SERUM AND URINARY CYTOKERATIN 19 AND BLADDER TUMOR ANTIGEN IN BLADDER CANCER IN EGYPTIAN PATIENTS

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Objective Evaluation of the usefulness of cytokeratin 19 and bladder tumor antigen (BTA) in comparison to conventional urine cytology in the diagnosis of bladder cancer and early detection of recurrence during follow up of superficial disease in Egyptian patients.

Patients and Methods Ninety-five cases were studied and classified into three groups: 20 patients with normal urothelium (Group I), 20 patients with reactive urothelial lesions (Group II) and 55 patients with bladder cancer (Group III). In Group III, 30 patients had squamous cell carcinoma (SCC), while 25 patients had transitional cell carcinoma (TCC). The serum samples were subjected to CYFRA 21-1 immunoassay and the urine samples to routine urine cytology, CYFRA 21-1 immunoassay and BTA stat immuno-chromatographic assay.

Results The sensitivity of urine cytology, urinary CYFRA 21-1, serum CYFRA 21-1 and BTA was 63.6%, 90.9%, 92.7% and 87.5%, respectively. The specificity for the same parameters was 80%, 87.5%, 62.5% and 81.8%, respectively. The results were matched to pathological types, grade and stage.

Conclusion Urinary CYFRA 21-1 and BTA stat are valuable non-invasive urinary markers for the detection of bladder cancer with a high sensitivity compared to urine cytology.

Key Words cytokeratin, complement H, BTA, CYFRA 21-1, BTA stat

INTRODUCTION

While cystoscopy is the most definite mode of investigation for diagnosing bladder cancer, yet, its cost, invasiveness, need for special expertise, infection risk and unavailability in many areas restrict its use as a screening tool for bladder cancer[1]. Voided or washed urine cytology is still the gold standard for screening patients for urothelial cancer. However, apart from the fact that specialized experienced pathologists are needed, the major inter-observer variations and the low sensitivity and specificity of urine cytology especially in low-grade non-invasive forms of bladder cancer indicate the necessity for supplementary markers with a higher sensitivity[2,3]. Furthermore, the different biological and antigenic behaviour of squamous cell carcinoma (SCC) in Egypt[4] presents an additional diagnostic problem for the conventional markers developed mainly for the common western type of bladder cancer.

A variety of non-invasive techniques have been developed, correlating the expression of molecular markers with the clinicopathologic status and eludicating their interrelationships, thus facilitating a non-invasive early diagnosis. Cytokeratin 19 (21-1 fragment) and bladder tumor antigen (BTA) are potential novel markers eligible for clinical testing of bladder cancer.

Cytokeratins (CKs) are water insoluble intermediate filaments that are expressed by all epithelial cells and appear to be a useful marker of epithelial differentiation[5]. A total of 20 human CKs have been distinguished, and a given epithelium may be characterized by a specific pattern of CK expression. CK 19 is an acid type with a low molecular weight of 40 kDa that is expressed in the urothelium. During cell lysis, it is released as a soluble fragment (CYFRA 21-1) together with other cellular components in biological fluids including serum

and urine. Based on this fact, soluble CYFRA 21-1 can be detected and monitored in serum and urine with a reliable anti-CYFRA 21-1 antibody by using the commercial ELISA CYFRA 21-1 assay[6,7]. It has been found that all layers of the normal urothelium and low-grade transitional cell carcinoma (TCC) express all simple epithelial type CKs including CK 19. Squamous metaplasia and TCC with squamous differentiation express only minute amounts of CK 19[8,9]. Interestingly, a poorly differentiated SCC also expresses CK 19[9].

It has been demonstrated that the human complement factor H related protein is produced and secreted by several human bladder cell lines but not by the normal epithelium[10]. In addition, in situ hybridization has shown that bladder tumors produce a human complement factor H related protein[11,12]. The urinary human complement factor H related protein can be detected, and since it has been associated with bladder cancer, it has been given the name "bladder tumor associated antigen" (BTA). The BTA stat test is a one-step rapid immunochromatographic assay detecting BTA in urine[13,14].

