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INVITED OPINION

Prostate Cancer

Perspectives on the clinical management of localized prostate cancer

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If cure is necessary, is it possible and if cure is possible, is it necessary?

–Willet F. Whitmore

Defined broadly, prostate cancer has two states: An indolent histological manifestation of a locally proliferative and invasive process or a clinically relevant, potentially lethal disease. Likewise, the management of clinically localized prostate cancer must address two questions: what sort of disease is this and what needs to be done.

The protean nature of prostate cancer, summarized in a simple question by Dr. Whitmore, is becoming increasingly relevant in current disease management. Defined broadly, prostate cancer has two states: an indolent histological manifestation of a locally proliferative and invasive process or a clinically relevant, potentially lethal disease. Likewise, the management of clinically localized prostate cancer must address two questions: what sort of disease is this and what needs to be done. Dissecting Whitmore's conundrum – a riddle contained within a pun – is useful in structuring a perspective on clinically localized prostate cancer.

IS CURE REALLY NOT NECESSARY?

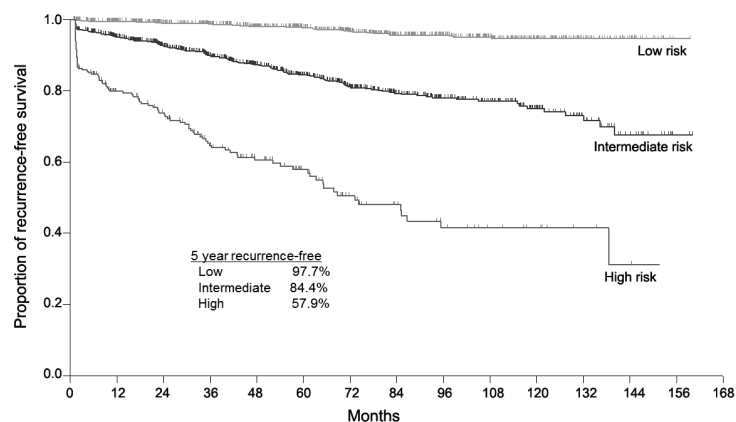
In the United States, death from prostate cancer is disproportionately populated by those who present with high risk features and in the elderly. For example, biopsy Gleason score 8–10 accounts for less than 10% of all men undergoing radical prostatectomy and yet is associated with more than a third of the 15-year prostate cancer-specific mortality.¹ Men with similar

high-grade disease undergoing conservative management (observation, immediate or delayed androgen deprivation therapy) were much more likely to die of prostate cancer than another cause.² Moving beyond a strategy to treat every prostate gland independent of the inherent disease risk – remarkably close to current practice – improvement in prostate cancer survival will require more effective management of high risk disease.

But what, exactly, is high risk disease? Most trace their understanding of risk categories to the work of D'Amico: 'patients with AJCC stage T2c disease or a PSA level of more than 20 ng ml⁻¹ or a biopsy Gleason score of 8 or more have a risk higher than 50% at 5 years of post-therapy PSA failure.'³ As is shown in the outcomes of men stratified by low-, intermediate- and high-risk disease from my own series (Figure 1), the strength of this classification scheme is the ability to significantly segregate the populations based on preoperative features. Although this

risk category certainly captures the largest fraction of bad cancers, it unnecessarily includes some without truly high-risk disease and simultaneously, excludes some destined to die of prostate cancer. Does that small nodule (or is it really a prostatic calcification?) contralateral to the palpable lesion, hence T2c, really make this cancer high risk? Doesn't that small nonpalpable cancer, so poorly differentiated it no longer makes PSA, become more lethal when it is not detected in an otherwise seemingly low-risk cancer? By the original D'Amico description, any PSA over 20, any Gleason 8–10 and any bilaterally palpable tumor placed that patient in the high risk category: as such, it is certainly the most inclusive of the three risk categories, the most open-ended, and hence, the most heterogeneous.

