Cancer diagnosis: Histopathology, cytology and tumour markers

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Introduction

Establishing a diagnosis of cancer begins with a thorough history and physical examination. There should always be a strong correlation between the clinical diagnosis of cancer and the results of diagnostic tests. If there is any concern regarding diagnostic “fit”, the case should be discussed with the reporting pathologist. This is as relevant in the diagnosis of recurrent or metastatic disease as it is in the primary setting.

There should be a high level of communication between the clinician and the pathologist to avoid error arising in the diagnostic phase. Accurate labelling of specimens (correct patient name, tumour side, site and specimen orientation) is extremely important, particularly when dealing with high specimen volumes (skin lesions, endoscopy specimens, multiple breast biopsies) where incorrect assignment of the result could have dire consequences for the patient.

Is tissue always necessary?

There are very few circumstances where the diagnosis of malignancy is made in the absence of pathological confirmation, particularly as diagnostic procedures have become less invasive over the past few decades. A clinical diagnosis alone is most often made in the context of advanced malignancy in a poor performance status patient where anti-cancer therapy would neither improve quality of life nor survival. Thus, the majority of patients have the diagnosis of cancer confirmed on tissue pathology. The diagnosis of recurrent and/or metastatic disease may be made on the basis of the pattern of relapse combined with knowledge of the initial tumour stage and underlying tumour biology. However, caution should be taken to consider “benign” pathology

that may mimic metastatic malignancy (e.g. pulmonary sarcoidosis, hepatic haemangioma, osteoporotic vertebral fracture, Paget's disease of bone, ischaemic cerebrovascular accident). Additionally, tumour heterogeneity may result in differential tumour behaviour between the primary and metastatic sites (such as hormone responsiveness or HER2 expression in breast cancer), giving rise to different treatment options for the metastatic disease compared with what might have been anticipated based on the pathology of the primary tumour.

Obtaining tissue

An important principle is to obtain diagnostic material via the least invasive approach. An example is the cytological evaluation of a palpable supraclavicular lymph node by fine needle aspiration biopsy (FNAB) in a patient with a lung mass or known intra-abdominal malignancy. The diagnosis of cancer by the least invasive procedure (FNAB or core biopsy) facilitates appropriate staging investigations, planning of the definitive treatment and discussion of these treatment recommendations with the patient and their support person(s). Specific consideration needs to be given to the amount of tissue required to direct treatment. For example, cytology on a neck node that confirms metastatic squamous cell carcinoma from an oropharyngeal primary would be sufficient to direct ongoing management, whereas in lymphoma, a larger biopsy or the entire node may be required to evaluate nodal architecture in order to decide optimal first-line management.

Histopathology/cytopathology

Historically, histopathology and cytopathology have been the main tools utilised in the diagnosis of cancer. These techniques have evolved from an era of diagnosis based on haematoxylin and eosin (H&E) stained slides (Figure 1) to the current regular evaluation of tumours by immunocytochemistry (IHC) to confirm tumour histogenesis and subtype. In breast cancer, this means the routine IHC evaluation of hormone receptors (oestrogen (Figure 2) and progesterone receptors) as well as evaluation of HER2 expression (Figure 3) and Ki67 (a marker of tumour proliferation). These factors strongly influence prognosis and the selection of anti-cancer treatments. Molecular histopathology using in-situ hybridization (ISH) techniques also provides additional information influencing prognosis and treatment in breast cancer (Figure 4) and other cancers. More recently, gene profiling technology (Figure 5) has been used to define subgroups of breast cancer patients. For example, it has identified the Luminal-A breast cancer subtype for whom adjuvant chemotherapy is unlikely to be of benefit. These gene profiling techniques are likely to be used in the management of other tumours over coming years.

