

## Prognostic Role of Human Epididymis Protein 4 (HE4) in Ovarian Cancer Treatment: Our Point of View

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### Introduction

In the last 10 years, the marker “Human Epididymis protein 4 (HE4)” for the management of gynecological tumors has entered powerfully in the world literature. At the moment, carrying out an accurate research in the main scientific portals such as PubMed, we can find more than 2,000 works concerning Cancer antigen-125 (Ca125), but those concerning HE4 are less than 400. The assessment of the prognostic significance of Ca125 has been described in more than 1000 scientific papers, whereas in the case of HE4 such works are only about 100. The HE4 gene product is an N-glycosylated protein which is secreted into the extracellular environment and can be detected in the bloodstream of patients with ovarian cancer. Diagnostic strategies for discriminate benign neoplasm from malignant Epithelial Ovarian Cancer (EOC) use tumor markers, imaging exams and combination algorithms. Ca125 is the best documented circulating marker and the most frequently recommended by clinical practice guidelines, despite its low specificity. To compensate for the low specificity of Ca125, new markers were studied: HE4 is one of the most promising; HE4 has demonstrated good sensitivity and specificity in detecting EOC, overcoming the traditional role of Ca125. So, the role currently assumed by HE4 marker has been to aid in the diagnosis of malignant ovarian neoplasm. In recent years, however, these markers (HE4 and Ca125) have assumed an important significance in the assessment of prognosis and response to chemotherapy.

### Prognosis

There are about twenty articles on the prognostic potential

of HE4 in the world literature. Peak and his group, in 2011, were the first that evaluated Progression Free Survival (PFS) and its correlation with HE4 values, finding out that in advanced stage, the median PFS of patients with elevated serum HE4 levels was about 20 months, whereas that of patients with normal serum HE4 level was about 24 months, resulting in a statistically significant difference ( $p=0.029$ ) [1]. Also Kong et al. in 2011 confirmed these results, demonstrating that HE4 was an independent prognostic factor for PFS ( $p=0.036$ ) [2]. Another group guided by Bandiera concluded that HE4 represented an independent prognostic factor for shorter OS, disease free survival (DFS) and PFS [3]. Overall Survival (OS) was also studied in relation to the levels of HE4 and the first group to publish the data was the one led by Kalapotharakos, in 2012, they reported that high levels of HE4 were an independent prognostic marker for worse prognosis with an Hazard Ratio (HR) 2.02, suggesting the predictive role of preoperative HE4 for OS [4].

In 2012, Steffensen et al. found that the combined score of HE4 and CA-125 was highly predictive of both PFS and OS in multivariate survival analysis [5]. In 2014, Braicu and his group reported that HE4 and platinum response were the only independent prognostic factors for OS ( $p<0.001$  and  $p=0.044$  respectively) [6]. Kayser in 2014 evaluated the association between the pretreatment serum HE4 levels or the Risk of Ovarian Malignancy Algorithm (ROMA) scores with PFS and Disease-Specific Survival (DSS) concluding that both are not independent prognostic factors [7]. Some studies have also evaluated the combination of the two markers Ca125 and HE4. For example in 2016, Nassir et al. reported that the combination of elevated levels of CA125 and HE4 revealed significantly worse estimated

