ESR1 Overexpression is Associated with Recurrence on Stage I Endometrioid Endometrial Carcinoma

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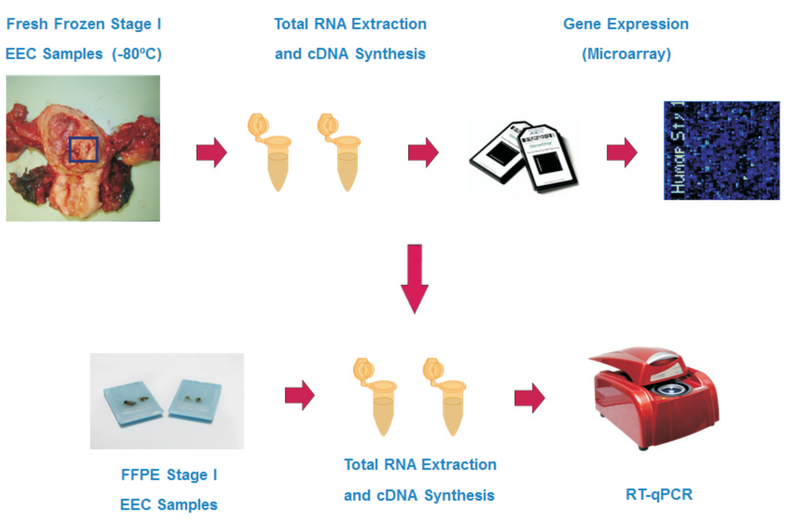
INTRODUCTION

Endometrial cancer is classified into two subtypes of tumors with different clinicopathological features and prognosis. Endometriod endometrial carcinoma (EEC) is the most frequent subtype. Most of these tumors are diagnosed in early stages and have a favorable prognosis, but some may present an unexpected recurrence, with limited responsiveness to treatment. As prognosis is based solely on clinicopathological features, this study was designed to analyze the EEC global gene expression profile in stage I cases which presented relapse comparing to non-recurrent cases.

OBJECTIVES

- Analyze the global gene expression profile of stage I EEC cases with and without recurrence, in an exploratory sample set.
- Analyze gene expression of the genes that are differentially expressed between these sample groups, in a confirmatory set.

METHODS

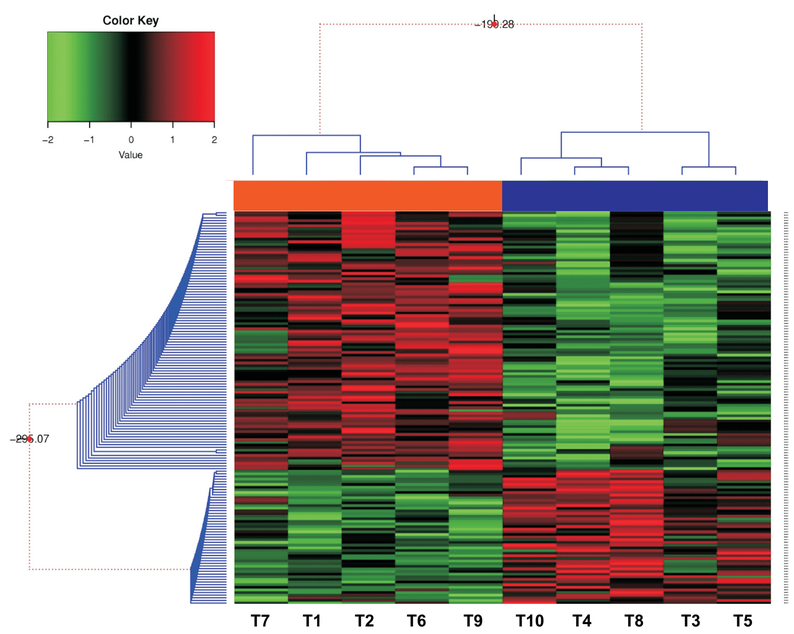


DNA microarray platform was applied in tumor samples of 10 stage I EEC cases, from which 5 presented relapse and 5 didn't (investigational set). An enrichment analysis of differentially expressed genes (DEG) and a transcriptional factor network assessment were performed in recurrent cases, where one overexpressed factor was identified. Therefore, a quantitative PCR (RT-qPCR) of its encoded gene was performed with a larger number of formalin-fixed paraffin-embedded (FFPE) samples of stage I EEC (n=64): 22 recurrent and 42 not recurrent (n=42) cases (validation set)

RESULTS

The gene expression profile of the investigational set pointed out 149 differentially expressed genes (DEG) among samples from patients with and without relapse (98 overexpressed and 51 underexpressed in tumors from cases who presented relapse). Hierarchical clustering of tumors was performed applying unsupervised Bayesian Hierarchical Clustering (BHC), with the expression values of the identified 149 DEG. It was possible to observe two distinct groups, where the samples with relapse are showed on orange bars and the non-recurrence ones on blue bars (Figure 1). The estrogen receptor, encoded by *ESR1*, presented overexpressed in recurrence. *ESR1* expression was 4.3-fold higher in relapse cases compared to no recurrence cases in DNA microarray analysis (n=10).

