

Carcinoembryonic Antigen, Carbohydrate Antigen 19-9, Cancer Antigen 125, Prostate-Specific Antigen and Other Cancer Markers: A Primer on Commonly Used Cancer Markers

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Abstract

Cancer markers are molecules produced by cancer cells which may serve to identify the presence of cancer. Cancer markers can be differentiated as serum-based, radiology-based and tissue-based, and are one of the most important tools in diagnosing, staging and monitoring of treatment of many cancers. The most used cancer markers are serum cancer markers due to its relative ease and lower cost of testing. However, serum cancer markers have poor mass screening utilization due to poor positive predictive value. Several markers such as prostate-specific antigen (PSA), beta-human chorionic gonadotropin (B-hCG), alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH) are used to aid in diagnosis of cancer in cases of high suspicion. Serum markers such as carcinoembryonic antigen (CEA), AFP, carbohydrate antigen 19-9 (CA 19-9), and 5-hydroxyindoleacetic acid (5-HIAA) play a significant role in assessing disease prognosis as well as response to treatment. This work reviews the role of some of the biomarkers in the diagnosis and treatment of cancer.

Keywords: Tumor markers; Serum markers; CA 19-9; CEA; AFP; Cancer screening; Prognostic markers; CA-125; PSA; CA 27-29; B-hCG; Calcitonin; 5-HIAA; LDH

Introduction

Cancer markers are molecules produced by cancer cells which may serve to identify the presence of cancer. Cancer markers can be differentiated as serum-based, radiology-based and

tissue-based, and are one of the most important tools in diagnosing, staging and monitoring of treatment of many cancers. The most used cancer markers are serum cancer markers due to its relative ease and lower cost of testing. However, serum cancer markers have poor mass screening utilization due to poor positive predictive value. Radiological modalities such as mammogram, low-dose computed tomography (CT) scans are useful tools in screening for cancer in certain patient populations. Evidence of radiological markers such as the presence of “spiculated calcifications” on a mammogram can lead to further malignancy investigations. Lastly, tumor tissue markers provide insight into characteristics of the cancer by means of genetic mutation or a receptor overexpression. Examples of tissue markers include p53 mutation, estrogen and progesterone receptors and human epidermal growth factor receptor 2 (HER2) receptor. Tissue markers are often used to determine tissue-specific cancer treatment regimens and may also be used as predictors of overall prognosis in cancer patients. This article focuses on the common serum cancer markers and their current use in clinical practice.

Carcinoembryonic Antigen (CEA)

CEA is a glycoprotein involved in cellular adhesion normally produced in fetal development. The production of CEA stops prior to birth and as such, CEA levels are not generally observed in significant quantities after birth [1]. A normal CEA result is typically < 2.5 ng/mL in non-smokers and < 5 ng/mL in smokers [1]. The most common use of CEA in clinical setting is for disease monitoring in metastatic colorectal cancer during systemic therapy. Elevated CEA levels are also observed in other malignancies including but not limited to pancreatic cancer, gastric cancer, hepatobiliary cancer and lung cancer (Table 1 [2-13]). Many non-malignant conditions such as smoking, peptic ulcer disease, inflammatory bowel disease and pancreatitis also lead to elevated CEA levels [2]. While specificity of CEA test for identifying future colorectal cancer patients is 99%, it carries poor sensitivity of 12%, making it a futile tool for mass screening purposes [14]. Due to the poor sensitivity and diverse prevalence of CEA in non-malignant conditions, the American Society of Clinical Oncology does not recommend the use of CEA as a screening test for colorec-

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Table 1. List of Markers, Reference Levels and Their Associated Cancers

