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HOTSHEET

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A SYSTEMS PATHOLOGY APPROACH TO POST-SURGICAL PATIENTS WITH ANXIETY

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Introduction

In 2010, approximately 218,000 men were diagnosed with prostate cancer and, based upon available data, approximately 50% of men opted for surgery.[1,2] Radical prostatectomy (RP) is considered the gold standard by many physicians and it is indeed effective for the vast majority of those treated. However post-surgery, a number of men have higher risk features such as positive surgical margins (incidence ranges from 11% to 46%) or extracapsular extension which cause these men concern and require physician counseling.[3]

Typically, positive surgical margins (PSMs) are defined as the presence of tumor at the inked margin of the removed specimen and extracapsular extension (ECE) is defined as tumor extending from the prostate into the periprostatic tissue.[4] After RP, the prostate is sent to the pathology laboratory. Technicians process the tissue and a pathologist examines the specimen, grading the tumor and assessing the extent of the disease. Often the prostatectomy Gleason score differs from the Gleason score assigned at biopsy. This is because the biopsy view is an extremely narrow perspective of the tumor whereas, after surgery, the entire prostate can be assessed. It is during the pathologic review of the prostatectomy tissue that the presence of PSMs or ECE is determined.

There are several obstacles to understanding the actual risk posed by a PSM. The presence of a PSM is determined by a pathologist but it is a subjective assessment and can be difficult to unequivocally ascertain due in part to variables such as anatomic location and specimen processing. A PSM can be due to an extensive tumor but, in certain locations (such as posteriorly against the rectum or laterally against the pelvic sidewall), there is a limit to the amount of tissue a urologist can remove; in these sites pathologists cannot be certain how much tumor, if any, is truly at the inked margin and therefore still in the patient.[4] In addition, a PSM can result from an incision through a tumor that is outside the prostate capsule, or by an accidental incision into the prostate in a case that is actually organ confined disease. Other research has suggested that the tissue preparation method, used in the pathology laboratory, may result in different PSM rates.[5]

Given the subjective and variable nature of what may constitute a PSM, it is not surprising that the association of increased risk between a PSM and post-RP prostate cancer recurrence (measured primarily as biochemical or PSA recurrence) has resulted in variable outcomes in the literature. Most studies, but not all, find an association between PSM and PSA recurrence.[6,7] Studies have analyzed the possible cancer recurrence risk with many aspects of PSMs. Many believe that positive margins in specific locations place a patient at higher risk but research conflicts on this point.[5, 8-10]

Other studies suggest that margin length or the number of positive margin sites may or may not be associated with higher risk.[5,11-12] Some have found an association between PSM, the need for salvage therapy and decreased risk of survival.[13,14] However, PSMs typically become less predictive when other factors such as high Gleason score ($\geq$8) or seminal vesicle invasion (SVI) are factored into the analysis.[6, 14]

Regardless of the exact nature of the positive margin or the link to cancer recurrence, margin status can affect treatment management.[15] Some advocate adjuvant therapy for patients with PSMs and although results are controversial more studies continue to be published on the potential benefits of adjuvant therapy for patients with pathologically advanced prostate cancer.[16-19]

Post-RP patients, who experience a high-risk feature, regardless of its nature (PSM, ECC or high Gleason score) or have any concern, benefit from having an objective, comprehensive and more accurate understanding of their real risk of serious disease progression. New tools that incorporate a patient's molecular and cellular information provide a personalized risk assessment that can be very important during counseling post-surgery. One such 'tool' is Aureon's Systems Pathology approach: an objective integration of multiple types of data that results in personalized patient risk assessment. Traditional pathology bridges both basic and clinical biomedical sciences. However, there is a degree of subjectivity to these analyses, and they lack the ability to provide measurable results. Aureon's Systems Pathology approach overcomes these deficiencies by integrating information from tissue shape and patterns, clinical data and the cellular localization and measurement of molecular information.

What is Post-Op Px?

Post-Op Px™ is an innovative test, based upon Systems Pathology that provides each post-surgical patient with an objective, comprehensive and personalized assessment of their risk. When a urologist orders Post-Op Px, Aureon sends a request to the pathology laboratory that processed the prostatectomy sample. The laboratory sends the tissue and the results of their pathology determination to Aureon for subsequent prognostic analysis. Aureon pathologists and scientists use a patented technological approach that combines image analysis, protein detection, clinical/pathologic information and mathematics to uniquely measure:

- The tissue patterns of each patient's surgically removed prostate tumor
- Biologically-relevant proteins in the tumor specimen

Post-Op Px helps predict:

- Patients likely to have serious disease progression (metastasis, or salvage therapy failure) within 5 years of RP
- Patients likely to have PSA recurrence within 5 years of RP

Patients with PSMs may be anxious. These men or their loved ones do research on the Internet. They ask their doctor many questions about their status and the extent to which they should be concerned. There is a range of medical responses to PSMs: some physicians wait for the PSA to rise before becoming concerned, others watch the patient closely or are not concerned, and yet others consider adjuvant therapy. The difficulty arises from the subjective nature of surgical margins (see intro) and the extent of risk that a PSM may or may not pose for the individual. Post-Op Px provides an additional and objective perspective about the person's likelihood of serious disease progression.

