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To study the expression of estrogen, progesterone receptor and p53 immunohistochemistry markers in subtyping endometrial carcinoma

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Abstract

Background: Endometrial cancer is one of the most commonly diagnosed cancers in women worldwide. **Aim and Objectives:** To study the expression of estrogen receptor (ER), progesterone receptor (PR) and p53 immunohistochemistry (IHC) markers in subtyping endometrial carcinoma. Materials and Methods: A total of 100 cases of carcinoma endometrium submitted during January 2016 to October 2018 were included in our study. The ER, PR and p53 expressions were scored as per the adopted scoring system. Agreement between ER, PR and p53 IHC expression and the consensus HE diagnosis, FIGO grading and tumour staging were assessed using Chi square tests. **Results:** There was a statistical association between ER, PR and p53 status and tumour histologic type with a P value < 0.01. There was no statistical significance observed between ER and PR expressions and different FIGO grades. Statistical significance (P = 0.036) between p53 and different FIGO grades seen. No statistical significance was observed between ER, PR and p53 expressions and different tumour stages and tumour invasiveness. There was a statistical association between ER and PR status and lymph node metastasis. p53 did not show a statistical significance. **Conclusion:** Combination of ER, PR and p53 IHC markers can be used to distinguish type 1 and type 2 endometrial cancers. PR expression is more specific than ER in endometrioid carcinomas. p53 expression is more specific in serous carcinoma, however, p53 IHC alone cannot be used to distinguish different grades of endometrioid carcinomas as there is variability of staining in endometrioid carcinomas.

Keywords: Endometrial carcinoma, estrogen receptor, progesterone receptor, p53, subtypes

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Introduction

Endometrial cancer is one of the commonly diagnosed cancers in women globally.[1] In patients of Lynch syndrome, it is the second frequent common cancers.[2] Endometrial carcinoma occurs in 8 per 10,000 women globally and is the tenth most frequent reason for cancer deaths.[1] In India, it is seen in 4.3 per 100,000 women.[3]

Endometrial carcinoma usually occurs in elderly women. The incidence is rare in less than 50 years age, about 9%. Lynch syndrome-related endometrial carcinomas are seen in patients with mean age of 49 years.[4]

The pathogenetic classification of endometrial carcinoma was first given by Bokhman depending upon its clinical course, its biological properties and the progress of the disease.[5] Endometrial carcinoma based on tumour histology is classified into two clinicopathological types: Type I (Endometrioid cancer) and Type II (Non-Endometrioid cancer).[6]

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Abstract
Introduction
Materials and Me...
Results
Discussion
References
Article Figures
Article Tables

The gain of function events in endometrial carcinoma includes the oncogenes, namely K-ras, β-Catenin and loss-of function events include PTEN and p53 genes. Other important causative factor for endometrial cancer is genomic instability which occurs because of DNA mismatch repair gene (DNA MMR) deficiency, detected as microsatellite instability. It may be sporadic or may be due to germline mutation of MMR genes which includes MLH1, MSH2, MSH6 and PMS2.[7]

Higher level of estrogen receptor (ER), progesterone receptor (PR) reflects favourable prognosis and higher level of HER2, reflects poor prognosis in endometrial carcinoma. These hormone receptors help in predicting the hormone therapy response in endometrial cancer.[8]

Type-I endometrial carcinoma shows strong positivity for ER/PR. High grade endometrial carcinoma expresses variable intensity of p53, in less than 75% of neoplastic cells but some high grade endometrioid carcinoma can harbour p53 mutation. Type-II endometrial carcinoma shows weak positivity or stain negative for ER/PR. One of the most important somatic mutations in uterine serous carcinoma is Tp53 mutation. Intense and diffuse staining of p53 in at least 75% of the tumour cells correlates with Tp53 mutation and helps in diagnosis of uterine serous carcinoma. Clear cell carcinoma is usually negative for p53 or rarely overexpresses p53.[9]

ER and PR content in endometrial tumours correlates with the clinicopathological parameters like histologic stage, grade, prognosis and survival.[10]

p53gene mutations in uterine serous carcinoma are missense detected by immunohistochemistry. Strong nuclear staining in more than 75% of tumour cells indicates p53 mutations. However, complete negativity of p53 may be indicative of p53 mutations, as frameshift or nonsense mutations in p53 can result in a protein which remains undetected by Immunohistochemistry (IHC).[3]

Thus, in our study, we studied the expression of estrogen, progesterone receptor and p53 immunohistochemistry markers in subtyping endometrial carcinoma.