Serial no.	Marker	Associated cancers	Reference level	Reference
1	CEA	Colorectal cancer, pancreatic cancer, gastric cancer, hepatobiliary cancer, lung cancer	< 2.5 ng/mL in nonsmokers; < 5 ng/mL in smokers	[2]
2	CA 19-9	Pancreatic ductal adenocarcinoma, gastric cancer, colorectal cancer, lung cancer, thyroid cancer	37 U/mL	[3]
3	AFP	Hepatocellular carcinoma, non-seminomatous germ cell tumors (NSGCTs), gastric cancer, pancreatobiliary cancers	< 20 ng/dL	[4]
4	CA-125	Ovarian cancer, endometrial cancer, breast cancer, gastric cancer	< 35 U/mL	[5]
5	CA 27-29	Breast cancer, colon cancer, lung cancer, pancreatic cancer, ovarian cancer	< 38 U/mL	[6]
6	PSA	Prostate cancer	Aged based: 40 - 49 years: < 2.5 ng/mL; 50 - 59 years: < 3.5 ng/mL; 60 - 69 years: < 4.5 ng/mL; 70 - 79 years < 6.5 ng/mL	[7]
7	B-hCG	Non-seminomatous germ cell tumors, gestational trophoblastic tumors, neuroendocrine cancers, prostate cancer, lung cancer, gastrointestinal tract cancers, cancers of cervix, uterus and vulva	< 5 - 10 IU/mL in men	[8]
8	Tg	Thyroid cancer	1.40 - 29.2 ng/mL males; 1.50 - 38.5 ng/mL females	[9]
9	Calcitonin	Medullary thyroid cancer, neuroendocrine tumors, small cell lung cancer, prostate cancer	< 10 ng/mL	[10]
10	LDH	Testicular germ cell cancers, lung cancer, liver cancer, lymphomas, leukemias	140 - 280 U/L	[11]
11	5-HIAA	Neuroendocrine tumors (particularly small intestinal NETs and metastatic lung NETs)	2 - 8 mg/24 h	[12]
12	β 2M	Multiple myeloma, chronic lymphocytic leukemia, lymphomas	< 2 mg/L	[13]

CEA: carcinoembryonic antigen; CA 19-9: carbohydrate antigen 19-9; AFP: alpha-fetoprotein; CA-125: cancer antigen 125; CA 27-29: cancer antigen 27-29; PSA: prostate-specific antigen; B-hCG: beta-human chorionic gonadotropin; Tg: thyroglobulin; LDH: lactate dehydrogenase; 5-HIAA: 5-hydroxyindoleacetic acid; β 2M: beta-2 microglobulin; NETs: neuroendocrine tumors.

tal cancer [15].

There is increased utilization of CEA as a prognostic marker. Elevated preoperative CEA levels correlated with increase in danger of death compared to normal preoperative CEA levels in a study of 131,181 patients with stage I-III colon cancer (hazard ratio (HR) 1.62, 95% confidence interval (CI) 1.53 - 1.74) [16]. CEA levels typically return to normal in 4 - 6 weeks after successful surgical resection. Although the guidelines recommend postoperative serum CEA testing every 3 months in patients with stage II or III disease for 3 years after diagnosis to screen for metastatic disease, there is variation among clinicians on the serum CEA threshold to trigger further investigations [15, 17]. However, a Cochrane review of 52 studies concluded that 10 ng/mL ought to be used as a threshold to trigger additional investigations due to sensitivity of 68% and specificity of 97% [17]. CEA also remains the marker of choice for monitoring disease activity in metastatic colon cancer while undergoing systemic therapy. CEA levels are measured every 1 - 3 months during active treatment. Rising levels above the patient's baseline can be suggestive of progressive disease despite the absence of evidence on radiographical imaging [2]. As such, CEA proves to be a valuable tool in monitoring of disease after the diag-

nosis of colorectal cancer despite poor utility in screening purposes.

Carbohydrate Antigen 19-9 (CA 19-9)

CA 19-9 is a sialylated Lewis (Lewis^{ab}) blood group antigen, synthesized in normal pancreatic parenchyma and biliary tract as well as epithelial cells of the gastric, colon and uterine mucosa [18]. CA 19-9 is the most used biomarker for pancreatic ductal adenocarcinoma (PDAC) but is also found elevated in other malignancies such as gastric cancer, colorectal cancer, lung and thyroid cancer [19]. Serum levels of CA 19-9 have sensitivity of 81% with specificity of 90% for diagnosis of PDAC in symptomatic patients with a typical cutoff value of 37 U/mL [3]. However, due to low prevalence of PDAC, its utility as a diagnostic marker is limited. Furthermore, false positive results are seen in benign conditions including pancreatobiliary diseases such as pancreatitis, cholangitis and obstructive jaundice as well as autoimmune diseases, pulmonary disease and thyroiditis [3, 19]. Meanwhile, patients with Lewis negative phenotype (approximately 5-10% of population) do not produce CA 19-9 leading to falsely low levels even in the presence

of advanced pancreatic cancer [3]. A large prospective study of 70,940 patients in South Korea showed positive predictive value of pancreatic cancer to be 0.9% in asymptomatic population rendering it an ineffective screening marker [20].

