**Figure S1. Spatial mapping of cell type annotations for all fields of view (FOVs) on TMA1.** Main panel depicts FOV-wise spatial maps (see Figure S3A for context). Bottom panel shows a UMAP embedding with cells pseudo-colored by cell type annotation for all cells on TMA1.

**Figure S2. Spatial mapping of cell type annotations for all fields of view (FOVs) on TMA2.** Main panel depicts FOV-wise spatial maps (see Figure S3B for context). Bottom panel shows a UMAP embedding with cells pseudo-colored by cell type annotation for all cells on TMA2.

**Figure S3. Acquisition of spatial molecular imaging (SMI) data for two HCC FFPE TMAs allows for quantitative isolation of specific cell type subsets.** (**A**) Left: H&E staining for TMA1 with the region selected for SMI enclosed in black. Second from left: immunofluorescent staining for the selected region in S3A. Each white rectangle depicts a field of view (FOV), within which SMI was conducted. Pink arrows indicate FOVs filtered due to QC. White arrows indicate kidney control FOVs. Staining matches that in Figure 1B. Second from right: spatial map of relative TMA1 FOV locations with cells pseudo-colored by cell type annotation inside each FOV. Right: UMAP embedding for TMA1 with cells pseudo-colored by patient identity. (**B**) Replication of S3A, for TMA2. Note that core 22 was filtered entirely due to QC. (**C**) UMAP embedding for the complete SMI dataset with cells pseudo-colored by patient identity. (**D**) UMAP embedding for all tumor cells identified in the SMI dataset with cells pseudo-colored by patient identity. (**E**) UMAP embedding for all stromal cells identified in the SMI dataset with cells pseudo-colored by patient identity (top) and by cell type annotation (bottom).

**Figure S4. Validation of cell-typing with differentially expressed marker genes for cell type clusters.** One-sided volcano plots depicting significant differentially expressed positive marker genes for each cell type cluster (see methods). Each cluster was compared to all other clusters. P-values computed by Wald test and FDR-adjusted. Significance threshold = 0.05. Effect size threshold = logFC value of 1.5.

**Figure S5. Continuation of differential expression analysis in endothelial cells and extended information for RNA-ISH validation.** (**A**) Volcano plot summarizing differential expression analysis comparing endothelial cells in LINE1-ORF1 high patients and LINE1-ORF1 low patients, as defined in Figure 3A. P-values are FDR-adjusted. Significance threshold = 0.05. (**B**) Schema of RNA-ISH data collection and quantification workflow. For each cell, the nucleus is pseudo-colored purple, the cytoplasm is pseudo-colored grey, and confidently identified RNA-ISH spots are pseudo-colored red (bottom). (**C**) Representative images of HERVK, HERVH, and HSATII RNA-ISH staining (left to right). (**D**) Bar plot depicting the definition of LINE1 HIGH and LOW patient groupings in the RNA-ISH dataset. The dashed line represents the upper tercile for LINE1 RNA count density (per µm2) across all patients.

**Figure S6. Extended information for neighborhood enrichment analysis.** (**A**) Differences in LINE1-ORF1 high and low tumor cells’ colocalization patterns with themselves, one another, and other cell types across the complete SMI dataset. ER = enrichment ratio (see methods). P-values computed by paired Wilcoxon Rank Sum Test and FDR-adjusted. \* = nominal p-value < 0.05. \*\* = adjusted p-value < 0.05. (**B**) Observed differences in all pairwise cell type colocalizations between LINE1-ORF1 high patients and LINE1-ORF1 low patients in the SMI dataset (See Figure 4C). Differences were computed as high minus low. P-values computed empirically. \* = nominal p-value < 0.05.