Guidelines for the use of tumour markers

ACBI
Scientific
Committee
Guidelines

Guidelines for the use of tumour markers

Association of Clinical Biochemists in Ireland

MJ Duffy P McGing

Produced by the
Scientific Committee
of the
Association of Clinical Biochemists in Ireland
(ACBI)

Fifth edition: November 2018

Other booklets in this series

Guidelines on the use of biochemical cardiac markers and risk factors
Guidelines on the use of therapeutic drug monitoring
The biochemistry of body fluids

Contents

Preface

This is the 5th edition of the well-known and much used publication 'Guidelines for the use of Tumour Markers', and is part of a series commissioned and produced by the Scientific Committee of the Association of Clinical Biochemists in Ireland to promote appropriate and effective use of the laboratory service. It is intended to be a concise reference document to assist both practitioners in the Clinical Biochemistry field and those who are users of the laboratory service. Further to the previous edition, this fifth edition contains additional reference to recent scientific evidence and expert consensus and incorporates guidance from the National Cancer Prevention Programme's GP referral guidelines for ovarian and prostate cancer. There is a new section on Companion Diagnostics whereby Therapy Predictive markers enable a personalised approach to cancer treatment.

On behalf of ACBI Council, I would like to express our gratitude to the individual authors for their work on this project. In particular, we are honoured to have Prof Joe Duffy as the lead author. Prof Duffy continues to publish extensively in this field and has been a lead contributor to major international guidelines for the use of Tumour Markers. Council is also grateful to the Diagnostics Division of Abbott Laboratories Ireland for their generous financial contribution to the printing costs of this new edition.

Dr Graham Lee,
President, ACBI

November 2018

Introduction

The purpose of this booklet is to give a brief background to enable the judicious use of seven widely performed serum cancer markers. The format used here is similar to that in previous editions.

In addition to these marker specific sections, the fourth edition saw the introduction of guidance on the difficult issue of Use of Tumour Markers in Diagnosing Cancer of Unknown Primary Origin (Occult Cancers).

In this 5th edition we have added a section on Therapy Predictive markers, commonly known as Companion Diagnostics.

Although use of serum marker half-life has declined in use, we have retained this information as it can be useful in determining response to treatment, particularly for markers AFP, hCG, and CA125.

While this booklet gives specific details relating to the most frequently used markers, we feel that it is important to make some general points about tumour marker tests. These are listed in Serum Tumour Markers - Key Points section.

Serum Tumour Markers - Key Points

- No serum marker in current use is specific for malignancy.
- Generally, serum marker levels are rarely elevated in patients with early malignancy. With a few exceptions, high levels are usually found only when patients have advanced disease.
- No cancer marker has absolute organ specificity. PSA, however, appears to be relatively specific for prostate tissue, but not for prostate cancer.
- Apart from possibly hCG in choriocarcinoma, no marker is elevated in 100% of patients with a particular malignancy.
- Requesting of multiple markers (such as CEA and the CA series of antigens) in an attempt to identify metastases of unknown primary origin is rarely of use (see below).
- Requesting of multiple markers in cases of query cancer (such as 'unexplained weight loss') is inappropriate and ineffective.
- Tumour markers assays should not be carried out on biological fluids such as peritoneal fluids, pancreatic juice and ovarian cystic fluids as reliable reference ranges are currently unavailable for these types of specimen. Furthermore, assays for the existing biomarkers have only been validated for serum or plasma. If tumour markers are analysed in such fluids the report should include comment on the lack of validation in that fluid and also lack of reference values.
- Reference ranges for cancer markers are not well defined and are used only for guidance. Please note that a level below the reference range does not exclude malignancy while concentrations above the reference range do not necessarily mean the presence of cancer. Changes in levels over time are likely to be more clinically useful than absolute levels at one point in time.
- As many tumour markers lack agreed International Reference Preparations (e.g. CA125, CA15-3, CA19-9), different assay kits may give different results for the same sera.
- Laboratories carrying out tumour marker tests should always state the assay used on their report form.

General References on Tumour Markers

1. Duffy MJ, Sturgeon CM, Sölétormos G, Barak V, Molina R, Hayes DF, Diamandis EP, Bossuyt PM. Validation of New Cancer Biomarkers: A Position Statement from the European Group on Tumor Markers. Clin Chem 2015;61:809-820
2. Duffy MJ. Use of Biomarkers in Screening for Cancer. Adv Exp Med Biol. 2015;867:27-39.
3. Duffy MJ. Tumor markers in clinical practice: a review focusing on common solid cancers. Med Princ Pract. 2013;22(1):4-11.
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Alpha-Fetoprotein (AFP)

Structure
AFP is a 70 kDa glycoprotein homologous to albumin.

