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# Clinical Utility of Tumor Markers: What the Guidelines Recommend

# Kliniczna użyteczność markerów nowotworowych; wskazania i rekomendacje

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*Summary*

*Although a myriad of markers have been proposed for malignancy, only a minority have been adequately validated for routine clinical use. Apart from PSA in prostate cancer, markers are of little value in the detection of early malignancy. Several markers however, are currently used in the post-operative management of patients with diagnosed malignancy. Markers generally recommended for the management of patients with malignancy include CEA in colorectal cancer, AFP and HCG in patients with non-seminomatous germ cell tumors, AFP in hepatocellular cancer, CA 125 in ovarian cancer, CA 15-3 in breast cancer and CA 19-9 in patients with pancreatic cancer. Although widely used, the impact of PSA screening in reducing mortality from prostate cancer is inconclusive. Emerging markers include PCA3 and -2proPSA for prostate cancer, proGRP for small-cell lung cancer and HE4 for ovarian cancer.*

*Streszczenie*

*Spośród wielu markerów rozważanych w diagnostyce chorób nowotworowych, użyteczność w praktyce klinicznej tylko nielicznych została zwalidowana w odpowiedni sposób. Za wyjątkiem PSA dla raka stercza, markery są mało przydatne dla wykrywania nowotworów we wczesnych stadiach zaawansowania. Jednakże niektóre markery są obecnie wykorzystywane w pooperacyjnym prowadzeniu chorych na nowotwory złośliwe. Do markerów zalecanych w tym zakresie można zaliczyć CEA w raku jelita grubego, AFP i HCG u chorych na nienasieniakowate nowotwory zarodkowe, AFP w raku wątroby, CA 125 w raku jajnika, CA 15-3 dla raka piersi oraz CA 19-9 u chorych na raka trzustki. Należy podkreślić, że opinie odnośnie wpływu szeroko rozpowszechnionych badań przesiewowych z wykorzystaniem PSA na zmniejszenie śmiertelności z powodu raka stercza nie są przekonywujące. Do obecnie ocenianych markerów można zaliczyć PCA3 i [-2]proPSA dla raka stercza, ProGRP dla drobnokomórkowego raka płuca i HE4 dla raka jajnika.*

**Key words:** tumor markers, biomarkers, AFP, HCG, CEA, PSA, CA 15-3, CA 125

**Słowa kluczowe:** markery nowotworowe, biomarkery, AFP, HCG, CEA, PSA, CA 15-3, CA 125

The optimum management of patients with several different types of cancer requires measurement of specific tumor markers. Although generally of little value in the early detection of cancer, tumor markers are particularly useful following a diagnosis of malignancy such as in deciding which patients should have systemic therapy, choosing the optimum form of systemic therapy, surveillance following curative surgery for primary disease and monitoring therapy in advanced disease. Over the last few decades multiple markers have been proposed for clinical use [1,2,3]. However, only a small proportion of these have been validated for clinical use (Table 1). The aims of this article are to review the most widely used serum markers in clinical practice and summarise guidelines for their use.

## Clinically Used Markers

### *PSA in Prostate Cancer*

*Screening*

World-wide, the most widely used cancer marker is PSA. Most of this use involves screening for prostate cancer [4].

**Table 1.**
**Existing and emerging serum markers for solid cancers.**

| Cancer | Existing marker(s) | New Marker(s) |
|---|---|---|
| Prostate | PSA, free PSA | PCA3, proPSA |
| Colorectal | CEA, TPA, TPS | TIMP1 |
| Hepatocellular | AFP | DCP |
| Ovarian | CA 125 | HE4 |
| Breast | CA 15-3, CEA, TPA, TPS, soluble HER2 | |
| Testicular | AFP, HCG, LDH | |
| Pancreatic | CA 19-9, CEA | |
| Thyroid (differentiated) | Thyroglobulin | |
| Thyroid (medullary) | Calcitonin | |
| Lung (non-small cell) | CYFRA 21-1, CEA, SCC | |
| Lung (small-cell) | NSE | ProGRP |
| Melanoma | S100 | |

Although widely practised, screening for prostate cancer is controversial. One of the reasons for the controversy is that PSA is a less than an ideal marker in this setting. In particular, there is no cut-off point that clearly separates patients with cancer from men without cancer, i.e., there is no cut-off point below which a man can be reassured that he does not have prostate cancer. In most centers, the cut-off point for deciding whether or not a man should have a prostate biopsy following a PSA assay is 4 µg/L. However, at this cut-off point, prostate cancer was detected in about 15 % of men studied [5]. Importantly, about 15% of these had high grade disease (Gleason score of 7 or higher), suggesting a possible poor outcome.