The main objective of our study was to investigate the role of these innovate biological markers in the diagnosis of bladder tumors and in the detection of early recurrence during the follow up of patients with superficial disease. We compared the validity of CYFRA 21-1 and BTA stat with voided urine cytology in Egyptian patients with bladder cancer of two different pathological types: TCC and SCC.

PATIENTS AND METHODS

A total of 95 patients (72 males and 23 females) were divided into three main groups. Group I included 20 healthy patients with a normal urothelium serving as a control group, while Group II included 20 patients with reactive urothelial lesions including urinary tract infection, lithiasis and squamous metaplasia (disease control group). Group III included 55 patients with bladder cancer, 30 of them with SCC and 25 with TCC. Cancers in the pathological stages Ta and T1 were regarded as non-invasive (Group IIIa, 17 cases), while those with stages T2 and T3 were regarded as invasive[15] (Group IIIb, 38 cases). The median age was 48.83 ± 1.14 years. The healthy controls were recruited from

Table 1: Distribution of Patients According to Pathological Stage and Histological Grade and their Correlation

Stage	Grade			Total
	Grade 1	Grade 2	Grade3	
Pta	3	1	0	4
PT1	0	6	7	13
PT2	0	13	15	28
PT3	0	4	6	10
Total	3	24	28	55

$X^2 = 20.49$, p=0.002

asymptomatic paramedical personnel with no signs or past history of urological disease.

All patients and controls were subjected to a thorough clinical history and examination, as well as to routine investigations including urine analysis, plain X-ray and pelvi-abdominal ultrasound. For the members of Groups II and III excretory urography and cystoscopy were performed. After cystoscopic biopsy, the Group III patients were graded according to the WHO[16] and staged according to the TNM classification[15]. In all cases, venous blood and freshly voided urine samples were collected at inclusion. For CK assessment, the serum samples were obtained by centrifugation and the urine samples were filtered by means of a nitro-cellulose membrane. The serum and urine samples were stored at –80°C until assayed. Positive urine cytology was defined according to the Papanicolaou classifications[17]. All specimens were evaluated in duplicate. The laboratory team performing the assays was blinded with regard to the patients' clinical status.

Procedures

Cytokeratin:

Serum and urinary CK 19 (21-1 fragment) was measured using the mouse monoclonal antibody 21-1 assay kit ELISA-CYFRA (Cis Bio International, Gif-sur-Yvette, France) which is a solid phase sandwich immunoradiometric assay.

Table 2: Mean Values (±SEM) of CYFRA 21-1

	Group I (n=20)	Group II (n=20)	Group III (n=55)				
			Total (n=55)	Invasive (n=38)	Non-Invasive (n=17)	TCC (n=25)	TCC (n=30)
Urine (ng/ml)	5.21±2.92	30.51±7.24	595.65±24.17	358.95±27.79	154.16±23.89	340.28±39.95	258.47±28.07
Serum (ng/ml)	1.56±0.95	8.88±1.95	17.06±2.73	21.81±3.68	6.42±1.11	17.59±4.17	16.61±3.67

Table 3: Sensitivity and Specificity Values of CYFRA 21-1 in Diagnosing Bladder Cancer

		Area under the curve	Sensitivity (%)	Specificity (%)
Urinary CYFRA 21-1	Total cases (n=55)	0.964	90.9	87.5
	non-invasive (n=17)	0.922	82.4	87.5
	Invasive (n=38)	0.983	94.7	87.5
	TCC (n=25)	0.991	100	87.5
	SCC (n=30)	0.942	83.3	87.5
Serum CYFRA 21-1	Total cases (n=55)	0.793	92.7	62.5
	Non-invasive (n=17)	0.696	88.2	62.5
	Invasive (n=38)	0.836	94.7	62.5
	TCC (n=25)	0.797	100	62.5
	SCC (n=30)	0.789	86.7	62.5

Bladder Tumor Antigen (BTA):

BTA detection was achieved by the commercial immunochromatographic BTA stat assay kit (Bion Diagnostic Sciences, Redmond, Washington, USA). According to the manufacturer's instructions 5 drops of untreated voided urine were added to the disposable test device using the disposable pipette provided. Five minutes later, the qualitative interpretation was done.

