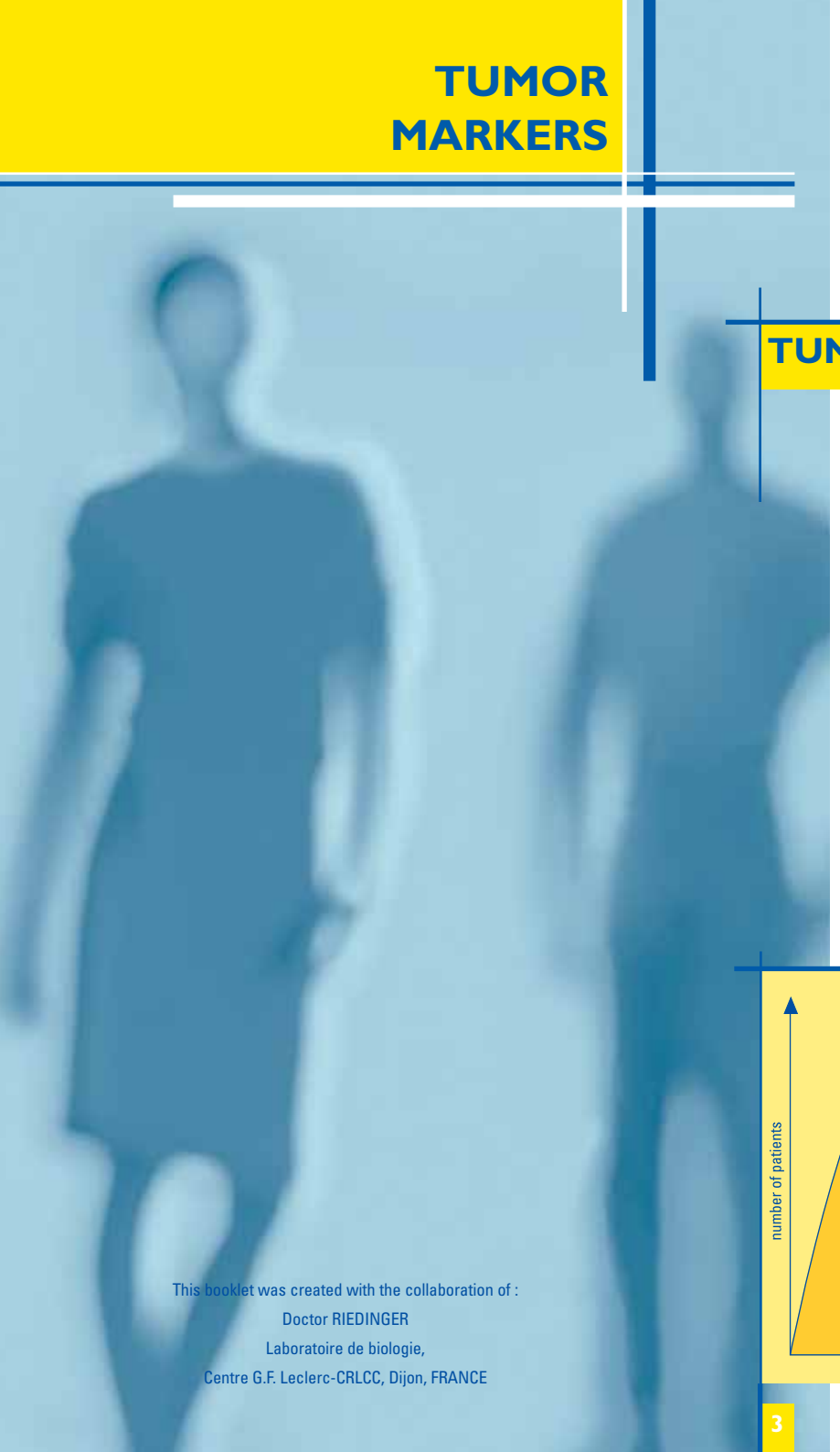
Diagnosis & Monitoring of CANCER

from diagnosis,
the seeds of better health

BIOMÉRIEUX

TUMOR MARKERS



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TUMOR MARKERS

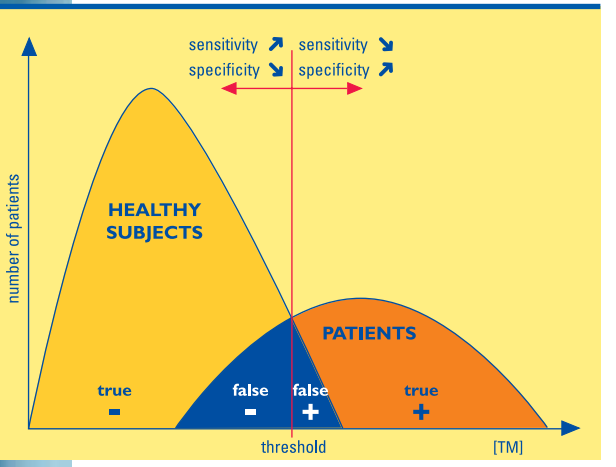
From dreams…

An ideal tumor maker (**TM**) would be a substance produced only by the neoplasic cells, specific to one type of tumor (no false positives) and detectable right from the initial stage of the disease (no false negatives).

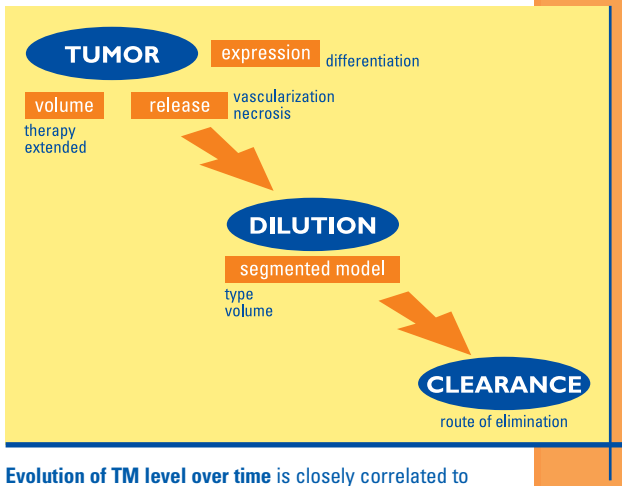
It would be undetectable in healthy subjects, and enable the screening and diagnosis of cancer. The [TM] level would correlate closely with tumor size, contribute to the initial extension of the profile and evaluation of therapeutic efficacy, as well as the early detection of recurrent diseases.

…to reality

Most TMs are also produced by normal cells, and have only average sensitivity and specificity levels which depend on the decision-making threshold chosen.



The TM level is influenced by a large number of parameters.



Evolution of TM level over time is closely correlated to variations in the size of the tumor.

Non-specific increases in TM levels other than tumor pathologies	
CEA	Smoking, benign pulmonary and digestive pathologies, chronic renal insufficiency
CA 19-9	Benign pulmonary and digestive pathologies (cholecystitis and pancreatitis ++)
AFP	Benign hepatic pathologies, multiple pregnancies
PSA	Prostate adenoma, prostatitis, prostate manipulations
ßhCG	Pregnancy
CA 15-3	Benign hepatic, digestive, pulmonary and ovarian pathologies, auto-immune disease
CA 125	Serosa pathologies, cirrhosis, ascitis, endometriosis, end of pregnancy
CT	Apudoma, chronic renal insufficiency, hyperparathyroidism, Paget's disease
Tg	Benign thyroid diseases
NSE	Apudoma, renal tumors, benign pulmonary pathologies
ß2-M	Rheumatoid arthritis, AIDS, lupus, crohn's disease, renal tubular dysfunction.

