The Prostate Supplement 7:48–57 (1996)

Review on the Simultaneous Determination of Total Prostate-Specific Antigen and Free Prostate-Specific Antigen

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BACKGROUND. The total prostate-specific antigen (t-PSA) in serum measured by PSA assays represents the sum of free (f-PSA) and PSA complexed with α1-antichymotrypsin. The f-PSA/t-PSA (F/T) ratio in prostate cancer (PCA) patients is lower than in patients suffering from benign prostatic hyperplasia (BPH). This review summarizes the currrent literature on the clinical relevance of measurement of the F/T PSA ratio.
METHODS. Discussed are: physiology of PSA, assays for t-PSA and F/T ratio, factors which bias the F/T PSA ratio, use of F/T PSA ratio in the detection of PCA, correlation with histological features, and pathological stage.
RESULTS. Using the F/T ratio in the intermediate t-PSA range, a reduction of approximately 30% in biopsies can be accomplished in the detection of prostate cancer.
CONCLUSIONS. The F/T PSA ratio could become a valuable tool in the differentiation of BPH from PCA. To accomplish this goal, an international standardization not only for the t-PSA measurement but also for the F/T PSA ratio must be a priority for manufacturers of PSA assays.

KEY WORDS: **prostate-specific antigen, free, complexed, antichymotrypsin, benign prostate hyperplasia, prostatic carcinoma**

INTRODUCTION

Prostate cancer (PCA) is the second leading cause of cancer death in men [1]. Fortunately, after curative radical prostatectomy, men with organ-confined disease have a survival rate that is equal to men without PCA [2]. High incidence and possibility for curative treatment are important prerequisites for a possible value of screening for PCA. Further conditions that have to be fulfilled for the application of a test in a screening population are tolerability, accuracy, and acceptable cost. An accurate blood test would meet these requirements. Papsidero et al. [3] were the first to report high serum concentrations of prostate-specific antigen (PSA) in patients with PCA. Since then, several studies have shown that the determination of serum PSA is more reliable to predict PCA than either transrectal ultrasound (TRUS) or digital rectal examination (DRE) alone [4]. The American Cancer Society has recommended yearly determinations of PSA combined with DRE for men above the age 50 years for the purpose of detecting prostate cancer at an early stage [5]. However, because PSA is a protein expressed in the normal prostate gland, PSA is organ-specific but not disease-specific. Especially in the intermediate range of serum PSA (2.0–20.0 ng/ml), there is a great overlap between serum PSA values of patients with benign prostate hyperplasia (BPH) and PCA. In this range, a high percentage of unnecessary biopsies is performed when the criterion for taking biopsies is a PSA elevation above normal reference range. To enhance the accuracy of PSA in the inter-

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mediate PSA range, Benson et al. [6] introduced PSA density (PSAD), representing PSA divided by gland volume. They advocated a cutoff level for PSAD of 0.15 in patients with PSA between 4.0–10.0 ng/ml. Several authors have raised objections against the use of this cutoff value [7,8]. PSA velocity (PSAV), the change in serum PSA over time, was subsequently introduced by Carter et al. [9]. They found a PSAV ≤0.75 ng/ml/year to be indicative for the presence of PCA. Because of the high intrapatient variability in PSA measurements, the calculation of PSAV must be done using PSA measurements taken at least 1 year apart and with at least three separate measurements [10]. In summary, the clinical value of PSAD and PSAV in differentiating between BPH and PCA in the intermediate PSA range is disputed. Based on the observation that the aging prostate increases in size, resulting in a rise in PSA production [11], Oesterling et al. [8] constructed age-specific reference ranges for PSA. Using a different reference range for each age-decade rather than regarding an upper limit of 4.0 ng/ml as normal for all ages, the accuracy of PSA could thus be enhanced. However, in a trial involving 6,630 men conducted by Catalona et al. [12], no difference was found in accuracy using age-specific reference ranges for PSA.

FREE-TO-TOTAL PSA RATIO, A NEW PARAMETER

In serum, PSA forms complexes with α1-antichymotrypsin (ACT) and several other protease inhibitors. The total PSA (t-PSA) measured by PSA assays represents the product of reactivity with free PSA (f-PSA) and PSA complexed to ACT (ACT-PSA). The proportion of t-PSA that forms a complex with ACT appears to be higher in patients suffering from PCA. As a result, the f-PSA/t-PSA (F/T) ratio in PCA patients is lower than in BPH patients. The establishment of a reference range of this new parameter in men with BPH and in men with PCA could give the practicing urologist a valuable new tool in the differentiation of BPH from PCA in the intermediate PSA serum range (2–20 ng/ml). This review summarizes the literature about the clinical use of the F/T ratio of PSA.