While men with PSA levels < 4 µg/L generally do not progress to prostate biopsy, many men with levels > 4 µg/L are recommended to undergo such a procedure. However, for men with levels between 4 and 10 µg/L, only approximately 25-30% have a positive biopsy. In order to increase specificity in this grey area, additional tests such as free and complex PSA assays may be used [6]. Indeed, the National Academy of Clinical Biochemistry (NACB) (USA) now recommend use of % free PSA for reducing the number of biopsies in men with total PSA levels 4-10 µg/L [7]. Other markers that are currently undergoing evaluation for increasing specificity in the 4-10 µg/L concentration range for PSA, include PCA3 [8,9] and -2 proPSA [10,11].

As well as problems with the accuracy of PSA in detec -ting early prostate cancer, PSA screening is controversial for several other reasons. These include the possibility of over-detection and thus overtreatment of indolent prostate cancer and lack of clarity on the optimum treatment for patients with localized disease (i.e., whether it should be radical prostatectomy, radiotherapy or indeed just active surveillance). The most important reasons however, as to why prostate cancer screening is controversial relates to its potential to reduce mortality, i.e., it is still unclear whether PSA screening reduces mortality from prostate cancer.

In order to address this issue, 2 major randomized prospective trials have been in progress for in excess of 10 years [12,13]. Preliminary results from these 2 trials were published in 2009. One of these trials was carried out in the USA and the other at 7 sites in Europe [12,13]. In the American trial, 76,693 men were randomized to either annual screening or standard care [12]. Following analysis, similar rates of death were found in the 2 groups. A limitation of this study was that approximately 50% of men in the control group underwent screening during the study. This trial might thus be regarded as a comparison between frequent and infrequent screening. A further problem with this trial was the relatively short follow-up period, i.e., a median of 7 years.

In the European study, 162,243 men were randomly assigned to PSA screening at an average of once every 4 years or to a control group not subjected to screening [13]. After a median follow-up of 9 years, death rates from prostate cancer were 20% lower in the screened compared to the control group. However, the authors calculated that 1410 men would have to be screened and 48 additional cases of prostate cancer would have to undergo treatment to prevent one death from prostate cancer.

The main conclusion from these trials is that PSA screening has at best only a modest impact on decreasing mortality from prostate cancer. Furthermore, any possible benefit to some patients may be negated with overdetection and overtreatment [14]. It is thus unclear whether PSA screening does more good than harm. Clearly, further follow-up of both the above mentioned trials will be necessary before definite conclusions can be reached as to whether screening with PSA reduces mortality form prostate cancer.

Because of the lack of reliable evidence that PSA screening reduces mortality, guidelines published by different expert panels vary in their recommendations regarding population-based prostate cancer screening [for review, see ref. 7]. While some expert panels recommend screening others are opposed to the practice [7]. Most organizations however,

recommend a shared decision between doctor and patient and that a discussion take place between the 2 parties regarding the benefits and limitations of the early detection of prostate cancer. Only following such a discussion, should measurement of PSA be requested.

### *CEA in Colorectal Cancer*

*Postoperative surveillance*

The primary use of CEA in colorectal cancer (CRC) is in the postoperative surveillance of patients who have undergone curative surgery for this disease [15]. The aims of surveillance in these patients are to investigate possible therapeutic complications, identify a recurrence that is potentially respectable for cure and to detect new metachronous neoplasms at a preinvasive stage [16]. Several small studies have addressed to impact of intensive follow-up on patients with diagnosed CRC. Although the results from these trials have been mixed, meta-analyses of individual studies have shown that CRC patients undergoing intensive surveillance have a better outcome that those undergoing less intensive follow-up [17-22]. Regular determination of CEA, as part of the intensive surveillance, was shown to be essential for achieving this improved outcome [17,20].