CLINICAL USE OF MARKERS

Organ	Histological type	Main or secondary marker
Breast	Adenocarcinoma	CA 15-3 - CEA
Ovary	Serosa	CA 125
	Mucosa	CA 19-9 (CEA - CA 72-4)
	Germinal	AFP - ßhCG
	Granulosa	Inhibin (estradiol)
Uterus (neck)	Epidermoid	SCC or CYFRA 21-1
Endometrium	Adenocarcinoma	CA 125 - CA 19-9
Placenta	Trophoblastic	ßhCG
Prostate	Adenocarcinoma	PSA - free PSA (PAP)
Bladder	Adenocarcinoma	TPA
Testis	Seminoma	ßhCG
	Non seminoma	ßhCG - AFP
Oesophagus	Epidermoid	SCC or CYFRA 21-1
	Adenocarcinoma	CA 19-9 (CEA)
Stomach	Adenocarcinoma	CA 72-4 (CA 19-9 - CEA)
Liver	Hepatocarcinoma	AFP - DCP (CEA)
	Metastasis (unknown primitive)	CEA - AFP - CA 19-9 - CA 15-3 - NSE
Bile ducts	Adenocarcinoma	CA 19-9 (CEA)
Pancreas	Adenocarcinoma	CA 19-9 (CEA - CA 50)
	Endocrine	Digestive hormones - NSE
Small intestine	Carcinoid	5-HIAA* (CEA - CA 19-9)
Colon/rectum	Adenocarcinoma	CEA (CA 19-9)
Anus	Epidermoid	SCC or CYFRA 21-1
Medulo-adrenal	Pheochromocytoma	VMA* - metanephrines* - catecholamines*
Lung	Adenocarcinoma	CEA
	Epidermoid	SCC or CYFRA 21-1
	Small cells	NSE
ENT	Epidermoid	SCC or CYFRA 21-1
Thyroid	Medullary	Calcitonin - CEA
	Differentiated	Thyroglobulin
Nervous system	Neuroblastoma	NSE - HVA* - catecholomines*
Hemato-lymphoid	Lymphoid malignancies	β2-M

* assays using urine

The clinical use of TMs has 5 main indications

CEA	Carcinoembryonic Antigen
AFP	α-Fetoprotein
CA	Cancer Antigen
ß2-M	β2-Microblobulin
CT	Calcitonin
5-HIAA	5-Hydroxyindoleacetic Acid
5'Nu	5'Nucleotidase
DCP	Decarboxyprothrombin
γGT	γ-Glutamyl Transferase
hCG	Human Chorionic Gonadotropin
HVA	Homovanillic Acid
LDH	Lactate Dehydrogenase
NSE	Neurone Specific Enolase
ALP	Alkaline Phosphatase
BAP	Bone Alkaline Phosphatase
PAP	Prostatic Phosphatase Acid
PSA	Prostate Specific Antigen
SCC	Squamous Cell Carcinoma
Tg	Thyroglobulin
TPA	Tissue Polypeptide Antigen
VMA	Vanillylmandelic Acid

SCREENING

PSA is the only maker that is used for screening of prostatic cancer in conjunction with digital rectal examination in males above the age of 50. In addition, **targeted screening** of thyroid medullary cancer using CT and hepatocarcinoma using AFP is justified.

DIAGNOSIS

The diagnostic use of TM is rare and is limited to the following assays :

- ßhCG for germinal tumors,
- AFP for hepatocarcinomas,
- CT for thyroid medullary cancer,
- PSA for prostate cancer.■

■ *To improve the diagnostic performance of PSA, different criteria have been proposed : The free PSA/total PSA ratio, the PSA density (ratio of PSA to gland size), the PSA velocity (annual increase of PSA) and the level of PSA linked to patient age.*

PROGNOSIS

The prognostic value of TMs is generally linked to the tumor size and often indicates the extent of disease. The only TMs with an independant prognostic value for the extent of disease are :

- CEA in colorectal cancer,
- ßhCG and AFP for germinal tumors,
- CYFRA 21-1 in non-small cell pulmonary cancer,
- LDH in germinal tumors and lymphoma.

THERAPEUTIC MONITORING

Therapeutic monitoring is evaluated by tracing the evolution of TM levels measured using the same technique within the same laboratory. Each patient is considered to be their own control and any reference to normal values should be abandoned.

Individual kinetics of the marker level

Integration of clinical and therapeutic data to the TM individual kinetics graph, as logarithmic coordinates, enables the different kinetic parameters to be calculated.

To evaluate therapeutic efficacy, the TM half-life ($T_{1/2}$) and its minimum level obtained during treatment (min[TM]) are measured.

Apparent half-life ($T_{1/2}$)

The half-life is the time taken for the TM concentration to decrease by half in the initial phase of therapy. This parameter measures the rate at which the size of the tumor size is reduced.
Its value depends on the type of therapy administered, as well as its efficacy. After radical surgery, the $T_{1/2}$ reflects only the clearance of TM.
While administering chemotherapy, radiotherapy or hormone therapy, the $T_{1/2}$ also reflects the transitory residual tumor secretion.