median PFS with an HR 8.14 and slightly worse PFS in patients with only one biomarker elevated (HR 1.46,  $p=0.292$ ) compared to those patients with any biomarker was elevated. For the estimated median OS, their analysis revealed similar results [8]. In 2016, Steffensen reported that patients with an increase in HE4 of  $>50\%$  at 3- and 6- month follow-up compared to the end-of-treatment sample had significantly poorer PFS HR, 2.82 ( $P=0.0052$ ) and HR, 7.71 ( $P<0.0001$ ), respectively. The corresponding CA125 levels ( $>50\%$ ) showed HRs of 1.86 ( $P=0.0512$ ) and 2.55 ( $P=0.0011$ ), respectively. Multivariate analysis confirmed HE4 as a predictor of short PFS, with an HR of 8.23 ( $P<0.0001$ ) at 6-month follow-up [9]. In addition, in 2012, Trudel et al. reported that HE4 levels above the median value of 394 pmol/L were significantly associated with mortality (HR=2.17) and progression (HR=1.81) [10]. Data on HE4-related ovarian cancer recurrence have been published by Nassir, they reported that the combined use of HE4 and CA125 at follow-up with cut-off values of 49.5 pmol/L and 25 U/ml, respectively, within 12 months after first-line chemotherapy performed better than HE4 or CA125 alone. HE4 at FU could predict recurrence within 6 months after second-line chemotherapy [8]. Several studies also report the correlation between HE4 levels and response to surgical treatment. Kong et al. in 2011 demonstrated that HE4 was significantly associated with residual tumor size and operative time ( $p = 0.003$  and  $p=0.033$ ) [2]. In 2013, Braicu et al. confirmed these results reporting that higher plasma HE4 levels correlated with poor surgery outcome in terms of macroscopically residual tumor mass ( $p<0.001$ ). Plasma CA125 and the risk index (HE4 and CA125 together) were independent predictive factors for surgical outcome Odd Ratio (OR)=3.37 ( $p=0.001$ ) and OR=6,041 ( $p<0.001$ ), respectively, concluding that the combination of HE4 and CA125 might predict the surgical outcome, with a possible prognostic impact on PFS and OS [6]. In 2013 we found that HE4 at cut-off of 262 pmol/L was able to better identify patients candidate to optimal cytoreduction with a sensitivity of 86.1% and a specificity of 89.5% (PPV=93.9% and NPV=77%). In addition, the combination of HE4  $\leq 262$  pmol/L and ascites  $<500$  mL improved our results with a sensitivity of 100% and a specificity of 89.5% (PPV=94% and NPV=100%) [11]. In 2013, Yang et al. found as demarcation criterion a HE4 value of 600 pmol/l, where a value  $>600$  pmol/l indicates a lower possibility of optimal debulking, with a sensitivity of 77% and a specificity of 32% of incomplete cytoreductive surgery [12]. In a subsequent paper of 2014, Braicu reported that at a HE4 cut-off value of 250 pmol/L, a sensitivity of 52% and a specificity of 93.8% ( $p=0.001$ ) were reached in predicting total macroscopic tumor clearance. Moreover, together with ascites, HE4 was the only independent predictive factor for surgical outcome (odds ratio [OR] 7.2,  $p=0.029$ , and OR 10.18  $p=0.036$ , respectively) [13]. Chudecka-Glaz et

al., in 2014, evaluated the usefulness of different markers, including HE4, in predicting optimal cytoreduction. At the HE4 cut-off of 218.43 pmol/L, the sensitivity, specificity, PPV and NPV of optimal debulking surgery were 86.6%, 91.3%, 92.9%, 84%, in comparison to CA125 (83.3%; 75%; 80.6%; 78.3%), respectively [14]. In 2015 Tang et al. evaluated the ability of preoperative HE4 in predicting the primary cytoreductive outcomes in advanced EOC. They used a HE4 cut-off value of 473 pmol/L. Suboptimal cytoreduction was obtained in 66.7% (38/57) of cases with HE4  $\geq 473$  pmol/L compared with only 27.3% (9/33) of cases with HE4  $<473$  pmol/L. At this threshold, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for diagnosing suboptimal debulking were 81%, 56%, 67%, and 73%, respectively [15]. Another work of our group consisted in developing a predictive model, named SeC-Score (SeC-s), to assess the risk of optimal secondary cytoreductive surgery, including residual tumour (RT) at primary cytoreduction (0 vs.  $>0$  cm), ascites, preoperative CA125 and HE4, for the first time in literature. Using 0.4375 as cutoff, we tested the score firstly in a training set (TS) where we correctly classified 48 of 52 patients cytoreducible and 30 of 38 not cytoreducible, reporting 92% of sensitivity and 83% of specificity (PPV=0.85, NPV=0.90;). The AUC of SeC-s in TS was 0.92. These data were confirmed in a verification set (VS) consisting of 45 patients: 25 (56%) cytoreducible and 20 (44%) not cytoreducible. In the VS, we correctly classified 19 of 25 patients cytoreducible and 16 of 20 not cytoreducible, reporting 76% of sensitivity and 80% of specificity (PPV=0.82, NPV=0.72). The AUC of SeC-s in VS was 0.88. If we consider the overall performance (135 patients) of SeC-s in TS and VS, we correctly classified 66 of 77 cytoreducible patients (86%) and 46 of 58 not cytoreducible patients (80%), reporting 82% of sensitivity and 83% of specificity (PPV=0.79, NPV=0.81) [16].

