Monitoring Response, Prediction Methodology, Staging, and Imaging in Prostate Cancer

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The predictive values of various tests and examinations are assessed as they relate to prostate cancer progression and treatment. The usefulness of post-treatment biopsy specimens is greatest 2 years after radiation therapy completion. Gleason grading is not reliable in the setting of hormonal ablation therapy. For patients with extracapsular extension, the survival curves separate depending on whether positive or negative surgical margins are obtained. Prostate-specific antigen doubling time is increasingly used as an indicator of disease recurrence after local therapy and prostate cancer–specific survival.
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At the 16th International Prostate Cancer Update, Session 5 was titled "Monitoring Response, Prediction Methodology, Staging, and Imaging." Dr. Gerald Chodak introduced the session with a short case presentation. He described a 58-year-old gentleman presenting with a prostate-specific antigen (PSA) level of 2.1 ng/mL. The patient is being considered for a prostate biopsy and he wants to know the likelihood that he has a life-threatening cancer. This raises the issue of PSA nomograms and their predictive value. Additionally, this raises the issues of screening, predictive modeling, and staging in prostate cancer.

Post-treatment Biopsy

Dr. M. Scott Lucia lectured on the interpretation of post-treatment prostate biopsy specimens. It is now clear that benign prostate, post-radiation changes, and viable prostate cancer can all be distinguished after radiation therapy. Staining for basal cell cytokeratins is indicative of benign glands only. In the radiation therapy literature, it is clear that the usefulness and significance of post-treatment biopsy specimens are greatest 2 years after completion of radiation therapy.[1] The frequency and extent of Gleason score differences between biopsy and prostatectomy are roughly the same in either the presence or absence of prior radiation therapy.

Post-treatment Gleason Grading

After androgen withdrawal, a number of morphologic changes occur, and Gleason grading is simply not reliable in the setting of hormonal ablation. An example was shown in which a biopsy specimen showed Gleason $3 + 3 = 6$, and after neoadjuvant hormone therapy the prostatectomy specimen showed Gleason $5 + 5 = 10$.[2] The 5α reductase inhibitors such as finasteride do not seem to compromise the assignment of Gleason grade as do the leuteinizing hormone–releasing hormone (LHRH) agonists. An expert panel of genitourinary pathologists concluded that finasteride does not cause distinctive generalized histopathologic changes to prostate cancer tissue that can distinguish finasteride-treated from untreated cancers.[3] However, the panel would not rule out that in some cases, finasteride could cause pathologic changes that mimic high-grade cancer. The Gleason score is still not validated in the setting of finasteride. Should Gleason grade be reported after treatment? Dr. Lucia concluded that Gleason grade should probably be reported after radiation therapy, should definitely not be reported after LHRH agonists and anti-androgen therapy, and could be reported after 5α reductase therapy.