- *Some paradoxal increases in the TM level in the initial phase of efficient systemic therapy result from massive cytolysis or regeneration of hepatocytes.*

  When a heterogenous tumor secretes several TMs, a discrepant evolution of these markers can indicate a different sensitivity of the secreting cell clones to the therapy administered.

Minimum level obtained during therapy min[TM]

The min[TM] is a good indicator of residual disease. Its value and the time taken to obtain the result depends on the type of therapy administered and its efficacy.

- *The persistence of a high min[TM] level reveals the existence of a remaining secreting tumor. A return to usual values is not always associated with sterilization of the tumor. The value can correspond to the persistence of small remaining tumors or the disappearance of the only secreting cell clone.*

  For TMs for which the half-life is short, the persistence of a detectable level 3 weeks after complete surgical resection indicates the persistence of residue, probably due to a tumor.

Characteristics of main tumors

TM	$T_{1/2}$ (therapy)	Normal values
CEA	several weeks	< 2.5-5 µg/l
CA 19-9	8.5 days (surgery)	< 37 kU/l
AFP	4-5 days (surgery)	< 10 µg/l
PSA	2.2-3.2 days (surgery) 1.4-2.6 months (radiotherapy)	< 2.5 to 6.5 µg/l*
ßhCG	24 to 36 hours (surgery)	< 5-10 U/l
CA 15-3	8-15 days (surgery)	< 25-35 kU/l
CA 125	4.8 days (surgery) 9.2 days (chemotherapy)	< 35 kU/l
CT	20 minutes (surgery)	< 10 ng/l
Tg	2.7 days (surgery)	< 25 µg/l
SCC	20 minutes (surgery)	< 1.5 µg/l
CYFRA 21-1	4 days (surgery)	< 1.8 µg/l
TPA	7 days (surgery)	< 95 U/l

* 40-49 yrs old < 2.5 µg/l ; 50-59 yrs old < 3.5 µg/l ; 60-69 yrs old < 4.5 µg/l ; 70-79 yrs old < 6.5 µg/l (Standard Hybritech)

EARLY DETECTION OF RECURRENT DISEASE AND METASTASES

Biological recurrent diseases is characterized by the appearance of the evolutive TM profile.

Individual kinetics of the TM level

An exponential increase in TM levels, even within normal values, indicates renewed evolution. The evolution increase rate can be evaluated by the TM doubling time.

Doubling time (dT)

The doubling time is calculated using 3 points, and reflects the initial increase rate of the recurrent disease.

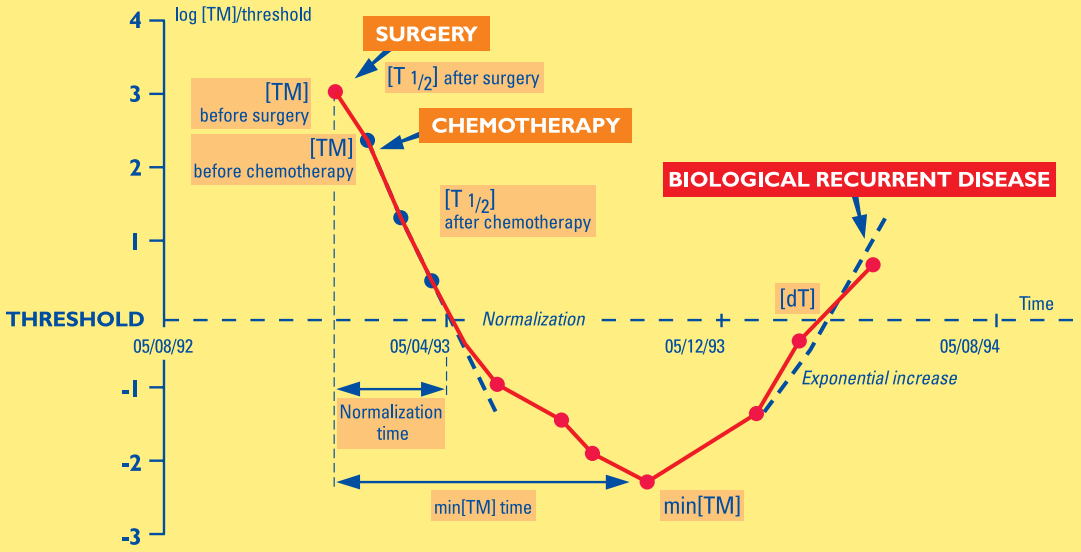
It also enables the monitoring schedule, therapeutic strategy, and type of therapy administered to be adapted early to the agressivity of the recurrent disease.

