What Are the Outcomes of Radical Prostatectomy for High-risk Prostate Cancer?

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OBJECTIVES To examine the long-term survival following radical prostatectomy in the population with high-risk prostate cancer. Despite considerable stage migration associated with widespread prostate-specific antigen screening, as many as one-third of incident prostate cancers have high-risk features. These patients are often treated with combined radiation and androgen deprivation therapy, and less is known about the long-term survival in this population after radical prostatectomy (RP).

METHODS Between 1992 and 2008, 175 men underwent RP by a single surgeon with D'Amico high-risk prostate cancer (clinical stage ≥T2c, biopsy Gleason score 8-10, or prostate-specific antigen >20 ng/mL). In this population, we examined the rates and predictors of biochemical progression, metastatic disease, and cancer-specific mortality.

RESULTS Among 175 high-risk patients, 63 (36%) had organ-confined disease in the RP specimen. At 10 years, biochemical recurrence-free survival was 68%, metastasis-free survival was 84%, and prostate cancer-specific survival was 92%. The 10-year rate of freedom from any hormonal therapy was 71%. Of the high-risk criteria, a biopsy Gleason score of 8-10 (vs ≤7) was the strongest independent predictor of biochemical recurrence, metastases, and prostate cancer death.

CONCLUSIONS National data suggest that RP may be underutilized for the management of high-risk clinically localized prostate cancer. Our data suggest that surgical treatment can result in long-term progression-free survival in a subset of carefully selected high-risk men. Further prospective studies are warranted to directly compare the outcomes of RP vs combined radiation and hormonal therapy in high-risk patients. UROLOGY 76: 710–714, 2010. © 2010 Published by Elsevier Inc.

In 1998, D'Amico et al[1] proposed a risk classification scheme for prostate cancer, wherein patients with a prostate-specific antigen (PSA) level >20 ng/mL, Gleason score of 8-10, or clinical stage ≥T2c were considered "high-risk." Since that time, numerous studies have validated this classification, and it is widely used in the literature. Moreover, the prognostic value of the D'Amico classification seems similar to other high-risk definitions.[2]

According to the American Urological Association Treatment Guidelines, patients with clinically localized high-risk disease have numerous possible management options: watchful waiting, radiation therapy (with or without hormonal therapy), and radical prostatectomy (RP).[3] The relative use of these different treatment options may vary in different populations.

In the observational CaPSURE population, Meng et al[4] reported that approximately 26% of patients met the D'Amico high-risk criteria. Overall, 31% elected external beam radiation therapy (EBRT), 36% underwent RP, 29% received androgen deprivation therapy, and 4% chose watchful waiting.

On the basis of Surveillance, Epidemiology, and End Results data, patients with clinical stage T3 prostate cancer were most frequently treated with EBRT in 2001 (60.2%).[5] By contrast, the proportion of clinical stage T3 patients undergoing RP decreased from 18.1% in 1995 to 9.3% in 2001.

There is now considerable evidence showing improved outcomes using hormonal therapy in conjunction with EBRT for intermediate disease to high-risk disease.[6,7] Less is known about the relative advantages and disadvantages of surgical management for men meeting the D'Amico high-risk criteria. Thus, our objective was to examine the long-term treatment outcomes among high-risk patients after RP by a single surgeon.

MATERIAL AND METHODS

Between 1992 and 2008, 3052 underwent radical retropubic prostatectomy and pelvic lymphadenectomy (PLND) by a single surgeon (P.C.W.). Of these men, we retrospectively identified 186 who met the D'Amico high-risk criteria: PSA level

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>20 ng/mL, Gleason score of 8-10, or clinical stage ≥T2c.[1] All men were considered to have a life expectancy of at least 10-15 years. On digital rectal examination, patients with clinical stage T3 disease had evidence of neither seminal vesicle invasion nor fixation at the apex or pelvic sidewall.

