

Understanding *and* Applying Risk Assessment *for* Prostate Cancer

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INTRODUCTION: THE HETEROGENEITY OF PROSTATE CANCER

With over 200,000 new diagnoses every year, prostate cancer is by a wide measure the most common cancer among men in the United States. Over 30,000 men will die of the disease this year.¹ This number is surpassed only by lung cancer among cancers affecting men in this country, yet is clearly dwarfed by the number of diagnoses. These numbers summarize the challenge of prostate cancer: screening programs based on measurement of prostate specific antigen (PSA) levels among otherwise healthy men are intended to identify and offer early curative treatment to the men at risk of dying of prostate cancer — and indeed, since PSA screening started in earnest in the early 1990s, prostate cancer mortality rates at the population level have fallen about 40%.¹ But in the course of identifying the potentially



lethal prostate cancers, many more tumors are found that are indolent, i.e., that would never cause symptoms or reduced lifespan if they were never detected. Most men with prostate cancer in fact die of heart disease — just like men who have

not been diagnosed with prostate cancer. The side effects and costs of over-treating these low-risk prostate tumors amount to one of the most substantial public health problems related to the disease.

The obvious solution is to treat only those prostate cancers that are likely to cause problems and ignore the rest. In fact, the last several years have seen significant progress toward this paradigm of *selective* and *risk-adapted* treatment. Men with low-risk prostate cancer — tumors unlikely to progress — are now offered *active surveillance*: careful monitoring of the tumor with serial PSA tests and repeat prostate biopsies. With large cohorts of hundreds of men now reported from major centers across North America, this strategy is increasingly accepted as safe and effective: for the large majority of men with low-risk tumors, the window of opportunity for cure lasts for years, so treatment after a period of surveillance (e.g., if the PSA is rising consistently) is as likely to cure as immediate treatment. In the interim, the risks and side effects of surgery, radiation therapy, hormonal therapy, etc. may be avoided.² Men with intermediate-risk cancer generally should receive surgery or radiation therapy, and those with higher-risk prostate cancer often need combination therapy — either surgery followed by radiation or radiation together with hormonal therapy.

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The Key Players: PSA, Gleason Grade, and Tumor Extent

Risk-stratifying prostate cancer — determining which are at low-, intermediate-, or high-risk—is thus absolutely critical to effective treatment. How exactly to use risk stratification in practice is at once simple and complex. The simple part is what factors to consider, as there is broad agreement on the key determinants of prostate cancer risk. First is the blood level of **PSA**. For all the controversy surrounding PSA testing for prostate cancer *screening*, the test is quite reliable in predicting outcomes among men who have already been diagnosed with cancer. Except in rare cases, the lower the PSA, the lower the cancer risk. PSA levels under 10 are usually considered low-risk, but even within the <10 category, lower is better. When the PSA is over 20 at time of diagnosis, there may be detectable cancer outside the prostate, so imaging tests such as bone scans are ordered to rule out metastatic disease.

The second key risk factor is the **Gleason grade**, which is a measure of the aggressiveness of the cancer cells as determined by the pathologist examining prostate tissue (e.g., from a biopsy) under the microscope. The Gleason grade is assigned on a 1 to 5 scale, but in contemporary practice grades 1 and 2 are rarely seen, so for practical purposes, Gleason grade 3 indicates low-grade cancer, Gleason 4 indicates intermediate-grade, and Gleason 5 indicates high-grade. Prostate cancer can be heterogeneous even within an individual prostate, so the Gleason score is expressed as two numbers: the first number is the primary pattern—i.e., the most common pattern—and the second number is the secondary pattern.

The two numbers are sometimes added for a final score, but are better expressed as a primary + secondary score. A Gleason 3+3 (or Gleason 6) tumor, for example, is uniformly low-grade. A Gleason 3+4 tumor is mostly low grade with some intermediate-grade, whereas a Gleason 5+4 tumor is mostly high-grade with some intermediate-grade. In terms of grade, the major driver of prostate cancer risk is the primary pattern. Thus Gleason 4+3 tumors are significantly more aggressive than Gleason 3+4 tumors—which is why lumping all such cases as “Gleason 7” is not ideal.

The PSA and Gleason score are the most important risk parameters in most cases. The third is some

measure of **tumor extent**—how much cancer there is and where it is. There are different ways to articulate extent. The most common is tumor *clinical stage*, and is expressed with three letters: T, N, and M. A tumor which is not palpable on rectal exam or visible on imaging tests (e.g., ultrasound) is designated T1, one which is palpable or visible but is confined to the prostate is T2 (with subtypes T2a, 2b, and 2c depending on how large the palpable tumor is), and one which is felt or seen to extend beyond the edge of the prostate is T3. If there are involved lymph nodes, the cancer is N1, and if there are metastases in the bones or elsewhere, it is M1. Metastatic (i.e., N1 or M1) cancer is very uncommon at diagnosis in the era of PSA screening, and the large majority of tumors are stage T1 or T2.