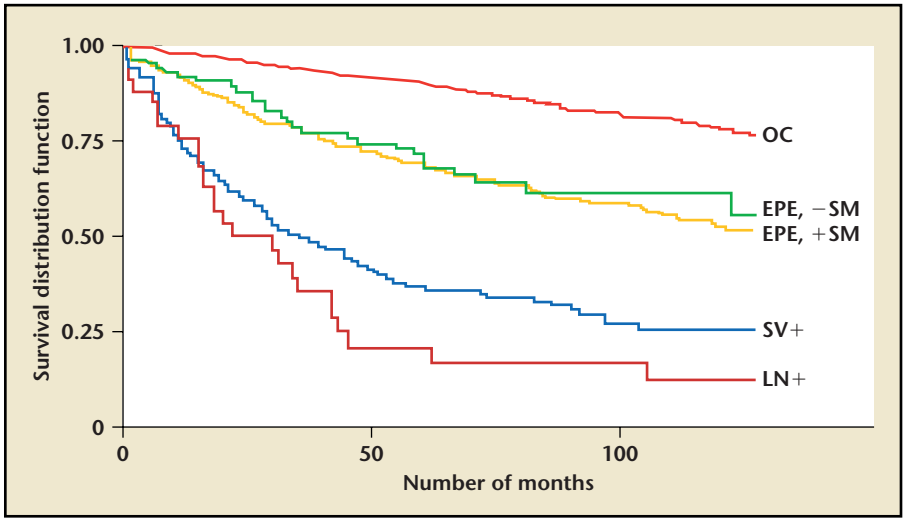
Predictive Modeling

Dr. Nicholas Vogelzang discussed predictive modeling for prostate cancer. He introduced the subject by reviewing and affirming the importance of the usual prognostic indices: PSA,[4] clinical stage, Gleason score, pathologic stage, and the presence or absence of distant metastases. Almost 25% of lymph node–positive patients and approximately 35% of seminal vesicle–positive patients are alive 5 years after surgery. Even for these subgroups, who are generally assumed to have a dismal prognosis, the survival curves flatten out, and approximately 15% to 25% are alive beyond 10 years from diagnosis. Local failure is often the first site of failure for lymph node–positive and seminal vesicle–positive patients; therefore, postoperative radiation therapy should be considered.

Of particular interest to surgeons is the fact that for patients with extracapsular extension, the survival curves separate depending on whether positive or negative surgical margins are obtained. This begs the question of whether postoperative radiation therapy for patients with positive margins could cause the curves to overlap. It is important to realize that extraprostatic extension, surgical margin status, seminal vesicle involvement, and lymph node involvement are independent predictors of outcome, even though they are frequently associated with each other (Figure 1).

PSA doubling time (PSADT) is increasingly used as an indicator of disease recurrence after local therapy and prostate cancer–specific survival.[5] Several large, retrospective databases have demonstrated the predictive value of PSADT. Dr. Vogelzang's analysis of Radiation Therapy Oncology Group (RTOG) trial 92-02 validates the value of PSADT in a prospective fashion.[6] RTOG 92-02 randomized T2c-T4 radiation therapy patients to short-term androgen deprivation (2 months neoadjuvant and 2

Figure 1. *Probability of nonprogression survival after radical retropubic prostatectomy, stratified by pathologic stage (P < .0001). OC, organ confined; EPE, −SM, extraprostatic extension, negative surgical margins; EPE, +SM, extraprostatic extension, positive surgical margins; SV+, seminal vesicle tumor involvement; LN+, pelvic lymph node tumor involvement. Reprinted from* Journal of Urology, *volume 172, Roehl KA, Han M, Ramos CG, et al, Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results, pp. 910-914, copyright 2004, with permission from the American Urological Association.*



months concurrent) versus long-term androgen deprivation (2 months neoadjuvant and 2 months concurrent plus 24 months adjuvant). Applying Prentice's criteria to this prospective database, it is shown that PSADT is a surrogate endpoint for cause-specific survival.[7] The 4 criteria met are as follows. First, treatment is prognostic for the true endpoint, cause-specific survival. Second, treatment is prognostic for the surrogate endpoint, PSADT. Third, the surrogate is prognostic for the true endpoint; PSADT is prognostic for cause-specific survival. And fourth, the full effect of treatment on cause-specific survival is explained by the effect on PSADT. PSADT of 12 months meets all of Prentice's criteria and therefore should be considered as a surrogate endpoint for clinical trials and considered as a stratification factor (Table 1).

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Effective clinical trials for men with hormone-refractory prostate cancer depend on appropriate risk stratification, so it is important to identify the various prognostic indices for these patients. Using data from 1101 patients enrolled on 6 Cancer and Leukemia Group B protocols between 1992 and 2002, a multivariable model predictive of overall survival of men with hormone-refractory prostate cancer has been developed.[8,9] Variables include performance status, Gleason sum, lactate dehydrogenase, alkaline phosphatase, PSA, hemoglobin, and the presence of visceral disease. From these indices a nomogram predictive of overall survival has been developed. This nomogram has been appropriately calibrated and can be used for predicting survival, stratifying patients in new trials, and treatment selection.

