

Oncological and Functional Outcomes Following Open Radical Prostatectomy: How Patients May Achieve the “trifecta”?

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ABSTRACT

Purpose: The desirable outcomes after open radical prostatectomy (RP) for localized prostate cancer (PC) are to: a) achieve disease recurrence free, b) urinary continence (UC), and c) maintain sexual potency (SP). These 3 combined desirable outcomes we called it the “Trifecta”. Our aim is to assess the likelihood of achieving the Trifecta, and to analyze the influencing the Trifecta .

Materials and Methods: A total of 1738 men with localized PC underwent RP from 1992-2007 by a single surgeon. The exclusion criteria for this analysis were: preoperative hormonal or radiation therapy, preoperative urinary incontinence or erectile dysfunction, follow-up less than 24 months or insufficient data. Post-operative Trifecta factors were analyzed, including biochemical recurrence (BR).. We defined: BR as PSA \geq 0.2 ng/mL, urinary continence as wearing no pads, and sexual potency as having erections sufficient for intercourse with or without a phosphodiesterase-5 inhibitor.

Results: A total of 831 patients met the inclusion criteria. The mean age of the entire cohort was 59 years old. The median follow-up was 52 months (mean 60, range 24-202). The BR, UC and SP rates were 18.7%, 94.5%, and 71% respectively. Trifecta was achieved in 64% at 2 year follow-up, and 61% at 5 year follow-up. Multivariate analysis revealed age at time of surgery, pathologic Gleason score (PGS), pathologic stage, specimen weight, and nerve sparing (NS) were independent factors.

Conclusions: Age at time of surgery, pathologic GS, pathologic stage, specimen weight and NS were independent predictors to achieve the Trifecta following radical prostatectomy. This information may help patients counseling undergoing radical prostatectomy for localized prostate cancer.

Key words: Radical Prostatectomy; treatment outcome; prostate cancer; recurrence

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INTRODUCTION

Open Radical prostatectomy (RP) is an effective treatment for clinically localized prostate cancer. In the era of PSA screening, patients are often diagnosed with low grade, low stage prostate cancer. Consequently, disease free survival (DFS) rates approach 90% at 5 years post TP. (1). Other approaches, like radiation therapy, provide similar DFS. Treatments with comparable DFS rates should be evaluated in terms of quality of life (QoL) including continence and erectile function, as well as cancer control.

Better knowledge of pelvic anatomy, improvements in surgical technique (2), and early detection (PSA), have led to improved oncological results and reduced adverse functional outcomes (3). Full continence, erectile function, and absence of biochemical recurrence (BR) represent the Trifecta, the most desired outcomes following TP (4). BR is assessed with serial serum PSA measurements. However, QoL outcomes being subjective in nature are tabulated as an objective endpoint. Although the methodology of assessing the outcome is critical, there are no universally accepted guidelines for

quantifying and reporting urinary incontinence and erectile dysfunction (ED) after RP.

Several endpoints have been used to evaluate postoperative UC. The rates following RP vary from 70-95% (5-10). Although different definitions have been applied, urinary incontinence is more accurately reported than ED given that it can be quantified and qualified (pads or no pads, leakage or not).

Assessment of erectile function lacks uniformity. Erectile function encompasses different factors: partial recovery, adequate rigidity, ability for intercourse and overall sexual satisfaction. In addition, reported rates need to be correlated with age, preoperative function, oncologic outcomes, surgical technique and use of medication or devices to assist in the treatment of ED.

The aim of our study is to present our Trifecta results and to analyze the factors that may influence these results. The ultimate clinical objective is to better inform patients by assessing each individual's risks and his probability of achieving Trifecta using preoperative and postoperative variables.

MATERIALS AND METHODS

A total of 1738 men with localized PC underwent RP from 1992-2007 by a single surgeon (MSS). RP is performed through a Pfannenstiel incision with bilateral standard pelvic lymphadenectomy and "en-bloc" resection of the prostate. A unilateral or bilateral nerve-sparing approach was performed when feasible (3). The exclusion criteria for this study were: neo-adjuvant hormonal (n = 310) or radiation therapy (n = 24), preoperative urinary incontinence (n = 6) or erectile dysfunction (n = 320), follow-up less than 24 months or incomplete data on UC, SP or BR (n = 247). Our final cohort included 831 patients. The factors affecting UC, SP or BR were analyzed. We defined: a) BR as PSA \geq 0.2 ng/mL, b) urinary continence as wearing no pads and c) sexual potency as having erections sufficient for intercourse with or without phosphodiesterase-5 inhibitors. The ability to perform a nerve sparing procedure was assessed from the surgeon's operative note defining whether one

or both neurovascular bundles were spared. A procedure was recorded as "non-nerve sparing" when there was no intention to spare the neurovascular bundles and when there was uncertainty the nerves were preserved. Quality of Life (QoL) data was collected during each clinical encounter and subsequent chart review. During the past 2 years, patients completed the sexual health inventory for men (SHIM) (11) and International Consultation on Incontinence Questionnaire (ICIQ), (12) on each postoperative visit and data was collected. Patients were considered potent if their SHIM score was 3-5 on the third question of the questionnaire. Urinary continence was defined as bother score of "0" and/or no pads. A patient was considered to have achieved Trifecta if he had UC, SP and was free of BR.

