, 126). Because of the relative inactivity of this prohormone, clinical manifestations of Cushing's syndrome are uncommon (127). Ectopic secretion of ACTH can be differentiated from ACTH that originates in the pituitary gland by the dexamethasone suppression test. Failure to suppress plasma cortisol levels with high dose dexamethasone suggests ectopic secretion of ACTH (123).

ACTH has no value in screening for carcinoma, and pretreatment levels demonstrate no correlation to patient survival time or stage of disease (121, 123). The usefulness of serial measurements of ACTH to monitor response of tumor to therapy remains controversial (127, 128). ACTH lacks the sensitivity and specificity to be clinically useful for screening, staging or predicting response to therapy.

ANTIDIURETIC HORMONE

Small-cell carcinoma of the lung is the malignant disease most commonly associated with ectopic secretion of antidiuretic hormone (ADH) (129, 130). Secretion of ADH may be detected biochemically or may present clinically as the syndrome of inappropriate ADH (SIADH) (129, 131). Approximately 80 per cent of the instances of SIADH associated with malignant disease occur with small-cell carcinoma of the lung (130); however, SIADH occurs in less than 10 per cent of patients with small-cell carcinoma of the lung (131, 132).

Other malignant disease found to secrete ectopically ADH include carcinoma of the pancreas, bronchial carcinoid tumors, carcinoma of the adrenal cortex, thymomas, carcinoma of the bladder and prostate (130, 133). Benign causes of ADH production include pulmonary disease, disorders of the central nervous system, anesthetics and ingestion of drugs (134). ADH is not a useful marker for screening of carcinoma, staging or monitoring response to therapy (129, 131).

POLYAMINES

The polyamines consist of a group of organic cations, including putrescine, spermidine and spermine. Levels of polyamines increase in response to growth of tissue, cellular replication and numerous benign and malignant conditions (135). Benign diseases associated with elevated levels of polyamines include rheumatoid arthritis, polymyositis, psoriasis, tuberculosis, chronic obstructive pulmonary disease and pernicious anemia (136). Elevated urinary excretion of polyamines has been documented in patients with a variety of malignant diseases, including leukemia, lymphoma, melanoma, carcinoma of the colon and rectum, pancreas, bladder, prostate and lung and primary tumors of the brain (137, 138).

In patients with malignant disease, levels of polyamines seem to correlate with tumor burden, activity of the disease and cell loss (138, 139). In 1979, higher levels of polyamines were observed in patients with actively progressive disease and in patients with large tumor burdens (140). Other studies have documented higher urinary levels of polyamines in patients with metastatic carcinoma of the breast compared with patients with localized carcinoma of the breast (141, 142). Furthermore, recurrence of disease may be preceded by increasing urinary levels of polyamines (138). In patients with medulloblastoma, increasing levels of putrescine in cerebrospinal fluid have accurately predicted recurrence (143).

Response of hematologic and solid tumors to chemotherapy has been associated with an immediate increase and subsequent decrease in levels of polyamines (140, 144). An immediate twofold or greater increase in urinary levels of spermidine correlated with objective response of tumor to chemotherapy in one study. In patients with no significant increase in excretion of spermidine, no response to therapy was observed (140). These findings are preliminary, however, and require confirmation by subsequent clinical investigation.

ADDITIONAL MARKERS

A number of enzymes, proteins, hormones and antigens are currently being investigated as potential markers of tumors in the future. The recent development of monoclonal antibodies has lead to the discovery of numerous tumor-associated antigens in the serum and tissue of the tumor in patients with malignant disease. Chromosomal changes, including deletions, segmental duplications and trismony, have been documented in human malignant disease and may provide important diagnostic and prognostic information (145, 146). These markers require further study to determine the role in screening for carcinoma, assessing tumor burden and monitoring the response of the tumor to therapy. The most promising markers of tumor of the future are listed in Table II.

SUMMARY

This state-of-the-art review identifies the clinical usefulness and limitations of currently available tumor markers. The role of specific tumor markers in screening, assessing extent of disease and monitoring the response of the tumor to antineoplastic therapy is discussed. Recent technologic advances, including monoclonal antibodies and genetic analysis, may identify additional tumor markers and provide insight into the developmental process of neoplasia by characterizing the biologic changes associated with malignant disease.

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