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Review

Kinetics of Serum Tumor Marker Concentrations and Usefulness in Clinical Monitoring

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Only a few markers have been instrumental in the diagnosis of cancer. In contrast, tumor markers play a critical role in the monitoring of patients. The patient's clinical status and response to treatment can be evaluated rapidly using the tumor marker half-life ($t_{1/2}$) and the tumor marker doubling time (DT). This report reviews the interest of determining these kinetic parameters for prostate-specific antigen, human chorionic gonadotropin, α-fetoprotein, carcinoembryonic antigen, cancer antigen (CA) 125, and CA 15-3. A rise in tumor markers (DT) is a yardstick with which benign diseases can be distinguished from metastatic disease, and the DT can be used to assess the efficacy of treatments. A decline in the tumor marker concentration ($t_{1/2}$) is a predictor of possible residual disease if the timing of blood sampling is soon after therapy. The discrepancies in results obtained by different groups may be attributable to the multiplicity of immunoassays, the intrinsic characteristics of each marker (e.g., antigen specificity, molecular heterogeneity, and associated forms), individual factors (e.g., nonspecific increases and renal and hepatic diseases) and methods used to calculate kinetics (e.g., exponential models and timing of blood sampling). This kinetic approach could be of interest to optimize patient management.

Only a few markers have been instrumental in the diagnosis of cancer; they include α-fetoprotein (AFP),[9] human chorionic gonadotropin (hCG), and calcitonin. Although the concentration of an isolated tumor marker before any treatment may have a prognostic value, they are not widely used in comparison to conventional prognostic factors. In contrast, tumor markers play a critical role in the monitoring of patients. However, recourse to tumor markers as a yardstick of treatment or to signal the emergence of a recurrence or a metastasis has been based only on a succession of values with no regard for knowledge of the exponential nature of tumor growth, which is a theoretical and practical basis of cancer therapy. In an economy-conscious environment in which cost-effective medicine is an overriding concern, physicians treating cancer patients need convenient, efficient methods to rapidly evaluate response to therapy and to offer alternative treatment when appropriate *(1–4)*. A challenging approach to rapid evaluation of clinical response and monitoring is the determination of tumor marker half-life ($t_{1/2}$) and tumor marker doubling time (DT), kinetic parameters associated with changes in marker concentrations. The $t_{1/2}$ is calculated according to the formula $dt/\log(tm_1/tm_2)$, where tm_1 and tm_2 are the tumor marker values at times 1 and 2, respectively, and dt the interval between the two dates. The DT is determined according to the interval required to double the serum concentration. This report reviews the interest of determining kinetic parameters of the tumor markers that are the most relevant for the monitoring of patients. The main characteristics of prostate-specific antigen (PSA), hCG, AFP, carcinoembryonic antigen (CEA), cancer antigen (CA) 125, and CA 15-3, are presented in Table 1.

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[9] Nonstandard abbreviations: AFP, α-fetoprotein; hCG, human chorionic gonadotropin; $t_{1/2}$, half-life; DT, doubling time; PSA, prostate-specific antigen; CEA, carcinoembryonic antigen; CA, cancer antigen; BPH, benign prostatic hyperplasia; hCGβ, hCG β subunit; and NSGCTT, nonseminomatous germ-cell testicular tumor.

Dynamic Aspects of Tumor Markers

PSA

Serum PSA concentrations increase with age at a rate of 0.04 μg/L per year in healthy adult males *(5)*. The rate at which PSA increases annually is between 0.07 and 0.27 μg/L in patients with benign prostatic hyperplasia (BPH), between 0.47 and 3.08 μg/L for patients with localized cancers, and between 1.02 and 26.49 μg/L for patients with metastatic disease *(6)*. The serum PSA concentration is generally proportional to intra- and extracapsular growth of prostate carcinoma *(7)*. A linear relationship has been reported between serum PSA and the size of prostate cancer *(6, 8, 9)*. BPH provokes a rise of 0.3 μg/L per gram of hyperplastic tissue, whereas a rise of 3.5 μg/L per gram is observed for tumor tissue *(8)*. This relationship between tumor size and PSA production is not unanimously accepted. Brawer et al. *(10)* reported that the PSA_{index}, defined as the ratio between the serum PSA value and the tumor mass, is linked to the extent of the cancer but not correlated with the PSA concentration. The PSA concentration is a biological yardstick distinguishing patients with BPH from patients with localized, loco-regional, or advanced metastatic adenocarcinomas *(5, 11, 12)*.

There is a clear relationship between the DT and the International Union against Cancer tumor-node-metastasis classification before any treatment *(8)*. The DT apparently exceeds 48 months in stages T_1, T_2, and is less than 24 months for stages T_3 and T_4 *(8)*. This slow progression makes it possible to monitor therapy over 3- to 6-month periods. DT values vary from 73.9 to 98.9 years in controls and from 12.4 to 16.9 years in BPH patients *(6)*. In patients with prostate cancer, the pattern is biphasic. The first phase is linear, with an identical DT for localized and metastatic disease (13.6–18.6 years), and the second phase is exponential, with a DT of 2.4 years for localized cancers and 1.8 years for metastasis. DT values must be determined before starting therapy because prostate tumors grow very slowly, particularly when the initial concentration is low. The initial PSA concentration and DT should not be considered as isolated prognostic factors because their values are correlated with the tumor volume and grade *(13)*. Carter and Pearson *(14)* focused their study on trends in PSA with age, gland volume (measurement of PSA density), and time (measurement of PSA velocity). These tools are used for the screening of adenomas and localized cancers and to assess tumor extension in conjunction with other variables (e.g., biopsy and Gleason score).