Most expert panels in Europe and the USA thus currently recommend serial measurements of CEA following curative surgery for CRC [7,16,23-25]. According to the European Group on Tumor Markers (EGTM), "CRC patients with stage II and III (Dukes' B and C) CRC that may be candidates for either liver resection or systemic treatment in the event of recurrence in that organ, should have CEA measured every 2 to 3 months for at least 3 years after diagnosis [23,24]. Although serial measurements of CEA are widely recommended as part of a surveillance regime, agreement is lac-king as to the extent of concentration change that constitutes a clinically significant increase in marker levels. According to the EGTM group [23,24], "a significant increase in CEA levels occurs if the elevation is at least 30% over that of the previous concentration". This organization also state that prior to initiating therapy, this increase must be confirmed by a second sample taken within approximately one month. If the second sample is also increased, the patient should undergo further investigations such as imaging [24].

It is important to bear in mind that the above definition of CEA increase has not been clinically validated or indeed the optimum for predicting early recurrence. For example, small consistent increases in CEA concentration (e.g. 15-20% maintained over at least three successive assays) may also prompt intervention [24]. Doctors should also be aware that low concentrations of CEA concentrations do not necessarily exclude progression, and in patients with clinical symptoms of disease recurrence, additional tests such as CT-scan, X-rays, and colonoscopy are required, irrespective of the CEA concentration [24].

Some patients undergoing surveillance may show increasing CEA levels in the absence of any symptoms, i.e., measurement of the marker provide a lead-time. Increasing CEA levels in an asymptomatic patient creates a dilemma as to whether or not to initiate new treatment. According to the National Comprehensive Cancer Network (NCCN) [16] in the USA, colonoscopy, chest, abdominal, pelvic CT scans and physical examination should be performed while a PET scan should be considered. If imaging is normal, CT scans should be repeated every 3 months until either disease is identified or CEA concentrations stabilize or declines.

It should be stated that not all patients with metastatic CRC release high levels of CEA into blood. For monitoring these patients, other markers such as CA 19-9, CA 242, TIMP-1 or TPA/TPS may be used [24]. None of these markers however, have been as extensively evaluated as CEA and indeed, none have been shown to be superior to CEA.

*Monitoring Therapy in Advanced Diseased*

The second main use of CEA in CRC is in monitoring therapy in patients with advanced CRC. The rationale for using CEA in this setting is based on the findings that serum levels generally increase with progressive disease and decline with regressing disease. As with surveillance, most guidelines recommend use of CEA in monitoring therapy in patients with advanced CRC [7, 23-25]. Ideally, this should be done in conjunction with other modalities such as imaging. There is however, no data suggesting that monitoring therapy in patients with advanced CRC enhances outcome or quality of life.

### *AFP in Hepatocellular Cancer*

*Screening High-Risk Subjects*

A frequent use of AFP is in surveillance for hepatocellular cancer (HCC) in subjects at high-risk for this disease. Subjects at increased risk of developing HCC include those with cirrhosis due to infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), genetic haemochromatosis or biliary cirrhosis [26]. One of the problems in using AFP in this setting is limited sensitivity and specificity for early HCC. In a recently published multicenter study, involving 419 cases of HCC and 417 controls with cirrhosis, AFP had a sensitivity of 66% and a specificity of 82% for early HCC [27]. The optimum cut-off point for AFP was found to be 10.9 μg/L. In this study, the presence of cirrhosis was verified by histology or evidence of portal tension with chronic liver disease. Histology and imaging but not AFP was used to diagnose HCC.

Different views exist on the value of AFP screening in screening for HCC in subjects at increased risk of developing this malignancy [26,28-30]. Thus, the American Association for the Study of Liver Disease (AASLD) [26] state that surveillance should be performed using ultrasound and that AFP should only be used when ultrasound is not available. On the other hand, NCCN [28] recommends the use of both AFP and ultrasound in screening high risk subjects for HCC. According to the NACB guidelines [30], "AFP should be measured and abdominal ultrasound performed at six-monthly

intervals in patients at high risk of HCC, especially in those with hepatitis B and hepatitis C-related liver cirrhosis. AFP concentrations that are >20 μg/L and showing consistent increases in concentration should prompt further investigation even if ultrasound is negative".

