High risk prostate cancer: evolving definition and approach to management

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CHUGHTAI B, MIAN BM. High risk prostate cancer: evolving definition and approach to management. The Canadian Journal of Urology. 2008;15(6):4375-4380.

Advances in the early detection and treatment of prostate cancer have progressed far beyond our ability to identify patients with high risk prostate cancer. In general, designation of high risk prostate cancer implies the presence of disease that is likely become progressive or lethal if not managed aggressively. Without proper risk stratification, there is a significant likelihood of both overtreatments of men with low risk disease and undertreatment for men with high risk cancer. The major issues surrounding the clinical management of high risk prostate cancer revolve around the definition of high risk disease as well as the benefits of multiple modality therapy. Over the years, numerous attempts have been made to develop risk assessment tools such as risk categories, scoring systems and nomograms, but a widely accepted definition is yet to be determined. The benefits of routine clinical utility of these risk assessment tools remain somewhat difficult to ascertain. We will discuss several multimodality therapeutic approaches, especially in combination with androgen ablation, to improve the outlook for men with high risk or locally advanced prostate cancer. This review focuses on the potential limitations of the risk assessment tools available to the clinicians and the approach to management of high risk prostate cancer.

Key Words: prostate cancer, high risk, prostatectomy, androgen ablation

Introduction

Prostate cancer remains the most commonly diagnosed solid malignancy and the second leading cause of cancer related deaths for men in the United States.[1] In 2008, an estimated 186,320 men will suffer from newly diagnosed prostate cancer and 28,660 men will die of the disease. Clinical tools are needed to educate the patients about their disease, determine the prognosis and plan a course of action in order to change the natural history of the cancer. The debate regarding the true benefits of early detection and the best treatment modality is ongoing. However, it's mostly geared towards the increasing number of men with low risk prostate cancer because these men are likely to do well with any single therapeutic modality, including active surveillance.[2] The need and benefits of active treatment for high risk prostate cancer are less controversial.

Accepted for publication October 2008

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The issues surrounding the clinical management of high risk prostate cancer revolve around the definition (which determines the incidence) of the high risk disease as well as the additional benefits (and potential harms) from multiple modality therapy.

Several clinical scenarios may be categorized as "high risk" disease. This may include traditionally defined locally advanced prostate cancer (cT3-4)[3,4] at initial diagnosis or recurrent prostate cancer following initial treatment or the newly diagnosed prostate cancer which is likely to become progressive or lethal if not managed aggressively i.e. high grade, large volume disease. In this article, we will focus on only the clinically localized high risk prostate cancer.

Defining high risk prostate cancer

Prospective identification of patients with high risk prostate cancer should allow us to select those men whose cancer can be cured with a single modality treatment from those whose cancer is likely to be locally advanced, possibly with regional or distant micro metastases, hence necessitating multi modal therapy. A universally accepted definition of high risk prostate cancer does not exist. Despite two decades of PSA based screening, early detection and curative treatment of prostate cancer, the clinical parameters that are used to identify high risk cancer have remained unchanged i.e. PSA, Gleason score and clinical stage. Although terms such as locally advanced, cT3-4, high Gleason score or poorly differentiated cancer imply high risk disease, no single factor can reliable predict the response to treatment and subsequent failure.[5-7] Clinical stage based on DRE is notorious for interobserver variability and underestimating extra prostatic disease.[8] Gleason grading is also subject to interobserver variability and has been associated with significant over and under grading, especially depending upon the biopsy technique.[5,9] The PSA level, in the contemporary era, may be a reflection of benign prostatic hyperplasia (BPH) rather than cancer and many poorly differentiated cancers are associated with normal PSA levels.[10]

Multivariable assessment tools

Due to the limitations associated with the individual parameters mentioned above, these have been used in various combinations to develop numerous risk assessment tools including nomograms, categories, neural networks and guidelines. Medline search for "prostate cancer risk assessment tools" yields a dizzying array of published reports which claim to reliably predict the presence of high risk disease. A review and critical evaluation of some of these tools is warranted in order to understand the usefulness and limitations associated with incorporating these into routine clinical practice.