PHYSIOLOGY OF PSA

Originally identified in seminal plasma in 1971 by Hara et al. [13], PSA was first isolated from prostatic tissue by Wang et al. in 1979 [14]. PSA is also named human glandular kallikrein 3 (hK3) and shows a restricted chymotrypsin-like specificity. It is produced only in the prostatic secretory epithelium. Secreted in the seminal plasma at concentrations in the range of 0.2–5.0 mg/ml [15], it plays a role in the liquefaction of semen through hydrolysis of semenogelin [16]. In vitro, proteolytic active PSA slowly forms stable complexes with several extracellular protease inhibitors [17]. In vivo, the release of active PSA in intercellular fluids or blood plasma also results in inactivation of enzymatic activity [18]. PSA occurs in serum in different forms: free PSA (f-PSA, MW (molecular weight) 30 kDa), PSA bound to alpha-2-macroglobulin (A2M-PSA), MW 780 kDa, and PSA bound to alpha-1-anti-chymotrypsin (ACT-PSA), MW 90 kDa (Fig. 1). A2M and ACT are extracellular protease inhibitors, referred to as serpins. PSA molecules which form a complex with A2M are engulfed by this protein, resulting in sterical shielding of all its epitopes. The lack of exposure of epitopes therefore prevents the detection of A2M-PSA by PSA assays. On the other hand, ACT does not cover all epitopes of the PSA molecule. Whereas A2M is the major binder of PSA when it reaches circulation [19], in 1991 Lilja et al. [20] showed that ACT-PSA is the predominant immunoreactive form in serum. A smaller immunoreactive fraction (5–30%) occurs as f-PSA; most likely this represents an enzymatically inactive form of the enzyme [20,21]. The proportion of f-PSA in serum does not correlate with the concentration of t-PSA nor with that of ACT [22].

Similarity to Other Glandular Kallikreins

The amino-acid sequence of PSA is closely similar to those of hK1 and hK2 (77% sequence identity) [23]. In 1995, hK2 was isolated from seminal fluid by Dephertes et al. [24], but its function remains unknown. The extensive similarity suggests that PSA immunoassays may crossreact with hK2 to a various extent. Using 25 different monoclonal antibodies (Moabs) in all possible two-site combinations (capture- and detection-Ab), Piironen et al. [25] constructed epitope maps on PSA and hK2. Of the 25 Moabs, seven showed crossreaction with hK2. Only low concentrations of hK2 were measured in serum samples as compared to PSA. However, until any influence of PSA measurement in serum by occasionally elevated hK2 concentrations is excluded, proper selection of Moabs remains essential to avoid cross-reactivity with hK2 in clinical assays.

Metabolism of PSA

The metabolism of PSA is largely unknown. A pilot study performed by Agha et al. [26] indicates that the main site of metabolism of PSA is in the liver. Clearance data from studies measuring serum PSA after radical prostatectomy indicate a two-compartment model for f-PSA elimination, with an initial

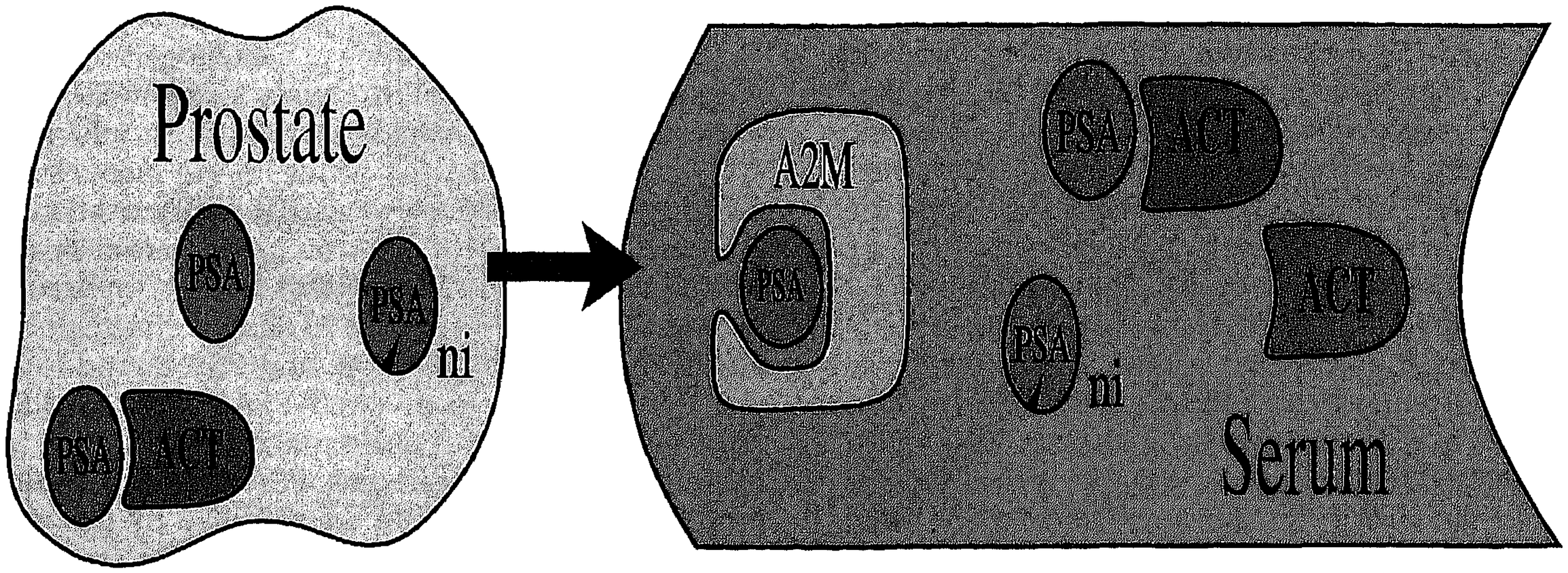


Fig. 1. Schematic representation of the two major protease inhibitors in serum, A2M and ACT. Also indicated is local production of ACT in the prostate by prostatic tumor and production of nicked form of PSA (PSA-ni) by BPH.

half-life of approximately 2–3 hr for the first 4 hr after removal of the gland, followed by a half-life of approximately 20–25 hr thereafter [27]. This is shorter than the half-life of t-PSA, which has been reported to be 2–3 days [11].

