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UNIVERSITY OF CALIFORNIA,
IRVINE

Validation of 90-Day Percent Erection Fullness as a Predictor of Long-Term Potency
Recovery after Robot-Assisted Radical Prostatectomy

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

Linda My Huynh

Thesis Committee:
Professor Dr. Thomas Ahlering, Chair
Professor Dr. Sheldon Greenfield
Assistant Professor Dr. Cory Hugan

2018

DEDICATION

To my family, mentors, colleagues, and friends
in deep recognition of their support

The fact that progress has actually been made,
in the most part,
by ordinarily clever people,
building step by step from the work of their predecessors
makes the story more remarkable.

John Gribbin
"Science: A History"

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LIST OF KEY ABBREVIATIONS

CI	: Confidence Interval
HIPAA	: Health Insurance Portability and Accountability Act
ED	: Erectile Dysfunction
ESI	: Erections Sufficient for Intercourse
EPIC-CP	: Expanded Prostate Cancer Index for Clinical Practice
IIEF-5	: International Index of Erectile Function 5
IRB	: Institutional Review Board
Pca	: Prostate Cancer
RARP	: Robot-assisted radical prostatectomy
RP	: Radical prostatectomy
SPSS	: Statistical Package for Social Science
UCIMC	: University of California, Irvine – Medical Center

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<https://onlinelibrary.wiley.com/doi/full/10.1111/bju.14190>

ABSTRACT OF THE THESIS

Validation of 90-Day Percent Erection Fullness as a Predictor of Long-Term Potency
Recovery after Robot-Assisted Radical Prostatectomy

By

Linda My Huynh

Master of Science in Biomedical and Translational Science

University of California, Irvine, 2018

Professor Thomas E. Ahlering, Chair

Objective: To introduce a patient-reported percent erection fullness scale (% fullness) following robot-assisted radical prostatectomy (RARP) as a qualitative adjunct to the International Index of Erectile Function - 5 (IIEF-5) questionnaire and as a 90-day predictor of two-year potency outcomes.

Patients and Methods: Prospective data was collected from 540 men with normal preoperative sexual function (defined as an IIEF-5 score between 22 and 25) who underwent RARP by a single surgeon, of which 299 had complete data at all follow-up time points. In addition to standard assessment tools (IIEF-5 and erections sufficient for intercourse), patients were asked to "indicate the fullness you are able to achieve in erections compared to before surgery?" (0-10...100%). The primary outcome was prediction of potency (defined as ESI) at 24 months, based on 90-day % fullness tertiles (0-24%, 25-74%, and 75-100%).

Results: 299 men with complete follow-up were included in initial analysis. Significant predictors of 24 month potency included age, BMI, pathologic stage, nerve-sparing status, and % fullness tertiles. In multivariable analysis, % fullness demonstrated excellent prediction of 2-year potency recovery ($R^2=0.89$) and internal validation suggests good

discrimination (AUC = 0.83). Repeated analysis in the full patient cohort (n=540) yielded similar results.

Conclusions: We introduce % fullness as a qualitative adjunct to the IIEF-5 and as a 90-day predictor of two-year potency recovery post-RP. This initial report is hypothesis-generating such that the use of % fullness enables the identification of men most likely to benefit from early, secondary intervention.

I. INTRODUCTION

1.1 Background

Erectile dysfunction (ED) is commonly encountered following radical prostatectomy (RP), varying dramatically from 12 to 96% of patients and dependent upon patient demographics, surgical technique, and surgeon skill and experience. [1-4] While the need to use validated questionnaires to assess preoperative sexual function has already been established, there is a lack of consensus regarding assessment of sexual function recovery following RP. [5-8] This is particularly problematic in men with normal preoperative sexual function (as defined as an International Index of Erectile Function-5 score between 22 and 25) as erectile dysfunction post-RP is of major consequence to patients' quality of life. [9] While men with early (within 90-days post-RP) recovery of potency maintain long-term potency, men with partial erection recovery have no early predictors of long-term potency recovery. [6-7]

1.2 Current Methods of Assessing Potency Recovery

In recent years, the management of post-RP patients has experienced a paradigm shift from objective, quantitative methods of assessing perioperative sexual function to subjective, qualitative patient-reported outcomes [1, 4-5]. Presently, there are three methods of assessing potency recovery post-RP, each with its own advantages and disadvantages (Table 1).

The most heavily used assessment tool for postoperative sexual function is the International Index of Erectile Function-5 questionnaire (IIEF-5) [6]. Originally developed as an appended version of the IIEF-15, the IIEF-5 measures a patient's confidence,

frequency, and satisfaction with regard to sexual function over the past four weeks (Appendix A). While well validated to assess the efficacy of erectile dysfunction medications such as sildenafil and tadalafil [7], the IIEF-5 has not been validated for the assessment of sexual function recovery in post-RP patients. Other limitations of the IIEF-5 include partial responses, a lack of consensus in recovery thresholds, and a narrow distribution of patients scoring IIEF-5 < 3 immediately post-RP. Patients who do not have a sexual partner, for example, cannot answer IIEF-5 questions 2 through 5, which reduces the maximum score from twenty-five to five, thus decreases the ability of the scale to capture clinically significant changes in sexual function recovery. In this regard, it has been suggested that a categorical assessment of patients with the IIEF-5 may be advantageous when considering men for secondary interventions for erectile dysfunction [7]. However, there is little consensus regarding the thresholds that offer the highest sensitivity, specificity, and predictive values. Categorization of IIEF-5 scores 15, 17, and 22 are commonly suggested, but the clinical significance of an IIEF-5 score 15 versus a 17 remains debatable [5]. Furthermore, at 90-days post-RP, 65-75% of men report scores <15, poorly discriminating partial return of erections or, more importantly, the ultimate likelihood of potency recovery [9].

At present, the only validated questionnaire for the assessment of sexual function recovery post-RP is the Expanded Prostate Cancer Index for Clinical Practice (EPIC-CP). Seldom used in a clinical setting, however, the EPIC-CP is long, cumbersome, and results are difficult to interpret [10]. An alternative is two questions extracted from the EPIC-CP, commonly referred to as "erections sufficient for intercourse" (ESI): "are your erections

firm enough for penetration?" and "are they satisfactory?" [12]. As the most commonly used questionnaire among robotic surgeons, an affirmative ESI is associated with durable recovery of sexual function after robot-assisted RP [10, 12]. Although these two questions effectively distinguish patients who have recovered functional potency at any given time point, interpretation remains limited to a dichotomous "yes" or "no". As such, patients who answer Yes/No or No/Yes to the two questions may or may not have partial return of erections, making it significantly more difficult to track partial recovery and establish need for further treatment.

