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PCa Commentary

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HIGH-RISK PROSTATE CANCER: *Not a Uniform Disease And A Management Challenge*

The optimal management of men with high-risk prostate cancer often occupies the majority of discussions at tumor boards despite the fact that this presentation occurs in the minority of cases. In the Prostate Cancer Prevention Trial a Gleason score ≥7 was found in only 6.4% of men diagnosed with cancer. In unscreened populations that figure rises to 20% - 30%.

Why is high-grade disease a major focus?

Answer: Because the choice of management is still quite controversial and requires the integration of multiple risk factors each with differing weight affecting treatment outcome. The inherent heterogeneity of prostate cancer is maximally apparent as the disease become more aggressive, and best management requires informed individualization usually involving multimodal treatment.

Many schema have been suggested to identify this group having a high likelihood of recurrence after primary therapy. Probably the most succinct is attributed to D'Amico: PSA ≥20 ng/ml, OR clinical stage >T2c or greater, OR Gleason score >7. In a 2009 report D'Amico removed tumor category cT2c from "the standard high-risk classification ... based on a recent report [by Cooperberg (Cancer 2010 Nov 15)] documenting outcomes similar to intermediate-risk PC for men with category T2c tumors."

Greater risk of recurrence is conferred by having an *increasing* number of the high-risk elements or higher risk elements in each of the three categories, i.e. a Gleason sum of 9 or 10 confers greater risk than Gleason 8. However, in a PSA/DRE screened population the likely entry into the high-risk category results from finding a

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Gleason score of 8 or more in a minimally deformed gland associated with a PSA of <10 ng/ml or a bit more. A consensus of opinion supports the belief that a Gleason score of 8 or higher is the *strongest independent predictor* of recurrence among D'Amico's three categories.

Useful as it is, the D'Amico three-part criteria in its simplicity omits the additional clinical, pathologic, and biochemical risk factors that also contribute individually and collectively to failure after primary treatment for localized prostate cancer. A fuller list comes from an excellent review by Scott et al. "Additional therapy for high-risk prostate cancer treated with surgery: what is the evidence?" (Expert Reviews 2009) which adds: obesity, African American race, tertiary Gleason pattern 5, pelvic lymph node involvement, extracapsular extension, positive surgical margins, percentage positive cores on biopsy, small gland size, pretreatment PSA, pretreatment PSA velocity of >2 ng/ml in the year prior to diagnosis, free-to-total PSA ratio, and PSA density.

I will present and discuss the results from two series of "high-risk" patients treated by recognized experts, one employing brachytherapy and the other, surgery. These studies allow noting how the risk composition of the treated groups affects outcome and how a clinician's awareness of those elements might affect the choice of primary therapy.

FIRST: A BRACHYTHERAPY STUDY

Stock and Stone, Mount Sinai, NY, report excellent results in "Outcomes for patients with high-grade prostate cancer treated with a combination of brachytherapy, external beam radiotherapy and hormone therapy." (BJU Int 2009) The study dealt with 181 men all having Gleason scores of 8-10. Clinical T1 and T2 cancers were present in 85% and PSA was >20 ng/ml in only 18%. Seminal vesicle (SV) involvement was found in 29 men, and laparoscopic pelvic node biopsy was positive in 3 of 31.

Treatment consisted of 3 months of an LHRH agonist followed by a 100 Gy 103-Paladium implant. Two months later, external beam radiotherapy of 45 Gy was given covering the prostate and margins, in some instances the SVs, and, if positive, pelvic nodes. The total duration of HT was 9 months.

Relevant points:

1) This trial addresses the currently common "high-risk" presentation, i.e. mostly lower PSA values (median 9 ng/ml in Stone's study) in a population mainly of cT1-2 tumors, whose entry into "high-risk" was a Gleason score of 8, 9,or 10.

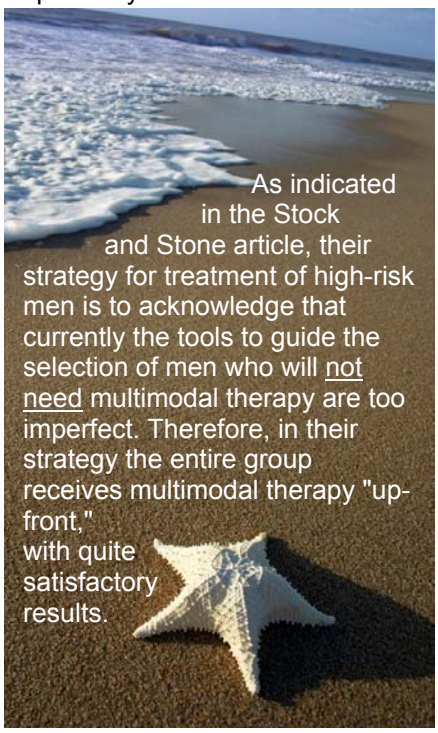
2) Radiation dose matters. The best cell-kill is achieved by delivering the highest safe dose. The mean treatment dose to the prostate in this study was 206 Gy, far exceeding 80 Gy, the maximally safe dose deliverable by external beam radiotherapy (EBRT) alone.