Imaging

Dr. Priya Werahera presented the use of optical spectroscopy for prostate cancer diagnosis.[10] Dr. Werahera's techniques involve tissue interaction with light: absorption, fluorescence, phosphorescence, and Raman scattering. These properties depend both on the molecular composition and cellular morphology of tissues; cancer affects cells at both levels. These properties vary with the wavelength of light used, and the pattern of these properties as a function of wavelength is sometimes different for malignant tissues compared with benign tissues. Elastic scattering and fluorescence spectra can distinguish benign from malignant prostate tissue, and work is in progress for in vivo diagnosis of prostate cancer.

Dr. Mack Roach presented a talk on the various uses of new imaging modalities for prostate cancer, with an emphasis on staging and radiation therapy for local disease. Positron emission tomography (PET) with fluorocholine seems to be more sensitive than PET with fluorodeoxyglucose.

Lymph node size as seen on computed tomography (CT) is a very poor predictor of pathologic involvement. Better tools for determining the risk of lymph node involvement are the Partin tables and the Roach equations, which both estimate risk on the basis of clinical stage, Gleason score, and PSA. Using receiver operating characteristic curves, we see that the predictive value of Partin tables and the Roach equations is improved by the addition of ProstaScint scanning (Figure 2). As with any test, ProstaScint scanning adds the most benefit for patients at intermediate risk of a positive result. In this case, ProstaScint scanning is probably most informative for patients with an estimated risk of nodal involvement greater than 20%.

Dr. Roach presented intriguing data from Harisinghani on the use of lymphotropic nanoparticles to increase the sensitivity and specificity of magnetic resonance imaging in the detection of pathologic nodal involvement; positive predictive value is approximately 95%.

A discussion of intensity-modulated radiation therapy (IMRT) for prostate cancer came next. Dr. Roach explained how traditional 3-dimensional conformal treatment has defined nodal volumes according to bony landmarks.[11] IMRT requires

Table 1
Prognosis for Patients With a Rising Prostate-Specific Antigen Level

Prostate-Specific Antigen Doubling Time (mo)	Median Time to Metastases (y)	Median Survival (y)
3	2	6
6	4	8
9	6	10
12	8	12

Data from D'Amico et al.[5]

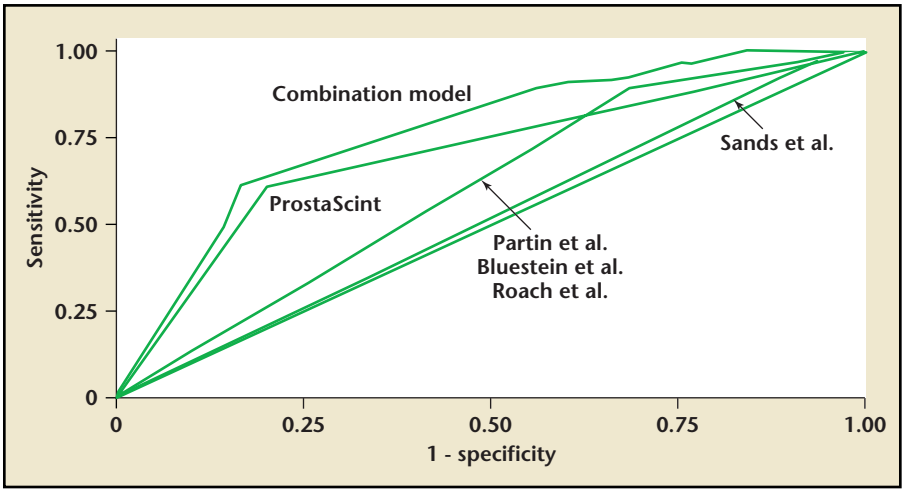
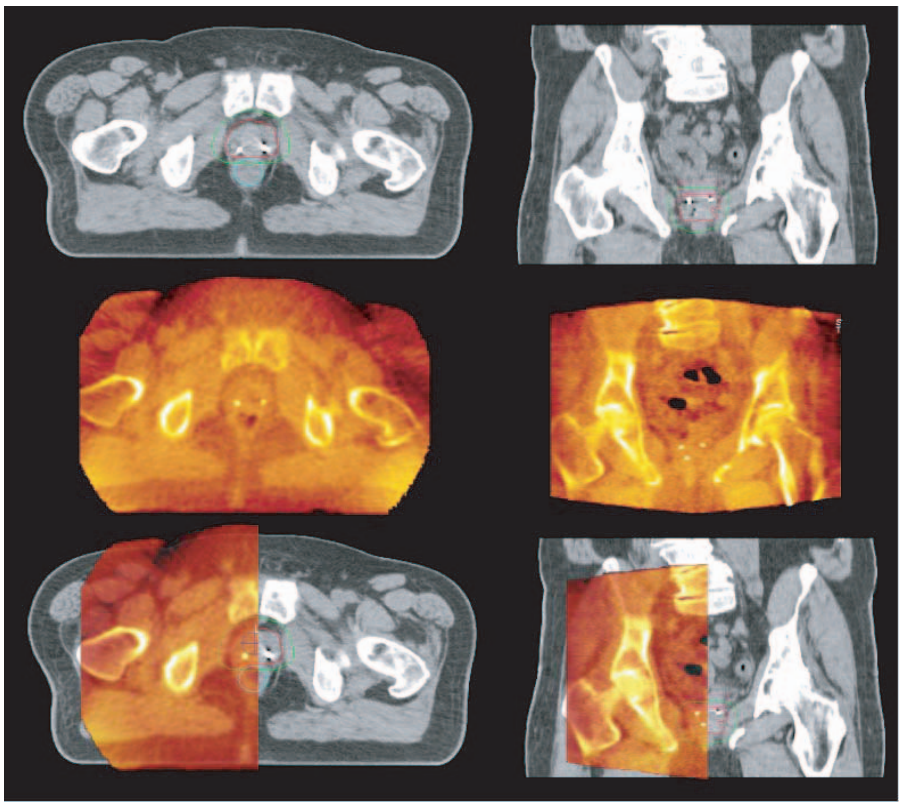


