Translational research/biomarkers

2022-RA-205-ESGO CIRCULATING HPV DNA IN CERVICAL CANCER: A MARKER FOR EARLY DETECTION OF RELAPSE

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Introduction/Background Almost all cervical cancers (CC) are caused by human papillomavirus (HPV) and patients with advanced stage are at high risk for relapse. Studies has shown that most patients with HPV-associated tumors have detectable circulating HPV DNA (HPV ctDNA) in the blood at time of diagnosis, before treatment. Development in sensitive technologies led to the use of cell-free DNA for monitoring patients. In the present study, we investigated if HPV ctDNA may serve as a residual tumor marker at the end of chemo-radiation or to predict relapse during the follow-up period.

Methodology We analyzed serum samples from 94 HPV16- or HPV18-related CCs from the BioRAIDs (NCT02428842) prospective cohort. Samples were collected before and after treatment and during an 18-month follow-up period. Using digital droplet PCR (ddPCR), we assessed the relevance of circulating HPV E7 gene as a marker for residual disease. Finally, the prognostic impact of circulating HPV E7 gene was assessed with its prediction value of relapse.

Results Circulating HPV DNA (HPV ctDNA) was detected in 63% (59/94) of patients, before treatment. HPV ctDNA detection in serum sample was associated with high FIGO stage ($p=0.02$) and para-aortic lymph node involvement ($p=0.01$). The level of HPV ctDNA was positively correlated with HPV copy number in the tumor ($R=0.39$, $p<0.001$). Complete clearance of HPV ctDNA by the end of treatment was significantly associated with a longer PFS ($p<0.0001$). Patients with persistent HPV ctDNA in serum relapsed with a median time of 10 months (range, 2–15) from HPV ctDNA detection.

Conclusion HPV ctDNA detection is a useful marker to predict relapse in cervical cancer.

2022-RA-366-ESGO CALCIUM ACTIVATED POTASSIUM CHANNELS (KCNMA1) AS BIOMARKER OF PRE INVASIVE AND INVASIVE CERVICAL CANCER

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Introduction With rising incidence of cervical cancer, novel biomarkers need to be developed. One such biomarker are ion channels and voltage gated channels which are known to be regulated by HPV oncogene and estradiol. Potassium channels including calcium- activated potassium channels (KCNMA1) are also involved in tumor cell proliferation, migration, invasion and angiogenesis and are over-expressed in cancers like glioma, breast, ovary and prostate. The primary objective was to study and compare the mRNA and protein expression of calcium-activated potassium channels (KCNMA1) in pre-invasive and invasive cervical cancer.

Methodology In a prospective comparative study women with biopsy proven diagnosis of CIN 1/2/3 and cervical carcinoma were recruited as cases (n=45). Cervical tissue from hysterectomy specimen done for benign gynaecological indication with normal cervical cancer screening tests were taken as controls (n=15). Women were allocated equally into four groups on the basis of histopathology, i.e. control (Group1), cervical intraepithelial neoplasia 1 (CIN1; Group2), CIN 2/3(Group 3) and invasive cervical carcinoma (Group 4). KCNMA1 mRNA level estimation was done by real-time quantitative PCR (RT-qPCR) and protein expression was studied by immunohistochemistry using anti- KCNMA1 rabbit polyclonal antibody against Maxi Potassium channel alpha. Main Outcome Measures estimated were KCNMA1 protein expression and mRNA expression in four groups: control, CIN1, CIN 2/3 and cervical cancer.

Results The mean KCNMA1 mRNA levels in Groups 1, 2, 3, 4 was 0.2253(SD±0.5798), 271.40(SD±1050.21), 298.84(SD ±1153.33) and 326.545(SD±861.97) respectively; ($p=0.039$). Protein expression was positive in 34% in CIN1, 80% in CIN2/3 and 100% in the cervical cancer group($p\leq0.001$). On subgroup analysis in cancer, KCNMA1 channel mRNA levels and protein expression was higher in tumour size >4 cm, poorly differentiated tumours, deep stromal invasion and non keratinising squamous cell carcinoma.

Conclusion KCNMA1 channel expression has promising role as a biomarker of cervical precancer and cancer.

2022-RA-457-ESGO PROGNOSTIC ROLE OF TGF-β SIGNALLING PATHWAY ALTERATIONS IN ENDOMETRIAL CANCERS – A PROSPECTIVE CLINICAL STUDY

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Introduction/Background Transforming growth factor-beta (TGF-β) has a crucial role in inducing endometrial cancer invasion and metastasis. Studies assaying this signalling pathway in endometrial cancers have been conflicting. Most of these have utilised cancer cell lines. Our research was to assess the TGF-β signalling pathway alterations in fresh tumour tissue specimens, including all subsets of endometrial cancers employing quantitative RNA assay techniques.