CA 19-9 is however used extensively in monitoring response to treatment of pancreatic cancer and is often useful in monitoring for recurrence. Many studies point to elevated serum levels of CA 19-9 to correlate with unresectable disease, but cutoff values differ significantly [3, 21, 22]. Guidelines recommend against using only perioperative CA 19-9 to determine operability [15]. In resectable PDAC, elevated perioperative CA 19-9 levels have shown to correlate with staging and survival but threshold levels vary among studies [23, 24]. A study of 176 patients with PDAC showed that patients with postoperative decrease in CA 19-9 levels and with values of < 200 U/mL were independent prognostic factors despite adjusting for stage [23]. In patients treated with surgical resection receiving adjuvant chemotherapy, CA 19-9 levels may be used to evaluate patient's response to therapy or in monitoring for recurrence. While both European Society for Clinical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) recommend measurement of CA 19-9 levels after surgical resection and prior to adjuvant therapy to guide treatment, there is no consensus on the magnitude of change or the frequency of monitoring [3, 25, 26]. However, rise in CA 19-9 is usually accompanied by other investigative modality such as imaging to confirm progressive or recurrent disease. Additionally, patients with Lewis null factor again do not benefit from CA 19-9 monitoring, as such many patients may exhibit low CA 19-9 levels despite progressive disease.

Alpha-Fetoprotein (AFP)

Serum AFP is the most widely used biomarker in diagnosis of hepatocellular carcinoma (HCC) with upper limit of normal < 20 ng/dL. When used alone to screen for HCC in patients with coexisting liver disease, AFP has suboptimal sensitivity of 41-65% and specificity of 90-94% in diagnosis of HCC with a cutoff value of 20 ng/mL, although higher cutoff values show significantly improved sensitivity [4]. Elevated AFP levels are also seen in other malignancies including non-seminomatous germ cell tumors (NSGCTs), gastric and pancreatobiliary cancers while non-malignant causes of AFP elevation may include viral hepatitis, chronic liver disease and pregnancy [4]. The value of AFP as a solitary screening marker for HCC is heavily debated. Up to 20% of HCC may not have elevated AFP levels at the time of diagnosis [27]. There is a disagreement among international professional societies regarding the use of AFP in screening for HCC. The Asian Pacific Association for the Study of Liver (APASL) and the Japan Society of Hepatology (JSH) guidelines recommend using AFP as a screening marker, while the European Association for the Study of the Liver (EASL) recommends against the screening [28]. Meanwhile, the American Association for the Study of Liver Diseases (AASLD) recommends screening for HCC in high-risk patients with ultrasound and leaving the decision to use AFP to clinician's discretion [29]. While studies have shown AFP as an

independent prognostic marker in patients with HCC, it does not have significant use in staging or treatment protocols [30, 31]. AFP may be used for post-treatment monitoring and as a prognostic tool. A meta-analysis of 4,726 HCC patients showed post-treatment AFP response to be significantly associated with overall survival as well as recurrence-free survival in HCC patients [32]. The use of AFP in NSGCTs is discussed with the tumor marker beta-human chorionic gonadotropin (B-hCG).

Cancer Antigen 125 (CA-125)

Due to unspecific onset of symptoms and poor early detection methods, ovarian cancer is typically diagnosed in advanced stages in 75% of cases [33]. Although the CA-125 has been used in ovarian cancer to monitor treatment response, its role as screening and prognostic marker is rather unclear. The normal value for CA-125 is typically less than 35 U/mL. The sensitivity of CA-125 for ovarian cancer detection is 78.9% with 86.9% specificity with positive predictive value of 63.8% [34]. While up to 80% of women with epithelial ovarian carcinoma have elevated serum CA-125 levels with frequency of the elevation often correlating with tumor burden, only 50% of patients with stage I disease showed elevated CA-125 levels [35, 36]. Elevated levels of CA-125 are also found in various benign gynecological conditions including ovarian cysts, endometriosis, cervicitis as well as benign liver disease and gastrointestinal disorders. Elevated CA-125 results are also associated with other malignancies including malignancies of endometrium, breast and gastrointestinal tract [5].

Although majority of patients with advanced disease carry poor prognosis, no American society currently recommends for routine ovarian cancer screening in general population. Elevated CA-125 levels have poor utility in early-stage diseases. A recent randomized controlled trial (RCT) in UK evaluated routine screening in postmenopausal women aged 50 - 74 years using CA-125, transvaginal ultrasound versus no screening. No significant reduction was noted in ovarian and tubal cancer deaths despite screening measures [37].

CA-125 levels are often measured perioperatively prior to debulking surgery and during chemotherapy to monitor response. Some studies have identified perioperative CA-125 cutoff value of 500 U/mL to predict successful primary debulking surgery; however, there is no consensus on this threshold value [33]. Despite its significant limitations, CA-125 is used to monitor treatment response by serial measurements. Successful response is determined as > 50% reduction in CA-125 level after initiation of treatment. Patients with persistently high and unchanged CA-125 levels during and after chemotherapy showed poor prognosis in advanced epithelial ovarian cancer [38, 39]. Additionally, rising CA-125 levels are noted to precede signs of symptoms of disease recurrence in up to 70% of cases, making it a useful marker for recurrence [40].

