# Liquid based endometrial cytology in diagnosis of high-grade endometrial carcinoma with emphasis in recent advances and tissue correlation

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**Abstract:** Background: Invasive endometrial cancer is the most common cancer of the female genital tract and from clinico-pathologic standpoint endometrial serous carcinoma as a prototype of type II endometrial carcinomas, has poor prognosis and 46% of these tumors are going to be diagnose in metastatic and high stages. The aims of this research is comparison of endometrial cytological findings in high grade endometrial carcinoma with tumor histology and achieve accuracy, sensitivity, specificity, positive predictive value and negative predictive value of this method in diagnosis of high grade endometrial tumors. Methods: Seventy patients, who had been candidate for hysterectomy, underwent for endometrial brush cytology before surgery. The prepared liquid based cytology smears examined by gynecological pathologist and the cytologic findings compared with histologic results and stages in a blind fashion. Results: All 12 cases of high- grade malignant lesions diagnosed by permanent histologic sections were diagnosed by cytological smears except one. There was complete correlation between cytologic and histologic findings regarding to tumor type and nuclear grades. The accuracy, sensitivity, specificity, PPV and NPV of endometrial brush cytology were calculated as 98%, 91%, 100%, 100% and 98% respectively. Conclusion: Endometrial cytology is a simple and feasible method for diagnosing of endometrial malignant lesions and if this high sensitivity and specificity be achieved in diagnosis of endometrial premalignant lesions such as endometrial intraepithelial neoplasia (EIN) and endometrial glandular dysplasia (EmGD) in large studies, it may be useful in early diagnosis and screening of endometrial lesions.

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**Keywords:** Endometrial Cancer, Endometrial Intraepithelial Neoplasia, Endometrial Cytology

## 1. Introduction

Endometrial carcinoma is the most common invasive cancer of the female genital tract in the U. S .A. and accounts for 7% of all invasive cancers in women, excluding skin cancer (Crum et al., 2006).The incidence of endometrial cancer in postmenopausal women with abnormal uterine bleeding (AUB) is 3.7% to 17.9% and an increase in its incidence has been observed in recent decades (Tinelli et al., 2008). Endometrial cancers usually arise in postmenopausal women and although in over 80 of cases it is associated with postmenopausal bleeding, which often allows detection and cure at an early stage, however 7470 deaths attributed to uterine corpus malignancies estimated for 2008 (Jemal et al., 2008). This relatively high mortality rate suggests that prevention and/or early detection remain highly essential approaches to the prevention of endometrial cancer-related mortality (Fadare and Zheng, 2008). From clinicopathologic point view, endometrial carcinoma can be divided into two groups, type I and type II. Tumors in type I category usually develop in perimenopause women, show association with hyperestrogenism, usually preceded by atypical endometrial hyperplasia or endometrial intraepithelial neoplasia (EIN) and have favorable clinical outcome. Microsatellite instability, mutations in *PTEN* and *K-ras* genes and nuclear B-Catenin accumulation are the most known molecular- genetic alterations associated with these tumors (Fadare and Zheng, 2008). In contrast type II cancers, the prototype of which is uterine serous carcinoma typically occur in older age group, arising in the background of resting endometrium and display chromosomal instability, frequent mutation in p53 gene and over expression of mutant p53 protein and low frequency of expression of hormone receptors (Prat et al., 2007; Lax, 2004; Lax and Kurman, 1997). Type II endometrial carcinomas are more likely to present with metastatic disease at diagnosis and carry a poorer prognosis (Chan et al., 2003). Although cervical cytology created a significant change in cervical cancer incidence in western countries and although cervical channel is far only two centimeter from uterine

corpus mucosa, the endometrium has not be screened for neoplastic lesions to the same extent as the uterine cervix which is surprising that the endometrial cytological sampling is exceedingly easy. As a result, in last two decades, some of the gynecological pathologists provided convincing evidences that endometrial cytology can be used as an effective methods for diagnosis of endometrial neoplasms and preneoplastic lesions (Hagiwara et al., 2005; Maksem and Knesel, 1996). In this prospective study, our aim was to detect the accuracy, sensitivity, specificity, positive predictive value and negative predictive value endometrial cytology in diagnosis of endometrial high -grade carcinoma and compare the cytological findings with tumor histologic grade and stage.