How was Post-Op Px developed?

A cohort of 881 patients and associated outcome data was assembled from Memorial Sloan-Kettering Cancer Center. After review, there were 758 evaluable cases in the cohort. The median time to disease progression was 5 years post-RP. The cohort was split into demographically balanced data sets. One data set was used to design and develop Post-Op Px and the second data set was used to independently validate the test's ability to predict disease recurrence and progression.

Post-Op Px Reimbursement

Aureon currently bills all commercial, private, third party carriers, and Medicare. Our Aureon Patient Care Program – APCP can be helpful to patients in understanding the reimbursement process. Aureon feels very strongly that no patient should ever be penalized financially while working through their battle with Prostate Cancer. Aureon's billing dept does offer an up-front benefit investigation if required to get general info regarding deductibles and coinsurance.

Comparison of Systems Pathology with Post-Surgical High Risk Features

In initial studies, Post-Op Px was able to accurately separate low-risk and high-risk patients for both advanced disease progression and PSA recurrence using the patient's own RP sample. [20, 21]

Given the possible significance of PSMs and ECE with disease progression an analysis was conducted utilizing the Post-Op Px validation data set to investigate the comparison of these pathologic features with the Post-Op Px integrated, Systems Pathology approach for predicting outcome. A sub-cohort study was conducted utilizing the Post-Op Px validation data set to investigate the comparison of these pathologic features with the Post-Op Px integrated, Systems Pathology approach for predicting outcome.[22]

Prognostic accuracy was measured by both hazard ratio (HR) and concordance index (CI). The HR is a measure of the effectiveness of a factor/variable to stratify patients into different risk populations: low- and high-risk. An HR of 1 means there is no difference in risk between the two groups. An HR of >1 means patients in the predicted high-risk group are indeed at higher risk than the predicted low-risk group. As the HR increases, the more accurate the low/high risk stratification.

The CI is the probability that, given two randomly selected patients, the patient with the worse outcome is, in fact, predicted to have a worse outcome. This measure, similar to an area under the receiver operating characteristic curve, ranges from 0.5 (i.e., chance or a coin flip) to 1.0 (perfect ability to rank patients). The higher the CI the more accurate the test performs.

An analysis of the disease progression endpoint (Table 1) in the validation cohort (N=385) examined the HR, CI and associated p values of clinical and pathologic variables in comparison to the Px SCORE.

As Table 1 shows, age, clinical stage, pre-op PSA, RP Gleason sum, PSM, and ECE have poor prognostic value for disease progression, which in some cases, is not statistically significant (p-value >0.05). The Px SCORE has the best HR (11.4), which was highly statistically significant (p-value <0.0001), as well as the most favorable CI (0.84).

A similar analysis of the PSA recurrence endpoint (Table 2) in the validation cohort (N=340) examined the same performance metrics. As seen with disease progression, Table 2 also demonstrates that the Px SCORE possessed the best hazard ratio (HR 5.56), which was highly statistically significant (p-value <0.0001), as well as the most favorable concordance index (CI 0.77).

Table 1: Px SCORE Compared with Post-RP High-Risk Features

Predictor	CI	HR	P-value
Age	0.51	0	0.99
Clinical Stage	0.61	1.72	0.15
Pre-RP PSA	0.57	1.51	0.37
Post-RP Gleason score	0.68	2.28	0.08
SVI	0.64	5.90	<0.0001
PSM	0.60	2.34	0.03
ECE	0.61	2.29	0.03
Px SCORE	0.84	11.4	<0.0001

Another way of comparing high-risk features and the Systems Pathology approach is a Kaplan Meier survival curve. As seen in Figure 1, Post-Op Px is better able to separate high from low risk patients for disease progression in 5 years than surgical margin status.

Conclusion

Post-surgical patients with a high risk feature(s) have understandable questions and concern. The literature demonstrates the difficulty in extrapolating from a patient's risk feature to actual disease prognosis. Better tools are needed to help provide more information about each patient's specific circumstance. Aureon's System's Pathology approach, exemplified by Post-Op Px, supports the belief that more comprehensive, advanced prognostic tools require the integration of multiple features at the molecular and cellular level.

