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Original article

Significance of Sex Determining Region Y-Box Transcription Factor 4 (SOX4) Expression and Nuclear Morphometry in Endometrial Carcinoma

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Abstract:

Background: Endometrial carcinoma (EC) is the 6th most common cancer worldwide. SOX4 has been used as an immunohistochemical marker. Expression of SOX4 by cancer cells has been demonstrated in EC. Nuclear morphometry is an imaging technique that plays important roles in endometrial hyperplasia (EH) and EC. **Aim**: This work aimed to evaluate SOX4 expression and nuclear morphometry in EH and EC and the relation between its expression and different clinicopathological variables. **Material and method:** This is a selected retrospective study including 60 different cases of EC and EH. SOX4 immunostaining and nuclear morphometry were performed for all cases. **Results**: There was a highly significant statistical difference between SOX4 expression in studied cases according to type, FIGO grade, depth of myometrial invasion, LVSI (lymphovascular space invasion), T/B (Tumor/Border) configuration, desmoplasia, mitotic count, T, N, M components, TNM and FIGO stage (P<0.001, <0.001, <0.001, <0.001, <0.001 <0.001, <0.001, <0.001, =0.003, <0.001, <0.001 and <0.001 respectively) and highly significant statistical relation between MNA and clinicopathological parameters of studied cases. **Conclusion**: strong SOX4 expression was associated more with SEC (serous endometrial carcinoma), higher grade of EC, deeper myometrial invasion, LVSI, infiltrative tumor border, evidence of desmoplasia, higher mitotic count T, N, M components, TNM and FIGO stage. Nuclear morphometry is useful in diagnosis and differentiation of EC from premalignant lesions. SOX4 and Nuclear morphometry can be used together to diagnose and predict the outcome of EC.

Keywords: Endometrial hyperplasia; endometrial carcinoma; SOX4; nuclear morphometry.

Introduction

Endometrial carcinoma is one of the deadliest cancers in the world with an increasing incidence and disease-associated mortality. It is the 2nd most common gynaecological cancer and the 6th most common malignant tumour in females worldwide **(1)**. According to Egyptian National Cancer institute, it is third most common gynaecological cancer. It represents 22.83% of female genital system malignancy and 72.37% of primary uterine corpus malignancy in Egypt **(2).**

Endometrial carcinoma is a multifactorial disease. The risk factors are classified into non-modifiable and modifiable risk factors including age, race, early menarche, late menopause, hereditary syndromes unopposed excess oestrogen, Type II diabetes mellitus, oestrogen-producing ovarian tumours, lifestyle, and Alcohol **(3).**

According to the 5th edition WHO classification, endometrial hyperplasia (EH) is considered a precursor lesion of EC and classified according into hyperplasia without atypia and atypical endometrial hyperplasia (AEH)/ endometrioid intraepithelial neoplasia (EIN). EC is classified into several subtypes including endometrioid, serous, clear cell type, undifferentiated/dedifferentiated, mixed cell type and carcinosarcoma. Some subtypes have been added to the classification such as mesonephric-like adenocarcinoma and gastric (gastrointestinal-type) mucinous carcinoma **(4).**

Endometrioid carcinoma is classified into four groups according to TCGA molecular classification. They include ultra-mutated endometrial cancer with mutations in the exonuclease domain of DNA polymerase epsilon (POLE-mutated), tumours with microsatellite instability (MSI) (hypermutated), tumours harbour TP53 mutations with high copy number alterations and tumours with no specific molecular profile (NSMP) **(5)**

Sex Determining Region Y-Box transcription factor 4 (SOX4) belongs to C subgroup of SOX family. It has a role in development, cell differentiation and tumorigenesis. It is overexpressed in several human cancers, including breast, prostate, bladder, and lung cancers **(6),** but its role in EC is not elucidated yet.

Nuclear morphometry is a quantitative objective and reproducible results that could be a useful supplement in diagnosis, prediction of prognosis and treatment planning for certain types of cancer using nuclear parameters including the mean and standard deviations (SD) of the nuclear area (MNA), longest (MLNA) and shortest (MSNA) nuclear axis **(7). However,** its role is not fully elucidated in endometrial lesions.