The American Urological Association Guidelines for the management of clinically localized prostate cancer used the risk assessment classification which is based on the D'Amico classification.[11,12] In these classifications, individual risk factors (PSA or Gleason grade or clinical stage) alone may potentially assign individual patients to the high risk category. This approach may overestimate the risk e.g. cT2c alone *or* a single focus of Gleason score 8 alone would be sufficient to classify the patient into high risk category, with potential for overtreatment. In an update of the initial D'Amico classification, the high risk cohort was classified as those men with any combination of Gleason score ≥ 7, PSA > 10 ng/ml, and clinical stage ≥ T2b. While this classification was an improvement, it still allowed overestimation of risk due to arbitrarily assigning equal weights and categorical cutoffs of various risk factors. For example, a patient with PSA of 11 and Gleason score 7 may potentially be assigned to the same risk category as a patient with cT3 and multifocal Gleason score 9 prostate cancer. This degree of overlap in risk assessment is clinically suboptimal as it may potentially lead to overtreatment for the former or undertreatment for the latter patient scenario mentioned above.

In order to minimize the heterogeneity associated within the risk groups, several multivariable risk assessment tools have been developed where the weight assigned to each variable in the model is proportional to its likely contribution to the risk of cancer recurrence. The most publicized of the multivariable risk assessment tools are the Kattan nomograms which were developed to predict outcome in both pretreatment and post treatment settings.[13] These nomograms utilize complex statistical calculations to assign proportionally weighted points to each variable. The initial preoperative model was based only on the PSA, Gleason grade and clinical stage, an updated version utilizes systematic biopsy information to enhance the ability to predict recurrence.[14] The UCSF Cancer of the Prostate Risk Assessment (CAPRA) score, which was based on the CaPSURE registry, utilizes additional clinical variables to predict the risk of recurrence.[15] The CAPRA score is calculated by assigning up to three points for Gleason score, up to four points for categorized PSA level, and one point each for age > 50, clinical stage T3a, and > 33% positive of biopsy cores. The CAPRA score ranges from 0 to 10, and every two point increase in CAPRA score roughly doubles the risk of biochemical recurrence following surgery.

Critical evaluation

Despite using multivariable approach for risk stratification, there are significant potential limitations associated with the clinical use of these models. Experienced urologists may find some of the assumptions and calculations made by the risk assessment tools difficult to reconcile, especially in certain clinical scenarios. For example, in the Kattan "preoperative" nomogram, a PSA 9 ng/ml is assigned a higher score than Gleason score 9, and in the prebrachytherapy nomogram, Gleason score 8 carries the same weight as PSA 3 ng/ml. In the CAPRA model, it is not clear why the age of 51years should carry the same score as clinical stage T3. Additional questions arise when one compares the ability of various assessment tools to predict survival after treatment. Mitchell et al applied the Kattan nomogram and the D'Amico risk categories to the CaPSURE registry and noted a significant difference in the predicted biochemical recurrence free survival.[16] In addition, the 95% CI for D'Amico model and the ranges for Kattan nomogram were quite wide, thus further limiting the clinical utility. Yossepowitch et al compared eight published definitions of high risk disease by analyzing the outcome of 4708 patients treated with radical prostatectomy. Based on the definition that was applied to their study cohort, 3%-38% of the patients could be classified in the high risk category.[17] Of the high risk subgroup (depending upon the definition) 22%-63% had organ confined disease and 41%-74% remained free of PSA recurrence for 10 years after surgery.

There are several potential reasons for the suboptimal performance of these tools including the fact that these, by design, are based on retrospective data, and the relative weights assigned to each clinical variable are based on historic data. While external cohort validation is often performed, most of the risk assessment tools have not undergone prospective validation, and the outcomes prediction of the contemporary patients is based on the assumption that the current clinical variables have similar implications as those from 10-15 years ago. This assumption is quite invalid, given our understanding of the shift in stage, tumor volume and Gleason grade which has taken place since the advent of PSA screening. Furthermore, most risk assessment tools do not utilize quantitative pathological information which has been shown to be predictive of outcome e.g. number of biopsy samples with high grade cancer, percent core with cancer etc. Another caveat to remember is that most of the prediction models are based on biochemical recurrence which may precede clinical recurrence, or metastases, or death by decades.