ASSAYS FOR DETERMINATION OF PSA

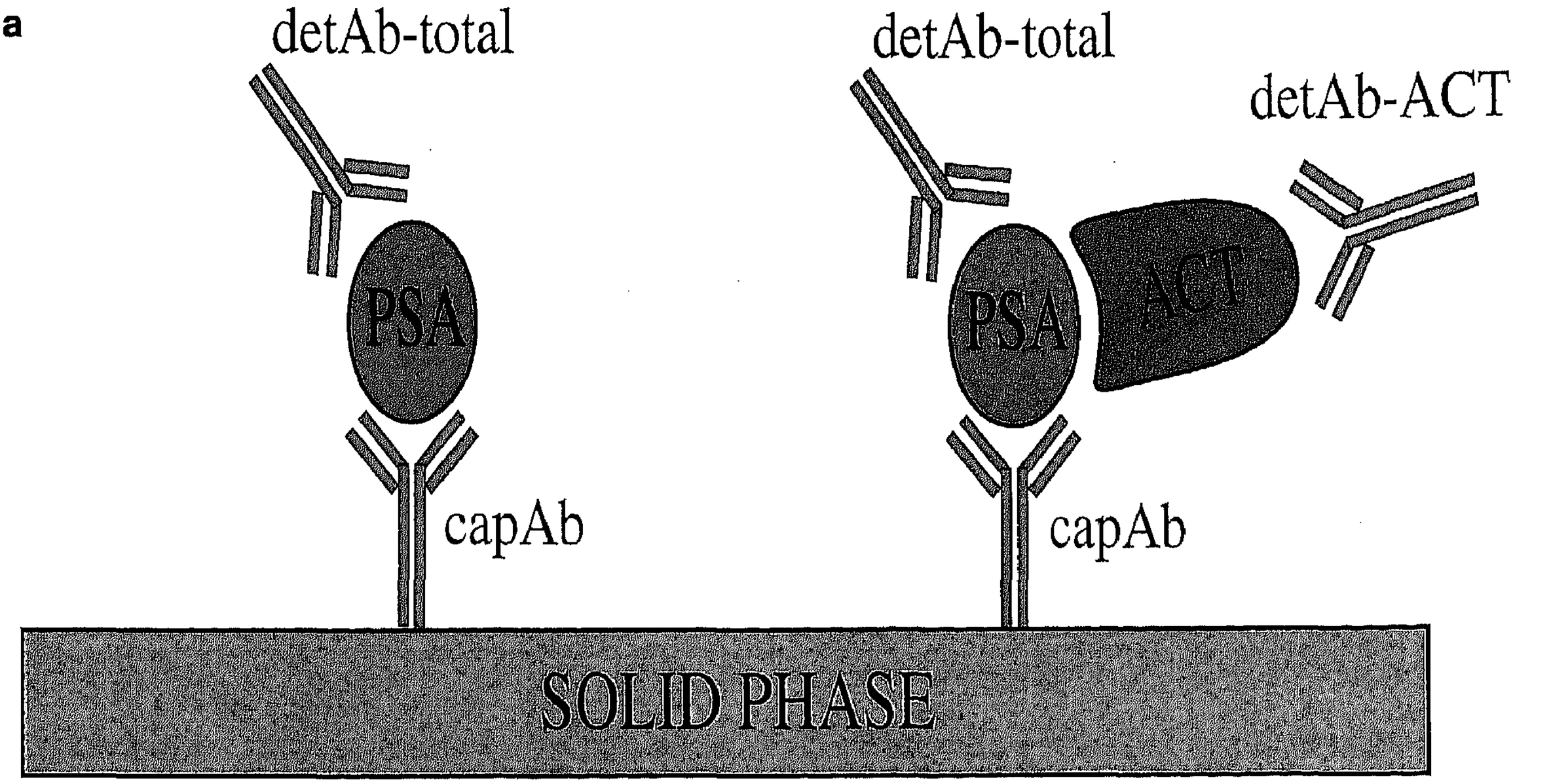
Assays for t-PSA

The presently used commercial assays for the measurement of PSA are double-determinant, "sandwich-type," noncompetitive immunoassays. Except for the IMx PSA assay (Abbott, Abbott Park, IL) which is a monoclonal-polyclonal assay, these sandwich assays make use of a monoclonal capture antibody and a monoclonal detection antibody. The capture Moab is fixed with its constant region to a solid phase (e.g., a tube or bead). It "captures" with its variable region the protein measured, in this case PSA, from the added serum by binding to a unique epitope. The detection (or tracer) Moab then binds to a different, structurally unrelated epitope. The amount of bound PSA is measured by chemiluminescence, fluorescence, radiation, or an enzymatic reaction of a label that is chemically bound to the detection antibody. If the label is an isotope, the method is called IRMA (immunoradiometric assay). For enzyme or fluorescent labels, it would be called IEMA (immunoenzymetric assay) or IFMA (immunofluorometric assay).

