PROTOCOLS & PRACTICES
Perspectives on cancer management

RISK STRATIFICATION IN PROSTATE CANCER

Trends in preoperative clinical assessment

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Top-line summary

The introduction of prostate-specific antigen (PSA) into the paradigm of early detection has resulted in a stage migration towards more localized, and curable, prostate cancers. This has led, however, to an unfortunate trend to over-diagnosis and over-treatment of biologically insignificant disease. One challenge we face in the modern PSA era is to differentiate men who have disease destined to progress and cause morbidity/mortality from those who will not require immediate, or possibly even delayed, therapeutic intervention. Researchers are attempting to develop a prognostic marker of some type — via molecular, biochemical, imaging and other routes — that will be able to meet this challenge.

Once patients undergo radical intervention for what is thought to be significant cancer, a second challenge is how to predict, *preoperatively*, which of these men carry a higher risk of developing postoperative recurrence. The current standard of practice is to combine possible predictive factors to broadly "risk stratify", piecing together preoperative clinicopathologic factors that may suggest the likelihood of recurrence after surgery and the possible need for adjuvant therapies.

This paper reviews the application of *preoperative clinical information* to determine *postoperative risk*. We assess different schemas of risk stratification of men with prostate cancer that will give urologists and oncologists the most useful and practical information to plan pre- and post-treatment care.

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The definition of risk in the preoperative context includes the odds of adverse pathologic outcomes, postoperative biochemical recurrence or persistence and, ultimately, decreased length of survival. Risk assessment may help determine which patients are operable, which need to be treated with multimodality therapy, and which may be treated expectantly under watchful waiting.

RATIONALE FOR BETTER RISK ASSESSMENT

Clinicians can currently give men information regarding the probability of success with surgery in terms of rates for positive margins and extracapsular spread, chances of distant metastasis, and predicted biochemical failure. These data also determine the aggressiveness of surgery (nerve-sparing or not), the need for pelvic node dissection and the nature of an individual's postoperative followup.

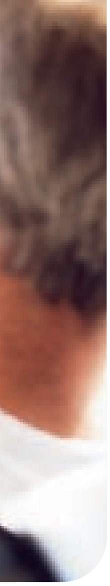
More refined ways to identify the high-risk patient are essential to help clinicians provide therapeutic options that may employ multiple, often aggressive, therapies to achieve maximal cancer control. These men can also be given the option to enroll in clinical trials that offer novel therapies. Categorization of patients into established and consistent risk categories is also key to making comparisons between patients in clinical databases.

PROGNOSTIC TOOLS: PROS AND CONS

Sophisticated prognostic instruments include risk grouping, tables and nomograms, all of which use similar preoperative clinicopathologic parameters: pretreatment serum PSA, biopsy grade and volume parameters, and clinical tumour stage. Exciting research in proteomic and genomic characterization of prostate cancer may one day provide more accurate and individual-specific risk assessment.

Serum PSA

In the current PSA era, the majority of men with prostate cancer present with normal digital rectal examination (DRE) but an abnormal PSA, representing clinical tumour stage T1c.[1] But the level of PSA considered to be "abnormal" is uncertain, especially considering the relatively high rates of cancer observed in men with a PSA < 4.0 ng/mL in the



Prostate Cancer Prevention Trial.[2] In this very important study, Thompson et al demonstrated that men with normal DRE and PSA between 0–1.0 and 1.1–2.0 ng/mL have a prostate cancer detection rate of 8.8% and 17%, respectively. This high rate of carcinoma in men with low PSA levels reflects the sizeable disparity between incidence and mortality rates due to large numbers of tumours which are "biologically insignificant" and not destined to cause morbidity and possible mortality.

