SUMMARY:

The evolutionary features of clear-cell renal cell carcinoma (ccRCC) have not been systematically studied to date. We analysed 1209 primary tumour regions from 101 patients recruited into the multi-centre prospective study, TRACERx Renal. We observe up to 30 driver events per tumour, and show that subclonal diversification is associated with known prognostic parameters. By resolving the patterns of driver event ordering, co-occurrence and mutual exclusivity at clone level, we show the deterministic nature of clonal evolution. ccRCC can be grouped into seven evolutionary subtypes, ranging from tumours characterised by early fixation of multiple mutational and copy number drivers, with disseminated metastases; to highly branched tumours with >10 subclonal drivers and extensive parallel evolution, presenting with solitary metastases. We identify genetic diversity and chromosomal instability as determinants of patient outcome. Our insights reconcile the variable clinical behaviour of ccRCC, and suggest evolutionary potential as a biomarker for both intervention and surveillance.

Renal cell carcinomas have the highest pan-cancer proportion and number of indel mutations. Evidence suggests indels are a highly immunogenic mutational class, which can trigger an increased abundance of neoantigens and greater mutant-binding specificity.