3) The treatment schema incorporated the awareness of the positive synergistic effect of concomitant radiation and HT.

4) It is recognized that if the men in this group had undergone RP the pathology reports would have shown a substantial amount of extracapsular extension, perineural invasion, some unexpected lymph node and seminal vesicle involvement (a distribution as was seen in the Loeb/Walsh article below); and likely there would have been a moderate number of Gleason upgrades, and possibly a few down-grades.

Results:

The 8-year actuarial estimates were: freedom from biochemical failure (FBF), 73%; likelihood of remaining free of distant metastases, 80%; prostate cancer-specific survival (PCSS), 87%; and overall survival, 79%. Each step higher in the Gleason score was associated with a progressively worse outcome: the 8-year FBF for Gleason 8, 9, and 10 were 73%, 55%, and 30%; and the PCSS was 92%, 80%, and 62.5%, respectively.



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DISCUSSION

The Stock and Stone data sets a high benchmark for other treatment modalities, suggesting that the other modalities should reach at least 73% long-term relapse free survival. The challenge for surgeons is to successfully accomplish that careful and challenging selection process, offer surgery alone as primary treatment in the hope that those selected men will either never need supplemental radiation or hormonal therapy, or at least delay their application for a lengthy period, thus avoiding additional toxicity.

In common practice, however, for a large number - possibly a majority - of men the surgical pathology report will reveal unwanted adverse findings, or an unsatisfactory post surgical PSA value will be found and these will merit additional radiation (adjuvant or salvage) and hormonal therapy to improve outcomes.

Dr. Martin Gleave, urologic surgeon, Vancouver Prostate Centre (Current Oncology, 2010) emphasizes the benefit in high-risk patients of a multimodal approach and its effect of delaying to some extent the onset biochemical progression.

Gleave cited 3 brachytherapy series all of which incorporated EBRT and short-term ADT: Dattoli (Cancer 2007), Sylvester (Int J Radiat Oncol Biol Phys 2007), and Stock (see above) which respectively showed biochemical progression-free (BPFS) results of 72% (14 years), 73% (15 years) and the Stone report of 73% at eight years.

The exposure to ADT in these studies was relatively brief, mainly employed to reduce prostate size to accommodate ease of seed implantation or to radiosensitize the cancer. Merrick speaks for the general experience and discounts the long-term effects of early ADT ("High-Risk Prostate Cancer With Gleason Score 8-10 and PSA Level ≤15 ng/ml Treated With Permanent Interstitial Brachytherapy," Merrick et al. Int J Radiat Oncol Biol Phys 2010 Oct) and reports "The use of ADT did not significantly impact biochemical progression-free survival, CSS, or OS."

Gleave cited 3 surgical series, each incorporating either adjuvant or salvage EBRT but no ADT before biochemical progression: Ward, Hsu, and Loeb (see below). The BPFS in these studies were 43% (10 years); 51.5% (10 years); and 68% (10 years), respectively.

Gleave offers two advantageous features associated with surgery. "Only RP can provide pathological staging to discern those patients in whom monotherapy may be the only treatment required ...", e.g. identifying organ confined disease or recognizing Gleason "down-staging." Secondly, he cites Zelefsky et al. (J Clin Oncol Mar 2010) which presents a complex analysis of the outcomes of patients with clinical stages T1c-T3b cancer and found that the onset of metastases was delayed (but not necessarily prevented) by 7.8% at 8 years in the high-risk RP group compared to those receiving contemporary dose EBRT. (97% v. 93% at 8 years in the overall study.)

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SECOND, A SURGICAL SERIES

The study by Loeb and Walsh is a excellent example of an effort by well respected surgeon whose intent was to offer surgical monotherapy to a carefully selected group of men in the high-risk category: "What Are the Outcomes of Radical Prostatectomy in High-risk Prostate Cancer"(Loeb, UROLOGY 76, 2010)

In this series 175 men were chosen for surgery after *excluding* 11 men who were found to have positive pelvic lymph nodes on laparoscopic investigation or by frozen section intraoperatively. The PSA was >20 ng/ml in 33%; clinical stage ≥T2c in 38%; Gleason score 8-10 in 36% (a difference from the Stock and Stone study in which 100% were Gleason 8-10). Biochemical progression was defined as a PSA >0.2 ng/ml. Postoperative RT was given to 9% of men. "Because men with multiple high-risk features are infrequently managed at our institution with surgery alone, only 6% of men had more than 1 risk factor," an important point which places this series in the lower range of the "high-risk" spectrum.

"At RP, 63 (36%) had organ-confined disease, whereas extracapsular extension and seminal vesicle invasion were present in 79 (45%) and 8 (5%) respectively. Positive surgical margins were reported in 32 (18%) and lymph node metastases in 25 (14%)."

