Risk stratification in clinically localized prostate cancer

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Clinical outcomes in patients with localized prostate cancers are heterogeneous. In recent years, analyses of large datasets from multiple centres have yielded a better understanding of how to measure risk in localized prostate cancer. Regardless of whether patients are treated with prostatectomy, radiotherapy, brachytherapy, or expectant management, three factors appear correlated with clinical outcome: biopsy Gleason score, clinical T stage, and serum prostate-specific antigen (PSA). Partin Tables, derived from these parameters and recently updated and refined, may be used to estimate the risk of metastasis and to assess certain aspects of surgical management in clinically localized disease. Partin tables, however, are limited by the fact that pathologic stage does not always predict clinical outcome. Nomograms that employ serum PSA, biopsy Gleason score, and clinical T-stage have been developed with the aim of predicting clinical recurrence after radical prostatectomy or radiation therapy. Three risk categories for clinically localized prostate cancer have recently been developed by the Canadian Genito-Urinary Radiation Oncologists Consensus Conference, which group cases according to serum PSA, T-stage, and biopsy Gleason score. Additional factors have been assessed in the hopes of improving the prediction of outcome in clinically localized disease, but none of these has consistently been demonstrated to add independent value to the principal parameters of serum PSA, T-stage, and Gleason score. Virtually all predictive nomograms, algorithms, and tables incorporate a combination of these three parameters. While these tools may be useful in prognosticating an individual case, several limitations preclude their widespread use. The greatest benefit to date of risk stratification is its use in comparing outcomes of series of patients treated with various modalities, and in clinical trial design and analysis.

Key Words: prostate cancer, risk stratification, clinical outcome prediction

All clinically localized prostate cancers are not the same. The clinical outcome of patients with localized cancer is heterogeneous. Attempts at defining the potential risk of cancer progression have focused on clinical, pathological and biological factors. In recent years, analyses of large datasets from multiple institutions have resulted in a better understanding of how to measure risk.

Regardless of treatment (radical prostatectomy, external beam radiotherapy, brachytherapy, or

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expectant management), the three statistically significant, independent, and consistent factors that correlate with clinical outcome appear to be:

1. biopsy Gleason score
2. clinical T-stage
3. serum prostate-specific antigen (PSA)

The combination of these three parameters has been incorporated into table form (Partin Tables) in order to estimate the final pathologic stage after radical prostatectomy. Thus, one can use Partin Tables to help estimate the risk of extraprostatic spread, seminal vesicle involvement, and lymph node metastases with some reliability, by knowing the three parameters. Partin tables were originally described in 1997 based on a large pool of radical prostatectomy cases from various academic institutions across the United States. These tables were subsequently assessed in a general community-based dataset from the United States and the reliability of Partin Tables was somewhat diminished. Nevertheless, if one wishes to know the risk that an individual cancer was organ-confined or not, Partin Tables can be used.

Partin Tables have been recently updated and refined and include two major changes. Specifically, the biopsy Gleason score of 7 is now subdivided into 4+3 and 3+4, indicating the prognostic importance of primary Gleason pattern 4. In addition, PSA ranges have been sub-divided to include 0–2.5, 2.6–4.0, 4.1–6.0, 6.1–10, and >10 ng/ml. Interestingly, Partin Tables are available on the internet for patients to consult and assess the cancer risk for themselves.

Partin Tables may be used to help decide certain aspects of surgical management in clinically localized disease. For example, if the risk of lymph node involvement is very low, then one may consider avoiding a pelvic staging lymphadenectomy. In addition, if the risk of extraprostatic spread is judged to be very high, then one may consider wide excision of neurovascular bundles as opposed to nerve-sparing prostatectomy. With respect to radiation therapy, the need for staging pelvic lymphadenectomy can also be assessed using these tables.

The limitation of Partin Tables lies in the fact that pathologic stage does not always predict clinical outcome. For example, many patients with extraprostatic spread (p3a) without seminal vesicle involvement or lymph nodal metastases are cured after radical prostatectomy. In addition, approximately one-third of patients with seminal vesicle involvement and negative lymph nodes will be free of disease on long-term follow-up. Moreover, approximately 15% of patients with microscopic nodal metastases will not recur biochemically after radical prostatectomy. Thus, knowing the risk of finding extraprostatic spread is not as important as knowing the risk of recurrence.

