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Original article

The value of touch imprint cytology of prostate core needle biopsy specimens – Kuwait experience

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Abstract
Objectives: Touch imprint cytology (TIC) is a reliable, cost-effective technique for the diagnosis of cancer. The aim of this study was to determine the diagnostic value and accuracy of TIC of prostate core needle biopsy (CNB) specimens in predicting the final histology in patients with suspected prostate cancer.
Subjects and methods: TIC was carried out on 354 core needle biopsy specimens taken from 59 patients with suspected prostate cancer as indicated by a high prostate serum antigen (PSA) level or abnormal findings on rectal examination. All biopsies were taken under transrectal ultrasound (TRUS) guidance. Two touch imprints were prepared from each CNB. The TIC results were correlated with CNB.
Results: TIC revealed evaluable results in 336/354 (94.9%) CNB specimens analyzed, with the following cytological diagnosis: malignancy in 40 (11.9%), atypical features in 47 (14%) and benign results in 249 (74.1%) specimens. Histopathological examination of the 40 CNB specimens showing malignant features on TIC confirmed the diagnosis of prostate cancer. In 24/47 (51.1%) cases with atypical cytology, histopathological assessment of the CNB specimens revealed benign features in 7 and prostatitis in 17, while high-grade prostatic intraepithelial neoplasia (HGPIN) and carcinoma were seen in 3 and 20 specimens, respectively. In 12/249 (4.8%) cases showing benign results on TIC, histopathological examination of the CNB specimens revealed an abnormal histology in the form of HGPIN in 9 (75%) and carcinoma in 3 (25%) cases. TIC accurately predicted the final histology in 336 cases with a sensitivity of 84% and a specificity of 90.8%. When excluding atypical cytology on TIC and HGPIN on CNB, the sensitivity and specificity were 93% and 100%, respectively. A strong correlation was seen between TIC and CNB ($p < 0.001$).

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Conclusions: The routine use of TIC complements CNB reports and helps to provide an immediate and reliable cytological diagnosis of prostate lesions. TIC and serial sectioning of CNB specimens significantly improve the diagnostic accuracy.

Introduction

Prostate cancer is the most common non-cutaneous cancer in men in the United States with an incidence of 126.1 per 100,000 men of all races and Hispanic origin, and it is also one of the leading causes of cancer mortality [1]. An estimated 1 in 6 white men and 1 in 5 African-American men will be diagnosed with prostate cancer in their lifetime, with the likelihood increasing with age [2]. The current incidence of carcinoma of the prostate among indigenous Kuwaitis is 17.8 per 100,000 men per year [3]. The risk of getting prostate cancer increases with age. According to a recent report, 6.4, 12.6 and 14.9 percent of men sixty years of age in the United States will develop prostate cancer in 10, 20 and 30 years respectively [4]. The most important tools helping in the early diagnosis of prostate cancer are the use of prostate – specific antigen (PSA) as a screening tool and transrectal ultrasound (TRUS) – guided prostate biopsy [5]. The risk of disease increases as the PSA levels increase, however, no PSA level guarantees the absence of prostate cancer [5]. Diagnosis relies on TRUS and core needle biopsy (CNB). According to the usual biopsy protocol, 10–12 core needle biopsy specimens are taken for systematic mapping of the prostate, including any palpable or radiological target lesions [5]. However, some studies have revealed a 20–40% false negative rate of sextant biopsies [6], and it has been felt that touch imprint cytology (TIC) may provide additional information to CNB interpretation [7–9]. The aim of this study was to evaluate the accuracy of TIC in the diagnosis of prostate cancer.

Subjects and methods

Over a period of 6 months, TIC was carried out on 354 core needle biopsy specimens taken from 59 patients with suspected prostate cancer as indicated by a high PSA level or abnormal findings on rectal examination. The study was performed according to the guidelines of the local ethics committee which conforms to the Helsinki Declaration. The biopsies were taken under TRUS guidance using a 17–gauge coaxial introducer and an 18-gauge Tru-cut core biopsy needle. The median number of CNBs per patient was 12 (range 5–12). According to the study protocol, 10–12 CNBs were to be taken from each patient, however a smaller number of CNBs was taken in patients unable to tolerate the procedure. These patients were normally rescheduled for biopsy under local anesthesia at a later date.

