Can Ki-67 Predict Pelvic Node Status in Endometrial Adenocarcinoma?

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Abstract

Background: The Ki-67 marker is a nuclear protein that has a direct correlation with the degree of cells proliferation that often expressed in human neoplasm.

Objective: To evaluate utilization of Ki-67 expression as predictor for pathological nodal positivity in endometrial endometrioid adenocarcinoma.

Design: A retrospective case control study.

Settings: Tertiary cancer center.

Materials and methods: We evaluated 12 histopathological slides for patients with endometrioid adenocarcinoma of the uterus for percentage of expression of Ki-67. We defined high expression as Ki-67 stained > 50% of tumor cells.

Main outcome measures: The correlation of Ki-67 high expression rates and pelvic node positivity in endometrioid adenocarcinoma.

Results: Our sample mean age at diagnosis is (58.25 years) and median age is (57 years). The rate of high expression of Ki-67 in tumor cells among cases with positive lymph nodes vs controls were significantly higher (83%) vs (17%), with (p-value = 0.04). There were no significant differences between the mean age in cases and controls (59.8 vs 56.67) with (p = 0.67), tumor grade (p = 0.3), myometrium invasion (p = 0.1), cervical stromal invasion (p = 0.2), lymphovascular invasion (p = 0.2). On multivariate analysis a high expression of Ki-67 continued to be independent predictor for lymph node positivity (p = 0.02).

Conclusions: This finding suggests that a high expression of Ki-67 plays an important role as predictor for lymph node positive in endometrioid adenocarcinoma. The level of expression of Ki-67 can be utilized for preoperative or postoperative risk assessment to predict for lymph node metastasis for cases with borderline indications for postoperative pelvic irradiation. Further prospective larger study is needed to validate this preliminary data.

Background

Endometrial cancer (EC) is the most common malignancy of the female genital tracts and the fourth most common cancer occurring in women after breast, bowel and lung cancers [1]. Total abdominal hysterectomy and bilateral salpingo oophorectomy (TAHBSO) is the standard surgical intervention for early endometrial adenocarcinoma. Addition of pelvic lymph node dissection remains controversial issue, several meta analyses and database analysis showed no differences in overall or recurrence free survival between females who had lymphadenectomy and those who did not undergo for lymphadenectomy with higher surgical morbidities in lymphadenectomy patients [2-4]. Although in early stage endometrial cancer patients the risk for lymph node metastasis is low, still adjuvant pelvic radiation is widely recommended following TAHBSO aiming to reduce pelvic recurrence. The Gynecology Oncology Group -33 study (GOG 33) identified several pathological risk factors significantly predict for lymphatic metastasis which are

currently used in different algorithm to recommend adjuvant therapy which are: tumor grade, depth of myometrial invasion, and vascular space invasion [5].

Immunohistochemical (IHC) method has been very useful for detecting several markers of possible prognostic importance for a number of cancer types. The Ki-67 protein is an (IHC) marker of cell proliferation associated nuclear antigen which is expressed in dividing cells during cell cycle (G1, S, G2 and M) but not on (G0) [6,7]. The labeling index of Ki-67 has a direct correlation with the degree of cells proliferation, and has prognostic value in several types of cancer [8-12]. The Ki-67 is a commonly used proliferation marker in breast cancer. Some data showed a high Ki-67 was significantly associated with a short disease free interval [13]. Recently, a high Ki-67 expression is being utilized as IHC marker to predict for a better response to systemic therapy in subgroup of patient with luminal-B ductal carcinoma of breast and borderline indication for chemotherapy [14,15].

Several publications on utilization of IHC markers and other biomarkers in endometrial disorders found that expression of Ki-67 may play an important role in identifying endometrial cancer transformation and cell differentiation [16-21]. Other found that high levels of proliferation and expression of Ki-67 with other biomarkers were predictive of recurrence in low grade Endometrial Stromal Sarcomas [22].

Since Ki-67 is a nuclear protein that has a direct correlation with the degree of cell proliferation, we hypothesized that Ki-67 marker be highly expressed in pathologically nodal positive endometrial adenocarcinoma.

Study Objective

To evaluate if high expression of Ki-67 in endometrial endometrioid adenocarcinoma can predict pathological lymph nodes positivity.

Patients and Methods

We conducted a retrospective case control study on adult patients' samples who presented with histologically confirmed endometrioid

Table 1: Study population characteristics.