Statistical Evaluation

The results were tabulated and analyzed using commercial PC statistical software (Statistica, release 5.0 A, StatSoft Inc., USA). The numerical variables were compared by the independent sample t-test and an analysis of variance (ANOVA) and correlated by the Pearson correlation test. The categorical variables were analyzed, compared and correlated using the 2 x 2 Chi-square test. A value of $P < 0.05$ demarcated the level of significance. For urinary and serum CYFRA 21-1, a receiver operator characteristic (ROC) curve analysis and a selection of cut-off values were done by the PC software program SPSS (release 9.0, SPSS Inc.) with estimation of the area under the curve. Sensitivity, specificity and total accuracy for both BTA stat and cytology were calculated.

RESULTS

Table 1 shows the distribution of pathological stage and histological grade among our Group III patients. A significant correlation between stage and grade was noted.

Table 4: Values of BTA Stat and Voided Urine Cytology in Diagnosing Bladder Cancer

		Sensitivity (%)	Specificity (%)	PPV* (%)	NPV** (%)	Total Accuracy (%)
	Total cases (n=55)	81.8	87.5	90.0	77.8	84.2
	Non-invasive (n=17)	70.6	87.5	70.6	87.5	82.5
BTA Stat	Invasive (n=38)	86.8	87.5	86.8	87.5	87.2
	TCC (n=25)	90.0	87.5	84.4	92.1	88.6
	SCC (n=30)	72.2	87.5	78.3	83.3	81.5
	Total cases (n=55)	63.6	80.0	81.4	61.5	70.5
	Non-invasive (n=17)	35.3	80.0	42.9	74.4	66.7
Urine Cytology	Invasive (n=38)	76.3	80.0	78.4	78.0	78.2
	TCC (n=25)	52.2	80.0	61.9	72.7	69.2
	SCC (n=30)	73.3	80.0	73.3	80.0	77.1

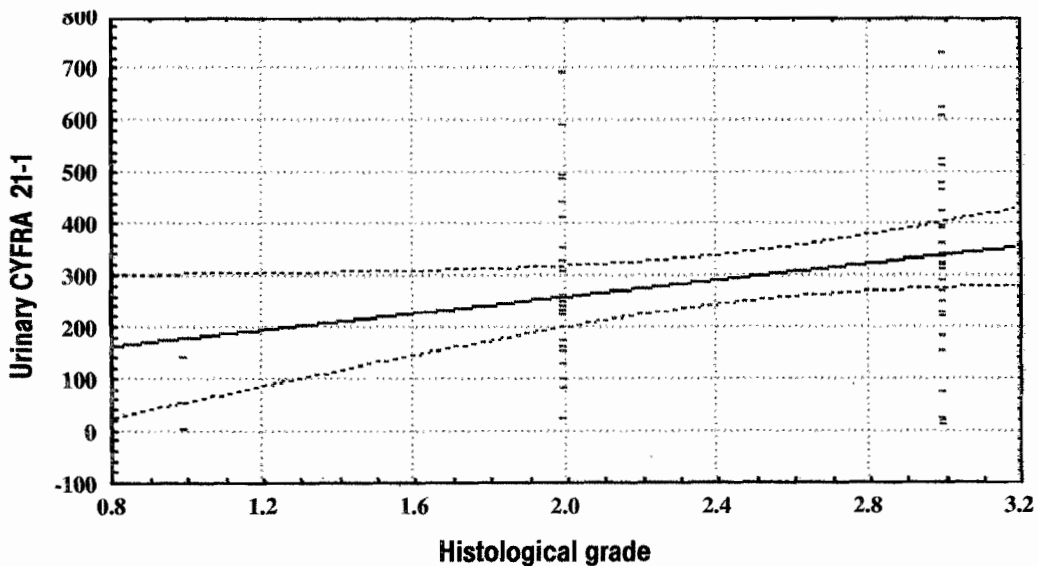* = positive predictive value; ** = negative predictive value

Fig. 1: Graph showing the correlation between urinary CYFRA 21-1 and the pathological stage in the patients of Group III (r=0.618)

Table 2 lists the results of the CYFRA 21-1 measurements in the urine and serum samples of all studied subjects. For Group III, the values for invasive and non-invasive cancer as well as for TCC and SCC are mentioned separately.