CA 27-29

CA 27-29 is a monoclonal antibody that detects circulating gly-

Table 2. Serum Markers by Cancer Type, Advantages and Disadvantages

Cancer	Agent	Advantages	Disadvantages
Colon cancer	CEA	Marker of choice for monitoring disease activity and for metastatic disease	Poor sensitivity, diverse prevalence of CEA in various nonmalignant conditions
Pancreatic ductal adenocarcinoma	CA 19-9	Monitoring treatment response; Postoperative decrease strongly correlates with improved survival	Not useful in patients with Lewis null phenotype; Not a useful screening marker
Hepatocellular carcinoma	AFP	Independent prognostic factor; Useful for post-treatment monitoring	Suboptimal sensitivity, use in screening is controversial; No use in staging or treatment protocols
Epithelial ovarian cancer	CA-125	Perioperative levels predict successful debulking surgery; Can be used for monitoring treatment response	Low levels in patients with stage I disease hinder early diagnosis
Breast cancer	CA 27-29	Early detection of asymptomatic recurrence	Poor positive predictive value in early stage of disease; Multiple benign disorders increase levels
Prostate cancer	PSA	Useful marker in monitoring for recurrence and metastasis free survival; Prognostic marker	Falsely elevated in benign conditions. Increased screening does not translate to improved overall survival
Non-seminomatous germ cell tumors	B-hCG	Useful in assessing tumor burden, risk stratification and treatment regimen based on degree of marker elevation; prognostic marker	False positive rates seen in tumor lysis, marijuana use and multiple other malignancies
	AFP	Useful in assessing tumor burden, risk stratification and treatment regimen based on degree of marker elevation, prognostic marker	Present in variety of malignant and nonmalignant conditions
	LDH	Useful in assessing tumor burden, risk stratification and treatment regimen based on degree of marker elevation, prognostic marker	Degree of elevation highly nonspecific and may be caused by variety of benign and malignant conditions
Thyroid cancer	Thyroglobulin	Useful in monitoring recurrent and metastatic disease, response to therapy, prognostic marker	Limited screening utility due to association with benign conditions
Medullary thyroid cancer	Calcitonin	Degree of elevation correlates with degree of tumor burden and metastasis, important for postoperative monitoring and evaluation of metastasis	Not available in US, poor positive predictive value due to low prevalence of disease
Neuroendocrine tumors	5-HIAA	Useful in evaluation of carcinoid heart disease, serves as a prognostic factor	Not effective screening marker for all NETs. Levels affected by wide range of foods and medications
Multiple myeloma	β 2M	Useful in staging multiple myeloma, prognostic factor, correlates with disease stage and tumor burden	Not specific for multiple myeloma, may be seen in other malignancies and benign conditions

CEA: carcinoembryonic antigen; CA 19-9: carbohydrate antigen 19-9; AFP: alpha-fetoprotein; CA-125: cancer antigen 125; CA 27-29: cancer antigen 27-29; PSA: prostate-specific antigen; B-hCG: beta-human chorionic gonadotropin; LDH: lactate dehydrogenase; 5-HIAA: 5-hydroxyindoleacetic acid; β 2M: beta-2 microglobulin; NETs: neuroendocrine tumors.

coprotein mucin 1 (MUC-1) antigen in peripheral blood which has been used in monitoring of breast cancer [6]. Elevated levels of CA 27-29 are typically considered > 38 U/mL and are highly associated with breast cancer. However, elevated levels can also be seen in healthy individuals with benign conditions as well as other malignant conditions (Table 2) [6].

Due to poor positive predictive value in early stages, CA 27-29 does not have a role in screening, diagnosing or staging breast cancer, although the sensitivity rises considerably in metastatic disease [6, 41]. Mammography remains one of the modalities of choice for breast cancer screening. There are insufficient data to recommend the use of CA 27-29 to moni-

tor recurrence of breast cancer after primary treatment. While some studies showed early detection of asymptomatic recurrence after curative treatment with elevated CA 27-29 levels, no clinical trial has shown whether early detection of asymptomatic recurrence improved overall survival, progression-free survival or quality of life [41-43].