Lymph Node	Age	Histopathology Type	Tumor Grade	Cervical stromal Involvement	Myometrial Invasion	LVI	Ki-67 Expression	Surgery	Radiation after surgery	CTH
Negative (controls)	Mean=56.67 Median=53.5 SD =12									
1	47	Endometrioid Adenocarcinoma	Grade III	absent	<50%	Positive	≤50%	Yes	Yes	No
2	51	Endometrioid Adenocarcinoma	Grade I-II	absent	<50%	Negative	≤50%	Yes	No	No
3	46	Endometrioid Adenocarcinoma	Grade I-II	absent	<50%	Negative	≤50%	Yes	Yes	No
4	56	Endometrioid Adenocarcinoma	Grade I-II	absent	<50%	Negative	≤50%	Yes	Yes	No
5	62	Endometrioid Adenocarcinoma	Grade I-II	present	<50%	Positive	≤50%	Yes	Yes	No
6	78	Endometrioid Adenocarcinoma	Grade I-II	present	>50%	Negative	> 50%	Yes	Yes	No
Positive (Cases)	Mean=59.8 Median=63.5 SD =13.5									
1	69	Endometrioid Adenocarcinoma	Grade I-II	present	<50%	Negative	> 50%	Yes	Yes	Yes
2	70	Endometrioid Adenocarcinoma	Grade I-II	present	>50%	Positive	≤50%	Yes	Yes	Yes
3	47	Endometrioid Adenocarcinoma	Grade III	present	>50%	Positive	> 50%	Yes	No	Yes
4	58	Endometrioid Adenocarcinoma	Grade I-II	absent	<50%	Negative	> 50%	Yes	No	Yes
5	41	Endometrioid Adenocarcinoma	Grade I-II	absent	>50%	Positive	> 50%	Yes	Yes	Yes
6	74	Endometrioid Adenocarcinoma	UnSP	UnSP	UnSP	UnSP	> 50%	No	No	No
Total Population = 12	Mean=58.25 Median=57 SD =12.3									

SD: Standard Deviation; CTH: Chemotherapy; LVI: Lymphovascular Invasion; UnSP: UnSpecified

adenocarcinoma of the uterus. The study was conducted in tertiary cancer center at King Abdullah Medical City. The protocol was reviewed and approved by institutional review board. Population was identified via search of hospital Electronic Medical Records between June of 2014 and June of 2016. We identified 48 cases with endometrial adenocarcinoma, then we identified 6 cases with pelvic node positive disease with no distance metastasis and we identified 6 matched controls of node negative. We match the cases and control for age and other clinicopathological characteristics including: tumor grade, lymphovascular space invasion, myometrial invasion and cervix invasion. The Immunohistochemical stain of Ki-67 was carried on unstained pathological slides taken from formalin-fixed, paraffin-embedded tissues by standard automated immunohistochemistry on Ventana machine.

We defined high expression as Ki-67 staining > 50% of tumor cells. All readings of the percentage of Ki-67 were carried out by one pathologist to overcome observers' variation (Figures 1 and 2).

Statistical analysis

Collected data was transferred and analyzed by using SPSS ver. 24 (SPSS Inc.). The correlation of high expression of Ki-67 with pelvic node positive and other factors was tested using the Pearson chi-square test and Fisher exact test. Multivariate model was estimated using the back-ward logistic regression method for statistical significance of a P-value < 0.05.

Result

All 12 patients had confirmation of endometrial endometrioid adenocarcinoma; all underwent TAHBO and pelvic lymph node dissection (Table 1). Population mean age at diagnosis is (58.25 years) and median age is (57 years). We found the rate of high expression of Ki-67 in cells among cases with positive lymph nodes (83%) vs controls with negative lymph nodes (17%), which was significantly higher (p-value = 0.04). There were no significant differences between the mean age in cases and controls (59.8 vs 56.67) with (p = 0.67), tumor grade (p = 0.3), myometrial invasion (p = 0.1), cervical stromal invasion (p = 0.2), lymphovascular invasion (p = 0.2). On multivariate analysis a high expression of Ki-67 continued to be independent predictor variable for lymph node positivity (p = 0.02).

