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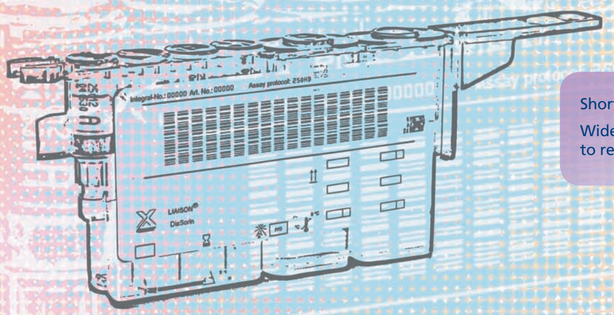

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Oncology

Ordering Information

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LIAISON® CA 125 II™	(code 314211)
LIAISON® CA 15-3®	(code 314301)
LIAISON® CEA	(code 314311)
LIAISON® Ferritin	(code 313551)
LIAISON® hCG	(code 312311)
LIAISON® β_2 microglobulin	(code 314501)
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LIAISON® Control Calcitonin II Gen	(code 310651)
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Oncology

LIAISON® Tumour Markers

A complete panel for Cancer Management

Oncology

Cancer is the uncontrolled growth and spread of cells that may affect almost any tissue of the body. Lung, prostate, breast, colorectal and stomach are the five most common cancers in the world.
More than 10 million people are diagnosed with cancer every year.

Tumour markers are biological substances produced by the tumour cells, generally found in very low concentrations in normal individuals, which can be measured in blood and other body fluids. Increased concentrations indicate the presence of a tumour. An ideal tumour marker should be used for screening, diagnosis and monitoring of disease progression. Unfortunately there is no ideal tumour marker.

Screening

Due to the low sensitivity of most tumour markers, none is currently recommended for screening the general population. The most likely candidate is PSA for prostate cancer, however there is no agreement whether screening reduces premature mortality.

Diagnosis

Tumour markers are occasionally useful as pointers towards a specific diagnosis. Very high concentration of a specific marker will make some cancer forms exceedingly likely. However tumour markers should never be used alone to establish a diagnosis.

Prognosis

Prognosis may be of help to assess optimal therapeutic regime. Several tumour markers have additional value to the traditional staging system and often a correlation between tumour marker concentration and survival time exists.

Monitoring of Treatment and Follow-up

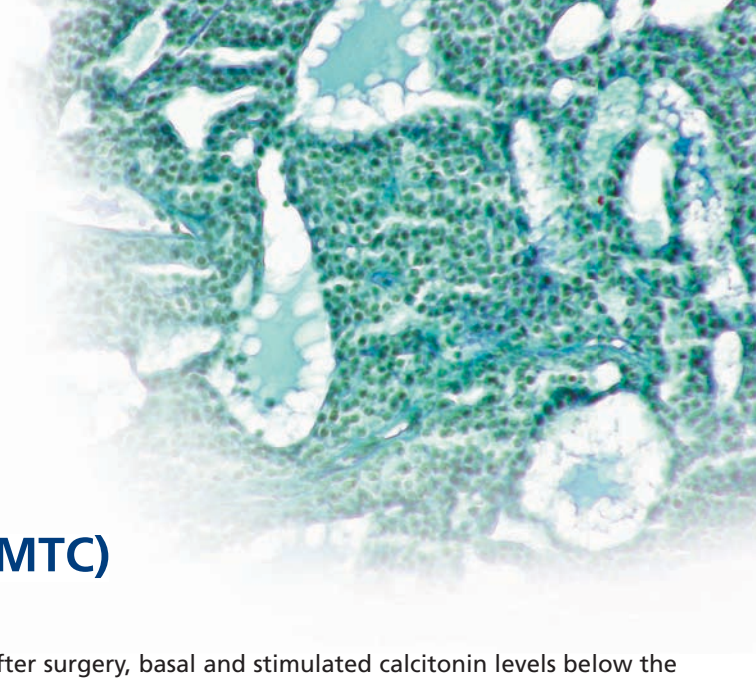
Monitoring of disease progression is the main clinical use of tumour markers. Regular measurements of tumour markers assist in demonstrating the effectiveness of a treatment intervention. Reduced levels of the marker indicate successful treatment, increased levels indicate progressive disease. In the follow-up the markers may detect progression prior to the appearance of clinical symptoms.

LIAISON® Tumour Markers Assays

Cancer form	Tumour Marker
Brain	S100, NSE
Thyroid	Tg, CEA, Calcitonin
Lung	CEA, TPA®, NSE
Breast	CA 15-3®, CEA, TPA®
Blood	TK, $ß_2$-microglobulin, Ferritin
Liver	AFP, CEA
Stomach	CEA, CA 19-9™
Pancreas	CA 19-9™, CEA
Colorectal	CEA, CA 19-9™, TPA®
Bladder	TPA®
Ovary	CA 125 II™, AFP, hCG
Prostate	PSA, fPSA
Cervix, Uterus	CA 125 II™, CEA, TPA®
Testes	AFP, hCG
Skin	S100

LIAISON® Tumour Markers Characteristics

Tumour Marker	Substance	DiaSorin Reference range	Clinical Indication	False positives
AFP Alpha-fetoprotein	Glycoprotein MW 68 000	< 5.5 IU/mL	Liver cell carcinoma Germ-cell tumours	Liver disease, Crohn´s disease, polyposis
$ß_2$-microglobulin	The light chain of the MHC class I antigens MW 10 800	0.9-2.0 mg/L	Lymphoproliferative disease, myeloma	Renal insufficiency
Calcitonin	Polypeptide MW 3600	<10 pg/mL	Medullary thyroid cancer	Renal insufficiency
CA 15-3	Glycoprotein defined by two monoclonal antibodies (115 D8 and DF3)	<30 U/mL	Mammary carcinoma	Liver disease Diseases of the ovaries, lung and breast
CA 19-9	Glycolipid, hapten of the Lewis-a-blood group determinant defined by the monoclonal antibody 1116NS-19-9	<19 U/mL with greyzone up to 37 U/mL	Carcinomas of the gastro-intestinal tract especially pancreatic carcinoma	Hepatitis, biliary disease, pancreatitis, cystic fibrosis
CA 125	High molecular weight glycoprotein defined by the monoclonal antibodies OC 125 and M11	<35 U/mL	Carcinomas of the ovaries	Benign gynaecological disease, endometrioses, liver disease, pancreatitis
CEA Carcinoembryonic antigen	Glycoprotein MW 180 000	< 4 µg/L	Colorectal carcinoma, secondary marker in pancreas, lung, breast, prostate	Liver disease, Colitis ulcerosa, Lung emphysema
Ferritin	Iron containing protein MW 460 000	Male: 18.2-341.2 µg/mL Female:4.0-104.2 µg/mL (< 45 years) 4.9-232.3 ng/mL (> 45 years)	Leukaemia, Hodgkin, non-Hodgkin, breast, bronchial carcinoma, neuroblastoma	Idiopathic haemo-chromatosis, Intrathecal haemorrhage
hCG Human chorionic gonadotropin	Dimeric glycoprotein consisting of an α-and β-subunit MW 37 000	Female: < 2.4 mIU/mL Male: < 1.1 mIU/mL	Germinal tumours of testis and ovary	Pregnancy
NSE Neuron-specific enolase	The γ-form of enolase, an enzyme in the glycolytic pathway MW 87 000	< 18.3 µg/L	Small-cell bronchial carcinoma, neuroblastoma	Head trauma
PSA Prostate-specific antigen	Glycoprotein, a serine protease MW 34 000	< 3 ng/mL with grey zone up to 10 ng/mL f/t PSA < 0.1 in prostate cancer patients	Carcinoma of the prostate	Acute prostatitis and benign prostate hyperplasia. Determination of free PSA/total PSA improves discrimination
S100B	Protein, member of the S100 family consisting of 20 proteins MW subunits 11 000	< 0.15 µg/L	Malignant melanoma	Brain damage
Thyroglobulin	Glycosylated iodoprotein MW 660 000	0.2-70 µg/L	Thyroid carcinoma (papillary, follicular)	Goitre, Basedow´s disease
TK Thymidine kinase	Cellular enzyme involved in DNA synthesis MW subunits 58 000	< 8 U/L	Haematological malignancies	Infections
TPA Tissue polypeptide antigen	Circulating complex from cytokeratin 8, 18 and 19	< 75 U/L	Carcinomas of the lung, breast, gastro-intestinal tract	Liver disease, Infections



Calcitonin

For accurate monitoring of Medullary Thyroid Carcinoma (MTC)

Calcitonin is a 32 aminoacid polypeptide produced by the parafollicular C-cells in the thyroid. High circulating levels of calcitonin are found in patients with medullary thyroid carcinoma (MTC), the most aggressive form of differentiated thyroid carcinomas (papillary, follicular, medullary).[1]

Early diagnosis and complete surgical removal of the tumour before metastatic spread are the main factors determining patients' survival. The detection of high concentrations of calcitonin in serum is the most sensitive and specific marker for the primary diagnosis and postsurgical follow up of MTC.[2]

Calcitonin secretion by normal and neoplastic C-cells is stimulated by gastrin, so intravenous administration of pentagastrin followed by measurements of calcitonin in samples collected at 0, 2, 5 and sometimes 10 minutes is commonly used as stimulation test.[3]

Histologically confirmed MTC cases have basal and stimulated calcitonin values that are highly correlated with tumour size.[4, 5]

After surgery, basal and stimulated calcitonin levels below the detection limit are indicative of cure.

