Defining high-risk prostate cancer: current status

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Defining men at high risk for prostate cancer treatment failure and death continues to evolve. Identifying these men allows for better disease prognostication, patient decision treatment making and facilitates accrual for appropriate clinical trials. Men at traditional high risk for prostate cancer progression and death include men with advanced clinical stage, higher levels of PSA and Gleason pattern 4. Utilizing accepted methods of risk stratification including nomograms can aid in case identification. Softer risk factors such as obesity, race, socioeconomic status, and genetic polymorphisms are increasingly being studied. Ultimately high-throughput genomics will aid in identification of these men.

Key Words: prostate cancer, high-risk, risk stratification

Introduction

Prostate cancer is the most common human malignancy. In North America it represents the most commonly diagnosed cancer among men and ranks as the second most common cause of cancer deaths among this gender.[1] The past 15 years has been revolutionary with respect to prostate cancer prevention, detection and treatment. Death rates have dropped since 1999[1] and the morbidity of radical therapies continues to fall. One of the most prolific areas of research directly affecting patient care has been in the field of defining and treating men with high-risk prostate cancer. Most investigators would agree that risk stratification strategies have dramatically altered the practice of urologic oncology. The purpose of this review is to outline the benefits of risk stratification, define patients at "high-risk" and review both traditional and softer risk factors for prostate cancer progression and death.

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Benefits of risk stratification

A host of aids and markers have been developed to help us stratify patients who present with newly diagnosed prostate cancer into sub –cohorts of men more or less likely to do well. The benefits of this approach are numerous. First, they facilitate the decision making process for the treating physicians, surgeons, patients and their family members. The common use of adjuvant hormone therapy in conjunction with radiotherapy is a good example of this.[2] Second, risk-stratification provides patients with valuable information regarding disease prognosis allowing them to better plan for their futures. A third benefit of risk stratification criteria is that they allow us to best practice evidence-based medicine where credible evidence exists. Finally, risk-

TABLE 1. **Risk factors in disease continuum**

Pathological features	
	Extracapsular extension
	Surgical margin involvement
	Upgrading of Gleason score
	Seminal vesicle/bladder neck involvement
Features at relapse	
	Post operative detectable PSA
	PSA velocity
	Time to PSA failure

stratification allows for identifying sub-cohorts of patients for clinical trials and testing with novel agents, especially if they are within a sub-cohort likely to do poorly with current treatment regimens.

Definition of high-risk prostate cancer

Although no formal definition exists regarding high-risk disease, men at high risk represent a subset of men who possess known variables either in isolation or combination, which put them at high likelihood of treatment failure and death from prostate cancer. It is important to mention that historically, high-risk definition applied to covariates defined at initial disease presentation. This approach however may not be as relevant in the context of prostate cancer that has a long disease continuum. Many men may start out in a low risk category and subsequently attain high-risk features as more information is learned (such as pathological stage) or he begins to exhibit disease progression (i.e. rapid prostate specific antigen {PSA} failure). Table 1 lists well recognized factors that place patients at high risk at later time points than initial presentation. It is also important to note that the with respect to pathological stage, only surgically treated patients provide this information.

Traditional markers for high-risk disease

Data from large single series cohorts and randomized trials have identified four traditional risk factors Table 2 defined at presentation that place patients at high risk for treatment failure and potentially prostate cancer death: clinical stage, PSA, biopsy Gleason grade and some measure of tumor volume.

TABLE 2. **Traditional risk factors**

Clinical stage
PSA
Gleason score
Volume

Clinical stage

The utility of the staging systems in prostate cancer has been well recognized for over a generation. Many systems have been used with the TNM system most widely utilized today. Clinical stage remains the most important predictor of survival in prostate cancer. Patients with M+ disease typically die in 30-36 months.[3] Patients with node positive disease live on average 7-9 years.[4] Aside from N+ and M+ disease, the contribution of T-stage becomes less clear, particularly among men with clinical T1-2 disease. In most cohort studies,[5] T stage remains important but perhaps not as important as other parameters.

Prostate specific antigen

PSA has dramatically altered the approach to prostate cancer treatment and detection. It remains an excellent cancer marker. In the early PSA era, data from numerous centers[6-10] published consistent data showing that a higher PSA at presentation was associated with worse surgical outcomes. Similar data emanated from the radiation oncology literature.[11] More recently, data from Stamey[12] suggest that in low levels (<9 ng/ml) PSA may better reflect benign prostatic hyperplasia than prostate cancer. Clearly these data challenge our current concept of PSA, but suffice it to say that at least in levels above 10 ng/ml PSA is an important marker of outcome in prostate cancer.