Prostate-Specific Antigen (PSA)

PSA is produced by epithelial cells of both benign and prostate gland. Elevated PSA levels are seen in patients with prostate

cancer as well as other benign conditions such as prostatitis and benign prostatic hyperplasia [44]. Serum PSA concentrations are correlated with increasing patient age and prostatic volume. In order to make PSA a more discriminating tumor marker for detecting clinically significant prostate cancer, different age-based cutoffs for serum PSA levels have been proposed. In general, the recommended upper reference range for serum PSA for men aged 40 - 49 years is 2.5 ng/mL; for 50 - 59 years, it is 3.5 ng/mL; for men aged 60 - 69 years, it is 4.5 ng/mL; and 70 - 79 years, it is 6.5 ng/mL [7]. Despite adjusting for age, ethnicity is also an independent factor influencing serum PSA levels. Among men with no evidence of prostate cancer, African American males had higher serum PSA levels and PSA densities compared to Caucasian or Hispanic males [45]. Similarly, African American males with non-metastatic cancer at diagnosis also had higher serum PSA levels than Caucasian males with non-metastatic disease [46].

Despite age-adjusted ranges for serum PSA, screening for prostate cancer with PSA remains a highly controversial issue. The US Preventative Service Task Force (USPSTF) recommends shared decision making based on individual risk factors to utilize prostate cancer screening in men aged 55 - 69 years (grade C recommendation) whereas for men aged 70 years or above, prostate cancer screening is not recommended (grade D recommendation) [47]. Although PSA-based screening programs in men aged 55 - 69 years have shown to prevent 1.3 deaths from prostate cancer in 1,000 men screened over 13 years as well as three cases of metastatic cancer per 1,000 men screened, the trials did not show any reduction in all-cause mortality from screening [47].

Meanwhile, the incidence of prostate cancer is higher in African American males with increased incidence of transformation to aggressive disease compared to the general population [48]. Consequently, African American men have two- to threefold higher mortality rate compared to general population [48]. Despite poorer outcomes, data from RCTs do not show adequate evidence to recommend screening due to poor enrollment of African American patients in the studies. For example, the PLCO trial which found no significant difference in all-cause mortality in prostate cancer screening programs included 4.3% African American patients [49]. Additionally, African American males are at a risk of increased harm from screening testing as well. Complications data from the PLCO trial showed that African American patients had a higher infectious complications rate following prostate biopsy [50].

While prostate cancer screening remains a debate, serum PSA is a useful marker in patients with established diagnosis of prostate cancer. Although no clinical trials have defined the optimal frequency for measuring serum PSA levels, the NCCN guidelines recommend treatment monitoring with serum PSA every 6 months for the first 5 years and then annually [51]. Following radical prostatectomy, rising PSA levels may indicate evidence of recurrent or metastatic disease [52]. Additionally, the prostate-specific antigen doubling time (PSADT) of ≤ 7.5 months has been reported as an independent predictor of metastasis-free survival [53]. Following radiotherapy, serum PSA levels require careful interpretation. Serum PSA levels can initially fluctuate after radiation therapy before reaching post-treatment nadir. Therefore, the American Society for

Therapeutic Radiology and Oncology (ASTRO) consensus panel defines three successful elevations in serum PSA compared to nadir, regardless of PSA value as biochemical failure after radiotherapy [54].

B-hCG

B-hCG is a glycoprotein normally produced by the placenta in pregnancy. In men, the normal value of B-hCG is $< 5 - 10$ IU/L. Elevated levels are frequently seen in germ cell tumors (GCTs) and gestational trophoblastic disease, although mild increases have also been reported with other malignancies (Table 2) [8]. Additionally, non-malignant conditions such as hypogonadal state, presence of heterophilic antibodies and marijuana use have also been linked to false positive results [8]. B-hCG, along with AFP and LDH are the best studied tumor markers for patients with GCTs. While these tumor markers are not effective in screening asymptomatic men for testicular tumors due to low incidence and low mortality rate. In patients with testicular mass suspicious of GCT, these serum markers can help establish initial diagnosis, provide risk stratification and assist with post-orchietomy management [55].

Histologically, GCTs are divided into seminomas and NSGCTs. Testicular NSGCTs produce AFP or B-hCG, whereas pure seminomas do not produce AFP [55]. Serum LDH is not a reliable tumor marker in aiding in diagnosis as elevations in LDH can be highly non-specific. Among patients with NSGCTs, frequency of elevation in serum B-hCG and AFP correlates with advancing clinical stage and tumor burden. Elevated serum B-hCG levels are seen in 10-20% of stage I disease, 20-30% of low volume stage II disease, and 40% in advanced disease [55]. Elevated AFP levels are also similarly seen in 10-20% of stage I disease, 20-40% of low volume stage II disease, and 40-60% in advanced disease [55]. While increased levels do not alone establish diagnosis of GCTs, in patients with testicular or retroperitoneal tumor who have extensive disease burden requiring urgent initiation of treatment, substantial elevation in serum B-hCG and/or AFP may be considered sufficient for diagnosis of GCT [8].