PSA + pathology

Despite its limitations as a screening tool, preoperative PSA testing may still supply valuable clues to the risk of tumour recurrence. In older series, PSA was shown to be proportional to tumour volume, biopsy and pathologic Gleason scores, and tumour stage.[3] Freedland et al reported that, in a cohort of 1582 men who underwent radical prostatectomy, lower preoperative serum PSA was associated with decreased incidence of positive surgical margins, extracapsular disease, seminal vesicle invasion and lymph node involvement. Multivariate analysis suggested that only serum PSA levels and the biopsy Gleason score predicted time to recurrence. These results support previous studies linking lower preoperative PSA with reduced biochemical failure rates.[4-6]

In contrast, Stamey's group conjectured that PSA values may only presage pathologic Gleason scores if PSA values are either extremely high or low.[7] These researchers showed that between 2 and 9 ng/mL, PSA was less reliable as a prognosticator of tumour pathologic grade or biochemical recurrence.[7-8]

When combined with biopsy Gleason score and clinical tumour stage, the preoperative serum PSA level consistently proves to be a strong predictor of the risk of biochemical recurrence. In the Partin series of men with T1c disease, biochemical recurrence-free survival at 10 years in men with PSA 10.1–20 ng/mL was between 61% and 94%. For levels between 4.1 and 10 ng/mL the 10-year biochemical-free survival was between 71% and 97 %.[3] D'Amico assessed whether different PSA cutoffs could further substratify T1c tumours into defined risk groups.[9] He concluded that in T1c disease, PSA values < 10, 10.1–20, and > 20.1 ng/mL separated men into low-, intermediate- and high-risk disease categories.

Velocity

Several studies have reported that the pretreatment rate of change in PSA over time, known as PSA velocity, may be a better tool than absolute PSA levels in predicting pathologic stage, grade and time to biochemical recurrence.[10-12] In their study of over 1000 men, D'Amico et al calculated PSA velocity using linear regression of all PSA values within 1 year prior to treatment, with a median postoperative followup of 5 years. His group showed that a pretreatment PSA velocity of 2 ng/mL per year was associated with lymph-node metastasis, advanced pathologic stage and high-grade disease; a PSA velocity of > 2 ng/mL per year correlated with shorter time to recurrence and death from prostate cancer.[12] These authors recommend that men who undergo radical prostatectomy with a preoperative PSA

Evolutions in Gleason score

First introduced in 1966, Gleason grading assesses prostate glandular architecture rather than cytological morphology.[16] In many multivariate analyses, the Gleason score proves to be an independent predictor of both pathologic tumour stage and time to biochemical recurrence,[3,17-19] with some experts suggesting that biopsy Gleason grade may be the most powerful preoperative prognostic factor.[18,19] D'Amico et al stratify Gleason score as:[9]

- 6 or less as low-risk
- 7 as intermediate-risk
- 8 or above as high-risk

Also, Gleason 7 tumours can be subclassified into either 3+4 or 4+3, depending on which grade is most prevalent in the cores.[20] Along with many others, D'Amico has validated that this type of Gleason score classification and subclassification predicts postoperative outcomes.[9,21]

The PSA era has seen an upswing in grade migration towards moderate differentiation, even while relative rates of poorly and well-differentiated disease remain fairly stable.[22,23] This apparent increase in moderate-grade tumours may be due to either a true rise in their incidence relative to high- or low-grade tumours in men with T1c disease or, as Smart et al have suggested, may rather be due to contemporary changes in pathologists' interpretations of slides.[23] Further, intra- and inter-pathologist variations of interpretation are not uncommon, reported in up to 64% of cases.[24-26] The significance of this variability was highlighted in the Nguyen study,[26] which reviewed over 600 prostate biopsies initially graded between 1989 and 2001 and rescored in 2004. In 44% of cases, Gleason score changed, with upgrading of 88%. The researchers estimated that over 10% of these men might have received a different treatment if choice had been based on the updated rescoring of their biopsies.

Another limitation of biopsy Gleason score as a predictor of outcome is its poor correlation with pathologic Gleason score of the surgical specimen obtained at prostatectomy. Discordance rates of 43% to 46%, with upgrading in 35% of cases, have been reported.[27] Suggestions to improve concordance rates include increased sampling of prostate tissue and a consensus evaluation of 2 or 3 pathologists. Still, despite all these confounding variables of pathologic interpretation and sampling errors, Gleason score continues to be a powerful and accurate predictor of treatment outcome.

velocity of > 2ng/mL per year should consider enrolling in clinical trials involving adjuvant systemic therapy.