Calcitonin in Nodular Thyroid Disease

MTC affects about 1% of patients with thyroid nodules. Many European authorities support the importance of screening patients with nodular thyroid disease, based on the high positive predictive value for MTC diagnosis of calcitonin levels above 100 pg/mL.

The German Society for Endocrinology (DGE) recommends the algorithm depicted in Fig.1.[6]

Basal calcitonin levels below 10 pg/mL practically exclude MTC, while levels above 10 pg/mL should be confirmed by pentagastrin stimulation test, provided use of proton pump inhibitors and renal insufficiency have been excluded as confounding contributors to the calcitonin level.

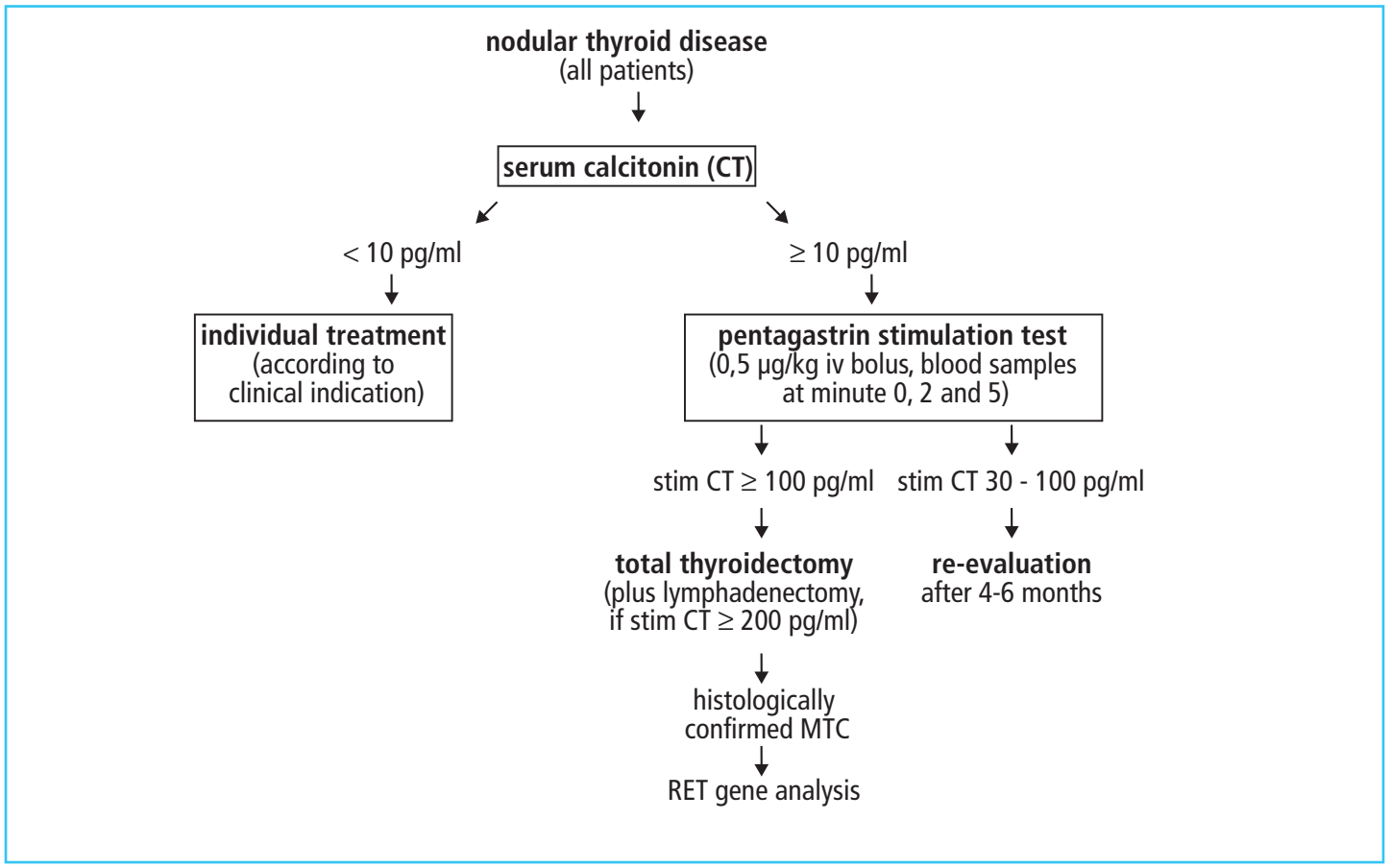


Fig. 1 - Calcitonin measurement in nodular thyroid disease (Ref. 6) .

Thyroidectomy is advised in patients with stimulated levels above 100 pg/mL and strongly recommended (with additional lymphadenectomy) when calcitonin levels exceed 200 pg/mL.
The risk of MTC in patients with stimulated levels between 30 and 100 pg/mL is around 3%, therefore regular biochemical follow up is recommended.
About 25% of MTC cases are hereditary and are caused by mutations of the RET protooncogene, which can be detected by genetic tests.[3]

Elisei et al. demonstrated that screening nodular thyroid disease by serum calcitonin measurement is more sensitive than fine needle aspiration cytology (FNAC) in the preoperative diagnosis of unsuspected sporadic MTC. The outcome of patients diagnosed by calcitonin determination (group 1) was compared to that of a historical group of MTC patients diagnosed and treated before the introduction of calcitonin screening (group 2). As shown in Fig.2, group 1 had a significantly better outcome, with a 10-yr survival rate of 86% versus 43.7% for group 2.

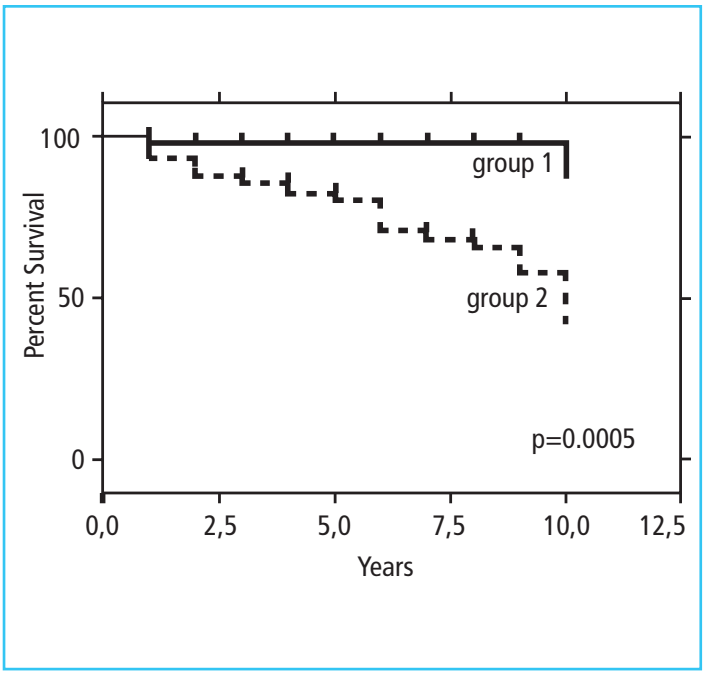


Fig. 2 - Survival curves of MTC patients diagnosed after (group 1) and before (group 2) the introduction of calcitonin screening in nodular thyroid disease (Ref. 7).

