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FOX A1 Immunohistochemical Expression as a Prognostic Factor in Cases of Invasive Serous and Mucinous Ovarian Carcinoma in Correlation with p53 Status

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Abstract

Aim: The objective of the present work was to evaluate FOX A1 immunohistochemical expression in correlation with p53 status in invasive serous and mucinous carcinomas to determine prognostic value.

Methods: This retrospective study was carried out on paraffin embedded blocks of 46 and 21 invasive serous and 15 mucinous ovarian carcinomas respectively. Sectioning and immunohistochemical staining using anti-p53 and anti-FOX A1 antibodies was conducted.

Results: p53 expression was detected in approximately two third of all cases (65.7%), score 4 was the most frequent score (52.2%) and only significant association could be detected between p53 expression and histologic type as all positive cases were of serous type. FOX A1 showed high expression (80.6%) in all cases and score 2 & 3 represented 38.8% and 35.8% respectively. FOX A1 showed significant association with old age (p=0.048), stage (p=0.001) and high grade (<0.001), also with capsular rupture and ascites (<0.001). No agreement could be detected between FOX A1 expression and p53, still, (82.6%) of negative p53 cases showed positivity for FOX A1 and (65.2%) of negative p53 cases showed FOX A1 score 3.

Conclusion: FOX A1 is highly expressed and has a poor prognostic indication in invasive serous and mucinous carcinoma cases regarding significant association with old age, high grade, stage, capsular rupture and ascites, p53 helps to differentiate serous type and FOX A1 over expression in cases of negative p53 could be used as a marker for prognosis and potential targeted therapy.

Keywords: FOX A1; p53: Immunohistochemistry; Serous ovarian carcinoma; Mucinous ovarian carcinoma; Cancer ovary

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Introduction

Ovarian Cancer (OC), which is mostly epithelial derivative, represents a major concern worldwide since it is the most fatal gynecologic malignancy in women [1]. The estimated global new cases of cancer ovary were 295,414 in 2018, matching 3.4% of all new cancer cases in females. However, there is a considerable geographical variance in the drain of cancer ovary as the rates differ from Africa to Europe (5.0/100,000 individuals/year to 9.5 per 100,000 individuals/year respectively) [2,3]. The elevated cancer ovary death rate is endorsed to silent growth of such tumor, late appearance of symptoms, delayed discovery, and absence of appropriate screening test. All these factors cause late diagnosis after disease progression into late stages [4].

Depending on clinical, pathological and molecular criteria, ovarian carcinomas are classified into two types (1&2), the 1st type includes serous carcinoma of low-grade, clear cell, endometrioid, mucinous and transitional cell carcinomas, and the 2nd type includes High-Grade Serous Carcinoma (HGSC), carcinosarcoma, and undifferentiated carcinoma [5]. Whereas HGSC is the most common type seen histologically, mucinous type is a distinct entity that has different clinical history, prognosis, genetic profile and response to chemotherapy [6]. Serous carcinoma of low grade type (type I) mostly exhibits rather stable genetic pattern and more indolent clinical sequence in contrast to type II (HGSC) which is linked to a worse clinical sequence [7]. The genetic profiling report of

HGSC publicized a different spectrum of mutation among HGSC and proposed for the potentiality of targeted treatments [8].

The main stream of HGSC type originated from the epithelium of fallopian tube through a sequence of antecedent lesions that aim the secretory type of cells. Normally, a fallopian tube epithelial cell encloses both ciliated and secretory type, and is classically negative for p53. The benign "p53 signature" is formed totally of secretory cells with p53 strong expression and indication of damage to DNA but with no evidence of proliferation. With development of intra epithelial carcinoma of serous type, there is gaining of pleomorphism, loss of polarity and mitosis. HGSC exhibits all the previous criteria and symptomatic presentation classically arises with disease progression [9]. Studies have been dedicated to inspecting if mutations and protein expression of p53 are related to invasiveness and its resistance to chemotherapy mainly because TP53 gene mutations are the commonest alteration in genes in ovarian type of cancers [10].