Indication	Biological criteria	Significance
Therapeutic monitoring	[TM] before therapy	Reference value
	$T_{1/2}$	Therapeutic efficacy
	min[TM] (normalization)	Residual disease
	min[TM] deadline (normalization)	Therapeutic efficacy
Early detection of recurrent disease	Exponential increase in TM (3 levels)	Biological recurrent disease
	dT	Increased rate of recurrent disease

$T_{1/2}$ = - Log(2)/decreasing TM curve
dT = + Log(2)/increasing TM curve

THEORETICAL EVOLUTIO N CURVE OF A MARKER*

There are several parameters which enable the interp retation of individual kinetics of an initially high TM level



*These kinetics cannot be generalized to all markers and clinical situations

PRACTICAL QUESTIONS

When to prescribe TM ?

Before therapy : to obtain a reference value.

During therapy : according to a rhythm adapted to the type of therapy, the half-life and the initial level of TM.

During therapeutic monitoring : with a frequency adapted to

- the risk of recurrent disease,
- the average time lapse before the onset of recurrent disease,
- the therapeutic alternatives available.

During evolving recurrent disease : according to a rhythm adapted to the doubling time of the TM.

Analysis of discrepancies

clinical :

- modification of the filtration functions of TM (hepatic or renal insufficiency),
- tumor heterogeneity,
- massive tumor cytolysis or regeneration of hepatocytes,
- inadequate evaluation (even dissociation) of the clinical response.

analytical :

- problem of reagent standardization,
- variable sensitivity of reagents to the hook effect or interfering substances,
- problem of international standardization,
- molecular heterogeneity of TM,
- presence of HAMA*.

* mouse anti-human immunoglobulin antibodies

Can TMs be detected elsewhere than in blood ?

After surgery, the expression of TM in tumor cells can be detected in tissue using the immunohistochemical technique.

TMs can also be assayed in biological fluids such as :

- urine (catecholamines and NSE in neuroendocrine tumors),
- pleural fluid (hyaluronic acid in mesotheliomes),
- ascite fluid (CA 19-9 and CEA in peritoneal carcinosis),
- CSF (NSE in organic neurological pathologies),...

What is the interest of the enzymatic assays in cancerology ?

They can usefully complete the information linked to TMs. If the increase in some enzymatic activities (ie. ALP, 5'Nu, γGT, LDH) indicates a non-specific response of the liver parenchyma to the invading tumor, other hyperactivities are a more specific result of the existence of a tumor : BAP (primary or metastatic bone tumor), PAP (prostatic tumor), lysozyme (myeloproliferative syndromes) etc...

ALWAYS REMEMBER

1. A normal TM level does not exclude cancer.
2. A high TM level does not always indicate cancer.

ESSENTIAL DO'S...

1. Assay the TM level before administering therapy.
2. Interpret the TM level taking into account the clinical and radiological context.
3. Control all positive results indicating the need for therapeutic decision making using a new sample.
4. Monitor patients using the same technique in the same laboratory.
5. Store sera in a serum bank.
6. Examine the background history when changing assay technique.
7. Integrate the individual evolution kinetics of the TM in the patient report.

...ESSENTIAL DON'TS

1. Assay a marker when no therapy is available.
2. Monitor the tumor site using several TMs which are not really complementary.

Blood Tumor Markers assays :

VIDAS® CEA	ref. 30412
VIDAS® AFP	ref. 30413
VIDAS® TPSA	ref. 30428
VIDAS® FPSA	ref. 30440
VIDAS® CA 15-3®	ref. 30429
VIDAS® CA 19-9™	ref. 30427
VIDAS® CA 125 II™	ref. 30426
VIDAS® ß2-M	ref. 30420

VIDIA® TPSA*	ref. 38500
VIDIA® FPSA*	ref. 38510
VIDIA® CEA*	ref. 38520
VIDIA® AFP*	ref. 38530

* in development

Availability of some VIDAS tests may be restricted in certain countries due to registration requirements. Consult our local representatives for further information.

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