The problem is that neither rectal exams nor imaging tests are particularly accurate in identifying tumors which are confined to the prostate, and as a result clinical stage offers little information when considered in context of other variables such as PSA and Gleason grade for tumors which are confined to the prostate.³ A more accurate measure of tumor extent is to quantify how much cancer is seen on biopsy. This can be measured as the number or percent of biopsy cores positive—for example, if a 12-core prostate biopsy is performed and 10 cores are involved with cancer, the volume of cancer is greater than if only 2 cores are involved. Some pathologists will also report the extent of cancer involvement within each needle core.

Putting It All Together

Once the PSA, Gleason score, and tumor extent is determined, the question becomes how to integrate this information to give an overall sense of cancer risk. This question is more complicated than identifying the variables: by one count there are over 100 formulae, calculators, nomograms, and other instruments intended to determine risk at various prostate cancer decision points.⁴ Most are based on PSA, Gleason, and clinical stage and/or some measure of biopsy core involvement; some add other parameters such as patient age, year of diagnosis, or prostate size (which can impact interpretation of the PSA).

One of the first widely-adopted approaches to risk stratification is a 3-level risk group classification published by Anthony D’Amico and colleagues at

Harvard University⁵ and formally adopted by the American Urological Association’s practice guideline for localized prostate cancer treatment.⁶ In this classification, men are assigned to one of three groups as follows:

Low-risk: PSA ≤10, Gleason ≤6, and clinical stage T1 or T2a

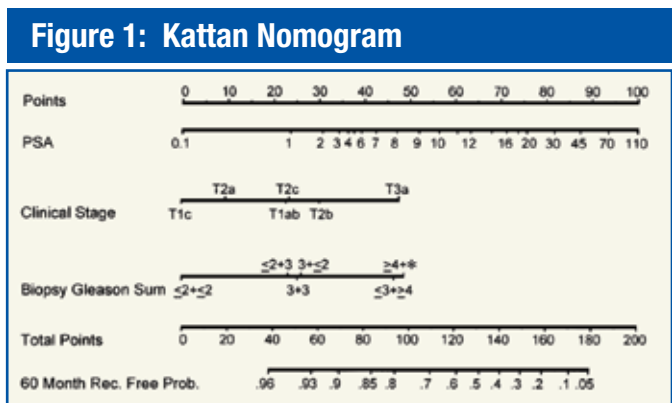
Intermediate-risk: PSA 10-20, Gleason 7, or clinical stage T2b

High-risk: PSA >20, Gleason 8-10, or clinical stage T2c or T3a

The major advantage to this system is its simplicity, and it is used very commonly. However, it has significant drawbacks. First, it over-weights T stage which, as noted above, is not a very accurate measure of tumor extent within the T2 category. Second, it does not distinguish between Gleason 3+4 and 4+3 tumors which (again, as noted above) behave very differently within the Gleason 7 category. Finally, and most importantly, it does not *combine* information from the risk variables. A PSA 18, Gleason 4+3, stage T2b tumor and a PSA 4, Gleason 3+4, stage T1c tumor are both “intermediate-risk” in this classification, but would be expected to behave quite differently.

Multivariable models combine PSA, Gleason grade, and other parameters, integrating information from each to give a more accurate overall impression of risk. There are many such models, and though the math underlying them tends to be similar, there are several different ways to present the data. For example, Alan Partin and colleagues at Johns Hopkins University published a set of *lookup tables* to predict outcomes after surgery such as extra-prostatic extension of tumor.⁷ The tables simply list likelihoods for the outcome of interest for men with a given set of risk factors (again, PSA, Gleason score, and T stage), and are used as a reference.

Nomograms are another popular way of presenting information from multivariable risk models. Popularized by Michael Kattan and Andrew Stephenson and colleagues at Memorial-Sloan Kettering and the Cleveland Clinic, nomograms are graphs on which a patient is assigned a set number of points for each variable of interest; the points are then summed to predict the outcome of interest, which is given with a ±10% margin of error.



For example, using the original nomogram published by Kattan,⁸ which predicts likelihood of remaining free of recurrence 5 years after surgery, the patient mentioned above with PSA 4, Gleason 3+4, stage T1c disease would receive 84 points (37 + 47 + 0) corresponding to a roughly 84% ±10% likelihood of recurrence-free survival. The patient with PSA 19, Gleason 4+3, stage T2b would receive 155 points (74+50+31), indicating a 25% ±10% likelihood of recurrence-free survival. An updated version incorporates data on the number of biopsy cores involved with cancer.⁹

Many other nomograms have been published since, intended to predict pathologic outcomes (similar to the Partin tables), biochemical outcomes after surgery or radiation therapy, or longer-term outcomes like metastasis or mortality.⁴ Two important caveats should be noted. First, a given nomogram is developed based on data from a specific cohort of men, usually treated in one or a few academic centers in which a small number of highly-trained surgeons or radiation oncologists treat large volumes of patients. A great deal of caution must be exercised in calculating specific risks of recurrence for patients treated in other settings by different clinicians, and ideally nomograms should be formally validated in a given setting before they are used routinely in that setting.