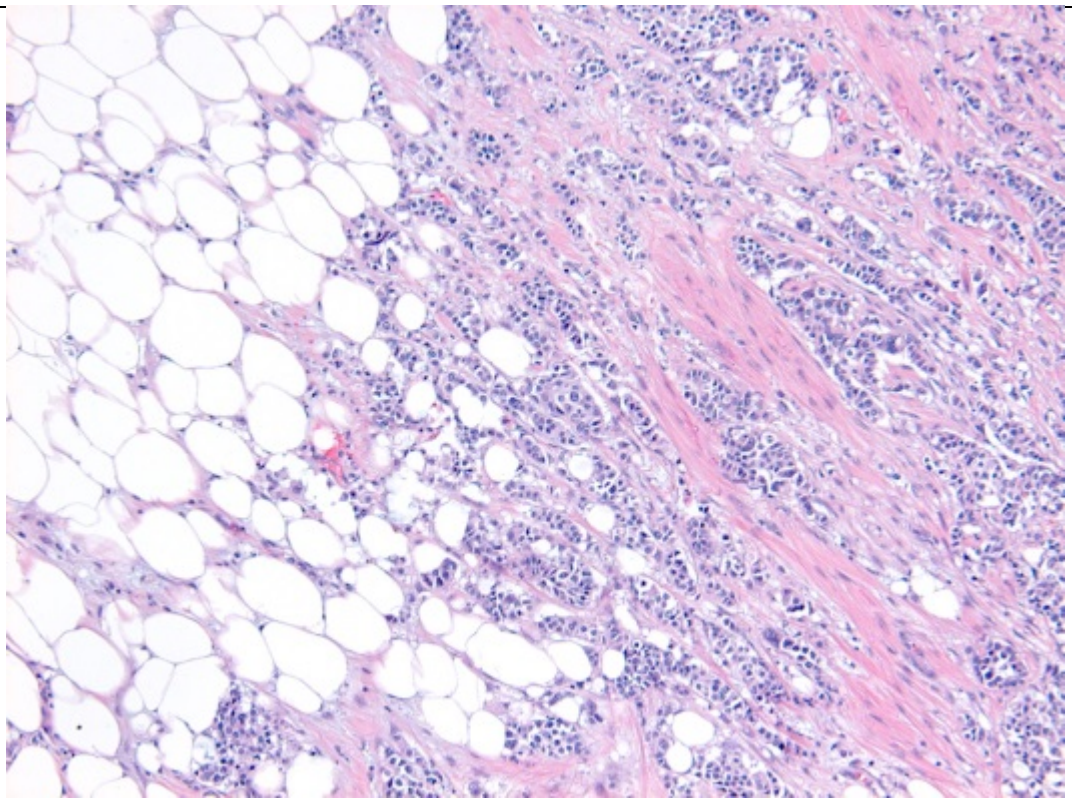

Figure 1: High grade breast cancer H&E section Source: Dr Ala Enno Consultant Histopathologist at Liverpool Hospital

