Table 3: Evaluation of hTERT immunoreactivity in biopsy confirmed malignant and non-malignant specimens

Malignant cases			hTERT		
			Positive	Negative	TOTAL
Cytological diagnosis	Positive		27	2	29
	Atypical		1	3	4
		TOTAL	28	5	33
Non-malignant cases			hTERT		
			Positive	Negative	TOTAL
Cytological diagnosis	Negative/Reactive		1	10	11
	Atypical		7	5	12
		TOTAL	8	15	23

we had confirmatory information from bladder tissue biopsy evaluation. Histological examination of tissue bladder biopsy is considered the gold standard for the diagnosis of bladder malignancy. The biopsy correlation data are shown in Table 3. The availability of this data enabled the calculation of the diagnostic accuracy of the hTERT immunoassay. Overall, the hTERT immunoassay demonstrated a positive predictive value of 77.8% and a negative predictive value of 75% in this study. No correlation of hTERT expression was observed with the mode of specimen collection i.e. urine collection through voiding or instrumentation. Of 4 cytologically atypical cases subsequently proven to carry a bladder tumor burden through cystoscopy and biopsy, one case expressed hTERT (Table 3). Thus, in this case hTERT detection may have aided diagnosis, however, of 12 cytologically atypical cases with no evidence of a bladder lesion at the time of sampling, 7 cases exhibited hTERT expression. Notably, 4 of these 7 positive atypical cases were from patients who had a history of bladder cancer, indicative of a possible 'field-effect' which alters the phenotype of the entire bladder urothelia without resulting in an actual focal lesion. Finally, it is noteworthy that umbrella cells were occasionally positive for hTERT expression (Figure 1K). These superficial cells were commonly identified in urine sediments and exhibited hTERT in seven cases, all of which had negative reactive urothelial cells. In this study, cases were only considered positive if urothelia other than umbrella cells exhibited nucleolar hTERT staining.

Discussion

Carcinoma of the urinary bladder is the most common malignant tumor of the urinary tract and, after prostatic carcinoma, the second most common malignancy of the urogenital system. Furthermore, bladder carcinoma shows a very high recurrence rate (50–70%) and recurrent disease, when it does occur, is associated in 15–25% of patients with progression to a more advanced tumor stage. Thus, careful and frequent follow-up is of prime importance. Due to factors such as size or localization, the great majority of carcinomas of the urinary bladder are either undetectable with standard imaging techniques, or cannot be definitively differentiated from non-malignant, reactive processes. Thus, the invasive method of instrumental cystoscopy remains the standard detection mode in the clinic. A non-invasive method of comparable diagnostic quality would significantly facilitate the initial diagnosis of carcinoma of the urinary bladder and greatly simplify the follow-up of treated patients. The commonly utilized cytological examination of urine sediments is specific and readily available, but it is not sufficiently sensitive for the detection of the subtle morphologic changes that occur in well-differentiated carcinomas of the urinary bladder. Furthermore, inter-observer variability can create additional diagnostic pitfalls, thus, the need for non-invasive techniques for the diagnosis and follow-up of carcinoma of the urinary bladder remains.

Recent evidence has suggested that the presence of the enzyme telomerase in urine is a potentially useful marker for the early detection of urothelial neoplasia [15-19]. Comparative analyses of non-invasive methods for the diagnosis of bladder cancer have shown that telomerase has the highest combination of sensitivity and specificity with respect to urine cytology and other biochemical marker determinations [16,18-25]. The detection of telomerase activity and the expression of the associated genes has been customarily achieved through the telomere repeat amplification protocol (TRAP) and RT-PCR methodologies respectively. Sanchini et al recently demonstrated the ability of telomerase activity levels in urinary sediments to accurately detect the presence of