GUIDELINE FOR REQUESTING TUMOUR MARKERS

INTRODUCTION

A tumour marker is a biomarker found in blood, urine or body tissues that can be elevated by the presence of one or more types of cancer. Although cancer cells often produce tumour markers, healthy cells in the body may produce them as well.

Tumour markers are relatively expensive tests and are generally over-requested.

These guidance notes aim to provide information on the most appropriate use of specific tumour markers, as both over- and under requesting of these tests can have detrimental effects on patient care.

IMPORTANT POINTS TO NOTE[1]

- No single tumour marker in current use is specific for malignancy
- In general, serum tumour markers are rarely elevated in early malignancy
- No tumour marker has absolute organ specificity
- Although reference ranges are provided on the laboratory report, these are not well defined and should be used for guidance only
- Benign conditions and other factors such as lifestyle and medical investigation can influence results
- Measurement of tumour markers is not recommended in patient with vague symptoms where likelihood of cancer is low
- Requesting multiple tumour markers in an attempt to 'screen' for cancer is rarely of value
- Tumour markers should only be requested when results can influence clinical practice with a consequent favourable outcome for the patient and should only be used in areas where there is sufficient expertise to interpret the results
- The main use of serum tumour markers is in monitoring of patients with diagnosed malignancy
- When interpreting results, it is important to be aware that results obtained by different analytical methods are not necessarily comparable

SCREENING

In patients presenting with non-specific symptoms (e.g. tiredness) but no known malignant disease, it is inappropriate to request tumour markers. Due to their non-specific nature, tumour markers should not be used to screen, diagnose or exclude malignancy in isolation.

Tumour marker results within normal limits do not exclude malignancy or progression of disease.

METASTATIC DISEASE OF UNKNOWN PRIMARY ORIGIN[2]

Patients with 'cancer of unknown primary origin' (CUP) or 'malignancy of undefined primary origin' (MUO), have metastatic disease without an identifiable primary site. During the initial diagnostic phase, selected tumour markers (see table below) may be used to investigate these patients, guided by clinical symptoms:

Tumour marker	Indication
Myeloma Screen (serum protein electrophoresis, serum free light chains)	Isolated or multiple lytic bone lesions
PSA	In men with presentations compatible with prostate cancer
CA-125	In women with presentations compatible with ovarian cancer (including those with inguinal node, chest, pleural, peritoneal or retroperitoneal presentations). Carefully interpret these results due to limited test specificity
AFP & hCG	In patients with presentations compatible with germ-cell tumours (particularly those with mediastinal and/or retroperitoneal masses and in young men)
AFP	In patients with presentations compatible with hepatocellular carcinoma

APPROPRIATE USE OF TUMOUR MARKER

The table below summarises the appropriate use of tumour markers:

Marker	Elevated in Cancer	Indication	Uses	Other causes of increased levels
CA-125	Ovarian	*Females only* Persistent abdominal distention (bloating), early satiety/loss of appetite, pelvic/abdominal pain, increased urine urgency/frequency. Symptoms of IBS within the last 12 months	Diagnosis in symptomatic women aged >18 Monitoring response to treatment, detection of recurrence	Endometriosis, menstruation, pregnancy, ascites, benign ovarian pathology, pelvic inflammation, heart failure, liver disease, pancreatitis, malignancy of lung, GI tract, breast

PSA	Prostate	*Males only* Lower urinary tract symptoms – nocturia, increased frequency, hesitancy, urgency, retention. Erectile dysfunction. Visible haematuria	Diagnosis in symptomatic men	UTI, BPH, prostatitis, digital rectal examination, needle biopsy, ejaculation within 48 hours of test
Faecal occult blood (FOB) - Guiac	Colorectal	Bowel cancer screening programme (asymptomatic) for men and women aged 60 to 74 years		Diet, rectal bleeding, ulcers, polyps
Faecal Immunochemical Test (FIT)	Colorectal	Unexplained symptoms (weight loss, change in bowel habits, anaemia, abdominal pain, blood in faeces) without rectal bleeding, not meeting the criteria for a suspected cancer pathway referral	Screen prior to referral for colonoscopy	Rectal bleeding, ulcers, polyps
CEA	Colorectal	Known malignancy. Pre- and post-operative	Staging, prognosis, monitoring treatment, detecting recurrence	Most advanced adenocarcinomas, hepatitis, cirrhosis, obstructive jaundice, ulcerative colitis, Crohn's, pancreatitis, renal disease
FBC	Leukaemia	Pallor, persistent fatigue, unexplained fever, persistent/recurrent infection, generalised lymphadenopathy, unexplained – bruising, bleeding, petechiae, hepatosplenomegaly	Diagnosis in symptomatic adults and children	
LDH	Lymphoma	Suspected malignancy	Screening, diagnosis, staging, recurrence, monitoring	Megaloblastic anaemia, pernicious anaemia, abdominal & lung cancer, AMI, leukaemia, liver & renal disease