Recent attention has been brought to PSA kinetics prior to prostate cancer detection. D'Amico and colleagues[13] assessed PSA change in the year prior to prostate cancer detection among a surgically treated cohort of men. In that analysis, men with PSA rise greater than 2 ng/ml in the year prior to disease detection did poorly with a ten fold higher risk prostate cancer specific death. Clearly more work is needed in this area and heightened attention needs to be paid to PSA change from primary care doctors.

Tumor grade

Histological grade at biopsy has been recognized as an important predictor of outcome from prostate cancer for many decades. The Gleason system is most widely used and was developed, in part, because of the known heterogeneous nature of prostate cancers. It must also be noted that many prostate cancers at true pathology differ from the biopsy grade,[14] although this has diminished in recent years. Aside from patients with obvious N+ or M+ disease, most analyses

place Gleason pattern 4 disease as the strongest predictor of outcome.[6-8]

Cancer volume

A number of approaches have been used to estimate cancer volume from procured biopsy specimens. These include number of positive cores, volume of cancer as well as mm (length) of cancer. Much refinement of these systems are required but clearly these data are helpful in planning nerve bundle sacrifice as well as prognosis in general.

Assessing risk in clinical practice

Physicians who treat men with prostate cancer have an array of tools available to assess risk in the clinical setting. The tools most utilized in clinical practice are the Partin[15] and Kattan[16] nomograms as well as the D'Amico classification.[17] All of these risk stratifications schema have their advantages and disadvantages. The Partin tables are particularly useful in selecting men for non-nerve sparing surgery but it must be emphasized that they have no time function. Thus they can only predict pathological findings. It should also be noted that many men with extracapsular extension can be cured with surgical therapy.[8] The Kattan nomogram has the added benefit of predicting recurrence free survival. Finally the D'Amico classification utilizes grade, stage and PSA to predict men at low (PSA<10 and Gleason <7 and T1-2), intermediate (PSA<20, and T1-2 and Gleason 7) or high (any Gleason 8 or T3/4 or PSA>20) risk. Unfortunately the range for men at high risk is tremendous. For example a man with a T3 Gleason 6 tumor and PSA of 26 would be similarly classified as a man with Gleason 9/T3 disease. Clearly they have vastly different prognoses. Despite these limitations, risk stratification is encouraged and helps facilitate patient's care.

Softer risk factors

A host of additional risk factors deserve comment. These risk factors are being increasingly recognized as important in predicting outcome and in some cases are modifiable.

Obesity

Obesity is at epidemic-type levels an increasingly being recognized as a risk factor not only for disease incidence but outcome as well.[18] A variety of mechanisms may explain this observation including altered androgen metabolism[19] as well as more difficult delivery of radical therapies as evidenced by a higher incidence of positive surgical margins.[18] Obesity is also confounded somewhat by race and African Americans have the highest obesity rates.[20] In one recent study,[21] men with organ confined cancers were examined for risk of biochemical failure. It was noted that obese men were four–fold more likely to fail compared to slim men. Clearly this observation points to biological factors in addition to technical ones as all patients had organ confined disease. More work is needed in this area.

Smoking

Smoking is not a traditionally recognized risk factor for prostate cancer. A recent review suggests that smoking is a likely risk factor for disease progression but not incidence.[22] A variety of biological mechanisms may be responsible for this including altered hormonal milieu, generation of reactive oxygen species and genotoxicity. Roberts and colleagues[23] have shown that young men with prostate cancer who smoke are more likely to fail biochemically. In addition, Pickles and colleagues have shown that men who smoke during radiotherapy respond worse than quitters or never-smokers.[24]

Race/socioeconomic status

The impact of race on outcome in prostate cancer reveals an inconsistent association.[25-27] Although African Americans with prostate cancer have worse outcomes, most data suggest that socioeconomic status is probably more important and, in fact, confounding much of these datasets.

Androgen metabolism

A variety of polymorphisms exist that modulate hormonal activity at the cellular level.[28-29] These include CAG repeats, SSR5A2 polymorphisms and many others. The data implying these as predictors of outcome are both inconsistent and in some case bi-directional. Clearly more data are needed.

The future: molecular profiling

Given the heterogeneous nature of prostate cancer, the era of modern genomics and bio-informatics hold great promise in allowing us to predict biological outcome from pathological specimens as well as host DNA with much greater accuracy than current approaches. Recent publications from pathological specimens suggest that this approach is feasible[30-32] however securing this information from biopsy material is at the present, problematic. Clearly this approach will continue to flourish in the coming decade. □

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