Other tools for risk estimation for the newly diagnosed prostate cancer patient have been developed and independently validated (Table 1). Risk categories, despite



Number at risk	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168
Low	1251	1123	995	901	792	674	547	430	335	251	164	87	38	3	
Intermediate	1298	1081	892	751	614	483	364	275	200	143	90	51	24	2	
High	263	167	138	102	77	58	41	32	23	17	11	6	3		

Figure 1: Prostate cancer recurrence after open radical prostatectomy (defined as PSA ≥ 0.2 ng ml⁻¹ or use of any adjuvant treatment) stratified by D'Amico risk categories.

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Table 1: Tools for risk estimation for newly diagnosed prostate cancer patients

Tool	Description	Example
Risk categories	Uses PSA, clinical stage and biopsy Gleason score to separate patients into broad risk groups	D'Amico Risk Groups (low, intermediate or high risk of 5-year biochemical recurrence)
Probability tables	Uses PSA, clinical stage and biopsy Gleason score to predict final pathological stage	Partin tables (probability of organ-confined cancer, extracapsular extension, seminal vesicle invasion, lymph node metastases)
Risk score	Uses age, PSA, clinical stage, Gleason score, percent positive biopsy cores to predict 5-year recurrence-free survival estimates	UCSF-CAPRA score (risk score 1–10: higher number—increased probability of 5-year recurrence)
Nomograms	Calculate probability of an event based on continuous and categorical input	Kattan nomograms (probability of 5- and 10-year freedom from biochemical recurrence; indolent disease or pathological stage)

PSA: Prostate-specific antigen; UCSF-CAPRA: University of California, San Francisco Cancer of the Prostate Risk Assessment. *Adapted from reference⁴

their inherent broadness and lack of resolution, have been widely adopted in clinical practice because they are intuitive and easy to apply. Probability tables suffer from the unknown surrogacy of final pathological stage in overall outcome and the need to be regularly updated with contemporary cohorts. Risk scores attempt to improve on risk categories by including age and volume of cancer, but, in the process, become more unwieldy. Nomograms, particularly those accessed and calculated by computer, are the most widely used in risk prediction and provide the most individualized results compared with the other tools.

All these tools were developed to predict an event: biochemical failure, final pathology and likelihood of indolence, but not the one that matters most to those with high risk features, namely, death from prostate cancer. Recently with the longer-term follow-up necessary to collect enough prostate cancer deaths to be meaningful, a tool for predicting prostate cancer-specific mortality after radical prostatectomy has been developed.¹ Interestingly, even in those with high risk disease (as defined by D'Amico), the 15-year prostate cancer-specific mortality was only 19% (95% confidence interval (CI) 14–24) meaning either such men were either cured by surgery, were alive with disease or died of another cause. How high risk is a disease when less than 20% have died of it within 15 years?

In the United States, the median age of death from prostate cancer is 80-years-old and more than half of the deaths from prostate cancer occur in men over 75-years-old.⁵ The challenge is to determine who will live long enough to be at risk to die of prostate cancer. The natural history of early, localized prostate cancer over 30 years was recently reported.⁶ The risk of prostate cancer-specific death

increased between years 20 and 30, indicating that healthier men are at greater risk. Indeed, even men with low-grade, untreated prostate cancer can die of their disease.

WHEN IS PROSTATE CANCER 'BENIGN'?