Aim of the work

This study aimed at conducting immunohistochemical evaluation of (SOX4) expression in EC and precursor lesions and its correlation with histopathological features. Also, assessing the role of nuclear morphometry and investigating the correlation of immunohistochemical and morphometric findings trying to assess their combined possible role in endometrial carcinoma.

Material and methods:

Study group:

This is a retrospective study including 60 cases of endometrial lesions as follow: 37 cases of endometrioid endometrial carcinoma (EEC), 7 cases of serous endometrial carcinoma (SEC) and sixteen cases of endometrial hyperplasia of which 9 cases of AEH and 7 cases EH without atypia.

The material included archival formalin fixed paraffin embedded blocks processed during the years 2010 to 2015 as well as stained Hematoxylin and Eosin (H&E) slides for review. The blocks were collected from Department of Pathology and Early Cancer Detection Unit; Faculty of Medicine, Benha University, Egypt.

Clinicopathological data were collected from the files of patients. Being a retrospective study, a written informed consent was not needed.

The cases were selected according to the availability of paraffin blocks and clinical records. The study was approved by the Research Ethical committee of Faculty of Medicine, Benha University, Egypt (MSC 26/1/2022).

Histopathological examination:

Re-evaluation of sections from all selected cases was performed. The cases were re-evaluated for their type according to fifth edition of the WHO Classification of tumors of the uterine corpus **(4)**, graded according to FIGO grading and staged according to FIGO and TNM staging systems **(8 and 9).**

Evaluation of mitosis count was carried out using Leica ICC50 HD light microscope with wide angle (field diameter: 0.636 mm2; Leica ICC50 HD, Germany). The mitotic count was calculated as total number of figures counted in per 2 mm^2 **(10).** T/B (Tumor/Border) configuration was categorized as infiltrative or pushing tumor border **(11and 12)** and presence of surrounding desmoplastic stromal reaction was also recorded **(13).**

Immunohistochemical studies:

Slides were stained according to manufacturer's instructions with SOX4 rabbit polyclonal antibody (**ABclonal, USA**) at a dilution 1:50 at 4°C overnight. Immunodetection was carried out using a standard labelled streptavidin-biotin system (**Genemed, CA 94080, USA, South San Francisco**). Antigen retrieval was done by using solution of 10 mmol/L of Tris/EDTA (pH 9.0) and heating for 3 cycles, 10 minutes each in the microwave. Freshly prepared chromogen diaminobenzene (DAB, Envision TM Flex /HRP-Dako, REF K 8000) was used. Negative (Phosphate- buffered Saline) and positive control (breast and colonic cancer tissue) were enclosed in each run **(14 and 15).**

Interpretation of SOX4 expression:

Positivity was considered as brownish homogenous nuclear staining of tumour cells **(16).** The expression level of SOX4 was defined by the sum of the staining-intensity and staining-extent scores as follows: "0" (negative, score of 0), "1" (weakly positive, score of 1-2), "2" (positive, score of 3-4), and "3" (strongly positive, score of 5-6) **(17).**

Nuclear morphometry is performed as follow:

Morphometric analysis was carried out by using Olympus® software imaging system (Analysis® LifeScience Series, Olympus Corporation, Hamburg, Germany) **(18)**. The morphometric analysis was carried out on H&E-stained slides to measure the nuclear parameters blindly regarding the histopathologic diagnosis **(7)**. Approximately 50 nuclei were examined in the most representative areas per slide with non-overlapping nuclei and their contours were traced manually using 40 x objectives to measure mean nuclear area **(19).**

Statistical analysis

Data analysis was performed by SPSS software, version ٢٥ (SPSS Inc., PASW statistics for windows version ٢٥. Chicago: SPSS Inc.). Data was presented and suitable analysis was done according to the

type of data obtained for each parameter. Mean, standard deviation (± SD), median, standard error (±SE), and range were used for description of numerical data. Frequency and percentage were used for description of non-numerical data. The significance of the obtained results (p value) was considered at the (≤0.05) level.