Two CNB specimens on average were taken from each of the six sites sampled. As soon as the CNB was obtained, it was carefully smeared on the slide by the cytopathologist. The imprint smears were air-dried and stained using the May–Grünwald–Giemsa staining method. After preparing the touch imprints, the CNB specimens were fixed in buffered 10% formaldehyde for further fixation and staining with hematoxylin and eosin. The CNB specimens were independently and blindly reviewed by an experienced histopathologist (SH), while TIC was carried out by an experienced cytopathologist (KK) who categorized the results as benign, atypical cytology, positive and unsatisfactory. The criteria for a positive cytology (i.e. malignancy) included nuclear pleomorphism, a high nuclear cytoplasmic ratio, nuclear molding and prominent nucleoli with loss of polarity at the edge of clusters in an acinar arrangement (Fig. 1A and B). TIC was considered benign when mono-layered sheets of uniformly distributed nuclei with fine chromatin and small nucleoli were observed (Fig. 1C and D). The cases were labeled as atypical cytology when the morphologic features were not sufficient to label the cells as malignant. Finally, the cytological diagnosis was correlated with the histological diagnosis. To ease the correlation, one morphological diagnosis was taken from each of the two CNB specimens taken from one site. TIC-positive but histologically negative biopsies underwent serial sections.

Statistical analysis

Comparing the results of cytologic and histopathologic examination, the sensitivity, specificity, positive predictive value and negative predictive value were calculated. In order to prepare a two-way tables worksheet for statistical analysis, benign conditions and inflammation were classified as negative results, while an atypical or positive TIC was considered as malignant. HGPIN and carcinoma cases were grouped together in the group of malignant cases for histological diagnosis. Patients with non-diagnostic TIC as well as patients with atypical TIC and HGPIN on CNB were excluded from the calculations of sensitivity, specificity, positive predictive value and negative predictive value. The following definitions were used in this analysis:

Sensitivity: True positive/(True positive + False negative)
Specificity: True negative/(True negative + False positive)
Positive predictive value: True positive/(True positive + False positive)
Negative predictive value: True negative/(True negative + False negative).

All statistical calculations were performed using IBM SPSS Statistics 19 for Windows. The Chi-square test was used to assess the association between the histopathological and cytological tests. Significance of the statistical tests was based on a 95% confidence interval.

Results

The patients' age ranged from 51 to 83 years with a median age of 67 years (Table 1). The serum PSA levels were correlated with the histological diagnosis (Table 2). No significant correlation