Materials and Methods

A total of 100 cases of carcinoma endometrium (both endometrioid and non-endometrioid) submitted during January 2016 to October 2018 were included in our study. The proposed sample size in our study was 74 cases. However, diligent retrieval of cases helped us attain a final sample size of 100 cases. All the cases diagnosed as carcinoma endometrium in hysterectomy specimens and endometrial curetting's in department of histopathology of our hospital. The cases excluded included diagnoses other than carcinoma endometrium in hysterectomy specimens, tissues not well processed, cases where clinical details like age were not available.

After staining, the cases were examined and reported by both the primary investigator and the co-investigator separately. Haematoxylin and eosin (HE) diagnosis was formulated.

Categories of ER, PR and P53 as depending on the nuclear positivity and the intensity of staining [Table 1].

Categories	Number of cases			Percentage		
	ER	PR	P53	ER	PR	P53
I	13	15	68	13.0	15.0	68.0
II	25	21	18	25.0	21.0	18.0
III	62	64	14	62.0	64.0	14.0
Total	100	100	100	100.0	100.0	100.0

Table 1: Categories of ER, PR and P53 as depending on the nuclear positivity and the intensity of staining

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Immunohistochemical staining was evaluated with the use of a double grading system: percentage of stained cells and intensity of nuclear stain. The percentage of positive cells was graded as 1 when 0% of the nuclei stained, 2 when 1-25% of the nuclei stained, 3 when 26-75% of the nuclei stained and 4 when more than 75% of the nuclei were stained.

Stain intensity was defined as follows: 1, absent or weak; 2, moderate; and 3, strong. The sum of both parameters gave the immunohistochemical score (IS). Tumours were divided into three categories according to this score: category I included the cases with an IS of 2 or 3, category II the cases with an IS of 4 or 5 and category III the cases with a score of 6 or 7.

ER, PR and P53 were assigned categories as I, II and III depending on the nuclear positivity and the intensity of staining as shown in the accompanying tables.

Agreement between ER, PR and p53 IHC expression and the consensus HE diagnosis, FIGO grading, tumour staging was assessed using Chi-square tests.

Results

A total of 100 cases were selected and studied, after careful application of inclusion and exclusion criteria. The study had a wide range of age distribution from third to ninth decade (30-84 years). Majority of the cases were of more than 50 years of age (81%). 19 out of 100 cases (19%) were in less than 50 years of age group.

Based on the HE diagnosis, the cases were grouped into 4 diagnostic categories as Endometrioid carcinoma (83%), Serous carcinoma (10%), Clear cell carcinoma (3%) and Others which included Carcinosarcoma and Mucinous carcinoma (4%) [Figure 1].

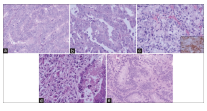

Figure 1: (a) Endometrioid Carcinoma, (H and E Stain, 40x) (b) Serous Carcinoma, (H and E Stain, 40x) (c) Clear Cell Carcinoma, (H and E Stain, 40x) The inset shows cytoplasmic positivity for Napsin A (IHC, 40X) (d) Carcinosarcoma-Epithelial and sarcomatous components, (H and E Stain, 40x) (e) Mucinous Carcinoma, (H and E Stain, 40x)

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Among the 100 cases of endometrial carcinoma, FIGO grading was done for 83 cases of Endometrioid carcinoma. 61 out of 83 cases (73.5%) were categorised as FIGO grade 1, 19 out of 83 cases (22.9%) were categorised as FIGO grade 2 and 3 out of 83 cases (3.6%) were categorised as FIGO grade 3.

A cross-table was made enlisting the diagnoses on HE and the diagnosis as per the ER, PR and p53 interpretation of the cases. The data were analysed for ER, PR and p53 categories according to Histologic type [Figure 2] and [Figure 3]. The *P* value was less than 0.05 in our study which was statistically significant, calculated using the Chi-square tests. The most occurring ER and PR category in Endometrioid carcinoma was category III. Out of all cases, 6 cases showed abnormal/aberrant/mutation-type pattern with p53 expression—3 cases showed 100% nuclear positivity and 3 cases showed complete absence of nuclear staining with p53 IHC. Rest 94 cases showed wild type pattern of p53 staining. The most occurring p53 category in Endometrioid carcinoma was category I and p53 category III being the most common in serous carcinoma. There was significant difference for all types of carcinomas. Our study showed a statistical association between ER, PR status and tumour histologic type. Higher levels of positivity was seen in endometrioid adenocarcinomas.

