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Molecular Expression of p53 in Endometrial Carcinoma and Its Correlation with Clinicopathological Factors

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Abstract

The mutational status of TP53 is the single most important molecular factor, which predicts prognosis in endometrial carcinomas; nonsynonymous TP53 missense mutations result in nuclear accumulation of p53 protein that can be detected as overexpression by immunohistochemistry. A cross-sectional study was conducted in the Department of Gynaecological Oncology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, between January and December of 2023, to evaluate the immunohistochemistry findings of p53 protein and its correlation with clinicopathological factors in endometrial carcinoma. A total of 54 endometrial carcinoma patients diagnosed by fractional curettage or diagnostic curettage admitted in the BSMMU Hospital were enrolled in this study. Patient's complete history including age, BMI, family history, parity, menstrual pattern, comorbidities, clinical complaints, investigations and operation notes were recorded in the data collection sheet. After surgery, blocks were made from pathological specimens for histopathological examination. After regular histopathological examination, immunohistochemistry was performed on all tumours using monoclonal mouse antibodies against p53 proteins (Dako Envision method according to manufacturer protocol) in the Department of Pathology of the same institution. Aggressive histological variety (non-endometroid) was more prevalent (87.5%) in p53 mutant cases ($p<0.01$). Deeper myometrial invasion (≥50%), cervical extension and lymphovascular space invasion (LVSI) were also significantly associated with p53 mutations ($p<0.05$, $p<0.01$ and $p<0.01$ respectively). Moreover, higher tumour grade and lower FIGO stage were significantly associated with p53 mutations ($p<0.05$ and $p<0.01$ respectively). However, tumour size, adnexal and lymph node involvement showed no significant difference ($p>0.05$).

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Introduction

Endometrial carcinoma (EC) is one of the most common gynecological malignancies worldwide, particularly affecting postmenopausal women. Its incidence is rising globally due to increasing life expectancy, obesity and associated metabolic disorders, family history of cancer.[1] Understanding the molecular (genetic) characteristics of affected patients is essential for early detection, effective management, and improved outcomes.[2] The World Health Organization (WHO) endorsed the molecular classification of endometrial carcinomas using surrogate markers and following a stepwise diagnostic procedure.[3] The mutational status of TP53 is the single most important molecular factor, which

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predicts prognosis in endometrial carcinomas; nonsynonymous TP53 missense mutations result in nuclear accumulation of p53 protein that can be detected as overexpression by immunohistochemistry.[4,5]

The wild-type p53 staining pattern is characterized by nuclear staining of 1–80% of tumour cells with variable intensity. Abnormal p53 expression patterns include overexpression, complete absence, and cytoplasmic localization. Abnormal overexpression is typically caused by nonsynonymous missense mutations in the *TP53* gene, resulting in excessive nuclear accumulation of p53 protein.[4-6] In immunohistochemistry (IHC), this appears as diffuse, strong nuclear staining in more than 80% of tumour cells. Tumors showing a complete absence of p53 staining are usually associated with frameshift or nonsense mutations that produce truncated, nonfunctional p53 protein. The cytoplasmic staining pattern is defined by tumor cells exhibiting distinct moderate to strong cytoplasmic staining with variable or absent nuclear staining, often linked to mutations affecting the nuclear localization or tetramerization domains of p53.[3-5] Abnormal p53 expression is strongly associated with high-grade, aggressive behaviour, and the poorest clinical outcomes of endometrial cancer.[5,6]

Although several western reports are available, we lack evidence of p53 IHC study on Bangladeshi women suffering from different gynaecological cancers. Therefore, we proposed this study involving Bangladeshi patients having endometrial carcinoma admitted in a tertiary level specialized hospital to evaluate the immunohistochemistry findings of p53 protein and its correlation with clinicopathological factors.

Methods

This cross-sectional study was conducted in the Department of Gynaecological Oncology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, between January and December of 2023. Sample selection was done following purposive sampling technique. A total of 54 endometrial carcinoma patients diagnosed by fractional curettage or diagnostic curettage admitted into the BSMMU Hospital were enrolled in this study. At the time of their entry into the study a complete personal and family history was taken and recorded. Their age, BMI, parity, menstrual pattern, comorbidities, clinical complaints were noted in the data collection sheet. Preoperative investigations included some imaging modalities like transvaginal sonography (TVS) and magnetic resonance imaging (MRI) scans. All of the enrolled patients were treated by hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic and para aortic lymphadenectomy and/omentectomy as per staging. Peroperative findings and the findings of the cut section of the uterus (myometrial invasion, cervical extension, tumour size, ascites, omental metastasis) were noted. After surgery was done, pathological (endometrial carcinoma) specimens are routinely fixed with formalin and embedded in paraffin; then blocks were made for histopathological examination. For immunohistochemical study, from paraffin embedded blocks 4 micrometer thick sections were cut, deparaffinized with xylene and rehydrated through a graded series of alcohol. Standard molecular testing was performed on all tumours using monoclonal mouse antibodies against p53 using Dako Envision method according to manufacturer protocol (Dako EnVision by Agilent Technologies, Inc., Santa Clara, CA, USA). Immunohistochemical staining of p53 was

evaluated as abnormal/mutant-like in case of: (i) protein overexpression, (ii) “null” phenotype, or (iii) positive cytoplasmic staining; otherwise, it was considered normal (wild-type).[8] Molecular expressions are shown in Fig. 1 & Fig. 2. Both regular histopathological examination and immunohistochemistry were done in the Department of Pathology of the same institution. The analysis of immunoreactivity was analyzed by the Consultant Pathologist. All were noted in the data sheet.

