REVIEW ARTICLE

HE4 tumor marker as a predictive factor for lymphatic metastasis in endometrial cancer

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KEYWORDS

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SYNOPSIS

As a preoperative tumor marker, human epididymis protein 4 (HE4) seems to be useful for managing endometrial cancer and is associated with lymphatic metastasis.

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ABSTRACT

Endometrial cancer is the most common genital cancer in high-resource countries. Treatment is essentially surgical, but the role of lymphadenectomy in the treatment of low-stage and low-grade tumors has not been defined. Although no tumor factors have been validated for use as preoperative prognostic markers of endometrial cancer at yet, human epididymis protein 4 (HE4) has received much interest as a potential diagnostic and prognostic tumor marker. Since 2008, several studies have explored its utility in the management of endometrial cancer: HE4 may be a useful preoperative prognostic marker because it is associated with lymphatic metastasis and other unfavorable factors in endometrial cancer. In addition, some studies have explored a HE4 cutoff value to classify patients according to lymph node involvement. HE4 might be beneficial as a serum marker that helps clinicians in the decision-making algorithm for treatment of endometrial cancer, enabling them to perform individualized operations and decrease the adverse effects of unnecessary surgery.

1 INTRODUCTION

Endometrial cancer is the sixth cause of cancer among women, with a global incidence of 380 000 cases in 2018 [1], accounting for 2% of deaths due to cancer among women in high-resource countries [2]. Human epididymis protein 4 (HE4) was discovered in 1991 by Kirchhoff et al. [3] as a 25-kDa protein secreted in the distal part of the epididymis. More recently, it has been shown to play a role in the regulation and growth of ovarian and endometrial tumors [4]. HE4 is currently used as a marker in ovarian cancer, and has been used in the management of this disease since the FDA approved the ROMA algorithm in 2009 [5].

A serum tumor marker that can predict lymphatic involvement, advanced-stage disease, or myometrial invasion before surgery would be useful for personalizing the type of surgery. At present, however, no tumor marker has been validated as a preoperative prognostic marker for endometrial cancer, although some studies have reported the utility of HE4 in this disease. It seems that HE4 preoperative values and prognostic variables of endometrial cancer may be correlated [6-9]; however, evidence that relates serum HE4 levels to prognostic factors of endometrial cancer is limited with conflicting results.

Following the ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer in 2016, it was concluded that “There is evidence that the serum tumor markers cancer antigen 125 (CA125) and, more recently, human epididymis protein 4, are significantly correlated with histological grade, FIGO stage, lymph node metastasis, myometrial invasion and cervical involvement. However, the appropriate cutoff has not been established and evidence that serum marker assessment is clinically useful is lacking” [10]. This conclusion indicates that there remains a lack of evidence on the role of HE4 in endometrial cancer.

There are several well-defined factors for a poor prognosis in endometrial cancer, including myometrial invasion more than 50%, high histologic grade (G3), and advanced FIGO stage (III–IV) [10]. The presence of lymphatic metastasis is also an important factor for poor prognosis, not only because it indicates advanced FIGO stage, but also because it represents a potential focus of disease recurrence and metastasis, reducing long-term survival [6].

The main risk factors for lymphatic node involvement are histologic grade and myometrial invasion [11, 12]. The relevance of lymphatic involvement is reflected in the survival rate. Thus, the 5-year survival rate in endometrial cancer is approximately 80%–85%, but it decreases to 68% and 17% if regional spreading and metastasis, respectively, are present [10]. Todo et al. [12] previously suggested that lymphatic invasion may be estimated at the preoperative stage because it is related to the tumor volume on MRI and the histologic grade determined by preoperative biopsy; however, it is important to identify other predictive factors for lymphatic metastasis. The aim of the present review was therefore to summarize the evidence on the use of the HE4 tumor marker in endometrial cancer and its correlation with the presence of lymphatic metastasis.

2 METHODS

The present review was based mainly on publications in PubMed identified by using an advanced search by title with the following terms: (endometrial cancer [Title] OR endometrial carcinoma [Title]) AND (HE4 [Title] OR human epididymis protein 4 [Title]).

