Preoperative Risk Stratification Predicts Likelihood of Concurrent PSA-Free Survival, Continence, and Potency (the Trifecta Analysis) After Radical Retropubic Prostatectomy

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OBJECTIVES
To assess the likelihood of biochemical disease-free survival, urinary continence, and sexual potency after radical retropubic prostatectomy (RRP) as an aggregate outcome, the “trifecta” analysis.

METHODS
From the Columbia University Urologic Oncology Database of 2522 patients from 1988 to 2005, 503 had undergone RRP by a single surgeon. Of these, 87 patients were excluded: 31 with inadequate follow-up, 47 who had undergone additional confounding therapy, and 9 with insufficient data for the trifecta analysis. The final sample of 416 patients was stratified according to preoperative prostate-specific antigen level, Gleason sum, and clinical stage. Biochemical disease-free survival, continence, and potency were defined, respectively, as a prostate-specific antigen level of less than 0.2 ng/mL, not requiring daily pads, and having an erection sufficient for intercourse with or without oral pharmacotherapy. Patients achieving all three positive outcomes, the trifecta, were analyzed using analysis of variance.

RESULTS
Risk stratification identified 225 low-risk, 144 intermediate-risk and 47 high-risk patients whose biochemical disease-free survival rate was 96.4%, 90.3%, and 78.7% at a median follow-up period of 4.4, 4.8, and 7.1 years, respectively. The corresponding continence rates were 93.8%, 94.4%, and 93.3% and the potency rates were 81.3%, 67.7%, and 69.6% with at least 1 year of follow-up. Of the 314 analyzable patients, 130 (72.6%) of 179 low-risk, 61 (58.1%) of 105 intermediate-risk, and 12 (40.0%) of 30 high-risk patients achieved the trifecta. The trifecta rates were significantly different between the low and intermediate-risk (P = 0.04) and low and high-risk (P = 0.001) groups.

CONCLUSIONS
Preoperative (RRP) low-risk patients are more likely to remain disease-free, continent, and potent after surgery than are patients of higher risk. Physicians should consider aggregate outcomes when counseling patients regarding the clinical outcomes after RRP.

Radical retropubic prostatectomy (RRP) has been the mainstay of definitive oncologic treatment for early-stage prostate cancer for decades. The primary oncologic outcome after RRP, regardless of the approach or technique, is disease-free survival (DFS). In the prostate-specific antigen (PSA) era, biochemical recurrence or the maintenance of an undetectable PSA level has become the standard metric. With improvements and innovations in surgical technique and stage migration have come improvements in DFS, which has approached 90% in short-term, 5-year series. With the understanding that benefits from surgery are not realized for at least 5 years, the focus for postoperative clinical outcomes has shifted toward the associated side effects and quality-of-life (QOL) considerations.

The appreciation that attaining optimal simultaneous outcomes in cancer control, continence, and erectile function has been gradual, and it was not until June 2004, at the Challenges in Laparoscopy Conference in Rome, Italy and the Evolving Strategies in Prostate Cancer Meeting in New York...
York in September 2005, that the concept of the “trifecta” was first introduced.4,5 The trifecta, as an aggregate outcome, represents the three-pronged results of cancer-free survival and maintenance of erectile function and urinary continence, considered to be the ideal result for a man undergoing RRP. Discussing these outcomes together acknowledges the holistic concept that QOL issues are surgical outcomes equally important to cancer control. Bianco et al.6 first analyzed the trifecta after RRP and found that 60% of patients were continent, potent, and cancer free at 24 months.

Many pitfalls exist in collecting QOL data, some of which have been described specifically for prostate cancer, as researchers have attempted to reconcile patient-reported outcome measures with validated QOL questionnaires.7,8 Ideally, QOL outcomes should be measured with a validated questionnaire. However, this study was initiated at a time when validated questionnaires were not in widespread use and therefore used the available patient-reported and physician-determined clinical information. Additionally, combining urinary continence and erectile function (“gain-of-function” parameters) with biochemical failure (a “loss-of-function” parameter) complicates the statistical analysis and subsequent clinical interpretation of the results. Despite its methodologic shortcomings, this study was designed to answer an important question that incorporates cancer and QOL-specific outcomes into an aggregate outcome to more comprehensively inform patients about the risks and benefits of RRP. Recognizing the limitations associated with the capture of QOL data, we sought to examine the likelihood of achieving the aggregate trifecta outcome stratified by preoperative risk.