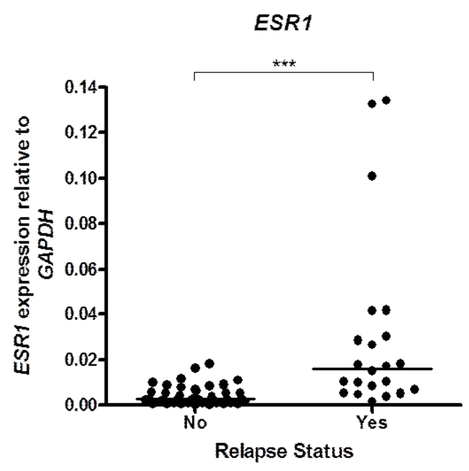
Figure 1



Assessment of *ESR1* expression by RT-qPCR in the validation set showed 4.29-fold higher expression in recurrent tumors (p<0.001). ROC curve demonstrated 81.4% of specificity and 65.9% of sensitivity, with 87% of accuracy (figures 2A and 2B). Univariate analysis showed a significant association between high expression of *ESR1* and worse prognosis in disease-free survival (p=0.001) and overall survival rates (p=0.013), increasing the risk of relapse in 5.48 fold and the risk of death in 4.188-fold (figures 3A and 3B). In multivariate analysis, high expression of *ESR1* was reported as independent prognosis variable for both disease-free survival (p=0.003) and overall survival (p=0.023).

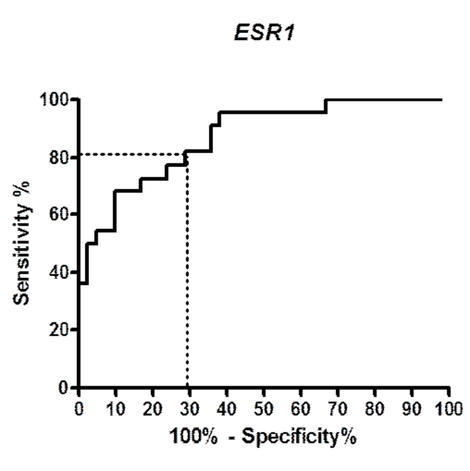
Figure 2

Fig 2 A



***p<0.001

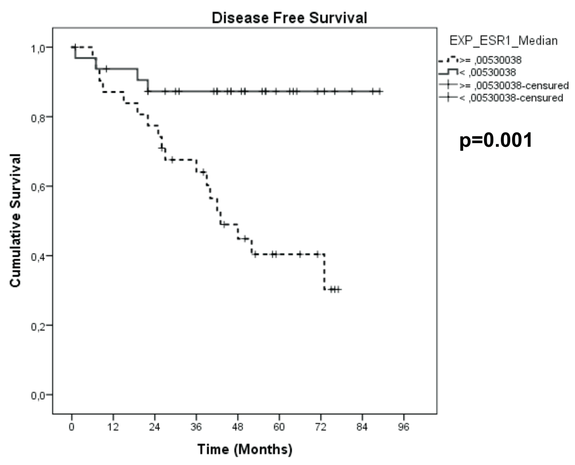
Fig 2 B



Specificity=81.4%
Sensitivity=65.9%
Accuracy=87%

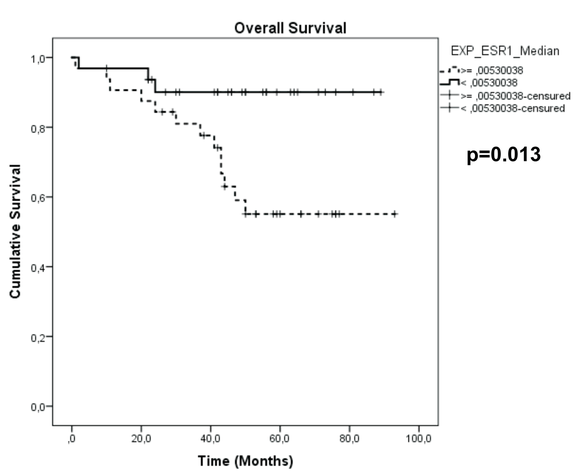
Figure 3

Fig 3 A



p=0.001

Fig 3 B



p=0.013

CONCLUSION

ESR1 overexpression is associated with worse prognosis in stage I EEC.

REFERENCES

Bokhman JV. Two Pathogenetic Types of Endometrial Carcinoma. Gynecol Oncol; 15(1):10–17, 1983.

Li C, Wong WH. Model-Based Analysis of Oligonucleotide Arrays: Expression Index Computation and Outlier Detection. Proc Natl Acad Sci USA, 98(1): 31-36, 2001.

Creasman WT et al. Carcinoma of the Corpus Uteri. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obst, 95 Suppl 1:S105-143, 2006.

Jongen V et al. Expression of Estrogen Receptor-Alpha and -Beta and Progesterone Receptor-A and -B in a Large Cohort of Patients with Endometrioid Endometrial Cancer. Gynecol Oncol,112:537–42, 2009.

Reynaers EAEM et al. Comparable Outcome Between Endometrioid and Non-Endometrioid Tumors in Patients With Early-Stage High-Grade Endometrial Cancer. J Surg Oncol, 111:790–794, 2015.

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