

## Newly Diagnosed Prostate Cancer: Evaluating the Options -- Part 1 of 3

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Newly diagnosed prostate cancer is a disease in transition. Historically, because it was diagnosed in the advanced stages, the diagnosis of prostate cancer portended an early death just like many other common cancers. Over the last 10 years, however, the widespread use of [PSA testing](#) and [ultrasound directed biopsies](#) has dramatically changed the nature of this disease for the better. These advances have, in a sense, created an entirely new entity, a cancer that is not very life threatening.

This is not to say that the risk of a prostate cancer death has been totally eliminated. A small percentage of newly diagnosed patients have high-grade variants that are more dangerous. We also still see men who have not availed themselves of the benefit of early PSA screening, men who already have advanced disease when they are diagnosed. Fortunately, these sad circumstances become less common every year as more and more men get PSA screening. However, realizing that some forms of prostate cancer are indeed dangerous does not take away from the fact that for most men the danger of dying from this disease is low when it is managed properly.

The transformation of prostate cancer into a treatable disease creates a whole new arena of challenges. Side effects of treatment take on added importance, and the quality of life becomes a priority when survival is no longer the central issue. Side effects from treatment tend to be immediate, whereas the slow-growing effects of untreated cancer may not be felt for 10 to 15 years. Potential side effects such as impotence or incontinence are not trivial.

The number of treatment options is increasing as technology continues advancing. The choices available can generally be thought of in terms of four categories.

- **Local** treatment options ([radical prostatectomy](#), [brachytherapy](#), [external radiation](#), [cryotherapy](#)) are directed at the eradication of the prostate gland and the cancer it contains. Modern technology in expert hands can accomplish the sterilization of the prostate gland from cancer with a high degree of consistency. However, there are two potential drawbacks to the local treatment options. One is the potentially irreversible side effects to the adjoining structures (e.g. the erectile nerves, bladder or rectum). The other is the disheartening possibility of undergoing the risks of local therapy only to later have a relapse because the cancer had already spread to elsewhere in the body.
- **Systemic** treatment options (surveillance with dietary modification, [antiandrogen](#) monotherapy or [combined hormone blockade](#) for 12 or more months) treat the whole body but are suppressive, not curative in nature. The selection of one of these options is based on the philosophical belief that prostate cancer is a low-grade process. Therefore, effective suppressive treatment may

be able to convert it into a chronic, non-progressive condition. The advantage of these options is that the side effects are usually reversible. The disadvantage is the absence of the possibility to get closure and move on; a systemic approach requires one to remain educated about the disease and watch the situation closely as it evolves.

- **Combination** options (systemic plus local treatment) provide the best chance for outright eradication of the disease but using two treatments instead of one incurs a higher risk of side effects.
- **Conditioning** options usually consist of some form of hormone blockade administered for three to six months as a lead-in to local therapy. Hormone blockade given in this fashion has not been shown to improve the cure rates of state-of-the-art local treatment. However, by reducing the size of the prostate gland prior to therapy, **neoadjuvant** hormone blockade reduces the potential side effects of the local therapy.

The tension between the risk from the cancer and the risk from treating the cancer mandates a process of robust education that enables men to be fully aware of the short and long-term implications to the various options before they make irreversible choices. Fortunately, newly diagnosed early prostate cancer is a slow growing disease, permitting sufficient time for the problem to be studied.

The progressive educational process, which hopefully leads to selecting optimal treatment, can break down for a variety of reasons. This disease is unusual because patients themselves make the treatment decisions. Patients should be aware of some pitfalls inherent in a situation where they are selecting their own cancer strategy. Many patients are in a state of shock and grief for a few months after diagnosis. Strong emotions are also stirred up as patients reflect on the dramatic personal consequences attendant to a high-stakes situation that can affect sexual and urinary function permanently. The clear and objective reasoning that is needed can be difficult under these circumstances, but patients should be encouraged to persevere and weigh all the relevant factors.

This shift of responsibility from physicians to patients results from the fact that there are multiple different treatment choices with indistinguishable survival rates. Therefore, **examining the potential side effects of each treatment option and comparing it with the other choices is the only logical way to make distinctions among these many options.** Since it is the side effects that distinguish these alternatives, patients themselves must decide which type of side effects they are willing to personally risk.