Results

Clinicopathological results:

The age of 60 studied cases ranged from 42-75 years with the mean age was 57.33±10.56. endometrial carcinoma cases included 54.5 % of the studied patients < 55 years old while 45.5% were ≥55 years old (Mean±SD 55±7.21). The characteristics of the patients and tumors are listed in **(Table 1)**

Immunohistochemical Results:

SOX4 expression in studied groups:

For EH cases, all cases were SOX4 negative, 32 % of EC cases were of score 0, 11% were of score 1, 34% were of score 2 and 23% were of score 3. There was a statistically significant difference of SOX4 expression in studied groups (P<0.001).

Relation between SOX4 expression score and different clinicopathological parameters of studied EC cases:

There was a statistically significant relation between SOX4 expression score and; histopathological type, FIGO grade, depth of myometrial invasion, LVSI, T/B configuration, Evidence of desmoplasia, mitotic count, T, N, M components, TNM and FIGO stage **(Table 1 & Figure 1)**

Nuclear Morphometry results:

Relation between MNA results in EH studied and EC cases:

The MNA among AEH cases was higher than EH without atypia cases (73.17±1.68 versus 60.37±2.29 µm2) with statistically significant difference between them (P<0.001). The MNA among EH cases were lower than EC cases (67.57±6.83 versus 134.93±46.31 µm2) with a significant difference of MNA between EH and EC cases (P<0.001).

Relation between morphometric results and the clinicopathological parameters of EC:

There was a statistically significant relation between MNA and Histopathological type, FIGO grade, depth of myometrial invasion, LVSI, T/B configuration, desmoplasia, mitotic count, T, N, M components, TNM and FIGO stage (Table 1& Figure 2).

