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RESEARCH ARTICLE

Evaluation of CK903 and P40 in distinguishing questionable prostatic lesions

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ABSTRACT

Background: Prostatic carcinoma is considered the 2nd cause of death of cancers; the first is the lung cancer. Many pitfalls in the diagnosis of adenocarcinoma in cases of small foci of atypical glandular proliferations and high grade PIN. Immunohistochemistry play an important role in differentiating those lesions by staining basal cells. Basal cells recognition is extremely helpful in excluding a diagnosis of prostatic carcinoma. **Aim:** **Aim:** This study aimed to compare the expression of CK903 and P40 by benign and malignant prostatic lesions as well as their sensitivity and specificity as biomarkers to differentiate between benign and malignant glands. **Results:** CK903 showed cytoplasmic staining of the basal cells in all cases of benign prostatic hyperplasia, six out of seven HGPIN cases and only one case of prostatic adenocarcinoma. P40 showed nuclear staining of the basal cells in all cases of benign prostatic hyperplasia and HGPIN while all adenocarcinoma cases were negative to P40 immunostaining. P40 showed higher specificity, sensitivity and diagnostic accuracy than Ck903. **Conclusion**: P40 can be a reliable basal cell marker in questionable foci of prostatic biopsy specimens. CK 903 is better used in combination with other basal cell markers for more accurate diagnosis.

Keywords: Blo BPH, HGPIN, Prostatic adenocarcinoma, Ck903, P40

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INTRODUCTION

Prostatic carcinoma is the second common cause of cancer-related morbidity and mortality in men after lung cancer, and in several developed countries it is the commonest non skin cancer (Ceder et al., 2017). Prostatic carcinoma usually affects men over 50 years old. The incidence rises from 20% in men in their fifties to about 70% in men between the ages of 70 and 80 (Kalantari et al., 2014).

Immunohistochemistry is very essential in the diagnosis of prostate carcinoma. Specifically, in prostatic needle biopsies presenting with few atypical glandular proliferations whereas minute atypical foci may increase the doubt for malignancy, so the problem with needle biopsy seems not only from the small quantity of tissue offered for histopathological examination, but also from the point that only a few malignant glands or many benign mimics of cancer could be present (Molinie´ et al., 2004). So, basal cells recognition is extremely helpful in excluding a diagnosis of prostatic carcinoma.

It is in these cases that pathologists want a specific marker to distinguish benign from malignant glands. The existence of a basal cell layer in prostatic glands is a must to be called benign (Brustmann, 2015). On the other hand, studies have shown that some adenocarcinomas show basal cell layer at least partially by p63 and CK 903 staining (Kalantari et al., 2014).

CK903 (34betaE12) is a high-molecular-weight cytokeratin. It is a cytoplasmic marker that

marks intermediate cytokeratin filaments in glandular basal cells and is specific for basal cells in the prostate. CK903 is the time-honored basal cell marker used since 1985 (Fadel, 2004). However, CK903 immunoexpression differ among benign glandular proliferation and its staining pattern may not be circumferential. Even though CK903 was the first prostatic marker offered in the differential diagnosis between cancer and atypical benign glands, now most laboratories do not depend on it alone but mostly used together with the more specific prostate cancer marker alpha-methylacyl coenzyme racemase (AMACR) or with other basal cell–associated markers (Paner et al., 2008). Although the tumor cells may not show CK 903 immunoexpession, diffuse p63 positivity may unclear the loss of HMWCK when using a multiple stain (comprising antibodies against p63, racemase, and high-molecular-weight keratin) therefore making a diagnostic difficulty (Uchida et al., 201).

P63 is the most famous basal cell marker of stratified epithelia. It consists of numerous isoforms. They arranged into two main groups: TAp63 and DNp63. TAp63, is a full-length protein entertaining an N-terminal transactivation domain (TA), and its isoform DNp63, which features a transcriptionally inactive DN domain (Crum et al., 2010). Most laboratories distinguish p63 protein using the monoclonal antibody 4A4, that reacts with a core domain shared by both isoforms. On the contrary, the DNp63 isoform- specific DN domain is identified exclusively by the antibody p40 (Bishop et al., 201) .