### **Determining the Appropriate Intensity of the Treatment Plan**

Carefully comparing and contrasting treatment options prior to finalizing a plan is certainly important. But even more important, the initial step must be to determine the appropriate intensity of the treatment plan. In other words, how do we decide when the disease is serious enough to warrant the use of a combination of treatment options? When is the disease situation low-grade enough to be treated with a single modality therapy? Clearly a single modality approach, when it can be safely used, is always preferable since there are fewer associated side effects. So before picking a local or systemic treatment option, patients must first determine their risk that their cancer has

spread outside the gland, i.e. the risk of having micro metastatic disease. When the risk of [micromets](#) is low, single modality therapy is best. When the risk of micromets is high, combination therapy is best.

Understanding the concept of [metastasis](#) is essential to making correct decisions about what kind of treatment is appropriate. Cancer can enlarge and grow through the capsule of the prostate (increasing the risk of [positive margins](#) at surgery), but this is not what we are talking about when we use the term micromets. Prostate cancer cells also have the potential to separate from the primary tumor, enter the blood stream, and end up in other areas of the body – usually the bones or [lymph nodes](#). The concept of metastasis is a little challenging because it is impossible to know with absolute certainty whether or not microscopic nests of metastatic cells exist in a given patient. There is no technology presently available that can scan your whole body and unflinchingly detect the presence of a few prostate cells outside the gland; [bone scans](#) are positive only when the metastases are large enough to provoke an [osteoblastic](#) reaction resulting in new bone formation. Our lack of ability to definitely rule in or rule out the presence of metastasis is a severe disability when it comes to making treatment recommendations. Absolute information would, of course, be useful because we could then select the individuals who have no metastatic disease; these patients would certainly then be the best candidates for local therapy alone.

Since we cannot measure micromets directly our next best alternative is to estimate the likelihood that they are present. **When such an estimate is available, patients then can at least use this information to decide whether they personally feel that a combination approach is warranted.** One process for determining one's risk of micromets is via the Kattan nomograms.

The Kattan nomograms were developed by Dr. Michael Kattan, a biostatistician at Memorial Sloan Kettering in New York. These nomograms generally use a combination of three factors to determine the probability of PSA relapse after local therapy. These factors are PSA, [Gleason score](#), and [Clinical stage](#). Nomograms exist for surgery, [conformal radiation](#), and for brachytherapy. Generally, the predicted relapse rates (the risk of micromets) is fairly consistent when the nomograms are compared with each other. The nomograms are derived from the results of treatment of thousands of patients who have been treated at reputable university centers. Hence, the relapse rates generally do not reflect the effects of poorly performed local therapy. Rather, the statistical likelihood of relapse is dependent upon the presence of micro-metastatic disease preexistent at the time the local therapy was performed. Therefore, the relapse rates determined by the Kattan nomograms can be taken as an indication of the likely presence of micromets at the time of local therapy.

Of course, the danger of micromets is that they eventually grow to larger dimensions and, when fully developed, impair function and ultimately lead to death. Patients are generally aware that for most common cancers (such as colon, lung, stomach etc.) micromets portend an almost certain early death within a couple of years. However, this is certainly not the case for prostate cancer. **Early relapse after local therapy (as detected by a rise in PSA) can, on the average, be controlled with the early administration of hormone blockade for up to 11 years!**<sup>1</sup> And even when hormone blockade loses effectiveness, a variety of additional therapeutic alternatives are available.

Men need to keep in mind the relatively low-grade nature of prostate cancer relapses when weighing the pros and cons of using combination therapy to reduce the risk of relapse; clearly, elderly patients need not be unduly concerned about relapse (because of the efficacy of hormone blockade in controlling relapses), whereas for younger men the risk of a relapse translating into an eventual prostate cancer death (rather than from old age) should be taken quite seriously.

For decision-making and counseling purposes we have found it useful to initially categorize patients into four risk categories with the statistical information provided by the Kattan nomograms (see Table 1). As shown, we categorize patients who are less likely to have micro metastatic disease (less than 50% chance) as Risk Category I patients. We categorize patients who are more likely to have micro metastatic disease (more than 50% chance) as Risk Category II patients. Risk Category III describes patients with a documented spread to the lymph nodes. Risk Category IV represents patients with a documented spread to the bones. Risk Category I patients are further subdivided to IA (a less than 10 % risk of micromets), to IB, (a 10–25% risk of micromets), and to IC, (a 25–50% risk of micromets).