Table 1: Current questionnaires assessing post-radical prostatectomy sexual function

	Description	Advantages	Disadvantages
Erections Sufficient for Intercourse (ESI)	Two questions: <ul style="list-style-type: none"> - Are your erections firm enough for penetration? - Are they satisfactory? 	<ul style="list-style-type: none"> - Highest response rate - Most effective in identifying potent patients 	<ul style="list-style-type: none"> - Does not discern partial erection recovery
International Index of Erectile Function -5 (IIEF-5)	Five questions assessing confidence, frequency, satisfaction, firmness, and maintaining erections during sexual intercourse	<ul style="list-style-type: none"> - Most commonly used - Can be assessed continuously or categorically - Common categorical cutpoints 15, 17, or 22 	<ul style="list-style-type: none"> - Limited use in sexually inactive patients - Variable definitions for potency
Expanded Prostate Cancer Index for Clinical Practice (EPIC-CP)	Sixteen questions, with five sub-sections for urinary, obstructive, bowel, and vitality / hormonal symptom scores.	<ul style="list-style-type: none"> - Validated for use in prostate cancer - Includes subsections on bowel , vitality, and hormonal symptoms 	<ul style="list-style-type: none"> - Lowest response rate - Difficult to interpret and target interventions

A priori, the ideal questionnaire for assessing sexual function recovery post-RP should have three characteristics. First, the questionnaire must be simple, easy to use and

easy to interpret. Second, the questionnaire should be an early predictor (within 90-days post-RP) of long-term recovery outcomes. While sexual function recovery post-RP may take up to 24 months, secondary therapies for erectile dysfunction are most effective and will greatly enhance patient quality of life as early as 3 months post-RP [10]. Finally, and along similar lines, the questionnaire should be able to distinguish between those with partial erection recovery, as early risk stratification can significantly enhance patient counseling and decision-making. Such a questionnaire could and would be a useful adjunct to the IIEF-5: capturing the five domains of sexual function via confidence, frequency, satisfaction, firmness, and maintenance of erections, while also providing the sensitivity of “sliding scale” to assess partial erection recovery post-RP.

1.3 Specific Aims and Objective

In 2004, we recognized the need for a qualitative adjunct in assessment of post-RP sexual function recovery and introduced a single-item percent erection fullness scale (% fullness): “please indicate the fullness you are able to achieve in your erections at this time, compared to before surgery: 0, 10, 20 ... 90, 100%”. Over time, we recognized the potential of percent erection fullness as a more complete description of partial erection recovery at 90 days post-RP and, therefore, expanded our experience to utilize 90-day % fullness as a metric for 2-year potency outcomes. The present study seeks to validate the use of 90-day % fullness as a qualitative adjunct to existing measures of erectile function (i.e. the IIEF-5 and ESI questionnaires) and as a stand-alone metric to predict 2-year potency recovery post-RP, as defined as two affirmative answers to ESI.

II. PATIENTS AND METHODS

2.1 Study Design

This is a retrospective cohort analysis of prospectively collected data. Data were prospectively collected and entered into an electronic database under approval from an institutional review board protocol (HS# 1998-84) and compliance with the Health Insurance Portability and Accountability Act was maintained. From 2004 through 2014, all men with pre-operative IIEF-5 scores between 22 and 25 undergoing robot-assisted radical prostatectomy (RARP) by a single surgeon at our institution were initially enrolled. Perioperatively, all patients were prescribed a standard of care, daily low dose of phosphodiesterase-5 (PDE-5) inhibitors (tadalafil and sildenafil) to enhance blood flow and encourage sexual function recovery post-RP. All men using any other erectile dysfunction therapies, including penile rehabilitation and/or erectile dysfunction medications beyond the daily dose of PDE-5 inhibitors were excluded from analysis.

2.2 Outcome Measurement

Pre-operative erectile function was assessed via the IIEF-5 questionnaire. Post-operative recovery of erectile function was assessed post-RP at Months 3, 9, 15 and 24 using the three patient-reported and self-administered assessment tools: (1) two components of the erections sufficient for intercourse (ESI) questionnaire: "*are your erections firm enough for penetration?*" and "*are they satisfactory?*", (2) the IIEF-5 questionnaire, and (3) percent erection fullness: "*please indicate the fullness you are able to achieve in your erections at this time, compared to before surgery: 0-100%.*" All responses were obtained via paper surveys mailed directly to our office; secondary phone calls were

conducted by study staff to maximize response rates. Response rate was defined as responses both to primary survey questionnaires and secondary interventions; similarly, patients were only defined as a loss to follow-up if they did not answer either method of follow-up.

Potency was defined by two affirmative answers to ESI. Patients were assessed for sexual function at all time points, such that should a patient have achieved potency at an early visit, he would still have been reassessed for sexual function at subsequent follow-up visits through the 24-month period. If a patient achieved potency at Month 9 or Month 15 and did not respond to Month 24 questionnaires, it was assumed that he would have maintained potency. This method of assessment is consistent with previous studies, as ~99% of men who recover ESI post-RP maintain ESI long-term [10].

2.3 Statistical Analysis

Prior to analysis, a set of variables posited to be potential confounders of sexual function recovery were identified from literature review and expert comment. These included: age, pre-operative IIEF-5 score, pre-operative prostate specific antigen (PSA) level, body mass index, pathologic stage, pathologic Gleason grade, and nerve-sparing status. All variables were normally distributed via visual assessment of histograms, and thus were summarized with frequencies and proportions (Fisher's Exact Test) and means and standard deviations (independent samples t-test).

Pair-wise t-tests and comparison of proportions were used to identify significant covariates and a correlation matrix was examined to test for associations between each variable and potential confounder. A simple regression was used to assess unadjusted

correlation between 90-day percent erection fullness and 2-year potency recovery.

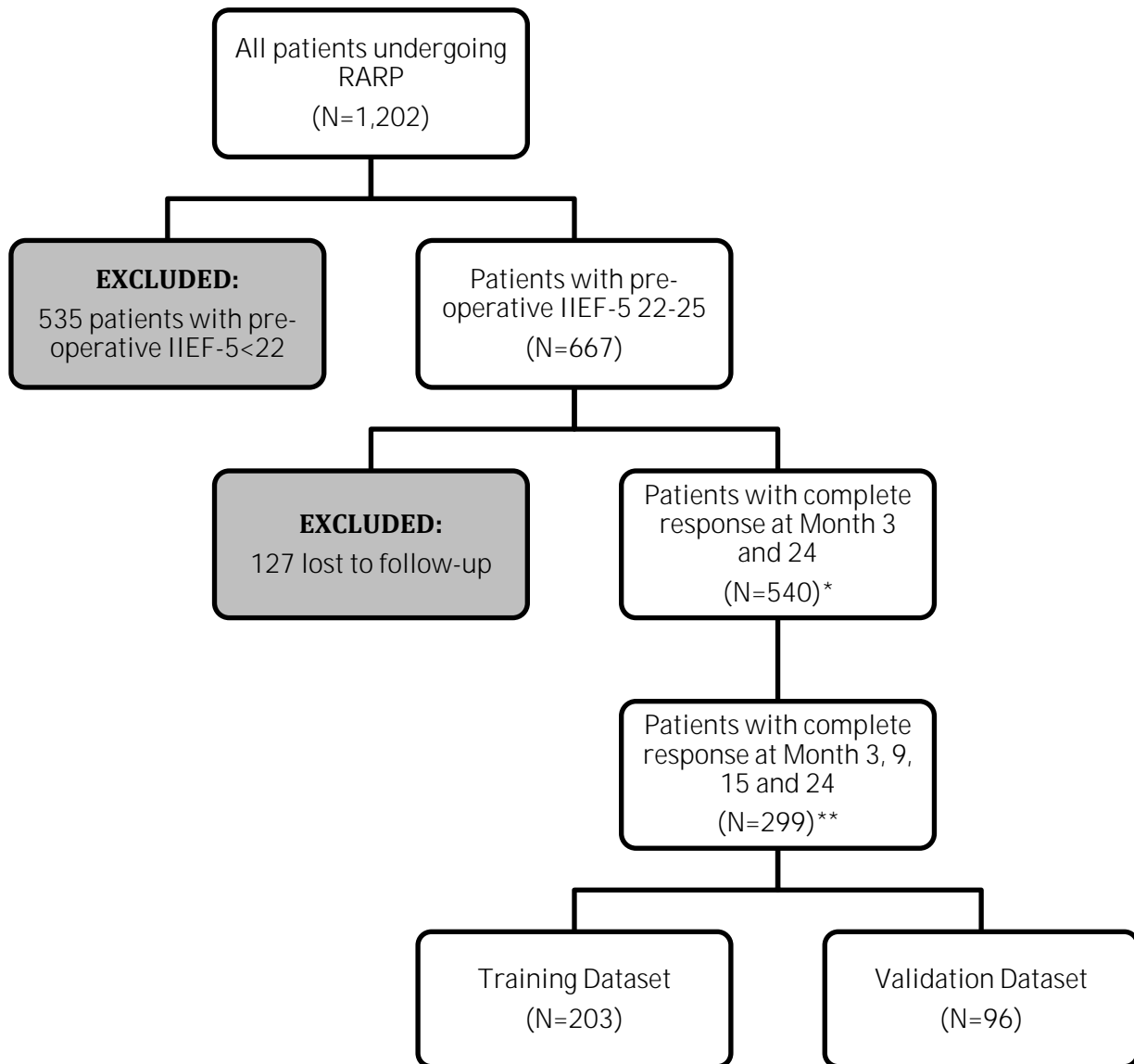
Following, a multivariable logistic regression model was utilized to adjust for significant covariates.

