Immunohistochemistry (IHC) Evaluation of a Novel 4-Protein Prognostic and Predictive Biomarker Panel in Endometrial Cancer (EC)

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Background: EC is common and incidence has increased by 65% in 40 years. There are no validated biomarkers or approved targeted therapies in clinical use. This study evaluates a novel biomarker panel in EC by correlating clinico-pathological features and tumour tissue expression levels of p53, PTEN, phospho-P70S6K (pS6), phospho-Stathmin (pSTMN). pS6 and pSTMN activity is influenced by PI3K/Akt pathway activation which frequently occurs in EC.

Methods: The 144 EC patients who had primary surgery from January 2006 to December 2010 at University College London Hospital were retrospectively identified and included in this analysis. Patient characteristics are shown in Table 1. Antibodies for p53, PTEN, pS6 and pSTMN were optimised for use in this study. IHC was performed on surgical resection specimens. Standard scoring methods incorporating percentage of cells stained and staining intensity were applied.

Results: Univariate analysis for disease specific survival (DSS) showed, as expected, non-endometrioid histology, grade (G)3 tumour, presence of lymphovascular invasion or myometrial invasion (MI) and advanced FIGO stage conferred poor DSS. The overexpression of p53 and pSTMN was also associated with poor DSS. In multivariate analysis G3 histology, MI, p53 and pSTMN overexpression were the only factors that remained significantly associated with poor DSS.

Conclusions: We demonstrate for the first time that p53 and pSTMN overexpression are independent predictors of DSS in EC and may be useful prognostic biomarkers. Overexpression of pSTMN may predict sensitivity to PI3K pathway inhibitors in EC. Prospective evaluation is warranted in clinical studies.

Variables	Categories	Univariable Analysis				Multivariable Analysis	
		n	Deaths	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value
Age	<65	59	7	1.91 (0.79-4.62)	0.15	3.43 (0.33-35.14)	0.3
	≥65	85	17				
Histological sub-type	Endometrioid	128	16	4.90 (2.09-11.48)	<0.001	0.18 (0.008-3.99)	0.28
	Non-endometrioid	16	8				
Grade	1 and 2	94	5	9.02 (3.36-24.19)	<0.001	47.14 (2.02-1097.86)	0.02
	3	50	19				
Size	<3 cm	55	8	1.18 (0.51-2.77)	0.69	NA	NA
	≥3 cm	88	16				
Lymphovascular Invasion	Absent	98	10	4.16 (1.83-9.42)	0.001	2.51 (0.44-14.31)	0.3
	Present	46	14				
Myometrial Invasion	<50%	74	8	2.85 (1.21-6.71)	0.02	129.09 (4.99-3341.45)	0.003
	≥50%	67	16				
FIGO	1 and 2	118	12	5.73 (2.41-13.65)	<0.001	1.03 (0.09-11.57)	1.00
	3 and 4	22	9				
Adjuvant Radiotherapy	Didn't receive	82	8	2.23 (0.92-5.38)	0.07	0.31 (0.03-2.9)	0.3
	Received	57	13				
Adjuvant Chemotherapy	Didn't receive	112	13	2.79 (1.19-6.53)	0.02	0.33 (0.03-3.61)	0.36
	Received	28	9				
p53 Expression	Negative	74	7	2.9 (1.18-7.11)	0.02	64.68 (1.59-2637.75)	0.03
	Positive	55	15				
PTEN Expression	Negative	99	13	2.22 (0.92-5.37)	0.08	4.44 (0.85-23.12)	0.07
	Positive	28	8				
phospho-P70S6K Expression	Negative	32	5	1.27 (0.47-3.41)	0.64	NA	NA
	Positive	96	18				
phospho-stathmin Expression	Negative	98	5	12.34 (4.48-34.00)	<0.001	17.23 (1.03-286.91)	0.047
	Positive	32	15				

Table-1. Cox proportional hazard regression model comparing clinico-pathological features and biomarker expression with DSS. NA – not applicable. HR-hazard ratio.