Clinical and genomic indolence in lung-recurrent metastatic hormone-sensitive prostate cancer

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Background and objective
Pulmonary involvement without synchronous bone involvement is rare in metastatic hormone-sensitive prostate cancer (mHSPC) that recurs after primary disease surgery or radiation. Guidelines recommend intensive systemic therapy, but case series suggest that patients with lung-recurrent mHSPC have relatively good outcomes. Therefore, we aimed to characterize outcomes and genomic alterations present within primary and metastatic tumours of lung-recurrent mHSPC. We hypothesized that a relatively indolent disease course would be reflected in genomic features.

Materials & methods
We performed a retrospective cohort study in 10 mHSPC patients with metastatic lung recurrences who underwent thoracic surgery (n=9) or fine-needle biopsy (n=1) in the years after curative-intent treatment for primary disease. After histopathological review, distinct primary tumour (n=46) and metastatic lesions (n=24) were selected. From each sample, genomic features were analysed using deep multi-gene targeted sequencing and whole exome sequencing.

Results
All patients remained alive despite a median follow-up of 139.3 months (range 97.5-170) following initial diagnosis and 55 months following lung-recurrence. Progression to metastatic hormone-resistance occurred in 2 patients. The lung-recurrent mHSPC driver landscape resembled localized prostate cancer with frequent PTEN, SPOP and chromosome 8p alterations; deleterious TP53 and DNA damage repair mutations were absent. Despite the long median time to recurrence (76.8 months), copy numbers and clonal mutations between metastases and matched primary tumours were highly similar, suggesting intra-patient homogeneity and that archival biopsy specimens are representative of late relapses.

Conclusions
Our results reveal the indolent genomic etiology underlying the relatively good clinical outcomes in this and prior cohorts of lung-recurrent mHSPC. We propose that treatment of lung-recurrent mHSPC with immediate or delayed androgen-deprivation therapy alone may be sufficient for long-term disease control. Prospective evaluation of lung-recurrent mHSPC
as distinct from aggressive visceral disease, and inclusion in therapy de-intensification clinical trials is warranted.