In the hopes of predicting clinical recurrence after radical prostatectomy or radiation therapy, nomograms have been developed from large clinical datasets. To date, there exist two pre-treatment nomograms which employ serum PSA, biopsy Gleason score, and clinical T-stage in a point-based formula that estimate the 5-year biochemical-free rate as well as 95% confidence intervals. These nomograms are available for daily clinical use on computer or hand-held devices. The nomograms developed for radical prostatectomy and radical radiotherapy are from different datasets and institutions, and therefore the temptation to compare potential outcomes between radiation and surgery in an individual patient should be resisted.

Recently, the Canadian Genito-Urinary Radiation Oncologists Consensus Conference defined three risk categories for clinically localized prostate cancer, which group cases according to serum PSA, T-stage and biopsy Gleason score. These groups have been defined as low-risk (PSA 0–10 and Gleason 2–6 and T1-2a), intermediate-risk (PSA 0–20 and Gleason 2–7, if not low-risk) and high-risk (PSA > 20 or Gleason 8 or greater or T3). Furthermore, various treatment recommendations have been proposed for each of the risk categories, which renders this risk stratification clinically useful.

Several additional factors have been studied in the hopes of improving the prediction of outcome in localized disease. These include 1) number of biopsies containing cancer, 2) % cancer per biopsy, 3) % Gleason pattern 4 or 5, and 4) family history status, none of which has been shown consistently to add independent value to the three principal parameters of PSA, Gleason score, and T-stage. Intuitively, patients with low serum PSA (< 10 ng/ml), low stage (T1c) and low Gleason scores (< 7) will do well, and patients with high serum PSA (> 20 ng/ml), high stage (T2b) and high Gleason scores (> 7) will not do well. Finally, several biologic markers of prognosis are actively being studied in the hopes of improving on the traditional triad of PSA, grade, and stage. Of course, one must always assess the risk of cancer progression within the context of the individual patient's co-morbidities and physiologic age.

To date, several nomograms, tables, and algorithms have been created in order to assist in predicting pathologic stage or clinical outcome in an individual patient. Although many of these tools do help in prognosticating a particular case, several limitations

preclude their widespread use. Specifically, virtually all tools incorporate a combination of Gleason score, T-stage, and PSA, which have inherent variability that can affect the performance of the test. In addition, not all tools will perform the same when transferred from the originating institution to community practice. Furthermore, tables that help predict pathologic stage are only somewhat useful since the important end-point remains clinical recurrence and survival. Nomograms appear helpful in assessing the risk of biochemical recurrence at 5–7 years after treatment such as radical prostatectomy or radiotherapy. Although this is valuable information, the endpoint of PSA recurrence is not as critical as the risk of clinical recurrence, metastases, and survival. In fact, many cases with biochemical recurrence post-radical prostatectomy do not fail clinically for many years when left untreated. Finally, although it is tempting to use nomograms to compare an outcome in an individual patient when treated by radical prostatectomy versus radiation therapy, until the outcome of rising PSA post-definitive therapy is clearer, the knowledge of the risk of biochemical failure will only be moderately helpful. Nevertheless, these tools do provide the clinician with some assessment of risk of progression, and this can be used to counsel patients. The greatest benefit in risk stratification to date is its use in comparing outcomes of series of patients undergoing various therapies and in the design and analysis of clinical trials. □

Suggested reading

1. Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. *JAMA* 1998;280:975-980.
2. Kattan MW, Eastham JA, Stapleton AM, Wheeler TM, Scardino PT. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst* 1998;90:766-771.
3. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, Tomazewski JE, Renshaw AA, Kaplan I, Beard CJ, Wein A. Biochemical outcome after radical prostatectomy, external beam radiotherapy, interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969-974.
4. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh P.C. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591-1597.
5. Kattan MW, Zelefsky MJ, Kupelian PA, Scardino PT, Fuks Z, Leibel S.A. Pretreatment nomogram for predicting the outcome of three-dimensional conformal radiotherapy in prostate cancer. *J Clin Oncol* 2000;18:3352-3359.
6. Partin AW, Mangold LA, Lamm, DM, Walsh PC. Epstein JI, Pearson JD. Contemporary update pf prostate cancer staging nomograms (Partin Tables) for the new millennium. *Urology* 2001;58:843-848.
7. Lukka ., Warde P, Pickles T, Morton G, Brundage M, Souhami L, Canadian GU Radiation Oncologist Group. Controversies in prostate cancer radiotherapy: consensus development. Can J Urol 2001;8(4):1314-1322.
8. Kattan MW, Potters L, Blasko JC, Beyer DC, Fearn P, Cavanagh W, Leibel S, Scardino PT. Pretreatment nomogram for predicting freedom from recurrence after permanent prostate brachytherapy in prostate cancer. *Urology* 2001;58:393-399.