

## The D'Amico Article Reviewed: The CPDR/CaPSURE Recurrence Equation

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**D**r. D'Amico has written an outstanding overview of risk stratification in localized prostate cancer using a combination of prognostic factors such as prostate-specific antigen (PSA) value, Gleason score, and clinical or pathologic stage to group patients as to their likelihood of having occult locally advanced or developing advanced disease. Using nomograms, equations, or tables, the clinician can "plug in" the patient's individual factors to de-

termine his risk group. At the time of initial diagnosis or after initial primary treatment, the risk stratification can help the clinician make decisions about additional local or systemic therapy or better tailoring of the patient's follow-up care.

Because clinically localized prostate cancer may be truly localized or, in actuality, more advanced, these risk stratifications are critically important. Dr. D'Amico and other recent investigators such as Partin, Kattan, and Bauer (who is from my group) have taught us to think about combining prognostic factors to better "stage" the patient, rather than relying only on traditional staging factors such as tumor size and radiographic imaging. Furthermore, a by-product of risk stratification is broadened thinking about treatment—ie, an awareness that surgery alone or radiation alone may not be sufficient for many higher risk men and that a combination of treatments may be indicated.

### Choosing the "Best" Nomogram or Equation

Having said these positive things about risk stratification, it is also important to point out the major current problem: What is the best nomogram or equation to use? There are now at least 42 published prostate cancer nomograms according to a recent article by Ross, Scardino, and Kattan.[1] It is difficult enough for a busy clinician to make the philosophical leap of incorporating nomograms into practice. Ross et al correctly point out that the field is currently hampered by a lack of comparisons of predictive accuracy. In other words, how do we know that the groupings proposed by Dr. D'Amico, or for that matter, any investigator, are "better" or more clinically useful or applicable than a risk-stratification nomogram touted by someone else.

In the article by Ross et al,[1] our own work in this area was criticized. Specifically, in 1998, Bauer et al from

Table 1

### Validation of Original Post-Radical Prostatectomy Risk-of-Recurrence Stratification Model in Updated CPDR and CaPSURE Radical Prostatectomy Cohorts

#### Center for Prostate Disease Research (CPDR)

Risk Group	Number of Patients	Number of Recurrences	3-Year Disease-Free Survival Rate	5-Year Disease-Free Survival Rate	7-Year Disease-Free Survival Rate
Low	143	14 (9.8%)	96.0%	92.5%	85.1%
Intermediate	193	31 (16.1%)	92.7%	84.9%	70.6%
High	167	56 (33.5%)	80.6%	62.3%	37.7%

#### Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE)

Risk Group	Number of Patients	Number of Recurrences	3-Year Disease-Free Survival Rate	5-Year Disease-Free Survival Rate	7-Year Disease-Free Survival Rate
Low	441	36 (8.2%)	93.8%	83.5%	72.0%
Intermediate	409	97 (23.7%)	85.5%	67.6%	42.1%
High	162	68 (42.0%)	74.8%	46.8%	27.6%

Adapted, with permission, from Moul et al.[4]

Table 2

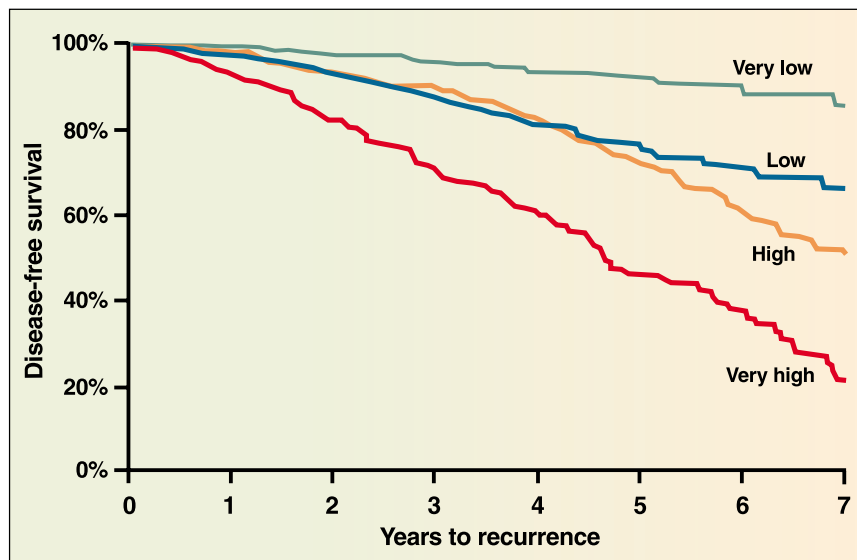
**Updated CPDR/CaPSURE Risk-of-Recurrence Equation: Kaplan-Meier Disease-Free Survival Rates at 3, 5, and 7 Years After Radical Prostatectomy, by Risk Group**

Risk Group	Risk of Recurrence	Number of Patients	Number of Recurrences	Disease-Free Survival Rates		
				3-Year	5-Year	7-Year
1	1.6–3.9	188	10	97.3%	93.8%	85.6%
2	3.9–4.7	191	13	94.6%	89.5%	83.5%
3	4.7–5.6	190	32	89.4%	76.2%	62.3%
4	5.6–7.1	188	26	90.5%	74.9%	71.9%
5	7.1–8.9	190	37	90.1%	74.5%	54.4%
6	8.9–12.3	190	47	86.6%	74.5%	43.8%
7	12.3–16.7	189	47	86.6%	67.2%	54.4%
8	16.7–56.3	189	90	70.3%	46.3%	21.3%
<b>Consolidated Groupings</b>						
1 and 2 = very-low-risk group	1.6–4.7	379	23	96.1%	91.9%	85.4%
3 and 4 = low-risk group	4.7–7.1	378	58	89.9%	75.5%	66.0%
5,6, and 7 = high-risk group	7.1–16.7	569	131	87.8	71.9%	50.6%
8 = very-high-risk group	16.7–56.3	189	90	70.3%	46.6%	21.3%

<sup>a</sup> For the combined CaPSURE and CPDR cohorts (N = 1,515).

CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor; CPDR = Center for Prostate Disease Research.

Adapted with permission from Moul et al.[4]



**Figure 1: Survival Curves**—Biochemical disease-free survival curves for postprostatectomy patients in four risk groups, based on the 2001 CPDR/CaPSURE risk-of-recurrence equation. CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor; CPDR = Center for Prostate Disease Research.

my institution developed a prognostic equation that used pretreatment PSA value, surgical Gleason sum, pathologic stage, and patient ethnicity to stratify risk of recurrence after radical prostatectomy.[2] The equation was based on data from 378 patients treated at Walter Reed Army Medical Center in the early PSA era and was validated with an independent group of 91 patients from another military hospital. Ross et al correctly pointed out that the group at intermediate risk of recurrence was not significantly different from the low- or high-risk groups in the validation.[2] Truthfully, I had overlooked this fact in 1998 when the article was published, and the peer reviewers of the article for the *Journal of Urology* overlooked it as well.

I mention this because our 1998 work was an honest yet rather “first-pass” effort to risk stratify our post-surgery patients. Despite the small size of the study (N = 378) and suboptimal validation, it taught my clinician colleagues and me to think in terms of risk stratification. Furthermore, the equation was placed on our website at [www.cpdr.org](http://www.cpdr.org) and has been used extensively in our daily practice to counsel patients who have undergone radical prostatectomy about their risk of recurrence and appropriate degree of vigilance for follow-up. It has even been incorporated into an ongoing clinical trial of a HER2/neu vaccine for high-risk men after surgery.

### The CPDR/CaPSURE Equation

Even before the article by Ross et al was published,[1] we embarked on further validation and updating of the equation developed by Bauer et al.[2] Collaborating with the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database[3] and increasing our Center for Prostate Disease Research (CPDR) cohort, we validated the Bauer equation with data from 1,515 patients with a mean follow-up of 47 months (CPDR) or 36 months (CaPSURE). Table 1 shows the 3-, 5-, and 7-year disease-free survival

rates for the low-, intermediate-, and high-risk groups. Differences among all of these rates are statistically significant.

We then developed a modified multivariable Cox regression model for risk of recurrence (RR), based on this combined cohort of 1,515 patients:

$$\text{RR} = \exp[(0.54 \times \text{race}) + (0.05 \times \text{PSA}_{\text{st}}) + (0.23 \times \text{postop Gleason}) + (0.69 \times \text{pathologic stage})]$$

In this equation, race = 1 if the patient is African-American, and 0 if white.  $\text{PSA}_{\text{st}}$  is calculated using a sigmoidal transformation of highest pretreatment PSA. The postoperative Gleason sum enters the equation as a continuous integer value ranging from 2 to 10, with 10 being the highest or worst sum in the radical specimen. Pathologic stage = 1 if there was extracapsular penetration and/or a positive margin (ie, pT3 disease) or 0 if organ confined (pT2).

Table 2 lists eight risk groups, which are then consolidated into four risk groups (very low, low, high, and very high) with the corresponding 3-, 5-, and 7-year disease-free survival rates after radical prostatectomy. Figure 1 illustrates the disease-free survival curves for these four risk groups.

We believe this new equation will help improve patient care and have made this new equation available on our website at [www.cpdr.org](http://www.cpdr.org) for others to use. As with the original Bauer equation,[2] one simply enters the four variables in the fields provided on the Web page, and the program calculates the risk of recurrence for the individual patient. The risk-of-recurrence value can then be “fit” into one of the eight risk groups for comparison with our published disease-free survival (Table 2).

### Conclusions

Although we believe our new model is an advance, we admit that we do not know if it is “better” or even as good as the risk groupings proposed by Dr. D’Amico and others.[1] Our model needs to be compared in a pro-

spective fashion with other nomograms that predict recurrence after radical prostatectomy. Furthermore, additional prognostic factors, most notably the percentage of cancer-containing biopsy cores as a surrogate of tumor volume (touted by D’Amico), will undoubtedly improve risk stratification in the future.

There is still much fine-tuning needed to help sort out intermediate-risk patients. For example, risk groups 3 to 7 have a 7-year disease-free survival ranging from 71.9% to 43.8% (Table 2). Despite the fact that these groups represent 947 of our 1,515 patients (62.5%), the risk stratification is not ideal. It may represent the most prognostic power available from our four factors (PSA, pathologic stage, Gleason score, and race), but it is not enough for intermediate-risk assessment. In the future, we must develop and validate nomograms that are simple and based on easily obtained variables, but they must also serve to better stratify the risk of patients in the intermediate-risk group.

As Dr. D’Amico’s article shows, we have made great strides in risk stratification as a new paradigm for clinically localized prostate cancer. However, much work remains to be accomplished.

—Judd W. Moul, MD

### References

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*A second review, by Drs. Ray and Sandler, appears on page 1064.*