The mean urinary CYFRA 21-1 in Group III (cancer group) (295.65±24.17 ng/ml) was significantly higher compared to Group II with reactive urothelial lesions (30.51±7.24 ng/ml, p<0.001) and Group I (control group) (5.21± 2.92 ng/ml, p<0.001). Furthermore, the values were statistically higher when comparing Groups I and II (p<0.002). A comparison between the 17 patients in subgroup IIIa (stages Ta and T1) and the 38 patients in subgroup IIIb (stages T2 and T3) revealed a statistically significant difference (154.16±23.89 ng/ml versus 358.95±27.79 ng/ml, respectively, p<0.001). However, a comparison between pa-
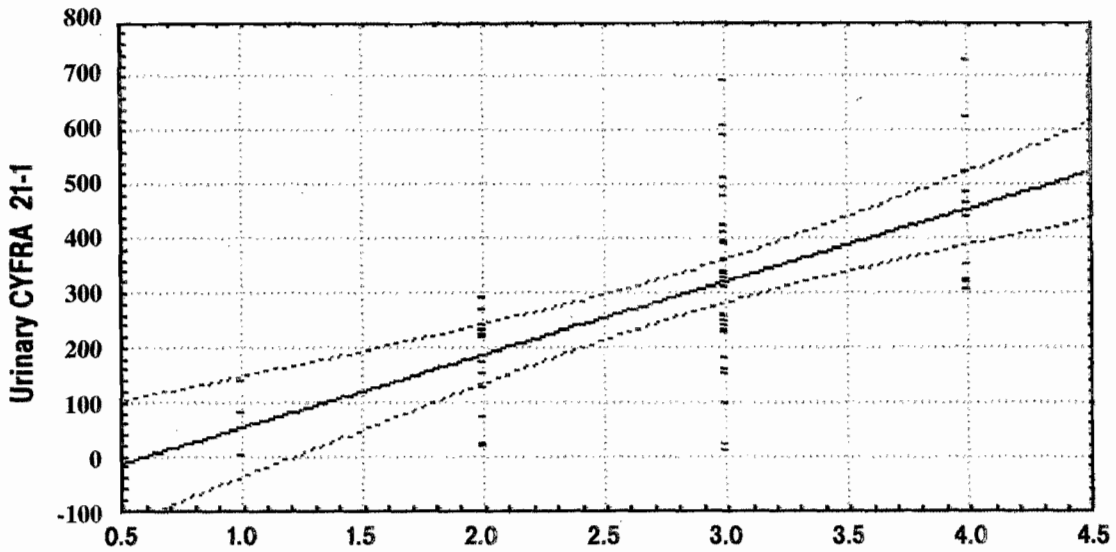
Fig. 2: Graph illustrating the correlation between the urinary CYFRA 21-1 and the histological grade in the patients of Group III (r=0.272)
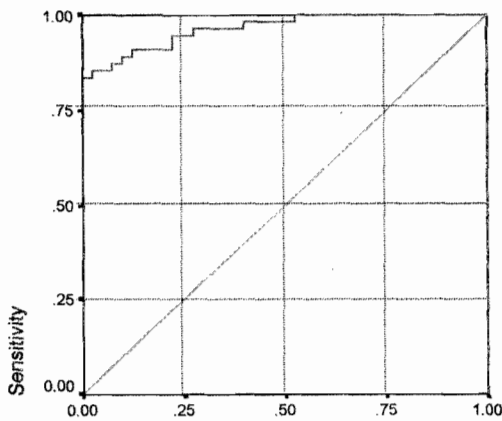

Fig. 3: Receiver operator characteristic (ROC) curve used to determine sensitivity and specificity of urinary CYFRA 21-1
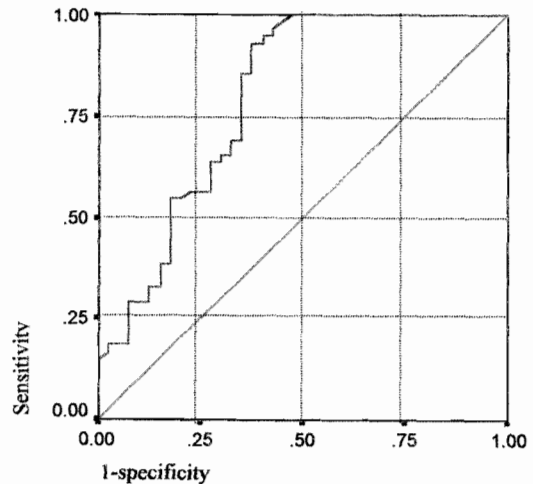