Assays for Simultaneous Determination of Free and Total PSA

New assays are developed which give simultaneous measurement of different molecular forms of PSA in serum, giving separate results for two forms of PSA and also the ratio between them. This dual measurement is made possible by utilizing chelates of lanthanide metals, which have mutually exclusive light-emission spectra and which are measured using time-resolved fluorometry. Depending on the Moabs used, t-PSA, f-PSA, or ACT-PSA can be measured. With these measurements, either the ACT-PSA/t-PSA (C/T) or the f-PSA/t-PSA (F/T) ratio can be determined. Pioneering work was done by Stenman et al. in 1991 [21], who by using an anti-ACT-detecting antibody developed an assay specific for ACT-PSA in serum (Fig. 2a). They showed that the C/T ratio is higher in patients with PCA than in patients with BPH. This was confirmed by Wood et al. [28], Christensson et al. [22], and Stamey et al. [29]. Theoretically, the F/T ratio equals 1 minus the C/T ratio. This would indicate that measurement of the F/T ratio would give no additional information to the measurement of the C/T ratio. However, assays of the ACT-PSA complex can severely overestimate the concentration of ACT-PSA in serum because of nonspecific adherence of ACT or cathepsin-G complexed to ACT to the solid phase of the assay [30], proportionally more so at lower concentrations of PSA. Instead of measuring ACT-PSA with an anti-ACT antibody, it is possible to selectively measure f-PSA using an antibody against an epitope which is obscured after complex formation to ACT (Fig. 2b). The accuracy of f-PSA assays in comparison with assays of the ACT-PSA complex suggest that better discrimination is obtained by using the F/T instead of the C/T ratio [22,30].

The reason for the relatively low F/T PSA ratio in prostate cancer patients is unknown. ACT is pro-