The primary outcome measure was the goodness of fit and coefficient of multivariable regression modeling of 2-year potency outcomes, as adjusted for covariates. The secondary outcome measure was sensitivity of the final multivariable model, as compared to the current standard of care IIEF-5 questionnaire. All patients who were impotent at 3 months were subsequently assessed in an exploratory subset analysis to examine the utility of 90-day percent erection fullness as an adjunct to the 90-day IIEF-5 questionnaire.

2.4 Validation Dataset

Initial statistical analysis and internal validation was performed only in patients with complete follow-up at Months 3, 9, 15, and 24 post-RP (N=299). Confirmatory analysis and supplemental modeling was subsequently performed in patients with complete follow-up at Months 3 and 24 post-RP (N=540), regardless of varying response rates at Month 9 and 15. Because this is the first study to formally assess percent erection fullness as a measure of partial recovery of sexual function, however, patients with complete responses at all intermediate time-points are prioritized in data presentation and discussion. Figure 1 depicts the inclusion and exclusion criteria for each dataset and the subsequent datasets used for internal validation.

Figure 1: Inclusion and Exclusion Criteria



* Predictive model of 90-day % fullness was developed in this dataset

**Predictive model of 90-day % fullness was validated in this dataset.

Internal validation of the 299 patients with complete responses was performed by splitting the original data set into two portions via random number generation in Statistical Package for the Social Sciences, Version 2.4 - a "training dataset" (N=203) and "validation

data set" (N=96). A logistic regression model was developed after accounting for significant covariates in the training set and was then used to estimate 2-year potency recovery for each patient in the validation set. A risk score was calculated by multiplying each variable in the multivariate model by its coefficient (natural logarithm of odds ratio) and summing the products. This risk score (RS) was then used to compute the odds of 2-year potency recovery using the formula, $\text{Odds}(2\text{YearPotency}) = e^{\text{RS}}$. Odds were then converted to a probability using the formula, $[\text{Pr}(2\text{YearPotency})], \text{Pr}(2\text{YearPotency}) = \frac{\text{Odds}(2\text{YearPotency})}{1 + \text{Odds}(2\text{YearPotency})}$. ROC analysis was used to evaluate the performance of the continuous risk models in discriminating patients who would ultimately recover potency at their 24-months post-RP.

III. RESULTS

3.1 Study Cohorts

From 2004 to 2014, 1,202 patients underwent robot-assisted RP by a single surgeon at our institution, of which 667 (55.5%) had normal pre-operative sexual function as defined by an IIEF-5 score between 22 and 25.

Of the 667 patients, 540 (81.0%) had sexual function recovery follow-up in all three methods of assessment at Month 3 and Month 24 post-RP. A total of 299 (44.8%) patients had complete follow-up at Month 3, 9, 15, and 24 post-RP and were included in the main analysis presented below. Of note, prior to exclusions, 90-day response rates to percent erection fullness (96%) and ESI questionnaires (92%) were significantly higher as compared to complete responses to the IIEF-5 questionnaire (81%). In this regard, there were no patterns to confirm ordering bias or fatigue effects of these questionnaires.

3.2 Baseline Characteristics

Of the 299 patients with complete sexual function follow-up at all time points, 216 (72.2%) regained potency by 24 months, as defined as two affirmative answers to the ESI questionnaires. Table 2 depicts significant differences between the 24-month potent versus non-potent patient groups, with regard to age, pre-operative IIEF-5 score, pre-operative prostate specific antigen (PSA) levels, pathological stage, seminal vesicle invasion, and nerve-sparing status ($p < 0.05$). While pathologic Gleason score did not differ significantly between the two groups, the impact of disease grade was considered to be a potential confounder of sexual function recovery and was ultimately included as a covariate in the final regression model.

Table 2: Baseline characteristics of patients with complete follow-up (N=299).