## 2. Materials and Methods

In a prospective study, all cases that have been candidate for hysterectomy during March 2010 to March 2011 underwent endometrial cytological sampling by standard sterile cytobrush (Endo brush standard, Laboratories' C.D.D Paris-France). The endometrial brushing was done by inserting of endobrush into the endometrial cavity and brushing all aspects of the endometrium according to the recommended instruction. After remove of the brush the head of brush transferred to preservative solution (Specimen Preservative- LGM international, INC. FL. USA) for preparing of liquid based thin layer smear. The prepared smears were studied for cellularity, presence or absence of malignant cells, architectural patterns, the severity of nuclear atypia, presence of nucleoli and mitotic count. The patient's clinical and pathologic information were extracted from pathology department file. The above mentioned cytology findings then compared with histologic results including histologic subtype, histologic grade and tumor stage. Finally data were analyzed by using Exact Fisher Test in *SPSS 16* software and $P < 0.05$ considered significant. Ethical approval was received from the ethical review board before this study was undertaken.

## 3. Results

The median patient age was 44.7 years (range, 34-69 years). 11 out of 70 prepared smears were malignant and showed high grade nuclei, papillary structures, mitotic figures, tumor giant cells and psammoma bodies in various proportion. Low grade tumors were excluded from this study. In comparison with histologic findings all of the high grade endometrial carcinomas were diagnosed by liquid based cytology except one. Statistical analysis by exact Fisher test revealed that data distribution was significant ($P<0.05$) and accuracy, sensitivity, specificity, positive predictive value and negative predictive value were calculated as 98%, 91%,100%, 100% and 98% respectively.

## 4. Discussion

High grade endometrial carcinoma composed of endometrial serous carcinoma, clear cell carcinoma and grade 3 endometrium carcinoma. Although the two former cancers categorized as type II endometrial carcinoma and showing aggressive clinical course and poor prognosis, the grade 3 endometriod type often shows deep myo-invasion and higher stage at the time of diagnosis also. Type II endometrial carcinoma typically seen in older patients, arise from resting endometrium and usually shows metastasis in first diagnosis. Most of these tumors are associated with chromosomal instabilities, P53 mutation and products of mutant gene product and loss of steroid hormone receptors (Prat et al., 2007; Creasman et al., 2004; Dunton et al., 1991). Creasman et al. in survey of FIGO annual report noticed that 46% of these tumors represent in stage II-IV, while this rate was 21% for endometriod type (Lax, 2004; Creasman et al., 2004). Otherwise when the five year survival rate in some studies has been reported 50-80% for stage I serous carcinoma, this rate was 80-90% for stage I endometriod tumors (Creasman et al., 2004; Lax and Kurman, 1997; Dunton et al., 1991; Slomovitz et al., 2003; Maksem et al., 2007). Therefore the early diagnosis of these tumors has more impact on the patient outcome. Although a few numbers of these tumors can be detected in Pap smear, this test has no enough specificity and sensitivity for screening of these tumors. In our study the achieved high sensitivity and specify of endometrial cytology for detecting of high grade endometrial carcinoma highlights the fact that this method can be used easily for detection of endometrial tumors in the expert hands. Higawara et al. in alimited study identified 5 endometrial serous carcinoma by applying the cytological criteria in comparison with 10 low grade cancers (Hagiwara et al., 2005). It seems that the high potential of this methods in identifying high grade endometrial cancers depends on the presence of obvious high grade nuclei(fig 1A, 1B, 1C), papillary structures (fig 2A,2B,2C), easily found mitotic figures, rare atypical mitosis (fig3), and rare psammoma bodies (Maksem et al., 2009). Although based on the major genetic and clinical differences between type I and type II endometrial cancers this classification has its own diagnostic value, presence of several pitfalls in FIGO grading system, low reproducibility in nuclear grading and similar clinical outcome in the most cases of high grade tumors, encouraged many investigators to suggest other grading systems with high interobserver and