P40 is the chief p63 transcript in squamous lung cancers and in basal cells of prostatic acini and carcinomas of other sites. Recently, p40 expression in prostatic basal cells is as dependable as p63 in most cases. In addition, abnormal p40 immunostaining by tumor cells is hardly observed than with p63 staining (Sailer et al., 2013). Sailer et al., 2013 compared the commonly used p63 clone, 4A4, with the p40 polyclonal antibody in a semi quantitative method, by immunostaining done on 640 malignant and normal prostate tissues. They reported identical staining pattern of normal tissue for p40 and p63. However, they found significant differences in the staining pattern of carcinomas: as 1.4 % of the nuclei were p63 positive versus only 0.6% for p40. So they reached a conclusion that p40 is as reliable in the diagnosis as p63 and highlighted the higher specificity of p40 in displaying less than half the false positive staining of aberrant cells

Thus, the diagnostic difficulty encountered with the rare p63-positive prostate carcinomas cases can be managed by a basal cell marker with a higher specificity. As the significance of p40 in the diagnosis of prostatic carcinoma is uncertain, we investigate its diagnostic value as a basal cell marker in direct comparison to CK903.

MATERIALS AND METHODS

Materials

The materials of this study included 45 specimens from prostatic tissue. The specimens were divided into of 3 groups as follows. Group 1 represented cases of benign prostatic hyperplasia (20 cases). Group 2 represented cases of HGPIN (7 cases). Group 3 represented cases of prostatic adenocarcinoma (18 cases). All cases were collected from archive of pathology department, Tanta University as paraffin embedded blocks, and were subjected to hematoxylin and eosin staining and histopathological re-evaluation by 3 different pathologists.

Immunohistochemistry staining

It was performed on 4 mic-thick sections using immune-peroxidase method. Sections were incubated with mouse monoclonal antibody of p40 (Catalog Number: ACI 3066 A, C Description: 0.1, 1.0 mL, conc., Dilution: 1:100. BIOCARE MEDICAL) and CK903 (Cytokeratin HMW [34βE12]) (Catalog Number: CM 127 A, C, Description: 0.1, 1.0 mL, conc. Dilution: 1:100 (BIOCARE MEDICAL). After deparaffinization and hydration in graded alcohol, the initial step binds the primary antibody to its specific epitope, a secondary antibody added to bind to the primary antibody. An enzyme-labeled polymer is then added to bind to the secondary antibody. Lung squamous cell carcinoma was used as a positive tissue control for p40. Skin, prostate or squamous cell carcinoma Positive Tissue Control for ck903.

Table 1. Clinico-pathological parameters of the studied cases

Variables		BPH (N=20)	HGPIN (N=7)	Adenocarcinoma (N=18)
Age (mean)		(45 – 70) mean 54	(50-80) mean 68.7	(50-82) mean 61.8
Operation	TURP	9(45%)	4(57.1%)	10(55.5%)
	TRUS	6(30%)	2(28.6%)	3(16.7%)
	OPEN	5(25%)	1(18.4%)	5(27.8%)
Gleason score	4			2(11.1%)
	6			3(16.7%)
	7			4(22.2%)
	8			5(27.8%)
	9			3(16.7%)
	10			1(6.5%)
PSA (mean)		(1.5 - 12 ng/ml) mean 4.96 ng/ml	(5-15 ng/ml) mean 10.7 ng/ml	(7-75 ng/ml) mean 44.4 ng/ml

Table 2. Immunohistochemical results of the studied cases

Immunohistochemical results		BPH (N=20)	HGPIN (N=7)	Adenocarcinoma (N=18)	*p*-value
CK903	-ve	0(0.0%)	1(14.3%)	17 (94.4%)	0.001*
	+ve	20(100%)	6 (85.7%	1(5.5%)	
P40	-ve	0(0.0%)	0(0.0%)	18(100%)	0.001*
	+ve	20(100%)	7(100%)	0(0.0%)	

Table 3. Sensitivity and specificity of CK903 results

Diagnosis/ck903	Sensitivity	Specificity	PPV	NPV	Accuracy
Malignant lesions vs. Benign prostatic lesions	96%	90%	85%	96%	93%
Prostatic Adenocarcinoma vs. HGPIN	90%	87%	79%	95%	89%

Table 4. Sensitivity and specificity of P40 results

Diagnosis/p40	Sensitivity	Specificity	PPV	NPV	Accuracy
Malignant lesions vs. Benign prostatic lesions	100%	93%	89%	100%	91%
Prostatic Adenocarcinoma vs. HGPIN	100%	100%	100%	100%	100%

Immunohistochemical interpretation

P40 and Ck 903 cases were considered positive if brown nuclear staining in 5% or more of the tumor cells. Cases with staining less than 5% or cases with no areas of positive staining were considered as negative (Abrahams et al., 2002 and Bishop et al., 2012).

