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ACTIVE SURVEILLANCE AND MULTIPARAMETRIC MRI: A PROMISING COMBINATION FOR A NEW PARADIGM — mpMRI Targeted Biopsy for Patient Selection; mpMRI for Sequential Monitoring. A vision of the future.

A technically well performed and expertly interpreted multiparametric MRI combining standard T2 and diffusion weighted, and contrast enhanced imaging is the most accurate method of assessing the true size and location of cancer within the prostate gland short of a pathologist's assessment of a whole-mount prostate specimen. A biopsy targeted into a region of high suspicion on a mpMRI confers a greater likelihood of establishing the true Gleason score of the cancer as compared to a random 12-core TRUS guided biopsy. Therefore, it is not surprising that mpMRI is assuming a primary role in the selection of men for active surveillance, and being evaluated as the preferred tool for monitoring during the course of active surveillance (AS).

Maxwell Meng, MD, (UCSF) at the meeting of the Society of Urologic Oncology (SUO), Bethesda, December 2013, weighed in on this topic with his presentation: *"Role of MRI: Can MRI replace the biopsy or not?"* He answered his own question with data supporting the substitution. The thrust of his remarks was summarized for UroToday:

"The potential benefits of MRI in AS include improvement in preoperative risk stratification, increased acceptance of AS by low risk patients, identification of candidates for early intervention, and improved monitoring during follow-up."

MRI AND PATIENT SELECTION FOR ACTIVE SURVEILLANCE:

An abundance of studies has established that patients initially considered as good candidates for AS based on a TRUS-guided biopsy undergo a 20-30% reclassification on a confirmatory biopsy or on a prostatectomy specimen. Dr. Meng (UCLA) cited his study of 500 men thought to have low-risk disease on initial work-up. At 6 - 12 months thereafter these men underwent an MRI and biopsy. Meng confirmed what others have found: a baseline MRI score indicating low suspicion for cancer (≤2 on a scale of 1, definitely no tumor, to 5, definitely tumor) was associated with an excellent negative predictive value (0.98-1.0) for predicting *subsequent* upgrading and the presence of significant cancer. Of the men classified as low-risk at the initial assessment, 38% showed no region of suspicion on subsequent MRI. Rebiopsy in this group led to a reclassification rate of only 3.5%.

MRI AND PATIENT SELECTION FOR ACTIVE SURVEILLANCE continued:

The study supported the added value of a MRI guided biopsy as compared to the standard 12-core sampling. In 582 patient (320 with a negative first 12-core biopsy) the MRI targeted biopsy upgraded 32% overall; 22% in men with an initial Gleason score of ≤3+4.

The superiority of a targeted MRI guided/fusion biopsy over the standard 12-core was again supported in a presentation at the 2014 SUO meeting in a report by Dr. Salami (The North Shore Institute for Urology, Hofstra North Shore, N.Y.). The study focused on 140 men in whom the initial TRUS biopsy(s) was negative. The second biopsy session employed an MRI fusion guided biopsy and a random 12-core TRUS guided biopsy. The cancer detection rate was 65% for those men with one prior negative biopsy. Although the detection of cancer of *any* grade was similar with both techniques, i.e., ~50%, the fusion biopsy detected significant cancer in 48% vs 31%. The standard technique missed 19 of 91 clinically significant cancers whereas the fusion biopsy missed only 3.5%.

As seen in previous studies, the cancers missed by the TRUS technique were predominantly located in the anterior and central portions of the gland, regions reached with difficulty in the standard transrectal biopsy but well within the range of a transperineal approach.

Considering the studies cited above, and supported by an abundance of other studies with the same conclusion, patient selection for AS based on an mpMRI targeted biopsy would appear to be the preferred technique.

Pathologic diagnosis of the specimen obtained at prostatectomy is unquestionably the reference standard for comprehensive information about the location, size, and Gleason score of prostate cancer. But an initial prostatectomy can not be performed and then later choose AS for only favorable candidates. However, the MRI-guided method has the better record than TRUS-guided for determining both significant cancer (i.e. those greater than 1cm in diameter) and cancer prompting reclassification (and possible intervention).

A comparison of the index tumor biopsied using image-guided MRI/fusion with the step sectioned prostatectomy specimen in 135 men was reported by Ukimura, Eur Urol Sept 2014. The index tumor (IT) was “defined as lesion with the highest Gleason score or largest volume or extraprostatic extension. Their conclusion: The concordance between IT location on biopsy and RP specimens was 95% (128-125). … [and] “The concordance of primary Gleason pattern between targeted biopsy and RP specimen was 90%.”