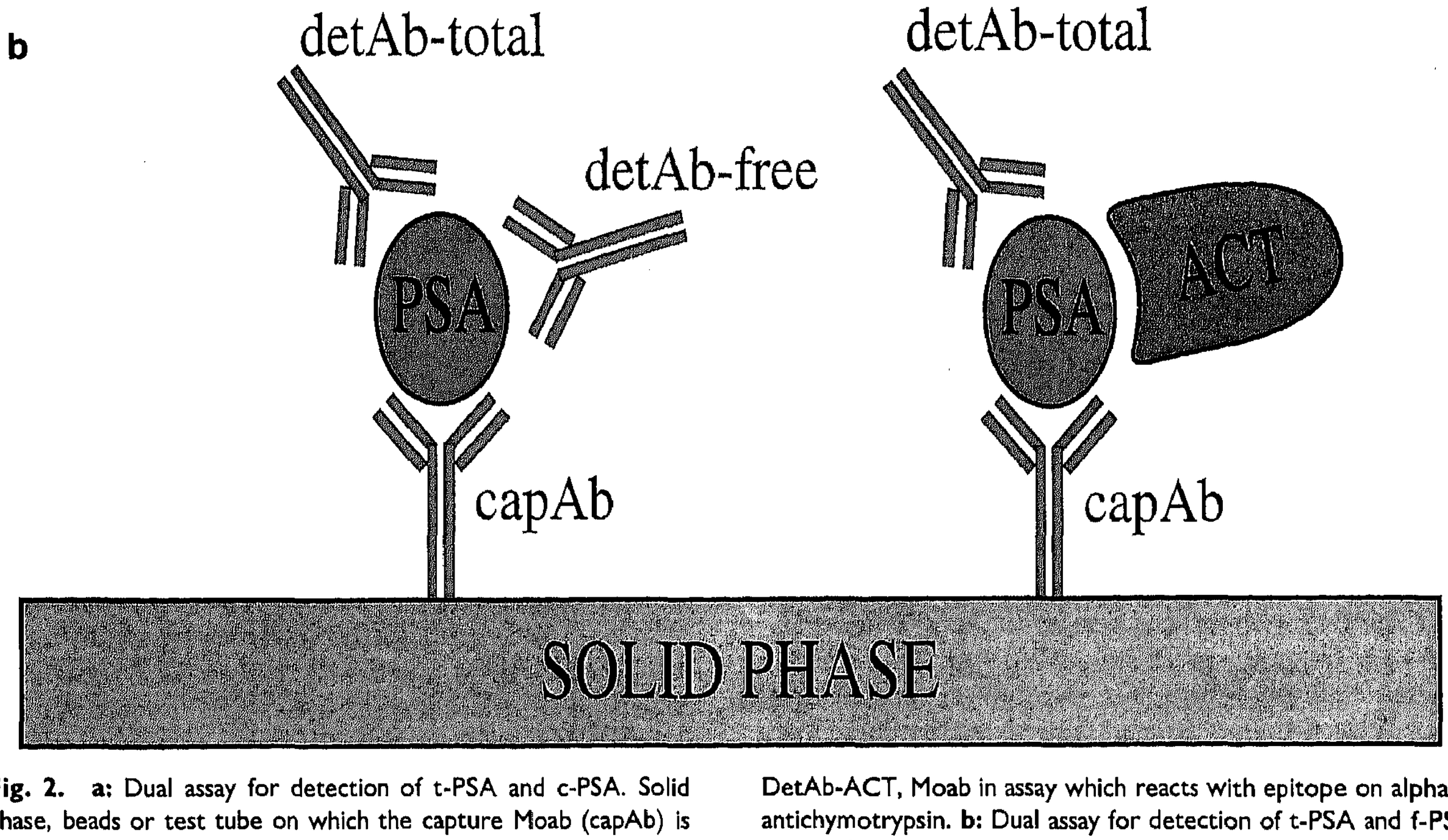


Fig. 2. **a:** Dual assay for detection of t-PSA and c-PSA. Solid phase, beads or test tube on which the capture Moab (capAb) is attached. ACT, alpha-1-antichymotrypsin from serum sample complexed to PSA. DetAb-total, antibody in assay which reacts with epitope not obscured by complex formation of PSA with ACT. DetAb-ACT, Moab in assay which reacts with epitope on alpha-1-antichymotrypsin. **b:** Dual assay for detection of t-PSA and f-PSA. DetAb-free, Moab in assay which reacts with epitope which is obscured after complex formation of PSA with ACT.

duced in the liver and circulates in the blood at a 10^4–10^5-fold molar excess compared to PSA. Björk et al. [31] showed that besides the liver, ACT is also produced by the normal prostate and prostate carcinoma cells but not by BPH cells. They stated that complex formation between PSA and ACT occurs locally at the point of secretion. In Bostwick et al. [32], the difference between ACT-stained cells in benign epithelium and carcinoma was modest (40% compared to 48%). Igawa et al. [33] found a significantly *higher* proportion of cells immunostaining for ACT in tissue from BPH compared to that from prostate cancer. Another explanation for the low F/T ratio in patients with PCA compared to BPH could lie in the

observation that PSA aspirated from BPH nodules occurs mainly in the "nicked-form" (PSA-ni) [34]. This form of PSA has multiple internal proteolytic cleavages. Because of these alterations, PSA-ni may have a different three-dimensional structure from that of seminal fluid PSA. It has lower chymotrypsin-like activity than PSA from seminal plasma, but still has affinity to the protease inhibitors ACT and A2M. Of the nicked form, 4–19% complexed with ACT in vitro, whereas 54–67% reacted with A2M in a study by Leinonen et al. [19]. Overall, the nicked form seems to complex to a lesser degree as compared with PSA without cleavages. It is still unclear whether the lower enzymatic activity of BPH-PSA or the local production of ACT by PCA cells explains the higher F/T ratio in BPH patients. The finding that BPH-PSA is of a specific molecular structure could imply a possible production of specific Moabs against this nicked form of PSA. In this way, assay kits could be developed with a selective affinity for BPH-PSA, and these may prove useful in the discrimination between PCA and BPH.

INFLUENCE OF F/T PSA RATIO ON T-PSA ASSAY READINGS

One of the reasons that different assays for serum t-PSA have failed to produce the same PSA values on identical specimens is a variability in affinity of the detection antibodies to either f-PSA or ACT-PSA [29]. A t-PSA assay must be accurate independent of the relative amounts of free and complexed PSA in different patient samples. Antibodies used for a t-PSA assay should recognize an epitope on the PSA molecule that is not shielded after complex formation to ACT, as this would result in preferential binding to free PSA. Brawer et al. [35] demonstrated significantly lower t-PSA readings in sera when analyzed with the IMx (Abbott Laboratories, Abbott Park, IL, USA) t-PSA assay as compared to the Tandem Hybritech (Hybritech Inc., San Diego, CA, USA) t-PSA assay. The IMx bias appeared to be highly correlated with the proportion of f-PSA. This may be the result of the presence of a subpopulation of antibodies in the (polyclonal-monoclonal) IMx assay that binds to the same epitope of PSA as that to which ACT binds. The response of such a t-PSA assay which is dependent on the F/T ratio is called "skewed." This in contrast to a t-PSA assay with an equimolar response, in which the results are independent of the F/T ratio. The clinical implication of this finding is that when compared to the Hybritech assay, serum specimens measured with the IMx assay are less likely to exceed a certain cutoff value for t-PSA, and when they do, this will be more often due to a high F/T ratio. This is the case in benign conditions, resulting in the tendency of an inferior diagnostic capacity to differentiate BPH from PCA. Mean measured concentrations in identical serum samples may differ up to 36% between different t-PSA assays [36]. Interpreting t-PSA concentrations therefore requires awareness of the applied method and accurately determined reference ranges. Efforts to reach an international standard for measurements of PSA are currently being determined by Chen et al. [37]. Besides a careful selection of antibodies, a universal calibrator for the construction of the response curve, using a combination of 90% PSA-ACT complex with 10% f-PSA, is recommended [36].