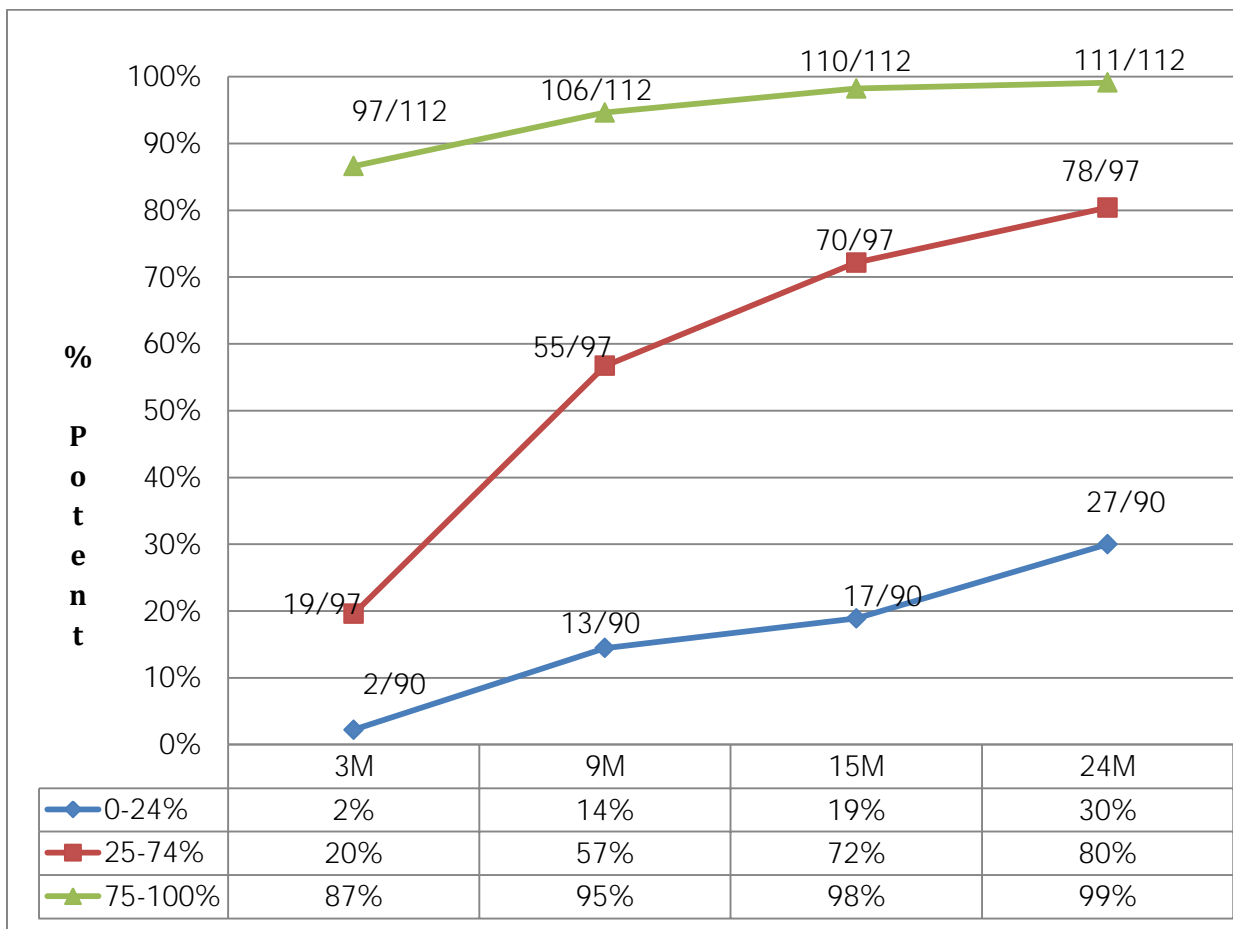
	Not potent (N = 83)		Potent (N = 216)		p-value
	Mean	SD	Mean	SD	
Age (years)	61.8	7.0	57.5	6.5	<0.0001
Pre-operative IIEF-5	24.1	0.9	24.4	0.9	0.0103
PSA (ng/mL)	6.9	6.3	5.6	3.5	0.0245
AUASS	7.2	6.7	7.3	6.6	0.9071
Bother Score	1.4	1.5	1.4	1.4	0.9786
Prostate Weight (g)	53.6	19.5	49.6	18.3	0.0976
Estimated Blood Loss	103.6	27.4	105.3	35.9	0.6969
Body Mass Index	27.3	3.2	26.7	3.2	0.1476
	N	%	N	%	p-value
Pathological Stage					0.0280
pT2	56	67.5	172	79.6	
pT3/pT4	27	32.5	44	20.4	
Pathological Gleason					0.0968
3+3	27	32.5	76	35.2	
3+4	31	37.3	94	43.5	
4+3	16	19.3	35	16.2	
4+4	9	10.8	11	5.1	
Seminal Vesicle Invasion					0.0114
Yes	5	6.0	2	1.0	
No	78	94.0	214	99.1	
Surgical Margin					0.7539
Positive	6	7.2	18	8.3	
Negative	77	92.8	198	91.7	
Nerve-sparing status					0.0067
None	2	2.4	0	0.0	
Unilateral	15	18.1	21	9.7	
Bilateral	66	79.5	195	90.3	

*AUASS = American Urological Association Symptom Score

At Month 3 post-RP, patients were subsequently stratified into three percent erection fullness tertiles: 0-24%, 25-74% and 75-100%, with 90 (30.1%), 97 (32.4%) and 112 (37.5%) patients, respectively. Figure 2 demonstrates the potency recovery curves of

these 3-month % fullness tertiles for patients with complete responses at all follow-up time points (N=299). While patients reporting 0-24% fullness at 3 months demonstrated poor recovery (19%) throughout the first 15 months postoperatively, 30% ultimately regained potency by 24 months. Patients reporting 25-74% fullness at 3 months had low rates of potency recovery (72%) through 15 months, of which 80% regained potency by 24 months. Patients reporting 75-100% fullness at 3 months had low rates of potency recovery (72%) through 15 months, of which 80% regained potency by 24 months. Finally, for patients reporting 75-100% fullness at 3 months, 87% and 99% were “potent” at 3 and 24 months, respectively.

Figure 2: Potency recovery curves based on % fullness reported at 3 months, for patients with complete responses at 3, 9, 15, and 24 months (N=299)



3.3 Adjusted Potency Models

Table 3 depicts a multivariable logistic regression model of 2-year potency recovery, as predicted by Model 1, 90-day percent erection fullness tertile and Model 2, 90-day IIEF-5 score. In the 90 day percent erection fullness model, there were no significant covariates associated with recovery of 2 year potency, after accounting for 3 month percent erection fullness (OR 6.637, $p < 0.0001$). In contrast, in the 90 day IIEF-5 model, pathologic stage was a significant indicator of potency recovery (OR -2.287, $p = 0.023$), in addition to 3-month IIEF-5 score (OR 8.145, $p < 0.0001$). Overall, the 3-month percent erection fullness model had an adjusted R^2 of 0.378, while the 3-month IIEF-5 model had an adjusted R^2 of 0.294.

Table 3: Multivariable Logistic Regression Model of 2-year Potency, after adjusting for Significant Covariates

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	0.417	0.746		0.559	0.577
Age (continuous)	-0.005	0.004	-0.084	-1.342	0.181
Nerve-sparing (uni-[ref] vs. bilateral)	0.128	0.067	0.101	1.92	0.056
1 Pre-operative IIEF-5 (continuous)	0.024	0.027	0.047	0.877	0.381
BMI (continuous)	-0.009	0.007	-0.063	-1.229	0.22
p-stage (pT2 [ref] vs. pT3/T4)	-0.145	0.063	-0.143	-2.287	0.023
90-day month IIEF-5	0.022	0.003	0.44	8.145	<0.001
(Constant)	-0.224	0.963		-0.232	0.817
Age (continuous)	-0.011	0.006	-0.148	-1.908	0.058
Nerve-sparing (uni-[ref] vs. bilateral)	0.16	0.085	0.126	1.89	0.06
2 Pre-operative IIEF-5 (continuous)	0.049	0.035	0.091	1.427	0.155
BMI (continuous)	-0.009	0.011	-0.056	-0.877	0.382
p-stage (pT2 [ref] vs. pT3/T4)	-0.023	0.081	-0.023	-0.289	0.773
90-day % fullness (<24 [ref] vs. >25)	0.008	0.001	0.434	6.637	<0.001

a. Dependent Variable: Potency at 24 months

In addition to the above logistic regression models assessing predictability in all patients, subset analysis of patients who were impotent at 90 days was also conducted and depicted in Table 4. When utilizing only 90-day IIEF-5, the adjusted R² for Model 3 was 0.160. However, when combining both 90-day IIEF-5 and 90-day percent erection fullness, the adjusted R² for Model 4 increased to 0.251. This suggests that not only was percent erection fullness a strong predictor of long-term sexual function recovery, but also that it was a useful adjunct to the 90-day IIEF-5 score in determining those who were most likely to suffer from long-term impotency.