MATERIAL AND METHODS

The Columbia University Comprehensive Surgical Urologic Oncology Database consists of 2522 patients who underwent RRP from 1988 to 2005. Of these patients, 503 were identified from a single surgeon’s experience with complete information regarding preoperative PSA level, biopsy Gleason sum, and clinical stage and a minimum of 1 year of follow-up. From this cohort, 87 patients were excluded for the following reasons: 31 had less than 1 year of follow-up, 46 had undergone radiotherapy or androgen-deprivation therapy within their first year of RRP, 1 had undergone radiotherapy before RRP, and 9 had insufficient data to include in the analysis.

For purposes of risk stratification of the 416 patients in the study, D’Amico’s criteria9,10 were used. Low risk was defined as clinical Stage T1c or T2a, a PSA level of 10 ng/mL or less, and a Gleason sum of 6 or less; intermediate risk was defined as either clinical Stage T2b, a PSA level greater than 10 but 20 ng/mL or less, or a Gleason sum of 7; and high risk was defined as clinical Stage T2c or greater, PSA level greater than 20 ng/mL, or a Gleason sum of 8 or greater.

For patients with palpable disease (clinical Stage T2 or greater) or whose preoperative magnetic resonance imaging study indicated local disease extension, wide resection of the neurovascular bundles was performed at surgery. Nerve-sparing surgery was scheduled for the patients who did not meet the criteria for wide resection, although the ultimate use of the nerve-sparing technique was determined by the intraoperative assessment of the tissues at the discretion of the surgeon. Differences in the use of a nerve-sparing surgical technique were assessed between each group using analysis of variance.

The three clinical outcomes were measured individually as described below and aggregated to create a combined score, the “trifecta.” Biochemical DFS (bDFS) required at least two postoperative PSA levels of less than 0.2 ng/mL during the first year after surgery. Urinary continence and erectile function were determined by patient report at postoperative office visits, by surgeon interview, and by physical examination to determine the presence of incontinence pads. Patients who were incontinent or impotent before surgery were excluded from our analysis. Continence was defined as not routinely using a pad, although the occasional use of a pad for anticipated vigorous activity was allowed. Potency was defined as having an erection sufficient for intercourse, with or without the use of oral 5-phosphodiesterase inhibitors. Patients who retained biochemical disease-free status, continence, and potency met the trifecta criteria.

Differences in individual outcomes and trifecta frequencies are reported using the rates of cumulative incidence and compared among risk groups using analysis of variance. The cumulative incidence was evaluated at a minimum of 12 months after RRP to allow ample time for the return of urinary continence and erectile function and to ensure that the intersection of the ascending QOL parameters and descending bDFS function had already occurred. Logistic regression analysis was used to determine the effect of the preoperative risk category on the likelihood of achieving the trifecta and was repeated, controlling for age and the use of nerve-sparing surgical techniques, either unilateral or bilateral. Within each risk category, the reason for not achieving the trifecta (biochemical failure, incontinence, or impotence individually or any combination of the three) was analyzed using analysis of variance.

The institutional review board approved the database, which was compliant with the Health Insurance Portability Act. Statistical significance testing was set at $P = 0.05$ for all analyses. The analyses were performed using STATA SE, version 9.0 (StataCorp LP, College Station, Tex).

RESULTS

Of the 416 patients, 225 were classified as low risk, 144 as intermediate risk, and 47 as high risk before RRP. The sample characteristics are given in Table 1. On average, patients in the high-risk group were older ($P < 0.001$) and had undergone surgery earlier in the surgeon’s experience ($P < 0.001$). The rates of bDFS, urinary continence, erectile function, and the trifecta are depicted in Figure 1.

Biochemical Disease-Free Survival

The median follow-up for the 416 patients was 4.7 years. In the low, intermediate, and high-risk groups, the bDFS rate was 96.4%, 90.3%, and 78.7% with a median follow-up period of 4.4, 4.8, and 7.1 years, respectively. A significant difference was found in the failure rates of bDFS among all groups ($P < 0.001$), with the intermediate and high-risk groups demonstrating incrementally greater rates of failure.
Urinary Continence

Five patients had incomplete data regarding continence and could not be evaluated. The cumulative continence rate for the low, intermediate, and high-risk groups was 93.8%, 94.4%, and 93.3%, respectively, with median follow-up of 1 year. The differences in the rates of postoperative continence among the groups were not significant ($P = 0.96$). Of the 25 patients identified as incontinent after RRP, 22 (88.0%) developed stress urinary incontinence requiring a daily pad and 3 (12.0%) had continuous incontinence. Of the 386 patients identified as continent after RRP, 12 (3.1%) were classified as having stress urinary incontinence not requiring the use of a pad and 16 (4.1%) were identified as having stress urinary incontinence requiring the use of a pad only with vigorous activity.