Two possible explanations were provided:
- calcitonin screening increases the preoperative diagnostic accuracy of MTC and alerts the surgeon to perform a more radical treatment which is fundamental for definitive cure
- the calcitonin test overcomes the frequent false negative result of FNAC, which might delay MTC diagnosis and treatment.[7]

Calcitonin in Clinical Guidelines

The American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi guidelines mandate the determination of calcitonin only in cases with a family history of MTC or multiple endocrine neoplasia type 2 syndrome (MEN2), based on cost-effectiveness considerations.[8]

Although the American Thyroid Association has declined to recommend for or against routine measurement of calcitonin in patients with thyroid nodules, the determination of calcitonin and CEA is recommended 2-3 months after surgery. In case calcitonin is undetectable, no further test is necessary. If it is detectable and imaging is negative, calcitonin and CEA should be tested every 6 months to determine their doubling times. During follow-up, calcitonin and CEA should be tested at 1/4th the shortest doubling time or annually.[9]

The European Thyroid Association consensus for the management of patients with differentiated thyroid carcinoma recommends serum calcitonin measurement in the initial diagnostic evaluation of thyroid nodules.[10]

The cost effectiveness of routine calcitonin screening in patients undergoing evaluations for thyroid nodules has been proven by different investigators.[11, 12] They concluded that the cost effectiveness is comparable or higher than for other widely accepted screening programs and it could be further increased by focusing on subgroups of patients.

Summary

- Calcitonin is the most sensitive and specific marker for the diagnosis and follow up of medullary thyroid carcinoma.
- Calcitonin measurement allows identification of MTC cases among patients with nodular thyroid disease and improves their survival rate.

1. Gharib H et al. Mayo Clin Proc 1992; 67: 934-940
2. Tashjian AH et al. N Engl J Med 1970; 283: 890-895
3. Demers LM, Spencer C 2002 NACB: Laboratory Support for the Diagnosis and Monitoring of Thyroid Disease
4. Iacobone M et al. World J Surg 2002; 26: 886-890
5. Kaserer K et al. Am J Surg Pathol 1998; 22: 722-728
6. Karges W et al. Exp Clin Endocrinol Diabetes 2004; 112: 52-58
7. Elisei R et al. J Clin Endocrinol Metab 2004; 89: 163-168
8. Gharib H et al. Endocrine Practice 2006; 12: 63-98
9. Kloos RT et al. Thyroid 2009; 9: 565-612
10. Pacini F et al. Eur J Endocrinol 2006; 154: 787-803
11. Borget I et al. J Clin Endocrinol Metab 2007; 92: 425-427
12. Cheung K et al. J Clin Endocrinol Metab 2008; 93: 2173-2180

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Oncology

Neuron-Specific Enolase

NSE

For therapy monitoring and follow up of neuroendocrine tumours

Enolase is an enzyme involved in glucose metabolism (glycolysis), which catalyzes the conversion of 2-phospho-D-glycerate into phosphoenolpyruvate. Enolase is made up of two out of three existing subunits (α, β and γ subunits), which form the physiologically active enzyme. NSE consists of an α γ or γ γ dimer, mostly found in neurons and neuroendocrine tissues. A high concentration of serum γ-enolase (NSE) is detected[1, 2] above all in neuronal and neuroendocrine cell neoplasms (APUD-cells), e.g. bowel and lungs, due to its high tissue specificity. About 20% of all cancer-related deaths in Europe are caused by lung cancer,[3] with the highest incidence reported in Hungary.[4, 5]

NSE in lung cancer

NSE as marker of choice for small-cell bronchial carcinoma

NSE sensitivity in small-cell lung cancer (SCLC) ranges between 60 and 87%.[6] Therefore, NSE is considered a crucial marker for small-cell bronchial carcinoma. NSE is more relevant with respect to other available markers[7] in the differential diagnosis between benign lung disease and nonsmall- cell lung cancer (NSCLC) or SCLC. NSE correlates well with the tumour size and spread. The course of the disease and its prognosis may be established trustworthy using NSE in both SCLC and NSCLC.[8] The response to treatment can be detected within seven days, because a rapid fall in NSE concentration may be observed 24-72 hours after the initial therapy session in therapy responders.[9, 6, 10]

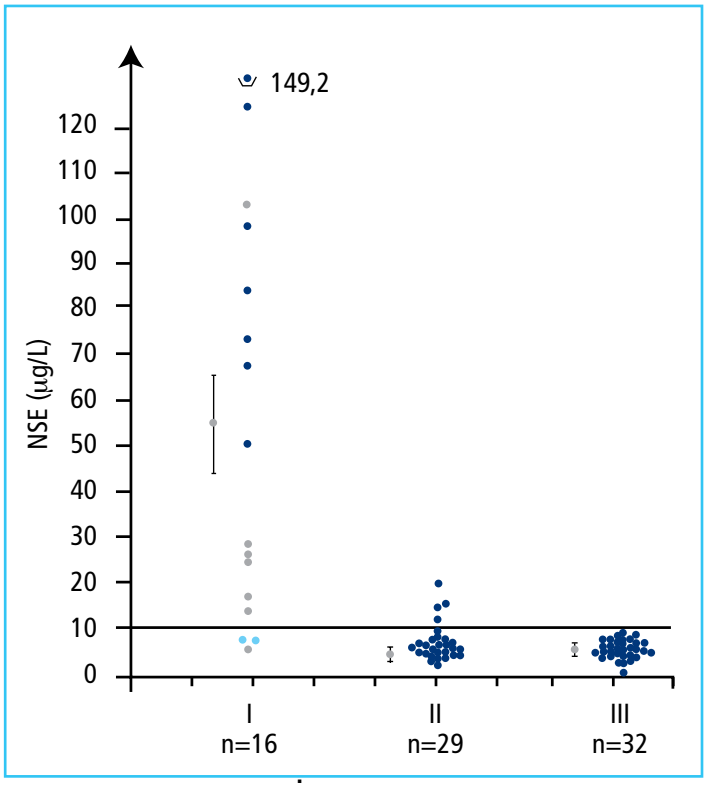

Fig. 1 - Pretreatment serum concentrations and mean value (x ± SE) of NSE in patients with SCLC (I), non-SCLC (II), and begin pulmonary diseases (BPD) (III)
• Limited disease; • extensive disease;
• extensive disease and diffuse metastatic spread (Ref. 7)

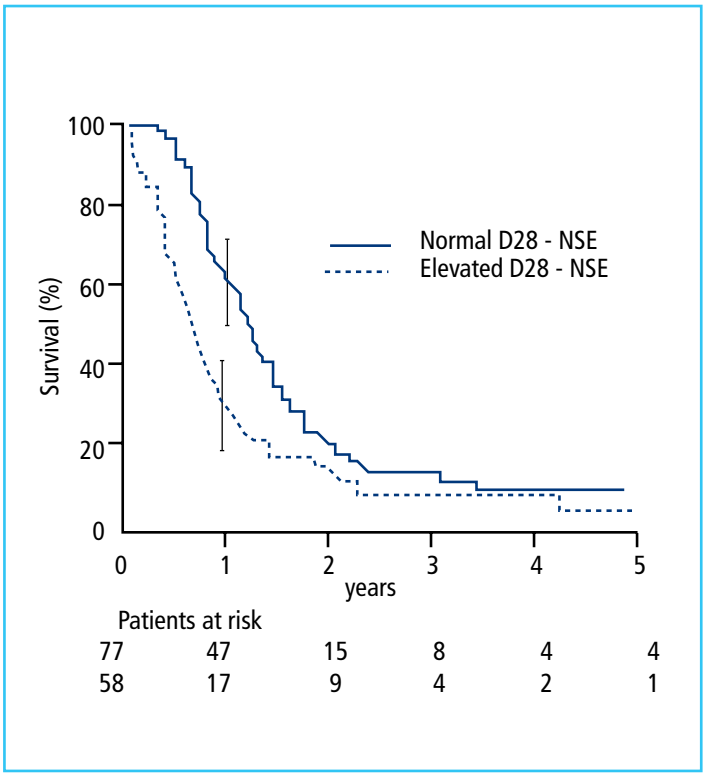

Fig. 2 - Overall survival of patients with small cell lung carcinoma is shown, according to the serum neuron specific enolase value measured on Day 28 after chemotherapy (D28-NSE) (Ref. 10)