Risk stratification was performed using the D'Amico criteria (13,14). Low risk included clinical stage T1c or T2a, PSA < 10 ng/mL and biopsy Gleason sum (GS) \leq 6. Intermediate risk included clinical stage T2b, PSA between 10 and 20 ng/mL or biopsy GS of 7. High risk was defined as clinical stage T2c or more, PSA > 20 ng/mL or biopsy GS \geq 8.

Statistical analysis was done using the SPSS software version 17. A two-sided p-value of 0.05 or less was considered statistically significant. Data were expressed as numerical values and percentages for categorical variables; and as mean \pm SD for continuous variables. For normally distributed data, analysis of variance (ANOVA) was used to analyze overall differences. For data that was not normally distributed, the non-parametric Kruskal-Wallis test was used to analyze overall differences. Chi-square or Fisher's exact test was used to compare the categorical data among the groups. Kaplan-Meier analysis was performed to estimate the long term outcome regarding biochemical recurrence (BR). Univariate and multivariate analyses were performed using logistic regression models with the intent of testing the independent effect of each predictor on the outcomes of interest that represent the Trifecta. Predictors included age at surgery, PSA, clinical stage, biopsy Gleason sum, pathologic Gleason sum and stage, nerve sparing procedure, and specimen weight.

RESULTS

A total of 831 patients were included in this analysis. Clinical and pathologic patient characteristics are shown in Table-1. Mean age was 59 (range 35 to 77) and median preoperative PSA was 5.8 ng/mL. 68% of patients had biopsy Gleason

score of 6 or less, and 85% were clinical stage ≤ T2a. Unilateral and bilateral nerve sparing procedures were performed in 17.5% and 63.5% of patients respectively, and 19% of patients were considered to have had a non-nerve sparing procedure. The following rates for pathologic Gleason sums were recorded: 49% for Gleason 6, 42% for

Table 1 - Preoperative and postoperative patient characteristics (n = 831).

Age	
Mean (median)	59.5 (60)
Range	35 - 77
< 65 years	652 (8.5%)
> 65 years	179 (21.5%)
Preoperative Biopsy Gleason score	
6 or less	568 (68.5%)
7	212 (25.5%)
8 or more	51 (6%)
Clinical T stage	
T2a or less	706 (85%)
T2b	84 (10%)
T2C or more	41 (5%)
PSA (ng/mL)	
Mean (median)	6.9 (5.7)
0 -4.0 ng/mL	132 (15.9%)
4.1 – 10.0 ng/mL	582 (70.0%)
> 10.0 ng/mL	117 (14.1%)
Nerve sparing	
None	159 (19%)
Unilateral	147 (17.5%)
Bilateral	525 (63.5%)
Risk group stratification	
Low	436 (52%)
Intermediate	288 (35%)
High	107 (13%)
Pathologic stage	
T2	688 (82.8%)
T3a	88 (10.6%)
T3b	55 (6.6%)
Pathologic Gleason	
6 or less	409 (49%)
7	350 (42%)
8 or more	72 (9%)

Gleason 7 and 9% for Gleason 8-10. 83% of the patients were pT2.

After a median follow-up of 52 months (mean 60, range 24-202), the rates of BR was 19%; SP was 71%; and UC was 94.5%. When stratifying patients according to the preoperative D'Amico classification, BR occurred in 12% of the low risk group, 21% in the intermediate group and 38% in the high risk group ($p < 0.001$). The Kaplan-Meier estimated biochemical recurrence free survival of 92% at 2 years post-op, 84% at 5 years and 66% at 10 years.

The overall UC rate had median follow-up of 54 months and UC rate of 94.5%. The UC rates were not significantly different ($p = 0.90$) in the low (94%), intermediate (94%) and high risk (93%) groups. The overall postoperative SP rate was 71%. The potency rates in the low, intermediate and high risk groups were 74%, 69% and 67% respectively ($p = 0.28$).