Fig. 4: Receiver operator characteristic (ROC) curve used to determine sensitivity and specificity of serum CYFRA 21-1

tients with TCC and SCC revealed no statistical significance (p>0.05). The correlation between urinary CYFRA with the cancer stage (Fig. 1) and grade (Fig. 2) revealed a statistical significance (r=0.62 and 0.27, respectively, P<0.05).

The mean serum CYFRA 21-1 in the cancer group (17.06±2.73 ng/ml) was higher although statistically not significant compared to the patients with reactive urothelial lesions (8.88±1.95 ng/ml, p>0.5). However, it was significantly higher compared to the control group (1.56±0.95 ng/ml, p=0.001). Also, the mean serum CYFRA 21-1 was significantly higher for Group II compared to Group I (p=0.002). A comparison between subgroup IIIa (21.81±3.68 ng/ml) and subgroup IIIb

(6.42±1.11 ng/ml) regarding serum CYFRA 21-1 revealed a statistically significant difference (p<0.008). However, the difference between patients with TCC (17.95±4.17 ng/ml) and SCC (16.61±3.67 ng/ml) was not significant (p>0.05).

The efficacy of urinary and serum CYFRA 21-1 as diagnostic tools for bladder cancer was assessed by the ROC curve analysis (Fig. 3, 4). For urinary CYFRA 21-1, the optimal combination of sensitivity (90.9%), specificity (87.5%) and confidence interval (CI = 0.93-0.99, the area under the curve = 0.96) was obtained at a cut-off value of 48.37 ng/ml. For serum CYFRA 21-1, 92.7% sensitivity and 62.5% specificity (CI = 0.69-0.89, area under the curve = 0.79) were obtained at a cut-off value of 2.38 ng/ml. The efficacy of urinary and serum CYFRA 21-1 at the same cut-off values for invasive cases and non-invasive cases with either TCC or SCC was assessed separately by ROC curve analysis. The values of sensitivity and specificity for each parameter together with the overall values for the whole group are recorded in Table 3.

Voided urine cytology was capable of diagnosing a total of 35 cases with bladder cancer (sensitivity = 63.6%), compared to a total of 45 cases diagnosed by BTA stat (sensitivity = 81.8%) with a statistically significant difference (p=0.005). While voided urine cytology failed in detecting 20 cases with bladder cancer (specificity = 80%), only 10 cases escaped diagnosis by BTA stat (specificity = 87.5%). However the difference was not statistically significant (p>0.05). The values of both tests in diagnosing invasive, non-invasive, TCC and SCC cancer are listed in Table 4.

There was a significantly higher overall accuracy in favour of BTA stat regarding the detection of all cases (p<0.001) and cases of TCC (p=0.007). Also a comparison of the accuracy of both tests showed a near significant level of diagnosing non-invasive (p=0.055) and invasive cases (p=0.057) in favour of BTA stat.

A correlation between urine cytology and the pathological stage and grade showed a statistical significance (X^2=6.3 and 18.99, respectively, p=0.036), while there was no statistical significance regarding the tumor type (TCC or SCC, p>0.05). For BTA stat, the correlation was significant regarding invasive-ness and type (p<0.05). Meanwhile, BTA stat and urine cytology showed a highly significant correlation (X=12.25, p=0.0005).

DISCUSSION

Cytological examination of voided urine or bladder washing in combination with cystoscopic examination is the gold standard for the diagnosis of bladder cancer and the detection of recurrence during the follow up of patients with superficial disease. However, the interpretation of urine cytology, especially in the case of low-grade tumors, highly depends on the skill of the examiner and, therefore, a high intraobserver variation in sensitivity may be noted[18,19]. Although more flexible materials have been introduced, yet, the procedure remains uncomfortable for a representative number of patients. Also, since the patients may initially present to a general practitioner or internist, a non-invasive, simple blood/urine test that detects bladder tumors with a high specificity would improve the early diagnosis. The newly developed molecular pathology techniques have prompted the search for a simple, cost-effective, non-invasive and more reliable urine-based diagnostic test to replace cystoscopy and cytology or to integrate and complement cytology with more specific markers[20,21]. In this study, two promising bladder tumor markers, namely CK 10 (CYFRA 21-1) and BTA, were evaluated in the diagnosis of bladder cancer in Egyptian patients with known tumor heterogeneity.