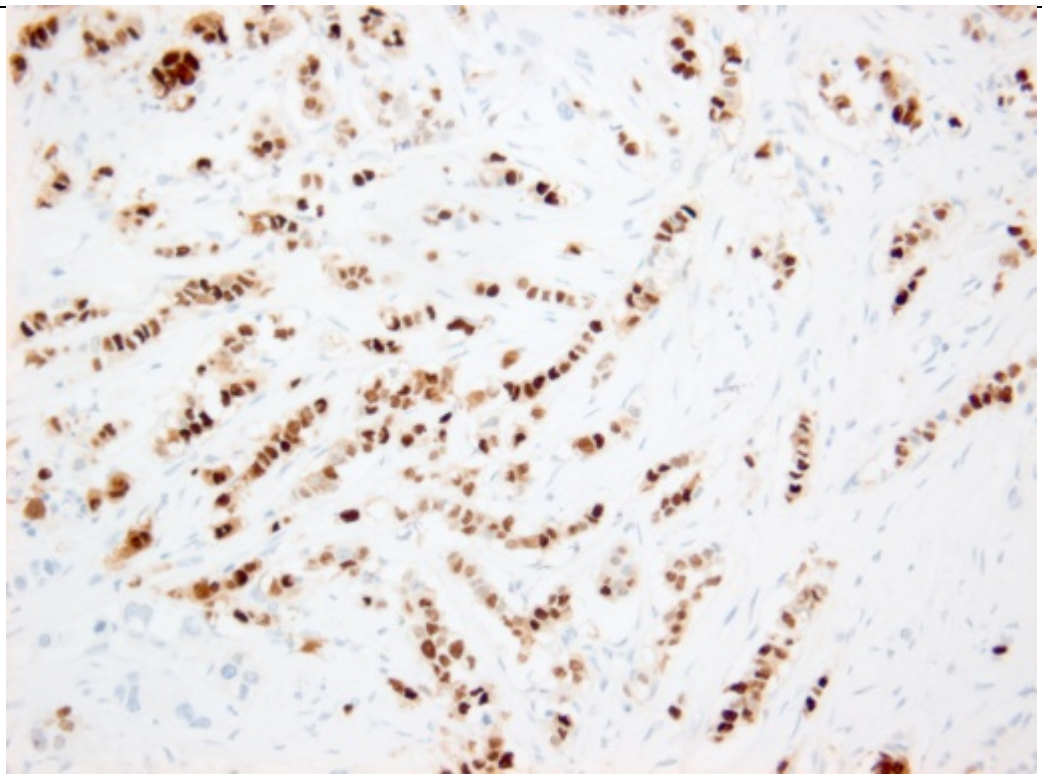

Figure 2: Breast cancer IHC ER positive Source: Dr Ala Enno Consultant Histopathologist at Liverpool Hospital

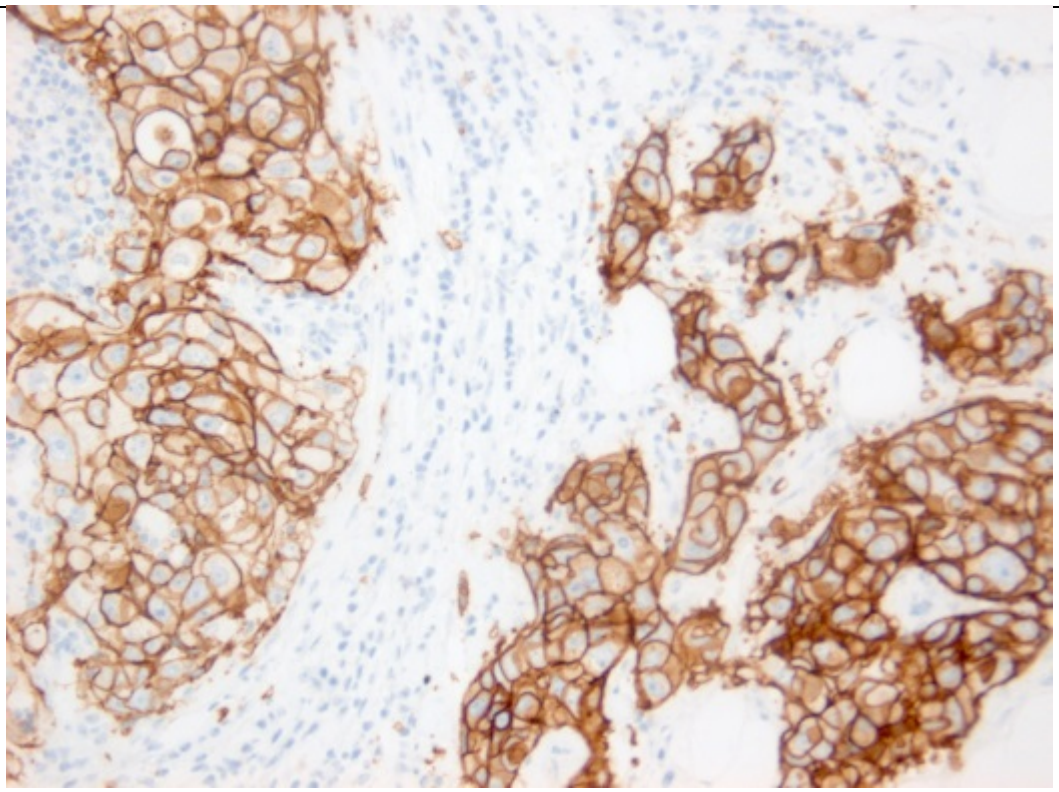

Figure 3: Breast cancer IHC HER2 positive Source: Dr Ala Enno Consultant Histopathologist at Liverpool Hospital. Permission to use.