While majority of the serum tumor markers are not used in staging of cancers, the TNM staging system for testicular GCTs incorporates serum tumor marker elevation as a distinct category [56]. The measurement of serum B-hCG and AFP after orchietomy provide guidance for risk stratification and determination of treatment plan [57]. For patients with advanced disease receiving chemotherapy, AFP and B-hCG levels are measured prior to each treatment cycle and upon completion of chemotherapy to assess for treatment response and for evidence of relapse or resistance to treatment. Initial increase in first cycle may be secondary to tumor lysis. Biological half-life of 24 - 36 h for hCG and 7 days for AFP need to be considered in evaluating the decline in serum hCG and AFP levels (Table 3 [2-5, 7-13]) [55]. However, lack of expected decline in tumor markers may be suggestive of resistance to treatment. A phase III trial of 263 patients with NSGCT treated with bleomycin, etoposide and platinum therapy were treated by an approach based on tumor marker response [58]. Patients with insufficient tumor marker decline underwent dose dense chemothera-

Table 3. Half-Lives of Serum Tumor Markers

Serial no.	Tumor marker	Half-life	Reference
1	CEA	3 - 5 days	[2]
2	CA 19-9	4 - 8 days	[3]
3	AFP	5 - 7 days	[4]
4	CA-125	5 days	[5]
5	PSA	1.83 h	[7]
6	B-hCG	24 - 36 h	[8]
7	Thyroglobulin	14 h	[9]
8	Calcitonin	30 h	[10]
9	LDH	24 h	[11]
10	5-HIAA	1.3 h	[12]
11	β 2M	2.5 h	[13]

CEA: carcinoembryonic antigen; CA 19-9: carbohydrate antigen 19-9; AFP: alpha-fetoprotein; CA-125: cancer antigen 125; PSA: prostate-specific antigen; B-hCG: beta-human chorionic gonadotropin; LDH: lactate dehydrogenase; 5-HIAA: 5-hydroxyindoleacetic acid; β 2M: beta-2 microglobulin.

py instead of standard dose. Among this group, patients treated with dose-dense therapy had 59% three-year progression-free survival compared to 48% in those with standard treatment dose [58]. Following successful treatment, serum B-hCG, AFP and LDH are monitored every 2 - 6 months to assess for recurrence as elevations in AFP and B-hCG may be the first signs of relapse. A sole rise in LDH is highly non-specific and must be interpreted carefully [57].

In addition to monitoring treatment response and recurrence, serum markers in NSGCTs also serve as independent prognostic factors based on the degree of elevation. Results from the International Germ Cell Cancer Collaborative Group (IGCCCG) of 5,202 patients with NSGCT showed that degree of elevation of AFP, hCG and LDH were independent predictors of risk along with mediastinal primary site and presence of non-pulmonary visceral metastases [59].

Thyroglobulin (Tg)

Tg is a glycoprotein produced exclusively by the thyroid follicular cells and is stored as colloid within the thyroid follicles [59]. Regulated by the thyroid-stimulating hormone (TSH), it is then iodinated and degraded to triiodothyronine and thyroxine. The normal range of TG varies based on gender, iodine intake as well as presence of anti-Tg antibodies (anti-Tg Abs). Gender-specific reference ranges of 1.40 - 29.2 ng/mL for males and 1.50 - 38.5 ng/mL for females have been proposed [9]. Notably, anti-Tg Abs are seen in up to 10% of patients with normal thyroid as well as up to 20% patients with Graves' disease, Hashimoto's disease and thyroid cancer, leading to falsely low levels of Tg [9]. The use of serum Tg as a screening and diagnostic tool is significantly limited due to low sensitivity of 70% and specificity of 80% [9]. In addition to differentiated thyroid cancers, benign conditions such as thyroiditis, Graves' disease may also lead to increased Tg levels. In peri-operative setting for thyroid cancer, measurement of Tg and anti-Tg Abs do not show significant association with disease staging or im-

proved overall survival [60].