In this prospective study, the mean urinary CYFRA 21-1 (295.65±24.17 ng/ml) in the cancer group was significantly higher compared to the group with reactive urothelial lesions (30.51±7.24 ng/ml) and the control group (5.21±2.92 ng/ml). Furthermore, the values were significantly higher in the patients with reactive lesions compared to the control group. This may be explained by the urothelial cell membrane damage that results in an expulsion of soluble fragments of intracellular CK 19 into the urine, particularly in lithiasis and infection. Nevertheless, urinary CYFRA 21-1 in the group with reactive lesions was 10-folds less than that in the cancer group, implying the usefulness of this marker in diagnosing bladder cancer. Our mean value for the control group is higher than the mean value of 2.4±0.14 ng/ml reported by Pariente et al.[7]. The significant 6-fold rise in patients with reactive urothelial lesions compared to the control group is,

however, close to that reported by Pariente et al.[7].

The comparison between subgroup IIIa (154.16±23.89) and subgroup IIIb (358.95± 27.79) revealed a statistically significant difference. However, the difference between patients with TCC (340.28±39.95) and those with SCC (258.47±28.07) was statistically non-significant denoting the usefulness of the marker in diagnosing bladder cancer of both types, with higher values in invasive cases. The relatively higher value for patients with SCC in our study goes with the report of Moll et al.[8] who proved that poorly differentiated SCC expressed CK 19. Also, it has been reported that bilharziasis has no effect on CK expression[8]. This can be explained by a possible retention of mRNA coding for CKs within epithelial cells showing squamous differentiation.

The power of urinary CYFRA 21-1 as a diagnostic tool for bladder cancer was assessed by an ROC curve analysis (Fig. 3). The optimal combination of sensitivity and specificity (90.9% and 87.5%, respectively, CI=0.93-0.99, area under the curve = 0.96) was determined at a cut-off value of 48.37 ng/ml. The sensitivity of CYFRA 21-1 was significantly higher compared to urine cytology for the total number of cases and invasive cancer, non-invasive cancer, TCC and SCC cases. Also, a higher specificity of urinary CYFRA 21-1 was noted when compared to urine cytology, but this difference was statistically non-significant (87.5% vs. 80%). These findings show a superiority of urinary CYFRA 21-1 over urine cytology in diagnosing bladder cancer. Our results are in agreement with other authors[7] who studied only TCC cases and reported an overall sensitivity of 96.6% and specificity of 67%.

The mean serum CYFRA 21-1 in the cancer group (17.06±2.73) was higher, even though without statistical significance, compared to the group with reactive lesions (8.88±1.95). However, it was significantly higher compared to the control group (1.56±0.95). This overlap between the group with reactive lesions and the cancer group decreased the specificity of serum CYFRA 21-1 when ROC curves were done (Fig. 4). The optimal combination of sensitivity and specificity was 92.7% and 62.5%, respectively (CI=0.69-0.89, area under the curve = 0.79) at a cut-off value of 2.38 ng/ml. Generally, the

sensitivity was significantly higher for serum CYFRA 21-1 compared to urine cytology for the total number of cases, the invasive and non-invasive cases and cases with TCC, but not for the cases with SCC. Unfortunately, that was on the expense of a significantly reduced specificity (62.5% for serum CYFRA 21-1 versus 80% for urine cytology).

Although serum CYFRA 21-1 failed to discriminate between TCC and SCC cases, significantly higher values were recorded for the invasive cases (21.81±3.68) compared to the non-invasive cases (6.42±1.11). This difference can be explained by the potential of circulating malignant cells which may release CK directly into the circulation of invasive cases[22].

