Algorithms Vie for Diagnostic Role in Prostate Cancer

To operate or not to operate is a question that often agonizes urologists and their patients with prostate cancer. In many cases it is impossible to determine whether the cancer has already escaped the gland, the point where, in the eyes of most urologists, a radical prostatectomy becomes far less likely to be curative.

"Right now, the ability of the urologist to predict organ-confined disease is 50%, a flip of the coin," said Robert Veltri, Ph.D., vice president and general manager, UroSciences Group, UroCor Inc., an Oklahoma City company that services urologists. In 13,000 cases, described in 17 articles, the correct pathology was identified in 6,800 cases, he said, and even the best medical centers will predict outcome with just 65% to 70% accuracy.

Furthermore, seminal vesicle biopsy, peripheral lymph node dissection, pelvic lymph node dissection, and bone scan — tests for metastasis that often follow positive biopsy — “are costly in today’s health care system, when you are not reliably getting the information you think you are getting,” added Veltri. For example, although a positive bone scan is virtual proof of metastasis, bone scans fail to detect more than three-quarters of metastatic prostate cancers. They cost $500 to $1,100.

UroCor has designed a new nomogram, a type of algorithm that Veltri said accurately identifies non-organ-confined disease status in nearly 86% of cases, and confinement to the prostate in more than 70% of cases. (Non-organ-confined means the cancer has escaped from the gland, but is in surrounding tissue, although not necessarily metastasized to other organs.) Several other groups also have advanced nomograms.

One goal of nomograms is to replace some of the costly and poorly predictive diagnostic procedures. Another is to “give [urologists] enough specificity so that they can avoid operating on some patients,” said Paul Lange, M.D., professor and chairman of urology, University of Washington School of Medicine, Seattle.

Uroscore Tested

UroCor’s nomogram, called UroscoreSM, was tested in a retrospective study of 210 pathologically staged patients, published in the Journal of Urology, October 1996, and conducted at Cerritton Hospital, Rochester Hills, Mich., and at Ohio State University Medical Center and the Arthur G. James Cancer Hospital and Research Institute, both in Columbus, Ohio.

Uroscore integrates seven measures that have been used independently to stage prostate cancer: prostate-specific antigen, quantitative nuclear grade, Gleason score (a measure of order, or lack of it, in the way the cells are stacked), the number of positive cores in six coordinated prostate biopsies, the percentage of tumor involvement in each, whether or not the tumor involves more than 5% of the base and apex of the gland, chromosome number, and quantitative nuclear grade (QNG).

QNG is a measure that has been refined by UroCor. Alan W. Partin, M.D., Ph.D., associate professor of urology at the Johns Hopkins University School of Medicine, Baltimore, traced the history of QNG.

Beginning more than 100 years ago, he said, pathologists diagnosed cancer by examining the shape of cell nuclei under a microscope. “A normal nucleus is round and homogeneous. When they get crinkly and out of shape, with dark spots, that’s a cancer.”

Until about two decades ago, “pathologists would just look under the microscope and say, ‘gee, that looks bad,’” said Partin. However, Partin, Veltri, and others have now used computers, microscopes, and image analysis to quantify this nuclear grade, which is made up of 11 different nuclear shape descriptors of the DNA texture.

“Quantitative nuclear grade was the most significant new prognostic indicator of non-organ confined prostate cancer,” the authors wrote in the October 1996 Journal of Urology. “Although significantly associated with preoperative PSA, quantitative nuclear grade was not related to any other prognostic factor, which suggests that quantitative nuclear grade provides unique information not available from other preoperative parameters.”

Lange, who reviewed it for the journal, said, “I thought the paper was worthy of publication and examination, but I didn’t think that everybody ought to
jump on the bandwagon. There are lots of combinations of preoperative markers said to be predictive of postoperative pathology."

**Very Accurate**

But Jeffrey I. Katz, M.D., managing partner at Associates in Urology, St. Barnabas Hospital in West Orange, N.J., said Uroscore “is very accurate.”

Katz said he has performed hundreds of biopsies and 50 radical prostatectomies on patients tested with Uroscore. The nomogram wrongly predicted non-organ-confine ment for only two of the 50 surgical patients, although Katz added that it will take many years of watching these patients to confirm that no metastasis occurred.

Thomas Bormes, M.D., in the Department of Urology, Rush-Presbyterian-St. Luke’s Hospital, Chicago, is also testing Uroscore. “It is too early to tell” whether the nomogram will ever stand alone, although it might if predictive values reached the high 90s, he said.