However, serum Tg has clinical utility in monitoring and management of recurrent and metastatic disease in postoperative setting as per guidelines from American Thyroid Association and NCCN [60, 61]. Not only can the postoperative Tg levels assist in risk stratification of thyroid cancer, Tg levels can also help assess biochemical response to therapy and assess for disease recurrence [61]. Serum Tg reaches nadir approximately 3 - 4 weeks postoperatively and is checked in most patients 6 - 12 weeks following total thyroidectomy [60]. High postoperative Tg values (> 10 - 30 ng/mL) are associated with poor overall survival and conversely, low Tg (< 1 - 2 ng/mL) is one of the strong predictors of remission [62]. Additionally, elevated postoperative stimulated Tg levels, typically > 10 ng/mL, help identify patients who may benefit from radioiodine ablation (RAI). The risk of recurrence and metastasis rises in patients with rising postoperative Tg levels [62]. Serum Tg is also used for long-term monitoring of differentiated thyroid cancers, initially every 6 to 12 months and then annually if the patient remains disease free [61]. It is important to note that serum Tg level is typically used in conjunction with anti-TG Abs levels since some recurrences may present with normal Tg level with high anti-TG Abs. Furthermore, utility of serum Tg is limited in cancers with mutations of the Tg gene [9]. Despite these limitations, overall Tg serves as an excellent monitoring and prognostic marker in diagnosed differentiated thyroid cancers.

Calcitonin

Calcitonin is a 32-amino acid monomeric peptide which is secreted by the parafollicular C cells of the thyroid gland [63]. Although elevated calcitonin levels are a distinct hallmark of medullary thyroid cancer, small elevations are also seen in patients with chronic renal failure, autoimmune thyroiditis and in various neuroendocrine tumors, small cell lung cancers and at times, prostate cancer [63]. Interestingly, the calcitonin levels

in patients with non-thyroid malignancies do not appear to increase in response to pentagastrin stimulation [10].

Currently, there is no consensus between the European and the American guidelines regarding the routine measurement of serum calcitonin to detect medullary thyroid carcinoma (MTC) in patients with thyroid nodules. Whereas in Europe, pentagastrin stimulation is used to measure calcitonin levels, pentagastrin is not available for use in United States [63]. The current reference range for calcitonin level is < 10 ng/mL with high sensitivity and specificity for MTC; however, due to low prevalence of the disease, it has poor positive predictive value [10]. The opposition to routine calcitonin measurement stems from the risk of false positives in the setting of low prevalence with long-term implications for patients who may undergo unnecessary thyroidectomy as well as cost-effectiveness and lack of confirmatory pentagastrin stimulation testing [10, 61, 63]. However, in patients with large thyroid nodules in whom the fine-needle aspiration (FNA) is inconclusive or suggestive of MTC, calcitonin measurements in FNA washout fluid are recommended for diagnostic accuracy [61, 63].

In patients with diagnosed MTC, the degree of elevations in basal calcitonin levels may correlate with the degree of tumor burden and metastasis [63]. Postoperatively, calcitonin levels and calcitonin doubling time are monitored along with CEA levels to assess treatment response and disease recurrence/progression [61]. After curative surgery, serum calcitonin levels fall to undetectable levels. If serum levels remain low postoperatively, this is considered a biochemical cure. Persistently elevated or rising levels indicate residual cancer or presence of metastasis which requires further diagnostic imaging [64]. Furthermore, calcitonin doubling time has also been found to be an independent predictor of survival in multivariate analysis [64]. After definitive treatment, serum calcitonin levels may be monitored every 6 to 12 months for recurrence [61].

Lactate Dehydrogenase (LDH)

LDH is one of the most common enzymes that normally appears throughout the body and small amounts. LDH is released in response to cell damage and is generally a marker of cellular metabolic rate and tissue injury [11]. Elevated LDH levels may be seen in conditions of acute or chronic inflammation, infection as well as in heart failure, lung disease or liver disease, and frequently in many malignancies [11]. Given that elevated LDH levels are highly nonspecific, it is not generally considered a reliable tumor marker in aiding in diagnosis of most cancers. However, LDH levels can be used in diagnosing testicular masses suspicious for GCTs [58]. While sole rise in LDH requires careful interpretation, along with B-hCG and AFP, it can help establish initial diagnosis and risk stratification [57]. Additionally, in testicular cancer patients, the degree of LDH elevation corresponds to high tumor burden in seminoma and recurrence in NSGCT, whereas low LDH activity is associated with high likelihood of remission and is considered a good prognostic factor [55, 57].