<b>I</b>	< 50% chance of micro metastatic disease
<b>IA</b>	< 10% chance
<b>IB</b>	10-25% chance
<b>IC</b>	25-50% chance
<b>II</b>	> 50% chance of micro metastatic disease
<b>III</b>	documented spread of PC to lymph nodes
<b>IV</b>	documented spread of PC to bones

### **Modifying Predictive Factors**

Besides PSA, Gleason score, and Clinical stage, other factors not included in the Kattan Nomogram provide additional predictive information about the risk of relapse. These include:

- A serum [PAP](#) elevated above normal range and confirmed with a repeat
- More than 50% of core biopsies positive for cancer
- An [endorectal MRI](#) showing seminal vesicle invasion
- A PSA > 0.5 after three months of conditioning hormone blockade.

In the interest of being systematic and consistent in providing patients with our best estimate of the likelihood of micromets, we modify the initial assigned Kattan stage accordingly.

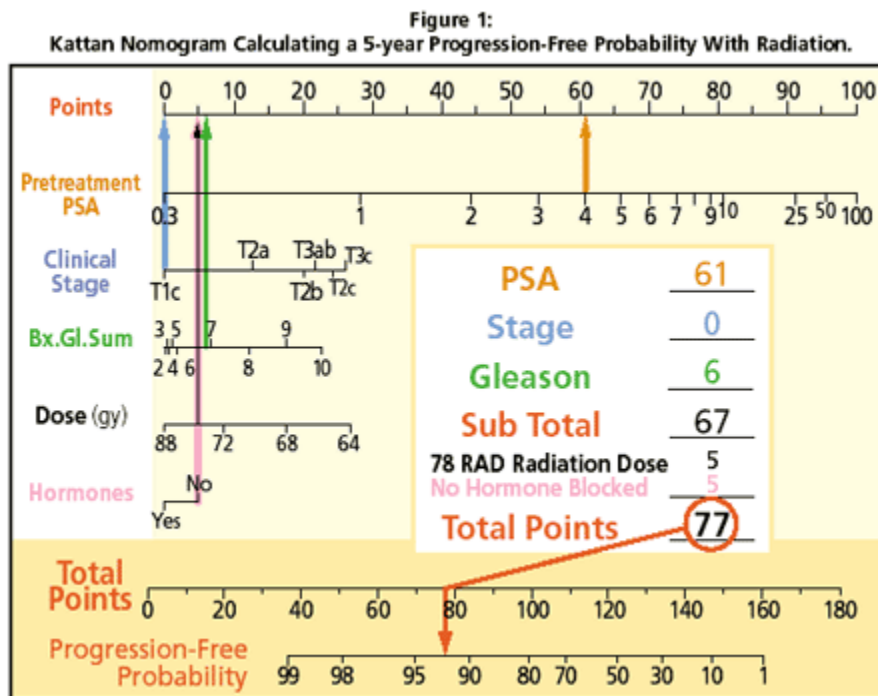
For patients who have more than 50% of core biopsies positive, we automatically raised one sub stage from that initially assigned by the Kattan nomogram. For example, when the nomogram indicates a Risk Category IB, we would raise the Risk Category to IC. Risk Category IC patients would be raised to Risk Category II.

We assigned Risk Category II automatically (unless Risk Category III or IV is documented) regardless of the Kattan prediction when any one of the following exists:

- A consistently elevated serum PAP
- Documented **seminal vesicle** invasion
- A PSA > 0.5 after three months of hormone blockade

This analysis, which provides an estimate of relapse risk (and an estimate of risk of underlying metastasis), is a tool designed to aid in determining the potential benefit of combining systemic hormone blockade with local therapy. Several randomized prospective trials adding hormone blockade to local therapy<sup>2,3,4,5,6</sup> conservatively indicate that relapse rates can be reduced by about 50% in patients treated with hormone blockade for an adequate period of time (the optimal time period is not known but appears to be between 12 to 24 months duration).