Prostate biopsy

Widespread use of PSA testing for early detection has resulted in a significant stage migration — such that clinical stage T1c tumours now predominate — which has put a greater emphasis on the Gleason score of a prostate biopsy in risk stratification of patients[13-15] (See the box on page 21). As well, looking beyond the Gleason score, analyzing the total number of positive cores and the percent of each biopsy core involved provides even greater prognostic information.

Percentages of positive biopsies + cores

Much has been published on the predictive value of tumour volume for outcome after radical prostatectomy.[28,29] In their cohort of 151 men, Poulos et al found that the percent of biopsy cores that are positive, the number of positive biopsy cores and tumour bilateralism all correlated with overall tumour volume.[30] Some studies suggest that the number of involved biopsy cores most accurately predicts tumour volume,[30-33] while others imply that the percentage of positive cores may be the better prognostic tool.[34,35]

Accordingly, combining both percent positive biopsy and number of positive biopsy cores not only improves prediction of pathologic stage but is also linked with the risk of positive margin status, seminal vesicle invasion and extracapsular extension.[31,34,36-38] Lotan's analysis of 605 radical prostatectomy and biopsy specimens, among other similar studies, additionally demonstrated an association with biochemical progression, distant metastases and overall mortality.[39]

COMBINED PROGNOSTIC TOOLS

Recognition of prognostic variables has led to the development of sophisticated tools that merge them in an array in an attempt to better predict postoperative outcome.[40] Currently, most of these employ a mix of biopsy Gleason score, clinical tumour stage and preoperative PSA levels.

Risk categories

The easiest and most commonly used method of risk stratification is the grouping developed by D'Amico et al,[9] which segregates patients diagnosed with prostate cancer into low-, intermediate-, and high-risk categories based on preoperative PSA, clinical stage and Gleason score. These sets have been validated for use in men treated with radical prostatectomy and radical radiotherapy.[9,41] Kattan, however, asserts that group risk stratification only serves to categorize patients with similar characteristics — those with inherent intragroup heterogeneity — which reduces its predictive accuracy.[42]

Tables

Use of the Partin Tables is another method of indirect determination of postoperative risk.[3] Introduced in 1993, this approach estimates a percentage risk of extracapsular extension, seminal vesicle invasion and lymph node metastasis. The tables have been independently validated, and were updated in 2001 to account for the grade, stage and the PSA migrations observed in the PSA era.[3,43-45] Augustin et al externally validated Partin Tables in a data set of 2139 European men. They deduced that the transition from the 1997 tables to the updated 2001 version was unnecessary, due to the powerful predictive power of the original tables, even though the observed population appears to be changing.[45]

Clinically, however, the Partin Tables have limited application: these tables do not directly predict the risk of biochemical recurrence or reduction in survival, because pathologic stage does not necessarily correlate with rate of disease progression.[46,47] These observations have led the same group to develop tables defining biochemical recurrence tailored to the specific characteristics of the individual patient.[48] Further external validation is required before this new set can be widely used.

Nomograms

Nomograms illustrate a statistical model by graphically incorporating several variables to predict a specific endpoint.[42] They allow calculation of the continuous probability of a particular outcome, which permits more accurate predictions than models based on risk grouping.[42] The most widely used preoperative nomogram was developed in 1998 by Kattan et al at Memorial Sloan Kettering Cancer Centre.[49] This nomogram applies "points" for:

- preoperative PSA levels
- clinical tumour stage
- biopsy Gleason score

Summation of points determines a total point score which corresponds to a 60-month recurrence-free probability after radical prostatectomy. Kattan et al believe that by bringing "continuous data" into play for risk recurrence, this nomogram is more specific, consistent and accurate.[42] While other authors view nomograms as being time-consuming and tedious,[41] the application of this tool may increase thanks to the development and free availability of PDA software, available at www.nomograms.com.