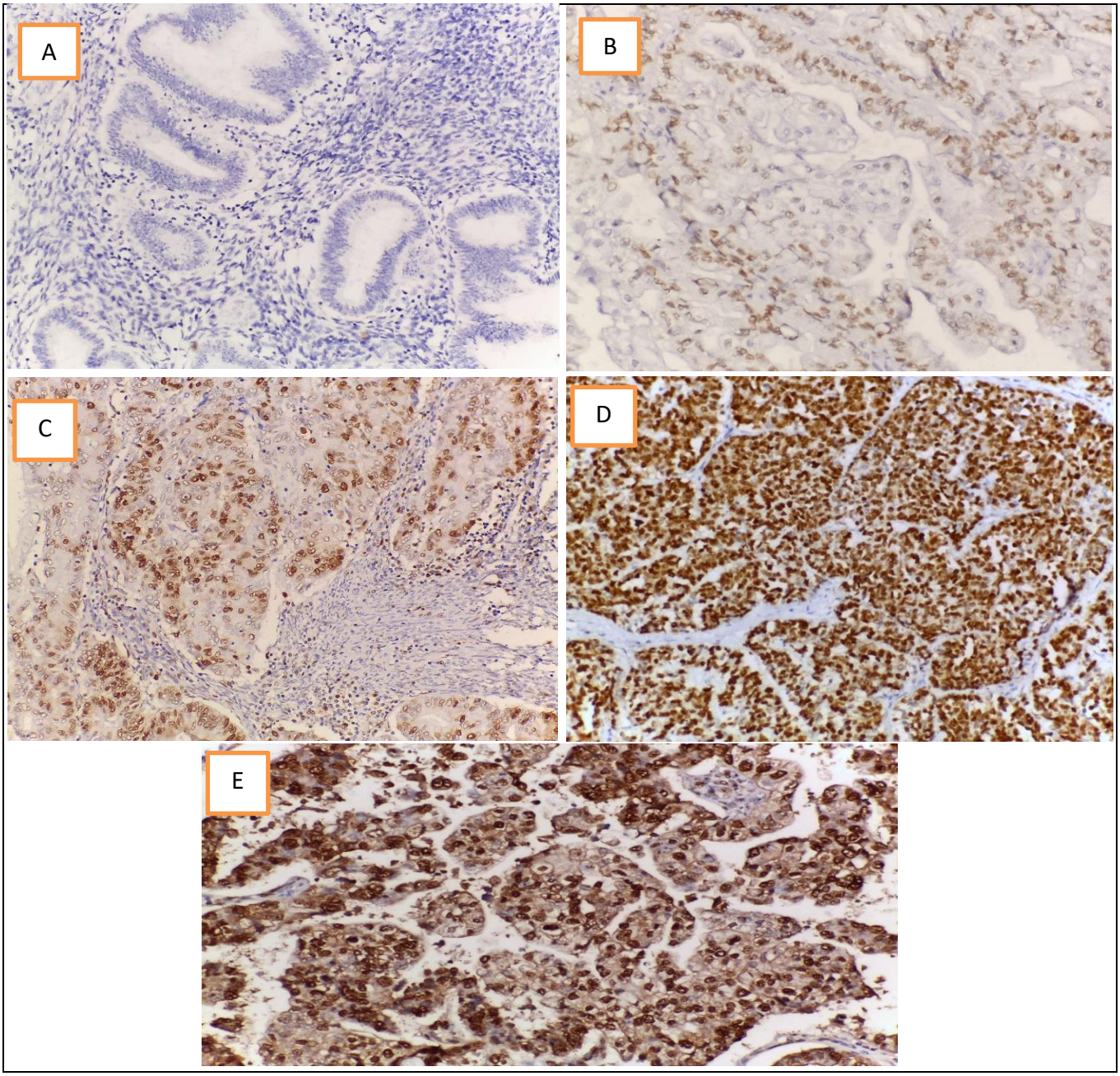

Figure (1): Immunohistochemical expression of SOX4 in studied cases: (A): EH showing negative expression of SOX4, score 0. (B) EEC, FIGO grade I, positive for SOX4 with score 1. (C): EEC, FIGO grade II positive for SOX4 with score 2. (D): EEC, FIGO grade III, positive for SOX4 with score 3. (E): SEC, positive for SOX4 with score 3. (Streptavidin-biotin / DAB, x200)

