Immunoexpression Status and Prognostic Significance of mTOR Pathway Members in Upper Tract Urothelial Carcinoma

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Background: Upper tract urothelial carcinoma (UTUC) accounts for 5-10% of all urothelial carcinomas. Despite many shared features, key clinical and molecular genetic differences between upper tract and bladder urothelial carcinomas are becoming apparent. We have previously demonstrated alterations of mTOR pathway in bladder carcinoma with potential impact on biological behavior. In the current study we evaluated the expression status and prognostic significance of mTOR pathway members in UTUC.

Design: Archival FFPE tissues from 99 primary UTUC were retrieved from one of the authors institution. Tissue microarrays (TMA) were constructed with triplicate tumor samples and paired non-neoplastic urothelium. TMAs were analyzed using immunohistochemistry for mTOR pathway members: PTEN, phos-AKT, phos-mTOR, phos-S6, phos-4EBP1 and related markers p27 and c-myc, as previously reported (Scultz et al; Cancer 2010). H score [sum of stain intensity (0-3+) by extent (0%-100%)] was calculated in each spot. Mean H score per tumor was used for analysis. Correlation with clinicopathologic parameters and outcome (recurrence and disease specific survival) was performed.

Results: Significantly lower PTEN expression was found in UTUC compared to paired benign urothelium (Median H Score 8.3 vs 90.5; P<0.001). The same was true for phos-4EBP1 (P<0.001). Median follow up was 47 months (range: 3 - 174 months). Forty-nine of 99 patients (49%) experienced recurrence. Four patients (4%) developed metastasis. We found no association between analyzed markers and any of the clinicopathologic parameters assessed. On univariate analysis, phos-AKT tumor expression was associated with disease specific survival (DSS) [Log-rank (Mantel-Cox) test P<0.05]. None of the other markers was associated with DSS. In a multivariate analysis model that also included grade, pT stage, lymphovascular invasion and patient’s age, phos-AKT did not maintain independent prognostic significance.

Conclusion: Activation of mTOR pathway was present in UTUC associated with markedly lower PTEN expression compared to paired normal urothelium. In our cohort, tumor phos-AKT expression levels correlated with disease specific survival. However, phos-AKT prognostic significance was not maintained when adjusting for standard clinicopathologic prognostic parameters.