Forms in serum
AFP exhibits microheterogeneity probably due to varying levels of glycosylation. AFP produced by malignancies appears to be more highly fucosylated than that formed by normal tissues.

Physiological function
Appears to perform some of the functions of albumin in the foetal circulation.

Malignancies with elevated levels
Mainly confined to three malignancies, i.e.

a. Non-seminomatous germ cell tumours (NSGCT) of testis, ovary and other sites.
b. Hepatocellular carcinoma (HCC).
c. Hepatoblastoma (in children, extremely rare in adults).
d. AFP may be occasionally elevated in patients with other types of advanced adenocarcinoma.

Benign conditions which may have elevated levels
Hepatitis, cirrhosis, biliary tract obstruction, alcoholic liver disease, ataxia telangiectasia and hereditary tyrosinaemia.

Physiological conditions with elevated levels
Pregnancy and the first year of life. Infants have extremely high levels which fall to adult values between 6 months and 1 year of age. A slower than normal rate of fall may indicate the presence of a tumour.

Main clinical applications
a. In combination with hCG, for monitoring patients with NSGCT (mandatory).
b. Independent prognostic marker for NSGCT (e.g. of the testis).
c. Diagnostic aid for hepatocellular carcinoma and hepatoblastoma. In patients with cirrhosis and a focal lesion >2 cm with arterial hypervascularization, an AFP level >200 µg/L is suggestive of HCC, and AFP>400 µg/L is strongly suggestive of HCC.
d. Screening for hepatocellular carcinoma in high risk populations (e.g. in patients with cirrhosis due to hepatitis B or C). Surveillance is

recommended using 6-monthly AFP measurement and abdominal ultrasound, with AFP>20 μg/L and rising prompting further investigation.

e. Note that AFP is not a useful marker for liver metastases; in such cases CEA is preferable marker.

Reference range

0 - 10 kU/L or 0 - 12 μg/L

Half life in serum

Approx. 5 days.

Comment on assay

Existing immunoassays appear to detect total AFP and do not discriminate between different glycosylated forms.

References

1. International Germ Cell Cancer Collaborative Group. International germ cell consensus classification: a prognostic factor-based staging system for metastatic germ cell cancers.
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   National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Liver, Bladder, Cervical, and Gastric Cancers.
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CA 125

Structure

CA 125 refers to the antigen originally detected by the OC-125 antibody. The protein detected by this antibody is Muc16, a mucin with a single transmembrane domain.

Forms in serum

The major forms in serum have molecular weights of 200 kDa to 400 kDa.

Physiological function

None established.

Malignancies with elevated levels

a. Epithelial ovarian cancer; 80 - 85% of all cases; but increased in only half of early (stage 1) cancer.
b. May be elevated in any adenocarcinoma with advanced disease.

Benign conditions which may have elevated levels

Endometriosis, acute pancreatitis, cirrhosis, peritonitis, inflammatory pelvic disease, chronic renal failure, acute hepatitis. The presence of ascites (of non-malignant origin) can also give rise to elevated serum levels of CA 125. Elevated levels may also be found in patients with pleural effusion.

Physiological conditions with elevated levels

Menstruation and pregnancy may be associated with moderately elevated serum CA 125 (usually not more than 100 kU/L)

Main clinical applications

a. While CA125 should not be used in screening asymptomatic women for sporadic ovarian cancer, its measurement, in combination with ultrasound, in postmenopausal patients with pelvic masses may help differentiate malignant from benign lesions.
b. The rate of decline during initial therapy is an independent prognostic indicator in ovarian carcinoma.
c. Monitoring treatment with chemotherapy.
d. Surveillance following initial treatment. The impact of this on survival is unclear.

Type of sample for assay

Serum is recommended.

CA 125 may be assayed on other fluid samples (e.g. ascitic fluid) but this cannot be recommended (outside of research projects), on analytical and interpretational grounds.

Reference range

0 - 35 kU/L (most frequently used range).

Please note however, that levels may be higher in premenopausal than postmenopausal women.

Half life in serum

Approx. 5-7 days.