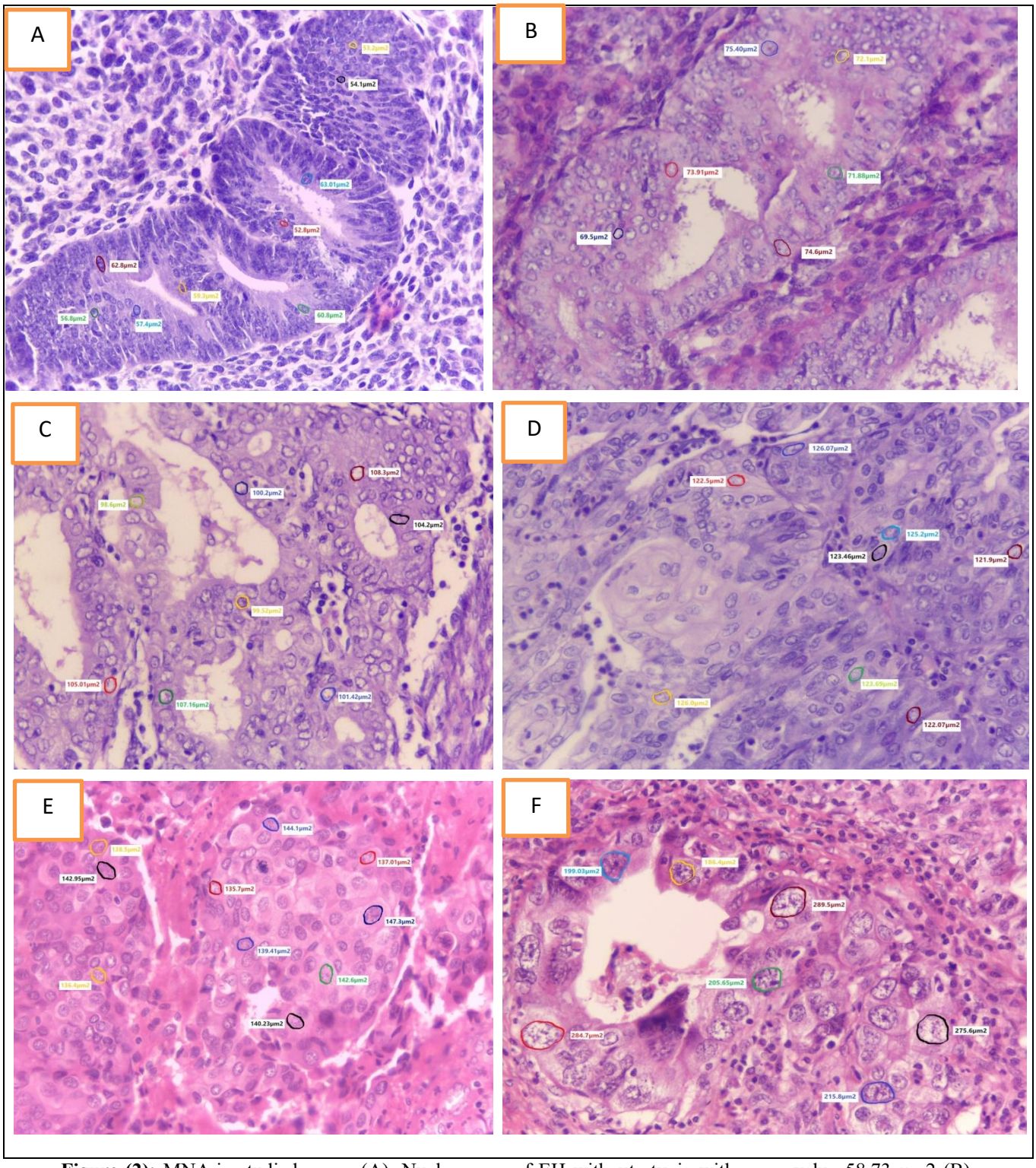

Figure (2): MNA in studied cases: (A): Nuclear area of EH without atypia with mean value 58.73 µm2 (B): Nuclear area of AEH with mean value 72.58µm2 (C): Nuclear area of EEC, FIGO grade I with mean value 103.05µm2 (D): Nuclear area of EEC, FIGO grade II with mean value 123.86 µm2 (E): Nuclear area of EEC, FIGO grade III with mean value 140.27 µm2 (F): Nuclear area of SEC, with mean value 236.66µm2 (H&E x400 with 100 zooming).

Table (1): Relation between SOX4 expression score, MNA and different clinicopathological parameters of studied EC cases:

Clinicopathological parameters	SOX4 score					p value	MNA (µm2)	p value
	Total n=44(%)	0 n=14(%)	1 n=5(%)	2 n=15(%)	3 n=10(%)			
Age/years								
<55	24(55)	10(42)	2(8)	9(37.5)	3(12.5)		121.64±32.72	
≥55	20(45)	4(20)	3(15)	6(30)	7(35)	P=0.200	147.52±57.03	P=0.07
Histopathological type								
EEC	37(84)	14(38)	5(13.5)	15(40.5)	3(8)	P<0.001*	116.47±13.89	P<0.001*
SEC	7(16)	0	0	0	7(100)		232.51±31.64	
FIGO grade								
I	14(32)	9(64)	5(36)	0	0	P<0.001*	100.86±5.07	P<0.001*
II	20(45)	5(٢٥)	0	15(75)	0		120.74±5.08	
III	10(23)	0	0	0	10(100)		204.29±52.21	
Depth of myometrial invasion								
<50%	23(52)	13(56)	5(٢٢)	5(٢٢)	0	P<0.001*	107.24±9.57	P<0.001*
≥50%	21(48)	1(4)	0	10(48)	10(48)		162.075±4.18	
LVSI								
Present	13(30)	0	0	4(٣١)	9(٦٩)	P<0.001*	184.07±59.19	P<0.001*
Absent	31(70)	14(45)	5(16)	11(36)	1(3)		112.16±11.99	
T/B configuration								
Infiltrative	24(55)	3(١٢.٥)	0	11(٤٦)	10(٤١.٥)	P<0.001*	157.49±53.82	P<0.001*
Pushing	20(45)	11(55)	5(25)	٤(20)	٠		107.02±10.09	
Desmoplasia								
Present	30(68)	4(١٣)	2(6.5)	14(٤٧)	10(٣٣.٥)	P<0.001*	146.98±51.02	P=0.004*
Absent	14(32)	10(71.5)	٣(21.5)	١(7)	٠		104.31±8.12	
Mitotic count								
≥10/2 mm2	15(34)	٠	0	5(٣٣)	10(٦٧)	P<0.001*	177.19±57.74	P<0.001*
<10/2 mm2	29(66)	١٤(48)	5(17)	10(35)	0		110.76±11.06	
T component								
T1	9(20)	8(٨٩)	1(١١)	0	0	P<0.001*	98.71±3.85	P<0.001*
T2	13(30)	5(٣٨)	4(٣١)	4(٣١)	0		109.64±9.79	
T3	16(36)	1(٦)	0	11(٦٩)	4(٢٥)		123.40±5.65	
T4	6(14)	0	0	0	6(100)		198.27±53.53	
N component								
N0	33(75)	14(٤٢.٥)	5(١٥)	11(٣٣.٥)	3(٩)	P=0.003*	122.47±38.82	P=0.002*
N1	9(20)	0	0	4(٤٤.٥)	5(٥٥.٥)		153.49±48.79	
N2	2(5)	0	0	0	2(100)		223.53±51.26	
M component								
M0	37(84)	14(38)	5(13.5)	15(40.5)	3(8)	P<0.001*	114.66±12.87	P<0.001*
M1	7(16)	0	0	0	7(100)		232.51±31.63	
TNM stage group								
Group 1	9(21)	8(٨٩)	1(١١)	0	0	P<0.001*	98.71±3.85	P<0.001*
Group 2	12(27)	5(٤٢)	4(٣٣)	3(٢٥)	0		111.07±7.29	
Group 3	15(34)	1(٧)	0	12(٨٠)	2(١٣)		125.70±6.27	
Group 4	8(18)	0	0	0	8(100)		220.38±45.10	