Prostatectomy is appropriate for a tumor recurrence when the DT is <9 months. When the DT is >1 year, antiandrogenic treatment is more appropriate *(15)*. Zagars and Pollack *(12)* used a percentage of decrease relative to pretreatment concentrations to decide whether additional therapy was required or not. Patients with stages B_1, B_2, and C prostate cancer whose DT is <3.8 months require prompt surgery. Patients with a DT exceeding 3.8 months can be treated less aggressively (e.g., antiandrogens) *(16)*. A DT attaining 12 months or less should be considered eligible for multimodal therapy, and a slow DT (5 years) eligible for watchful waiting without therapy *(17)*. According to Pollack et al. *(18)*, although a correlation exists between the PSA concentration, the DT, and the time to relapse, it is not considered judicious to select a particular course of treatment on the basis of the DT value given the large number of variables involved.

Radical prostatectomy is indicated for a clinically localized tumor, and the efficiency of the treatment is assessed by long-term monitoring. PSA is undetectable within 21 days after prostatectomy *(19–21)*, at which point, any PSA concentration above the lower limit of detection signifies the presence of residual tumor. This argues in favor of using ultrasensitive assays. The PSA $t_{1/2}$, calculated with t_0 measured 2 days after prostatectomy, is close to 2.5 days and similar in several studies *(21)*. In contrast, when the t_0 value is measured 5 min postoperatively, the $t_{1/2}$ value is equal to 1.5 days *(21, 22)*. Calculating $t_{1/2}$ values helps distinguish patients in complete remission from those likely to develop a recurrence ($t_{1/2}$, 2.98 ± 1.33 days), although they have undetectable concentrations, and from patients in whom PSA will never return to the baseline value. van Straalen et al. *(23)* found a biphasic pattern for the disappearance of PSA after prostatectomy, with a first phase presenting a $t_{1/2}$ of 1.6 days and a second phase with a $t_{1/2}$ of 4.6 days. The PSA concentration should therefore be measured at least 30 days postoperatively. Even with a $t_{1/2}$ value of 1.6 days, patients may be considered cured if PSA remains undetectable over 24 months postoperatively *(24)*. The elimination of free PSA also exhibits a biphasic kinetic profile *(25, 26)*. The $t_{1/2}$ of free PSA [0.5–0.8 h in fast phase (first phase), 7–14 h in slow phase (second phase)] is shorter than that of total PSA, and the ratio between free and total PSA can be a useful tool *(25)*. The elimination of PSA complexed to α_1-antichymotrypsin is nonexponential, and free PSA released during surgery does not form complexes with α_1-antichymotrypsin. Elimination of total PSA is a combination of these mechanisms *(26)*. PSA concentrations are undetectable in patients 3 days after surgery for BPH (open surgery; $t_{1/2}$, 0.55 ± 0.39 days), 28 days after radical prostatectomy ($t_{1/2}$, 2.5 ± 1.33 days for one compartment and 0.94 ± 0.8 days and 7.62 ± 6.35 days for two compartments), and 21 days after radical cystectomy ($t_{1/2}$, 1.92 ± 1.2 d for one compartment). For others, the PSA $t_{1/2}$ in BPH patients (1.4 days for free PSA; 2.4 days for total PSA) is shorter than the PSA $t_{1/2}$ in cancer patients (2.1 days for free PSA; 3.4 days total PSA) *(27)*. Cystoprostatectomy is a good model for a pharmacokinetic study of PSA *(28)*. Calculations of $t_{1/2}$ must take in account blood loss during surgery *(29)*. Adjuvant radiotherapy increases the percentage of patients with undetectable PSA concentrations after prostatectomy *(30, 31)*. All patients with documented clinical recurrences had previously displayed renewed PSA secretion during monitoring. It is therefore of interest to monitor slight variations in PSA. The PSA kinetic profile is a key to

Table 1. Main characteristics of tumor markers.