Several search filters were used, including the year of publication (2008 to 2019), the type of paper (guideline, meta-analysis, review, or clinical trial) and language (English). Among the studies retrieved, those on the prognostic value of endometrial cancer were selected. Those that did not examine the prognostic value of HE4 and those referring to the postoperative period were excluded.

A secondary search was conducted to analyze the evidence of lymphatic involvement and its relationship with prognosis in endometrial cancer. International clinical guidelines such as the ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer and the NCCN Clinical Practice Guidelines in Oncology were searched via PubMed.

The review did not require approval from an ethics committee or informed consent because it involved summarizing data published in recent studies, and neither patient information nor individual data were collected.

3 SUMMARY OF FINDINGS

3.1. Current use of HE4 as a prognostic marker of lymphatic metastasis

Existing evidence on the application of HE4 to detect lymphatic metastases is conflicting. Some studies have found no significant difference between preoperative HE4 level and lymphatic metastasis [13-15], whereas others have reported a significant rise in preoperative HE4 if lymphatic involvement is present [6, 8, 9,16-18].

In a notable study of 258 women, Wang et al. [6] investigated the predictive value of HE4 in the detection of lymph node metastasis, obtaining a sensitivity of 82.4%, specificity of 52.3%, positive predictive value of 10.9%, and negative predictive value of 97.7%, indicating that HE4 is a useful preoperative tool in the assessment of node involvement.

In 2019, Li et al. [17] studied the association between risk factors of endometrial cancer and the presence of lymphatic metastasis, considering both histologic risk factors (positive peritoneal cytology, myometrial invasion >50%, non-endometrioid histology, and lymph-vascular space invasion) and preoperative risk factors (serum CA125 >27.6 U/mL and serum HE4 >132 pmol/L). They found that the incidence of pelvic metastasis was 0%

in the absence of all six factors, but 100% if four or more risk factors were present. Li et al. [17] concluded that all six factors were independent risk factors for lymphatic metastasis and that, if none of these independent risk factors was present, the woman was unlikely to have pelvic metastasis and lymphadenectomy should not be recommended.

By contrast, studies reporting significant differences in HE4 values when analyzing other prognostic factors, such as deep myometrial invasion, did not find this correlation when studying lymphatic involvement [8,19]. One study suggested that the discrepancy in correlation with lymph node metastasis might be due to the small number of cases [19]. By contrast, another proposed that in some studies there are not enough women undergoing lymphadenectomy; therefore, the association with HE4 does not reach significance [8].

In recent years, many pathologic factors have been studied as predictors of lymphatic metastasis in endometrial cancer with the objective of identifying women with a low risk of lymphatic metastasis, and thereby reducing overtreatment and the complications associated with lymphadenectomy. Other researchers have studied factors other than HE4 to predict lymphatic involvement preoperatively for women with endometrial cancer. For example, Todo et al. [12] carried out a multivariate analysis, identifying serous adenocarcinoma subtype, a volume index of 25 or higher, a preoperative grade of 3 by biopsy, and high serum CA125 levels as independent risk factors for lymphatic metastasis. Their study suggests that lymphadenectomy should be avoided for women without risk of para-aortic node involvement, but would be necessary in cases of serous adenocarcinoma.

In line with Li et al. [17] and Todo et al. [12], the ASTEC trial [20], a multicentric randomized study of 1400 women, demonstrated that lymphadenectomy had no benefit on survival for women with stage I disease. Thus, the need of lymphadenectomy in early stage disease remains unclear. Current evidence on the association between preoperative HE4 values and other prognostic factors in endometrial cancer is summarized in Table 1.

3.2. Finding a cutoff value of HE4 for detecting lymphatic involvement

In ovarian cancer treatment, there is consensus on an HE4 cutoff value of 150 pmol/L for predicting lymphatic involvement [6]; by contrast, no HE4 cutoff value currently exists in the management of endometrial cancer. Some studies have tried to identify an HE4 cutoff value to classify women in accordance with the presence of lymphatic involvement with varied results.

In 2013, Antonsen et al. [18] reported a cutoff of 70 pmol/L to classify women with lymphatic involvement with a sensitivity of 75.9% and specificity of 48.8%. To obtain a sensitivity of at least 80%, the cutoff value was lowered to 57 pmol/L with a corresponding specificity of 37.8%.