Statistical analysis

Results were tabulated and statistical analysis was performed with Statistical Package for Social Science (SPSS version 19). The difference between two groups was statistically analyzed using Kruskal Wallis test, 2-tailed Fisher exact test or the $\chi 2$ test with Yates continuity correction. A P value of less than 0.05 was considered statistically significant.

RESULTS

Clinicopathological results

This study included 45 specimens from prostate. Specimens were divided as follows (20 cases of benign prostatic hyperplasia, 7 cases of HGPIN and 18 cases of prostatic adenocarcinoma). The age of patients of BPH ranges from 45 to 70 years with a mean of 54. For HGPIN the age ranges from 50 to 80 with a mean of 68.7. For prostatic adenocarcinoma the age ranges from 50 to 82 with a mean of 61.8. Nine specimens of BPH were taken by TURP, six cases by TRUS and five cases were taken by open prostatectomy.

In HGPIN, 4 cases were taken by TURP, two cases by TRUS and only one case by open prostatectomy. For prostatic adenocarcinoma, ten cases were diagnosed by TURP biopsy, 3 cases by TRUS and five cases were diagnosed by open prostatectomy.

Among 20 cases of BPH, the total serum PSA ranged from 1.5 to 12 ng/mL with a mean of 4.96 ng/mL, while the PSA level in HGPIN ranged from 5 to 15 ng/ml with a mean of 10.7 ng/mL. Also the 18 cases of prostatic adenocarcinoma, the total serum PSA ranged from 7 to 75 ng/mL with a mean of 44.4 ng/mL.

The eighteen cases of adenocarcinoma were graded using Gleason grading system and scoring was divided as follows, 2 cases of score 4, 3 cases of score 6, 4 cases of score 7, 5 cases of score 8, 3 cases of score 9 and only one case of score 10.

Immunohistochemical results

CK903 (Cytokeratin HMW [34βE12]) was detected by cytoplasmic staining of the basal cells. All cases of benign prostatic hyperplasia showed CK903 positivity. Six out of seven cases of HGPIN showed CK903 immunostaining. On the other hand only one case of prostatic adenocarcinoma was positive and 17 cases were negative to CK903 (Fig 1-4) and (Table 2). P40 was detected by nuclear staining of the basal cells. All cases of benign prostatic hyperplasia and HGPIN showed P40 positivity. All adenocarcinoma cases were negative to P40 immunostaining. (Fig 5-8).

Statistical relations

CK903 (Cytokeratin HMW [34βE12]) immune-staining regards sensitive and specific marker and of high value in distinguishing prostatic adenocarcinoma from benign prostatic lesions and HGPIN. As all cases of BPH and 85.7% of HGPIN were positively stained, while 94.4 % of adenocarcinoma lesions showed negative immunostaining in basal cell distribution (Table 3). P40 immunostaining is considered highly sensitive and specific valuable marker in differentiating prostatic adenocarcinoma from BPH and HGPIN cases. All cases of BPH and HGPIN were positively stained, while all cases of prostatic adenocarcinoma showed negative P40 immunostaining in the basal cells (Table 4).

DISCUSSION

In summary, miR-155 expression was difficult, especially when faced with the challenge of discriminating between prostatic intraepithelial neoplasia and well differentiated carcinoma in small tissue samples. Basal cell layer is absent in invasive prostatic carcinomas. Therefore, complete absence of immune staining in basal cell markers is indicative of a malignant interpretation. With H&E histopathological examination, basal cells may be mistaken for prostatic stromal cells adjacent to glandular-basement membrane, the vascular endothelial cells closely situated to the acini or tangentially sectioned tumor cells. This unrelenting challenge encountered especially in limited-volume prostatic carcinoma samples increased the use of ancillary immunohisto-chemistry for highlighting basal cells of benign prostatic glands or glands with PIN (Gladell et al., 2008).

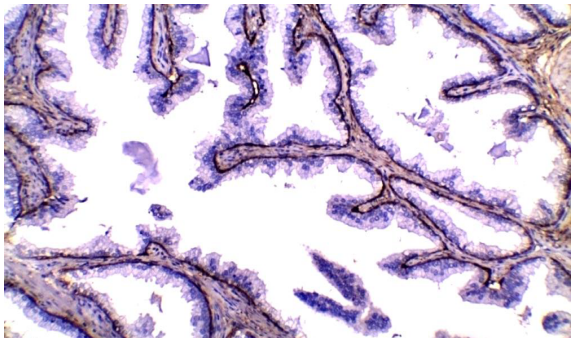

Figure 1. A case of BPH showing cytoplasmic staining of CK903 in the basal cells completely encircling the hyperplastic glands (Immunohistochemistry X200).