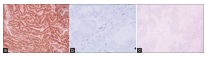

Figure 2: (a) ER and PR in Endometrioid carcinoma (ER and PR IHC, 10x) (b) ER and PR in Serous carcinoma, (ER and PR IHC, 40x) (c) ER and PR in Clear cell carcinoma, (ER and PR IHC, 4x)

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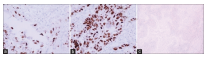

Figure 3: (a) p53 in Endometrioid carcinoma, (p53 IHC, 40x) (b) p53 in Serous carcinoma, (p53 IHC, 40x) (c) p53 in Clear cell carcinoma, (p53 IHC, 10x). (H and E = Haematoxylin and eosin, ER = Estrogen receptor, PR = Progesterone receptor, IHC = Immunohistochemistry)

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Our most remarkable findings were ER and PR total negativity in 2 cases of Clear cell carcinoma and weak positivity in 7 of the 10 Serous carcinoma cases for ER and 9 of the 10 cases of Serous carcinoma for PR. ER and PR expression was weak to moderate in the epithelial component of carcinosarcoma, with one case showing strong ER and PR expression. Occasional clear cell carcinomas and serous carcinomas showed strong PR staining. In our study, we found a statistical association between p53 status and tumour histologic type. Serous carcinomas gave the higher levels of positivity (7 cases out of 10).

In our study, though we have observed strong ER and PR expression in FIGO grade 1, there was no statistical significance ($P = 0.322$ for ER and $P = 0.181$ for PR) observed between different FIGO grades. This could be because of less number of cases in FIGO grade 3. We have observed that there was statistical significance ($P = 0.036$) between different FIGO grades with p53.

We report that there was no statistical association between the tumour stage and the ER, PR and p53 interpretation of the cases. The *P* value was more than 0.05 in our study ($P = 0.126$ for ER, $P = 0.245$ for PR and $P = 0.07$ for p53) which was statistically insignificant, calculated using the Chi-square tests. This could be because of less number of cases in stage pT2, pT3a and pT3b in our study.

We report that there was no statistical association between the tumour invasiveness and the ER, PR and p53 interpretation of the cases. The *P* value was more than 0.05 in our study ($P = .0.27$ for ER, $P = .0.234$ for PR and $P = 0.61$ for p53) which was statistically insignificant, calculated using the Chi-square tests.

Our study included 71 hysterectomy specimens and 29 endometrial curetting's. Only 50 cases of the 71 hysterectomies had pelvic lymph node dissection. These 50 cases were included in the present evaluation. We report that there was statistical association between the lymph node metastasis and the ER and PR interpretation of the cases. The *P* value was less than 0.05 in our study ($P = 0.004$ for ER and $P = 0.022$ for PR) which was statistically significant, calculated using the Chi-square tests. There was no association between the lymph node metastasis and the p53 interpretation of the cases ($P = 0.521$).

The sensitivity of ER, PR and p53 in our study was 98.00%, 97.59% and 70.00%, respectively and specificity of ER, PR and p53 was 41.18%, 58.82% and 85.56%, respectively [Table 2], [Table 3], [Table 4].

Table 2: Sensitivity and Specificity of ER

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Table 3: Sensitivity and Specificity of PR

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Table 4: Sensitivity and Specificity of p53

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Discussion

The range of age distribution was from 30-84 years. The maximum numbers of cases were seen in the age group more than 50 years forming 81% of study group. Most of the reported literature concurs with our finding of an older age and mean age of presentation of endometrial carcinomas. Goswami in 2017 conducted a study which included 34 cases of endometrial carcinoma. The age of the cases ranged from 35 to 85 years, mean age being 60.36 years [Table 5].[11] According to Garg K (2014) in a study stated that endometrial carcinoma is a disease of older postmenopausal women and is relatively uncommon in patients younger than 40 years.[12] Sunanda B (2011) reported that the median age group of patients with endometrial carcinoma is 61 years with 75-80% being post-menopausal. Only 3-5% is less than 40 years.[13]

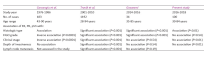

Table 5: Comparison of the present study with reported literature for comparison of ER, PR and p53 IHC markers and HE diagnosis.