Table 4: Multivariable Logistic Regression Model of 2-year Potency for men who are impotent at 90-days, after adjusting for significant covariates

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
	-0.224	0.963		-0.232	0.817
	-0.011	0.006	-0.148	-1.908	0.058
	0.16	0.085	0.126	1.89	0.06
3	0.049	0.035	0.091	1.427	0.155
	-0.009	0.011	-0.056	-0.877	0.382
	-0.023	0.081	-0.023	-0.289	0.773
	0.008	0.001	0.434	6.637	0
	0.074	0.703		0.105	0.916
	-0.004	0.004	-0.067	-1.133	0.258
	0.119	0.063	0.094	1.907	0.058
	0.027	0.026	0.053	1.053	0.293
4	-0.007	0.007	-0.047	-0.982	0.327
	-0.093	0.06	-0.092	-1.557	0.121
	0.003	0.004	0.059	0.723	0.47
	0.006	0.001	0.49	6.005	0

a. Dependent Variable: Potency at 24 months

Figure 3 shows receiver operating characteristic (ROC) curves demonstrating sensitivity and specificity analysis of 90-day % fullness and 90-day IIEF-5 in predicting 24-month recovery of ESI. Trade-offs between sensitivity and specificity were considered within the context of patient counseling for (1) suspected long-term impotency versus (2) high likelihood of potency recovery. If specificity was optimized to 98.5%, both the IIEF-5 and % fullness scales had similar sensitivity (at cut-points IIEF-5 score of 13 and 75% fullness, respectively). In contrast, if sensitivity was optimized to 82% (at cut-points IIEF-5 score 2 and 25% fullness, respectively) the specificity of % fullness was 70.1%, while the specificity of the IIEF-5 was 44.6%.

Figure 3a: ROC Curve of 90-day % Fullness as a Predictor of 24-month Potency; cut-points of 25% and 75% fullness (AUC = 0.81)

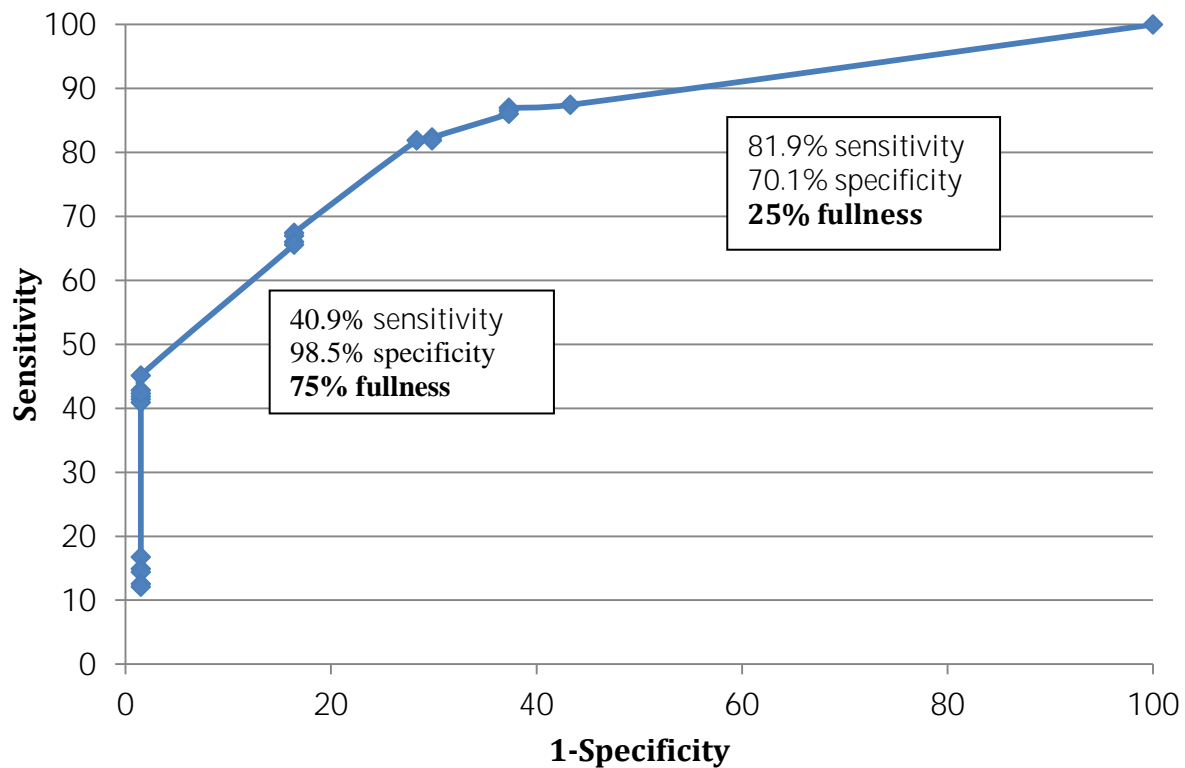
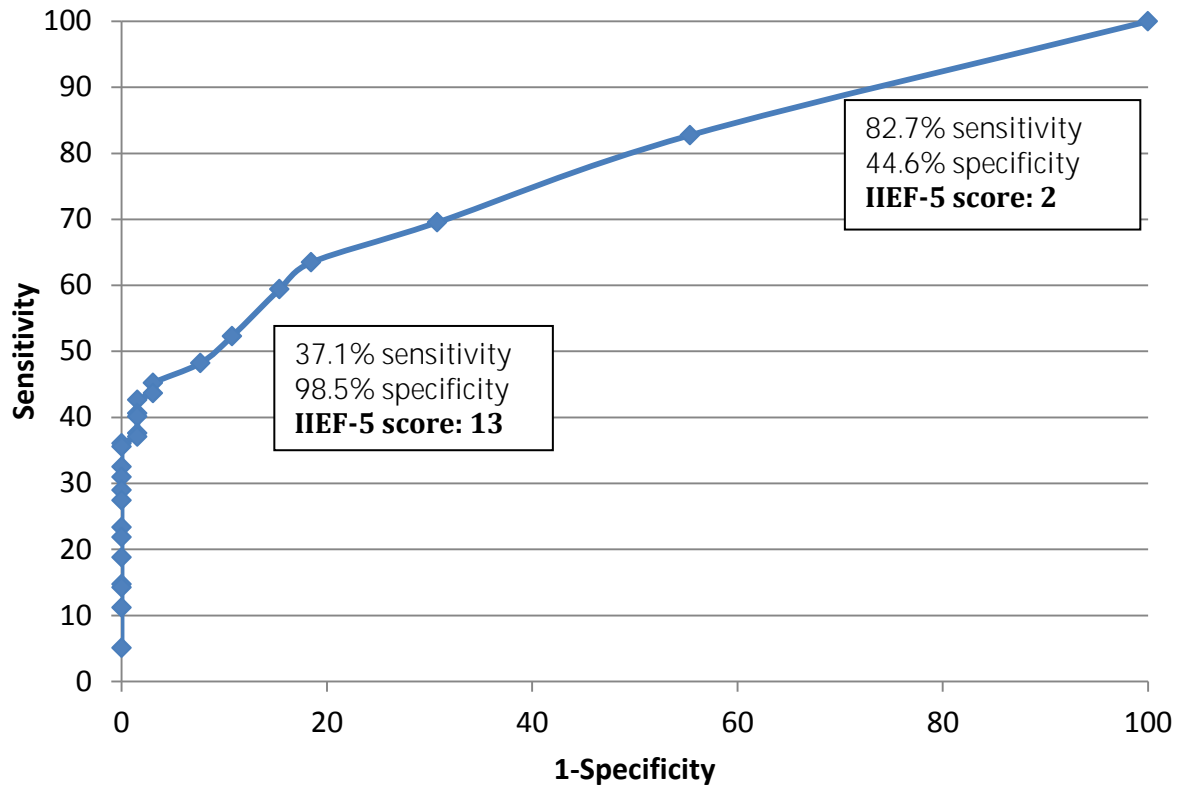


Figure 3b: ROC Curve of 90-day IIEF-5 as a Predictor of 24 month Potency; cut-points of IIEF-5 2 and IIEF-5 13 (AUC = 0.78)



3.4 Assessing Model Performance

Internal validation was conducted in the dataset with complete responses of at Months 3, 9, 15, and 24 post-RP. Random number assignment in this subset of 299 patients with complete responses yielded a “training dataset” of 203 patients and a “validation dataset” of 96 patients.