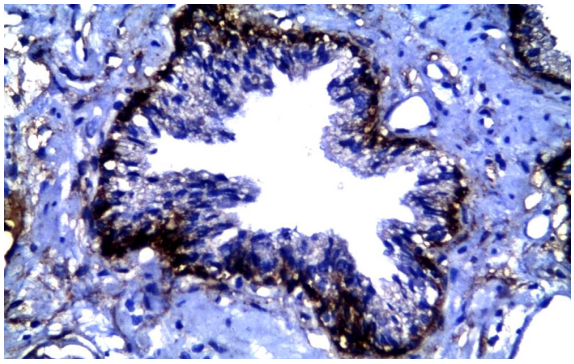

Figure 2. A case of HGPIN (tufting pattern) showing positive cytoplasmic expression of CK903 in basal cells surrounding involved glands (Immunohistochemistry X 400).

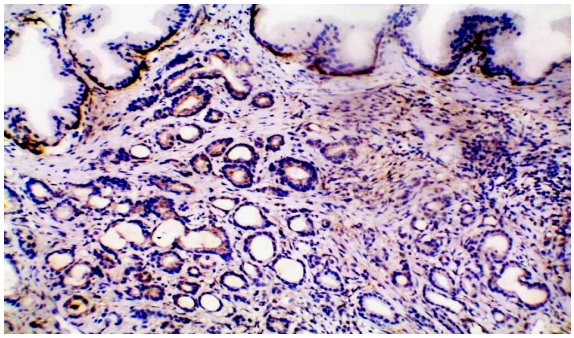

Figure 3. A case of prostatic adenocarcinoma Gleason grade 3 ((a component of score 6) showing positive expression of CK903 in the basal cells of some neoplastic glands and positive cytoplasmic staining in the basal cells of the adjacent non-neoplastic glands (Immunohistochemistry X 200).

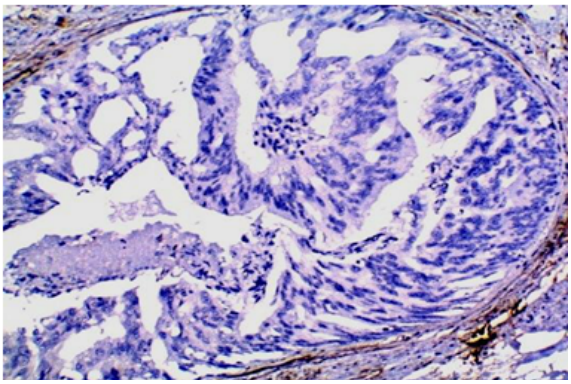

Figure 4. A case of ductal adenocarcinoma Gleason grade 4 (a component of score 8) showing negative staining of CK903 in the basal cells of neoplastic glands (Immunohistochemistry X 400).

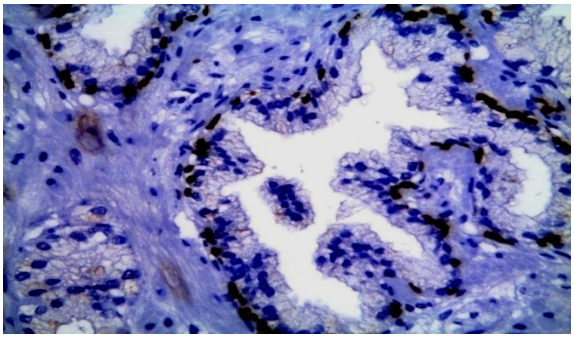

Figure 5. A case of BPH showing nuclear expression of P40 in the basal cells encircling the hyperplastic glands (Immunohistochemistry X 400)