Our staging evaluation included a bone scan and computed tomography of the pelvis. In addition, patients with biopsy Gleason 8-10 prostate cancer were recommended to undergo staging PLND with permanent section evaluation of the lymph nodes. These were performed either laparoscopically or through a mini-lap incision. Overall, 11 patients were found to have positive lymph nodes either through staging PLND (n = 5) or because of intraoperative findings of suspicious lymphadenopathy confirmed by frozen section (n = 6). Accordingly, RP was not performed. Of note, in all remaining patients bilateral PLND was performed at the time of surgery, using a standard previously described technique.[8]

Our postoperative follow-up protocol included PSA measurements at 3-month intervals for the first year, 6-month intervals for the second year, and annually thereafter. Biochemical progression was defined as a PSA level >0.2 ng/mL. Among men with biochemical recurrence, the follow-up protocol included PSA measurements every 6 months and an annual bone scan. Hormonal therapy was not advised until the development of radiographically detectable metastatic disease. A total of 16 patients received postoperative radiation therapy, given in either an adjuvant (n = 3) or salvage (n = 13) manner.

In the 175 high-risk men who underwent RP, the Kaplan–Meier method was used to calculate the progression-free survival (PFS), metastasis-free survival (MFS), and cancer-specific survival (CSS) rates, which were compared using the log rank test. In addition, multivariable Cox proportional hazards models were used to evaluate whether the 3 criteria defining high risk—PSA (>20 vs ≤20 ng/mL), clinical stage (T2c/T3 vs <T2c), and biopsy Gleason score (8-10 vs <8)—could identify subgroups with varying risk of these outcomes within this high-risk cohort. Separate "intent-to-treat" survival analyses were also performed including the 11 patients with positive lymph nodes who did not undergo RP. Statistical analysis was performed using SAS.

RESULTS

The median age of the study population was 59 years (range, 38-71) at the time of RP, and the majority of men were white. The PSA level at diagnosis was <10, 10-20, and >20 ng/mL in 93 (53%), 24 (14%), and 58 (33%) men, respectively. Clinical stage was T1 in 68 (39%), T2a/T2b in 41 (23%), and ≥T2c in 66 (38%). The biopsy Gleason score was ≤6 in 71 (40.6%), 3 + 4 = 7 in 29 (16.6%), 4 + 3 = 7 in 12 (6.8%), and 8-10 in 63 men (36%). Thus, only 6% of men had more than 1 high-risk factor.

At RP, 63 (36%) had organ-confined disease, whereas extracapsular extension and seminal vesicle invasion were present in 79 (45%) and 8 (5%), respectively. Positive surgical margins were reported in 32 (18%) and lymph node metastases in 25 (14%) patients.

At a median follow-up of 8 years (range, 1-16), 51 (29%) had biochemical progression, 6 (3.4%) had local recurrence, 23 (13%) developed metastatic disease, and 10 (6%) died of prostate cancer. Figure 1 shows the Kaplan–Meier curves for PFS, MFS, and CSS in the overall study population. At 10 years, biochemical recurrence-free survival was 68%, MFS was 84%, and prostate CSS was 92%. In addition, the 10 year rate of freedom from any hormonal therapy was 71%.

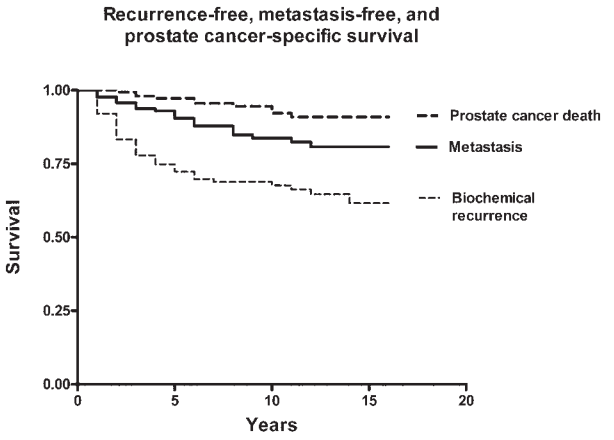

Figure 1. Kaplan–Meier Curve for progression-free survival, metastasis-free survival, and cancer-specific survival in 175 men with D'Amico high-risk prostate cancer treated by radical retropubic prostatectomy.