Mullins, Partin, Epstein *et al.,* at Johns Hopkins*, (BJU Int.* 2013 June) reported that mpMRI “demonstrated excellent specificity (0.974) and a negative predictive value (0.897) for the detection of pathological index lesions.”

In his report in BJU Int. 2014, “Mutiparametric magnetic resonance imaging (MRI) and active surveillance for prostate cancer: future directions,” Mullins stated: “It is currently the practice at our institution [Johns Hopkins] to refer eligible men for multiparametric MRI before enrollment in AS.

MRI IN MONITORING PATIENTS DURING ACTIVE SURVEILLANCE:

The application of monitoring the course of AS with multiparametric MRI alone (with biopsy only as indicated) is a work in progress requiring evaluation and validation. However, substituting mpMRI for sequential TRUS-guided biopsies has great potential and is well worth pursuing. Routine monitoring biopsies are recommended at various intervals in different regimens ranging from yearly to as long as every four years.

MRI IN MONITORING PATIENTS DURING ACTIVE SURVEILLANCE continued:

Considering that many well-selected men for AS may be followed without intervention for 7 to 10 years, this substitution would avoid repeated trauma, risk of infection, biopsy related scarring complicating subsequent surgery, and would address patient inconvenience and distaste for biopsies.

In his SUO 2013 presentation Meng offered his opinion on this subject:

> "The best way to incorporate MRI may be by using an initial MRI targeted biopsy to find clinically significant tumors. This will allow more accurate risk assessment prior to initiation of AS. MRI provides a high NPV [negative predictive value], the ability to avoid the need for confirmatory biopsy, and the potential to identify patients who may have more favorable outcomes based on the absence of MRI-detected lesions."

MRI studies with low suspicion scores, i.e. scores of 1 -2, have a high negative predictive value (NPV) for ruling out significant cancers. In various studies the NPVs range from 90%, 96%, 98%, to 100%.

With a baseline MRI as comparison, subsequent MRIs have the interpretative advantage of evaluating *patient-specific* changes in the size of the index lesion and changes in its density (i.e. the 'apparent diffusion coefficient' on which the grade of the lesion is determined). This information could be augmented by the rate of change of the PSA (PSA velocity) and change in the calculated PSA density.

A review article on the role of MRI in AS by Schoots, Klotz *et al., Eur Urol.* Nov 2014, states,

> "There are few data to assess the use of MRI as a monitoring tool during surveillance, so there is a need to define significant disease on MRI and significant changes over time."

In personal communication, Dr. Klotz, Professor, Department of Surgery, University of Toronto, kindly indicated studies that are in progress attempting to define and validate the issues which are necessary to support MRI at various points in a schema for AS relying on MRI:

1) the Canadian 'ASIST' trial, NCT01354171, currently 80% accrued, designed to evaluate the rate of upgrading of patients with an AS entry Gleason score of 6 to a score higher than 7 by comparing systematic TRUS-guided biopsies with MRI-targeted biopsies at one year;
2) the English 'PROMIS' trial, NCT01292291, designed to evaluate whether additional TRUS-guided systematic biopsies from regions beyond the MRI index lesion are necessary for diagnostic accuracy compared to MRI-targeted biopsies alone. A second objective is to determine the "proportion of men who could safely avoid biopsy as determined by specificity and negative predictive values;"
3) and a third planned large randomized Canadian trial of men with elevated PSA values comparing systematic TRUS biopsies with MRI biopsies only into regions of MRI suspicion.

CAVEAT:

The use of mpMRI pre-biopsy and its substitution for a TRUS-guided biopsy in monitoring AS are issues currently fraught with controversy. At the recent SUO14 meeting a panel was conducted and moderated by Dr. Klotz in which arguments pro and con were presented: "Should MR be the standard of care before biopsy?" The pro, argued by Dr. Taneja, NYU School of Medicine, closely followed the material presented above.

CAVEAT continued:

Dr. Stephenson, Cleveland Clinic, assumed the role of the 'devils advocate' saying: not all studies report greater accuracy of MRI over standard systematic biopsy; a MRI targeted biopsy misses 14% of significant cancers and may need to be combined with systematic biopsies; the data regarding upgrading and missing cancer has wide variation when comparing the MRI and TRUS systems; the negative predictive value for MRI in finding significant disease can be as low as 19-48% in comparison to much higher values reported to be in the 90+ range — and at the Cleveland Clinic adding an MRI to guide an initial biopsy MRI raises the cost by 25%.