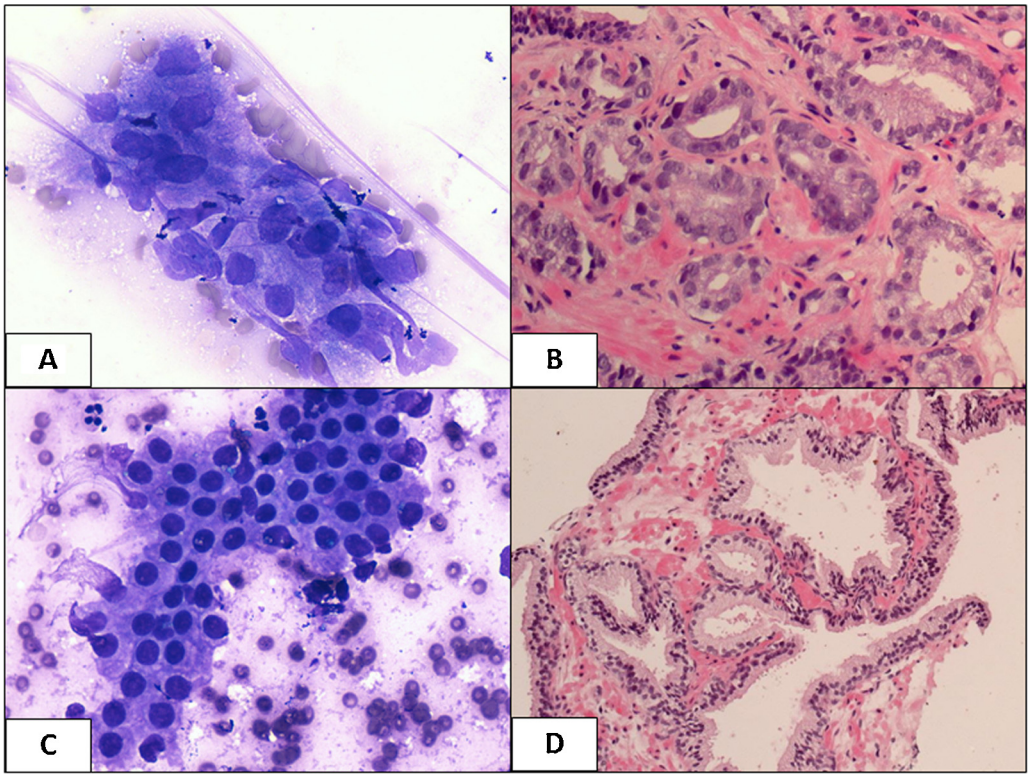

Figure 1 (A) TIC revealing carcinoma of the prostate showing a loose cluster of pleomorphic cells with vesicular nuclei having prominent nucleoli (May–Grünwald–Giemsa 400×). (B) CNB showing carcinoma (H&E 400×). (C) TIC revealing benign cytology showing a monolayered sheet of cells with uniform rounded nuclei (May–Grünwald–Giemsa 400×). (D) CNB showing benign prostatic tissue (H&E 200×).

Table 1 Age distribution and histological diagnosis of patients undergoing transrectal ultrasound (TRUS)-guided prostate biopsy.

Age group (years)	Number of patients	Number of CNB specimens (%)	Benign (BPH)	Histological diagnosis		
				Inflammation	HGPIN	Carcinoma
50–54	6	36 (10.2)	11	12	1	12
55–59	5	30 (8.5)	18	6	2	4
60–64	13	78 (22)	37	30	4	7
65–69	15	90 (25.4)	38	33	1	18
70–74	13	78 (22)	28	27	3	20
75–79	3	18 (5.1)	6	11	1	0
80–84	4	24 (6.8)	11	9	0	4
Total	59	354	149 (42.1)	128 (36.2)	12 (3.3)	65 (18.4)

Values in ( ) indicate percentages; CNB: core needle biopsy; BPH: benign prostatic hyperplasia; HGPIN: high-grade prostate intraepithelial neoplasia.

Table 2 Correlation of serum PSA levels with the histological diagnosis.

Serum PSA (ng/ml)	Number of patients	Histological diagnosis			
		Benign (BPH)	Inflammation	HGPIN	Carcinoma
0.2 to <4.0	4	1	1	1	1
4.0 to <10.0	21	3	11	5	2
10 to <20	13	1	7	0	5
≥20	9	1	1	0	7
Not available	12	2	6	1	3
Total	59	8 (13.6)	26 (44.1)	7 (11.8)	18 (30.5)

Values in ( ) indicate percentages; BPH: benign prostatic hyperplasia; HGPIN: high-grade prostate intraepithelial neoplasia; PSA: prostate specific antigen.

Table 3 Correlation of TIC with histological diagnosis.

TIC	Number of CNB specimens (%)	Histological diagnosis			
		Benign	Inflammation	HGPIN	Carcinoma
Benign	249 (70.3)	132 [53] (88.6)	105 [42.2] (82.0)	9 [3.6] (75)	3 [1.2] (4.6)
Atypical cytology	47 (13.3)	7 [14.8] (4.7)	17 [36.2] (13.3)	3 [6.4] (25)	20 [42.6] (30.8)
Carcinoma	40 (11.3)	–	–	–	40 [100] (61.5)
Unsatisfactory	18 (5.1)	10 [55.6] (6.7)	6 [33.3] (4.7)	0	2 [11.1] (3.1)
Total	354	149 (42.1)	128 (36.2)	12 (3.3)	65 (18.4)

TIC: touch imprint cytology; CNB: core needle biopsy; HGPIN: high-grade prostate intraepithelial neoplasia; [ ] % within TIC; ( ) % within histological diagnosis.

was observed between the serum PSA levels and the histological diagnosis.

Out of 35 patients with no lesion on TRUS, 24 cases were found to be benign on CNB and 21 on TIC, while CNB revealed carcinoma/high-grade prostate intraepithelial neoplasia (HGPIN) in 4 out of 8 patients with a suspicious lesion on TRUS. TIC was abnormal in 6 of these 8 patients. Benign TRUS findings were seen in 16 patients, but CNB and TIC revealed carcinoma/HGPIN in 10 of them. Thus, TRUS findings were not found to be a good indicator for the detection of malignancy.