Figure 2. *Receiver operating characteristic curves using various algorithms and the ProstaScint scan. The best ROC curve supports the use of ProstaScint combined with various methods of estimating the risk of positive lymph nodes. Patients with a risk of affected nodes greater than or equal to 20% seem to be the optimal subset for performing this test. For lower-risk patients, the benefits are likely to be less. Reprinted, with permission, from Polascik et al.*[15]

specific identification and drawing of all target volumes; Dr. Roach presented Shih's data on the need to define nodal target volumes according to the pelvic vessels. Drawing target volumes in this way should result in decreased irradiation to normal pelvic tissues and therefore less toxicity.

The prostate displays inter-fraction changes in position during a typical 9-week course of radiation therapy. As we escalate doses, margins become smaller. Visualization of the prostate in real time for daily treatment setup is rapidly becoming popular in radiation oncology. Imaging can be performed with transabdominal ultrasound, electronic portal imaging, or cone-beam CT. Fiducial markers placed in the prostate can help determine appropriate patient shifts. Average patient shifts are on the order of 2 to 3 mm, and typical treatment margins are 5 to 10 mm. We must realize, though, that the fiducial marker seeds themselves can shift a bit within the prostate. Moreover, megavoltage cine shows there is intra-fraction prostate motion of approximately 2 mm or less during the delivery of a prostate treatment. Three-dimensional imaging is essential to accurate targeting of the prostate (Figure 3).

Figure 3. *Patient setup: prostate cancer imaging using megavoltage cone-beam computed tomography and gold marker seeds.*



PSA Kinetics as an Endpoint

Dr. Philip Kantoff discussed some of the difficulties associated with the use of PSA kinetics as an endpoint in clinical trials.[12,13] Patients with biochemical failure represent a heterogeneous group, and the time to specific clinical outcomes can be very long, making clinical trials difficult. The use of PSA as a surrogate for clinical outcomes is potentially of great value but also potentially fraught with difficulties. PSADT is a powerful predictor of time to clinical recurrence and overall survival. A PSADT of

3 months results in a median time to metastases of 2 years and a median survival of 6 years, whereas a PSADT of 12 months results in a median time to metastases of 8 years and a median survival of 12 years.