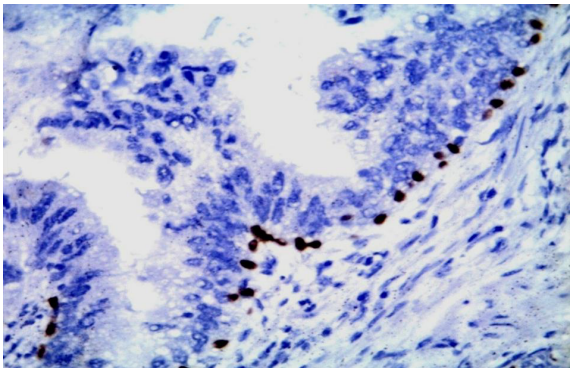

Figure 6. A case of HGPIN (micropapillary pattern) showing positive nuclear expression of P40 in basal cells surrounding the involved glands (Immunohistochemistry X 400)

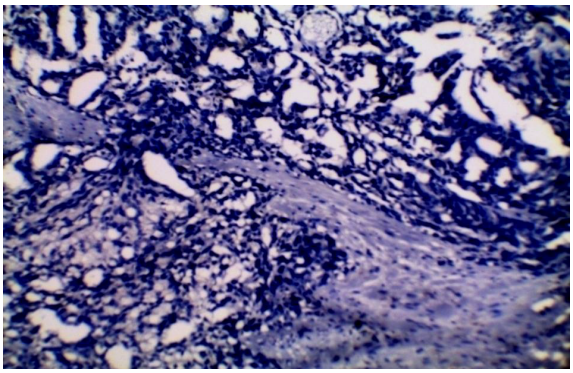

Figure 7. A case of prostatic adenocarcinoma Gleason grade 4 (a component of score 9) showing negative expression of P40 in the basal cells of neoplastic glands (Immunohistochemistry X200).

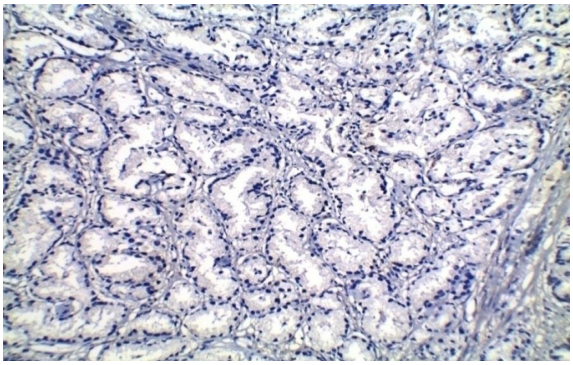

Figure 8. A case of prostatic adenocarcinoma Gleason grade 2 (a component of score 4) showing negative P40 immunostaining in the basal cells of neoplastic glands (Immunohistochemistry X 200).

This unrelenting challenge encountered especially in limited-volume prostatic carcinoma samples increased the use of ancillary immunohistochemistry for highlighting basal cells of benign prostatic glands or glands with PIN (Gladell et al., 2008).

Ck903 is one of the basal cell markers used in the identification of benign glands by positive staining. However, this doesn't rule out malignancy. Previous studies stated that the staining pattern of CK903 in prostatic biopsies was focal, patchy and occasionally failed to stain clearly benign glands, making the negative staining in the questionable glands unreliable (Wojno & Epstein, 1995, Googe et al., 1997 and Abrahams et al., 2002).

In our study, upon investigating effectiveness of CK903 in the evaluation of prostatic biopsies, we found high value of Ck903 in distinguishing prostatic adenocarcinoma from benign prostatic lesions and HGPIN with high specificity, sensitivity and diagnostic accuracy (96%, 90% and 93% respectively for benign vs prostatic adenocarcinoma) and (90%, 97% and 89% respectively in HGPIN vs adenocarcinoma). Ck903 showed cytoplasmic staining of the basal cells. While all cases of benign prostatic hyperplasia were positive, only one case of HGPIN was negative for Ck903. On the other hand only one case of prostatic adenocarcinoma was positive to CK903.

Similarly, Kalantari et al. (2014), noticed positive expression of CK903 in all cases of BPH and HGPIN. Two out of 40 cases of adenocarcinoma were excluded because of small limited foci; the remaining 38 cases were CK903 negative with high specificity and sensitivity of Ck903 in true adenocarcinoma and benign lesions.

In 2015, Brustmann found that benign prostatic specimens showed partial staining in 42%, diffuse staining in 46% and irregular reactivity was noted in one case only (2%). Acinar proliferations negative were termed atypical small acinar proliferations (ASAP). Out of six PIN lesions two cases showed partial, three cases showed diffuse reactivity and one case was stained irregular. All cases diagnosed as prostate carcinomas had no evidence of basal cell staining for Ck903. This also was approved by Hameed & Humphrey (2006) who stated that Ck903 can be very useful for demonstrating basal cells as their presence argues against a diagnosis of invasive carcinoma.

