Multifocality in prostate cancer: Implications for PAM50 subtyping using an index lesion-only approach

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Introduction & Objectives
PAM50 subtyping of prostate cancer harbours prognostic value and has emerged as a potential predictive biomarker. Molecular characterization of prostate cancer typically relies on a single core biopsy or resection specimen. However, it remains unclear if intra-tumour heterogeneity would impact PAM50 transcriptomic profiling, and an index lesion-only approach would be sufficient for PAM50 subtype classification. In this study, we determined to what extent different foci within a single prostate are concordant or discordant with each other for PAM50 luminal and basal subtyping.

Materials & methods
We performed a retrospective cohort study in patients with lymph node-positive prostate cancer (n=17) who underwent a radical prostatectomy. Histopathological evaluation of the prostate was performed upon which ≥1 index lesion plus different tumour foci (n=85, with a range of 2 to 6 primary samples per patient) were identified, representing distinct morphological features and histological grades. For each sample, RNA-sequencing with downstream PAM50 classification was used to classify each sample into luminal- and basal-like subtypes and investigate the extent of intra-tumour PAM50 transcriptomic heterogeneity.

Results
Among the 85 primary tumour foci, the PAM50 classifier identified 3 subtypes: Luminal A (57 [67%]), Luminal B (17 [20%]), and Basal (11 [13%]) (Figure 1). Molecular subtyping revealed intra-tumour PAM50 subtype heterogeneity in 11/17 (65%) patients. In 10/11 patients the Luminal A coexisted with Luminal B (n=5), Basal (n=2) or Luminal B and Basal (n=3). The Luminal B subtype coexisted with the Basal subtype in one case. In 7/9 patients with admixed Luminal B tumours, the index lesions captured the poor prognosis Luminal B subtype, which in 4 patients was only identified by profiling >1 index lesion. In two patients (ID10 and ID15) a single index lesion-only approach missed the detection of Luminal B-harbouring foci.

Conclusions
This hypothesis-generating study identified the co-existence of Luminal and Basal subtypes within the same patients’ primary high-risk prostate cancer. In the majority of cases an index lesion-only approach was sufficient to identify the poor prognosis Luminal B subtype. However, future studies on the prognostic and/or predictive value of intra-tumour PAM50 heterogeneity are warranted.
More information

Figure 1. PAM50 subtypes among prostate tumour foci (n=85) from patients with lymph node-positive prostate cancer post radical prostatectomy (n=17).
BOTTOM: PAM50 subtype distribution per patient, with annotation of the total number of samples per patient. TOP: PAM50 subtype distribution in matched index lesions.