Partin has developed his own nomogram, a series of four tables that predict organ-confined disease, capsular penetration, seminal vesicle involvement, and lymph node involvement.

“My tables are a lot simpler to use,” he claimed. They are based on an analysis of 1,000 prostate cancer patients at Hopkins. The physician simply plugs the stage, the Gleason score, and the PSA into each table, and finds the corresponding predictive number. Last year, the Partin tables on the Internet (http://rattler.cameron.edu/prostate/prostate.html) were hit 300,000 times, Partin said.

However, the Partin tables were designed using retrospective data from Hopkins patients, and others have found that, applied to other sets of patients, “they didn’t work very well at all,” said William J. Catalona, M.D., chief of urology at Washington University Medical Center, St. Louis.

The nomogram that currently predicts organ-confinement with the highest accuracy was developed by Perinchery Narayan, M.D., professor and chairman of urology, University of Florida, Gainesville. Using PSA, Gleason score, and staging based on needle biopsy, it correctly identifies 86% to 100% of cancers confined to the prostate, but only 50% of non-organ-confined cancers, Narayan said.

The new nomograms represent a significant improvement over Narayan’s earlier efforts, due partly to the use of neural networks, computer programs that analyze data by simulating human learning. Each time another patient’s data is added to the database, the neural network alters its predictions to account for the new information.
But the notion of relying exclusively on a nomogram scares some urologists. One reason is that in cases where prostate cancer has invaded the immediately surrounding tissues, patients have been cured by radical prostatectomy, said Peter T. Scardino, M.D., chairman of urology, Baylor College of Medicine, Houston. “If there is microscopic extracapsular extension the chance the cancer can be cured is still 70%, and if there is seminal vesicle invasion the chance is still 30%,” Scardino said.

Even if some cancer cells escape the knife, the operation can increase 5-year survival from 30% to 50%, said Bormes.

“Even if it’s only a 10% chance the guy is operable, you will take it,” added Lange.

**Trial to Begin**

To improve Urocore’s predictions, a multi-institutional trial is about to begin, with Johns Hopkins, Baylor, and the University of Michigan providing preoperative biopsy samples from patients who had radical prostatectomies. “We should know its performance characteristics with some degree of accuracy in the next 6 months, and have improvements to the algorithm in the next 12 months,” said Velti.

UroCor has also been developing a nomogram that can predict post-operatively whether cancer is likely to progress. This could help in deciding which patients should have adjuvant therapy following surgery, said Velti.

The ideal nomogram would make a science of predicting progression of prostate tumors. For the immediate future, at least, this small but critical corner of medicine will remain largely an art.

— David Holzman

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**Preparing for Life’s End: Do Health Professionals Need More Training?**

Are health professionals well trained to recognize the end stages of a fatal illness, and to share that awareness sensitively with patients and the people who mean the most to them? Or are many so poorly equipped to deal with these matters — and so uncomfortable with them — that they could profit from clinical guidelines on how to manage care at the end of life with greater compassion and skill?

These are some of the questions that a committee of the National Academy of Sciences’ Institute of Medicine has been grappling with since January 1996. Among the many other questions the 12-person panel has been exploring are the adequacy of the tools available for the assessment and symptom management of dying patients, the strengths and limitations of advance directives, and how better to determine and comply with the wishes of dying patients and their families.

“All these issues have taken on greater urgency as it has become evident that the advances of modern medicine can add to the discomfort of gravely ill patients without significantly prolonging their lives,” said Christine Cassel, M.D., who chairs the IOM panel.

“Yet it’s been almost a taboo among physicians to discuss the likely futility of heroic treatment with terminal patients for fear that it will deprive them of hope.

“Since many patients know perfectly well what is going on,” she continued, “the effect is to make them feel isolated when what they really want is the truth about what they can expect, and reassurance that the physician won’t abandon them at the end. When our report is ready for publication, as it will be next year, it will include a number of recommendations designed to encourage a change of physician behavior in this respect.”

But Cassel, who heads the Department of Geriatrics and Adult Development at the Mount Sinai Medical Center in New York, said the panel has also found that physician squeamishness about leveling with dying patients is understandable. For one thing, she noted, palliative care is not generally taught to medical students at either the undergraduate or postgraduate levels.

For another, there has been little systematic study of palliative care, which has given it a low profile in both the practitioner and research communities. Accordingly, Cassel reported, the IOM committee has been looking hard at whether palliative care should be a recognized medical specialty. The Committee will surely recommend that it get more attention from institutions that