After collection, data was checked for omission, inadequacy and inconsistency. Omission was corrected by re-taking history or re-examining the patient. Irrelevant and inconsistent data was discarded. Categorical variables was presented as frequency and percentage. Associations between molecular expression and clinicopathological factors was assessed using Pearson's chi-square test. Statistical significance was set at a two tailed p-value of <0.05. Data analysis was done using STATA software version 14 (StataCorp LLC, College Station, Texas, USA).

This study was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh (BSMMU/2022/9561-IRB Reg. No. 3956).

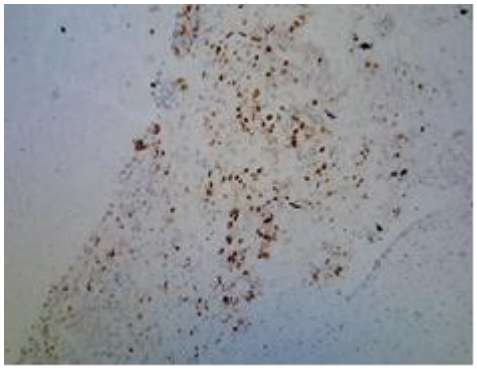

Fig. 1: Photomicrograph showing wild expression of p53 in tumour cells (×100).

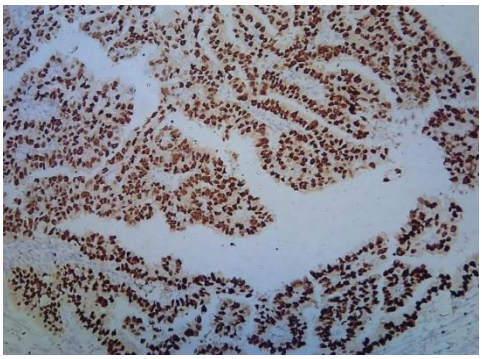

Fig. 2: Photomicrograph showing mutant type of reactivity of p53 in tumour cells (×100).

Results

Out of 54 patients, more than two-thirds (68.5%) were in the ≥60 years age group. Estimated BMI <25 was predominant (57.4%). The majority of the women were postmenopausal (79.6%), while most of them (61.1%) had both hypertension and diabetes mellitus as comorbidities. A positive family history of cancer was found in 20.4% cases (Table-I). Immunohistochemistry revealed that 46(85.2%) patients expressed wild type of p53, while 8(14.8%) had a mutant or abnormal expression of p53. Estimated BMI <25 showed more p53 mutation ($p<0.05$). However, no differences were observed in age group and menopausal status ($p>0.05$) (Table-II). Aggressive histological variety (non-endometrioid) was more prevalent (87.5%) in p53 mutant cases ($p<0.01$). Deeper myometrial invasion (≥50%), cervical extension and lymphovascular space invasion (LVSI) were also significantly associated with p53 mutations ($p<0.05$, $p<0.01$ and $p<0.01$ respectively). Moreover, higher tumour grade and lower FIGO stage were significantly associated with p53 mutations ($p<0.05$ and $p<0.01$ respectively). However, tumour size, adnexal and lymph node involvement showed no significant difference ($p>0.05$) (Table-III).

Table-I: Demographic characteristics of the patients (N=54)

Variables	Frequency	Percentage
Age group (in years)		
<60	17	31.5
≥60	37	68.5
BMI (kg/m^2)		
≥25	23	42.6
<25	31	57.4
Menopausal status		
Premenopausal	11	20.4
Postmenopusal	43	79.6
Comorbidities		
HTN and DM	33	61.1
HTN	6	11.1
DM	6	11.1
Others	9	16.7
Family history of cancer		
Yes	11	20.4
No	43	79.6

Table-II: Distribution of p53 mutant phenotype

Variables	p53 mutant (n=8)		p-value
	Frequency	Percentage	
Age group (in years)			
<60	2	25.0	0.547^{NS}
≥60	6	75.0	
BMI (kg/m^2)			
≥25	1	12.5	0.017^{S}
<25	7	87.5	
Menopausal status			
Premenopausal	3	37.5	0.726^{NS}
Postmenopausal	5	62.5	

Chi-square test was applied; S=significant, NS=not significant.