Clinically insignificant disease has moved from a pathological characterization to one describing a growing number – perhaps the majority – of newly diagnosed prostate cancers. Indeed, identifying minimal risk lesions as cancer is being openly questioned, as proposed by the term indolent lesion of epithelial origin (IDLE).⁷ For many, a prostate cancer diagnosis would be no more than a nuisance if it were not for the zeal of those bent on eradicating the disease, often at the expense of quality of life. In the PSA-era, only 4% of men treated with radical prostatectomy had a 15-year prostate cancer-specific mortality of greater than 5%.¹

The natural history of pathologically organ-confined (pT2) Gleason score 6 or less prostate cancer after radical prostatectomy in 2551 men at John Hopkins was recently reported.⁸ Biochemical recurrence occurred in 0.5% (13 patients) with an actuarial probability of 1.3% at 15 years. No patient in that cohort developed distant metastases, and obviously, none had a prostate cancer-specific mortality. The indolent nature of Gleason 3 + 3 = 6 prostate cancer was further supported by a study of over 14 000 fully embedded radical prostatectomy specimens when a pelvic lymph node dissection was also performed.⁹ There is no case of a pelvic lymph node metastasis in that series. In my personal series, observed recurrence (defined as a PSA \geq 0.2 or use of any adjuvant therapy) for Gleason 3 + 3 = 6 prostate cancer is 1.2% at 5 years (Figure 2). I perform a pelvic lymph dissection in all patients, but have no cases of lymph node

metastasis in a gland containing pure Gleason 3 + 3 = 6 prostate cancer.

If these indolent prostate cancers have no ability to metastasize, then diagnosis no longer requires treatment. For those who courageously abandoned the treatment imperative for active surveillance are now reporting 10-year actuarial prostate cancer-specific mortalities of less than 3%.¹⁰ The problem, of course, is the inability to accurately characterize a prostate cancer without actually removing it. In a series of 292 patients with favorable pathology on prostate biopsy (defined as 2 cores or less with cancer, less than 50% of any core with cancer and no Gleason pattern 4 or 5), 27% had upgrading in the radical prostatectomy specimen.¹¹ In that cohort, only 8% of the patients met the criteria of insignificant cancer. This means some men undergoing active surveillance do so at their peril: the reported PSA failure rates of men undergoing either radical prostatectomy or radiation therapy after a period of active surveillance are greater than if definitive treatment was used upfront.¹⁰ Furthermore, the pattern of PSA failure – namely, immediate – indicates these men had already developed metastases. In most larger active surveillance programs, the need for treatment grows over time and, in some younger, healthier men, seems inevitable.¹²

WHEN IS CURE NOT NECESSARY?

In the Prostate Cancer Intervention versus Observation Trial (PIVOT), the protocol required a life expectancy of at least 10 years from the time of randomization.¹³ When the results were reported, roughly 40% of men in both the observation and radical prostatectomy arms had died, indicating how poorly investigators and patients assessed the true life expectancies. It should be of no surprise that the trial, already modified from the ambitious accrual goals, was woefully underpowered to show a survival advantage in men undergoing radical prostatectomy. More importantly, PIVOT emphasizes the importance of reserving treatment for prostate cancer to those who will live long enough to gain a benefit. Sick men with low risk prostate cancer do not benefit from surgery. In my own radical prostatectomy series, the 10-year overall and cancer specific survival are 93.4% and 98%, respectively (Figure 3), demonstrating selection of healthier men is possible.

INCREASING THE POSSIBILITY OF CURE

Failure of the primary treatments for prostate cancer to cure the disease are the result of only three factors: tumor biology,

approach/technique or both. After radical prostatectomy, failure for cure can be a remote event (Figures 1 and 2) and the adequacy of surgical technique is often based on the presence or absence of positive surgical margins. Although margin status has not been shown to be an independent prognostic factor for prostate cancer-specific survival, it is clearly related to the biochemical recurrence and the use of adjuvant treatments.¹⁴ In my own series, the presence or absence of positive surgical margins was significantly associated with rates of recurrence (Figure 4). More importantly, there is clear evidence of reduced positive surgical margins for both pT2 and non-organ confined (pT3) disease with increases in experience. In my series, this ‘learning curve’ appeared to emerge after I had done more than 1000 open radical prostatectomies (Figure 5). I would argue the learning curve is continuous and mastery of technique is not possible without years of experience.

CURE WITH LESS MORBIDITY?

