Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

MP-MRI lesions suspicion scoring

Lesions identified on MP-MRI were examined on triplanar T2-weighted (T2W), diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE), and MR spectroscopy sequences. MRI suspicion was assigned to each lesion according to findings on these four sequences as outlined in **eTable 1**. MRI suspicion scoring has been correlated with both the presence of cancer (5% prevalence for low suspicion, 21% for intermediate suspicion, and 54% for high suspicion)[1] as well as an increased risk of high-grade disease[2].

Decision Curve Analysis

Decision curve analysis (DCA) is an analytic method for comparing different diagnostic strategies with regards to maximizing clinical utility[3]. The wider topic of decision analysis is often a challenging topic as comparing harms and benefits from a procedure such as a radical prostatectomy often requires deriving valuation on different harms and benefits. In the case of this study, harms of radical prostatectomy such as incontinence, impotence, and recovery from surgery in cases where surgery was perhaps not optimal (low-risk disease) would have to be compared against the benefits of treatment of intermediate/high-risk cancer. The topic becomes even more challenging with a heterogeneous population amongst whom individuals may have very different valuation on the different aspects of the analysis. For example, a man with poor erectile function may have different concern regarding impotence compared to a sexually active man with no erectile dysfunction.

DCA seeks to address these valuation challenges by utilizing a measure called the threshold probability (p_t). In this study, p_t is the probability of intermediate to high-risk prostate cancer at which an individual would believe the potential harms of side-effects from overtreatment of low-risk disease are equal to the potential benefits of treating intermediate/high-risk prostate cancer. This p_t can vary from individual to individual; the male with poor erectile function may be less concerned about side effects and have a p_t of 30% for example (i.e. if there was a 30% risk of intermediate- to high-risk prostate cancer, this individual would be willing to undergo the surgery knowing the risks of complications). On the other hand, a healthy, sexually active male may have a p_t of 60%. The benefit of using p_t rather than attempting to place valuation on the various aspects of the associated harms and benefits of treatment is that it allows for individual global processing of all the factors, measured and unmeasured, and express that personalized decision in the form of a summary variable that can be compared between individuals. The use of a summary variable such as the p_t allows for incorporation of any and all factors important to the patient (complications from surgery, comorbidities, age, life expectancy, social situation, etc.) to be captured in the form of an overall preference. The p_t can be analyzed over the full range from 0 to 1 thus incorporating all possible patient preference.

In this study, the DCA was used to compare five decision making approaches to determine which biopsy approach in patients biopsied for suspicion of prostate cancer would yield the greatest net benefit. The decision in question is whether an individual should undergo radical prostatectomy. A “good decision” for prostatectomy was determined to be if the patient had intermediate or high-risk prostate cancer on the final prostatectomy pathology specimen and underwent the surgery (True Positive). A “bad decision” for prostatectomy was defined to be if the patient had low-risk disease which could have been monitored by active surveillance, but for

which the patient underwent radical prostatectomy and was thus exposed to the potential complications of surgery unnecessarily (False Positive). The decision-making strategies compared in DCA shown in the **eFigure** were: 1. Treat everyone with any cancer detected using any of the biopsy techniques (Treat all). 2. Treat no one regardless of what any biopsy demonstrated (Treat none). Lastly, treat the patient if the biopsy technique of interest (3. Targeted MR/US fusion alone, 4. Standard extended-sextant biopsy alone, or 5. the two techniques combined) demonstrated intermediate to high-risk prostate cancer, but do not treat if the biopsy showed low-risk or no cancer.

Net benefit is measured as the rate at which the decision making approach guides the patient and physician to make a good decision minus the rate at which the decision making approach guides to make a bad decision with an adjustment factor based on the p_t to account for the relative harm due to the decision to not treat the cancer versus endure the side effects of a radical prostatectomy (living with the risk of cancer progression from intermediate/high risk cancer is not the same as living with erectile dysfunction and/or incontinence, and the p_t reflects the relative weight each individual puts on these types of competing risks). The result is a net rate at which true positive decisions are made without any harm to other men. In this way for example in this study, at a p_t of 0.5, the net benefit of using the MR/US fusion biopsy was approximately 0.3 **(eFigure).** This means that for every 100 men who are evaluated using targeted biopsy as compared to a treat no one strategy, 30 additional men would be treated appropriately with a radical prostatectomy for intermediate to high-risk disease without performing any additional prostatectomies on men with low-risk disease. At the same p_t of 0.5, the net benefit was approximately 0.15 for standard biopsy. Accordingly, at p_t of 0.5, the net benefit of using targeted biopsy versus standard biopsy is 0.3-0.15 = 0.15, or 15 additional men