NSE in neuroblastoma

Recommendations as tumour marker for diagnosis and follow-up

Neuroblastoma is the second most frequent malignant cancer among children. Neuroblastomas arise from degenerated cells of the autonomic nervous system and can occur along nerves in the entire human body. The use of NSE as a tumour marker is recommended in the interdisciplinary guideline of the German Cancer Society and the Society for Paediatric Oncology and Haematology,[11] since increased serum concentrations of NSE indicate higher probability of the presence of a neuroblastoma. Early neuroblastoma detection is of paramount importance to attain a more benign

course of the disease and favorable prognosis. Studies by Zeltzer[12] and Masseron[1] among others seem to indicate that serum values above 30 µg/L are associated with extremely unfavorable prognosis and are especially found in stage III and IV patients. Diagnostic sensitivity on neuroblastoma is 62%.[13]

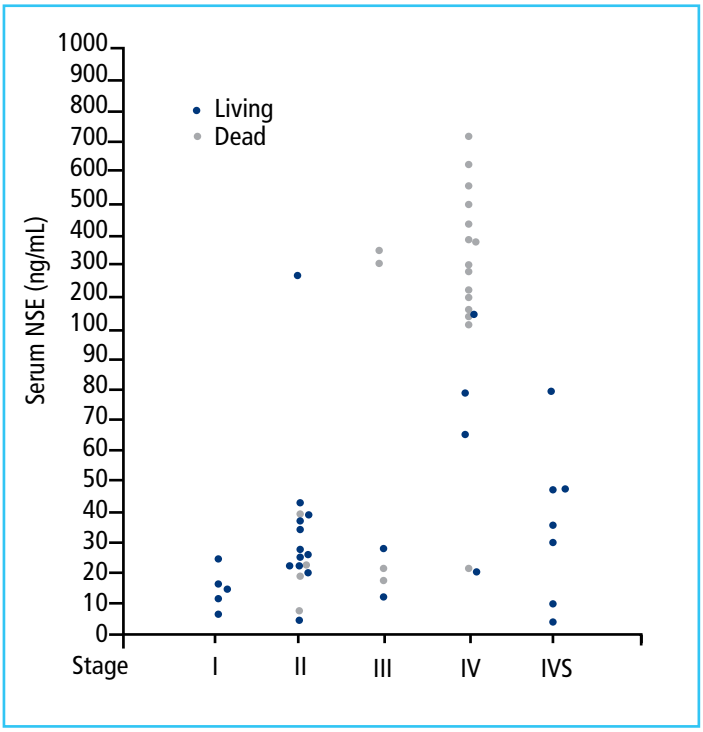

Fig. 3 - Serum NSE levels at diagnosis by stage in 54 patients with 2 or more years of follow-up with life status (survival). Disease-free survival was 79% (27/34) below and 10% (2/20) above the level of 100 ng/mL which was used to calculate the prognostic value of the test (Ref. 12)

NSE in APUDomas and seminomas

Improved correlation with clinical course

APUD-cells originate from the neural crest and are cells which take up amines and are capable of decarboxylation.
APUDomas form several tumours of different origin in the human body. These tumours are mostly of neuroendocrine origin, show a relatively slow growth and synthesize NSE in large amounts in serum.
Diagnostic sensitivity on APUDomas is 34%.[14] Germ-cell tumours are the commonest tumours among men in the age group of 20 to 40 years. They represent overall 1% of all neoplasms with increasing incidence in the last 40 years.[15] About 40-60% of seminomas are considered as the most frequent germ-cell tumours. NSE determination is of help in metastatic seminomas, although AFP and β-hCG are usually recommended as tumour markers, because increased NSE concentration is found among 68-73% of patients.[16, 17]

NSE in neurological impairment

Identification and prognosis of traumatic brain injury

Due to high tissue specificity of γ-enolase, brain injury can be identified by the enzyme release in the cerebrospinal fluid or blood. In particular, studies in children[18, 19, 20] as well as adults[21, 22] seem to indicate that increased NSE in serum or cerebrospinal fluid can lead to improved diagnostic and prognostic evaluation of the clinical course of the disease.

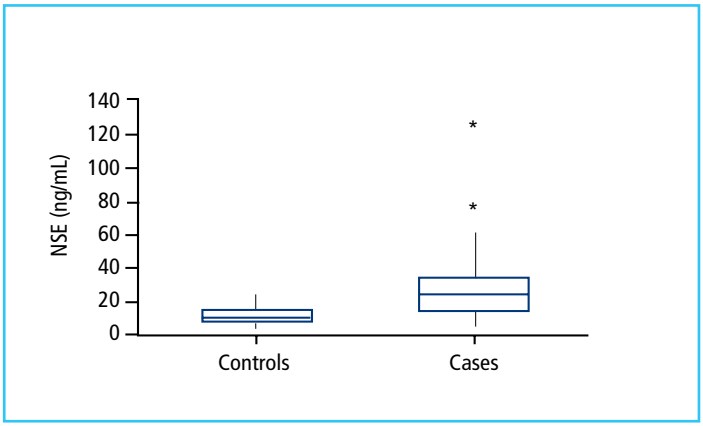

Fig. 4 - Box plots showing distribution of biomarker concentrations in controls versus cases with and without ICH. The horizontal line in each box represents the median concentrations. Asterisks represent outliers. NSE; p, 0.001 between groups (Ref. 20)

Summary

- NSE differentiates between benign and malignant disease and shows disease progression in small-cell bronchial carcinoma.
- Decreased NSE concentrations are generally indicative of successful treatment. If NSE concentrations are unaltered or increased, treatment strategy must be changed.
- NSE is a valuable diagnostic marker for neuroblastoma.
- Increased NSE concentrations for APUDomas and seminomas indicate metastatic disease.

1. Massaran S et al. Tumor Biol 1998; 19: 261-268.
2. Fujita K et al. Cancer 1987; 60: 362-369.
3. Europäische Union "eurostat" http://epp.eurostat.ec.europa.eu 2005.
4. Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (GEKID). www.rki.de/krebs 2006.
5. WHO European Office. http://data.euro.who.int/hfadb 2008.
6. Carney DN et al. Lancet 1982; 13: 583-585.
7. Fischbach W et al. Cancer 1989; 63: 1143-1149.
8. Jaques G et al. Cancer 1988; 62: 125-134.
9. Burghuber OC et al. Cancer 1990; 65: 1386-1390.
10. Fizazi K et al. Cancer 1998; 82: 1049-1055.
11. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF) www.leitlinien.net 2008; Pädiatrische Onkologie und Hämatologie.
12. Zeltzer PM et al. Cancer 1986; 57: 1230-1234.
13. Lamerz R in: Thomas L (ed.) Labor und Diagnose 2005; 1334-1338.
14. Fischbach W et al. Dtsch Med Wochenschr 1986; 111: 1721-1725.
15. Buse S et al. Praxis 2003; 92: 1989-1997.
16. Kuzmits R et al. Cancer 1987; 60: 1017-1021.
17. Kang JL et al. J Pathol 1996; 178: 161-165.
18. Berger RP et al. Pediatrics 2006; 117: 325-332.
19. Bandyopadhyay S et al. Acad Emerg Med 2005; 12: 732-738.
20. Berger RP et al. J Neurosurg 2005; 103(1 Suppl): 61-68.
21. Sawauchi S et al. No Shinkei Geka 2005; 33: 1073-1080.
22. Anand N & Stead LG. Cerebrovasc Dis 2005; 20: 213-219

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Oncology

S100

For the clinical management of malignant melanoma

The incidence of malignant melanoma is increasing with an annual rate of about 5%. Despite all efforts being made in the early detection of melanoma, 20% of the affected people will die as a result of tumour metastases. Immune modulating treatment with interleukin 2 induces long-term survival in 5-10% of patients with metastatic malignant melanoma, but at the expense of significant toxicity for the patients. Thus, a serum marker that reflects tumour load and can predict response and prolonged survival would greatly improve the clinical management.

Protein S100 with focus on S100B

S100B is a neuronal protein present in high concentrations in glial and Schwann cells. It is also found in significant amounts in malignant melanocytes.

Protein S100 has since long been known for its value in immunohistochemistry for detection of malignant tumours of melanocytic origin.

The S100 family consists of twenty members. The first member was isolated 1965 from bovine brain tissue and it was named S100 due to its solubility in 100% saturated ammonium sulphate.

S100B in Malignant Melanoma

Serum S100B has been shown to give valuable information regarding many aspects of the clinical management of malignant melanoma:

Staging - gives additional information to clinical staging.