In melanoma, serum LDH levels are incorporated into the

staging system [65]. The NCCN guidelines recommend obtaining serum LDH at the time of diagnosis of stage IV disease [65]. High levels of serum LDH are considered a surrogate for overall tumor burden and are an independent predictor of poor outcomes in patients with stage IV disease [66]. Additionally, prognostic scoring systems for several cancers have also incorporated the use of LDH levels to determine prognosis, including the international prognostic index (IPI) for prognosis of diffuse large B-cell lymphoma, FL international prognostic index (FLIPI) for follicular lymphoma as well as MCL international prognostic index (MIPI) for mantle cell lymphoma [67, 68].

5-Hydroxyindoleacetic Acid (5-HIAA)

5-HIAA, the main metabolite of serotonin, is one of the most commonly used biomarkers in evaluation and management of neuroendocrine tumors (NETs), especially when carcinoid syndrome (CS) is present [69]. 5-HIAA is considered a biochemical marker particularly in metastatic lung or small intestinal NETs since these tumors have the high secretion of serotonin and other vasoactive substances and are more likely to cause carcinoid syndrome which can present with symptoms of flushing, wheezing, diarrhea [70]. Although elevated production of 5-HIAA may aid in diagnosing some NETs, low or normal levels cannot rule out the presence of NETs. Thus, it does not serve as an effective screening marker and routine evaluation in asymptomatic individuals is not recommended [69].

Urine 5-HIAA excretion has been the preferred method of assessing elevated levels. A 24-h urine collection is required as random urine samples can produce varying concentrations [12]. In addition, a variety of foods rich in serotonin or tryptophan as well as certain medications including acetaminophen, naproxen, nicotine may affect 5-HIAA levels. Patients are advised to avoid these foods and medications for 48 h prior to the start of and during urine collection [70]. Evaluation of 5-HIAA levels may be useful in assessing response to treatment as well as monitoring for carcinoid heart disease in certain NETs [71]. Rising 5-HIAA levels may be indicative of poor or inadequate response to treatment whereas reduction in levels may indicate response to therapy [69]. A meta-analysis comparing urine 5-HIAA and mortality in patients with NETs showed a significant relationship, with every 10-fold increase in urine 5-HIAA associated with 11.8% increase in 1 year mortality among these patients [71]. This is likely due to development of carcinoid heart disease, which is associated with rising 5-HIAA levels and is an independent poor prognostic factor [72].

Beta-2 microglobulin (β 2M)

β 2M is a protein that forms one of the chains of the major histocompatibility complex (MHC) class I and plays a role in antigen presentation to cytotoxic T cells and immune homeostasis [13]. Elevated levels of β 2M may be seen in hematological malignancies such as multiple myeloma, chronic lympho-

cytic leukemia (CLL) and lymphomas. Elevated β 2M may also be observed in nonmalignant conditions such as inflammatory bowel disease, cytomegalovirus and human immunodeficiency virus (HIV) infection as well as dialysis related amyloidosis [13].

While β 2M is not utilized purely for screening of hematological malignancies, it plays a significant role in staging and as a prognostic factor. The Revised Multiple Myeloma International Staging System (R-ISS) incorporates serum β 2M levels in staging and prognosis of patients along with serum albumin, LDH and presence of high-risk genetic translocations [73]. Patients with high serum β 2M levels (> 3.5 mg/L) are noted to have significantly inferior survival compared to patients with low serum β 2M levels as elevated levels may possibly reflect greater tumor burden and renal involvement [73]. Additionally, serum levels of β 2M are also used to in determining prognosis in patients with CLL and is incorporated in the International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI) score as elevated β 2M levels are thought to correlate with advanced disease stage [74].

Conclusion

While many serum cancer markers are not recommended for use in screening for cancer, several markers such as PSA, B-hCG and AFP may be used to aid in cancer diagnosis. While serum cancer markers must be interpreted carefully due to poor sensitivity and association with multiple malignant and benign conditions, they are useful in patients with established cancers and play a significant role in monitoring for treatment response and assessing for relapse. Additionally, degree of elevation of many serum markers also serves as an independent prognostic marker in certain cancers.

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Conflict of Interest

The authors do not report any conflict of interest.

Author Contributions

Both authors AG and SD participated in conceptualization, methodology and literature search for the study. SD participated in the writing of the original draft. Both AG and SD were involved in editing and revision of the manuscript. All authors have read the final manuscript and agree to the content.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

CEA: carcinoembryonic antigen; CA 19-9: carbohydrate antigen 19-9; AFP: alpha-fetoprotein; CA-125: cancer antigen 125; CA 27-29: cancer antigen 27-29; PSA: prostate-specific antigen; B-hCG: beta-human chorionic gonadotropin; TG: thyroglobulin; LDH: lactate dehydrogenase; 5-HIAA: 5-hydroxyindoleacetic acid; β 2M: beta-2 microglobulin

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