In 2016, Prueksaritanond et al. [21] reported a similar cutoff of HE4 (79 pmol/L) to predict lymphatic involvement, differentiating women with high and low risk for lymphatic metastasis with a sensitivity of 83.3% and specificity of 80% (area under the curve [AUC], 0.88; *P*=0.003). Additionally in 2016, Dobrzycka et al. [22] conducted a study among 78 women with early stage endometrioid adenocarcinoma to identify a cutoff value to select women who would benefit from lymphadenectomy. They reported that an HE4 value of 78 pmol/L with an AUC of 0.814 (95% confidence interval, 0.72–0.89) had a sensitivity of 86.6%, specificity of 67.2%, negative predictive value of 88.4%, and positive predictive value of 51.2%.

In 2017, Wang et al. [6] reported a cutoff value of 72.9 pmol/L with a sensitivity of 82.4% and specificity of 52.3%, whereas in 2018 Abbink et al. [8] selected a cutoff value of 130 pmol/L with an AUC of 0.72, resulting in a sensitivity of 65% and specificity of 79%.

Based on the results of Abbink et al. [8], Li et al. [17] concluded that women who had a preoperative HE4 value of 132 pmol/L or higher were four times more likely to have lymphatic involvement as compared with women with HE4 values lower than 132 pmol/L.

In summary, the cutoff value for HE4 as a predictive factor of lymphatic involvement was

found to be approximately 70 pmol/L in most studies; however, Abbink et al. [8] reported a much higher HE4 value. It should be noted that the study populations are not homogeneous; for example, the study of Dobrzycka et al. [22] included only women with a good prognosis (i.e., endometrioid subtype and early stage disease).

4 CONCLUSION

A novel serum preoperative marker, HE4, is associated with the presence of lymphatic metastasis in endometrial cancer. Although it seems to have predictive value, it is necessary to carry out further research to validate a cutoff value before this marker can be implemented in daily clinical practice.

In the future, clinicians might be able to use preoperative HE4 together with other accepted tools (e.g., imaging test, endometrial biopsy) to individualize the type of surgery and even to avoid lymphadenectomy for selected women with endometrial cancer, but again, further studies will need to be performed. Lastly, it would be interesting to analyze the long-term prognosis value of HE4 in endometrial cancer and its role in the detection of relapses in the postoperative follow-up of women affected by this disease.

AUTHOR CONTRIBUTIONS

AER conceived and designed the review, and drafted the manuscript. TCG acquired the data and drafted the manuscript. MBV designed the review, analyzed the data, and drafted the manuscript. CDBT designed, structured, and revised the manuscript. PJCM designed of the review, interpreted the data, and revised the manuscript. LBM conceived the review, conducted the search, and revised the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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TABLE 1 Relationship between HE4 value and other prognostic factors in endometrial cancer

Study	Year	Association between HE4 and prognostic factor				
		Myometrial invasion	**Lymphatic metastasis**	**FIGO grade**	**Histologic type**	**FIGO stage**
Bignotti et al. [16]	2011	*P*<0.001	*P*=0.017	*P*<0.010	*P*=0.680	*P*<0.001
Moore et al. [14]	2011	*P*=0.002	*P*=0.293	*P*=0.022	NA	*P*=0.593
Kalogera et al. [23]	2012	*P*<0.001	NA	NA	*P*=0.830	*P*=0.005
Mutz-Dehbalaire et al. [15]	2012	*P*=0.010	*P*=0.480	*P*=0.999	*P*=0.791	*P*=0.485
Zanotti et al. [9]	2012	*P*<0.001	*P*<0.010	*P*<0.010	*P*=0.638	*P*<0.001
Angioli et al. [24]	2013	*P*=0.012	NA	NA	*P*<0.001	*P*<0.050
Saareleinen et al. [25]	2013	*P*<0.001	NA	*P*=0.012	NA	*P*=0.001
Capriglione et al. [13]	2015	*P*<0.050	NA	*P*<0.050	*P*<0.050	*P*<0.050
Wang et al. [6]	2017	*P*<0.001	*P*<0.001	*P*=0.008	NA	*P*<0.001
Abbink et al. [8]	2018	*P*<0.010	*P*<0.010	*P*=0.050	*P*=0.210	*P*=0.010

Abbreviation: NA, not available.