Urine cytology was capable of diagnosing a total of 35 cases with bladder cancer in Group III (sensitivity=63.3%) compared to a total of 45 cases diagnosed by BTA stat (sensitivity= 81.8%), and this difference was statistically significant. While urine cytology failed in detecting 20 cases of bladder cancer (specificity=80%), only 10 cases escaped diagnosis by BTA stat (specificity=87.5%), but this difference was statistically non-significant. These results are in accordance with previous studies that reported a sensitivity range of 11.4% - 66.7% for urine cytology[18,23,24,25] and of 74%-100% for BTA stat[26-28]. Moreover, Raitanen et al.[26] showed a near similar sensitivity of 81.5% for BTA stat. In the present study, there was a significantly higher overall accuracy in favour of BTA stat regarding the detection of the total number of cases and cases of TCC (Table 4). Also, the comparison between the sensitivity of both markers showed a significant level for diagnosing non-invasive cases in favour of BTA stat with a statistically similar specificity (87.5% for BTA stat and 80% for urine cytology). In agreement with Mayfield and Whelan[25], the correlation between urine cytology and tumor invasiveness was statistically significant. Meanwhile, there was a non-significant correlation between BTA stat and tumor invasiveness, indicating its value in the diagnosis of both early and invasive cases of bladder cancer compared to urine cytology which shows inferior results in early non-invasive bladder cancer.

The combined use of both urinary CYFRA 21-1 and BTA stat showed an overall sensitivity of 96.36% (53 out of 55 cases proved positive). When both tests were

negative for any parameter, the specificity was 100% (none of the patients of Groups I and II was positive for either marker).

In conclusion, serum CYFRA 21-1 is a sensitive marker for bladder cancer. However, it is short of specificity compared to urine cytology. Both urinary CYFRA 21-1 and BTA stat are valuable, easy-to-use, simple and non-invasive urine tests for detecting bladder cancer, particularly during the follow up of patients with superficial disease. They have a better overall sensitivity in diagnosing these cases with better results in the group of early non-invasive cancer compared to urine cytology. The higher sensitivity of CYFRA 21-1 and BTA stat, especially in view of the difficulties encountered in cytological examinations makes them superior to urine cytology in detecting bladder cancer. The combined use of both urinary markers may increase the sensitivity, and the combined negativity comforts the physician about the benign nature of the urologic presentation. However, more extended studies are needed to validate these markers on a large scale and to assess their value in the follow up of patients with bladder cancer and their reliability in detecting cancer recurrence.

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RESUME

Cytokeratin 19 Sérique et Urinaire et Antigen Tumoral Vésical dans le Cancer de la Vessie chez l'Egyptien

Objectif Evaluer l'utilité de la Cytokeratin 19 et l'antigen tumoral vésical (BTA) en comparaison avec la cytométrie urinaire conventionnelle dans le diagnostic du cancer de la vessie et la détection précoce des récidives dans le suivi des tumeurs superficielles de vessie chez les patients égyptiens. **Patients and Méthodes** Quatre vingt quinze cas ont été étudiés et classés en trois groupes. 20 patients avec épithélium vésical normal (Groupe I), 20 patients avec lésions urothéliales inflammatoires (Groupe II) et 55 patients avec un cancer de la vessie (Groupe III). Dans le Groupe III, 30 patients avaient un carcinome épidermoide de la vessie, tandis que 25 avaient un carcinome à cellules transitionnelles. Les échantillons sériques ont été analysés par Immuno-Essai au CYFRA 21-1 et les échantillons urinaires ont été examinés en cytologie urinaire de routine, une immuno-essai au CYFRA 21-1 et immuno-chromatographie au BTA stat. **Résultats** La sensibilité de la cytologie urinaire, du CYFRA 21-1 urinaire, du CYFRA 21-1 sérique et du BTA étaient respectivement de 63,6%, 90,9%, 92,7% and 87,5%. La spécificité pour les mêmes paramètres etait respectivement de 80%, 87,5%, 62,5% et 81,8%. Ces résultats concordaient avec le type cyto-pathologique, le grade et le stade tumoral. **Conclusion** CYFRA 21-1 urinaire et BTA stat sont des marqueurs de valeur dans la détection du cancer de la vessie avec une grande sensibilité comparée à la cytologie urinaire

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