References

1. Duffy MJ, Bonfrer JM, Kulpa J, et al. CA 125 in ovarian cancer: European Group on Tumor Markers (EGTM) guidelines for clinical use.
   Int J Gynecol Oncol 2005;15:679
2. Sölétormos G, Duffy MJ, Othman Abu Hassan S, Verheijen RH, Tholander B, Bast RC Jr, Gaarenstroom KN, Sturgeon CM, Bonfrer JM, Petersen PH, Troonen H, CarloTorre G, Kanty Kulpa J, Tuxen MK, Molina R. Clinical Use of Cancer Biomarkers in Epithelial Ovarian Cancer: Updated Guidelines from the European Group on Tumor Markers.
   Int J Gynecol Cancer. 2016 Jan;26(1):43-51.
3. NCCP Guideline Ovarian Cancer GP Referral For Symptomatic Women (Republic of Ireland): http://www.hse.ie/eng/services/list/5/cancer/profinfo/resources/gpreferrals/Ovarian%20Guidelines.pdf
4. NICE Guideline Ovarian cancer: recognition and initial management (UK): https://www.nice.org.uk/guidance/cg122/chapter/1-Guidance#detection-in-primary-care

CA 15-3

Structure

CA 15-3 is a transmembrane glycoprotein encoded by the MUC1 gene. It is defined by reactivity with 2 monoclonal antibodies, i.e., DF3 and 115D8 in a sandwich immunoassay.

Physiological function

May be involved in cell adhesion and cancer pathogenesis.

Malignancies with elevated levels

Breast and other adenocarcinomas, especially with distant metastasis. Rarely elevated in patients with local breast cancer.

Benign diseases with elevated levels

Benign liver disease, possibly benign breast disease.

Main clinical applications:

a. For preclinically detecting recurrences in asymptomatic patients with diagnosed breast cancer. Use of CA 15-3 in this setting is controversial.

b. For monitoring the treatment of patients with advanced breast cancer, especially in patients with disease that cannot be evaluated using standard criteria. Should not be used alone in monitoring treatment.

Reference range

0 – 25 to 0 – 40 kU/L

Half life in serum

Unknown

Comment about assay

Other assays such as BR 27.29 appear to measure the same antigen as CA 15-3

References

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2. Duffy MJ. Serum tumor markers in breast cancer: are they of clinical value?
   Clin Chem 2006;52:345-51.
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   J Clin Oncol 2015;33:2695-704.

CA 19-9

Structure
A mucin which reacts with monoclonal antibody 111 6 NS 19-9.

Physiological function
May be involved in cell adhesion.

Malignancies with elevated levels
Most pancreatic adenocarcinomas, approx. 50% of gastric carcinomas and approx. 30% of colorectal carcinomas. It has been reported that Lewis-antigen negative patients may not express CA19.9.

Benign conditions which may have elevated levels
Acute and chronic pancreatitis, hepatocellular jaundice, cirrhosis, acute cholangitis and cystic fibrosis.

Main clinical applications
a. As a diagnostic aid for pancreatic carcinoma. Inadequate sensitivity and specificity limit the use of CA 19-9 in the early diagnosis of pancreatic cancer. However, in non-jaundiced patients, CA 19-9 may complement other diagnostic procedures.
b. Monitoring treatment of patients with pancreatic adenocarcinoma.

Other potential uses
Diagnostic aid in gastric and cholangio carcinomas. For colorectal cancer, CEA is generally more valuable than CA 19-9.

Reference range
Very variable, from 0 - 37 kU/L to 0 - 100 kU/L

Half life in serum
Approx. 1 day but can vary from less than 1 day to 3 days.

Comment about assay:
Assays from different manufacturers can give markedly different results, particularly at elevated levels.

References

1. Duffy MJ, Sturgeon C, Lamerz R, *et al*, Tumor Markers in Pancreatic Cancer: A European Group on Tumor Markers (EGTM) Status Report.
   Ann Oncol 2010;21:441-447.
2. Scarà S, Bottoni P, Scatena R. CA 19-9: Biochemical and Clinical Aspects.
   Adv Exp Med Biol. 2015;867:247-60
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   Tumour Biol. 2017 Jun;39(6):1010428317692231.

CEA

Structure
A 200 kDa (approx.) glycoprotein.

Physiological function
Appears to play a role in cell adhesion and inhibition of apoptosis.

Malignancies with elevated levels
Can be elevated in almost any advanced adenocarcinoma, i.e., where distant metastases are present. Almost never elevated in early malignancy.