	PSA	hCG	AFP
First description	1971 by Hara et al. *(140)*	1927 by Ascheim and Zondek *(141)*	1956 by Bergstrand and Czar *(142)*
Structure	Glycoproteins *(143)*; Monomer, 34 kDa; carbohydrates 7%; five isomers *(146)*, pI 6.8 to 7.2 *(143)* Chymotryptic activity Antichymotrypsin and α-macroglobulin linked forms	Glycoproteins *(144)*; Heterodimer 45 kDa; carbohydrates, 30% (four N-glycan and four O-glycan chains); seven isomers, pI 3.8–4.7	Mucin-like glycoprotein *(145)*; 67–69 kDa (4–5% glycans); mono, bi, or trimer; two isomers (ph 4.85 and 5.2)
Gene	One gene on 19q3; 6 kb; four introns, five exons Homology with gene for kallicrein-1hGK1 at 12 kb from PSA gene *(146)*	α subunit: one gene on 6q21, 1-23; four exons β subunit: six genes on 19q13,3 (52 kb); three exons *(147)*	Chromosome 4 (long arm)
Site of production	Prostatic acini, breast, parotide	Trophoblastic cells of the placenta, pituitary	Liver, vitellus (fetal synthesis)
Half-life	1.5–3.2 days after radical prostatectomy	24–36 h ($t_{1/2}$ = 3.6, 18.0, 53.0 h) *(148)* β: 3–4 h ($t_{1/2}$ = 1.0, 23.4, 194 h) α: 2 h ($t_{1/2}$ = 0.6, 6.2, 21.9 h)	5–6 days *(149)*
Standard/calibrator	Yang or Hybritech	hCG: 75/537 (hCG CR119; 9286 kIU/g) hCGβ: 75/569 prepared from hCG CR119 hCGα:[a] 75/751 prepared from hCG CR119	
Reference values	4 μg/L *(150)* Increased production in men with age	hCG <10 IU/L; hCGβ <0.1 μg/L; hCGα <0.5 μg/L *(151)*	8.5–20 μg/L Increased at birth, 150 μg/L
Clinical interest in oncology	Monitoring of prostate cancer	hCG and free hCGβ: diagnosis and monitoring of patients with trophoblastic tumors and testicular cancers free hCGβ: monitoring of patients with nontrophoblastic cancers, particularly bladder cancer *(152)*	Diagnosis and monitoring of hepatocarcinomas, testicular cancer, teratocarcinomas, and germinal ovarian cancers *(153)*
	CEA	**CA 125**	**CA 15-3**
First description	1955 by Gold and Freedmann *(154)*	1981 by Bast et al. *(155)*	1984 by Kufe et al. *(156)*; 1984 by Hilkens et al. *(157)*
Structure	Glycoproteins; 180–200 kDa *(158)*; monomer; carbohydrates, 50–60% *(159)*	Mucin-like glycoprotein; 200–250 kDa	Glycoproteins
Gene	Chromosome 19 (long arm)	Chromosome 17 (long arm)	One locus (*DF3*), multiple alleles *(160)*
Site of production	Fetal gut, healthy colonic mucosa (differentiated surface epithelial cells)	Epithelial ovarian cells	Breast
Half-life	3–11 days *(161)*	5–10 days	Not determined
Standard/calibrator	WHO international reference preparation CEA (73/601)		
Antibodies	Very few specific epitopes *(162)*	Monoclonal antibody OC 125 *(163)*	Two monoclonal antibodies (mAb115-D8 and mAb DF3) *(164)*
Reference values	<5 μg/L	<35 kilounits/L	<30 kilounits/L
Clinical interest in oncology	Monitoring of early recurrence in colorectal adenocarcinoma	Prognostic value and monitoring in ovarian carcinomas	Monitoring of breast cancer

[a] hCGα, α subunit of hCG.

differentiation between local and metastatic recurrences (i.e., biological recurrences) several months before clinical signs.

In patients treated with radiotherapy alone, the use of PSA kinetics is controversial *(32)*. The tumor marker $t_{1/2}$ varies widely (11–275 days) among subjects *(33)* and is related to the activity of residual surviving cancer cells and to PSA-secreting cancer cells located outside the radiotherapy target volume. Fifty percent of biopsies performed 1 year after irradiation are PSA positive. Stage, grade, and pretreatment PSA concentrations are apparently not linked to PSA kinetics *(34, 35)*. These observations have been challenged by other authors *(12, 14, 18, 32, 36)*. Remission has been associated with normalization of PSA between 6 months and 3 years and recurrence in the absence of normalization *(37)*. A DT of <8 months may predict distant metastasis *(32)*.

In patients treated with hormonal therapy, the regulation of PSA synthesis is dependent on androgen activity. Hormonal therapy thus can modify PSA secretion. The androgen suppression syndrome, corresponding to increased PSA induced by nonsteroid antiandrogens is infrequent; consequently, monitoring of PSA is widely used in hormone therapy. After a treatment failure, the DT may be used for individual patients requiring androgen therapy *(17)*. A decrease in PSA, measured at 3 and 6 months, is a prognostic indicator correlated with survival. After 6 months of treatment, it is possible to separate subjects who are not responders from those who are *(38, 39)*. However, ~10% of nonresponders do not display an increase in PSA. Furthermore, the absence of a biological response revealed by the PSA concentration preceded clinical unresponsiveness by 6–12 months, over a mean evolution of 20 months.