## HE4 Levels and CT Response

There are also various works that consider the relationship between HE4 and the monitoring of primary therapy response (NACT or first-line chemotherapy). For example, in 2011, Hynninen et al. assessed that the profile of HE4 during primary chemotherapy was in line with radiologic and clinical responses. In the neoadjuvant chemotherapy group, HE4 better correlated with the radiologic response than CA125 [17].

In 2012, Steffensen et al. found that the positive predictive value in relation to platinum resistance was higher for the combination of markers (CA125+HE4) than for the markers individually [5]. In 2014, at least 5 articles were published regarding HE4 and response to first-line therapy. Braicu et al. reported HE4 and platinum response as the only independent prognostic factors for OS HR 18.77 ( $p<0.001$ ) and HR 3.33 ( $p=0.044$ ), respectively [13].

Chen et al. concluded that the change in HE4 was more closely related to the therapy response and recurrence than the change of CA125. Indeed, the reduction of HE4 (63.3%) was more significant than CA125 (33.3%,  $P < 0.01$ ). Moreover, among the recurrent patients ( $n=11$ ), HE4 predicted 8 recurrences (72.7%) and CA125 predicted 5 (45.5%); while neither HE4 nor CA125 were elevated in 3 patients [18]. Also our study group prospectively evaluated the role of HE4 and CA125 in the prediction of platinum response during first-line chemotherapy in EOC, reporting that HE4 reduction of almost 47% at third chemotherapy cycle reached the sensitivity of 83% with a specificity of 87% (PPV=0.86, NPV=0.85) in predicting chemoresistance. On the contrary, CA125 values during chemotherapy were not statistically significant [19]. Chudecka-Glaz found statistically significant differences in the mean concentrations of CA125 and HE4 between the group of patients sensitive and resistant to the first-line chemotherapy [14]. Finally, Vallius et al. reported that in patients with HE4 change  $>80\%$  and  $<80\%$  during NACT, the median OS was 3.38 and 1.60 years ( $p = 0.01$ ), respectively [20]. Lee et al. in 2016 evaluated how HE4 levels at the time of diagnosis could influence tumor response to chemotherapy HE4 induces chemoresistance against anti-cancer drugs and activates the AKT and Erk pathways to enhance tumor survival. HE4 expression in ovarian cancer tissue is associated with a worse prognosis for epithelial ovarian cancer patients [21]. Chudecka-Glatz in her prospective study on 90 patients affected by ovarian cancer published in 2018 found a significant effect of the normalization of the HE4 marker after therapy and 50% reduction of HE4 levels before interval cytoreductive surgery on PFS and OS, confirmed that HE4 might be an independent prognostic factor of treatment response. HE4 measurements performed during first-line treatment of ovarian cancer may have prognostic significance [22]. Liu et al. in 2018 evaluated how the levels of CA125 and HE4 in the ascitic fluid varied during chemotherapy treatment to evaluate the effect of drugs on the disease and therefore exploit it as a prognostic factor in patients affected by EOC (Epithelial Ovarian Cancer). They found that the level of human epididymis protein 4 in ovarian cancer ascites may reflect the therapeutic effect of ovarian cancer patients, and a high level of human epididymis protein 4 might predict chemoresistance and the possibility of ascites formation. The determination of the expression of human epididymis protein 4 alone or combined with carbohydrate antigen 125 levels in both serum and ascites in ovarian cancer patients with ascites may have important significance for guiding and improving the treatment regimen [23].

## Our Opinion

The world scientific literature, therefore, has not yet specifically clarified the role of the HE4 marker in the

management of patients with gynecological tumors. However, it seems clear that this marker can be used, with due care, in the evaluation and monitoring of ovarian cancer patients. To reinforce the notions tested so far, studies that have a greater scientific weight are needed. The scientific literature will have to produce randomized clinical trials to validate the data obtained so far. The future perspectives of our center are to start a prospective study in which all patients diagnosed with ovarian or endometrial cancer are performed with the dosage of the markers and, in accordance with the other cytoreducibility scores, initiated for the most suitable treatment, monitoring how HE4 levels vary at 3 months, 12 months and 36 months from the start of treatment. Hence, HE4 seems to play an important role not only in the diagnosis and initial evaluation of the patient, but also in the prognosis of the disease. The role it can play in predicting response to drug therapies, whether first-line or subsequent-line, also seems important. One could therefore think, as future prospects, of being able to use it also in the personalization of therapies.

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