Of the 354 touch imprints taken from 59 patients, 249 (70.3%) were diagnosed as benign, 47 (13.3%) as atypical, 40 (11.3%) as malignant and 18 (5.1%) as unsatisfactory. The 354 CNB specimens showed benign features in 149 (42.1%), prostatitis in 128 (36.2%), HGPIN in 12 (3.3%) and carcinoma in 65 (18.4%). The correlation of TIC with the histological diagnosis is shown in Table 3. In all the 40 cases where TIC had revealed carcinoma, malignancy was confirmed. Of the 47 cases with atypical cytology on TIC, 20 (42.6%) were found to be carcinoma and 3 (6.4%) were found to be HGPIN, while 7 (14.8%) were benign cases. Prostatitis was found in 17 (36.2%). Out of the 249 cases shown to be benign on TIC, HGPIN was reported in 9 (3.6%) and carcinoma in 3 (1.2%).

In this study, TIC was found to have a sensitivity of 84% and a specificity of 90.8% with positive and negative predictive values of 72.4% and 95.2%, respectively. However, when atypical cytology on TIC and HGPIN on CNB were excluded, TIC was found to have a sensitivity of 93% and a specificity of 100% with positive and negative predictive values of 100% and 98.8%, respectively. A strong correlation was seen between TIC and CNB ($p < 0.001$).

Discussion

The systematic sextant biopsy scheme recommended by Hodge et al. has significantly improved detection of prostate carcinoma [10]. For a higher prostate cancer detection rate, it is recommended to take 10–12 core prostate biopsy specimens. However, as a number of studies have revealed a 20–40% false negative rate, a repeat biopsy is suggested in cases with a negative biopsy result [11]. Several authors have tried to augment the positive biopsy rate by applying TIC in addition to CNB [6,8,9].

TIC is extremely helpful when evaluating malignancies, and it is increasingly being used in the evaluation of sentinel lymph node biopsies in cases of breast carcinoma [12]. When used as an adjunct to CNB in breast cancer cases, TIC has been found to improve diagnostic accuracy [13–15]. But TIC has also been helpful in the diagnosis of gastrointestinal, lung, lymph node and bone marrow tumors [8,16]. TIC in combination with CNB is cost effective and does not add any burden to the patient. The procedure simply requires applying the tissue sample on a glass slide. It not only helps to document adequacy of the specimen but also augments the diagnosis made on CNB. Tumor cell groups which are less cohesive may be selectively enriched in the tissue fluid covering the CNB, thus giving a unique source for cytological analysis [6]. The cytopathologist can immediately interpret the smears whereas the histological analysis of the CNB takes a minimum of 24 h [8].

In cases of carcinoma of the prostate TIC has helped to detect metastases in pelvic lymph nodes [17] and to provide an immediate diagnosis of prostate cancer [9]. TIC has also been found to be a useful adjunct to CNB, improving the accuracy of the diagnosis of prostate carcinoma [8]. The very few reports comparing the results of TIC with the diagnosis provided by CNB evaluation imply that TIC has a central role in the diagnosis and management of patients with prostate cancer [8,18]. In their study on 1210 CNB specimens taken from 121 patients under TRUS guidance, Aytac et al. reported a sensitivity, specificity, positive predictive value and negative predictive value of 100%, 98%, 90.2% and 100%, respectively [8]. However, in our study, when excluding atypical cytology on TIC and HGPIN on CNB, the sensitivity, specificity, positive predictive value and negative predictive value were 93%, 100%, 100% and 98.8%, respectively. In 24 cases showing atypical cytology on TIC, CNB showed benign features in 7 and prostatitis in 17. It is well known that inflammation can produce moderate to severe atypia of

the prostatic glands. Cancer was confirmed in all cases that were positive for malignancy on TIC.

In 10 out of 20 false-positive cases, Aytac et al. found that reactive atypia due to dense neutrophil infiltration caused the over diagnosis, while in the remaining 10 cases they failed to detect cancer in the CNB in spite of deep sectioning [8]. Lane et al. [19] demonstrated the necessity of cutting at least three levels of the prostate biopsy cylinder. In their study, sampling the cylinder at only one level missed an average of 23.4% of the total biopsy length, while sampling the tissue at three levels only missed an average of 7%.

In our study, 12 cases were found to be benign on TIC, whereas on CNB 9 of them turned out to be HGPIN and 3 carcinomas. The possible reasons for this discrepancy could be necrosis or very scanty tumor cells as is expected in cases of HGPIN.

In conclusion, our study reinforces that TIC is a reliable, easy method for the evaluation of prostate carcinoma in conjunction with PSA level assessment and TRUS-guided CNB.

Conflicts of interests

The authors declare there are no conflicts of interests.

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