hCG and afp

In gestational trophoblastic diseases, measurement of both the hCG concentration and the rate at which it decreases after surgery and/or chemotherapy have been demonstrated as essential for the management of patients. After evacuation of a molar pregnancy, the hCG concentration should be monitored every week until normalization and then every month during the first year. The disappearance of hCG is usually achieved within 8 weeks in ~40% of patients, within 9 to 22 weeks in ~55% of cases, and in >22 weeks in 5% of patients. In some cases, hCG concentrations remain stable or increase, suggesting the presence of persistent evolutive trophoblastic disease (molar retention, invasive mole, or choriocarcinoma). hCG regression curves have been used in several studies for early recognition of persistent disease in patients. Several reports propose normal regression corridors that allow the detection of 85–90% of patients with persistent disease within 4–6 weeks *(40, 41)*. Similarly, patients are identified within 8 weeks based on regression curves established from data including those of patients with a temporary hCG plateau. Yedema et al. *(42)* attempted to identify patients with persistent trophoblastic disease, based on a normal hCG regression curve constructed by fitting data from 130 patients with a hydatidiform mole with uneventful hCG regression. A biexponential regression model indicates two median hCG $t_{1/2}$ of 1.8 and 12.8 days. Using the 95th percentile limit, Yedema et al. *(42)* identified >90% of the 77 patients with persistent disease within 14 weeks and >50% within 6 weeks. Special attention must be paid to the 5% of disease-free patients who continue to have increased hCG concentrations 22–25 weeks after evacuation and to those who have persistent trophoblastic disease after initially spontaneous hCG regression to the reference value.

Patients who develop high-risk metastatic trophoblastic disease require intensive chemotherapy. These patients present one or several of the following factors: a pretreatment serum hCG concentration >40 000 IU/L, a diagnosis of choriocarcinoma, a history of a nonmolar pregnancy, metastases, and resistance to chemotherapy *(43)*. The ratio of free hCG β subunit (hCGβ) to total hCGβ (free hCGβ + hCG) is often higher in these patients than in patients with a hydatidiform mole or low-risk disease. During the first week of chemotherapy, marker values generally increase initially because of the destruction of tumor cells. Remission is achieved when marker concentrations are undetectable. Both hCG and hCGβ detection tests are among the most sensitive assays because they are capable of detecting 10^4 cancer cells. However, a recurrent tumor may arise from this small number of cells. Treatment must, therefore, be continued after the normalization of both hCG and hCGβ. Prolonged decay of either hCG or free hCGβ identifies patients who are unlikely to achieve a complete remission or long-term survival and indicates that additional chemotherapy or a switch to a different chemotherapy regimen is required *(44)*.

hCG, free hCGβ, and AFP are also the most useful markers for the diagnosis, prognosis, and monitoring of patients with testicular germ-cell tumors such as choriocarcinoma, embryonal carcinoma, and teratocarcinoma. Tumors may be located within the gonads or, on rare occasions, extragonadal. In nonseminomatous germ-cell testicular tumor (NSGCTT), increased concentrations of hCG and free hCGβ were found in ~60% and in 40–70% of cases, respectively *(45)*. Combining the three markers makes it possible to detect ~90% of patients with NSGCTT. hCG is of less interest as a marker in seminoma because it is increased in only ~16% of patients; serum values are generally <200 IU/L. Values exceeding 5000 IU/L indicate the presence of NSGCTT. Interestingly, 20–50% and 9–17% of patients with seminoma have increased free hCGβ and hCG α subunit, respectively. The prognostic value of both the hCG concentration before chemotherapy and its $t_{1/2}$ has been widely investigated, with the aim of identifying the 20–30% of patients with NSGCTT who fail to respond to therapy *(46–48)*. Several reports have indicated that the kinetics of both hCG and AFP are good indicators of patients likely to be refractory to treatment *(49, 50)*, whereas others conclude that the

analysis of tumor marker values cannot be used to predict who is at a higher risk or to tailor treatment accordingly *(48, 51)*. In fact, the tumor marker concentration before therapy appears to be a stronger predictor of treatment failure than marker $t_{1/2}$ *(52)*. Furthermore, after orchidectomy, patients with increased AFP relapse more frequently than patients with increased hCG *(53)*.

Currently, no firm conclusions can be drawn about the usefulness of markers for identifying poor risk patients. A major explanation for the discrepancies between the conclusions of the different studies is the methodology used. For example, unpredictable transient rises in hCG/hCGβ concentrations after chemotherapy may occur as a result of tumor lysis with a subsequent release of a given marker; consequently, comparisons of $t_{1/2}$ calculated from marker values before treatment and after the second cycle of chemotherapy are often unreliable. In a retrospective study, Toner et al. *(54)* showed that a prolonged marker $t_{1/2}$ (>7 days for AFP; >3 days for hCG) is a reliable indicator of residual tumor and a significant predictor of survival. In contrast to other studies, Toner et al. *(54)* determined the $t_{1/2}$ of each marker from the first two values measured within 3 months after the start of the treatment. Although markers were not measured systematically during initial treatment, this study provides a more reliable method for the use of serial measurements of markers in the management of patients with germ-cell tumors. Studies on AFP also confirm that the analytic strategy is crucial in attempts to improve the sensitivity of tests based on marker $t_{1/2}$. This critical point will be discussed later.

AFP is also used as a marker for both the diagnosis and monitoring of patients suffering from hepatocellular carcinoma *(55)*. Measurement of AFP is used to assess the completeness of surgical resection and response to therapy or recurrences. Hepatocellular carcinoma frequently recurs after surgery; with serial determination of serum AFP, such recurrences could be detected at least 3 and up to 18 months before the onset of symptoms. The interval between surgery and recurrence correlates with the AFP DT. A decrease in serum AFP indicates clinical response to chemotherapy; if DT does not decrease, serial measurement obviates prolonged ineffective therapy. However, a negative value does not exclude the presence of subclinical disease *(56)*. An increase in serum AFP signifies that chemotherapy should be changed *(57)*. Finally, measuring the $t_{1/2}$ of serum AFP has been useful for the management of patients with malignant germ-cell tumors of the ovary *(58)* and children presenting with teratoma, endodermal sinus tumor, or hepatoblastoma *(59, 60)*.