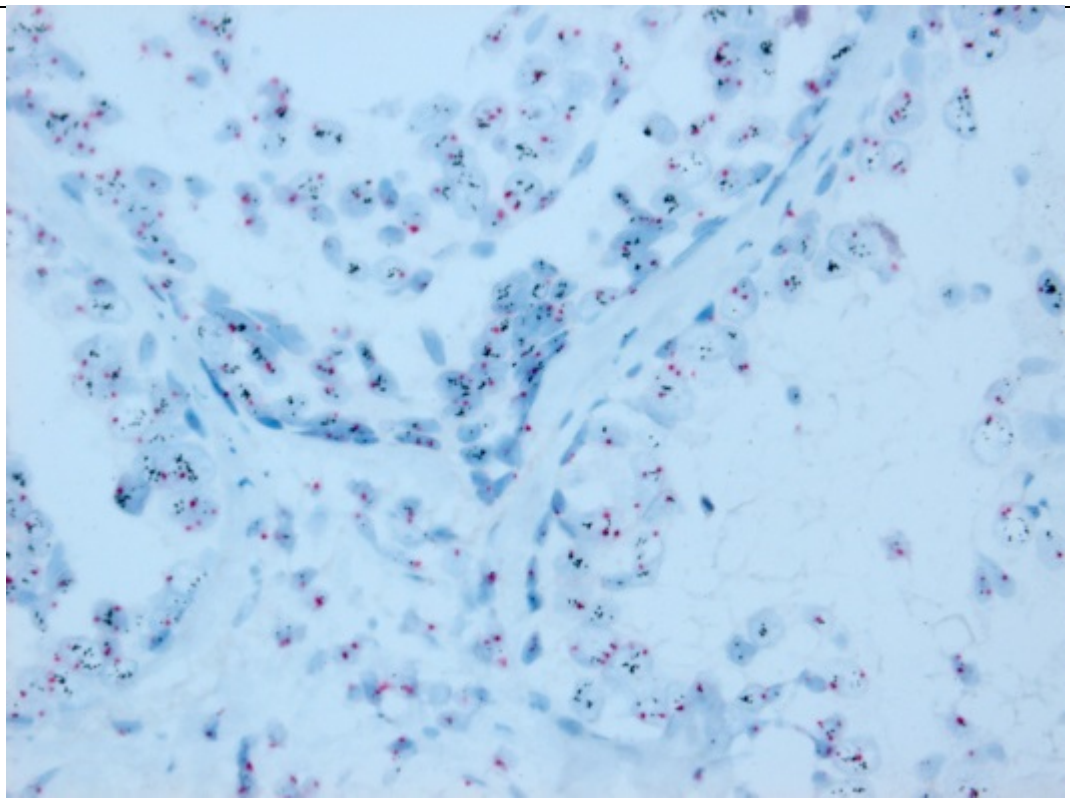

Figure 4: Breast cancer SISH HER2 gene amplification Source: Dr Ala Enno Consultant Histopathologist at Liverpool Hospital. Permission to use.