Clearly future studies will be required to resolve these different positions.

BOTTOM LINE: The use of a targeted mpMRI biopsy before patient selection for AS has substantial evidential support. A role for MRI in monitoring patients during AS is not ready as yet to become a recommendation in the NCCN guidelines. But the future for development and refinement in this area is promising. The goal of employing mpMRI to reduce unnecessary biopsies and achieve greater biopsy accuracy in diagnosis is worthy. It would be surprising if future developments did not proceed in that direction.

YOUR PSA IS "UNDETECTABLE: " What Does That Mean? How Does An "Undetectable" PSA Affect Management?

The Measurement:

It used to be simple. An "undetectable" PSA pf <0.1 ng/mL 4 - 6 weeks after surgery carried an encouraging bit of reassurance of a clean removal and a good prognosis.
But … no more!

The more sensitive the assay, the shorter the period of this reassurance. The values have steadily lowered from concern at levels >0.01 (beginning in the 1990s), then to >0.006 or even to >0.008, and currently to >0.003 (the AccuPSA). That represents 3 picograms/mL — an amazing 3 trillionth of a gram! Tests that report results in picogram range are termed 'fourth generation'.

Next came a remarkable radioimmune assay with a detection cutoff of <1 pg/mL.
Even more notable is a "fifth-generation" test employing a digital immunoassay with single-molecule counting, said to have a limit of quantification (LoQ) of <0.05 pg/mL!

Studies of each of these tests come replete with data on the prediction of biochemical recurrence in relation to values higher or lower than the test's lower limit of detection.

PSA 'Progression': What Is the Appropriate Threshold for Declaring 'Progression'?

In the 'old days' PSA progression after surgery, i.e. biochemical failure, was stipulated when a PSA rose above the comfortable but arbitrarily chosen level of >0.2 ng/mL. This continues as the definition currently used in reporting most clinical trials. A threshold of >0.4 ng/mL had even been suggested at the Mayo Clinic because of studies that showed that 50% of men between 0.2 and 0.4 ng/mL did not progress. Dr. Tom Stamey in l996 published data based on persisting PSA in men thought to be cured of prostate cancer after surgery.

PSA 'Progression': What Is the Appropriate Threshold…..continued:

Using a test sensitive to >0.002 ng/mL, he concluded that only PSA values above 0.07 ng/mL should be regarded as indicating residual prostate cancer.

However, now PSA progression may be declared at any level that exceeds the lower limit of detection in any of these ultra- and very ultrasensitive tests, since the application of the term 'undetectable' carries the reciprocal implication that PSA is 'detectable' above the lower test limit. What clinical interpretation and management decisions should result from test values above and below these lower limits of detection?

What About Assay Variability in Sequential Tests?

The utilization of ultrasensitive assays, such as the remarkable lower limit of detection of <0.003 ng/mL, raises the question of the utility and *interassay* reproducibility, i.e as in sequential testing. Drs. Wilson, Partin, *et al.* address this issue in their article,"Fifth-Generation Digital Immunoassay for Prostate-Specific Antigen by Single Molecule Array (SiMoA)Technology (*Clinical Chemistry.* Oct 2011 - free full text online). When discussing tests reported in the pg/mL range, i.e., <0.003 pg/mL, they indicate that the functional day-to-day limit of quantification may vary as much as +/- 20%.

Their motivation for pursuing a very ultrasensitive assay was evidence that "suggests, however, that more sensitive determination of PSA status following RP could improve assessment of patient prognosis and response to treatment and better target secondary therapy for those who may benefit most."

Studies Relating Ultrasensitive PSA Values to Prediction of Biochemical Recurrence (BCR):

Current studies have considerably lowered the bar for designating the nadir PSA level post-RP that should raise concern. In his article using the 'fifth generation' SiMoA test with a detection sensitivity in the 0.001 ng/mL range, Wilson seemed comfortable in regarding men whose post-RP PSA was below 0.01 ng/mL (correct as written) as likely cured, especially if the low value remains steady over time. This would represent a considerably lower bar than the 0.07 ng/mL suggested by Stamey.