CEA

CEA is the only useful marker for monitoring colorectal cancer *(61)*. For >25 years now, sequential CEA measurements have been used to monitor the response of colorectal cancer to surgery *(62–64)*. Serial measurements of serum CEA, instead of a single determination, are recommended for the detection of recurrences in colon cancer *(65, 66)*. The NIH Consensus Conference in 1981 emphasized that serial CEA determination, not a single determination, should be mandatory in clinical decision-making *(67)*. In Dukes stage A disease, which rarely recurs, CEA monitoring is not justified for monitoring purposes. Follow-up of CEA is recommended, however, for patients with Dukes B and C adenocarcinoma *(68)*. Recurrent disease occurs within 30 months and at a median time of 17 months in most patients. It rarely occurs after 5 years *(69)*. The postoperative CEA concentration is a significant prognostic factor for survival. When tumor resection is complete, the postoperative CEA value decreases to 2.5 μg/L or less within the first month *(65)*. When the postoperative CEA concentration falls to <5 μg/L, only 18% of patients will relapse. In contrast, recurrent disease occurs in 63% of the patients when the CEA concentration remains above 10 μg/L *(70)*. The median lead time from increase in marker concentration to clinical recurrence is from 3 to 8 months *(71)*. The sensitivity of postoperative CEA measurements varies according to the site of recurrence. The CEA test is inappropriate for the early diagnosis of localized recurrence *(72)*. CEA kinetics permit differentiation between local and metastatic liver recurrences, with mean slope values attaining, respectively, 0.17 and 2.2 μg/L in 10 days *(66)*. Calculating the CEA ascending slope in a computerized surveillance program has been shown to differentiate types of recurrent tumor *(66)*. Slope analysis has been used to predict the site of recurrence and to plan second-look surgery. Different decision rules have been proposed on the basis of the evolution of the CEA concentration *(73, 74)*. When Denstman et al. *(75)* compared various rules, they concluded that steadily rising concentrations (>12% per month) clearly indicated tumor recurrence. A linear relationship between log CEA and time exists during the logarithmic growth phase of recurrent tumors. This relationship is expressed by the DT, which varies according to the site of the metastatic lesions. The DT can be used to assess the efficacy of various treatments *(76, 77)* and is particularly correlated with the duration of survival *(78)*. Monthly CEA measurements during the first 3 years and then at 3-month intervals for 2 years are, therefore, recommended for postoperative monitoring *(69)*.

The calculated $t_{1/2}$ should be an earlier predictor than analysis of the CEA ascending slope. After complete surgical resection and in the absence of recurrent disease, CEA concentrations decrease exponentially to reference values, with a $t_{1/2}$ of ~5 days. In patients with a recurrence, a dissociation from the theoretical line of the $t_{1/2}$ is observed before the CEA concentration decreases to the reference interval *(79)*.

Postoperative chemotherapy and particularly combination fluorouracil-levamisole may be effective for metastatic tumors *(80)*. CEA appears to be a practical index and a criterion for evaluating the efficacy of treatment. A 20% decrease in the CEA concentration is considered a positive response to treatment, conferring a substantial

improvement of survival *(81, 82)*. The efficacy of regional chemotherapy has been assessed in patients with nonresectable liver metastasis from colorectal cancer: because CEA concentrations may vary considerably between patients, an individual reference value is first established as the arithmetical mean of serial CEA values during the first three courses of chemotherapy. The efficacy of the chemotherapy regimen is indicated by a decrease in the CEA curve to below the individual reference value *(83)*. In recurrent or nonresectable colorectal cancer, different indices, devised with serum CEA fluctuations over time, are helpful in assessing and comparing the effects of various treatments, especially the CEA DT ratio when the CEA DT is modified *(84)*. For the management of patients with hepatic metastases from colorectal cancer, measurement of CEA is mandatory before and after surgery to appreciate whether the resection was curative. Furthermore, postoperative CEA concentrations are among the criteria used to stratify patients for adjuvant treatment *(85)*.

Serial measurements of CEA provide a practical tool for patients undergoing chemotherapy for advanced colorectal cancer. However, scanning techniques are required to confirm the response suggested by any change in marker expression *(86)*.

CA 125

CA 125 is a useful marker for epithelial ovarian tumors *(87, 88)*. The preoperative serum CA 125 concentration is correlated with the tumor burden and stage, but its prognostic significance is controversial *(89, 90)*. The postoperative concentration is highly correlated with the residual tumor mass *(89)* and has a significant value that is predictive for survival *(91)*. It must be determined at least 3 weeks after surgery because CA 125 is released when the abdominal cavity is opened *(92, 93)*. Disease progression occurs in 61% of patients presenting with increased CA 125 concentrations before chemotherapy and in only 33% patients with values <35 kilounits/L *(94)*. After the first course of chemotherapy, the predictive value of the CA 125 concentration for disease-free survival is highly significant *(95)*.