Aiding Diagnosis

In contrast to the situation in surveillance of high risk groups, most expert panels recommend the use of AFP in aiding the diagnosis of HCC. According to the AASLD [26], detection of a hepatic mass > 2 cm in diameter in a patient with a cirrhotic liver is highly suspicious of HCC. If AFP is >200 μg/L and the radiological appearance is suggestive of HCC, the likelihood is that the lesion is HCC and biopsy is not essential. Similar statements have been published by other organizations [28-30]. AFP however, is of limited value in aiding the diagnosis of lesions < 2 cm in diameter.

### *AFP and hCG in Patients with Germ Cell Tumors*

*Surveillance and Monitoring Therapy*

Two main types of germ cell tumor exist, seminomatous and non-seminomatous. Non-seminomatous tumor may express both AFP and hCG but pure seminomatous types only produce hCG [31]. The use of AFP and hCG in monitoring patients with the non-seminomatous type is often regarded as approximating the ideal use of tumor markers. This is because these 2 markers are sensitive indicators of disease status, i.e., whether disease is stable, progressing or regressing. A further reason why these markers are particularly useful in patients with germ cell tumors is that these malignancies are highly chemosensitive. Indeed, it is now widely accepted that following orchidectomy for non-seminomatous testicular germ cell tumors, that increasing AFP or hCG levels in the absence of radiological or clinical evidence of disease suggests active disease and may provide sufficient reassurance to initiate treatment, provided likely causes of false positive marker levels can be eliminated [31,32]. Measurement of both AFP and hCG are essential in this setting as different clones of malignant cells may be associated with the different markers.

According to the 2010 ASCO guidelines, AFP and hCG should be measured during surveillance following definite therapy for NSGCT, regardless of stage [33]. These measurements may be carried out every 1 to 2 months in the first year, every 2 to 4 months in the second year, every 3 to 6 months in the third and fourth years, every 6 months in the fifth year and annually thereafter. Surveillance should continue for at least 10 years after therapy is completed. The organization states however, that there is no evidence that such monitoring improves survival or impacts on other health outcomes. Furthermore, the suggested frequency of monitoring is not evidence-based. The hCG assay used should detect the intact molecule as well as a broad range of its isoforms [30].

For monitoring patients with pure seminoma, ASCO recommends hCG and/or LDH [33].

*Determining Prognosis*

A further mandatory use of AFP and hCG in patients with non-seminomatous type tumors is in staging and determining prognosis. Indeed, measurement of hCG and AFP, as well as LDH, were the first markers to be included in the Union Internationale Contre le Cancer (UICC) TNM staging system for NSGCT [34]. Measurement of these markers for staging patients with metastatic NSGCT is therefore now recommended by multiple Expert Panels [30].

As well as static levels, dynamic levels of AFP and hCG may also be used to determine prognosis in patients with NSGCTs. After complete resection of these maligancies, AFP and hCG decrease in an exponential fashion with a half-life for clearance of approximately 5-7 and 1-2 days, respectively [32]. Some, but not all studies, have shown a significant independent association between a prolonged half-life for these markers and poor outcome [35-40].

The conflicting results on the relationship between marker half-life and prognosis may relate to the lack of a standardized approach for determining AFP and hCG half-lives. For determining AFP and hCG half-lives in patients with NSGCT, Mazumdar et al [39] recommended that markers levels be determined weekly during the first 2 cycles of chemotherapy. As some patients have transient markers increases immediately after the start of chemotherapy, values determined during the first week of treatment should be excluded from the marker decline calculation [39]. A further reason for the conflicting findings between AFP and hCG decline rates and prognosis in patients with non-seminomatous GCT may relate to the relatively small numbers of patients included in most of the published studies.