Paraprotein, urine BJP, SFLC	Myeloma & other B cell proliferative disorders	Unexplained anaemia, bone pain, weakness or fatigue, raised ESR, abnormal globulins, hypercalcaemia, renal failure, bone lesions	Diagnosis in symptomatic patients, recurrence, monitoring	Autoimmune or infective conditions may give rise to MGUS
B-2 microglobulin	Myeloma	Known malignancy	Staging, prognosis	Lymphoproliferative disorders, solid carcinomas, hepatitis, Crohn's, HIV
Ca-15-3	Breast	Known malignancy	Detecting recurrence, monitoring advanced disease	Non-breast pathology e.g. malignant - ovary, lung, myeloma & non-malignant – colitis, benign hepatitis
Ca-19-9	Pancreatic	Only in suspected malignancy in conjunction with imaging	Diagnosis, staging, monitoring	Chronic hepatitis, cholestasis, pancreatitis, gastric & colorectal carcinoma
AFP	Liver including hepatoblastoma in children (rare in adults)	Screening for HCC in high risk population e.g. cirrhosis, hepatitis	Screening, diagnosis, staging, recurrence, monitoring	Hepatitis, cirrhosis, biliary obstruction, alcoholic liver disease, tyrosinaemia. High until 12 months of age
	Germ cell (NSGCT)	In suspected malignancy. Diffuse testicular swelling, hardness and pain at any age	Diagnosis, staging, recurrence, monitoring	
hCG	GTD, NSGCT	In suspected malignancy. Diffuse testicular swelling, hardness and pain at any age	Diagnosis, staging, recurrence, monitoring	Pregnancy, after termination of pregnancy, ectopic pregnancy, pituitary adenoma
Thyroglobulin	Thyroid	Known malignancy	Detecting recurrence, monitoring	Benign thyroid disease (Grave's, thyroiditis)

Key: IBS; Irritable bowel syndrome. PSA; Prostate specific antigen. CEA; Carinoembryonic antigen. FBC; Full blood count. LDH; Lactate dehydrogenase. AMI; Acute myocardial infarction. BPH; Benign prostate hyperplasia. MGUS; Monoclonal gammopathy of unknown significance. BJP; Bence Jones Protein. SFLC; Serum free light chains. AFP; Alpha-fetoprotein. NSGCT; Non-seminomatous germ cell tumour. GTD; Gestational trophoblastic disease. UTI; Urinary tract infection.

Although no formal guidelines for their use exist, the tumour markers listed below are in routine clinical use for monitoring specific cancers. The information provided states the acceptance criteria as defined by the laboratory:

Marker	Applicable in malignancy	Acceptance criteria	Other causes of increased levels
S100	Malignant melanoma	Monitoring known melanoma	Central nervous system injuries, stroke, head trauma
Calcitonin	Medullary thyroid carcinoma (MTC)	Monitoring of MTC. In familial cases, calcitonin can be used as a screening test	Breast, lung, pancreatic cancer. Pheochromocytoma, renal failure, pagets, hyperparathyroidism
5-HIAA	Carcinoid syndrome	Suspected carcinoid	Serotonin rich foods
Chromogranin A/B	Suspected neuroendocrine tumour	Consultant request only	Hypertension. Renal failure (ChA)
Urine catecholamines / metanephrines	Pheochromocytoma	Suspected pheochromocytoma	Serotonin rich foods (bananas, pineapple, kiwi, nuts avocado), adrenaline-like drugs, recent caffeine intake

REFERENCES

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7. Guidelines for the diagnosis and management of multiple myeloma. British Society for Haematology. 2014.