Second, with computer software it is very easy to calculate multiple nomogram scores simultaneously, creating a temptation to use the nomogram scores to compare treatment options such as surgery or radiation. Nomograms cannot be used this way—the cohorts of patients used to develop each are very different, as are the definitions of the outcomes reported. In particular, with few exceptions nomograms predict likelihood of PSA recurrence after treatment, (Continued on page 6)



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which is defined very differently after radiation than after surgery. Thus nomograms may be useful to give a patient undergoing a specific treatment a sense of the likely outcomes, but cannot help guide treatment decisions.

The CAPRA Score

Because of these limitations—and the fact that nomograms are difficult to calculate for hundreds or thousands of patients in research settings and cannot be used to consistently identify low- or high-risk

cohorts—our group at the University of California, San Francisco developed the UCSF Cancer of the Prostate Risk Assessment (CAPRA) score, which is intended to combine the accuracy of nomograms with the ease of calculation of the a risk grouping system.¹⁰ To calculate the CAPRA score, points are assigned based primarily on the PSA and Gleason score, with lesser weights given to T-stage, percent of biopsy cores positive, and patient age:

Figure 2: CAPRA Score

Variable	Level	Points	Variable	Level	Points
PSA	≤6	0	T-stage	T1/T2	0
	6.1-10	1		T3a	1
	10.1-20	2	% of biopsy cores positive	<34%	0
	20.1-30	3		≥34%	1
	>30	4		Age	<50
Gleason (primary/secondary)	1-3/1-3	0	≥50		1
	1-3/4-5	1			
	4-5/1-5	3			

Points are added to yield a 0-10 score. Overall, every 2-point increase in score (e.g., from 2 to 4 or from 5 to 7) indicates roughly a doubling of risk. CAPRA scores in the 0-2 range indicate relatively low-risk disease, CAPRA 3-5 tumors are intermediate-risk and CAPRA 6-10 tumors are high-risk. Assuming they were over 50, with clinical stage T1 or T2 and <33% of biopsy cores positive, the two hypothetical patients described above would have CAPRA scores of 2 and 6, placing them in the low- and high-risk groups, respectively.

The CAPRA score was developed based on data from men in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry, which includes men treated at dozens of clinical sites, mostly community-based, across the U.S.. It has also been validated in a large academic center cohort,¹¹ and in multi-center cohorts of men in the Veterans Affairs system¹² and in Europe.¹³ It was recently found to offer better accuracy than competing instruments in an independent head-to-head comparison based on another European cohort.¹⁴ Moreover, it has been shown to predict metastasis and mortality as well as biochemical outcomes—after surgery, radiation therapy, and hormonal therapy.¹⁵

The CAPRA score can be determined without a complex table or software, and with a little practice can be calculated from memory. Moreover, it is easy to calculate for many patients at once and has been validated in multiple settings using the same definitions of low-, intermediate-, and high-risk, so is ideally suited for the research setting as well as for clinical practice. It is important to note that the CAPRA score is primarily meant to indicate *relative* rather than absolute risk. Thus a tumor with a CAPRA score of 4 has an intermediate-risk of recurrence or progression after surgery or radiation. This tumor will be *more likely* to progress than one with a score of 2, and *less likely* than one with a score of 6, regardless of treatment approach or setting. The *specific* risk (e.g., likelihood of being free of disease at 5 years after treatment), while roughly consistent across different cohorts, will depend at least in part on factors such as surgeon skill and experience, pathology grading practices, etc.

Conclusion: Risk Assessment In Practice

Data from the best available studies reported to date leave little question that prostate cancer screening saves lives.¹⁶ However, there is also no question that many men are harmed by over-treatment resulting in such screening efforts. High-quality treatment for prostate cancer entails *some* determination of overall risk, using the D’Amico classification at a minimum, but preferably using a multivariable tool such as a nomogram or the CAPRA score. Treatment in turn should be guided by cancer risk and an individual man’s overall health and life expectancy (*not necessarily*

by his chronological age). Though some trends are slowly improving, there is still too much variation in prostate cancer care, too much over-treatment of low-risk disease, and frequent under-treatment of high-risk disease.¹⁷

It is important to remember that even high-risk prostate cancer is slow to progress compared to lung, pancreas, and other aggressive malignancies. So there is almost always ample time to seek multiple treatment options and to make a carefully considered decision. Lower risk prostate cancers grow so slowly that some thought leaders are starting question whether they should even be called “cancer” at all,¹⁸ given the substantial psychological impact of the word itself. Consistent use of risk stratification tools will ameliorate both over-and under-treatment, will save millions of dollars in needless health care expenditures, and ultimately will improve both survival and quality of life for the hundreds of thousands of men diagnosed each year in the U.S. and worldwide.

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