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Carcangiu ML *et al.* in their study found a significant correlation between ER/PR status and tumour histologic type.[14] Our study, also showed a definite correlation between ER, PR and p53 status and tumour histologic type. Endometrioid carcinomas gave the higher levels of positivity for ER and PR with significantly low levels of p53. Though we in our study have found greater expression of ER and PR in low grade endometrioid carcinomas, we, however, did not find statistical significance in different grades [Table 5]. A study done by Mittal also showed similar results where grade 1 and grade 2 endometrial carcinomas expressed ER and PR positivity and strong p53 immunoreactivity was seen in more than 80% of serous carcinomas; in contrast, p53 is overexpressed in less than 20% of endometrioid tumours.[15] Study done by Suthipintawong C (2008), in which the authors found that ER status and PR-status were significant predictors with FIGO staging and grading.[16] Our results were similar to those of latter group of authors. A distinctive immunoprofile is seen in Clear cell carcinoma as compared to endometrioid and serous carcinomas. Lax concluded in a study that Clear cell carcinomas with serous features, showed total negativity for ER; only a few cases were weakly positive.[17] Similarly, we found negativity for ER in 2 out of 3 cases of Clear cell carcinoma. Reid Nicholson M *et al*. also quoted similar results in a study done in 2016.[18] The epithelial component in carcinosarcoma show very rare positivity (1/3) for ER/PR. We observed that with ER expression being weak to moderate in epithelial component of carcinosarcoma and one case showed strong ER expression.

Kounelis S *et al.* reported that the percentage of positive p53 in their study was 49 two-thirds of which showed either high grade or advanced stage.[19] Immunopositivity of p53 in our study was more common in serous carcinomas, 8 out of 10 cases, 7 showing weak positivity and one case showing total negativity. In the study by Wei, using a cut-off of greater than 70% expression and 0% expression for p53, an abnormal pattern of p53 expression was seen in approximately 80% to 90% cases of serous carcinoma.[20] Our p53 observation showed higher levels of p53 positivity in 7/10 cases (70.00%) of serous carcinomas. Mittal showed that p53 expression in endometrioid tumours was negative or weak in grade 1 to grade 2 tumours.[15] In our study, we found weak p53 positivity in grade 1 endometrioid carcinomas and in half cases of grade 2 endometrioid carcinomas. Lax concluded in a study that p53 expression was significantly higher in serous carcinoma compared with clear cell carcinoma[17] which was similar in our study. Our study also showed the heterogeneity of tumour cell for ER, PR and p53 content which was also seen in a study done by Carcangiu ML *et al.* in 1990.[14]

According to a study done by Swasti (2018), there exists a significant correlation between PR-positive tumours and grade, surgical stage, histology, adnexal spread, disease free survival and recurrence.[21] In the immunohistochemical study of Mutch DG *et al*. (1987), the clinical stage had no correlation with the ER status.[21] whereas, the study of Utaaker E (1987) also did not show corelation between these two parameters.[22] Though we found greater expression of ER and PR in lower stage tumour, it was not statistically significant. We report that there was no association between the tumour stage and the ER, PR and p53 interpretation of the cases. Trovik J *et al.* (2013), concluded in a study that pathologic p53 expression and loss of ER/PR expression, significantly predicted poor disease-specific survival, along with high age, non-endometrioid histology, high stage, high FIGO grade, deep myometrial infiltration and metastatic lymph nodes.[23] We also found that p53 expression and loss of ER/PR expression was associated with high age, non-endometrioid histology, high stage, high FIGO grade and deep myometrial infiltration.

A large multicentric study from a developed nation of 832 cases of endometrial carcinoma by Trovik J *et al.* (2013) has established independent correlation of ER/PR positive status with myometrial invasion [Table 5].[23] Similar results were also observed by Stoian SC *et al*. (2011)[24] and Ferrandina G *et al.* (2005).[25] Our study did not show any association between ER/PR and p53 status with tumour invasiveness, thus confirming the results previously obtained by Carcangiu ML *et al*.[14]

There are only few studies about the correlation between ER, PR and p53 status and lymph node metastases. Goswami (2017) in a study of 34 cases of endometrial carcinomas included 30 cases which had undergone hysterectomy with staging laparotomy to check the association of ER and PR status of cases of EC with incidence of nodal metastasis. The association was not found to be significant with $P = 0.19$.[11] A Chinese study by Yang B *et al*. (2016) of 200 patients at the Shanghai Cancer Centre too showed loss of ER/PR independently predicted nodal metastasis.[26] The study by Trovik J *et al.* (2013) had shown results similar to the previous study discussed.[23] Iwai K *et al.* (1999) concluded that PR IHC constitutes an independent prognostic marker of lymph node metastases. Intense p53 expression significantly correlated with lymph node metastases from endometrial carcinoma. p53 itself appeared to be an independent parameter of nodal involvement. The patients with endometrial carcinoma who showed previous negativity for PR immunohistochemistry have high chances of lymph node metastases.[27]

Immunohistochemistry with categories:

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Figures

[Figure 1], [Figure 2], [Figure 3]

Tables

[Table 1], [Table 2], [Table 3], [Table 4], [Table 5]

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