FACTORS THAT CAN BIAS MEASUREMENT OF F/T PSA RATIO

Prostatic Manipulations

Many studies have been performed to investigate the effect of various manipulations of the prostate on t-PSA serum level. After cystoscopy, no significant change is seen in the serum t-PSA level [38]. After prostate biopsies and after transurethral resection of the prostate (TURP), the median serum t-PSA rises, respectively, to 7.9 ng/ml and 5.9 ng/ml [38]. The results of these studies do not necessarily have to be transferable to measurement of f-PSA and the F/T PSA ratio. Glenski et al. [39] showed that DRE does not influence serum t-PSA, whereas Collins et al. [40], for instance, found a significant F/T ratio increase of 0.16 after DRE. In this study, the F/T ratio rose 0.20 after biopsy, and no significant change was found after cystoscopy. Hershman et al. [41] described a rise in F/T ratio after ejaculation. In view of the facts that in semen the ratio of f-PSA is much higher than in serum [15] and that the rise of t-PSA in men with prostatitis is caused by a disruption of the normal physiological barriers to PSA between ductal lumen and stroma in prostatic tissue [42], a relatively higher rise in f-PSA after prostatic manipulations could be caused by leakage of f-PSA originating from the intraluminal compartment after trauma of the basal membrane.

Stability of PSA After Venesection

The stability in daily laboratory practice of the F/T ratio after venesection might be different from that of t-PSA. Woodrum et al. [43] reported a stable F/T ratio when serum was processed within 3 hr of venesection, and stored at a maximum of −20°C during a 6-month period, for at least five freeze-thaw cycles. Serum which was stored at 4°C or processed 8 hr after blood draw showed a significant decrease in f-PSA.

USE OF F/T RATIO IN DETECTION OF PROSTATE CANCER

Using the F/T ratio, accuracy in the diagnosis of PCA can be enhanced [22]. In 422 randomly chosen men with no clinical signs of PCA, the lower limit of normal (95th percentile) of the F/T PSA ratio was found to be 0.15 [44]. This ratio was constant for men between age 40–79 years. In a study in which no restrictions were made on the basis of PSA levels, Klee et al. [45] found that the area under the receiver-operating curve (AUC) for the F/T ratio was less than or equal to the AUC for the total PSA for all age groups. (In a ROC (Receiver operator characteristic) curve, the x-axis represents 1 minus specificity, and the y-axis represents sensitivity. An AUC of 0.5 represents a noninformative test, and an AUC of 1.0 represents a perfect test.) The additional predictive power imparted by the measurement of f-PSA was very small (AUC rose 0.02) and only present in the age group between 50–70 years. This indicates that a possible gain in clinical differentiation between BPH and PCA may only be present in the intermediate PSA range, and that determination of the F/T ratio cannot replace t-PSA measurement.

F/T Ratio in the Intermediate t-PSA Range

An overview of several studies performed on the capability of the F/T ratio to differentiate between BPH and PCA in the intermediate PSA range is given in Table I. Compared to measurement of t-PSA only, measurement of the F/T ratio in studies performed by van Iersel et al. [66] (Fig. 3), Oesterling et al. [58] and Sagalowsky et al. [59] showed an increase of AUC of, respectively, 0.51 to 0.68, 0.53 to 0.73, and 0.52 to 0.72 for discrimination between BPH and PCA in the intermediate t-PSA range. This means that in this PSA range, differentiation between BPH and PCA using the t-PSA values is not significantly better than by chance (AUC = 0.5), and that by using the F/T ratio, a fair improvement in this differentiation can be made. Petteway et al. [62] measured the F/T for two different assays in the same group of patient sera. They concluded that different ratios of F/T PSA are necessary to achieve comparable sensitivities. This must be taken into consideration when extrapolating findings from one assay to another. As can be seen in Table I, a cutoff value for the F/T ratio in the range of 0.17–0.25 gives a sensitivity of approximately 90%, while a specificity of 20–45% is reached. Physician judgment must be involved in choosing F/T ratio cutoff, since one must choose between increased cancer detection rate (sensitivity) and increased biopsy rate (specificity), as evidenced in Table I. The final goal is to determine if F/T ratio is an accurate test for the selection of candidates for prostate biopsies in a screening population. In the study of Smith et al. [63], approximately 40% of biopsies could have been avoided while maintaining a 90% sensitivity for the presence of prostate cancer. The percentage of saved biopsies will vary among different studies according to the difference in prior probability of cancer incidence. An alternative approach was brought forward by Flemming et al. [46], who in a study on cost-effectiveness of screening tests for prostate carcinoma found the cost per life-year saved when biopsying all screenees was equal when only biopsying according to the outcome of DRE and serum PSA. However, most men are probably even more reluctant to undergo a routine prostate biopsy, as women are for having a cervical smear done. Consequently, the lack of tolerability to the screenees most likely will prevent this approach from gaining acceptance.