Table-III: Comparison of clinicopathological characteristics between p53 mutant and p53 wild groups (N=54)

Variables	p53 mutant (n=8) Frequency (Percentage)	p53 wild (n=46) Frequency (Percentage)	p-value
Histological type			
Endometroid	1 (12.5)	41 (89.1)	0.002^{S}
Non-endometrioid	7 (87.5)	5 (10.9)	
Size of tumour (cm)			
<2	2 (25.0)	9 (19.5)	0.898^{NS}
2–4	3 (37.5)	16 (34.8)	
>4	3 (37.5)	21 (45.7)	
Myometrial invasion			
<50%	-	23 (50.0)	0.015^{S}
≥50%	8 (100.0)	23 (50.0)	
Cervical extension			
Yes	6 (75.0)	9 (19.6)	0.004^{S}
No	2 (25.0)	37 (80.4)	
Adnexal involvement			
Yes	2 (25.0)	9 (19.6)	0.659^{NS}
No	6 (75.0)	37 (80.4)	
Lymphovascular space invasion (LVSI)			
Yes	7 (87.5)	16 (34.8)	0.008^{S}
No	1 (12.5)	30 (65.2)	
Lymph node involvement			
Yes	2 (25.0)	10 (21.7)	0.991^{NS}
No	6 (75.0)	36 (78.3)	
Grade			
Grade I	-	20 (43.5)	0.031^{S}
Grade II	3 (37.5)	15 (32.6)	
Grade III	5 (62.5)	11 (23.9)	
FIGO stage			
Stage I	-	23 (50.0)	0.005^{S}
Stage II	7 (87.5)	11 (23.9)	
Stage III	1 (12.5)	10 (21.8)	
Stage IV	-	2 (4.3)	

Chi-square test was applied; S=significant, NS=not significant.

Discussion

We studied on 54 Bangladeshi women having endometrial carcinoma confirmed by histopathological examination. Based on histological findings, endometrial carcinoma subtypes include endometrioid, serous, clear cell, undifferentiated, mixed cell, mesonephric, squamous cell, mucinous, mesonephric like, and carcinosarcoma. Endometrioid adenocarcinoma is the most common subtype (about 85% of cases), followed by serous and clear cell carcinoma.[7] In the present study, 14.8% of the study patients exhibited abnormal or mutated expression of p53 indicating potential genomic alterations in this subset, which is comparable with the findings of Da Cruz Paula *et al*., Koshiyama *et al*., and Huvila *et al*., where they observed 22%, 16.7% and 15.2% of patients exhibited abnormal or mutated expression of p53 respectively.[8-10] However, a higher rate of Abnormal p53 expression was observed by Vermiz et al. (32.1%).[11] Similarly, Tresa *et al*. observed a higher rate of p53 abnormalities (42.8%) among Indian women.[12] In China, Jia et al. observed much rate in non-endometrioid endometrial cancer (76.4%).[6]

However, there are challenges in molecular classification is interpreting p53 staining and understanding its clinical significance. The World Health Organization (WHO) characterizes abnormal p53 staining as diffuse, strong nuclear expression, complete absence of nuclear staining, or cytoplasmic expression, with a common threshold of 80% positive tumour cells.[3] In cases of mutant-pattern p53 staining, a ≥10% cutoff of tumor cells displaying the abnormal pattern is typically used to classify a tumor as p53 abnormal (p53abn).[10,13] However, the clinical relevance of this threshold remains unclear.[10] Our study found no association of p53 mutation with age and menopausal status except with BMI (<25 kg/m^2).

Similar results were reported by Jia *et al.* and Tresa *et al*.[6,12] In this study, aggressive histological variety (non-endometrioid), deeper myometrial invasion (≥50%), cervical extension and lymphovascular space invasion (LVSI). Stage and grade were associated with p53 mutation. Jia *et al*. observed differences among various histological types of non-endometrioid EC, including tumour size, myometrial invasion, and LVSI, while Tresa *et al.* reported a significant association between p53 mutation and histology, stage, cervical and adnexal involvement of the tumours, which are in congruence with the findings of the present study.[6,12]

Not a surprise, geographical differences are evident as an increased prevalence of abnormalites in p53 were observed in Asian countries,[14] which made our study more relevant (as no such report was available on endometrial cancer among Bangladeshi women to date).

However, our study has several limitations. The study population was selected from one selected hospital in Dhaka city; hence, the results of the study may not reflect the exact picture of the country. A small sample size was another limitation, which was due to time and budget constraint. Apart from that, we relied on IHC overexpression of p53 for detecting TP53 mutation mostly. However, splice site mutation can result in p53 wild-type staining and hence may be missed in this study.[15] Further studies are recommended with larger sample size and involving multicentres from different regions of the country.

Conclusion

Our data suggests that 85.2% of endometrial carcinoma (EC) patients expressed wild type of p53, while 14.8% had a mutant or abnormal expression of p53. Optimised p53 IHC is a reliable diagnostic

adjunct for histotyping and molecular subtyping in EC as well as an adjunct surrogate test for TP53 mutation in tumours, demonstrates excellent reproducibility and high clinical utility for molecular classification algorithms in EC.

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