Discussion

Endometrial adenocarcinoma of the uterus is the most common cancer of female genital tracts. Majority of cases present in early stage disease, and assessment of the risk for pelvic node metastasis is the most important prognostic factor that predicts for relapse. Currently in our clinical practice we offer pelvic lymph node dissection and/or pelvic node irradiation to almost all patients with early disease and this mainly because we could not identified patients with higher risk for pelvic nodal metastasis based on histopathological data alone.
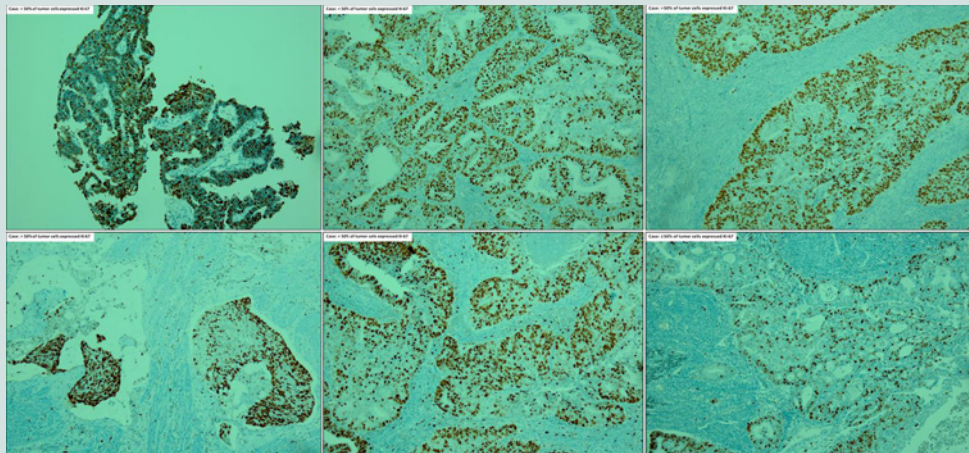
Figure 1: Immunohistochemical stain for Ki-67. In 5 out of 6 cases, there is high percentage of nuclear stains in tumor cells, more than 50%.
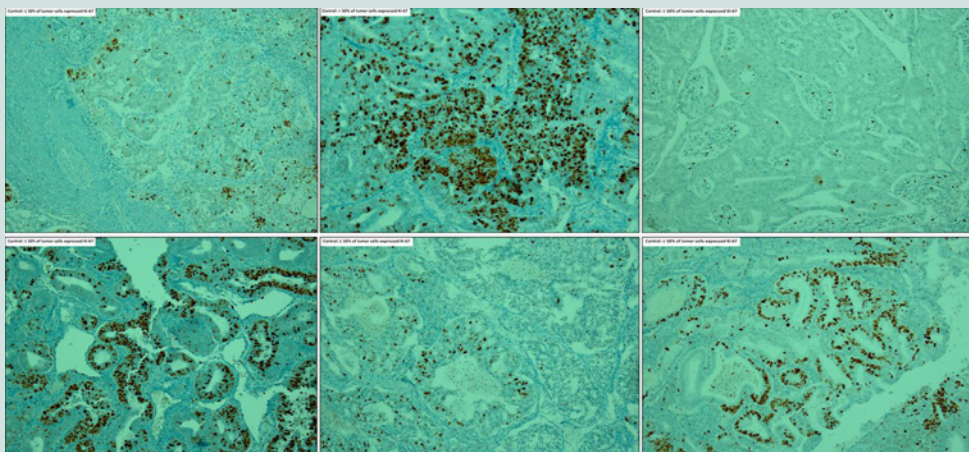

Figure 2: Immunohistochemical stain for Ki-67. In 5 out of 6 controls, there is low percentage of nuclear stains in tumor cells.

Tumor cells proliferation is an important biological parameter that reflects disease behavior, which might also predicts for disease prognosis. The nuclear protein Ki-67 is a proliferative marker and widely used prognostic indicator in several cancer diagnosis, including breast cancer, bladder cancer, gastrointestinal neuroendocrine tumor, oral cancer, lung cancer, astrocytoma, and pituitary adenoma [8-12,23,24].

In endometrial cancers, Ki-67 in addition to other biomarkers was found to be useful marker to distinguish benign proliferative conditions from cancer precursors and low grade endometrioid adenocarcinomas (16,25). In a study on 270 endometrial samples Ki-67 expression was found to be higher in samples with high-grade endometrioid carcinomas vs normal endometrial samples [26].

Conclusion

Our data suggests that high expression of Ki-67 (> 50% of tumor cells) is correlated with microscopic pelvic lymph node positive metastasis of endometrioid adenocarcinoma of the uterus. This IHC marker can be utilized as additional predictor to other histopathological prognostic factors to identify group of patients with true high risk pelvic nodal microscopic metastasis, whom are actually benefit from adjuvant pelvic nodal irradiation in early endometrioid adenocarcinoma.

Limitations

At the end we have to address some of the limitations of our results which are due to the retrospective nature of the study and small sample size. Our team is planning to validate this preliminary data by conducting a prospective analysis on a larger sample size.

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