Therefore, this analysis using modified Kattan nomograms enables patients to measure the potential benefit of adding hormone blockade to local therapy and to weigh that benefit against the potential toxicity of therapy. This can be demonstrated with two examples. As shown in Figure 1, a patient with a PSA of 4, a stage of T1c and a Gleason of 7 has a total of 67 points on the Kattan nomogram (for conformal radiation). Five points are added for removing the effects of conditioning hormone blockade. An additional five points are added by selecting a typical standard dose of radiation e.g., 7800 rads. Sixty-seven plus ten equals 77 points. On the Kattan nomogram 77 points indicate a 94% probability that the disease will not progress in five years. Stated another way, the risk of relapse is 6% (100% minus 94%).



This patient has Risk Category IA disease if less than 50% of the core biopsies are positive, the PAP is not elevated, there is no evidence of seminal vesicle invasion, and

the PSA is not greater than 0.5 after three months of conditioning hormone blockade (if it is being utilized). Since hormone blockade administered for 12 to 24 months cuts the risk of cancer relapse by 50%, the risk of relapse in this example is reduced from 6% down to 3%. In other words, in a patient with this particular profile, hormone blockade only improves the cure rate by 3%! In my experience, **most men eagerly forgo the potential side effects of hormone blockade when there is such a tiny chance it will have a beneficial impact.**

Another example may further illustrate these methods. In this example, the patient has a Gleason score of 8, a PSA of 15, and a clinical stage of T2b (a moderately sized nodule [new term] confined to one side of the prostate). This patient would have a total of 115 points on the nomogram. Again adding ten points for a dose of 7800 rads and no conditioning hormone blockade **results in a total point score of 125. This translates into a 60% relapse rate!** Hormone blockade for an adequate period of time is clearly indicated in such a patient and will reduce the risk of relapse by about half of 60% i.e. 30%.<sup>7</sup>

The Sloan Kettering Cancer Center website at [www.mskcc.org/nomograms/prostate](http://www.mskcc.org/nomograms/prostate) presents a nomogram calculator that permits a similar analysis for surgery, conformal radiation, and brachytherapy based upon a patient's own staging parameters.

### **Should Hormone Blockade Be Combined with Local Therapy?**

These two examples, because they are at opposite ends of the spectrum, lead to fairly straightforward conclusions about the advisability of using or forgoing hormone blockade in combination with local therapy. Patients with less polarized relapse rates, say in the 15 to 30% range, are not as easy to counsel. Ultimately, these individuals themselves must make a decision that they feel is in their best interests. **To make this decision, a patient in this situation must carefully weigh the implications and relative risk of relapse in the context of their age, preexisting sexual function, and overall health priorities along with the known potential side effects of hormone blockade.**

Patients who are ambivalent about the options facing them will occasionally elect to initiate hormone blockade to see how well they themselves tolerate the treatment. If inordinate side effects are encountered, they can stop the treatment with the expectation that the side effects will reverse. The only exception to this rule is for patients considering nerve-sparing surgery. About a third of patients treated with hormone blockade develop capsular thickening; this thickening can render the [nerve sparing](#) surgery somewhat more difficult, thereby increasing the risk of impotence.

Forced by circumstances to act as "amateur doctors," patients may finalize a treatment plan before they become aware of all relevant treatment options. This mistake can occur not only as a result of incomplete knowledge due to a lack of information about some aspect of one of the long list of alternatives, but also because of a natural human propensity to seek rapid resolution to a confusing situation. Despite reassurances, it is hard for patients to escape the lingering fear that "time's a wasting" while the cancer is growing and spreading.

Problems related to treatment selection do not merely originate from patient naiveté and lack of experience or a state of shock. Even doctors who contract this malady

bemoan the frustrating lack of clear data and consensus among prostate cancer experts. They, like all patients, struggle with the marked variability in treatment skills among surgeons and radiation therapists and the absence of any objective method for measuring these skills.

This first part of this three-part article has focused on the process used to decide whether or not to initiate **adjuvant** systemic hormone blockade with a view toward eradicating micro metastasis. This decision logically is based on the projected risk of micro metastatic disease being present; hence, I have described an approach enabling a newly diagnosed patient to make this risk determination. Risk alone is not the only deciding factor, however. The individual patient's age and specific preferences are also important. In parts two and three of this article, I will try to provide some guidelines that incorporate these additional factors and enable the patient to make the best decision for his specific situation.

**Part 2** deals with early stage disease (less than 10% chance of microscopic spread).

**Part 3** deals with higher risk of disease at diagnosis.

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**Source:** <http://www.prostate-cancer.org/pcricms/node/126>