for every 100 evaluated who undergo a radical prostatectomy correctly for intermediate/high-risk disease without any further surgery for low-risk disease. The net benefit can range from as high as the incidence of intermediate/high risk disease in the global population, but can also be negative in cases where the test leads to more false positive than true positive decisions. The net benefit can also be negative in cases where the dislike of complications and harms is much greater than the benefits of removing a prostate gland with intermediate/high risk prostate cancer such as at high values of p_t.

In such a way, the optimal strategy for maximizing clinical utility is to examine which approach yields the highest net benefit for each given p_t. We therefore see in the **eFigure** that for low values of p_t between 0 and 0.3 (i.e. in situations where the fear of the cancer is greater and the patient is willing to take the risk of complications even if there is just a small chance of intermediate to high-risk disease), the strategy to treat all men diagnosed on any biopsy with cancer, even low-risk disease, yields the optimal net benefit. Between the p_t range of 0.3 to about 0.75, the optimal strategy was to follow the targeted MR/US fusion biopsy result to guide treatment decision. In this range, a result of intermediate/high-risk prostate cancer on targeted biopsy should be treated with surgery, and no cancer or low-risk disease should not be treated with surgery. After a p_t of 0.75, the dislike of the complications from surgery are so great in the patient that no matter what the biopsy shows, the optimal decision is to not treat the tumor. In this way, within the clinically relevant range in which the optimal strategy was not either to treat all men or treat no one, targeted biopsy was superior to both standard biopsy, and also the two approaches combined in guiding decision making for radical prostatectomy.

Alternate risk stratification

Alternative methods of risk-stratification were examined to confirm that the outcome of the study was independent of the risk-stratification used. Equivalent results were obtained utilizing the various risk-stratification paradigms. When patients were stratified into low-risk as Gleason 6, intermediate-risk as Gleason 7, and high-risk as Gleason ≥ 8, targeted biopsy diagnosed 27% more high-risk tumors (143 versus 104, $p<0.001$) and 29% fewer low-risk tumors (147 versus 206, $p<0.001$). The same relationship persisted if the risk-stratification system of CAPRA scores[4] were examined in that targeted biopsy diagnosed 36% more high-risk (CAPRA score ≥6) tumors (162 versus 103, $p<0.001$) and 27% fewer low risk tumors (CAPRA score 0-2, 117 versus 161, $p<0.001$).