FIGO stage								
I	9(21)	8(٨٩)	1(١١)	0	0	P<0.001*	98.71±3.85	P<0.001*
II	12(27)	5(٤٢)	4(٣٣)	3(٢٥)	0		111.07±7.29	
III	15(34)	1(٧)	0	12(٨٠)	2(١٣)		125.70±6.27	
IV	8(18)	0	0	0	8(100)		220.38±45.10	

MC: Monte Carlo test, t: Student, F: One Way ANOVA test, *statistically significant

Correlation between SOX4 expression score and nuclear morphometric results in studied EC cases:

A statistically significant positive correlation was detected between SOX4 and MNA (r=0.852) with P value <0.001.

Discussion:

The current study revealed a statistically significant difference in SOX4 expression being only expressed in tumor cells suggesting that SOX4 may have a role in development of EC. SOX4 acts as an oncogene in activation of several pathways as PI3K/Akt and WNT/β-catenin pathways, which play a significant role in development of EC **(20).**

This agreed with studies on EC, lung adenocarcinoma and oesophageal squamous cell carcinoma, revealing that SOX4 was overexpressed in these tumours compared to normal tissues, respectively (**21, 22, 23 and 24)**.

This result contradicted to study of EC reporting that SOX4 is overexpressed in EH cases suggesting that high expression of SOX4 may lead to cellular transformation of endometrial lining (**25)**. This could be explained by using different technique to evaluate the expression levels of SOX4 gene by RT-PCR.

In the present study, a statistically significant positive relation was found between SOX4 overexpression and the histopathological type of EC with more expression in SEC than EEC. This was compatible with previous studies reporting SOX4 overexpression in small cell lung cancer, triple negative breast cancer and EC, respectively (**26,27 and 28)**. This could be contributed to the role of SOX4 activation of TGF-β and PI3K/Akt pathways that induce tumor progression and aggressiveness.

This disagreed with a study on melanoma reporting higher SOX4 expression in less aggressive histological types **(29)**. This may be contributable to the effect of SOX4 on specific promoters controlling expression of miRNAs through downstream transcription factors as P53 might be an explanation.

In this work, SOX4 overexpression was significantly related to FIGO grade. This may be pursuant to the critical role of SOX4 in promoting tumour progression. In accordance with this finding, similar results were reported in studies on osteosarcoma, EC and hypopharyngeal carcinoma, respectively (**30, 31 and 32)**.

In contrast, A study on EC reported a higher SOX4 expression in G1 than G2/3 EC **(33)**. This may be because of adopting different techniques in their study by using PCR not immunohistochemistry.