As AFP is never elevated in patients with pure seminomatous germ cell tumors, it cannot be used to help with prognosis for patients with this tumor type. Thus, the only markers potentially useful for determining prognosis in patients with seminomatous germ cell tumor are hCG and especially LDH. Based on pooled data from 660 patients with seminoma, the only independent prognostic factors for seminoma were the presence or absence of non-pulmonary visceral metastasis and LDH levels [34]. In contrast to the situation in NSGCT, levels of hCG were only of borderline statistical significance. This prognostic benefit of LDH in seminoma was recently confirmed in a large multi-center study using 803 patients [41]. The most important prognostic factor in patients with seminoma however, is the presence or absence of metastasis in an organ other than lung [33].

### *CA 125 in Patients with Ovarian Cancer*

*Differentiating Between Benign and Malignant Pelvic Masses*

A pelvic mass is an enlargement or swelling in the lower abdomen or pelvic region. Pelvic masses may originate from gynecologic organs (cervix, uterus, uterine adnexa) or from other pelvic organs (intestine, bladder, ureters, skeletal muscle, bone). In premenopausal women, almost all of these

masses are benign. However, in postmenopausal patients, such masses may be malignant in 15-20% of cases [42]. Differentiation between these 2 types of pelvic mass is important, as women likely to have ovarian malignancy should be referred to a hospital specializing in gynecological oncology surgery. This recommendation is based on multiple studies showing that women operated on by specialist gynecological oncologists have decreased morbidity and mortality as well as increased overall survival, compared to those operated on by a general surgeon [43-46]. Therefore, for optimum outcome, it is important that women presenting with pelvic masses suggestive of ovarian cancer should be referred to a specialist center.

Several expert panels including EGTM, NACB and American College of Obstetricians and Gynecologists [7,47,48] therefore now recommend measurement of CA 125, especially in postmenopausal women presenting with a pelvic mass. In general, patients with malignant masses have higher levels of this marker than those with benign masses. Thus, the EGTM recommend that postmenopausal women with a pelvic mass and an elevated level of CA 125 levels (e.g., > 35 U/L) should be considered for referral to a surgeon specialized in gynecological surgery [47].

For premenopausal women, CA 125 is less useful in differentiating between malignant and non-malignant pelvic masses, as several benign diseases may produce elevated marker levels. Despite this, the American College of Obstetricians and Gynecologists suggest that premenopausal patients with a pelvic mass and a highly elevated CA 125 level (e.g., > 200 U/L) should be considered for referral or consultation with a gynaecological oncologist [48]. An emerging marker that may be combined with CA 125 in distinguishing between benign and malignant pelvic masses is HE4, see below.

*Surveillance*

The role of CA 125 in post-therapy monitoring of patients with a history of ovarian cancer is unclear. Although serial measurement of the marker may detect early recurrences with median lead-time of 4-5 months [49], results of a recently-completed prospective randomized trial found no survival benefit from early treatment based on a raised serum CA125 level alone [50,51]. This trial involved 1442 women diagnosed with ovarian cancer but in clinical remission. CA 125 levels were measured every 3 months but the results were not made available to patients or their doctors. The women were randomized as soon as their levels reached twice the upper limit of normal, to receive treatment immediately or to continue with blinded CA 125 determinations. In this latter situation, women underwent treatment only when there was evidence of recurrence. No difference in overall survival was found in the 2 groups, even though second-line chemotherapy was initiated a median of 4.8 months earlier in the immediate treatment group [50,51].

This negative finding may relate to the relatively poor therapy currently available for recurrent ovarian cancer. Uncertainties therefore exist with respect to the value of surveillance and timing of treatment for relapsed disease. Patients should be informed of these uncertainties and become involved in decisions regarding their management [51].Whether or not to use CA 125 is this situation may therefore depend on the wishes of the patient who should be informed of the results of the above trial. A joint decision of the patient and her doctor should then be made as to the follow-up procedure [51]. Although the NACB panel currently recommends serial measurement of CA 125 following therapy for ovarian cancer [7], the EGTM panel are opposed to this practice [47].

*Monitoring Therapy in Advanced Disease*

Unlike the situation in post-therapy surveillance, it is generally agreed that CA 125 should be used in monitoring therapy in patients with ovarian cancer. Monitoring response to therapy in ovarian cancer can be particularly difficult as following surgery, many patients have low volume disease that may not be palpable or readily detectable by radiological procedures such as CT or ultrasound. In this situation, the use of serial determination of CA 125 has been recommended [52,53].