Training data set. A logistic regression model was generated utilizing the training data set to predict likelihood of 2-year potency recovery via 90-day percent erection fullness and significant covariates, yielding similar results to Table 3. Among covariates of age, nerve-sparing, pre-operative IIEF-5 score, BMI, and pathologic stage, only 90-day

percent fullness tertiles was a significant predictor of potency recovery at 24 months ($p < 0.001$). ROC curve analysis demonstrated good discrimination in potency recovery (area under the curve = 0.895).

Validation data set. The logistic regression model from the training set was applied to the validation set to assess the model's predictability. The mean \pm SD predicted probability of 2-year potency recovery was $69.0\% \pm 3.4\%$, compared to an actual 70.8% patients recovering potency at 2 years. The only significant contributor of 2-year potency recovery was 90-day percent erection fullness. In ROC curve analysis, the applied model demonstrated good discrimination in predicted potency versus impotency by 90-day percent erection fullness (area under the curve = 0.874).

3.4 Potency Recovery Modeling at 90 Days

Recognizing the difficulty of attaining complete follow-up at all four time points post-RP, all aforementioned analyses were repeated in the dataset of 540 patients with sexual function follow-up at Month 3 and 24 post-RP. Table 5 depicts a comparison of clinicopathologic demographics of both cohorts, with no statistically significant differences in baseline characteristics and covariates between the two groups.

Further, the distribution of 3-month percent erection fullness tertiles was similar in the 540 patients, with 172 (31.8%), 195 (36.1%), and 173 (32.0%) patients reporting 0-24%, 25-74%, and 75-100% erection fullness, respectively. As depicted in Figure 4, 24 month potency recovery rates in the three percent fullness tertiles were 42%, 83%, and 98%, respectively. Of note, those reporting 0-24% erection fullness in this overall cohort at 90-days had a significantly higher proportion of potency recovery at 24 months, as

compared to those in the sample of 299 patients with complete responses (42% recovery vs. 30% recovery; 95% CI: 5.21 - 18.47, p=0.006).

Table 5: Comparison of patients reporting 3 month % fullness and 24-month ESI (N=540) versus patients with complete responses at Month 3, 9, 15, and 24 post-RARP.

	All Patients (N = 540)		Complete Responses (N = 299)		p-value
	Mean	SD	Mean	SD	
Age (years)	58.7	6.7	58.7	6.9	0.9674
IIEF-5	24.3	1.0	24.3	0.9	0.4555
PSA (ng/mL)	6.3	5.3	5.9	4.5	0.2598
AUASS	7.5	6.7	7.3	6.6	0.6036
Bother	1.5	1.5	1.4	1.4	0.6308
Prostate Weight (g)	52.0	18.6	50.8	18.6	0.3520
Estimated Blood Loss	105	33.7	105	33.7	1.0000
Body Mass Index	26.8	3.2	26.8	3.19	0.7946
	N	%	N	%	p-value
Pathological Stage					0.6085
pT2	405	75.0	228	76.3	
pT3/pT4	135	25.0	71	23.7	
Pathological Gleason					0.1692
3+3	160	29.6	103	34.4	
3+4	239	44.3	125	41.8	
4+3	97	18.0	51	17.1	
8-10	44	8.1	20	6.6	
Seminal Vesicle Invasion					0.3520
Yes	19	3.5	7	2.3	
No	521	96.5	292	97.7	
Surgical Margin					0.4846
Positive	36	6.7	24	8.0	
Negative	504	93.3	275	92.0	
Nerve-sparing status					0.5626
None	22	4.1	2	0.7	
Unilateral	56	10.4	36	12.0	
Bilateral	462	85.6	261	87.3	

*AUASS = American Urological Association Symptom Score

Figure 4: Potency recovery curves based on % fullness reported at 3 months, for patients with responses at 3 and 24 months (N=540)

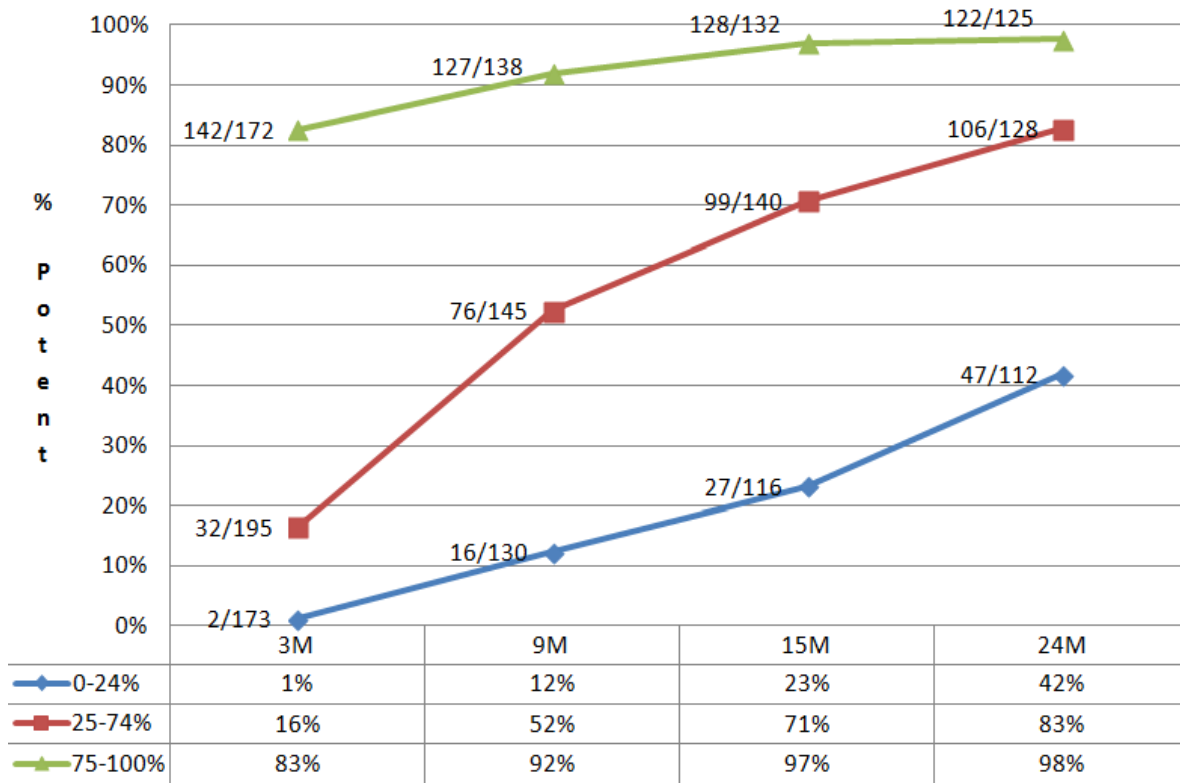


Table 6 displays the regression model of 24-month potency recovery via 90-day percent erection fullness in the 540 patients, which yielded similar results as previous comparisons of 90-day IIEF-5. Similar to prior analysis, the adjusted R² for Model 5 (90-day IIEF-5 and covariates) was 0.291, while Model 6 (90-day percent erection fullness and covariates) had an adjusted R² of 0.367. Similar to the initial model development, this increase in R² suggests that percent erection fullness can be used as a metric of two-year potency recovery.