Benign diseases which may have elevated levels
Hepatitis, cirrhosis, alcoholic liver disease, obstructive jaundice, ulcerative colitis, Crohn's disease, pancreatitis, bronchitis, emphysema and renal disease. Levels may also be mildly elevated in apparently healthy individuals who smoke.

Physiological conditions with elevated levels
None to our knowledge.

Main clinical applications
a. In surveillance following curative resection of colorectal cancer.
b. In monitoring therapy in advanced colorectal cancer. This is especially important when disease cannot be evaluated by standard criteria.

Other potential uses
May also be useful in other gastrointestinal malignancies and as a "general purpose" marker for adenocarcinomas. Please note however, that CEA is rarely elevated in patients with any type of local cancer.

Reference range
0 - 3.5 µg/L to 0 - 5.0 µg/L.

Half life in serum
Approx. 3 days but can vary from 1 to 5 days.

References

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   Int J Cancer 2014;134:2513-22.
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   Eur J Cancer 2003;39:718-727.
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   J Clin Oncol 2006;24:5313-27.
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   Eur J Cancer 2007;43:1348-1360.

Human Chorionic Gonadotropin (hCG)

Structure

hCG is a heterodimer composed of two glycosolated sub-units (alpha and beta chains) non-covalently bonded. The alpha chain is almost identical to the alpha chain in TSH, FSH and LH. The beta chain is distinct from the corresponding chains in TSH and FSH but has a high degree of homology with LH over the first 75% of the amino sequence. hCG however, possesses a distinctive 24 amino acid carboxy-terminal extension.

Forms in serum

hCG can exist in multiple forms including the intact 2-chain peptide, free alpha and beta chains, as well as various degradation products (e.g. beta core fragment).

Physiological function

To maintain progesterone production by the corpus luteum during early pregnancy. hCG can be detected as early as one week after conception.

Malignancies with elevated levels

a. Virtually all patients with gestational trophoblastic disease (GTD) (i.e. complete and partial molar pregnancy, choriocarcinoma and placental site trophoblastic tumours).
b. Non-seminomatous germ cell tumours (NSGCT) (e.g. of testis and ovary).
c. Seminomatous germ cell tumours of testis (approx. 20%).
d. Can be produced by a small number of other malignancies.
e. False positive pregnancy test can be due to atypical hCG production by various cancer types.

Benign Diseases With elevated levels

Very few, e.g. ectopic pregnancy, pituitary adenoma.

Physiological conditions with elevated levels

Pregnancy, after termination of pregnancy.

Main clinical applications

a. For monitoring patients with GTD.
b. In conjunction with AFP, for determining prognosis and monitoring patients with NSGCT of testis, ovary and other sites.

Other potential uses

Diagnostic aid for trophoblastic disease. Serum hCG levels do not usually differentiate between trophoblastic tumours and normal pregnancy. However, very high levels outside the range for twin pregnancies may lead to suspicion of a trophoblastic tumour. For diagnosing trophoblastic tumours,

hCG assays are usually used in combination with ultrasound.

Type of sample for assay

Serum or urine.

Reference range (serum)

- Pre-menopausal women: 0 - 5 IU/L.
- Post-menopausal women: 0 - 10 to 0 - 15 IU/L. Note there is limited data on hCG in peri- and post-menopausal women.
- Men: 0 - 5 IU/L.

Half life in serum

Approx. 16 - 24 hours; decline may be biphasic with a second half life of 13 days.

Comment about assay

When used as a tumour marker, assays for hCG should detect all the main forms, especially the intact molecule and beta-subunit.

Some hCG assays may give either false-positive or false-negative results. If false-positive results are suspected, then measure hCG in urine.

Note: some methods for hCG may cross-react with LH.

References

1. Stenman U-H *et al*. Human chorionic gonadotropin in cancer. Clinical Biochem 2004;37:549-561
2. Sturgeon C. Standardization of tumor markers - priorities identified through external quality assessment. Scand J Clin Lab Invest Suppl. 2016;245:S94-9.
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5. Ferraro S, Trevisol C, Gion M, Panteghini M. Human Chorionic Gonadotropin Assays for Testicular Tumors: Closing the Gap between Clinical and Laboratory Practice Clin Chem 2018: 64; 270-278.

Prostate Specific Antigen (PSA)

Structure

A 28.4 kDa single chain chymotrypsin-like serine protease containing 237 amino acids and a member of the glandular kallikrein family.