Prognosis - the expression of S100B is directly related to the degree of malignancy.

Treatment monitoring - studies have indicated that treatment outcome can be predicted in approximately 95% of all cases already after 4 weeks of treatment without additional clinical investigations.

Follow up - for early detection of recurrences

Staging

Several studies have demonstrated that S100B concentrations are significantly related to clinical stage as well as survival (Fig. 1). A review of multiple clinical studies indicated increasing sensitivity of serum S100B with clinical stage up to 70-80% in stage IV. Combining a positive serum S100B value and Breslow thickness > 4 mm resulted in sensitivity for the presence of secondary spread of 91% and specificity of 95%.

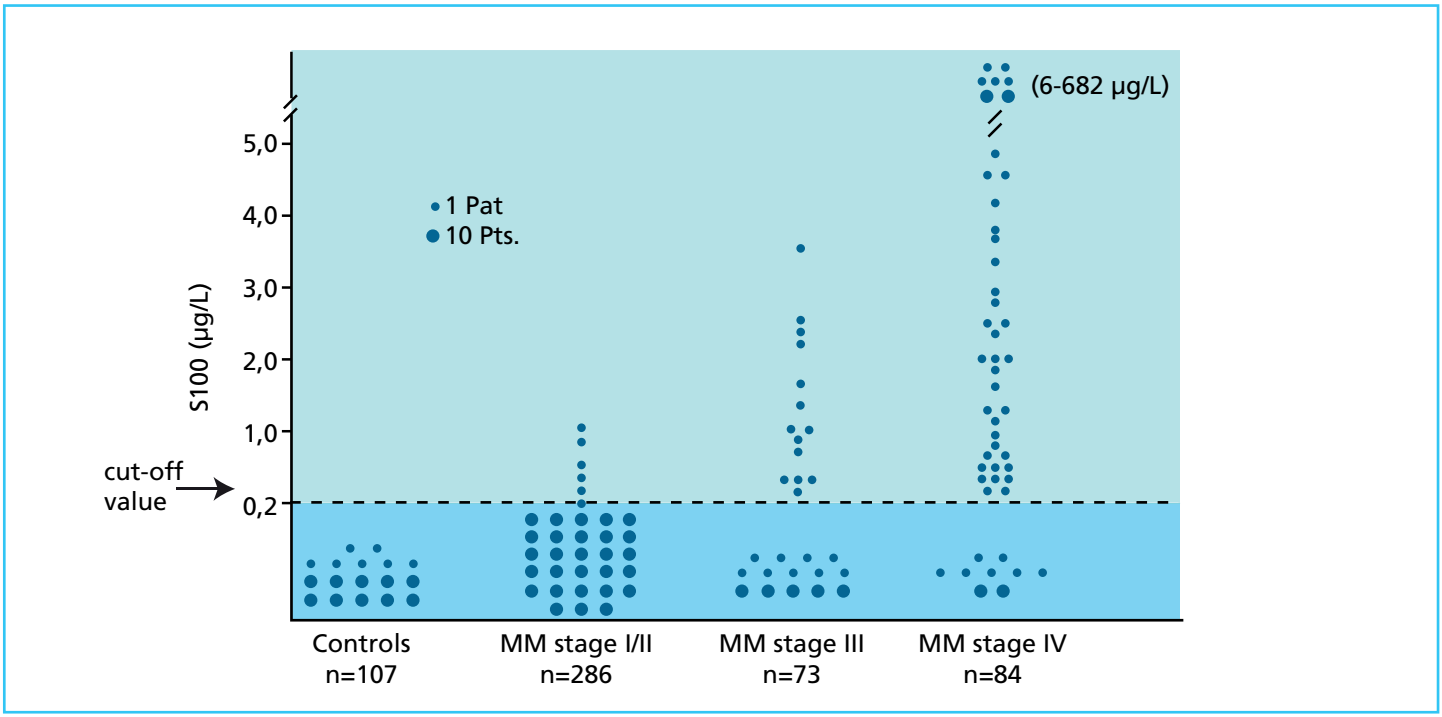

Fig.1 - S100B serum levels in melanoma (stages I-IV) and control patients (Ref. 8)

Prognosis

S100B is an independent prognostic factor. Pre-treatment levels of serum S100B predict survival time in melanoma patients. Survival is significantly longer in melanoma patients with normal S100B levels compared to those with elevated levels (Fig. 2, Table 1). Even within the same clinical stage survival is significantly influenced by the S100B level (Fig. 3). S100B is the only significant prognostic factor in a multivariate test for advanced-stage melanoma patients. In conclusion a large number of papers have shown that S100B is the most reliable prognostic marker for patients with stage III and IV melanoma.

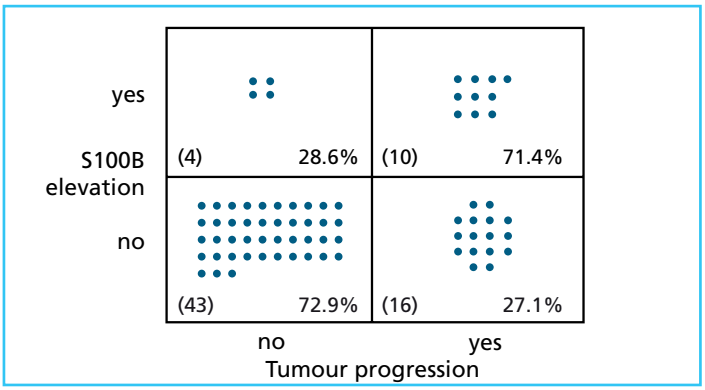

Fig. 2 - Correlation of tumour progression with initial serum S100B values (stage III patients) (Ref. 8)

Serum Level	Median Survival
< 0.2 µg/L	14 months
0.2 - 0.6 µg/L	10 months
0.6 - 3.0 µg/L	6 months
> 3.0 µg/L	3 months

Table 1 - Medium Survival in Stage IV patients (Ref. 8)

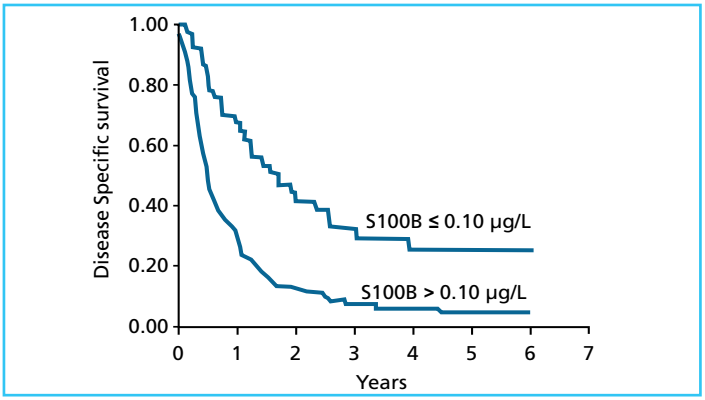

Fig. 3 - Melanoma-specific survival in patients (stages II and III) in relation to serum S100B levels (Ref. 4)

Treatment monitoring

Several studies indicate that serum S100B concentrations may be useful in treatment monitoring. Rising or falling serial serum S100B protein values correlate with disease progression or response to therapy (Fig. 4). The most interesting results are based on an interim analysis after 4 weeks of treatment. At this time the rate of adequate identification of responders was 95%. These studies imply that unsuccessful treatment can be terminated or altered early if serum S100B concentrations are increased.