Erectile Function

We excluded 43 patients from the erectile function analysis because they were impotent before surgery. Of these 43 patients, 19 (10.3%) were in the low-risk, 17 (14.7%) the intermediate-risk, and 7 (23.3%) the high-risk group. We excluded 85 patients because of incomplete erectile function data. Of the remaining 288 patients in the sample, the cumulative potency rate was 81.3%, 67.7%, and 69.6% for the low, intermediate, and high-risk groups, respectively, at a median follow-up of 1 year for all groups. The difference in potency rates was significant between the low and intermediate-risk groups ($P = 0.03$); however, no statistically significant difference in potency rates was noted between the low and high-risk groups ($P = 0.65$) or the intermediate and high-risk groups ($P = 1.0$). Pharmacotherapy to assist with erections was used by 197 (65.6%) of the 288 patients and 145 (94.8%) of 153 potent patients. The most commonly used agents were sildenafil (82.7%) and tadalafil (6.1%).

The Trifecta

Of the 314 analyzable patients, 130 (72.6%) of 179, 59 (56.2%) of 105, and 12 (40.0%) of 30 in the low, intermediate, and high-risk groups achieved the trifecta, respectively ($P < 0.0003$). Significant differences were noted between the low and intermediate-risk groups ($P = 0.01$) and the low and high-risk groups ($P = 0.001$). No difference was observed between the intermediate and high-risk groups ($P = 0.29$). The rates of bDFS, continence, potency, and the trifecta are depicted in Figure 1.

In the univariate logistic regression model, preoperative risk stratification was a significant predictor of achieving the trifecta ($P = 0.005$). Low-risk patients demonstrated one fourth the likelihood of failing the trifecta compared with the high-risk patients (odds ratio [OR] 0.25, 95% confidence interval [CI] 0.11–0.56, $P = 0.001$). Intermediate-risk patients demonstrated almost one half the odds of failure (OR 0.52; 95% CI 0.22–1.18, $P = 0.12$). On multivariate regression analysis, after controlling for age and nerve-sparing surgical technique, low-risk patients had nearly one half the likelihood of

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**Table 1.**

<table>
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<th>Overall</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
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<td>47</td>
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<td>58.1</td>
<td>59.7</td>
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<td>1999</td>
<td>1997</td>
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<td>Mean</td>
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<td>0.6–9.9</td>
<td>1.0–19.1</td>
<td>1.6–62.0</td>
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<td>Biopsy Gleason sum, n (%)</td>
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<td></td>
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<tr>
<td>$&lt; 7$</td>
<td>277 (71.0)</td>
<td>217 (100.0)</td>
<td>44 (33.3)</td>
<td>16 (39.0)</td>
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<td>88 (77.7)</td>
<td>8 (19.5)</td>
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<td>$&lt; 7$</td>
<td>181 (44.5)</td>
<td>136 (61.0)</td>
<td>36 (26.1)</td>
<td>9 (19.6)</td>
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<tr>
<td>$= 7$</td>
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<td>14 (7.3)</td>
<td>19 (18.1)</td>
<td>11 (32.4)</td>
</tr>
<tr>
<td>Total</td>
<td>279 (96.5)</td>
<td>165 (95.4)</td>
<td>93 (95.8)</td>
<td>21 (80.8)</td>
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</table>

* Complete data regarding this pathologic parameter was not available for all patients.
failure compared with the high-risk patients (OR 0.54, 95% CI 0.28–1.02, P = 0.06). Intermediate-risk patients had a likelihood of failing the trifecta that was statistically similar to that of the high-risk patients (OR 0.88, 95% CI 0.28–2.7, P = 0.99). A significant difference was found among the risk categories regarding the reason for not achieving the trifecta (P = 0.036; Fig. 2). Most patients in the low and intermediate-risk groups did not achieve the trifecta because of impotence (57.1% and 52.7%, respectively). Most high-risk patients did not achieve the trifecta because of biochemical recurrence (50.0%). The 102 patients excluded from the trifecta analysis because of missing data had an even distribution by risk: 48.4%, 47.0%, and 48.6% in the low, intermediate, and high-risk groups, respectively.