FREE PSA DENSITY

In 200 patients including 100 biopsy-proven PCA cases, Yemoto et al. [47] measured f-PSAD and t-PSAD. Mean t-PSAD was 0.23 and 0.15 for PCA and BPH patients, respectively. Mean f-PSAD was 0.026 and 0.025 for PCA and BPH patients, respectively. They suggested that cancer increases the complexed form of PSA in serum much more significantly than prostate volume increases the f-PSA in serum. Looking at these data, it seems that the difference in t-PSAD between PCA and BPH patients is mainly the result of a difference in ACT-PSA density. By using ACT-PSAD instead of t-PSAD, the accuracy of PSAD in differentiating between PCA and BPH in the intermediate PSA range might be enhanced. A similar advantage might be found using F/T velocity instead of t-PSA velocity.

CORRELATION OF PSA VALUES WITH PATHOLOGICAL STAGE

t-PSA and Stage

Patients with preoperative t-PSA levels below 10 ng/ml have a negligible risk for a positive bone scan [48]. Bleustein et al. [49] demonstrated in a retrospective study that 406 of 1,632 patients with clinically localized disease may be spared pelvic lymph node dissection when PSA is used in combination with local clinical stage and primary Gleason grade. The combination they used yielded a false-negative rate of 3%. Concerning organ confinement of the tumor, the significant overlap in preoperative PSA values precludes any useful predictive information for the individual patient.

TABLE I. Overview of Studies in Differentiation of Prostatic Cancer and BPH Using Assays for Simultaneous Measurement of f-PSA and t-PSA*

Authors	t-PSA	PCA/BPH	Cutoff F/T	Sensitivity	Specificity	Population	Assay
Elgamal et al. [57]	3–15	37/48	0.18	95	95	re T1c	1
		32/48	0.18	88	78	re ≥T2	
Oesterling et al. [58]	2–20	188/248	0.18	80	45	ni	2
			0.20	87	37		
			0.22	89	25		
			0.24	94	19		
Sagalowsky et al. [59]	4–20	23/19	0.11	42	88	pr	3
			0.15	74	75		
			0.18	84	38		
Saito et al. [60]	0–20	80/190	0.16	69	72	pr	ni
Reissigl et al. [61]	>4	45/101	0.18	75	48	pr	ni
			0.20	90	37		
Petteway et al. [62]	0–10	29/138	0.23	90	45	re	4
			0.30	93	30		
			0.33	100	25		
Petteway et al. [62]	0–10	29/138	0.25	90	26	re	3
			0.26	93	22		
			0.31	100	7		
Smith et al. [63]	4–10	50/63	0.20	90	38	pr	3
Marley et al. [64]	2.5–20	149/112	0.26	90	19	ni	5
Van Cangh et al. [65]	ni	163/290	0.10	41	96	ni	3
			0.15	75	82		
			0.17	82	76		
			0.20	88	60		
			0.25	96	36		
Iersel et al.**	4–10	50/216	0.18	70	54	re	3
			0.25	90	25		
Partin et al. [66]	4–10	88/47	0.17	90	46	pr	3
			0.20	91	28		
			0.25	100	14		

*t-PSA, range of t-PSA in study; n, number of cases histopathologically proven as respectively PCA and BPH; cutoff, F/T ratio below which cases were destined as BPH and above which cases were destined as having PCA; re, retrospective; pr, prospective. Assays: 1, Centrocor; 2, AxSYM, Abbott; 3, Tandem-R, Hybritech; 4, Dianon; 5, free with DPC-Immulite and total with TOSOH; ni, not indicated.
**Unpublished data.

F/T Ratio and Stage

Several studies have been performed to investigate whether the correlation of pathological stage with preoperative F/T ratio is superior to the correlation with t-PSA. In retrospective studies performed by Hendricks et al. [50] and Lerner et al. [51], the F/T ratio was measured of 70 and 178 men, respectively, who underwent a radical prostatectomy. They concluded that the PSA F/T ratio could not predict whether PCA has spread beyond the prostate gland at time of prostatectomy. Prospective studies carried out by Partin et al. [52] and Graefen et al. [53] in 288 and 53 men, respectively, brought the same result. In a study of 33 patients who underwent radical prostatectomy as a result of a screening program, Arcangeli et al. [54] found that F/T ratio <0.14 significantly correlated with a higher stage ($P = 0.05$). Regarding the limited number of cases included in the latter study, the outcome of the former studies suggests that F/T ratio provides no additional information on the prediction of pathological stage for men with clinically localized prostate cancer.

PSA Expression in Cells in Peripheral Blood

A future, better predictor for pathological stage might be PSA expression in cells in the peripheral blood. These can be detected by a PSA reverse transcriptase-polymerase chain reaction (RT-PCR) assay. Israeli et al. [55] concluded from their study that PSA expression is highly specific for the presence of prostate cancer. So far, PSA RT-PCR assays have failed to give additional prognostic information about the pathologically determined stage [56]. Also, as cells circulating in the peripheral blood do not necessarily