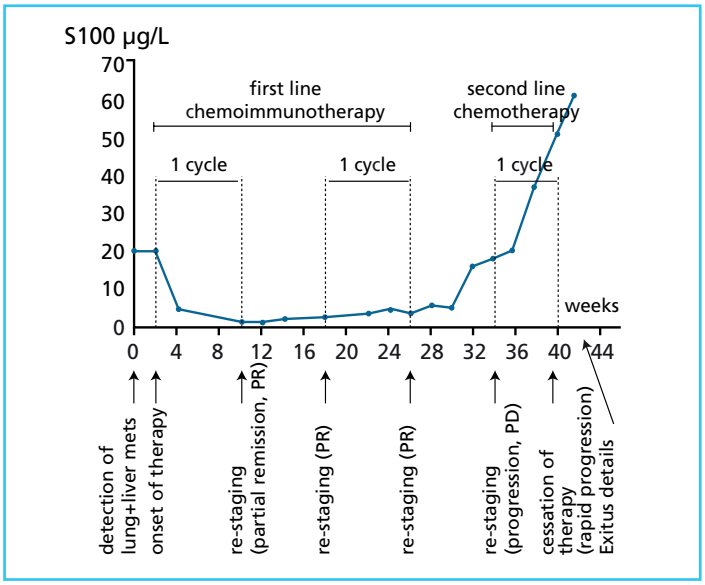

Fig. 4 - Serial measurements of S100B in a 26-year old man during the first line chemoimmunotherapy and second line polychemotherapy (Ref. 9)

Follow-up and early detection of recurrences

Rising levels of serum S100B protein have been shown to be a specific and sensitive marker of tumour progression, which precedes other evidence of melanoma recurrence. A rise in serum S100B may indicate melanoma progression 5-23 weeks before other evidence of metastatic spread. Repeatedly increasing serum S100B levels during follow-up should lead to further evaluation of the patient by chest X-ray, CT scan and clinical examination. Early detection of relapse could lead to earlier treatment and an overall better outcome of the disease. A recent paper has demonstrated that LIAISON® S100 has superior clinical sensitivity.

Summary

- Clinical evaluations of serum S100B protein have proved that S100B is an excellent marker for clinical management of malignant melanoma patients.
- LIAISON® S100 has demonstrated superior clinical sensitivity.

1. Abraha H.D. et al., Br J Dermatol 1997; 137:381-5
2. Bonfrer J.M. et al., Br J Cancer 1998; 77:2210-4
3. Bonfrer J.M. et al., Recent Results Cancer Res 2001; 158:149-57
4. Djureen-Mårtensson E. et al., J Clin Oncol 2001; 19:824-31
5. Donato R., Int J Biochem Cell Biol 2001; 33:637-68
6. Harpio R., Einarsson R., Clin Biochem 2004; 37:512-8
7. Heizmann C.W. et al., Front Biosci 2002; 7:1356-68
8. Hauschild A. et al., Oncology 1999; 56:338-44
9. Hauschild A. et al., Br J Dermatol 1999; 140:1065-71
10. Moore B.W., Biochem Biophys Res Commun 1965; 19:739-744
11. Smit L.H. et al., Eur J Cancer 2005; 41:386-92
12. Smit L.H. et al., Int J Biol Markers 2005; 28:34-42

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Oncology

Thymidine Kinase

TK

Reflecting proliferation in haematological malignancies

Thymidine Kinase reflects proliferative activity of the tumour

Thymidine Kinase is a cytosolic enzyme known to be involved in DNA synthesis.[1] DNA is synthesized following one of two possible pathways (Fig. 1): the de novo pathway or the Salvage pathway. In the latter thymidine kinase catalyzes conversion of deoxythymidine to deoxythymidine monophosphate. Subsequent steps lead to DNA-synthesis as shown in Figure 1. The pathway catalyzed by TK is called the Salvage pathway since it uses either exogenous or endogenous deoxythymidine. Mammalian cells contain two different Thymidine Kinase isoenzymes,[2] cytosolic Thymidine Kinase 1 (TK1) and mitochondrial Thymidine Kinase 2 (TK2). TK1 is associated with cell proliferation whereas TK2 is needed for mitochondrial DNA synthesis. TK1 activity increases markedly in the G1/S phase of the cell cycle. TK1 has therefore been shown to be a reliable marker of cell proliferation – the only proliferation marker that can be measured in serum (S-TK).[3]

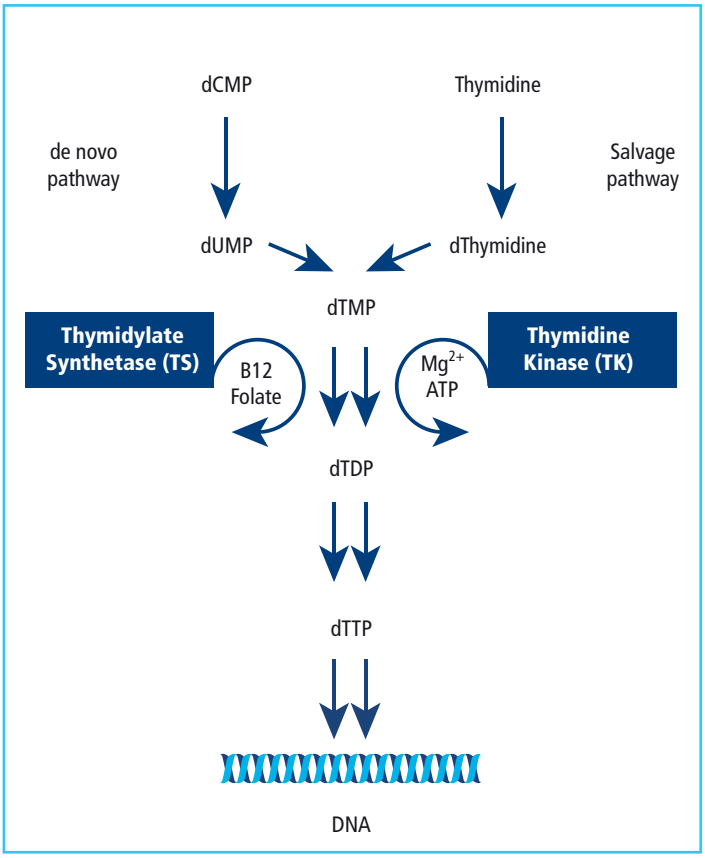

Fig. 1 - De novo and Salvage pathways

TK in Haematological Malignancies

Non-Hodgkin's Lymphoma (NHL)

Several studies have shown the value of S-TK as a prognostic marker.[5] Pretreatment levels have been found to be a powerful discriminator of disease stage and to provide prognostic information. S-TK levels are able to predict response to treatment and survival. S-TK values seem also to be higher in high-grade NHL than on low-grade NHL.[6-9]
Furthermore S-TK levels are useful in predicting the disease course in low-grade NHL. S-TK values are found to return to normal if the treatment is successful. A renewed increase indicates recurrence and/or transformation into a more malignant form of the disease.[10]

Chronic Lymphocytic Leukaemia (CLL)

The current staging systems in CLL such as Binet or Rai classification do not accurately predict the individual risk of disease progression. The S-TK levels in patients with CLL have been shown to have a remarkably prognostic capability. Patients with a serum level above 7.1 U/L have an average time of Progression-Free Survival of about 8 months, whereas patients with levels below this concentration have a Progression-Free Survival of almost 49 months, which is similar to that of patients with smouldering CLL (Fig. 2).[8,11]

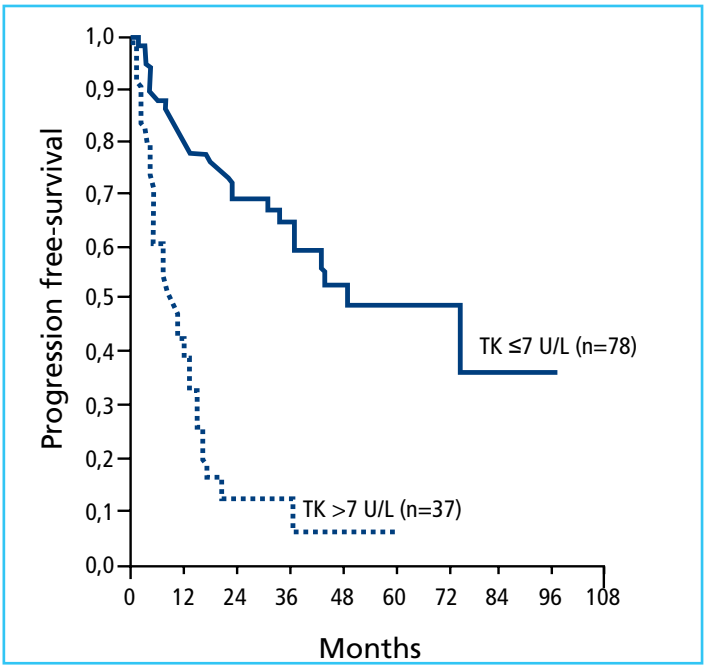

Fig. 2 - Progression-Free Survival of Binet stage A patients in relation to high versus low serum TK level. The cut-off used was 7.1 U/L (Ref. 8)

Multiple Myeloma (MM)

It has been shown that S-TK levels correlate with clinical stage and survival time. Furthermore S-TK levels have been found to be useful in distinguishing between MM and monoclonal gammapathy of undetermined significance (MGUS) (Fig. 3).[12,13]