Trifecta was achieved in 56% of patients in the entire cohort with a median follow-up of 54 months, in 64% at 2 years ($n = 831$) and in 61% at 5 years ($n = 352$). Trifecta rates in the low, intermediate and high risk groups were 62%, 52% and 43% respectively ($p < 0.001$) (Table-2). Patients with pathologic GS ≥ 8 infrequently achieved Trifecta due to a high rate of BR (33%) or a combined BR and ED (40%). In patients with pathologic Gleason 7 or less, the primary reason for not achieving Trifecta was due to ED.

We then performed univariate and multivariate analyses at the 2 year endpoint. In univariate analysis, the factors affecting the Trifecta was age, preoperative PSA, biopsy GS, NS procedure,

specimen weight, pathologic GS and pathologic stage (all $p \leq 0.001$) (Table-3). Clinical stage and BMI did not achieve statistical significance in predicting Trifecta in a univariate analysis. In multivariate analysis, age, NS procedure, specimen weight, pathologic GS and pathologic stage were independent predictors of achieving the Trifecta. Individual preoperative variables such as PSA, biopsy GS and clinical stage did not predict Trifecta in our analysis (Table-3). However, when stratified according to the D'Amico classification, patients with low risk features were more likely to achieve Trifecta (all $p < 0.016$) (Table-2).

DISCUSSION

Since the advent of PSA, patients are more commonly diagnosed with low grade and low stage prostate cancer. Radical prostatectomy is associated with high long term survival rates with the ultimate goal to maximize QoL and eradicate cancer. UC and erectile function are the two most frequent QoL alterations associated with RP. Improvements in understanding anatomy and surgical technique have refined this procedure so that blood loss is now well controlled, and the surgeon can focus on aspects of surgery to maximize continence and potency. The primary objective of RP is to eradicate prostate cancer but success is dependent on tumor stage and grade. Once prostate cancer control is achieved, the patient will focus on UC and SP. Therefore, the Trifecta represents the optimal desired outcome. Investigations regarding each individual endpoint, have been reported but only few studies have addressed these together.

Table 2 - Overall rates for BR, potency, continence and trifecta at median follow-up of 54 months according to the D'Amico preoperative risk group stratification.

	D'Amico risk group stratification			P
	Low (%)	Intermediate (%)	High (%)	
BR	12.7	22.4	40.8	< 0.001
Potency	73.5	69.5	67.0	0.28
Continence	93.7	94.2	93.1	0.902
Trifecta				
Overall	62.4	52.4	43.0	< 0.001
2 year	67.9	60.1	55.1	0.016
5 year	65.4	56.9	49.5	0.004

Factors Influencing The Trifecta Following Open Radical Prostatectomy

Table 3 - Univariate and multivariate analysis of clinical and pathologic factors affecting Trifecta.

Factor	Univariate	Multivariate		
	P	P	Odds ratio	95% CI
Age	< 0.001	-	0.003	
		0.008	referent	
			0.593	0.402-0.875
Preop Biopsy GS	< 0.001			
6 or less(ref)		-	-	
7		NS	-	
8 or more		NS	-	
Clinical T stage				
T2a or less(ref)	0.67	-	-	
T2b				
T2C or more				
PSA	NS		NS	
Nerve sparing	< 0.001			
Bilateral		-	referent	
Unilateral		0.001	0.505	0.337-0.757
None		< 0.001	0.408	0.268-0.622
Wet weight of prostate	< 0.001			
< 50		-	referent	
50 or more		0.009	0.647	0.466-0.897
Pathologic stage	< 0.001			
T2		-	referent	
T3a		NS	0.936	0.566-1.549
T3b		< 0.001	0.208	0.096-0.453
Pathologic GS	< 0.001			
6 or less		-	referent	
7		0.009	0.644	0.462-0.897
8 or more		< 0.001	0.256	0.133-0.493

GS: Gleason sum; NS: Not significant

Our cohort included 831 men with a median follow-up of 52 months. Trifecta at 2 and 5 years was achieved in 64% and 61% of patients respectively. When stratifying patients in subgroups using the D'Amico classification (14), there was a significant decrease from the low risk to the high risk category in the achievement of Trifecta at 2 years (15%) and 5 years (16%) with a 15% and 16% difference respectively (Table-2). The postoperative SP affected the most for not achieving Trifecta in the low and intermediate risk groups (74%

and 70% respectively). In the high risk group, failure of Trifecta was mainly due to BR (41%), while SP was similar across the risk groups (p = 0.28).

Patient and couple counseling needs to be done according to evidenced-based facts using preoperative and postoperative parameters (15). In multivariate analysis, age, pathologic GS, pathologic stage, specimen weight and NS procedure were independent factors affecting Trifecta. Individual preoperative parameters were not significantly associated with achievement of Trifecta in

the multivariate analysis. However, stratification of patients into preoperative risk groups demonstrated that higher risk groups were less likely to achieve Trifecta at 2 and 5 years.