The gene FOX or forkhead box family is derived from winged helix transcription factors family [11]. In mammalians, transcription factors of FOX are classified into A to S sub-classes depending on similar sequence not only inside but also outside of FOX [12]. The FOX A1 was called Hepatocyte Nuclear Factor 3α (HNF-3α) at first [13]. As other members of FOX family, FOX A1 regulates the transcription of gene by direct engagement to its consensus sequence, the forkhead motif. Furthermore, FOX A1 is able to open nearby chromatin, and consequently letting other factors transcription, such as androgen receptor, to be in approximation to their targets site, hence employing transcriptional regulation of gene expression [14]. The FOX A1 protein plays important roles in development of tumors depending on their complex actions, mostly in instability of genes and genomic mutation, stimulation of invasion and metastasis, and continuous signaling of proliferation. Moreover, FOX A1 is linked to variable cancer types that can be recognized as specific regarding tumor type, based on certain transcription interactions [15]. The up-regulation of FOX A1 is greatly associated with some tumors malignancy such as lung, esophagus, and prostate [16]. In cancer ovary, FOX A1 is proposed to act as an oncogene by prompting expression of numerous proteins [17].

Limited data are available in the literature regarding the expression of FOX A1 in invasive serous and mucinous carcinoma of the ovary, and to our knowledge no previous study demonstrated FOX A1 in relation to p53 expression in such cases. In this work we aimed to study FOX A1 in p53 immunohistochemistry positive and negative cases of invasive ovarian serous and mucinous carcinoma, and to explore the relation with clinicopathological data to reveal association with tumor prognosis.

Methods

This retrospective study was performed on 67 cases of invasive serous and mucinous ovarian carcinoma cases (46 serous and 21 mucinous). The cases were collected as paraffin embedded blocks from the archives of pathology department Aswan and Sohag University since January 2017 - December 2019 according to inclusion and exclusion criteria. Approval from ethical committee of Faculty of Medicine Aswan University was acquired (#408/9/19) and all cases were anonymous and handled according to legal and ethical standards.

Inclusion criteria

All received primary invasive serous and mucinous ovarian carcinoma specimens with confident histopathological diagnosis fulfilling clinical information on each patient were included.

Exclusion criteria

The following cases were not eligible for this study; inadequate material or missing tissue blocks. Other types including undifferentiated and mixed carcinomas were excluded. Patients received treatment was also excluded, in addition to cases with missing clinical data or unfit for immunohistochemistry (excessive fibrosis or necrosis).

Clinical data and pathological examination

Clinical data were obtained and recorded including age, laterality of tumor, ascites, capsule rupture, stage at presentation. Serial sections from each paraffin embedded block were cut at 4 microns thickness to be used for H&E and immunohistochemical staining.

All cases were examined using alight microscope to confirm the histologic diagnosis and assess histologic grade. Histological grade was done according to the scoring system endorsed by Shimizu et al. 1998 where the atypia of the nucleus was either mild, moderate or severe with scores 1, 2, 3 respectively, mitosis 0-9, 10-24, and >25 are scored 1, 2, 3 respectively, and architecture is regarded as glandular, papillary, and solid scored 1, 2, 3 respectively were recorded with calculation of their sum as total score where grade1 when score 3-5, grade 2 when score 6-7, and grade when score 8-9 [18]. Tumors of grade 1 were considered as low-grade, while tumors of grade 2 and 3 were both considered as high-grade according to two-tier WHO grading system [19].

Immunohistochemistry of p53 was conducted using Rabbit monoclonal antibody against p53; A11232, 1 ml concentration with dilution of 1:100 according to product data sheet with the use of streptavidin-biotin amplified system.

Immunohistochemistry of FOX A1 was conducted using Rabbit monoclonal antibody against FOX A1 A9793, 1 ml concentration with dilution of 1:100 according to manufacture guide. Omission of 1ry antibody was used as negative control. Breast tissue was used as positive control as endorsed in the datasheet.

Immunohistochemical evaluation

Immune reactivity of p53 in tumor cells: The evaluation of p53 was according to staining intensity and score depending on the percentage of positive cells.

Intensity of staining was recorded a scale from 0 to 3 according to negative, weak, moderate, and strong; and the proportion of positive tumor cells as follow; 0=10%, 1=11-25%, 2=26-50%, 3=51-75% and 4= more than 76% [20].

Immune reactivity of FOX A1 in tumor cells: Scoring of FOX A1 expression was as follow: negative =0; 1 to 50%=1; 51 to 75%=2; and >75%=3 and staining intensity was scaled from 1 to 3 (weak; intermediate; and strong). Both, percentage and intensity grades were multiplied to acquire a concluding score: 0= negative; 1-2=+1; 3-4=+2; 6-9=+3 [21].

Statistical analysis of the data

Data were fed to the computer and analyzed using IBMSPSS software package version 20.0. (Armonk, NY:IBM Corp). Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). Sensitivity, the capacity of the test to correctly identify diseased individuals' in a

Table 1: Distribution of the studied cases according to different parameters (n=67).