No hormone therapy was administered until radio-graphically demonstrable disease was found, and by 10 years an estimated 71% of men avoided hormone therapy.

Relevant points:

1) As with the BT example, in the Walsh study "...biopsy Gleason score of 8-10 was the strongest independent predictor of biochemical recurrence, metastases, and death.

2) In this select group (predominantly with only one risk factor, and only 33% having Gleason score of 8-10) by 10 years only an estimated 29% will have been exposed to the toxicity of HT, which was withheld until the diagnosis of metastases.

3) The freedom from biochemical progression reported by Walsh was superior to the generally reported experience as a result of selection. In less narrowly focused series, such as reported from the Mayo Clinic on 288 men with cT3 the actuarial freedom from PSA recurrence at 5 years was 58% and 43% at 10 years. The prostate cancer-specific survival 90% at 10 years. Adjuvant ADT was administered to 51%; adjuvant radiotherapy to 16%.(BJU Int 2005, Apr).

Results:

At 10-years the actuarial freedom from PSA failure was 68%; freedom from metastases, 84%; and prostate cancer-specific survival 92%.

DISCUSSION

Nguyen et al, (J Urol 2009 Jan) applied 6 different definitions of high risk to 3351 men operated at the Cleveland Clinic, using the less stringent criteria for PSA relapse of ≥0.4 ng/ml. He reported biochemical relapse-free survival rates at 5 and 10 years of 36% to 58% and 25% to 43%. Included in his article is the disclaimer: "However, we do not advocate summary exclusion of all high risk patients from RP as there are data indicting that surgery alone remains potentially curative in at least the subset of high-risk patients with organ confined disease," [which can only be determined after surgery].

In recognition of this common occurrence of PSA relapse following RP in high-risk patients, Dr. Walsh cautioned "...high-risk patients considering RP should be counseled on the possibility of multimodal therapy, depending on their pathology features and post-operative PSA."

Unfortunately, even men having pathologically determined organ confined disease are subject to disease recurrence no matter their mode of primary therapy.

Dr. Walsh stated what clinicians already know, "The results from the present study [see above] accentuate the importance of developing methods and models [including genetic biomarkers] to aid in identifying those patients who have extensive disease and a high number of adverse features, so that they can be better counseled regarding systemic and multimodal neoadjuvant and adjuvant treatment."

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SALIENT MESSAGE

What theme underlies these two reports? It is that even within the collective grouping termed "high-risk" there are significant gradations of risk, largely based on Gleason grade. The brachytherapy approach gives a uniform multimodal punch at the start, treating men with all "subsets" of risk, thereby accommodating the frequent extracapsular extension that is seen in Gleason 8 cancer. Whereas, radical prostatectomy as monotherapy for this entire high-risk group aims at identifying (post operatively) the minority of men with organ confined disease (in D'Amico' series 36%) who may, for a considerable period, avoid the additional toxicities of multimodal treatment. This strategy carries the acknowledgment that possibly 50% of men within 5 years will register a PSA rise and require additional therapy.

How can men in the "high-risk" category who have either lesser aggressive or more aggressive cancer be spotted so as to informatively counsel and manage patients individually? The development of imaging techniques that accurately identify seminal vesicle and lymph node disease would help a great deal. Of interest is a 2010 report (Menard BJU Int. Nov 2010) titled: "Endothelin-1: a predictor of extracapsular extension in clinically localized prostate cancer?" [!]

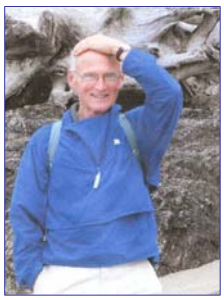
Many useful nomograms are available to predict aggressive disease after surgery, such as the well validated tool offered by Freedland, Moul et al. (BJU Int.104, 2009) But for pre-treatment estimations we need to fall back on the venerable Kattan nomogram and the Partin tables (2010 version: **file:///Users/edwardweber/Desktop/Partin%20Tables:2010.webarchive),** while adding nuance by considering percentage of biopsy cores positive, PSA density, and PSA velocity.

Even with this information there is plenty of room for the art of medicine, since there is no clear guidance as to what percentage estimate of risk for, say, extracapsular extension or seminal vesicle involvement should suggest the men best served by early multimodal treatment or surgery alone. Additionally, outcome predictions are always associated with fairly broad ranges.

BOTTOM LINE

D'Amico's high-risk categorization is the best criteria to date for identifying men at high risk for prostate cancer recurrence after primary therapy. Currently, however, preoperative studies can only suggest, but not clearly identify, those men having cancers with the fewest adverse pathologic features. Because of this predictive inability, the optimal management for the majority of men with high-risk cancer will usually result from multimodal therapy, except for a minority of men who, after surgery, are revealed as good candidates for initial monotherapy.

Your comments and requests for information on a specific topic are welcome at **ecweber@nwlink.com**



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