While several risk assessment tools have been developed, the clinical utility of these remains unclear due to the fact that often the range of predicted outcome is significantly wide and various tools yield disparate results. Inability to accurately predict high risk (and low risk) disease has significant implications for our patients as it may lead to overtreatment of those with lower risk disease or undertreatment for those with high risk disease. There are also broader implications for designing clinical trials. The definition or method used to assign high risk category will ultimately determine patient accrual and potential results. While significant advances have been made in the early detection and treatment of prostate cancer, our ability to predict high risk disease remain somewhat limited. This is quite evident from the fact that all of the risk assessment models today mostly depend on the same three variables that were used 20 years ago i.e. clinical stage, PSA and Gleason grade. Clearly, there is an urgent need to develop prediction tools that will incorporate novel molecular markers to enhance our ability to identify patients that are at high risk of disease progression and allow optimization of the therapeutic approach.

Management of high risk prostate cancer

Regardless of the definition used to signify the presence of high risk disease, it implies that local therapy alone may not cure or sufficiently control the cancer. In contrast to the localized low risk cancer, the standard approach to high risk cancer over the last 2 decades has been to employ systemic and/or combination therapy instead of local therapy alone. In an analysis of the CaPSURE registry for men with high risk prostate cancer (as defined by the CAPRA score), Cooperberg et al noted a steady decrease in the use of radical prostatectomy, brachytherapy and cryotherapy as the CAPRA score increased.[18] They also noted a corresponding increase in the use of luteinizing hormone releasing hormone (LHRH) alone or in combination with radiation therapy as the CAPRA score increased. Men in the highest risk group (CAPRA 8-10) were four times more likely to receive androgen ablation alone or with radiation therapy than any localized therapy alone, especially surgery. Analysis of Surveillance Epidemiology and End Results (SEER) database revealed that between 1995 and 2001, the number of men with localized T3 prostate cancer undergoing radical prostatectomy decreased by nearly 50%, with a corresponding increase in the use of XRT and/or androgen ablation.[19] Furthermore, nearly one quarter of patients under age 70 with T3 disease were not given any local therapy at all. Thus, it's long

been the standard practice to treat men with high risk disease with either a combination of systemic and local therapy (mostly radiation) or systemic therapy alone.

The primary reason for diverting patients with high risk cancer to androgen ablation alone or in conjunction with radiation therapy likely stems from the assumption that these men have incurable cancer. The increasing use of androgen ablation and/or radiation therapy is not necessarily due to any proven or perceived superiority in cancer control when compared to radical prostatectomy but rather from the complexity of the surgical procedure and high rates of incontinence and impotence. With the tremendous stage shift over the last 15 years due to early detection and improvements in the surgical technique, radical prostatectomy, either alone or with adjuvant therapy, may be a viable option for younger men with high risk prostate cancer.

Multimodality therapy

A review of literature for combination therapies for prostate cancer is striking for the large number of studies utilizing androgen ablation, radiation therapy, brachytherapy, prostatectomy and chemotherapy in every combination possible. A detailed analysis of the outcomes following the use of neoadjuvant and adjuvant androgen ablation therapy was outlined in a recent Cochrane review.[20] External beam radiation therapy along with concurrent, neoadjuvant and adjuvant androgen, androgen ablation was the most widely utilized combination therapy for high risk and/or locally advanced prostate cancer. Other less commonly utilized approaches included radical prostatectomy plus neoadjuvant androgen ablation or adjuvant radiation or androgen ablation. Neoadjuvant androgen ablation has also been utilized with brachytherapy, and at times in a trimodal approach using concomitant external radiation. A detailed discussion of each combination and the optimal duration of systemic therapy are beyond the scope of this review.