	No. (%)
Age (years)	
≤ 50	30 (44.8%)
>50	37 (55.2%)
Mean ± SD	52.1 ± 11.5
Median (Min.-Max.)	53 (31 - 71)
Site	
Unilateral	26 (38.8%)
Bilateral	41 (61.2%)
I	29 (43.3%)
II	11 (16.4%)
III	16 (23.9%)
IV	11 (16.4%)
Histologic type	
Serous	46 (68.7%)
Mucinous	21 (31.3%)
Grade	
I	18 (26.9%)
II	22 (32.8%)
III	27 (40.3%)
Capsule rupture	39 (58.2%)
Ascites	39 (58.2%)
P53 Expression	
Negative	23 (34.3%)
Positive	44 (65.7%)
P53 Score	
0	23 (34.3%)
1	2 (3%)
2	4 (6%)
3	3 (4.5%)
4	35 (52.2%)
FOX A1 expression	
Negative	13 (19.4%)
Positive	54 (80.6%)
FOX A1 score	
0	13 (19.4%)
1	4 (6%)
2	26 (38.8%)
3	24 (35.8%)

population TRUE POSITIVES. The greater sensitivity, the smaller number of unidentified case false negatives. Specificity, the capacity of the test to correctly exclude individuals who are free of the disease TRUE NEGATIVES. The greater the specificity, the fewer "false positives" will be included. PPV the probability of the disease being present among those with positive diagnostic test results. NPV the probability that the disease was absent among those whose diagnostic test results were negative.

Accuracy Rate of Agreement = (True positives + True negatives)/ Total tested × 100. Significance of the obtained results was judged at the 5% level.

Results

In this work we studied 67 cases of invasive ovarian carcinoma (46 serous types and 21 mucinous types). More than half of the studied cases (55.2%) were older than 50 years with mean ± SD (52.1 ± 11.5). Bilateral tumors were identified in 61.2% of the cases, and stage (I) was the most frequent stage (43.3%), still advanced stages (III, IV) were detected in (40.3%). High grade tumors (grade 2, 3) represented 73.1% of all cases. Capsule rapture was detected in (58.2%). Cases with positive p53 represented 65.7% of all cases, of which score 4 was the most frequent score (52.2%), while FOX A1 positivity was observed in 80.6% of studied cases, and score 2 & 3 represented 38.8% and 35.8% respectively (Table 1).

In the studied cases only significant association could be detected between expression of p53 and histology type, however, no significant association could be detected with neither the stage nor the grade (Table 2). Regarding the relation between FOX A1 and all studied parameters, FOX A1 showed significant association with age, 61.1% of positive cases were older than 50 years with significant difference as median age of positive cases was 54. Highly significant association was detected with stage (p=0.001) and grade (<0.001), also with capsular rupture and ascites (<0.001) (Table 3).

In this work, no agreement could be detected between FOX A1 expression and p53, still, (82.6%) of negative p53 cases showed positivity for FOX A1, and (65.2%) of negative p53 cases showed FOX A1 score 3 (Table 4, 5).

Discussion

Ovarian Cancer (OC) ranks the third most frequent gynecological cancer globally, and is considered as a chief cause of mortality due to cancer in females [2]. In contrast to other malignancies of reproductive systems, OC is deficient in availability of biomarkers. Recognizing biomarkers for OC may disclose innovative treatment targets and give a probable prognostic indication.

Immunohistochemical staining for p53 has been regarded as a crucial biomarker for clinical research trials targeting mutant TP53

Table 2: Relation between P53 expression with stage, grade and histologic type (n=67).

	Negative (n=23)	Positive (n=44)	χ^2	P
Stage				
I	12 (52.2%)	17 (38.6%)	6.263	MC_p=0.092
II	3 (13.0%)	8 (18.2%)		
III	2 (8.7%)	14 (31.8%)		
IV	6 (26.1%)	5 (11.4%)		
Grade				
I	8 (34.8%)	10 (22.7%)	2.995	0.224
II	9 (39.1%)	13 (29.5%)		
III	6 (26.1%)	21 (47.7%)		
Histologic type				
Serous	2(8.7%)	44(100%)	58.514*	<0.001*
Mucinous	21(91.3%)	0(0%)		

χ^2: Chi-square test; MC: Monte Carlo; p: p value for association between different categories

*: Statistically significant at p ≤ 0.05

Table 3: Relation between FOX A1 expression and different parameters (n=67).