The maintenance of a post RP PSA below 0.01ng/mL was also endorsed by Doherty *et al. (British Journal of Cancer* 2000) as a useful indicator of relapse free survival: "Only 2 patients with an undetectable [i.e. <0.01 ng/mL] prostate-specific antigen after radical prostatectomy had biochemical relapsed (3%), compared to 47 relapses out of 61 patients (75%) who did not reach this level." Their 5 year data suggests that maintenance of a PSA <0.01 for 2 years predicts a high likelihood of long-term disease free survival.

Partin *et al. (BJU Int* June 2012) have taken the issue to a further lower level. In a study of 31 patients they reported that 100% of men with a post-RP mean nadir AccuPSA of <0.003 ng/mL were free of biochemical recurrence compared (BCR) compared to 62% of men with a PSA above that level. "Those men without evidence of BCR had a minimum of 5 years' PSA follow-up." The mean nadir for non-recurrence was 0.0023 pg/ml compared to 0.047 pg/mL for those with BCR. Their conclusion: "The AccuPSDA assay predicts 5-year BCR-free survival after RP."

Studies Relating Ultrasensitive PSA Values to…Prediction of BCR continued:

All articles (see Wilson, Doherty, and Partin, above) agree that PSA doubling times in the ultrasensitive range are unreliable for supporting clinical management decisions. This was especially addressed by Carroll *et al.* (J Urol.*2011 Oct): "*Poor Agreement of Prostate Specific Antigen Doubling Time Calculated Using Ultrasensitive Versus Standard Prostate Specific Antigen Values" [i.e., PSA doubling times calculated in the range >0.2 ng/mL].

The only safe generalization continues to be that the lower the nadir PSA, the more likely the patient will enjoy long-term BCR-free survival" (Wilson, ibid).

What is the *Clinical Utility* of the Ultrasensitive PSA tests?

Clearly a post-RP PSA value above various ultra sensitive thresholds, i.e. ranging from >0.01 ng/mL to >.003 ng/mL have probability implications for biochemical recurrence in men with positive surgical margins and for the presence of residual cancer.

Furubayashi *et al. (Oncol Lett.* Nov 2014) addressed the implication of ultrasensitive PSA values as regards positive surgical margins. They reported a study of 239 men with one or multiple positive surgical margins. Of those whose PSA nadir was <0.008 ng/mL 93% of men with single or multiple positive margins remained free of recurrence while 46% with a higher value had a BCR. The median follow-up period was 53.8 months. The risk for recurrence was 11X for men with multiple positive margins whose PSA nadir was >0.008 ng/mL vs lower.

In *Urology* 1997 Oct Drs. Ellis, Lange *et al.,* assayed (with a sensitivity <0.008 ng/mL) sera from 29 men post cystoprostatectomy and compared the results with men post radical prostatectomy as controls. The surgical patients had been free of recurrent disease for 5 years. PSA levels for cystoprostatectomy patients were <0.008 ng/mL in 86.2% and <0.008 ng/mL in 96% of the 'cured' prostatectomy patients. These data supported the findings of Furubayashi using the same low PSA value.

Limited Practical Applications Currently Available.

The available clinical applications based on these very low ultrasensitive assays currently do not match this exquisite assay technology. Salvage radiotherapy would likely be chosen as the appropriate treatment when the prediction of recurrence is substantial. However, in their 2007 JCO study, "Predicting the Outcome of Salvage Radiation Therapy for Recurrent Prostate Cancer After Radical Prostatectomy," Stephenson *et al.* supported initiating radiation treatment at PSA levels of 0.5 ng/mL or lower, a value that is 2 logs higher than ultrasensitive levels. Current practice of initiating salvage radiation therapy follows that guideline today.

It is possible to speculate that immunotherapy, which is considered best applied when the tumor burden is lowest, may become an effective modality to be prescribed for men in whom BCR is predicted based on ultrasensitive assays. But the state of the art for this modality is not nearly ready to address this task.

BOTTOM LINE: It is becoming standard to measure postoperative PSA values with the almost unbelievable sensitivity of several picograms. Clearly values in this range can provide predictive information and can be satisfying (or not) for the surgeon. PSA values above or below a stipulated value can be a source of reassurance — or anxiety, for men, especially when a value might be edging upward in picogram increments. However, the state of the oncological art is not ready to effectively accommodate these very low values. Until then, a rise in PSA above 0.01 ng/mL is the value to appropriately raise concern.

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