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An integrated study of spatial dynamics and genomic alterations in renal cell carcinoma evolution

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Background

The multi-center prospective longitudinal cohort study, TRACERx Renal (NCT03226886) has revealed the evolutionary features of clear-cell renal cell carcinoma (ccRCC). However, the association of physical spatial location and genetically driven tumour subclones was unclear.

Methods

100 macroscopic tumour images taken at time of surgery were reviewed by a renal pathologist, and following quality control filtering accurate spatial data was available for 79 tumours. From these 79 cases, matched high-depth driver gene panel sequencing data was utilised from 756 individual biopsy regions (mean 9.6 biopsies per tumour). The boundaries between tumour and normal tissues were marked based on macroscopic photos by a renal pathologist, after which the positions of boundaries and biopsy regions were digitally extracted to X- and Y-coordinates. Spatial distances were calculated, with the correlations between spatial characteristics and genomic alterations investigated.

Results

We mapped the spatial location of 756 biopsies, across 79 ccRCCs, and integrated these coordinates with sequencing data. This enabled a resolution as to how genetically distinct subclones grow and evolve spatially. Compared with tumour margins, the level of somatic copy number changes was higher in tumour interiors. Moreover, metastasising clones were found to be more enriched in tumour interiors. The tumour subclones growing to largest physical size were characterised by gains of chromosomes 7q, 1q and and losses of chromosome 14q. The degree of discrepancy of genomic alterations across biopsy regions was positively correlated with spatial distances across biopsy regions. Tumour subclone growth was found to be predominantly spatially contiguous, with subclone dispersal a rare event found only in one case, which notably was associated with metastasis.

Conclusions

Spatial dynamics is strongly associated with genomic alterations and plays an important role in tumour evolution.

Clinical trial identification

NCT03226886.

Legal entity responsible for the study

Royal Marsden Hospital.

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