Both models were sensitive to potency status at 90 days post-RP. When analysis was restricted to patients reporting impotency at 90-days, the adjusted R² was 0.112 and 0.289 for models utilizing 90-day IIEF-5 and 90-day percent erection fullness, respectively.

Table 6: Multivariable Logistic Regression Model of Factors Contributing to Potency at 24 Months, after adjusting for covariates (N=540)

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	-0.002	0.695		-0.002	0.998
Age (continuous)	-0.004	0.004	-0.070	-1.188	0.236
Nerve-sparing (uni-[ref] vs. bilateral)	0.120	0.062	0.095	1.921	0.056
5 Pre-operative IIEF-5 (continuous)	0.030	0.025	0.058	1.183	0.238
BMI (continuous)	-0.006	0.007	-0.045	-0.927	0.355
p-stage (pT2 [ref] vs. pT3/T4)	-0.089	0.060	-0.088	-1.485	0.139
90-day month IIEF-5	0.007	0.001	0.536	10.529	<0.001
(Constant)	0.074	0.703		0.105	0.916
Age (continuous)	-0.004	0.004	-0.067	-1.133	0.258
Nerve-sparing (uni-[ref] vs. bilateral)	0.119	0.063	0.094	1.907	0.058
6 Pre-operative IIEF-5 (continuous)	0.027	0.026	0.053	1.053	0.293
BMI (continuous)	-0.007	0.007	-0.047	-0.982	0.327
p-stage (pT2 [ref] vs. pT3/T4)	-0.093	0.060	-0.092	-1.557	0.121
90-day % fullness (<24 [ref] vs. >25)	0.006	0.001	0.490	6.005	<0.001

IV. DISCUSSION

4.1 Clinical Integration of Percent Erection Fullness

Side effects of erectile dysfunction and urinary incontinence post-radical prostatectomy can severely alter patient quality of life and the recovery process. In this regard, for many patients, functional preservation of continence and sexual function hold similar importance as cancer control [4, 9].

Presently, potency recovery is frequently defined by IIEF-5 scores or erections sufficient for intercourse (ESI). A systematic review by Ficarra and associates previously noted ESI as the most commonly used definition of potency recovery [12]. In contrast, some have recommended defining potency using various categorical IIEF-5 scores 15, 17, and 22, or at least a 3 (approximately half the time) on component five of the IIEF-5 (when you attempted intercourse, how often was it satisfactory to you?). Although specific definitions of potency recovery have yet to be definitively settled, all of the above mentioned methods yield reasonably consistent, quantitative assessment for a large proportion of patients undergoing RP.

In an effort to add a qualitative component to assess partial recovery of erections and evaluate erection quality post-RP, we supplemented our standard follow-up questionnaires of ESI and IIEF-5 with a self-reported item of percent erection fullness. As a single adjunctive question, percent erection fullness is precise, easy to answer, and yields high patient response rates. Postoperatively, we noted that men reporting IIEF-5 scores between 15 and 21 typically had a percent fullness score of 75-85% and, logically, men with IIEF-5 scores between 22 and 25 generally had a percent fullness score of 95-100%.

However, it was not unusual to see an affirmative ESI, but an IIEF-5 8-10 - a combination of scores that was particularly common for men without sexual partners. Often, these men only answered components 1 and 2 of the IIEF-5 and indicated “no sexual activity” for the remaining components. While a low percent fullness score in these patients would support lack of potency consistent with the low IIEF-5 score, a high percent fullness score would likely indicate a potent man without a partner.

Overall, the most important finding of this study is the ability of percent erection fullness to provide an early, 90-day metric for long-term potency recovery – either as an independent predictor or as a qualitative adjunct to the IIEF-5 score. We suggest the use of percent fullness to identify those with high likelihood of long-term impotence post-RP, as 54% of all patients undergoing RP will report 0-24% fullness at 90-days, of which 72% will not recover sexual function within 24 months post-RP. This is not only statistically significant, but is also clinically relevant such that the use of 90-day percent erection fullness allows for the prediction of patients who can be counseled for early, secondary intervention.

4.2 Cavernosal Nerve Function and of Percent Fullness Tertiles

In current literature, Mulhall and associates have demonstrated that sexual function and potency are closely correlated with erection hardness [18-19]. As a single-item questionnaire, 90-day percent erection fullness presents as a capable predictor of long-term ED, with a notably higher sensitivity and specificity when compared to the IIEF-5 [18]. As a continuous measure of penile rigidity, the percent erection fullness scale is useful for several reasons. The ability of the percent fullness scale to discriminate between impotent

men compared to those with intermediate recovery of sexual function allows physicians to identify patients who would most likely benefit from early, therapeutic interventions such as injection therapy, penile implants, medication, etc.

To this effect, the recovery of potency, or more accurately, cavernosal nerve function seen in the present study, is illustrative of Seddon's description of the three classes of nerve injury and recovery: neurapraxia, axonotmesis, and neurotmesis [20]. Neurapraxia consists of a mild, concussion-like injury due to blunt impact or stretch injury to the perineural sheath without axonal structural damage. The recovery process is weeks to a few months, which is consistent with the recovery curve for patients who report 75-100% fullness at 3 months. For patients with axonotmesis (grade 2 injury), injury to the axon has occurred and, as long as the nerve sheath is intact, the nerve(s) will undergo Wallerian degeneration and regeneration from the point of injury to the end-organ. In this scenario, regrowth of the axon advances approximately 1 mm per day (or 2.54 cm per month), extending the recovery period to 6-24 months, as shown by the steady increase of potency in the 25-74% percent fullness quartile at 9-24 months post-RP [21]. Lastly, for the lowest tertile (0-24%), these patients have a blend of axonotmesis and neurotmesis; while some may recover, the majority likely will not. As the most severe injury resulting from significant injury to the axon and myelin sheath, neurotmetic injury causes the highest probability of neuronal death and, therefore, little capacity for axonal regrowth [21-22].

As such, the correlation between recovery from these types of peripheral nerve injuries and the results of the percent fullness predictive models further legitimize

quantifying percent fullness of erections to estimate recovery of potency and identifies patients at high risk for impotency post-RARP.