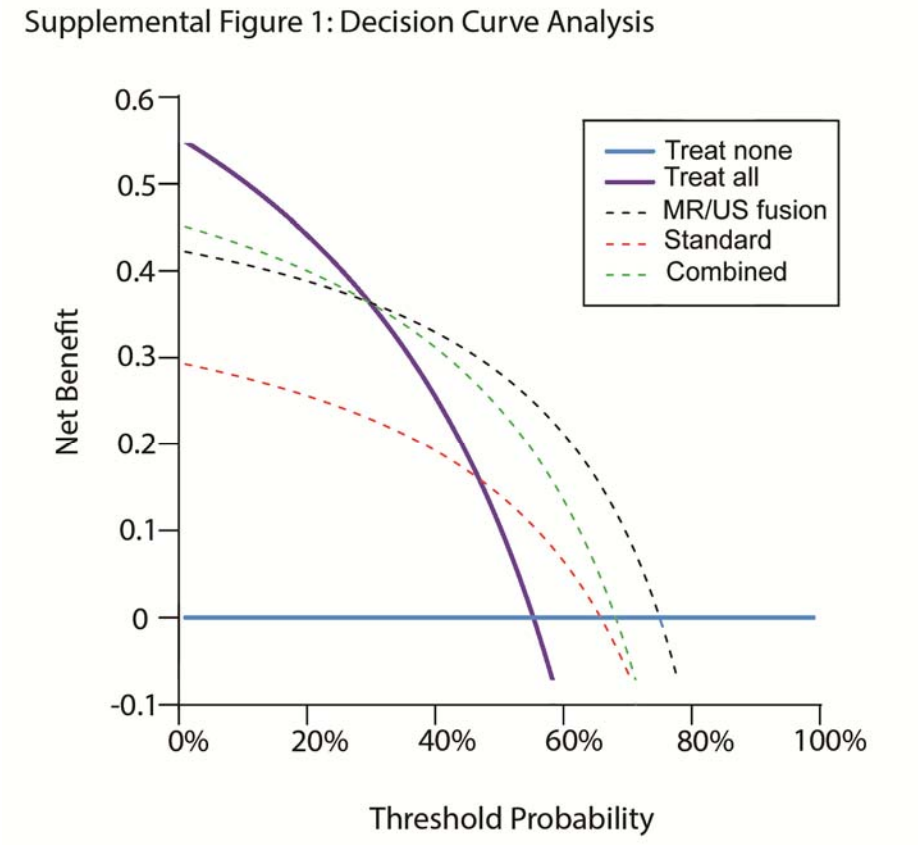
eTable 1: Chart of MP-MRI sequence findings to suspicion level

Findings on MP-MRI sequence				MP-MRI suspicion level
T2W	ADC Map of DWI	DCE	MR Spectroscopy	
-	-	-	-	Negative
+	-	-	-	Low
+	+	-	-	Low
-	+	-	-	Low
-	-	+	-	Low
-	-	-	+	Low
+	-	+	-	Moderate
+	-	-	+	Moderate
-	+	+	-	Moderate
-	+	-	+	Moderate
-	-	+	+	Moderate
+	+	+	-	Moderate
+	+	-	+	Moderate
+	-	+	+	Moderate
-	+	+	+	Moderate
+	+	+	+	High

eTable 2: Effect of adding standard extended-sextant biopsy to risk group stratification from a baseline risk determined by targeted MR/US fusion prostate biopsy. Risk groups were no cancer, low-risk, intermediate-risk, and high-risk cancer.

	Total Cohort (1003 patients)	**No Prior Biopsy Cohort (196 patients)**
No Change	857 (85.4%)	168 (85.7%)
Upgraded to Low-Risk	86 (8.6%)	10 (5.1%)
Upgraded to Intermediate-Risk	41 (4.1%)	11 (5.6%)
Upgraded to High-Risk	19 (1.9%)	7 (3.6%)

eFigure: Decision curve analysis demonstrating the net benefit, as measured by rate of treating men for intermediate to high-risk prostate cancer with no additional surgery for low-risk disease, using the five decision-making strategies as listed in the legend. Threshold probability is the threshold probability of intermediate to high-risk prostate cancer at which an individual considers the benefit of treatment for intermediate to high-risk disease equivalent to the harm of overtreatment for low-risk disease, and thus reflects how the individual weights the benefits and harms associated with this decision. The highest curve at any given threshold probability is the optimal decision-making strategy to maximize net benefit. Net benefit was maximized between threshold probabilities of 0%-30% by the "Treat all" approach, between threshold probabilities of 30% to 75% net benefit was maximized by the targeted MR/US approach, and between 75% and 100% net benefit was maximized by the "Treat none" approach.



References

1. Pinto PA, Chung PH, Rastinehad AR, et al. Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancer detection following transrectal ultrasound biopsy and correlates with multiparametric magnetic resonance imaging. *The Journal of urology.* Oct 2011;186(4):1281-1285.
2. Rais-Bahrami S, Siddiqui MM, Turkbey B, et al. Utility of multiparametric magnetic resonance imaging suspicion levels for detecting prostate cancer. *The Journal of urology.* Nov 2013;190(5):1721-1727.
3. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making.* Nov-Dec 2006;26(6):565-574.
4. Cooperberg MR, Pasta DJ, Elkin EP, et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. *The Journal of urology.* Jun 2005;173(6):1938-1942.