During chemotherapy, changes in CA 125 concentrations correlate with the evolution of the disease. The median time to normalization is 1.5 months in patients having attained a complete remission and 4 months in patients having achieved partial remission *(96)*. Increased CA 125 concentrations precede clinical detection of disease and are always associated with tumor progression, as substantiated by second-look surgery. However, in patients with normalized CA 125 concentrations, second-look surgery is still necessary because a CA 125 concentration within the reference interval does not exclude tumor. More than 40% of the patients with a serum CA 125 concentration within the reference interval still have microscopic or macroscopic tumor at second-look surgery *(87)*.

The prognostic value of the $t_{1/2}$ of CA 125 has been analyzed during induction therapy to identify high-risk patients. In patients with stage I and stage II disease whose tumor had been completely resected, the marker $t_{1/2}$ varied from 5.1 to 12 days in different studies *(96–101)*. The greatest difference in progression rate was found at a $t_{1/2}$ of 20 days. The median times to progression were 43–50 months and 11–23 months in stage I and stage II disease, respectively *(94)*. Patients with a marker $t_{1/2}$ <20 days have a good prognosis, those with a marker $t_{1/2}$ from 20 to 40 days have an intermediate prognosis, and those with a marker $t_{1/2}$ >40 days have a poor prognosis, with actuarial survival at 2 years attaining 76%, 48%, and 0%, respectively *(102, 103)*. The CA 125 $t_{1/2}$ is the most valuable prognostic factor for survival and for the probability of achieving a complete remission in stage III or IV ovarian cancer responding to initial chemotherapy *(104)*. The $t_{1/2}$ of CA 125 during early chemotherapy is an independent prognostic factor for achieving a complete response and for survival *(91)*. Evaluating the time required for normalization of CA 125 has also been proposed. A final model including the tumor size, performance status, and the time to normalization of CA 125 permits an accurate prediction of the prognosis *(105)*.

Additional monitoring of declining CA 125 concentrations is based on the exponential regression curve proposed by Buller et al. *(99)*, calculated as serum CA 125 = $e^{[i - s(\text{days after surgery})]}$, where i is the y-axis intercept and reflects the initial tumor burden, and s the slope of the regression curve, with s being dependent on the extent of cytoreductive surgery and on response to chemotherapy. In patients whose tumors had been completely removed, the marker $t_{1/2}$ was 10.4 days *(99)*. Comparing patients results with those obtained by this model permits an evaluation of treatment efficacy. Divergence from the ideal regression curve can be determined within 30 to 60 days of initial surgery and always leads to treatment failure. Therapy can, therefore, be modified without waiting for second-look findings. Comparison with the model also predicts the presence of residual disease, the risk of recurrence, and overall survival *(106, 107)*. After comparing these two exponential regression models, Yedema et al. *(100)* showed that survival correlates better with the $t_{1/2}$ calculated according to Buller et al. *(99)* than according to van der Burg et al. *(94)*. The CA 125 exponential regression curve was the most important prognostic factor for actuarial survival when analyzed with age, disease stage, grade, the intensity of chemotherapy, and residual disease in the Cox model. With the proportional hazard model, the disease stage was the most predictive variable for survival, and the CA 125 $t_{1/2}$ calculated according to Buller et al. *(99)* was the only additional prognostic factor for survival in stage III-IV patients early during the course of therapy *(100)*. During salvage treatment with Taxol, the regression rate did not correlate with the progression-free interval or survival *(108)*.

Rustin et al. *(109)* selected a specific percentage of decrease in the CA 125 concentration during chemotherapy as evidence for response to treatment. In a large

retrospective trial, two response rates were defined according to a reduction of either 50% or 75% in the serum CA 125 concentration from baseline. Three or four CA 125 measurements were required at the end of each cycle of chemotherapy to determine the response rates, the last sample being at least 28 days after the previous sample. The definitions proposed were based on 117 patients in a first trial and further tested on several hundred patients. The results showed better correlation with reduction of lesions in the patients than WHO, Eastern Cooperative Oncology Group, or Gynecologic Oncology Group criteria and were proposed for use in addition to or as replacements for these criteria. A few studies have been devoted to the CA 125 DT at relapse of ovarian cancer. There is no relationship between the $t_{1/2}$, DT, and survival, but the log cell kill, estimated by combining the marker $t_{1/2}$ and DT, was correlated with individual survival *(96)*. Riedinger et al. *(110)* studied the prognostic significance of the initial $t_{1/2}$ of CA 125 measured during first-line chemotherapy in 62 patients with epithelial stages III and IV ovarian cancer. The results showed a strong correlation between the $t_{1/2}$ and the DT, the slope representing initial CA 125 regression and disease-free survival as well as overall survival. The initial $t_{1/2}$, measured during the first cycles of first-line chemotherapy, appeared to be a critical predictor of response to therapy.