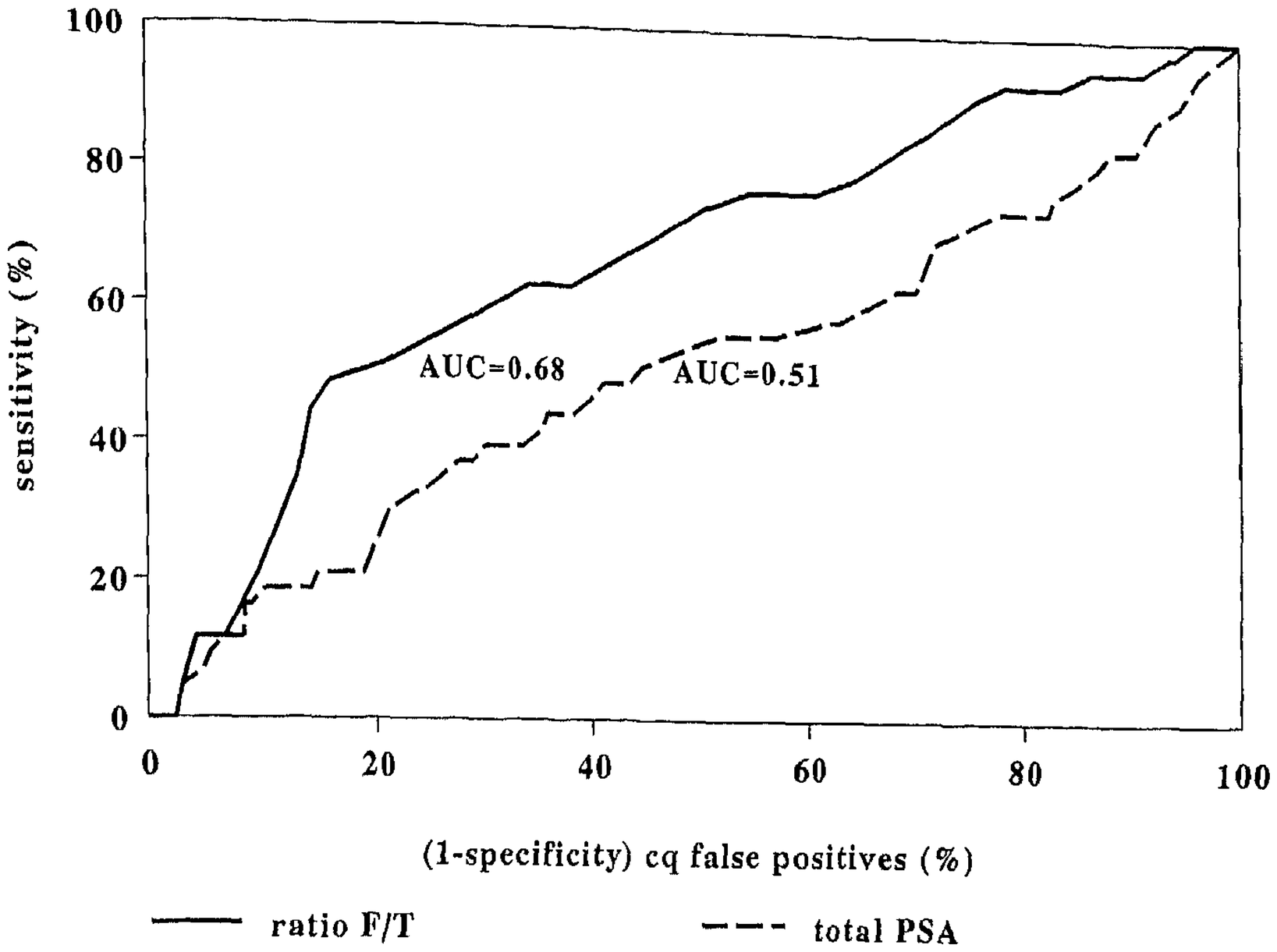


Fig. 3. ROC curve of t-PSA and F/T ratio in study of van Iersel et al. (unpublished data).

have the capability to form solid metastases, the clinical significance of the detection of circulating cancer cells remains to be assessed.

CORRELATION OF F/T RATIO WITH HISTOLOGICAL FEATURES: GLEASON GRADE, PERCENTAGE OF CANCER, AND DNA PLOIDY

No correlation was found between F/T ratio and Gleason grade in the studies by Graefen et al. [53] and Lerner et al. [51], whereas Arcangeli et al. [54] found that F/T ratio <0.14 was significantly correlated with a higher Gleason grade and high percentage of cancer ($P = 0.05$).

The use of the outcome of pathology on the basis of performed biopsies as a gold standard is not perfect. As reported earlier by several groups, false-negative results and an underestimation of Gleason grade are common in the pathologic evaluation of biopsies. To further evaluate a possible relationship between tumor volume and Gleason grade, a study on preoperative F/T PSA ratios must be performed in patients undergoing radical prostatectomy. No relationship between DNA ploidy and F/T ratio was observed by Lerner et al. [51].

CONCLUSIONS

The role of PSA in detecting early prostate cancer is undergoing extensive scrutiny. Because of the overlap in serum t-PSA in patients with BPH and PCA in the intermediate t-PSA range, any improvement in accuracy of serum PSA measurements will have a tremendous cost-savings potential. The F/T ratio seems to facilitate the differential diagnosis of PCA and BPH in this t-PSA range, saving approximately 30% of unnecessary biopsies. In this respect an international standardization of t-PSA measurements and of assays for the determination of F/T ratio would be most welcome. This would not only help the patients and physicians with a better differentiation between BPH and PCA, but would also help the manufacturers of PSA-assays in obtaining acceptance of the determination of F/T ratio for use in screening programs.

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