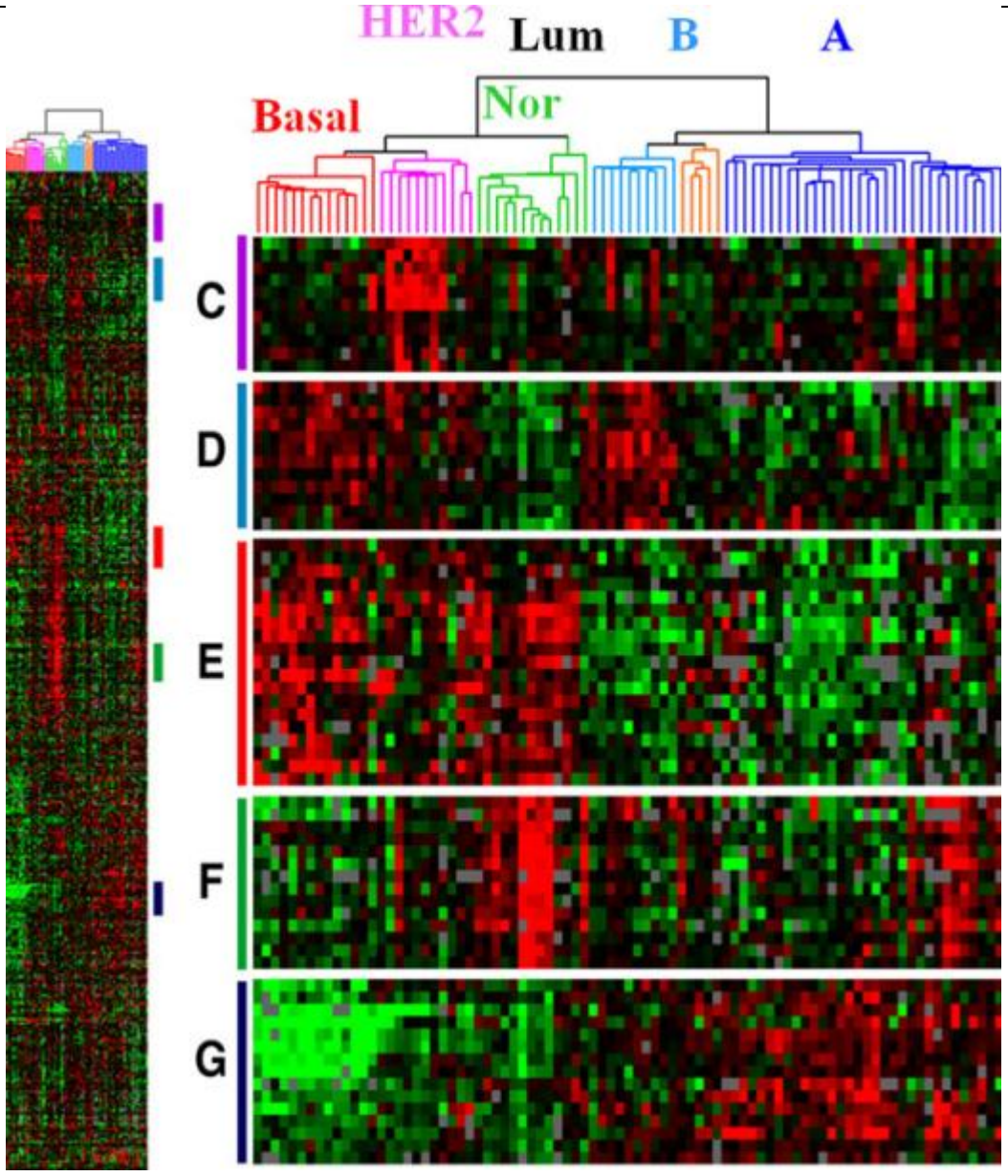

Figure 5: Classes of breast cancer based on gene expression profiles Source: Sørlie T et al : Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 2001, 98:10869-10874. Permission to use.

Molecular genetics/cytogenetics

Molecular and cytogenetic studies have demonstrated that the development and progression of human malignancies involves multiple genetic changes, and techniques identifying these changes have become major diagnostic tools in oncology. Studies have shown a specific gene translocation to characterise chronic myeloid leukaemia t(9;22) (Figure 6). Amplification and/or activation of tumour oncogenes such as c-myc, and deletion and/or inactivation of tumour suppressor genes such as p53 and Rb1, are identified with specific solid tumours. Cytogenetic results are increasingly important in confirming the diagnosis of malignancy and directing the optimum therapeutic strategy.

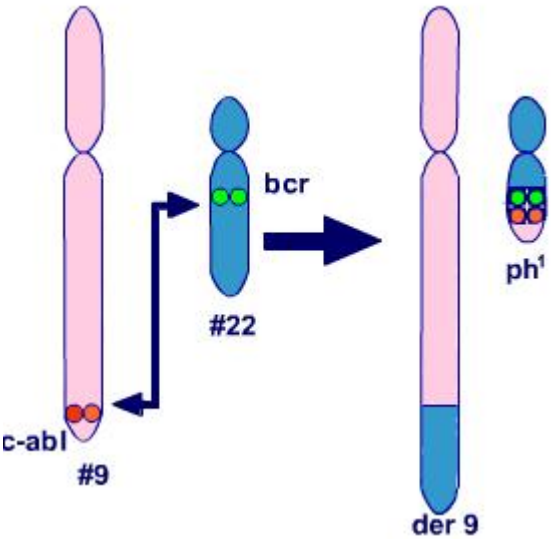

Figure 6: 9:22 Translocation Source: Medindia health. Permission to use.