CA 15-3

When breast cancer patients are monitored by serum CA 15-3 concentration, the serum antigen profile in each patient is the criterion during follow-up most indicative of recurrent disease and of response to various treatments. And yet, a third of breast cancer patients with metastasis have CA 15-3 concentrations within the reference interval *(111)*. The use of CA 15-3 kinetic parameters was proposed in patients at high risk of relapse: an increase in the tumor marker should be considered an early indicator of relapse. After radical resection of tumor, CA 15-3 exhibits substantial variation at abnormal concentrations *(112)*. CA 15-3 does not have a negative predictive value. The evolution during follow-up is based on the ratio of two serial CA 15-3 measurements over 1 month *(113)*. CA 15-3 is informative and biologically significant in a few cases if the variation between the preoperative determination and the determination 30 days after surgery is higher than threefold the analytical variation of the assay, even if values fall short of the cutoff. Both cutoff-based and dynamic criteria are used during the monitoring of breast cancer patients to detect early metastasis and even to assess the cure of relapses *(114)*. However, a clinical benefit has not been established, although an increasing CA 15-3 concentration can be considered synonymous with recurrence after primary treatment *(61)*.

DISCUSSION

Measuring tumor marker kinetics may be a useful way of improving the efficacy of cancer treatment, but at present there is no consensus as to the usefulness of determining marker dynamics during the monitoring of patients. Indeed, as illustrated by this review devoted to the main tumor markers used, the conclusions of distinct studies addressing the interest of measuring kinetics of a particular marker in a given cancer are frequently at variance. The discrepancies in comparisons of the dynamic results obtained by different groups may be attributable to several factors, including (*a*) the methodological approaches used to measure markers, which are often dependent on the nature and structure of tumor markers; (*b*) individual factors such as the pathophysiological state of the patient or the treatment regimen; and (*c*) the methods used to calculate kinetics and the interpretation of data.

Nature and Structure of Tumor Markers

During the last decade, invaluable efforts have been used to enhance the sensitivity and specificity of detection with tumor markers. Markers are now measured by immunochemical methods, most often based on the classic "two-site" sandwich immunoassay procedure. Its characteristics, particularly the affinity and the specificity of the monoclonal or polyclonal antibodies used, play a critical role in the design of the assay. Antibodies are usually selected for their high affinity to ensure better sensitivity in the immunoassay. Specificity is contingent on more selective recognition of the antigen structure by the antibody on the tumor marker molecule. Indeed, antigen proteins have several distinct antigenic determinants or epitopes protruding from their surface. The number of epitopes is roughly related to the molecular size of the protein. Extensive immunochemical analysis of protein antigens is a mammoth task, and only a few immunochemical maps of tumor markers have in fact been raised. These observations partly explain why two separate kits measuring the same molecule can yield different results. This is particularly true for the detection of hCG and PSA, for which ~40 commercial tests are currently available. Furthermore, the heterogeneous "faces" of tumor markers complicates the interpretation of data. Indeed, these molecules can exist in biological fluids as several entities, including subunits (hCG), associated forms (PSA), and degradation products (Table 1). There may also be variations in both their peptidic and carbohydrate structures that are attributable to either physiological or tumor processes. This has been particularly investigated for hCG-related molecules *(45)*. The structure of hCG is close to that of lutropin, which is detectable in healthy individuals. Not only must detection of hCG be specific in regard to potential cross-reactivity with lutropin (i.e., epitopic specificity), but tumors are capable of secreting various hCG-related molecules [free hCGβ, free hCG α subunit, and β-core fragment; for a review, see Ref. *(45)*], the clinical significance of which differs according to the tumor histologic type (i.e., structural specificity). In testicular and placental tumors, for example, should we analyze the rate at which either hCG or hCGβ declines or

both? PSA circulates in both a protein-linked form and as free PSA. The kinetics of PSA analyzed by methods measuring total PSA may differ from those measured by free-PSA assays. This question must be addressed because specific measurement of free PSA is now available *(115)*. Furthermore, part of the PSA is totally masked on the complex and is not accessible to the detection capacity of the kits currently available *(116)*. Changes in the only carbohydrate chain of AFP have also been described in patients with cancer, compared with that present on normal fetal AFP *(117)*. Some immunoassays bind differently to the two AFP molecules *(118)*. Pitfalls in the interpretation of the kinetics of CA markers are probably more related to their structural heterogeneity than to epitope specificity. Indeed, these markers are defined on the basis of their recognition by specific antibodies and their structure, i.e., the structure of the molecule bearing the "CA" determinant, which still remains unknown. These determinants are often large heterogeneous mucin-like molecules that vary in size according to the pathophysiological state of the individual. Thus, although immunoassays are comparable in terms of epitope specificity, the determination of kinetic parameters may be affected by changes in the structure of the CA-bearing molecule during the course of treatment. Improving the comparability of immunoassays, particularly those used to measure tumor markers, remains a challenge for the future. Through undaunted efforts, international societies have given concrete expression to better characterization of antibodies *(119, 120)*.