Neoadjuvant and concurrent androgen ablation for 3-8 months and radiation therapy demonstrated a significant improvement in biochemical disease free survival but did not reveal any improvements in overall survival.[10,21,22] Androgen ablation for 8 months was associated with a significant improvement in disease specific survival compared to only 3 months.[23] Neoadjuvant androgen ablation for 3-6 months prior to radical prostatectomy was associated with a significant downstaging and decrease in positive surgical margin rate but did not improve disease specific or overall survival.[24-26]

The use of concurrent and adjuvant androgen ablation (for up 3 years) with radiation therapy was evaluated in several studies.[27-29] All of these studies reported a benefit from hormonal ablation and increased disease free or biochemical recurrence free survival. However, there has been only one study that demonstrated a prolonged overall survival with the use of long term hormonal ablation.[27] A few studies of radical prostatectomy followed by adjuvant androgen ablation have been reported. Messing et al noted an increased overall survival in favor of hormonal ablation after surgery (in a randomized trial) whereas Wirth et al reported no such benefit, although both studies reported improved disease free survival.[30,31] The Early Prostate Cancer trial using antiandrogen following radical prostatectomy demonstrated an improvement in disease free survival, especially in the patients with locally advanced disease.[29]

Role of radical prostatectomy

In the early PSA era, most high risk patients presented with very high PSA levels and bulky stage T3 disease. Since then, there has been a trend favoring the use of hormonal ablation and/or radiation therapy and avoidance of radical prostatectomy for high risk or locally advanced prostate cancer due to fear of poor pathological outcomes and surgical complications. Previous studies of radical prostatectomy for high risk, poorly differentiated or locally advanced prostate cancer were associated with a high risk of positive surgical margins or lymph node metastases and low disease free survival.[6] Some centers have been strong proponents of wide surgical excision of locally advanced disease, along with adjuvant radiation or hormonal ablation.[7] These authors noted that clinical overstaging occurred in 24% of men who were thought to harbor cT3 disease, but had pT2 disease in the prostatectomy specimen. These patients required no additional therapy. Nearly two thirds of patients in this study required androgen ablation or radiation therapy at some point, yielding cancer specific and overall survival rates similar to those reported for radiation therapy and androgen ablation studies. However, this was not a randomized study and direct comparison between surgery and radiation is not possible.

In the contemporary, screening detected prostate cancer, the designation of high risk prostate cancer is often based on a single variable e.g. high Gleason score or PSA.[32,33] This, along with a better understanding of pelvic anatomy and the improvements made in surgical technique, may suggest that radical prostatectomy may be more feasible and effective in achieving adequate cancer control in the contemporary patients assigned to the high risk category.

Recent studies demonstrate encouraging pathological and disease free survival rates for men undergoing radical prostatectomy alone for poorly differentiated cancers. We and others have found that the cancer was confined to within the prostate in 26%-31% of the patients with high risk cancer defined as Gleason score 8-10.[34,35] Negative surgical margins or uninvolved seminal vesicles have been noted in as many as 50%-70% of men.[35-38] More importantly, the 5-year recurrence free survival, without any additional therapy, for these men with poorly differentiated cancer, ranges from 46%-71%, and 45%-82% in the subgroup with organ confined disease. It's clearly evident that surgical excision of high risk cancer is feasible and is associated with sufficient disease control in a large number of men with high risk disease treated with surgery alone. These men are able to avoid or safely postpone systemic therapies and the associated side effects from additional therapies.

Summary

Advances made in the early detection and active treatment of prostate cancer have progressed far beyond our ability to identify patients with high risk, potentially lethal cancers. Without proper risk stratification, there is a significant likelihood of both overtreatments of men with low risk disease and undertreatment for men with high risk cancer. Despite numerous attempts, the proper definition of high risk cancer remains elusive, and will likely remain so unless we are able to incorporate more sophisticated molecular markers in addition to the currently available clinical variables. Several multimodality therapeutic approaches have been utilized, especially in combination with androgen ablation, to improve the outlook for men with high risk or locally advanced prostate cancer. In addition, contemporary studies have highlighted the feasibility and efficacy of radical prostatectomy in the high risk cohort. Unfortunately, the heterogeneity of definitions, variations in inclusion criteria and the duration of systemic therapy preclude any meaningful or direct comparisons amongst various therapeutic modalities. Thus, the criteria for designation of high risk prostate cancer and defining the optimum treatment for this cohort remain fertile grounds for future research. □

Disclosure

None declared.

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