For monitoring response to initial chemotherapy, Rustin et al has proposed 2 separate definitions, i.e., either a 50% or a 75% decrease in CA 125 levels [52,53]. With the 50% response criteria, 4 separate blood samples are required, i.e., 2 initial samples showing an elevation with 2 subsequent samples showing a 50% decrease. For the 75% response definition, only 3 samples are necessary, which must exhibit a serial decrease of at least 75%. For the 2 definitions, the final sample must be taken at least 28 days after the previous sample. Both definitions are necessary as some responses are detected by only one of the definitions. It should be pointed out that patients with initial concentrations of CA 125 < 40 U/L cannot be evaluated using these definitions [52,53]. Whether these definitions can be used with the new biological therapies undergoing evaluation in patients with ovarian cancer remains to be investigated.

***CA 15-3 in Breast Cancer***

*Surveillance*

Although several serum markers have been proposed for breast cancer (CEA, TPA, TPS, CA 125 and the shed form of HER2), the most wisely used is CA 15-3 [54,55]. Unlike the situation in ovarian cancer however, no large prospective randomized has investigated the clinical impact of serially measuring CA 15-3 in the postoperative surveillance of women with diagnosed breast cancer. It is thus unclear whether regular measurement of this marker affects patient outcome or quality of life. Consequently, guidelines vary in their recommendations with respect to the role of CA 15-3 in monitoring asymptomatic women post breast cancer diagnosis. While organizations such as ASCO [56,57] and NCCN [58] recommend against routing use of CA 15-3 in surveillance, EGTM recommend its measurement in this setting [59]. According to the NACB guidelines, “CA 15-3 should not be routinely used for the early detection of recurrences/me-

tastases in patients with diagnosed breast cancer. However, as some patients, as well as some doctors, may wish to have these measurements, the ultimate decision on whether or not to use CA 15-3 must be taken by the doctor in consultation with the patient" [3].

Although the clinical value of CA 15-3 in the postoperative surveillance of patients with diagnosed breast cancer has not undergone evaluation in a larger prospective trial, a non-randomized prospective study is currently in progress [60]. This study involves serial measurements not only of CA 15-3 but also CEA and CA 125 in asymptomatic women who had undergone curative surgery for breast cancer. Of 681 patients participating in the study, 91 have so far developed metastasis. Of these 91 patients, 66 showed predefined increases (≥100%) of early CA 15-3, CEA or CA 125 at time of first metastasis. Of these 3 markers, CA 15-3 was the most sensitive in detecting early metastasis. Twenty five patients (27%) failed to show an increase in any of the 3 markers at the time of first metastasis. The effect of the preclinical detection of recurrence/metastasis on overall survival remains to be shown.

*Monitoring Therapy in Advanced Disease*

The main use of CA 15-3 in patients with breast cancer is monitoring therapy in patients with metastatic disease [54,55]. Ideally, in this situation, CA 15-3 should not be used alone but in combination with imaging. According to the EGTM guidelines, CA 15-3 should be used for monitoring therapy in patients with advanced breast cancer [59]. This Panel also state that, "marker levels should be measured prior to every chemotherapy course and at three monthly intervals for patients receiving hormone therapy" [59]. EGTM defines a clinically significant increase in marker level as an increase of at least 25% over the previous value. This increased concentration should be confirmed with a second sample taken within one month. A confirmed decreased marker concentration of more than 50% was stated to be consistent with tumor response [59]. It should be pointed out that these increases and decreases in markers levels have not been validated using high level evidence studies such as large prospective trials.

***CA 19-9 in Pancreatic Cancer***

*Postoperative Surveillance*

The most widely used serum marker in patients with pancreatic cancer is CA 19-9. Although of limited value in the detection of pancreatic malignancy, especially early disease, several studies have shown that serial determinations of CA 19-9 can detect progression of pancreatic cancer several months prior to finding clinical or radiological evidence [61]. As with CA 15-3 in breast cancer, the clinical impact of this lead-time is unclear, i.e., whether its availability improves patient outcome or increases quality of life. According to the ASCO guidelines, CA 19-9 measurements by themselves cannot provide definite evidence of disease recurrence without confirmation by imaging for clinical findings and/or biopsy [25].

