ISSN 2456-4400

Research Article International Journal of Medical Laboratory Research

PROGNOSTIC SIGNIFICANCE KI-67 EXPRESSION IN ENDOMETRIAL CANCERS: A POPULATION-BASED STUDY

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Received: 10 June 2016/Revised: 15 June 2016/Accepted: 26 June 2016

ABSTARCT: in the patient with endometrial carcinoma, there is a need for improved identification of high-risk groups that may be helpful after postoperative adjuvant therapy. We therefore studied the prognostic impact of markers for cell proliferation, cell-cycle regulation, and angiogenesis among endometrial carcinoma patients in a population-based setting. **Patients and methods**: patients diagnosed with endometrial carcinoma between 2012-2015 in Aligarh, AMU, were studied. The median follow-up for the survivors was 3 years (range 1 to 4 years), with no patient lost because of insufficient follow-up information. Paraffin-embedded tumor tissue were available in 96% of the cases (n = 22), was studied immunohistochemically for expression of *Ki-67*. The importance of this tumor markers was investigated in these patients for survival and prognosis. **Results**: The majority of cases was significantly associated with the tumor biomarkers. Age, International Federation of Gynecology and Obstetrics (FIGO) stage, histologic type, histologic grade, as well as *Ki-67* protein expression, all significantly influenced survival. Age, FIGO stage *Ki-67* expression, were the only variables with independent prognostic whereas histologic type, histologic grade, and had no independent influence. A group of high-risk patients with more than one unfavorable marker was identified. **Conclusion**: *Ki-67* protein expression showed an independent prognostic impact. Thus, information derived from routine histologic specimens identified a subgroup of high-risk endometrial carcinoma patients in this population-based study.

Keywords: Endometrial carcinoma, ER, PR, Ki-67

INTRODUCTION:

The endometrial carcinoma is the most found malignancy of the genital tract in female, with an increasing occurrence in socio-economic developed countries[1, 2]. The investigation of the immune markers that are involved in the endometrial carcinogenesis and establishing possible correlations between the studied parameters, may influence the early detection and treatment of these important lesions [3, 4]. The endometrial carcinoma is formed and develops in close relation to the plasma and tissue levels of sex steroidal hormones and their receptors.

Also, the connection with the atypical endometrial hyperplasia is recognized, associated with prolonged estrogen stimulation, of endogenous or exogenous origin, not being counterweight by progesterone [4, 5]. Out of the histological parameters with prognostic potential, the tumor stage, the tumor grade and the extent of myometrial and vascular invasion proved most useful in this regard [6,7]. The purpose of this study was to analyze the immune-expression of Ki67 in endometrial carcinomas, according to the histo-pathological parameters with prognostic value.

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MATERIAL AND METHOD:

We performed a retrospective study, in which we used post-hysterectomy specimens from 22 patients operated in the Obstetrics and Gynecology Clinics of JNMC medical college, AMU, Aligarh were used that were histopathologically diagnosed as endometrial carcinomas. The specimens were processed for histopathological and immunohistochemical examination. The histological preparation was performed by the classical method for inclusion in paraffin, followed by Hematoxylin–Eosin staining. The histopathological analysis was used in histological staging, and also for the assessment of myometrial and vascular invasion, the staging process following the FIGO system. Medical records were reviewed for age, FIGO stage, treatment, recurrence, and death. One investigator (C.S) reviewed all slides for the FIGO histologic type and grade of tumors, and the depth of myometrial invasion. The degree of the myometrial invasion was expressed as a percentage of the thickness of the myometrium. The immunohistochemical analysis was performed on serial sections, using an immune-enzymatic soluble complex and standard staining protocol. The percentage of ER, PR, Ki-67, positive cells was evaluated. Positive cells showed brown staining limited exclusively to the nuclei. In the case of ER and PR counts results were recorded as< 10%, 11-25%, 26-50%, 51-75%, and > 75%. Cases with > 10% positive nuclear staining were considered positive ER and PR.

Table.1 PI for the positive cases for ER and PR, according to the tumor grade, the myometrial invasion and the tumor stage and KI index:

Positivity index	Tumor grade			Myometrial invasion			Tumor stage		
	G1	G2	G3	Internal half	External half	No invasion	I	II	III
Ki index (%)	14	30	42	15	22	1	17	29	39
Deaths	1	2	12	5	20	0	3	3	15

RESULTS:

The mean age of the patients was 54.94 years with a range of 24 to 80 years. The 22 endometrioid carcinoma cases shows **ki** index (%) positivity in 14% were grade1, 30% were grade 2, and 42% were grade 3. The ki index(%) positivity for myometrial invasion were shown in 15%, 22% in internal half and external half while there was no invasion in 1% of the patients samples. 17% , 29% and 39% were the tumor stage I, II and III respectively for the ki index. The mean follow-up time was 12 months. There was 25% pateints died of the myometrial invasion while 21% of death were occurred in tumor garde stage during the follow-up period. Tumor grade stage and myometrial invasion showed higher Ki index also showed a higher correlation with patient deaths. (Table.1)

DISCUSSION:

The present study demonstrated that ER and PR to be independent prognostic factors for survival and recurrent tumor which was similar to many previous studies[11,12]. In a study Creasman et al[13] showed that ER-positive, PR-positive, and combined ER- and PR-positive status each implied significantly longer disease free survival times than a negative status. In a multivariate analysis of the ER status and PR status using various cut-off levels and FIGO grade of the tumor, Chambers et al[14] showed that either the ER status or the PR status was the most significant predictor of survival depending on the cut-off level chosen. This is similar to the present finding, the authors found that ER status and PR-status were significant predictors with FIGO staging and grading. Proliferative index determining with Ki-67 expression also showed independent prognostic significant similar to ER-PR status. This was in line with study of Steansson et al[15]. Other studies showed correlation with survival in endometrial carcinoma albeit only by univariate analysis19, or no prognostic significant in determining poor prognosis16, or associated with high-grade endometrial endometrioid carcinoma[17]. Fanning and associate[18] had found no association between Ki-67 expression and tumor recurrence in high-risk endometrial carcinoma. The authors explained that the lack of association might be due to exclusion of low-risk tumors and the small sample-size.

CONCLUSION:

Ki index is associated with poor prognosis and survival in endometrial patients. Also stage and tumor grade correlate with Ki index. In addition to age and FIGO stage, Ki-67 showed an independent prognostic impact. Thus, information derived from routine histological specimens identified a subgroup of high-risk endometrial carcinoma patients in this population-based study.

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CONFLICT OF INTEREST: Authors declared no conflict of interest**.**