but about 20% of screen-detected Gleason score 6 PCAs would evolve into higher-grade cancer over time. An alternative explanation for their observation of “true” grade progression could be the development of a “de novo” high-grade PCa in some of the patients with Gleason score 6 PCas. Nevertheless, their observations provide a strong rationale for early detection of the disease (eg, by PSA testing) to intercept the tumor prior to its development into a more aggressive cancer.

In contrast, the potential to transform into a higher-grade cancer—an event more likely to occur in older men [2]—would imply that men with low-risk PCa would need continued monitoring for their disease. Although, at a population level, this transformation may take about 6 yr, according to the data from the study by Inoue et al., the question remains whether this evolution is gradual or a sudden event (“saltationist”), particularly in molecular-genetic terms. Whole genomic-sequencing findings have demonstrated that PCa evolution is punctuated, that is, a sudden orchestrated burst of many molecular alterations involving multiple oncogenes and suppressor genes [4]. Such a sudden event would have consequences for the frequency of monitoring of men under AS. The holy grail of PCa biomarker research would then be the identification of markers predicting this saltationist molecular evolution to select those men who need frequent monitoring or definitive treatment.

Conflicts of interest: The author has nothing to disclose.

References

Re: Tracking the Clonal Origin of Lethal Prostate Cancer
J Clin Invest 2013;123:4918–22

Experts’ summary:
Prostate cancer (PCa) is known for its multifaceted nature, usually developing and progressing as a multifocal and multiclonal disease. In the context of overdiagnosis and overtreatment, correct characterization of PCa aggressiveness at diagnosis is crucial for therapeutic management.

To this end, Haffner and colleagues mapped the clonal origin of a mutistatic castration-resistant adenocarcinoma in a single patient treated with radical prostatectomy and multiple salvage therapies. Using whole-genome sequencing, they analyzed tissues from three anatomically different metastatic locations (lung, liver, and perigastric lymph node) collected immediately after the death of the patient. To trace the origin of the metastases, they compared their findings with those obtained from analysis of cancer foci in the prostatectomy specimen.

The authors confirmed the monoclonal origin of the metastases by detecting similar alterations of PTEN, SPOP, TP53, and ATRX. Surprisingly, the same genetic mutations were mapped not to large Gleason pattern 4 areas but to a small 2.2-mm by 1.3-mm Gleason pattern 3 area in the prostate, apart from ATRX alteration and AR upregulation that developed in later stages of the clonal expansion. In addition, the singular lymph node metastasis identified at the time of prostatectomy did not share the mutations of the distant and lethal metastatic foci.

Experts’ comments:
PCa management is heavily dependent on Gleason score grading, first assigned at the time of biopsy. Low-volume and well-differentiated disease is considered relatively benign with virtually no metastatic potential [1]. Hence, men with biopsy Gleason 6 disease are ideal candidates for active surveillance. Surprisingly, Haffner and colleagues have mapped the origin of deadly metastatic disease to a small Gleason 6 focus. Opponents of active surveillance and organ-sparing treatments might use these results to invalidate all theories regarding indolent disease; however, two points are to be noted. First, the patient did not have Gleason pattern 3 disease exclusively but also presented with Gleason pattern 4 disease, and the authors postulate that Gleason pattern 3 cells in close proximity to Gleason pattern 4 cells might be biologically different than isolated Gleason pattern 3 foci. Second, the prostatic DNA was 20 yr old, limiting more detailed analysis possibly linking the different cancer foci in the prostate.

Despite these data, active surveillance is an underutilized management option [2], perhaps due to varying extents of patients not being comfortable with the idea of living with cancer and to physicians’ lack of confidence in disease characterization at diagnosis. Indeed, PCa diagnosis has ample room for improvement. It date, PCa is the only solid malignancy that is randomly sampled at time of biopsy, and Gleason grading, regardless of its strong correlation with outcome, relies solely on morphological features.

We are in need of a novel diagnostic pathway that relies on image-guided targeted biopsies and genetic characterization. The former is already possible due to the development of multiparametric magnetic resonance imaging (MRI),
allowing for MRI–transrectal ultrasound fusion targeted biopsies that are able to diagnose more aggressive cancers with fewer biopsy cores [3]. The latter is still in process, with multiple markers being investigated [4]. By implementing these changes, over-detection and overtreatment might successfully be defeated.

Conflicts of interest: Thomas J. Polascik is a member of the board of the COLD registry and a consultant for Endocare; he is also an investigator for a clinical trial on Nanoknife (Angiodynamics). Niccolò M. Passoni has nothing to disclose.

References


Re: Impact of ABO Blood Type on Outcomes in Patients with Primary Nonmuscle Invasive Bladder Cancer
J Urol 2014;191:1238–43

Expert’s summary:
This multi-institutional retrospective study aimed to investigate the association between ABO blood type and the prognosis of patients with non–muscle-invasive bladder cancer (NMIBC). A total of 931 patients were enrolled: 130 low risk, 384 intermediate risk, and 417 high risk. The study results indicated that patients with blood type O experienced higher recurrence and progression rates than those with type A or B. The concordance index for predicting recurrence and progression in NMIBC patients increased by adding ABO blood type to the basic prediction model comprising well-established prognostic factors such as T stage, tumour grade, carcinoma in situ, tumour size, number of tumours, and intravesical instillation therapy with mitomycin C or the bacillus Calmette-Guérin (BCG) regimen. The authors concluded that ABO blood type, which is known for most patients, might be an ideal adjunctive marker to predict recurrence and progression in patients with NMIBC.

Expert’s comments:
ABO blood group antigens are found in a variety of epithelial cells including those of the urothelium, gastrointestinal mucosa, and lungs as well as in erythrocytes. The clinical implications of the ABO blood group system have thus extended well beyond transfusion medicine [1]. In this investigation, the authors demonstrated an increased risk of recurrence and progression in NMIBC patients with blood type O. However, subpopulation analyses indicated prognostic differences according to ABO blood type only in high-risk patients. Because loss or aberrant expression of ABO antigens has been reported to be associated with high-grade tumours, disease progression, and poor prognosis in bladder cancer [2,3], it might also be plausible that prognosis did not differ according to ABO blood type in high-risk NMIBC patients. No relevant association between ABO blood type and cancer-related prognosis has been observed in bladder cancer patients undergoing radical cystectomy [4]. In this study, approximately a quarter of all enrolled patients received adjuvant BCG therapy. The efficacy of BCG therapy might differ according to ABO blood type owing to the reported differing susceptibility to tuberculosis [5]. Thus, the efficacy of adjuvant instillation therapy might have affected the outcomes of NMIBC patients. Further research is warranted to verify the association between ABO blood type and bladder cancer prognosis and to clarify the underlying mechanism of this association.

Conflicts of interest: The author has nothing to disclose.

References