These results are comparable to the only other published reports on Trifecta. Bianco et al. (4) reported a Trifecta rate of 60% at 2 years in 758 men after open RP. Their patients responded a questionnaire reviewed with the physician. Eastham et al. (16) updated these results in 1577 men with a similar Trifecta rate of 62% at 23.5 months median follow-up. They then constructed a nomogram using preoperative variables. Pierorazio et al. (17) reported their Trifecta results in 314 patients after open RP. Their Trifecta rates were 72.6%, 56.2% and 40.0% in the low, intermediate and high risk categories at 1 year follow-up. Data collection relied on patient-physician interaction. Shikanov et al. (18) published their results in 380 patients after robotic assisted radical prostatectomy. Functional evaluations were based on subjective and objective UCLA-PCI index (19) definitions for UC and SP. The Trifecta rates at 2 years were 72% - subjective data and 44% - objective data ($p < 0.0001$).

Specimen weight has been shown to have variable impact on SP and UC. In this analysis, specimen weight was recorded as < 50 g or > 50 g. In our study, larger specimens (weight > 50 g) were associated with lower chance of achieving Trifecta (34% vs. 66%, $p < 0.001$) and specimen > 50 g was an independent predictor of higher rate of UC and ED in multivariate analysis ($p < 0.001$). Pettus et al. (20) evaluated specimen size with functional outcomes in 3067 patients who underwent open RP. BR and functional results at 1 year were not affected by prostate size. Other studies of open RP have not demonstrated a correlation between prostate size and SP or UC (21,22). Frota et al. (23) reported their results of 193 laparoscopic radical prostatectomy. Prostate weight had no significant impact on BR and UC yet prostates ≤ 30 g were associated with lower potency. However, according to Ahlering et al. (24) in 139 men who underwent robotic assisted radical prostatectomy, smaller prostates were associated with faster recovery of potency and larger prostates correlated higher risk of delay in potency recovery.

There are several limitations in our study. A large number of patients were excluded due to lack of data or a follow-up less than 1 year. As a large referral and tertiary center, patients often have their procedure performed at our center and follow-up done by their local urologist. However, our cohort comprised of 831 patients which compares favorably with other reports on Trifecta. QoL outcomes represent subjective data that is converted to objective quantifiable variables. Data were collected through the review of medical records. UC as per our definition has its limitations but can be easily reported and quantified i.e. pads or no pads. However, quantifying erectile dysfunction remains a challenge since there maybe neurologic, vasculogenic and psychologic factors to consider. Rigidity of erection and ultimately the capacity to have satisfactory intercourse is the desired endpoint. Patients' and surgeons' perceptions and expectations may have an impact on what is reported. Our results are tabulated from RPs performed by a single surgeon and caution should be used when extrapolating this data to a broader clinical setting.

CONCLUSIONS

Achievement of Trifecta represents the most desirable outcome after RP. Stratification of patients into preoperative risk categories may help clinicians discuss the many different options and the possible outcomes in the postoperative course. While patients often demand robotic prostatectomy, recent results have not shown any Trifecta advantages over the open RP. Adequate pre-operative counseling should focus on the probability of achieving the Trifecta in patients undergoing radical prostatectomy independent whether is done using open or other minimally invasive surgical approach.

ABBREVIATIONS

LTH = Lithotripsy Table Height; SWL = Shock-wave Lithotripsy; KUB = Kidney, ureters, bladder X-ray study; BMI = Body Mass Index; SSD = Skin-to-Stone Distance; HU = Hounsfield Units

NCCT = Non Contrast-enhanced Computed Tomography; ROC = Receiver Operating Characteristic; SF = Stone Free; RF = Residual Fragments OR = Odds Ratio; SE = Standard Error; SD = Standard Deviation; CI = Confidence Interval

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

In this study Antebi et al. [ref] report on a single surgeon experience with radical prostatectomy in nearly a thousand patients and analyzed the factors contributing to achieve the “trifecta” of UC, SP and biochemical disease free survival following surgery for prostate cancer.

In the era of widespread diffusion of robot-assisted prostatectomy it is of utmost importance to report on the contemporary outcomes of the open approach to better counsel patients with regards to the outcomes of the treatment. It is likely that no oncologically superior approach exists and the outcomes of surgical treatment are strongly related to surgeon’s skills.

In this series, 43-62% of men achieved the “trifecta”. One should bear in mind that most if not all published reports on the outcomes of surgical treatment (both open, laparoscopic and robotic) for prostate cancer originate in high volume centers with

highly experienced surgeons. These results therefore cannot be generalized. The outcomes of these reports are not a result of the approach to prostatectomy but of the surgeon performing it.

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