	FOX A1 expression		Test of sig.	P
	Negative (n=13)	**Positive (n= 54)**		
Age (years)				
≤ 50	9 (69.2%)	21 (38.9%)	χ^2= 3.901*	0.048*
>50	4 (30.8%)	33 (61.1%)		
Mean ± SD.	45.3 ± 10.94	53.8 ± 11.1	t=2.475*	0.016*
Median (Min. – Max.)	39 (31–63)	54 (33–71)		
Laterality				
Unilateral	4 (30.8%)	22 (40.7%)	χ^2=0.439	0.508
Bilateral	9 (69.2%)	32 (59.3%)		
Stage				
I	12 (92.3%)	17 (31.5%)	χ^2=14.726*	MC_p=0.001*
II	0 (0.0%)	11 (20.4%)		
III	0 (0.0%)	16 (29.6%)		
IV	1 (7.7%)	10 (18.5%)		
Histologic type				
Serous	10 (76.9%)	36 (66.7%)	χ^2=0.512	MC_p=0.74
Mucinous	3 (23.1%)	18 (33.3%)		
Grade				
I	12 (92.3%)	6 (11.1%)	χ^2=30.442*	MC_p<0.001*
II	0 (0.0%)	22 (40.7%)		
III	1 (7.7%)	26 (48.1%)		
Capsule rupture				
No	12 (92.3%)	16 (29.6%)	χ^2=16.921	<0.001*
Yes	1 (7.7%)	38 (70.4%)		
Ascites				
No	12 (92.3%)	16 (29.6%)	χ^2=16.921	<0.001*
Yes	1 (7.7%)	38 (70.4%)		

χ^2: Chi-square test; FE: Fisher Exact; MC: Monte Carlo; t: Student t-test
p: p value for association between different categories *: Statistically significant at p ≤ 0.05

and utilized in the diagnostic & prognostic examination of variable types of cancer, including ovarian ones [22]. While, FOX A1 mediates multiple actions including the nuclear steroid receptor signaling pathway by regulating androgen receptor and estrogen receptor activity [14]. Since ovarian carcinomas are likewise hormone-dependent, this provoked the evaluation of FOX A1 expression in such tumors. The present work evaluated FOX A1 in relation to p53 expression in invasive serous and mucinous carcinomas to determine prognostic value.

In the current study, p53 expression was detected using immunohistochemistry in approximately two third of the studied cases (65.7%) regardless of tumor grade or stage, and score 4 was the most frequent score since it was detected in (52.2%) of studied cases. In the studied cases only significant association could be detected between expression of p53 and histologic type as all positive cases were of serous type. Immunohistochemical expression of p53 in OC is a reflect of TP53 mutation with good indication as previously evident by many authors [10,23]. The expression of p53 in this study is in concordance with the study conducted by Razak Amanullah et al., who reported p53 expression in 65.2% of epithelial OC samples and all their positive cases were of serous type [24], which was also previously reported by Sylvia et al. [25]. P53 positivity was comparable to that reported by Ndukwe et al. [26] in 58% of epithelial OC. Furthermore, a previous meta-analysis stated that the expression of p53 in epithelial OC ranged from13.7 to 82.0% [27]. Moreover, strong expression was reported in 55% of cases studied by Havrilesky et al. [28].

In the present study, all the p53 positive tumors were serous malignancies. Malignant mucinous tumors were p53 negative. P53 positivity was seen in 95.65% of serous carcinomas; only two cases of the serous tumors were p53 negative. The expression of p53 was also detected in serous carcinoma cases and negative in mucinous carcinoma in previous studies [24,29]. Some authors well-thought-out that p53 expression is a substitute marker for the differentiation of HGSC from other OC [29]. It is worth mentioning that we found more expression of p53 in HGSC than low grade type as 77.3% of positive p53 were of high grade type although no statistical significance could be detected. Psyrri et al. [30] found that p53 immunohistochemical expression in OC had no statistical significance association with clinicopathological criteria including grade, stage, and histologic type, on contrary, Missaoui et al. [29], and Razak Amanullah et al. [24] showed significant association of p53 expression with stage and other clinical parameters, while, Ndukwe et al. [26] reported significant association with grade, and with histologic type. The variation in these results may be related to genetic mutation variation, and geographical distribution of the different studied groups. Larger scales of investigation may give clear idea about p53 expression as a marker for OC risk, prognosis, response to therapy, and targeted treatment.

In this work, FOX A1 showed high expression since positivity was observed in 80.6% of invasive serous and mucinous cases, and score 2 & 3 represented 38.8% and 35.8% respectively. This result of high expression is in concordance with the study conducted by Wang et al. [17] reporting that FOX A1 overexpression was detected in about 73.6% of epithelial OC. In contrast, Wang et al. [21] reported FOX A1 expression in epithelial OC to be about 32.03%; this difference in expression could be related to examine type of ovarian carcinoma as the later authors mentioned epithelial OC as targeted specimens without identification of specific subtypes while we studied only serous and mucinous types.