A therapy that results in an increase of the PSADT would yield the "broken arrow effect" on a graph of PSA versus time: a decrease in the slope of the line. Does an increase in PSADT caused by a therapeutic intervention reflect an improved clinical outcome? We are just beginning to evaluate the performance of PSADT as an endpoint in clinical trials. Responses can be measured as an increase in the PSADT by a given factor (eg, 150%–200%). Experiences from early trials have taught us some lessons. The PSADT must be precisely and accurately determined for a given patient during a sufficient lead-in period before entry on a trial: small differences in the measured PSA can result in large PSADT differences. The time a patient is exposed to the experimental treatment must be finite, and patients should be allowed to cross over from placebo arms to experimental arms to determine the effect on PSADT. Uniform guidelines for calculation of PSADT are needed. Trials must incorporate a placebo arm because placebo might affect PSADT. Ultimately, PSADT will have to be linked to clinical outcomes. ■

References

1. Litzenberg DW, Balter JM, Lam KL, et al. Retrospective analysis of prostate cancer patients with implanted gold markers using off-line and adaptive therapy protocols. *Int J Radiat Oncol Biol Phys*. 2005;63:123-133.
2. Bostwick DG. Grading prostate cancer. *Am J Clin Pathol*. 1994;102(4 suppl 1):S38-S56.
3. Reuter VE. Pathological changes in benign and malignant prostatic tissue following androgen deprivation therapy. *Urology*. 1997;49(3A suppl): 16-22.
4. Albertsen PC, Hanley JA, Penson DF, Fine J. Validation of increasing prostate specific antigen as a predictor of prostate cancer death after treatment of localized prostate cancer with surgery or radiation. *J Urol*. 2004;171(6 pt 1):2221-2225.
5. D'Amico AV, Moul JW, Carroll PR, et al. Intermediate end point for prostate cancer-specific mortality following salvage hormonal therapy for prostate-specific antigen failure. *J Natl Cancer Inst*. 2004;96:509-515.
6. Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol*. 2003;21:3972-3978 [erratum in: *J Clin Oncol*. 2004;22:386].
7. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med*. 1989;8:431-440.
8. Hudes G, Einhorn L, Ross E, et al. Vinblastine versus vinblastine plus oral estramustine phosphate for patients with hormone-refractory prostate cancer: a Hoosier Oncology Group and Fox Chase Network phase III trial. *J Clin Oncol*. 1999;17:3160-3166.
9. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. *J Clin Oncol*. 1999;17:2506-2513.
10. Richards-Kortum R, Sevick-Muraca E. Quantitative optical spectroscopy for tissue diagnosis. *Annu Rev Phys Chem*. 1996;47:555-606.
11. Shih HA, Harisinghani M, Zietman AL, et al. Mapping of nodal disease in locally advanced prostate cancer: rethinking the clinical target volume for pelvic nodal irradiation based on vascular rather than bony anatomy. *Int J Radiat Oncol Biol Phys*. 2005;63:1262-1269.
12. D'Amico AV, Moul J, Carroll PR, et al. Surrogate end point for prostate cancer specific mortality in patients with nonmetastatic hormone refractory prostate cancer. *J Urol*. 2005;173:1572-1576.
13. Aus G, Robinson D, Rosell J, et al. Survival in prostate carcinoma—outcomes from a prospective, population-based cohort of 8887 men with up to 15 years of follow-up: results from three countries in the population-based National Prostate Cancer Registry of Sweden. *Cancer*. 2005;103:943-951.
14. Roehl KA, Han M, Ramos CG, et al. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. *J Urol*. 2004;172:910-914.
15. Polascik TJ, Manyak MJ, Haseman MK, et al. Comparison of clinical staging algorithms and 111indium-capromab pendetide immunoscintigraphy in the prediction of lymph node involvement in high risk prostate carcinoma patients. *Cancer*. 1999;85:1586-1592.

Main Points

- Gleason grade should probably be reported after radiation therapy, should definitely not be reported after leuteinizing hormone–releasing hormone agonists and anti-androgen therapy, and could be reported after 5α reductase therapy.
- A nomogram multivariable model predictive of overall survival of men with hormone-refractory prostate cancer has been developed and appropriately calibrated and can be used for predicting survival, stratifying patients in new trials, and treatment selection.
- Prostate-specific antigen doubling time is a powerful predictor of time to clinical recurrence and overall survival.