



# He4 Marker in Endometrial Cancer: Reality or Fiction?

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## Abstract

**Purpose of the review:** HE4 has been recently studied in endometrial cancer, but no conclusive results have been obtained. The role of the marker to differentiate between benign pathology and cancer and its relationship with factors of poor prognosis in endometrial cancer has been studied in this review.

**Conclusions:** Clinicians could use HE4 marker in women with endometrial cancer to help them in the preoperative decision-making process.

**Keywords:** Endometrial Neoplasms; HE4; tumor marker

## Introduction

Endometrial cancer (EC) is the sixth cause of cancer in women in developed countries and the 2% of cancer deaths in woman [1]. Most cases of EC have good prognosis as they are usually diagnosed in early FIGO stage (80% in stage I). The survival rate in 5 years is about 80-85% [2] which decrease if metastasis or regional spreading appear (5 years survival of 68 and 17 % respectively) [3,4]. The most important poor prognosis factors in EC consist in [2] lymphatic node involvement, advanced FIGO stage (III-IV), myometrial invasion > 50 %, high histological tumor grade (G3) and non-endometrioid histological subtype. Other bad prognosis factors are: age over 60 years, lymph-vascular space invasion (LVSI), tumor size over 2 cm, uterine isthmus or cervical involvement or extra-uterine spreading [2]. At present time no tumor marker is validated for being used in the management of patients with EC. Even though several markers have been studied with unsatisfying results. HE4 is a 25 kDa protein secreted in distal part of epididymis which was discovered in 1991 by Kirchhoff [5]. It is an endogenous protease inhibitor detectable in the circulation, as it is a member of the whey-acidic-protein four-disulfide core domain family. High HE4 levels can be detected in vas deferens, salivary glands, respiratory system, mammary tissue and female genital tract [5].

In 1999 Schummer discovered that HE4 gene is overexpressed in ovarian cancer and, recently, it has been found out that HE4 plays a role on regulation and growth of ovarian and endometrial

tumors [5]. HE4 serum value can be disrupted by some factors like renal function, patient age, smoking habit and coexistence of certain tumors, as it has been told [5]. Thus, the normal ranges of this marker need to be defined among women of different ages, abnormal renal function and smoking habit [6]. The aim of this study is to review the current use of the preoperative HE4 tumor marker value in patients with EC.

## Use of He4 in Endometrial Cancer Diagnosis

The role of the HE4 and others tumor markers to differentiate between benign endometrial pathology like hyperplasia and cancer has been studied [7] first studied the application of HE4 value in EC in 2008. A sensitivity (SEN) of 45.5 % and specificity (SPE) of 95 % was found to separate women with EC from healthy women. Some studies compare the accuracy of HE4 and CA 125 in the diagnosis of EC [8,9]. The reviewed papers show the superiority of HE4 for the diagnosis of EC [10] performed a meta-analysis of 12 papers where it was demonstrated that HE4 value (SEN 71 %) performs better in the diagnosis of EC, compared to CA125 (SEN 35%) with no statistically differences in SPE. Huang et al. conducted a recent meta-analysis with 25 studies that analyzed the diagnosis value of HE4 and CA 125 together. They conclude that the combined detection of serum HE4 and CA125 is a highly accurate diagnostic tool for EC with a combined SEN and SPE for the diagnosis of 63% 90% respectively [4].

## Use of He4 as a Prognostic Marker in Endometrial Cancer

A review of the literature was made to analyze the potential association with HE4 as a preoperative marker and some of the most important prognostic factors in EC. A significant correlation between advanced stage disease (III-IV) and higher HE4 levels was showed in several studies [11,12] Although there is little evidence to find a lineal correlation between HE4 serum marker and the FIGO stages, Abdalla et al [13] found a significant rise of HE4 in patients with stage III-IV vs I-II, IB vs IA, II-III vs I, IB to IIIC vs IA and IIIC vs IA to IIIB. This finding demonstrated that HE4 can be used for differentiated stages II-IV from IA stage. Some authors found that the serum level of HE4 in patients with deep myometrial invasion (>50%) was significantly higher than that in women with superficial myometrial invasion (<50%) [6,11].

A statistically significant difference of HE4 level was found between G1 FIGO grade tumors and G2-G3 ones, which have a higher value of preoperative HE4 [12,13]. However, some of the studies did not find this difference [11,14]. The correlation of the marker depending on the subtype EC (endometrioid vs non endometrioid) is not so clear yet. The PORTEC 1- 2 trials [15] pointed LVSI as a risk factor for regional nodal recurrence and for distant metastasis as has been said previously. Evidence in the correlation of HE4 and LVSI is still limited with a reduced number of studies that refer to the relationship between HE4 and LVSI [16] showing all of them a significant rise of HE4 in patients who present LVSI in surgical specimen. It seems that there may be a relationship between the preoperative HE4 value and the presence of positive lymph nodes at the time of diagnosis. Wang et al. [6] in a broad and significant study of 258 patients, studied the predictive values of HE4 in the detection of lymph node metastasis and obtained a sensitivity (SEN) of 82.4 %, specificity (SPE) of 52.3 %, which reflects a useful preoperative tool in the study of node involvement. A recent study of [17] shows the relationship between risk factors of EC and lymphatic node involvement. They studied 6 risk factors in EC (serum CA 125 > 27.6 U/mL, serum HE4 > 132 pmol/L, nonendometrioid histology, myometrial invasion > 50 %, positive peritoneal cytology and LVSI). All of them were independent risk factors for pelvic node affectation. The incidence of pelvic metastasis was 0.0% in the absence of the above 6 factors, while the incidence was 100% in the presence of more than four risk factors.

## Conclusion

HE4, a novel preoperative serum marker, seems to be useful to diagnosis and manage EC and is related to the most important prognostic factors in EC (deep myometrial invasion, FIGO advanced stage, lymphatic involvement and FIGO tumor grade, among others). Further prospective studies are needed to validate HE4 as a preoperative prognostic tool and to apply this marker in the regular clinical practice.

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