Another statistically significant positive relation was reached, between SOX4 overexpression and depth of myometrial invasion of EC. This was referred to its ability to activate of TGF-β and the subsequent induction of numerous SOX4 target genes are involved in cancer cell

proliferation, survival, stemness, and EMT resulting in tumour invasion **(6)**. This agreed with studies on gastric carcinoma, EC, and oesophageal squamous cell carcinoma, respectively **(34, 35, 36 and 37)**

Despite of previous results, studies on skin and lung tumours, reported that SOX4 overexpression suppressed the invasion of melanoma and lung cancer **(38 and 39)**. This controversy could be due to the intrinsic differences in the biology of different tissue types or the ability of SOX4 to modulate the PUMA (p53 up-regulated modulator of apoptosis) transcription and expression, an inducer of apoptotic cell death, highlighting its role in tumour suppression **(40 and 41).**

The current study also revealed a significant positive relation between SOX4 overexpression and LVSI. These results could be explained by the acquisition of mesenchymal traits, enhanced cell migration and invasion on SOX4 overexpression **(42)**. This was consistent with studies on laryngeal squamous cell carcinoma, breast cancer and EC, respectively **(43, 44 and 31)**.

This contradicted to a study on hepatocellular carcinoma noting a significant relation between SOX4 overexpression and LVSI **(45)**. These contradictory results could be attributable to the role of SOX4 in mediating p53 activation resulting in induction of cell cycle arrest and tumor apoptosis.

The current study reached a statistically significant relation between SOX4 overexpression and T/B configuration with more expression in infiltrative than pushing tumor border. There was a statistically significant relation between SOX4 overexpression and T component in the current study. This agreed with studies on oral squamous cell carcinoma, lung and breast cancer, respectively (**46 and 47)**. This could be attributed to SOX4 activation of members of metalloprotease family responsible for the breakdown of the extracellular matrix, amplification of PI3K/AKT pathway and induction of EMT (**48)**.

Overexpression of SOX4 was significantly related to evidence of desmoplasia in studied EC cases. This was pursuant to similar results reported in a study on pancreatic cancer **(49)**. The effect of SOX4 on proliferation and differentiation of cancer associated fibroblasts and myofibroblasts through TGF- β/Smad pathway activation is a proper explanation (**50)**.

Inversely, a previous study on pancreatic ductal adenocarcinoma found that SOX4 can lead to tumour apoptosis and hence decrease desmoplastic reaction **(51)**. This could be explained by that strong activation of EMT by collaboration of TGF-β with oncogenic, hyperactive RAS signalling conflicts with a SOX4-dependent epithelial program, triggering apoptosis (**52)**.

In this work, SOX4 overexpression was significantly related to mitotic count. This agreed with a study on breast cancer **(53)**. This may be because of the possible role of SOX4 activating TGF-β pathway resulting in cellular proliferation.

In contrast, a study on glioblastoma multiforme found that SOX4 overexpression reduced cellular proliferation and mitotic rate **(54)**. This may be due to SOX4 reduction of AKT, results in inhibiting P53 degradation and

activation of downstream genes resulting in cell cycle arrest.

This result contradicted to a study of laryngeal squamous cell carcinoma which revealed no relation between SOX4 overexpression and T component **(55)**. This may be contributed to studying larger number of cases and different tumour biology.

This study also noted that SOX4 overexpression was positively related with lymph node metastasis, advanced FIGO and TNM staging of EC. This agreed with studies on breast cancer, colorectal carcinoma, and EC, respectively **(56), (57 and 31)**. This could be linked to the effect of SOX4 on EMT reducing the mRNA level of the epithelial marker, E-cadherin, and increasing the levels of the three mesenchymal markers, Vimentin, N-cadherin, and Fibronectin (**58)**.