There are several promising reasons to consider focal therapy for prostate cancer. It can effectively ablate the cancer while maintaining the remainder of the gland, a ‘lumpectomy’ approach. It can be applied in a minimally invasive fashion with the possibility of outpatient treatments. It may reduce morbidity by avoiding the continence mechanisms and neurovascular tissues, reducing urinary incontinence and erectile dysfunction. It has the ability to be repeated, retaining its cancer-destroying features. And it may prove to be the most cost-effective treatment from a global perspective.

Unfortunately, focal therapy faces several challenges. First, prostate cancer is multifocal.¹⁵ There is currently no imaging technique that can reliably detect all the prostate cancers within a gland, meaning focal treatments will miss some cancers. Second, prostate cancer arises as a result of a field effect. There is abundant evidence—much it coming from our institution – that the genetic alterations associated with the histologically benign prostate tissue in a gland containing cancer resemble the cancer much more closely than benign prostate tissue from a gland without cancer. One of the first demonstrations came from expression array data (mRNA): benign tissue adjacent to the tumor has a pattern of altered gene expression much closer to prostate cancer than to normal prostate tissues.¹⁶ The second observation examined copy number variants (DNA): amplifications and deletions

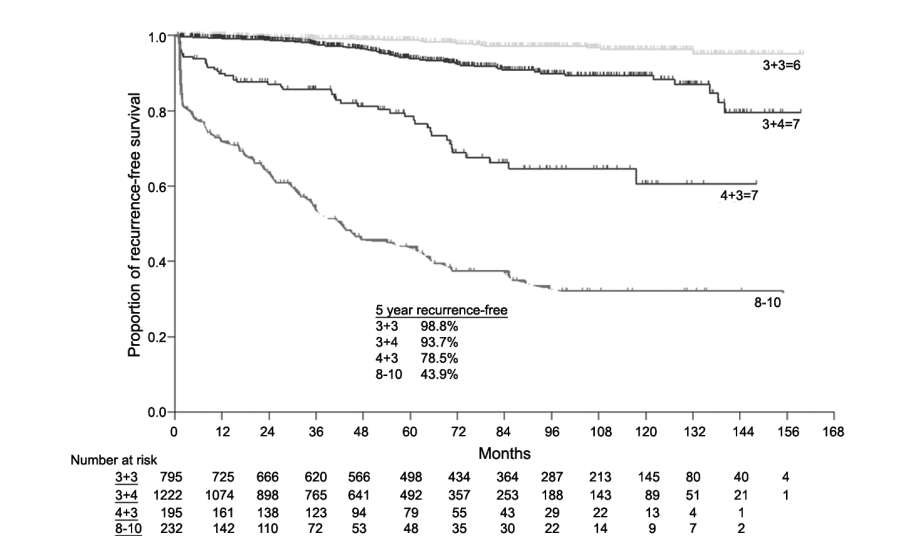


Figure 2: Prostate cancer recurrence after open radical prostatectomy stratified by final Gleason score.

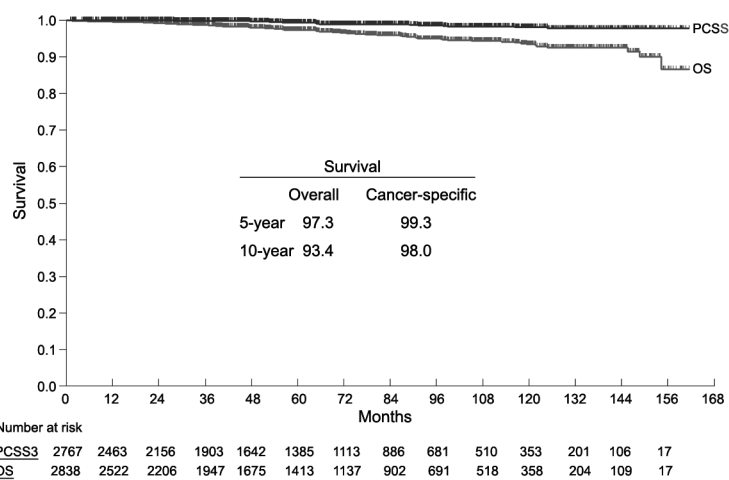


Figure 3: Overall and prostate cancer specific survival (OS and PCSS) after open radical prostatectomy.