4.2 Limitations

Although data were prospectively collected, there are inherent limitations to the retrospective nature of the present work. Firstly, present analysis was first conducted among men with IIEF-5 scores between 22 and 25 with complete responses at Month 3, 9, 15, and 24 post-RP to track partial recovery of erections. To model two-year potency with incomplete follow-up, a supplementary analysis of all patients reporting 90-day percent fullness and 24-month ESI was also included. While these two analyses confirmed a similar predictive capability of 90-day percent erection fullness, low response rates at Month 9 and 15 in the latter model limits assessment of partial erection recovery. Further, while inclusion of men with normal baseline sexual function is consistent with our effort to demonstrate proof of concept, it also limits the general applicability of our findings to men without pre-operative erectile dysfunction. In order to corroborate this limitation, we elected to define potency recovery as two affirmative answers to the ESI questionnaire and consistency between the ESI and IIEF-5 was assessed with a potency endpoint defined as IIEF-5 score \geq 15. This analysis yielded similar findings to the presented results, despite lower response rates to the IIEF-5 questionnaire. Further, these results are consistent despite changes in surgical technique and heterogeneous patient characteristics.

Overall, the results of the current study validate the use of percent erection fullness as a measure of potency recovery post-RP. Consistent with the pre-specifications made of an ideal post-RP questionnaire, percent erection fullness is simple, easy to use, easy to

interpret, and yields high response rates among patients undergoing RP. Even further, when assessed at 90 days post-RP, percent erection fullness provides both a qualitative adjunct to the IIEF-5 and an early predictor of 2-year potency recovery. Through these qualities, patient decision-making and physician counseling are significantly corroborated such that patients reporting 0-24% percent erection fullness can be referred for penile rehabilitation and secondary therapies for erectile dysfunction.

V. FUTURE DIRECTION

The average survival following radical prostatectomy (RP) is 22 years, which underscores the critical need to address improvements in the recovery of potency and urinary continence. Unsurprisingly, the primary limiting factor in managing patient outcomes is the challenge of securing reliable, time-sensitive data that surgeons can ultimately use to track their outcomes and accurately transmit them to their patients.

Of the data presented in this study, a systematic effort of two clinical research coordinators, two administrative assistants, and numerous research student interns were required to secure the 81% response rate for Month 3 and Month 24 sexual function questionnaires post-RP. Even further and, in spite of these efforts, still only 44.8% of patients had complete responses at all four time points of assessment. While the use of a 90-day metric of sexual function recovery post-RP may eventually alleviate the time devoted to patient outcome tracking, it is without a doubt that new efforts need be devoted to automate and summarize these data for use in real-time.

In 2016, the University of California - Irvine joined a consortium of over 500 academic institutions to adopt Research Electronic Data Capture (REDCap), a HIPAA-compliant, web-based patient survey system. Unique to REDCap's user interface are options to enable automatic survey invitations, reminder emails, and data summaries. With these tools at our disposal, we immediately moved our post-RP outcomes tracking to this system. While we originally intended to conduct a prospective study of 100 patients on both methods of tracking (i.e. a comparison of analog surveys versus automated email invitations), the improvements were strikingly evident within the first 50 patients [23]. In

contrast to the historic 78% response rates of the 90-day paper questionnaires, the electronic email invitations yielded response rates of 94%. Most remarkable, however, was a passive response rate of 76% - even without involvement or secondary interventions from our research staff, REDCap yielded comparable response rates to our previous systematic efforts, at a fraction of the time commitment required.

Given the efficacy and efficiency of this new system, external validation studies of 90-day percent erection fullness post-RP are currently underway, with promising results in 1-year follow-up of five surgeons across three academic institutions.

VI. CONCLUSION

The present study describes the first validation of a simple, single-item, and intuitive patient-reported scale of percent erection fullness following radical prostatectomy. In addition to its adjunctive and qualitative contribution to the current standard of the IIEF-5 questionnaire, percent erection fullness also functions as a means to identify patients at-risk for long-term erectile dysfunction. Percent erection fullness scores between 0-24% at 3 months, for example, was a strong predictor in that ~70% of these patients suffered long-term failure to recover potency. Given this, early counseling and pursuance of secondary interventions would greatly improve patient quality of life during the post-RP recovery process. Even further, automatic efforts via REDCap and validation efforts among other surgeon- and patient- populations offer promising potential of widespread integration into clinical practice.

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VIII. APPENDICES

Appendix A: International Index of Erectile Function - 5 (IIEF-5)

Over the past 6 months:					
1. How do you rate your confidence that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never or never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always or always 5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?	Almost never of never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always or always 5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never or never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always or always 5

Total Score: _____

1-7: Severe ED 8-11: Moderate ED 12-16: Mild-moderate ED 17-21: Mild ED 22-25: No ED

Appendix B: Expanded Prostate Cancer Index for Clinical Practice (EPIC-CP)

Patients: Please answer the following questions by circling the appropriate answer. All questions are about your health and symptoms in the **LAST FOUR WEEKS**.

Select ONE answer for each question:

1. Overall, how much of a problem has your urinary function been for you?				
No Problem	Very small problem	Small problem	Moderate problem	Big problem

2. Which of the following best describes your urinary control?				
0-Total control	1-Occasional dribbling	2-Frequent dribbling	4- No urinary control	
3. How many pads or adult diapers per day have you been using for urinary leakage?				
0-None	1-One pad per Day	2-Two pads per Day	4- Three or more pads	
4. How big a problem, if any has urinary dripping or leakage been for you?				
0-No problem	1-Very small problem	2-Small problem	3-Moderate problem	4-Big problem
<i>CLINICIANS: Add the answers from questions 2-4 to calculate the Urinary Incontinence Symptom Score (out of 12)</i>				

5. How big a problem, if any, has each of the following been for you?					
	No problem	Very small problem	Small problem	Moderate problem	Big problem
a. Pain or burning with urination	0	1	2	3	4
b. Weak urine stream/incomplete bladder emptying	0	1	2	3	4
c. Need to urinate frequently	0	1	2	3	4
<i>CLINICIANS: ADD the answers from questions 5a-5c to calculate the Urinary Irritation/Obstructive Symptom Score (out of 12)</i>					

6. How big a problem, if any, has each of the following been for you?					
	No problem	Very small problem	Small problem	Moderate problem	Big problem
a. Rectal pain or urgency of bowel movements	0	1	2	3	4
b. Increased frequency of your bowel movements	0	1	2	3	4
c. Overall problems with your bowel movements	0	1	2	3	4
<i>CLINICIANS: ADD the answers from questions 6a-6c to calculate the Bowel Symptom Score (out of 12)</i>					

7. How do you rate your ability to reach orgasm (climax)?				
0- Very good	1-Good	2-Fair	3-Poor	4-Very poor to none

8. How would you describe the usual quality of your erections?			
0- Firm enough for intercourse	1-firm enough for masturbation and foreplay	2-Not firm enough for any sexual activity	4-None at all

9. Overall, how much of a problem has your sexual function or lack of sexual function been for you?				
0-No problem	1-Very small problem	2-Small problem	3-Moderate problem	4-Big problem

10. How big a problem, if any, has each of the following been for you?					
	No problem	Very small problem	Small problem	Moderate problem	Big problem
a. Hot flashes or breast tenderness/enlargement	0	1	2	3	4
b. Feeling depressed	0	1	2	3	4
c. Lack of energy	0	1	2	3	4
<i>CLINICIANS: ADD the answers from question s10a-10c to calculate the Vitality/Hormonal Symptom Score(out of 12)</i>					

<i>CLINICIANS: ADD the five domain summary scores to calculate the Overall Prostate Cancer QOL Score (out of 60)</i>				
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