On the other hand, many other studies suggested the use of Ck 903 in combination with other basal cell markers for more accurate diagnosis of prostatic lesions. Abrahams et al., stated that the use of high molecular weight anti-keratin antibodies has been shown to decrease the number of equivocal diagnoses. They noticed positive focal and patchy Ck903 expression in all benign prostatic specimens with variable degrees except in four cases (13%), CK903 didn't stain any tissue on the slide and repeated staining showed similar results. The staining pattern was focal in a number of biopsies with the sensitivity of K903 being 40%. No adenocarcinoma cells demonstrated CK903 positivity (Abrahams et al., 2002).

Gladell et al. (2008), as well, noted that cytoplasmic basal cell Ck903 expression varied between glands of a benign glandular proliferation and the staining pattern may not be circumferential. Oliai et al (2002) also made it clear that the diagnosis of prostatic carcinoma in the face of positive Ck903 staining of basal cells should be made with extreme caution.

These differences encountered in the results of CK903 staining may be attributed to the extended formalin fixation of prostatic specimens which may affect Ck903 antigenicity, loss of suspicious glands on sections used for staining, too few glands to be reliable, technical problems, limited number of positive glands in a small focus and cautery artefact.

P40, a newly developed monoclonal antibody we intended to evaluate its usefulness in the diagnosis of prostatic specimens in comparison to Ck903. In the present study, we found P40 to be a more strongly valuable marker in differentiating prostatic adenocarcinoma from BPH and HGPIN cases as all cases of BPH and HGPIN were positively stained, while all cases of prostatic adenocarcinoma showed negative P40 immunostaining in the basal cells. In comparison with Ck903, P40 had higher specificity, sensitivity and diagnostic accuracy in differentiating benign prostatic lesion and HGPIN from prostatic adenocarcinoma.

Brustmann (2015) reached similar results as benign prostatic glands showed strong and diffuse basal cell staining as well as all PIN cases. All cases signed out as adenocarcinomas were negative basal cell staining. Immunostaining results of benign glandular proliferations and prostate carcinoma differed significantly (P < 0.0001). In a similar way, Tacha et al (2014) observed nuclear staining of P40 in prostatic basal cells in benign prostate and PIN glands, while none was observed in any cases of prostate carcinoma. Moreover, Zhang et al (2014) detected P40 positivity in 95.7% of BPH cases with no expression in prostatic carcinoma. This was also agreed by Uchida et al (2015) who found diffuse P40 positivity in 96% of benign cases and all conventional carcinomas were negative for p40.

More recently, a study by Kristiansen in 2018, suggested P40 as an alternative basal cell marker showing minimally lower rate of false-positive diagnosis of prostatic carcinomas. On the other hand, a study done by Sailer et al (2013), stated that P40 cannot be reliable for a diagnostic decision based on basal cell detection.

CONCLUSION

Basal cell markers can be helpful for improved differentiation between benign and malignant prostatic lesions. P40 is a high quality screening immunohistochemical antibody that can be employed diagnostically as a reliable basal cell marker in questionable foci of prostatic biopsy specimens. CK 903 is useful in the diagnosis of prostatic carcinoma but better used in combination with other basal cell markers as P40 for more accurate diagnosis. However, further validation and more comparative studies will be needed.

CONFLICT OF INTEREST

There is no conflict of interest.

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EACR is an NGO society that was declared by the Ministry of Social Solidarity (Egypt) No. 1938 in 19/11/2014 based on the initiative of Prof. Mohamed Labib Salem, the current Chairman of EACR. EACR aims primarily to assist researchers, in particular young researchers in the field of cancer research through workshops, seminars and conferences. Its first international annual conference entitled "Anti-Cancer Drug Discovery" was successfully organized in April 2019 (http://acdd.tanta.edu.eg). Additionally, EACR aims to raise the awareness of the society about the importance of scientific research in the field of cancer research in prediction, early diagnosis and treatment of cancer. EACR is also keen to outreach the scientific community with periodicals and news on cancer research including peer-reviewed scientific journals for the publication of cutting-edge research. The official scientific journal of EACR is "International Journal of Cancer and biomedical Research (IJCBR: https://jcbr.journals.ekb.eg) was successfully issued in 2017 and has been sponsored by the Egyptian Knowledge Bank (EKB: www.ekb.eg).

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