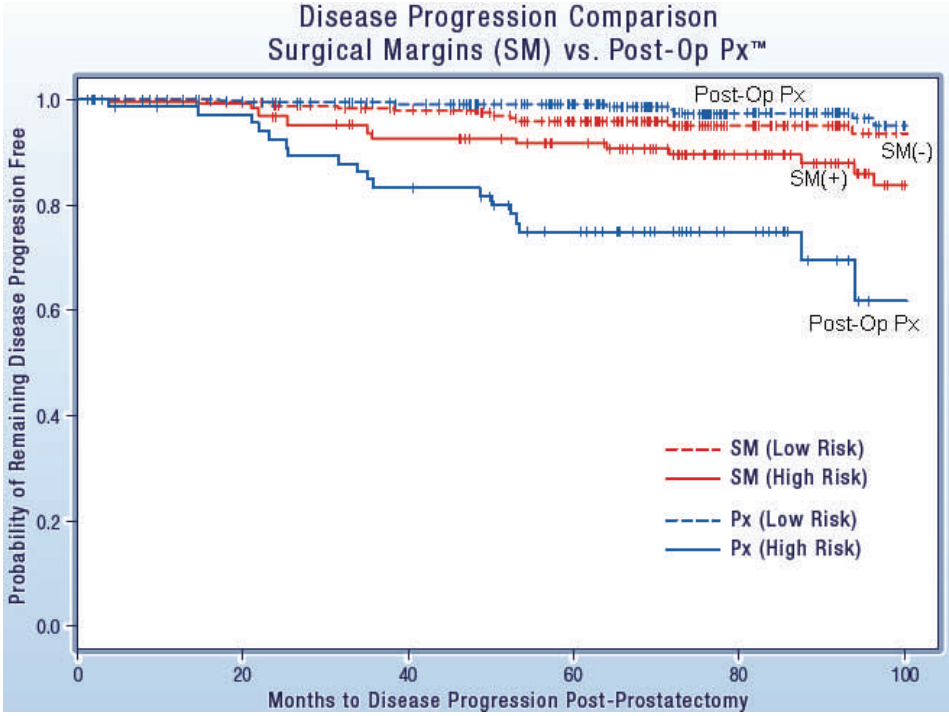
Systems Pathology provides a more accurate and objective prediction of serious disease progression than methods that rely primarily on clinical and pathologic features. Post-Op Px enables physicians to properly assess serious disease progression risk (metastasis, failure of surgery and salvage therapy within five years) post-RP.

Any surgical patient can benefit from this information but, especially, patients with a high risk feature(s) as well as their physicians will benefit from an objective perspective that provides new information for their personal risk assessment. Post-Op Px is an important tool during patient counseling.

Table 2: Prediction of Post-RP PSA Recurrence

Predictor	CI	HR	P-value
Age	0.59	0	0.99
Clinical Stage	0.64	1.99	0.02
Pre-RP PSA	0.65	2.60	0.01
Post-RP Gleason Score	0.70	4.70	0.001
SVI	0.56	3.38	0.003
PSM	0.65	3.75	<0.0001
ECE	0.68	4.29	<0.0001
Px SCORE	0.77	5.56	<0.0001

Figure 1: Comparison of Post-Op Px to Post-RP PSM Status



Editor's Note: Other tools are available to assist physicians in counseling a patient who is found to have high-risk features on final pathologic exam of the excised tumor. These include predictive algorithms and nomograms that estimate risk using a variety of pre-RP and post-RP risk factors collected from patient cohorts. Many utilized data from RP patients treated at one or more prostate cancer surgical centers of excellence and are accessible at no charge on the Internet. The CIs of such methods range from 0.7 to 0.85 depending on the model used[1] and showed comparable CIs to earlier Systems Pathology software versions.[2]
Like the Px SCORE, results with these nomograms have been independently validated. One drawback, however, is some models overestimate recurrence risk in men with higher risk features.[3]

Various tumor markers have been incorporated into the pre-RP and post-RP risk assessment models predicting post-RP PSA progression. Markers utilized in predictive models include human glandular kallikrein-2 (hK2),[4] PSA isoforms such as free PSA and [-2]pro-PSA[5] and serum proteomic biomarkers.[6]

Another exciting prognostic tool for predicting cancer outcome is the detection and quantification of the number of circulating tumor cells (CTCs) in patients with solid tumors (including prostate cancer).[7-9] Surprisingly, CTC detection rates and CTC numbers were independent from disease stage. Various immunocytochemical enrichment methods are available [7] and RT-PCR can be used to quantitate circulating levels tissue-specific mRNA transcripts.[8]

CTCs can be detected before, during and after RP for localized disease. However, the likelihood of developing biochemical progression or distant metastasis in early stage patients seems to be higher when tumors cells persistently reside in the patient bone marrow.[9] In advanced disease, CTC measurements serve as an excellent prognostic tool.

It is important to note, however, that all tests mentioned here predict PSA recurrence, and not serious disease progression that the Post-Op Px test does.

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Editor's Note: See also the Feb 2011 issue of the *Us TOO HotSheet*, pg 4, for an article on circulating tumor cells and a new, sensitive blood test, *Cancer Blood Test Closer to Market.*