We found that FOX A1 showed significant association with age, and highly significant association with stage and grade (p=0.001 and <0.001 respectively), also with capsular rupture, and ascites (both p<0.001). Whereas, no significant association could be detected between FOX A1 and laterality of the tumor or its type.

In this study, 61.1% of FOX A1 positive cases were older than 50 years, and 69.2% of negative cases were 50 years or younger with significant difference as median age and mean age of positive cases were 54 and 53.8 ± 11.1 respectively. This result is in line with the study of Wang et al. [17], they reported that FOX A1 expression was more in patients older than 55 years, however, their study showed no significant difference.

On correlation of FOX A1 expression with tumor staging; (48.1%) of positive FOX A1 cases were of advanced stage (III & IV) while (92.3%) of FOX A1 negative tumors were of stage (I). This result agrees with Wang et al. [17] who reported significant expression of FOX A1 in 41.8% of cases at stage III & IV tumors. Furthermore, this study goes hand in hand with their results regarding significant association of high expression with increased grading as we found

Table 4: Agreement (sensitivity, specificity and accuracy) for FOX A1 expression (n=67).

	P53 Expression		Sensitivity	Specificity	PPV	NPV	Accuracy
	Negative (n=23)	Positive (n=44)					
FOX A1expression							
Negative	4 (17.4%)	9 (20.5%)	79.55	17.39	64.81	30.77	58.21
Positive	19 (82.6%)	35 (79.5%)					
χ^2 **(FEp)**	0.091 (1.000)						

χ^2: Chi-square test; FE: Fisher Exact; NPV: Negative predictive value; PPV: Positive predictive value
p: p value for association between different categories

Table 5: Agreement (sensitivity, specificity and accuracy) for FOX A1 score of expression (n=67).

	p53 score				
FOX A1 score	0 (n=23)	1 (n=2)	2 (n=4)	3 (n=3)	4 (n=35)
0	4 (17.4%)	1 (50%)	0 (0%)	0 (0%)	8 (22.9%)
1	0 (0%)	0 (0%)	2 (50%)	0 (0%)	2 (5.7%)
2	4 (17.4%)	1 (50%)	2 (50%)	3 (100%)	16 (45.7%)
3	15 (65.2%)	0 (0%)	0 (0%)	0 (0%)	9 (25.7%)
K	-0.102 (no agreement)				

χ^2: Chi-square test; MC: Monte Carlo; κ: kappa test
p: p value for association between different categories *: Statistically significant at p ≤ 0.05

that (88.8%) of FOX A1 positively expressed tumors were of high grade. They also reported no significant association with laterality and subtype, which is in line with our results. Besides, according to the current work, there is high significant association between FOX A1 expression and tumors with ruptured capsule and ascites.

These results indicate the contribution of FOX A1 to bad prognostic parameters including advanced age, high grade, advanced stages, tumors with ruptured capsule and ascites regardless of laterality and type. Furthermore, these results support the suggestion of Wang et al. [17] that FOX A1 functions in epithelial OC as prognostic marker, and their proposal of being a targeted therapy, likewise Wang et al. [21] provided an evidence that FOX A1 plays a role as an oncogene in OC pathogenesis and progression .Moreover, with therapeutic lines, Rutten provided the evidence that FOX A1 expression in previously treated OC tissues was significantly associated with chemotherapy response since it was highly expressed in OC tissue with no response to chemotherapy in comparison to chemo-sensitive ones [31]. The high expression of FOX A1 suggests its implication in treatment of chemoresistant OC cases which requires further investigation to provide more evidence on targeted therapy like the recent work on role of FOX A1 in treatment resistance of breast cancer [32,33]. In this work, although no agreement could be detected between FOX A1 expression and p53, (82.6%) of negative p53 cases showed positivity for FOX A1, and (65.2%) of negative p53 cases showed FOX A1 score 3. This could indicate the implication of FOX A1 expression as a marker in cases of negative p53 and the suggestion of targeting FOX A1 as a new line of treatment in such cases.

In conclusion, FOX A1 has a poor prognostic indication in invasive serous and mucinous carcinoma as it is highly expressed in majority of such cases, significantly with advanced age, high grade, advanced stage, tumors with ruptured capsule, and ascites. Also, p53 showed high expression, and positivity was significantly associated with cases of serous carcinoma, however, no significant association could found between p53 expression and tumor grade or stage. P53 helps to differentiate serous type, and FOX A1 over expression in cases of negative p53 could be used as a marker not only in prognosis but also as a base for targeted therapy.

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