Individual Factors

Individual factors such as the pathophysiological state of the patient or the treatment regimen may also affect the measurement and interpretation of marker kinetics. During the monitoring of neoplastic disease, nonspecific increases in tumor marker concentrations can be caused by a variety of benign pathologies *(121–124)*. Inflammatory diseases are frequently the cause of nonspecific increases in the so-called CA markers. Tumor markers often increase after surgery because of a serous response. In contrast, a false decrease in tumor markers may be attributable to procedures leading to hemodilution (e.g., parenteral nutrition and blood transfusion). An increase in serum AFP may occur in cases of hepatic regeneration *(56)*. Kinetics may also be transiently affected by renal and hepatic diseases, because these tissues are involved in the metabolism of markers *(125, 126)*, and by the aging process *(127)*. Furthermore, tumor recurrences and metastasis may exhibit patterns of marker secretion that are different from that of primary tumors. This factor should be taken into account when interpreting the DT. Aggressive chemotherapy and radiotherapy may provoke massive destruction of cancer cells, leading to a transient increase in serum markers that should not be interpreted as the tumor escaping eradication via chemoresistance. Some therapies stimulate synthesis *(128)*. Increased CEA synthesis has been observed during interferon treatment *(129)*. PSA is controlled by androgens and gonadotropin-releasing hormone *(130)*. The potential effects on tumor marker concentrations of conventional drug therapy used to treat benign diseases in cancer patients remain to be established. Taxol is suspected of modifying CA 125 synthesis in ovarian cancer *(131)*. Finally, anti-species human immunoglobulins, particularly anti-mouse antibodies, are encountered in some patients *(132, 133)*. Human anti-mouse antibodies are sometimes observed in patients who have been submitted to immunoscintigraphy for the detection of recurrences. Human anti-mouse antibodies, autoantibodies, anti-idiotypic antibodies, and rheumatoid factor may generate false-positive results and, thus, interfere with marker dynamics.

Surgical intervention itself may amplify the shedding of markers into the circulation and therefore generate false-positive results. After abdominal surgery, CA 125 increases through tumor handling and peritoneal damage. During surgical intervention, the rupture of natural barriers facilitates the transfer of CA 125 into blood. Increases have been observed in postoperative CA 125 concentrations in malignant and benign diseases of the ovary as well as in diseases of the gastrointestinal tract. Consequently, caution should be exercised when interpreting CA 125 concentrations after abdominal surgery, and especially in patients whose pretreatment CA 125 concentrations were within the reference interval or moderately increased *(93)*.

Marker Determination Methods and the Analysis of Kinetics

The $t_{1/2}$ or DT of a marker can be calculated after repeated measurements only if the tumor marker is determined with the same method to avoid analytical variations attributable to different kits. Discrepancies between the conclusions of clinical studies may also be related to the methods used to evaluate kinetic parameters. Although tumor growth is exponential, most graphic representations are rarely based on logarithmic units. Logarithmic representation eliminates nonspecific variations. Furthermore, kinetics can be represented as a unique parameter, with the slope depicting either the $t_{1/2}$ or the DT. This parameter is a characteristic of the behavior of tumor growth. It could be included in a Kaplan-Meier model or any other suitable model to evaluate the efficacy of therapy during the monitoring of patients. Studies comparing two models, based on either linear or exponential regression, showed that the exponential model correlates better with clinical factors *(99, 107)*. However, for many authors *(111, 134, 135)*, there is no difference in the mathematical methods used to determine kinetic parameters.

In fact, the number of sequential measurements, the timing, and the interval between the measurements are probably the main source of variation in the establishment of kinetic factors. For example, a comparison of kinetics that were calculated after chemotherapy using either the

presurgery or prechemotherapy concentrations as the baseline value and either the first normalized concentration as the second value or all of the data available indicated that the exponential regression model including the presurgery and all other values correlated better with overall survival *(100)*. The timing of blood sampling is also critical, and it should be scrupulously respected. The marker concentration before treatment may have a prognostic significance, but this value should not be considered as the baseline value, i.e., the origin of the slope of the regression curve. Indeed, several factors contribute to the fluctuation of tumor marker concentrations between diagnosis and the beginning of treatment. As noted previously, chemotherapy as well as surgery induces either cytolysis and transient marker secretion or a reduction in the tumor volume. Thus, the kinetics of markers in patients treated with the same protocol may be particularly difficult to interpret *(92, 136)*. For example, kinetics during the monitoring of breast cancer show three distinct patterns: tumor regression, tumor progression followed by tumor regression, and tumor regression followed by resistance to therapy with major tumor progression. Kinetics evaluated immediately after treatment should not be used *(137)*. The first sample, which could be considered a legitimate value for the origin of the slope of the elimination curve, should be obtained after surgical excision or after induction chemotherapy. Other sequential samples can be collected following a sequence that will depend on the $t_{1/2}$ of the marker. As described previously for the measurement of PSA after radical prostatectomy *(21)*, if the t_0 value is measured 5 min after surgery, the PSA concentration will be higher and the $t_{1/2}$ shorter than if the t_0 is measured 2 days after surgery. Many authors do not agree with sampling 5 min after surgery *(138)*.

In conclusion, several questions and issues need to be addressed when applying dynamic evaluation of markers to the monitoring of patients, particularly the method used to calculate the kinetics and the choice of the data to be included in the mathematical model. However, using tumor kinetics appears to be a more rational way of using tumor markers than the common cutoff point. Indeed, the determination of the $t_{1/2}$ and DT often provides the most relevant predictive factors for the estimation of disease-free and overall survival, treatment efficacy, and for the decision regarding optimal treatment and cost-effectiveness in terms of toxicity and patient benefit. This approach could be a way to optimize patient management by limiting ineffective treatment and, consequently, the clinical costs of what may be pointless therapies once these dynamic data have clarified the clinical picture *(139)*.

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