Contemporary Active Surveillance

Candidate Selection, Follow-up Tools, and Expected Outcomes

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KEYWORDS

• Active surveillance • Prostate cancer • Risk stratification • MRI • Biomarkers

KEY POINTS

- The molecular genetics of Gleason pattern 3 resemble normal cells in most cases. In contrast, pattern 4 harbors numerous genetic abnormalities involving most oncogenic pathways.
- Gleason pattern 3 has no metastatic potential. Case series involving tens of thousands of cases have demonstrated no metastases when the presence of occult higher grade cancer is excluded.
- The main significant of higher volume Gleason pattern 3 is its association with a higher risk of co-existent occult higher grade cancer. This is reflected in a higher PSA density, cancer core volume, and number of cores involved. Higher volume pattern 3 should prompt a more aggressive search for occult cancer (MRI, repeat biopsy), not treatment.
- MRI and biomarkers are complementary, and clearly enhance the diagnostic pathway. Current guidelines vary in their recommendation regarding the role of MRI (from selective to routine) and biomarkers (from investigational only to selective use).

INTRODUCTION

About half of men diagnosed with prostate cancer by systematic biopsy are found to have low-risk disease, also called Gleason 6 prostate cancer, or grade group 1. The 2011 US Preventive Services Task Force's (USPSTF) recommendation against prostate-specific antigen (PSA) screening, owing to the risks of overdiagnosis and overtreatment,[1] reflected a compelling concern about overtreatment of low-risk disease. Since then there has been an emerging consensus that most men with low-risk prostate cancer do not derive any meaningful benefit from radical treatment, and an initial conservative approach is warranted. Importantly, this shift to expectant management has resulted in the USPSTF proposing to revise their recommendation regarding screening from D in 2011 to a C (neutral) in 2017.[2]

Prostate cancer develops in most aging men. In Caucasian men, the likelihood of harboring prostate cancer is approximately one's age as a percentage, beginning in the 30s.[3] This trend has been confirmed in many autopsy studies of Caucasians, Asians, and other ethnic groups. These lesions are usually small (<1 mm^3) and low grade. In an autopsy study in Japanese and Russian men who died of other causes, about 35% of both groups harbored prostate cancer, and 50% of the Japanese men older than 70 years had a Gleason score of 7 or higher.[4] Although the prevalence of histologic prostate cancer was lower in Japanese men between 30 and 60 years of age, there was essentially no difference in men older than 60 years.

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MOLECULAR HALLMARKS OF PROSTATE CANCER

This disparity between the prevalence of histologic prostate cancer and the lifetime risk of mortality from prostate cancer (3% in North America before the advent of screening and approximately 2% more recently) emphasizes the risks of overdiagnosis and the value of conservative therapy for low-risk patients. Molecular and genetic analyses have shown that the hallmarks of cancer differ profoundly between the two most common patterns of disease, Gleason 3 and Gleason 4. These hallmarks are a useful structure for determining the degree to which low-grade prostate cancer (Gleason pattern 3) looks like a true malignancy.[5,6]

In most cases, the molecular abnormalities associated with these characteristics are absent in Gleason pattern 3 and present in Gleason pattern 4 (**Table 1**). The differences are both qualitative and quantitative. It is remarkable how well the Gleason scoring system disaggregates prostate cancer between genetically normal and abnormal cells. According to those who knew him personally, Don Gleason himself thought that Gleason pattern 3 or less should not be called cancer.

Genetic aberrations are uncommon in Gleason pattern 3 and common in patterns 4 and 5. This finding is particularly true of genes regulating key oncogenic pathways. Genes involved in proliferation, including AKT and HER2, are expressed normally in Gleason 3 and abnormally expressed in Gleason 4 (see **Table 1**). Genes involved in cellular invasion and metastasis and genes regulating the cell cycle transition are not overexpressed in Gleason 3 but are in Gleason 4. Genes associated with resistance to apoptosis, angiogenesis, and the development of other proangiogenic factors, and genes involved in regulating cellular metabolism tend to be abnormally expressed in Gleason 4 but not in Gleason 3.[7–20]

Recent studies have indicated that the progression to higher-grade cancer is characterized by both qualitative and quantitative genetic differences. For example, about 10% of Gleason pattern 3 cancers have a PTEN deletion. This deletion is found much more commonly in Gleason 3 pattern cells in men with coexistent Gleason pattern 4, that is, Gleason score 7 cancers.[21] This may indicate that a field defect is present or that Gleason 3 cells harboring the PTEN deletion rapidly dedifferentiate to a higher Gleason pattern. An alternative explanation is that the deleterious genetic alterations present in the higher-grade cancers are transferred by exosomes into the lower-grade cancers.[22] This phenomenon of intertumoral and intratumoral communication and influence through extracellular circulating exosomes may explain several otherwise hard-to-understand observations in the field, for example, the effect of treatment of the primary in patients with metastatic disease.

POTENTIAL FOR METASTASIS

The data are very compelling that Gleason 6 cancer has little or no metastatic potential. One study of 14,000 men with pathologically confirmed Gleason pattern 6 identified only 22 cases with lymph node metastases.[23] All 22 men had higher-grade cancer on reexamination of the tissue. Thus, the rate of lymph node metastases in men whose prostate tissue contained no higher-grade cancer was zero. Another study of 12,000 men treated with radical prostatectomy whose specimen had

Table 1
Gleason 3 versus 4 and hallmarks of cancer

Pathway	Gleason 3	Gleason 4
EGF, EGFR[8]	No	Overexpressed
AKT, MAP2 kinase[7]	No	Aberrant
HER2neu[8]	No	Amplified
Insensitivity to growth inhibitory signals (cyclin D2, and so forth)[9–11]	Expressed	Absent
Resisting apoptosis, BCL2[13]	Negative	Strong expression
Absence of senescence, TMPRSS2-ERG[16–18]	ERG normal	Increased
VEGF, microvessel density, other proangiogenic factors[19,20]	Low expression	Increased
PTEN[21]	Present in 90%	Deleted in 70%–90%
Markers of tissue invasion and metastasis[14,15]	Normal	Overexpressed
Clinical evidence of metastasis/PCa mortality[23,24]	Virtually absent	Present

Abbreviation: PCa, prostate cancer.