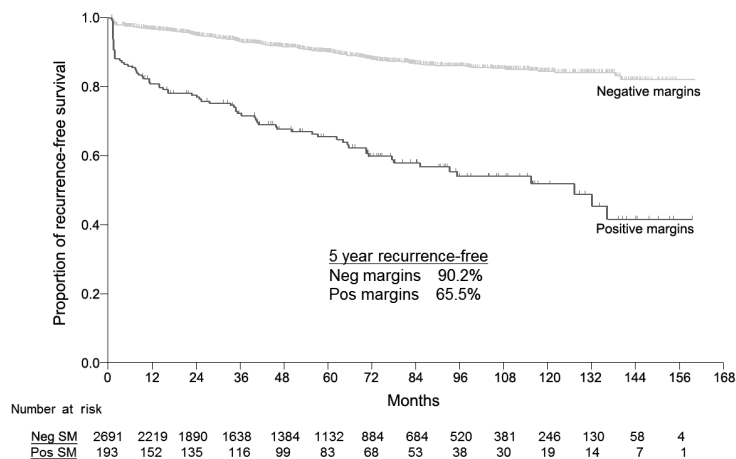


Figure 4: Prostate cancer recurrence after open radical prostatectomy stratified by surgical margin (SM) status.

in benign tissue adjacent to the tumor are much more similar to prostate cancer than peripheral blood DNA.¹⁷ Therefore, a gland containing prostate cancer is a gland that will



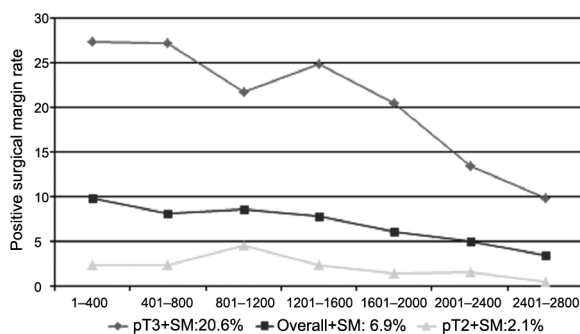


Figure 5: Change in positive surgical margins (SMs) over a series of 2800 consecutive open radical prostatectomies. pT2: pathologically organ-confined; pT3: non-organ confined.

continue to form prostate cancers. From the perspective of 20–30 years, this can be a real clinical challenge.

Third, targeted ablation is a misnomer. Only 25% of cancers are unilateral and there are no clinical or pathological features that will reliably detect them.^{18,19} Fourth, focal therapy needs to establish and validate criteria for success. Radiation-based definitions are for radiation. Fifth, there must be a demonstration of clinical benefit for most regulatory bodies. This will require designing and completing acceptable randomized clinical trials with appropriate endpoints and comparative arms. Finally, focal therapy must not irrevocably burn bridges: management of treatment failures (which are expected) cannot be at the expense of increased morbidity.

The game for focal therapy will change when there is imaging with cellular resolution, when success is based on imaging and not on PSA, when ablation is precise with no scatter and when retreatment is considered routine and not the sign of failure.

CONCLUSIONS

Given the dismal results of not treating poorly differentiated prostate cancer² and strong indication that local therapy can improve survival, the question becomes which local therapy, which systemic therapy and when? Although such questions will likely be answered first using our current

rudimentary tools to define prostate cancer, the future rests on a refined understanding of the entire spectrum of what is considered prostate cancer and selectively applying effective therapies. The answer to Dr. Whitmore will then be ‘we only cure when it is necessary’.

COMPETING INTERESTS

Author declares no competing interest.

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