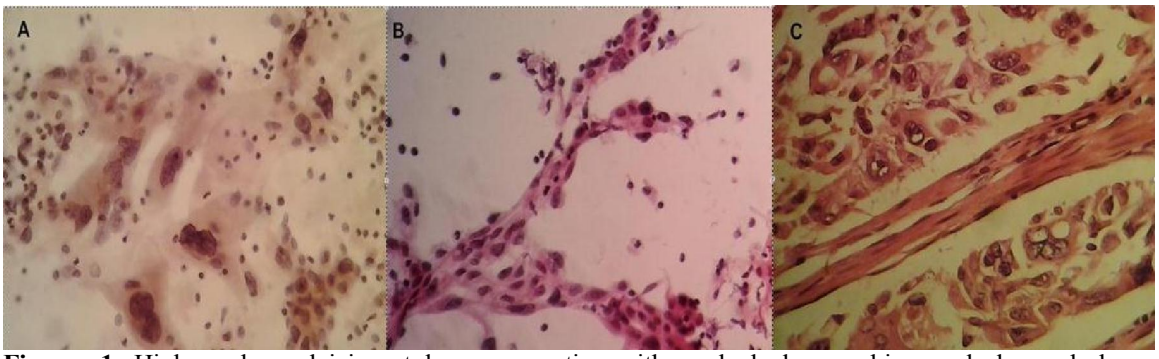
intraobserver agreement. In some of the recent studies, the researchers focused on relationship between tumor histologic grade and prognosis (Ambros et al., 1994; Takeshima et al., 1998; Zaino et al., 1995). In a large study conducted by Alkushi et al. including 202 cases of endometrial carcinoma, they suggested a new grading system and tried to correlate between each histologic findings and patient outcome (Alkushi et al., 2005). Based on this study all of the endometrial carcinoma can be grouped in a binary grading system as low grade and high grade tumors. In this study we applied the modified pattern of this system in cytologic specimens and can identified nearly all of the high grade tumors. In conclusion, we found that the endometrial brush cytology is an effective diagnostic procedure in experienced hands in outpatient's clinics for detecting high grade endometrial malignant epithelial tumors. Since the diagnosis of these tumors in early stages and pre-invasive phases has considerable improve in patient's outcome, we suggest large scale studies for assessment of the ability of this procedure in diagnosis of endometrial precursor lesions such as endometrial intraepithelial neoplasia (EIN) and endometrial glandular dysplasia (EmGD).

**Conflict of interest**

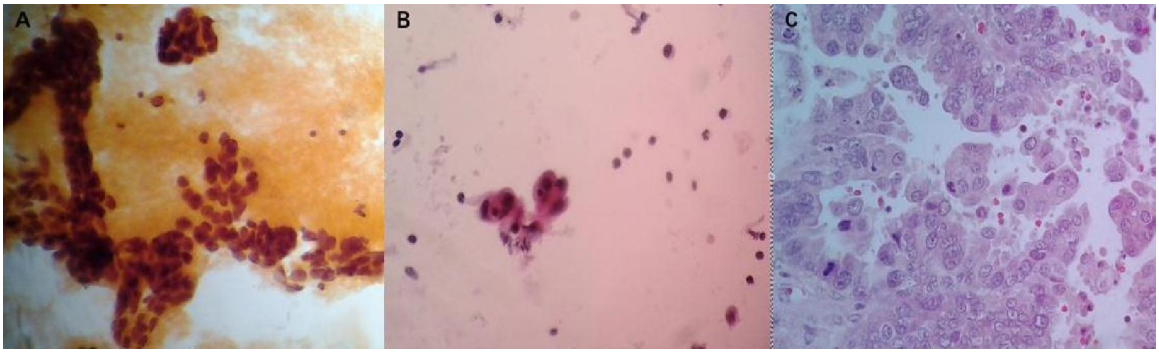
We declare that we have no conflict of interest.

**Acknowledgement**

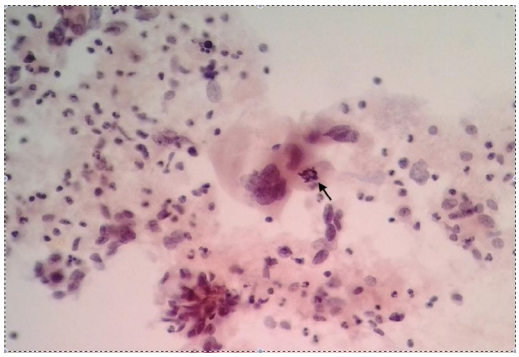
This study was supported by grant from the Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.




**Figures 1:** High grade nuclei in cytology preparation with marked pleomorphism and clumped chromatin (A), Obvious papillary structure with high grade nuclei (B), corresponding histology with myoinvasion (C).




**Figures 2:** Figure 2: Cytology preparation from a case of uterine serous carcinoma showing papillary structures (A and B), corresponding histology section (C).



**Figures 3:** An Atypical mitosis (arrow) found in cytology smear of high grade endometrial carcinoma.

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