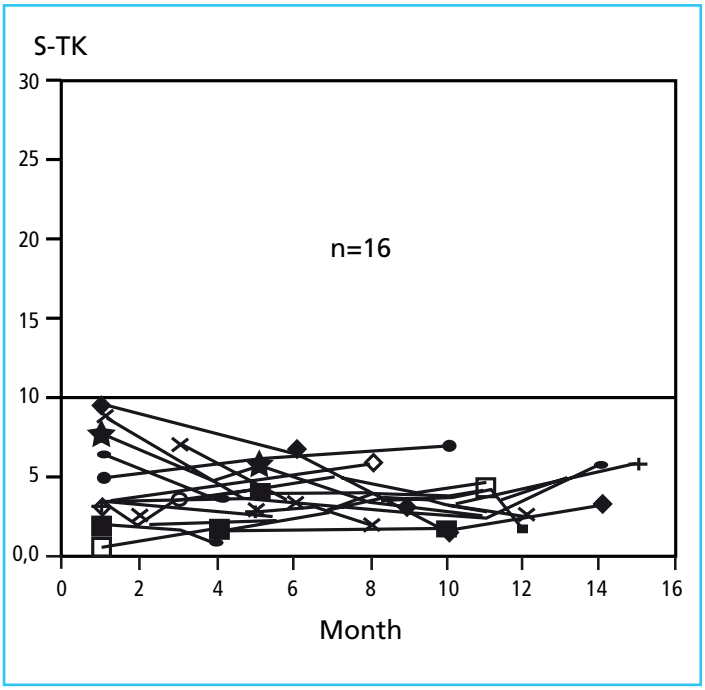

Fig. 3a - Follow-up of MM patients with smouldering myeloma (Ref. 12)

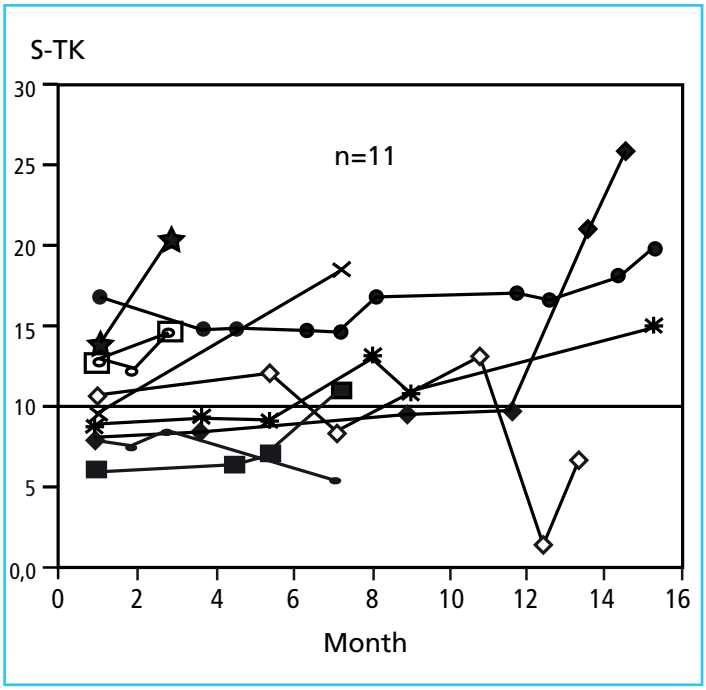

Fig. 3b - Follow-up of MM patients with active disease (Ref. 12)

Hodgkin's lymphoma

Significant correlations have been found between S-TK levels and the stage of the disease. When the prognostic ability was examined, patients in stages IA and IIA could be divided according to S-TK levels into two different groups in relation to Disease-Free Survival. This finding makes S-TK interesting as an additional tool in clinical evaluation and in the therapeutic decision concerning patients with Hodgkin's disease.[14]

Acute Myeloic Leukaemia (AML) and Acute Lymphocytic Leukaemia (ALL)

S-TK determinations detect recurrent disease at an early stage, before it can be detected microscopically. There is a close correlation between S-TK levels and the count of leukocytes, the percentage of blasts in the blood, the therapeutic response and the length of survival after the initial diagnosis. Therefore S-TK levels indicate the aggressiveness of leukaemic cells and predict the response to the treatment and the length of survival.[15-17]

MyeloDysplastic Syndrome (MDS)

High S-TK in MDS predicts transformation of MDS to Acute Myeloid Leukaemia. Multivariate analysis confirmed the independent prognostic value of S-TK for both overall survival and risk of acute transformation.
We conclude that S-TK may be an important prognostic factor in MDS, which is strongly correlated to development of AML.

Summary

- S-TK has proven to be a reliable marker of tumour cell proliferation
- S-TK provides a valuable tool to assess disease activity in untreated haematological malignancies and for monitoring of treatment, remission and smouldering disease
- S-TK predicts clinical relapse months before the onset of clinical syptoms

1. Reichard P et al. J Biol Chem 1951; 188: 839-846
2. Pardee AB. Science 1989; 246: 306-308
3. Hallek M et al. Ann H Hematol 1992; 65: 1-5
4. O'Neill KL et al. Expert Rev Mol Diagn 2001; 1: 428-433
5. Gronowitz JS et al. Br J Cancer 1983; 47: 487-495
6. Rehn S et al. Br J Cancer 1995; 71: 1099-1105
7. Hagberg H et al. Scand J Haematol 1984; 33: 59-67
8. Hallek M et al. Blood 1999; 93: 1732-1737
9. Ellims P et al. Blood 1981; 58: 926-939
10. Hallek M et al. Klin Wochenschr 1988; 66: 718-723
11. Matthews C et al. Eur J Hematol 2006; 77: 309-317
12. Poley S et al. Anticancer Res 1997; 17: 3025-3030
13. Luoni R et al. Cancer 1992; 69: 1368-1372
14. Eriksson B et al. Acta Radiol Oncol 1985; 24: 167-171
15. Sadamori N et al. Br J Haematol 1995; 90: 100-105
16. Hagberg H et al. Br J Cancer 1984; 49: 537-540
17. Archimbaud E et al. Leukaemia 1988; 2: 245-246
18. Musto P et al. Br J Haematol 1995; 90: 125-130

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Oncology

Tissue Polypeptide Antigen

TPA

Providing valuable information for prognosis and follow-up

Cytokeratin filaments

All eukaryotic cells have cytoplasmatic cytoskeletal structures known as intermediate filaments. Among the most important of these are the cytokeratin proteins found in epithelial cells. To date the human catalogue of cytokeratins comprises 20 distinct polypeptides.[1] An epithelial cell exhibits a characteristic combination of two or more cytokeratins. The pattern of expression is usually preserved during malignant transformation. The cytokeratins have become well-established markers of epithelial tumours.[2]

Tissue Polypeptide Antigen

Tissue polypeptide antigen or TPA is a circulating complex of polypeptide fragments of cytokeratins 8, 18 and 19. These three cytokeratins are characteristic of internal epithelium and are widely distributed in normal tissues and in tumours derived from them.[3]
Serum levels of TPA have been shown to correlate well with cell growth rate and tumour burden and are elevated in metastatic and disseminated disease. TPA is therefore valuable as a prognostic marker and for monitoring treatment of patients with different carcinomas.[4]

A variety of assays claim TPA reactivity

A number of assays for detection of cytokeratins exist on the market (Table 1). These tests vary in reactivity and the use of similar commercial names may generate confusion, since they do not show identical clinical results.[5, 6]

Marker	Cytokeratin		
TPA	8	18	19
TPS		18	
CYFRA 21-1			19
TPAcyk	8	18	

Table 1 - Reactivity of commercially available tests for cytokeratins

TPA in lung cancer

The overall sensitivity of TPA in the diagnosis of lung cancer, independent of histotype, is about 70% at 95% specificity level. The sensitivity for non-small cell lung cancer (NSCLC) is about 80%.[7, 8] TPA correlates well with tumour load and the extent of the disease. Furthermore TPA predicts disease progression and is an early indicator of relapse during follow-up in NSCLC. Changes in TPA often precede detection of relapse by conventional methods. Response to treatment can be detected within seven days since the halflife of TPA is less than one day.[9]