Forms in serum

Various molecular forms because of complex formation with protease inhibitors. Major immunoreactive form is PSA complexed with α_1-antichymotrypsin (PSA-ACT). Other complexes occur such as PSA linked to α_1-antitrypsin (trace quantity) and α_2-macroglobulin (undetectable by current immunoassays). A non-complexed free form (fPSA) represents 5 to 40% of the "total" PSA (fPSA + α_1-antichymotrypsin complex).

Physiological function

Partially responsible for the liquefaction of semen to promote the release and motility of spermatozoa.

Malignancy with elevated levels

Present data suggests that prostate cancer is the only malignancy giving rise to elevated PSA levels in serum. However, PSA has been found in cells from various cancer types and different normal tissues. PSA is thus not completely prostate specific.

Benign conditions with elevated levels

Benign prostatic hypertrophy (BPH), acute and chronic prostatitis, UTI, urinary retention.

A number of urological manipulations such as TURP, prostate biopsy, prostate massage and ejaculation may give rise to transient elevated levels. See Section *Effects of Urological Manipulations on PSA Levels* on the next page.

Physiological conditions with elevated levels

None described.

Main clinical applications

a. In combination with digital rectal examination (DRE), PSA can aid the diagnosis of prostate cancer.
b. Determining prognosis in patients with prostate cancer.
c. Surveillance following diagnosis of prostate cancer
d. Monitoring therapy in patients with diagnosed prostate cancer.

PSA in screening for prostate cancer

The value of PSA in screening for prostate cancer is controversial. As a screening test for prostate cancer, PSA lacks sensitivity and specificity for early disease. Furthermore, screening may lead to unnecessary biopsies, overdetection and overtreatment. It is thus unclear whether the benefits of screening outweigh the harms. Although published guidelines differ in their recommendation for PSA screening, almost all state that prior to PSA testing, men should be informed of the risks and benefits of the process. Most guidelines also state that men with a life expectancy of less than 10 years should not be screened.

Reference range:

0 - 4 µg/L (most frequently used) but some advocate age-related reference ranges as follows:

Age Range	PSA µg/L
40 - 49	0 - 2.5
50 - 59	0 - 3.5
60 - 69	0 - 4.5
70 - 79	0 - 6.5

In many countries, including Ireland and the UK, clinical decision thresholds for referral to urology are now used in place of, or in conjunctionwith, reference ranges.

In the UK, Public Health England recommends referral to specialist if age 50-69 years and PSA ≥3.0 µg/L.

In Ireland the National Cancer Prevention Programme (NCCP) recommend referral of asymptomatic men with non-suspicious DRE and PSA above the following thresholds (confirmed on repeat 6-12 weeks after initial test): Age<50 PSA ≥2.0 µg/L, age 50-59 PSA ≥3.0 µg/L, age 60-69 PSA ≥4.0 µg/L, age ≥70 PSA ≥5.0 µg/L

Half life in serum

Approximately 2.5 days after radical prostatectomy. Half life after radiotherapy may be many months.

Effects of urological manipulations on PSA levels.

It is advisable to take blood for PSA measurement before rather than after any of these manipulations.

DRE	May cause minor increases which are rarely of clinical significance.
Prostate massage	May cause minor elevations in some patients.
Ejaculation	Results conflicting but may increase PSA levels.
TURP	Increases PSA levels significantly. It is recommended to wait at least 6 weeks before drawing blood for PSA assay.
Needle Biopsy	As with TURP, increases PSA levels significantly. Wait at least 6 weeks before drawing blood for PSA assay.
Ultrasound	Increases PSA levels in a minority of subjects.
Cystoscopy	Flexible cystoscopy does not appear to increase PSA levels but rigid cystoscopy may increase levels.

Effect of drugs on PSA levels

Finasteride and Dutasteride, 5-alpha-reductase inhibitors used to treat BPH, reduce PSA levels by approx. 50%.

Comment about assay

PSA assays should detect the free and complexed forms on an equimolar basis. Furthermore, the assay should be standardised against the First International Standard for PSA.

Total PSA is stable for at least 6 hours at room temperature in uncentrifuged clotted blood. Five cycles of freezing and thawing caused no significant change.

References

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   Adv Clin Chem. 2014;66:1-23. Review.
2. Armstrong BK, Barry MJ, Frydenberg M, Gardiner RA, Haines I, Carter SM. PSA testing for men at average risk of prostate cancer.
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6. National Cancer Control Programme [Ireland]. National Prostate Cancer GP Referral Guideline. 2018.
   https://www.hse.ie/eng/services/list/5/cancer/profinfo/resources/gpreferrals/nccp-prostate-cancer-gp-referral-guideline.pdf

Free PSA (fPSA)

Form in serum

As stated above, PSA exists in serum in both a bound and free form. The free form includes enzymically inactive pre-PSA, pro-PSA, clipped-PSA and the enzymatically active form of free PSA. The lower the %fPSA, the higher the probability of prostate cancer.