Methodology A prospective observational study was done on patients who underwent surgical staging for endometrial cancer from November 2020 to March 2021 at a tertiary cancer centre. Tumour samples from hysterectomy specimens

were studied for mRNA levels of TGF-β1 ligand, TGF-β receptor1 & 2 (TGFβRI&II), Smad2 and Smad4 genes. mRNA expression was quantified by delta Ct (ΔCt) values obtained from quantitative PCR tests and fold change in expression by ΔΔCt values from ΔCt of reference endometrial sample. The association of these mRNA expressions with tumour-related characteristics and recurrences was assessed using non-parametric tests as Mann-Whitney U test & Kruskal Wallis test.

Results 49 patients were considered for analysis. Majority were of endometrioid histology, lower grade, and stage I. 84% of endometrial cancer samples demonstrated under-expression of Smad2. Loss of Smad2 was significantly associated with myo-invasive tumours and tumours >2 cm. Loss of TGFβRII expression was related to parametrial invasion and stage IV disease, while reduced TGFβRI expression to clear cell histology. During a median follow up of 15.4 months, there were three recurrences. Loss of TGFβRII expressions was significantly associated with recurrence. Mean ΔΔCt value of >1.950 for smad2 and TGFβRII expression was associated significantly with a reduced 1.5 year recurrence-free survival.

Conclusion TGFβ pathway components undergo changes in endometrial cancer. Impaired expression is observed at every level of signalling pathway, Loss of Smad mRNA expression and TGFβ receptor levels have certain associations with aggressive features and can predict recurrence risk.

2022-RA-627-ESGO PREOPERATIVE CIRCULATING TUMOR DNA LEVEL IS ASSOCIATED TO POOR OVERALL SURVIVAL IN PATIENTS WITH OVARIAN CANCER

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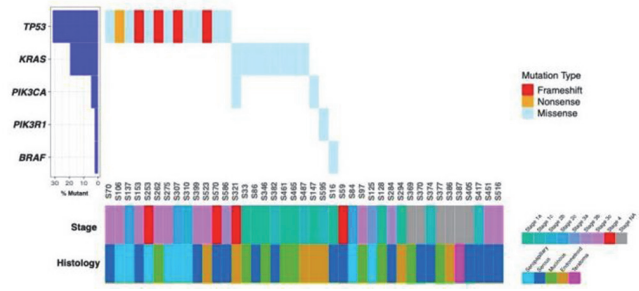
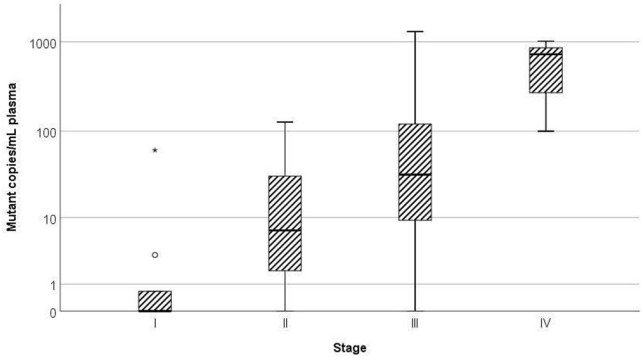
Introduction/Background Circulating tumor DNA (ctDNA), which is shed from tumor cells into the blood, is a promising minimal-invasive method for cancer diagnostics and monitoring. The aim of this study was to evaluate preoperative ctDNA levels in the plasma of patients with ovarian cancer and correlate the levels to clinico-pathological parameters and patient outcome.

Methodology Tumor DNA was extracted from ovarian tumor tissue from 41 patients. Targeted sequencing using a panel of 127 genes recurrently mutated in cancer was performed to identify candidate somatic mutations in the tumor DNA. SAGAsafe digital PCR (dPCR) assays targeting the candidate mutations were used to measure ctDNA levels in patient plasma samples, obtained prior to surgery, to evaluate ctDNA levels in terms of mutant copy number/mL and variant allele frequency.

Results Somatic mutations were found in 24 tumors, of which seven were from patients with borderline, and 17 with invasive cancer diagnosis. *TP53* was the most frequently mutated gene. Fifteen of 24 patients had detectable ctDNA levels in pre-operative plasma. Plasma ctDNA mutant concentration increased with higher stage (p_{trend} <0.001). Cancer patients with more than 10 ctDNA mutant copies/mL in plasma prior to surgery had significantly worse overall survival (p=0.008).



Abstract 2022-RA-627-ESGO Figure 1 Waterfall plot of validated somatic mutations in the patient tumors. Genes are indicated in rows and samples in columns. Mutated samples are show according to mutation type. Patient and tumor clinopathological variables are shown below the patient IDs



Abstract 2022-RA-627-ESGO Figure 2 Plasma circulating tum or (ctDNA) mutant concentration increased with higher stage (p_{trend}<0.001).Concentrations of circulating tumor DNA (ctDNA) in stage III and stage IV OvCa were significantly higher compared with stage I OvCa (p=0.025 and p=0.007 respectively) Bars include highest and lowest values, except outliers (o), which are 1.5 to 3 box lengths from the end of the box, and extremes (*) which are more than 3 box lengths from the end of the box

Conclusion Measuring ctDNA in pre-operative plasma may be useful as a predictive biomarker for tumor staging and prognosis in ovarian cancer patients.