Limitations

All the predictive tools described above were designed in accordance with retrospective studies of predominantly Caucasian men at academic centres, which curtails their suitability for widespread application. Although some studies have validated these tools in the community setting, outstanding questions and limitations remain:

- Can they be applied universally to men of different ethnic backgrounds, geographic locations and/or socioeconomic status?
- All preoperative risk assessment tools use an inherently subjective finding — clinical staging based on DRE — to predict outcomes. This restricts their "universal applicability" in terms of patient comparison.[50]
- Although prognostic tables and nomograms are occasionally updated, this does not account for the continuous changes in the tested cohort that occur with stage and grade migration, along with improvements in surgical techniques.

- The prognostic instruments do not take into consideration the varied experiences and skills of surgeons, which can affect outcomes.
- All currently available predictive tools determine the risk of survival surrogates, such as biochemical recurrence or pathologic stage.

FUTURE PROGNOSTIC TOOLS

Molecular characterization

Functional genomics, through gene expression profiling using cDNA microarrays, has permitted the characterization of genome-wide patterns of mRNA expression in prostate cancers.[51] Certain important genes have been profiled, including the antiapoptotic genes Bcl-2 and Bcl-xL,[52] heat shock protein Hsp-27[53] and other cell-survival genes, e.g. clusterin.[54,55] These have been suggested as being associated with worse prognosis, and may play important roles in prostate cancer progression and development of hormone-refractory disease. Unfortunately, the genomic heterogeneity of prostate cancer makes the identification and practical application of any 1 genetic tumour biomarker difficult.

But when linked with clinical data, including biochemical recurrence and pathologic outcomes, high-throughput technology may provide the ability to identify subsets of genes that function as prognostic markers or biologic predictors of therapeutic response.[50] Once these genomic identifiers are found, individual patients may be tested and can, thanks to individualized DNA microarray analysis, be accurately classified into a particular risk group.

Gene expression analysis is in fact becoming a reality. Glinsky et al recently identified "gene expression signatures" that are associated with recurrent prostate cancer or with poor-, intermediate- and high-risk disease.[56] Still, before this type of molecular signature profiling comes into widespread use, genomic and proteomic subgrouping must be validated, and molecular testing has to become more practical and economically affordable.

Pretreatment staging

Although the DRE has been traditionally used in pretreatment risk-assessment schemas, recent studies strongly imply that novel alternative tools may improve accuracy of preoperative clinical staging. Scardino et al have shown that preoperative endorectal magnetic resonance imaging (eMRI) significantly improved the surgeon's decision to preserve or resect the neurovascular bundle (NVB) during radical prostatectomy.[57] Interestingly, the impact of eMRI in decision-making was greatest in men with high-risk disease: prompted by eMRI, 78% of surgeons changed treatment in favour of resecting the NVB.

Other innovative methods that should help predict postoperative stage include biopsy image cytology and the use of artificial neural networks.[58-60] Poulakis and colleagues recently showed that artificial neural networks — after accessing and incorporating MRI data, preoperative PSA levels and biopsy Gleason scores — may accurately pinpoint pathologic stage.[58,59] In their cohort of 201 men, the researchers demonstrated that the artificial neural network was superior to both logistic regression and Partin Tables in predicting pathologic stage.

DNA image cytology and DNA ploidy may also aid in differentiating localized from nonlocalized disease.[60] Lorenzato et al determined that localized tumours were more frequently diploid compared to those that were non-localized. Although the sample size was small (74 prostate tumours), this study eloquently shows how molecular characterization of tumours can predict the clinical nature of disease.

CHALLENGES

A diagnosis of prostate cancer in a given patient is the beginning of many challenges that face urologists/oncologists in managing the treatment of men with this carcinoma. Complex decisions need to be made to tackle the disease on the part of clinician and patient alike. The ability to piece together pretreatment patient data that defines specific risk stratification — which both further determines risk of tumour recurrence and assesses overall survival probability — is essential in providing optimal patient care.

Today's clinical climate places significant value on early detection via PSA testing, resulting in a large pool of biologically insignificant cancers. It has become critical that clinicians use the best tools available to identify those tumours destined to cause morbidity and mortality. Œ

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continued on page 30

PROTOCOLS & PRACTICES

So & Goldenberg, continued from page 23

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