The 9:22 translocation brings together the breakpoint cluster region gene (BCR) on chromosome 22 and the Ableson leukaemia virus gene (ABL) on chromosome 9. The resulting BCR-ABL hybrid gene codes for a protein, endowed with tyrosine kinase activity, which has the ability to activate signal transduction pathways.

Mutations in genes involved in cellular signalling are common and these can be used to define patients that are more likely to benefit form a particular ‘targeted’ cancer therapy -- e.g. an epidermal growth factor receptor (EGFR) mutation in metastatic adenocarcinoma of the lung identifies a subgroup of patients that can be treated preferentially with first-line EGFR-targeted tyrosine kinase inhibitor therapy rather than chemotherapy. Similarly, patients with metastatic colorectal cancer exhibiting wild-type KRAS may benefit from EGFR-antibody therapy, whereas those with mutant-KRAS are resistant to such treatment.

Tumour markers/biomarkers

Tumour markers are substances released by cancer cells into the blood. They are used as an adjunct to other investigations in primary diagnosis and should not be used as blind screening tools in the absence of evidence to support their use in this setting. Tumour markers are most useful in the evaluation of how well a patient has responded to treatment and to check for tumour recurrence.

Biomarkers are physiological markers or substances expressed by the body that can indicate the presence of a tumour that is not necessarily expressed by tumour cells. Another distinction between tumour marker and biomarker is that biomarkers can also apply to non-solid tumour cancers.

Useful markers of internal malignancy

Prostate-specific antigen (PSA): An elevated PSA level in the blood may indicate prostate cancer, but other conditions such as benign prostatic hyperplasia (BPH) and prostatitis can also raise PSA levels. PSA levels are used to evaluate how a patient has responded to treatment and to check for tumour recurrence. The use of PSA as a screening tool for prostate cancer remains controversial.

Alpha-fetoprotein (AFP): This is normally elevated in pregnant women since it is produced by the foetus. In men, and in women who are not pregnant, an elevated level of AFP may indicate liver cancer or cancer of the testis or ovary. Noncancerous conditions such as chronic active hepatitis may also cause elevated AFP levels.

Human chorionic gonadotropin (HCG): This is another substance that appears normally in pregnancy and is produced by the placenta. If pregnancy is ruled out, HCG may indicate cancer in the testis, ovary, liver, stomach, pancreas and lung. Marijuana use can also “falsely” raise HCG levels.

Carcinoembryonic antigen (CEA): Colorectal cancer is the most common cancer where this tumour marker is used, but many other epithelial cancers can also raise levels.

CA 125: Ovarian cancer is the most common cause of elevated CA 125, but cancers of the uterus, cervix, pancreas, liver, colon, breast, lung and digestive tract can also raise CA 125 levels through peritoneal involvement. Several noncancerous conditions can also elevate CA 125 (e.g. non-malignant ascites). CA 125 is mainly used to monitor the treatment of ovarian cancer.

CA 19-9: This is associated with cancers in the colon, stomach, and bile duct. Elevated levels of CA 19-9 may indicate advanced cancer in the pancreas, but it is also associated with noncancerous conditions, including gallstones, pancreatitis, cirrhosis of the liver and cholecystitis.

CA 15-3: This is most useful in evaluating the effect of treatment for women with advanced breast cancer. Elevated levels of CA 15-3 are also associated with cancers of the ovary, lung, and prostate, as well as noncancerous conditions such as benign breast or ovarian disease, endometriosis, pelvic inflammatory disease and hepatitis. Pregnancy and lactation also can raise CA 15-3 levels.

There are many other markers used in monitoring specific cancers, e.g. calcitonin in medullary carcinoma of the thyroid, chromogranin-A (CgA) in neuroendocrine carcinoma, thyroglobulin in thyroid cancer, neuron specific enolase (NSE) in small cell carcinoma of the lung, immunoglobulins/light chains in multiple myeloma and beta-2-microglobulin in multiple myeloma and non-Hodgkin's lymphoma. Lactate dehydrogenase (LDH) is a non-specific marker that is of prognostic significance in metastatic melanoma, small cell lung cancer, germ cell tumours of the testis/ovary, non-Hodgkin's lymphoma and neuroblastoma.