**COMMENT**

RRP is the most common treatment choice for patients newly diagnosed with prostate cancer, with approximately 35% to 40% of men choosing surgery instead of radiotherapy or watchful waiting. Although surgery offers excellent cancer control, the nature of the operation puts men at substantial risk of incontinence and erectile dysfunction. Many patients may forego RRP and potential cure of prostate cancer armed with the knowledge that most men who are continent and potent before RRP will have significant dysfunction in the postoperative period, many patients may forego RRP and the potential cure of prostate cancer because of these side effects. Widespread PSA screening and the earlier diagnosis of prostate cancer have further magnified the issues of urinary and sexual function, because low-volume cancers are being detected in young men, often those of reproductive age and with long life expectancy. Given the substantial burden of the side effects, a thorough consideration of the risk factors for diminished QOL should be incorporated into the informed decision-making between physicians and patients.

The major finding from this study was that the preoperative risk predicts for QOL outcomes and biochemical recurrence as an aggregate endpoint, the trifecta. Borrowing the D’Amico’s risk stratification paradigm equating preoperative factors with bDFS, we have demonstrated that the expected decrease in bDFS by risk group mirrors the decrease in achieving the trifecta. The trifecta failure rates were accentuated by risk group compared with...
bDFS, with a 33-percentage point difference between the low and high-risk groups in the trifecta analysis compared with only a 17-percentage point difference in the bDFS analysis. This discrepancy could have been related to variations in surgical technique; specifically, how closely the surgeon approached the dissection near the prostatic capsule during the nerve-sparing portion of the procedure is likely associated with risk categorization. However, the use of a nerve-sparing technique cannot serve as a surrogate for all surgical decision-making nor differentiate among patients with small differences in preoperative risk. Furthermore, the discrepancy in the trifecta rates could reflect adverse biologic/pathologic parameters of high-risk disease. These adverse parameters can be considered intermediate endpoints toward the path of treatment failure and have been demonstrated to be associated with recovery of QOL functions.\textsuperscript{15,16}

A more detailed analysis of our principal findings revealed that among the low and intermediate-risk patients, erectile function was the primary determinant of achieving the trifecta, but bDFS drove the analysis among the high-risk patients. With increasing preoperative risk, the proportion of patients failing the trifecta for QOL outcomes decreased from 88% in the low-risk group to 75% in the intermediate-risk group and 50% in the high-risk group. Therefore, the attention of the surgeon should continue to focus on nerve sparing and preservation of potency in low-risk patients but aggressive surgical resection and cancer control should be prioritized in high-risk patients.

The postoperative continence rates did not vary among the risk groups and did not contribute differentially to achieving the trifecta. Hu \textit{et al.}\textsuperscript{17} found that the PSA level was the only significant predictor of urinary function assessed by the University of California, Los Angeles, Prostate Cancer Index among subjects from the Cancer of the Prostate Strategic Urologic Research Endeavor database 12 months after RRP. Furthermore, they demonstrated that Gleason sum and clinical stage had no bearing on QOL outcomes.\textsuperscript{17} In other studies, PSA level, Gleason sum, and clinical stage did not correlate with urinary or sexual function outcome.\textsuperscript{14,18,19} These studies’ findings contrast with our finding that the return of potency is related to preoperative risk. However, they agree with our finding that urinary continence is not a function of the extent of the disease or preoperative risk and perhaps is inherent in the disease process or the treatment. This extends the report by Bianco \textit{et al.},\textsuperscript{6} indicating that only two variables, bDFS and erectile function, are necessary to assess the long-term success of RRP.

This study had several limitations. The database included patients treated during the late 1980s, before the widespread use of validated QOL instruments. Therefore, the continence and potency data were physician reported and potentially biased. However, patient questioning was
confirmed during physical examination to verify pad use and added a degree of objectivity to the analysis. Furthermore, the high-risk population had a significantly longer follow-up period than did the low and intermediate-risk patients, potentially introducing bias into the analysis. Additionally, follow-up for all three groups was sufficient, allowing for interval comparisons of biochemical failure rates and for stabilization of the rates of urinary continence and erectile function.13

CONCLUSIONS
Patients classified as having low-risk disease before RRP according to the preoperative PSA level, Gleason sum, and clinical stage were more likely to remain disease free, continent, and potent (the trifecta) after surgery compared with those classified as having intermediate or high-risk disease. In addition to preoperative risk stratification, the trifecta is an important aggregate outcome measure with which to counsel patients regarding the comprehensive outcome after RRP.

References

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