*Monitoring Therapy in Advanced Disease*

Evaluating response to systemic therapy in patients with locally advanced pancreatic cancer may be difficult using imaging procedures due to extensive desmoplasia and surrounding inflammatory changes [62,63]. As a result, objective assessment of tumor response can be unreliable, imprecise and lack reproducibility. Furthermore, several new biological treatments for pancreatic cancer may be cytostatic rather than cytotoxic and thus may not shrink tumor size.

Because of these difficulties, a number of investigators have attempted to use serial CA 19-9 measurements in an attempt to assess response in patients with advanced pancreatic cancer undergoing treatment with systemic therapy [63-66]. Although different definitions of CA 19-9 response were used in the various studies (varied between 20% and 50%), most but not all found that patients with declining marker levels, following initiation of chemotherapy, had a better outcome than those showing no decrease [63-66].

Thus, according to the ASCO guidelines, present data are insufficient to recommend the routine use of CA 19-9 alone for monitoring response to therapy [25]. CA 19-9 however, can be assayed at the start of therapy for locally advanced or metastatic disease and every 1 to 3 months during active therapy. If serial levels of CA 19-9 increase, this may indicate disease progression. Confirmation of progression should be established with additional testing. The optimum frequency of CA 19-9 testing as well as the magnitude of change in concentration that is likely to be clinically significant remains to be established, see below.

***New Markers***

In recent years, several new cancer markers have emerged including PCA3 and -2proPSA for prostate cancer, HE4 for ovarian cancer and proGRP for small-cell lung cancer (SCLC). The PCA3 test detects a non-coding mRNA in urine. Unlike PSA, PCA3 levels are significantly increased in prostate cancer tissue compared with surrounding normal or benign prostate tissue [67]. Although PCA3 is unlikely to replace PSA as the frontline marker for prostate cancer, the combined measurement of both should result in enhanced specificity for prostate cancer diagnosis [8,9,68,69]. Assay of PCA3 may be of particular value in patients with elevated PSA levels but who have histologically-negative biopsies. In this situation, PCA3 could provide information in deciding whether or not to repeat a biopsy.

Another emerging marker for prostate cancer is -2proPSA. It is now known that the precursor of PSA exists as multiple forms. One of these proforms, known as -2proPSA form was found to be overexpressed in malignant compared to benign prostate cells. Subsequently, an assay was developed for the measurement of this protein in serum [10,11]. Using blinded samples from 123 men with no prior history of prostate cancer, Sokoll et al [10] showed that %-2proPSA was a better predictor of prostate compared to the %fPSA. This finding especially applied to men with total PSA in the

2-10 µg/L range. At a sensitivity of 90%, %-2proPSA had a specificity of 37% compared to 32% for %fPSA.

HE4 is a promising new marker for ovarian cancer. Its main use is likely to be in combination with CA 125 in differentiation between patients with benign and malignant pelvic masses [70-72]. An important point about HE4 is that it appears to be a more sensitive marker of early stage ovarian cancer than CA 125 [70,72]. Indeed, in one study HE4 levels were increased in > 50% of women with tumors and low levels of CA 125 [72].

Finally, proGRP has emerged as the most accurate marker for patients with SCLC [73-79]. Although not absolutely specific for SCLC, available data suggests that it is preferentially elevated in patients this specific malignancy. Its main use is likely to be in distinguishing SCLC from other types of lung cancers, especially when a histological diagnosis is not possible. It may also be useful in monitoring treatment in patients with small cell lung cancer. A relative common non-malignant disease that can give rise to elevated proGRP levels is benign kidney disease.

*Conclusion*

From the data presented above, it is clear that in certain situations, tumor markers play a critical role in the management of patients with certain types of cancer. Indeed, in some situations, markers can be used as the sole criterion for clinical decision making. A good example of this is the use of hCG and AFP in therapy decision making in patients with diagnosed NSGCT. In other situations however, the value of markers is less clear, e.g, role of PSA in screening for prostate cancer and assay of CA 15-3 in the surveillance of patients following the diagnosis of breast cancer. Hopefully, ongoing prospective studies will provide definite answers on the use of these markers, in the near future.

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