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Spatiotemporal Transcriptomic Analysis Reveals Clinically Relevant Tumor Heterogeneity In The Patient With Advanced Gallbladder Cancer.

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Background : Tumor heterogeneity is a well-known cause of therapeutic resistance and poor prognosis in pancreaticobiliary cancers. Recently, new emerging technology, especially spatial transcriptomics platform, has emerged in cancer research to reveal complex tumor biology harboring in situ pathologic information of tumor microenvironment. This study is to aim the identification of inter and intra-heterogeneity of advanced gallbladder cancer using the spatial transcriptomic technique with temporally collected patient samples.

Methods : A patient with advanced gallbladder cancer with formalin-fixed paraffin-embedded (FFPE) blocks from initial biopsy and post-mortem autopsy samples (gallbladder, liver, peritoneum, lung) was enrolled in this study. A total of 24 areas of interest (AOI) from six immunofluorescence slides with four morphology markers from the patient's FFPE blocks were selected and the RNA sample for tumor, stroma, and tumor-infiltrating lymphocytes (TILs) from each AOI was sequenced using GeoMx Human Whole Transcriptome Atlas platform (Nanostring Technologies, Inc., USA).

Results : Unsupervised clustering for sequenced data from spatial transcriptomics revealed remarkable temporal changes during cancer progression concordance with the patient's clinical course. Tumor stroma and TILs showed distinct gene expression patterns according to their unique tumor microenvironments. Interestingly, the tumor samples showing perineural invasion have unique and discriminative transcriptomic profiles with differentially expressed gene sets. Inter-tumoral and intra-tumoral heterogeneity harboring different molecular biology with distinct tumor phenotypes were identified from comprehensive pathway analysis using single-sample gene-set enrichment analysis. The in-silico analysis for drug response prediction showed differential responses for currently available cancer therapeutics according to temporal tumor progression and spatial tumor context with their unique environments.

Conclusions : Spatiotemporal transcriptomic analysis using cutting-edge technology with highly annotated tumor samples from a deceased patient reveals clinically relevant tumor heterogeneity in the patient with advanced gallbladder cancer. Inter and intra-tumoral heterogeneity showing different therapeutic opportunities warrant translational research for clinically relevant molecular deciphering with clinical samples in the era of precision surgical oncology.

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