Contrariwise, an inverse relation between SOX4 expression, nodal metastasis and advanced clinical stage, was reported in studies on melanoma and primary gall bladder carcinoma, respectively (**59 and 60)**. This controversy may be due to the role of SOX4 as a DNA damage sensor by blocking p53 degradation; SOX4 promoting cell cycle arrest and apoptosis inhibiting tumorigenesis **(40).**

In the present study, a statistically significant relation between SOX4 overexpression and distant metastasis was reached. This result agreed with previous studies regarding prostate cancer and gastric cancer, respectively **(61 and 62)**. Possible activation of C-MYC by SOX4 may play an important role in tumour progression **(37)**.

Inversely, A study on melanoma found that SOX4 overexpression decreased the metastasis **(63)**. Inhibition of tumour initiation through DNA damage signalling, activation of apoptosis and / or downregulation of certain oncogenic pathways as NF-κB signalling pathway were proposed as possible explanations **(64)**.

There was statistically insignificant relation reached between SOX4 overexpression and age of the studied cases being consistent with previous studies on gastric cancer and EC, respectively (**65 and 28)**. Inversely, another study on EC found a significant positive relation between SOX4 overexpression and the age of studied cases **(31)**. This could be explained by studying only EEC cases while the current study was applied to EEC and SEC cases.

The current study reached a statistically significant positive difference between nuclear morphometric parameters in EC and EH. The MNA was increasing along the progression of EH without atypia cases, to AEH to EC (60.37, 73.17 and 134.93 μm2). This could be clarified by that nuclear shape changed from elongated nuclei in EH without atypia to rounded nuclei in AEH and progression to EC by being larger, pleomorphic, and more rounded. This agreed with previous studies on EH and EC (**18 and 7)**.

This study also related the nuclear morphometric parameters with the clinicopathological findings of EC. The MNA showed a statistically significant relation with the type of EC in favour of SEC over EEC. This may be contributed to the higher grade and aggressiveness of SEC with large highly pleomorphic nuclei.

This agreed with previous studies reporting that MNA was related to histopathological type with higher values

detected in invasive duct carcinoma, poorly differentiated thyroid carcinoma, SEC, and papillary renal cell carcinoma**,** respectively **(66, 67**, **68, 69 and 70).**

Additionally, this study revealed MNA had statistically significant positive relation with tumour grade and consequently with mitotic count. This agreed with studies on EC and breast cancer, respectively **(71,72 and 73)**. This result could be interpreted by that histologic grade includes both cytological and architectural features with nuclear grade has been proved to be more important as stated in WHO classification 5th edition **(4).** The higher the tumour grade the more aggressive tumour behaviour is hence increased mitotic count **(74).**

This study revealed a statistically significant positive relation between MNA and T/B configuration with higher value of MNA in tumours with infiltrative than pushing borders and evidence of desmoplasia. This agreed with studies on lung adenocarcinoma and laryngeal carcinoma, respectively **(75 and 76)**. This may be indicative of more aggressive tumour behaviour.

A statistically significant positive correlations were reached between MNA and depth of myometrial invasion, T component, LVSI, lymph node, distant metastasis, FIGO stage and TNM stage in studied EC cases. This agreed with results noted in studies on EC, melanoma, breast cancer, gastrointestinal signet ring carcinoma, and colorectal carcinoma respectively (**77, 78, 79, 80, 81 and 82)**. These results suggested that tumour with large MNA, and high anaplasia, usually had deeper invasion and metastatic potential and consequently higher stage (**83, 84 and 85)**.

This was in contrary to a previous study on breast cancer revealing that the metastasis was associated with smaller nuclei **(86).** This finding could be due to a higher probability of small nuclei to enter through the wall of small arteries and capillaries and entering between dense collagen fibres.

There was statistically insignificant correlation between age of studied cases and MNA. This was in line with a previous study on EC **(87)**.

Upon correlating the SOX4 expression-and the morphometric parameters in this study, there is a significant statistical correlation between SOX4 and MNA (r=852, P<0.001). To our knowledge, this is the first study to reveal a positive correlation between SOX4 expression score and MNA results in EC.

Conclusion:

The significant correlation between SOX4 expression and MNA may imply the pivotal role of SOX4 in cancer development and progression specially in high grade tumours with aggressive behaviour. Also, MNA may distinguish between different tumour grades and types. Hence, our findings suggest that SOX4 and MNA may be used combined as an ancillary diagnostic tool to conventional histopathological findings and predict the prognosis of EC.

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