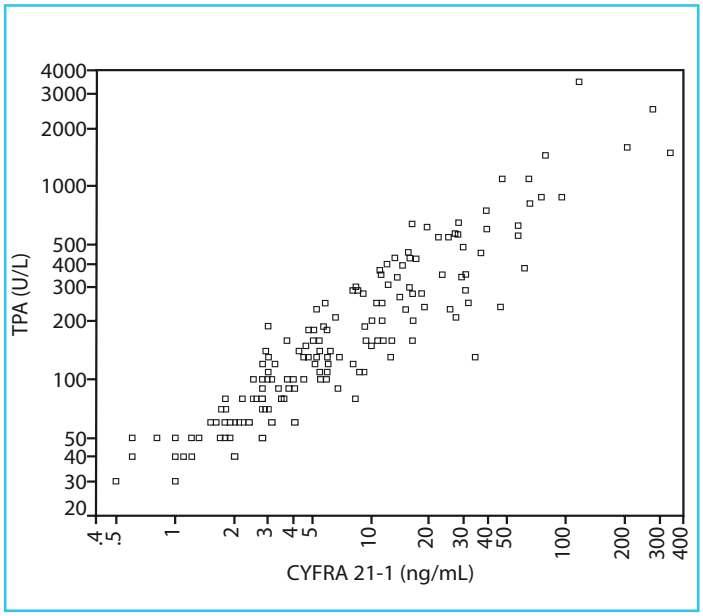

Fig. 1 - Scatter-plot showing pretreatment levels of TPA and CYFRA 21-1, measured, blind of clinical information, in 180 new NSCLC patients (Spearman r coefficient, 0.935)

TPA shows an excellent correlation to CYFRA in lung cancer (Fig. 1). Several studies have also demonstrated that TPA and CYFRA show the same clinical sensitivity for lung cancer of different histotypes (Table 2).[10]

Tumour Marker	Sensitivity (%)					
	SCLC	NSCLC	SCC	AC	ICC	Others
TPA	27	51	64	36	53	44
CYFRA	26	51	68	35	29	44
CEA	28	22	16	31	12	33
NSE	56	25	33	16	24	22
SCC	8	30	45	20	18	11
TPS	17	19	20	18	24	22

Table 2 - Clinical sensitivity at 95% specificity for the most frequently used lung cancer markers related to histology

TPA in breast cancer

TPA has been used in the therapeutic monitoring of breast cancer for several decades. A raise in serum TPA values has been shown to precede the clinical symptoms by several months.
Several studies showed that TPA has the highest sensitivity for breast cancer (Fig. 2).[11] In a recent study different combinations of tumour markers were assayed in all stages of breast cancer. The combination of a tumour marker with high specificity for breast cancer, CA 15-3, with the less specific but highly sensitive TPA increased the sensitivity by approximately 25% at all stages – a greater increase than for any other combinations tested.[12]

Using changes of marker levels, an increase of > 25% was judged as progressive disease and a decrease of > 50% as tumour response.
This demonstrated that the cytokeratin markers are superior to CA 15-3 in follow-up of chemotherapy (Table 3).[13]
The combination of CA 15-3 and TPA is therefore a valuable supplement to the conventional methods and the best combination of markers for evaluation of breast cancer patients.

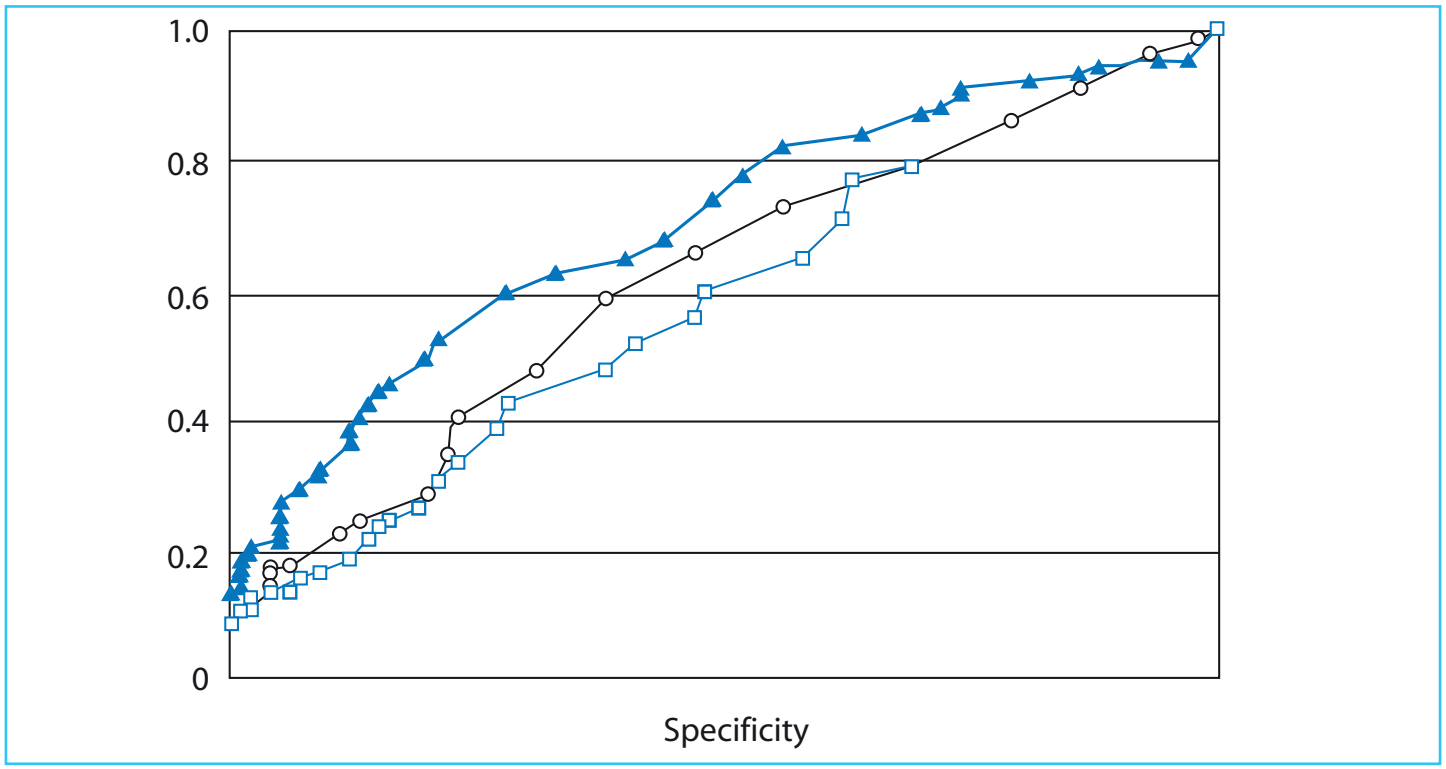

Fig. 2 - Receiver operating characteristic of curves of (–o–) CA 15-3, (–□–) CEA and (–◄–) TPA. Calculations based on values of the breast cancer group (n = 240) and the control group (n = 86). Area under the ROC curves: CA 15-3 = 0.623; CEA = 0.588; TPA = 0.702

Tumour Marker	Sensitivity (%)	
	CR, PR	PD
TPS	84	82
TPA	97	82
CA15-3	68	66

Table 3 - Correlation between clinical response according to UICC and tumour marker changes

Summary

- TPA discriminates between localised and metastatic disease
- TPA values normally decrease in response to successful treatment. If TPA values remain unaffected or increased, a change of treatment should be considered
- Increased TPA values during follow-up of treatment may indicate relapse

1. Moll R. Subcell Biochem 1998; 31: 205-262.
2. Einarsson R. Adv Clin Exp Med 2001; 10: 331-335.
3. Barak V. et al. Clin Biochem 2004; 37: 529-540.
4. Weber K et al.EMBO Journal 1984; 3: 2707-2714.
5. Bodenmüller H et al. Int J Biol Markers 1994; 9: 70-74.
6. Bombardieri H et al. Int J Biol Markers 1994; 9: 254-255.
7. Correale M et al. Int J Biol Markers 1994; 9: 231-238.
8. Mizushima Y et al. Oncology 1990; 47: 43-48.
9. Rapellino M et al. Int J Biol Markers 1994; 9: 33-37.
10 Buccheri G et al. Chest 2003; 124: 622-632.
11. Findeisen R et al Clin Chem lab Med 1998; 36: 841-846.
12. Niccolini A et al. Br J Cancer 1999; 79: 1443-1447.
13. Lindman H et al. J Tumor Marker Oncol 2000; 15: 177-186.

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