Main clinical applications

To enhance the specificity of total PSA in detecting prostate cancer, especially when total PSA values are between 4 and 10 µg/L. The use of free/total PSA in men with PSA levels can reduce the number of unnecessary biopsies.

Type of sample for assay

Serum or plasma.

Assays for both Total PSA and Free PSA should be carried out on same sample in the same laboratory; it is not appropriate to measure Total PSA in one laboratory and then refer sample to external laboratory for Free PSA.

Reference range

fPSA results can be used in two ways:

1. Use of a single cut-off point. In a large prospective multi-centre study with a cut off point of <25% fPSA (Ref 1), it was shown that unnecessary needle biopsies could be reduced by 20% while maintaining a 95% cancer detection rate with total PSA levels between 4 and 10 µg/L.
2. Probability of cancer: In the same multi-centre study, the following relationships were found between % fPSA and probability of prostate cancer.

% fPSA	% Cancer Probability
0 - 10	56
10 - 15	28
15 - 20	20
20 - 25	16
>25	8

Comment about assay

When using %fPSA, both the free and total PSA assay should be obtained from the same supplier. fPSA is less stable than total PSA, for medium and long-term storage, freezing at –70°C is recommended. Assay of complex PSA, i.e. PSA bound to ACT, appears to give similar information to the free/total ratio in men with PSA levels between 2 and 10 µg/L.

Effect of urological manipulations on fPSA

All the manipulations which increase total PSA levels also increase the level of free PSA as well as the percentage free.

Effect of drugs

While certain 5-alpha-reductase inhibitors, such as Finasteride and Dutasteride, reduce both total and free PSA levels, they do not significantly change the %fPSA level.

References

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2. Woodrum DL *et al.* Interpretation of free PSA clinical research studies for the detection of prostate cancer. J Urol 1998;159:5-12.
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Use of Serum Markers in Diagnosing Cancer of Unknown Primary Origin (Occult Cancers)

Cancers of unknown primary

Cancers of unknown primary origin or occult cancers are defined as histologically proven malignant metastatic tumours whose primary origin cannot be identified during pretreatment evaluation.

Overview of clinical utility

In general, serum markers are of little value in identifying the primary site. This is because, with a small number of exceptions, currently available serum markers are not organ-specific. Indeed, most of the available markers such as CEA, CA 125, CA 19-9 and CA 15-3 can be elevated in most types of advanced adenocarcinomas.

Main clinical applications

Markers that are potentially useful in diagnosing or excluding a likely site are:

- PSA in men for including or excluding prostate cancer.
- AFP and hCG for including or excluding a germ cell tumour.
- Thyroglobulin for including or excluding a differentiated thyroid tumour.

Reference

1. Sturgeon CM, Lai LC, Duffy MJ. Serum tumor markers: how to order and interpret them.
Br Med J 2009;339:852-858.

Therapy Predictive Markers (Companion Markers)

Therapy	Cancer	Biomarker
Hormone	Breast	ER, PR
Anti-HER2 (trastuzumab (Herceptin), lapatinib, pertuzumab, TDM-1)	Breast	HER2
Trastuzumab (Herceptin)	Gastric	HER2
Anti-EGFR (cetuximab, panitumumab)	Colorectal	*KRAS/NRAS
Anti-EGFR (gefitinib, erlotinib, afatinib)	NSCLC	*EGFR
Anti-BRAF (vemurafenib, dabrafenib)	Melanoma	*BRAF
Anti-ALK (crizitonib, ceritinib)	NSCLC	**EML4-ALK
Imatinib	GIST	KIT
***PARP inhibitors (olaparib)	Breast/Ovarian	*BRCA1/2
Immunotherapy (Pembrozilumab)	NSCLC	PD-L1

Table 1. Predictive markers for selecting treatment in patients with different cancers.

ER, estrogen receptors; PR, progesterone receptors; TDM-1, trastuzumab emtansine; NSCLC, non-small cell lung cancer.

*mutational status

**translocation

*** undergoing clinical trials in patients with advanced BRCA1/2-associated breast and ovarian cancers.

Reference

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