Next we performed an analysis to determine which of the high-risk features were most closely associated with treatment outcomes after RP. Both biopsy Gleason score and clinical stage were significantly associated with biochemical recurrence-free survival. Of note, progression was more likely among men with clinical stage <T2c, suggesting a greater contribution of other high-risk features (ie, Gleason score) to the ultimate prognosis. Figures 2 and 3 show the Kaplan–Meier curves for MFS and CSS stratified by each individual high-risk criterion. Similar to the results for PFS, patients with clinical stage T2a/b disease had the lowest MFS (P = .01). There were no significant differences in CSS on the basis of PSA, clinical stage, or biopsy Gleason score; however, the sample sizes were small.

Table 1 shows the multivariable proportional hazards models, including PSA (>20 vs ≤20 ng/mL), clinical stage (T2c/T3 vs <T2c), and biopsy Gleason score (8-10 vs <8). Biopsy Gleason score was the only statistically significant prognostic factor in each of the models, with multivariate-adjusted hazard ratio and P values of 3.2 (P = .025), 4.2 (P = .014), and 6.6 (P = .011) for biochemical recurrence, metastases, and prostate cancer death, respectively. Addition of age to the models had minimal effect on the parameters already in the model or on the model fit, indicated by the likelihood ratio (data not shown). Also, inclusion of the 11 men with positive lymph nodes who did not undergo prostatectomy in the analysis did not change the results (data not shown).

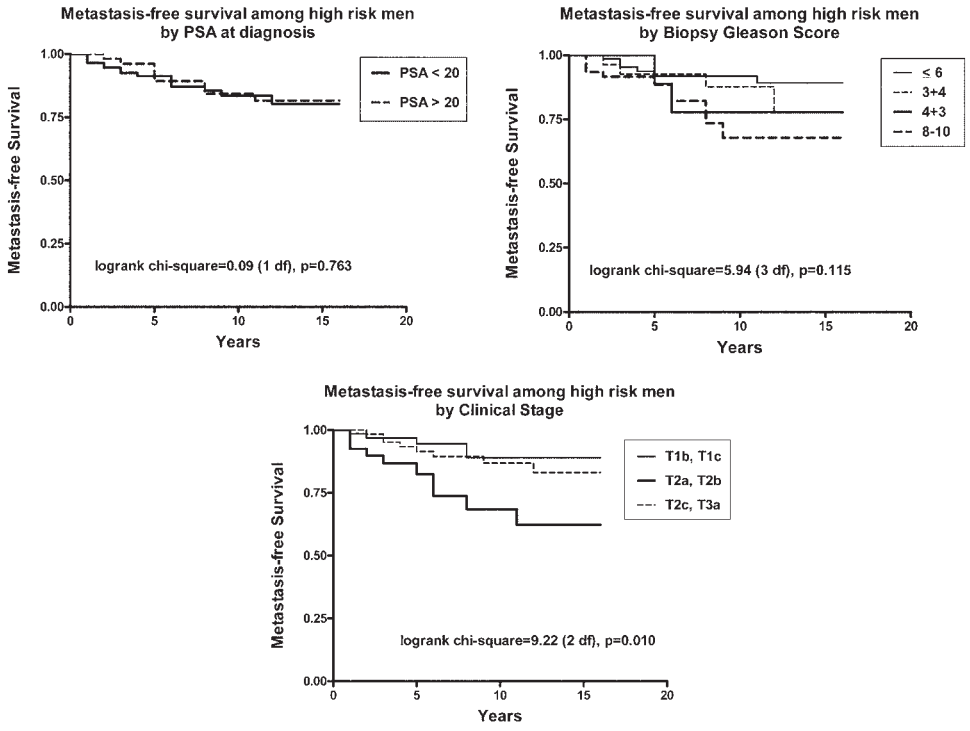

Figure 2. Metastasis-free survival after radical retropubic prostatectomy in men with D'Amico high-risk prostate cancer, by preoperative prostate-specific antigen, biopsy Gleason score, and clinical stage.

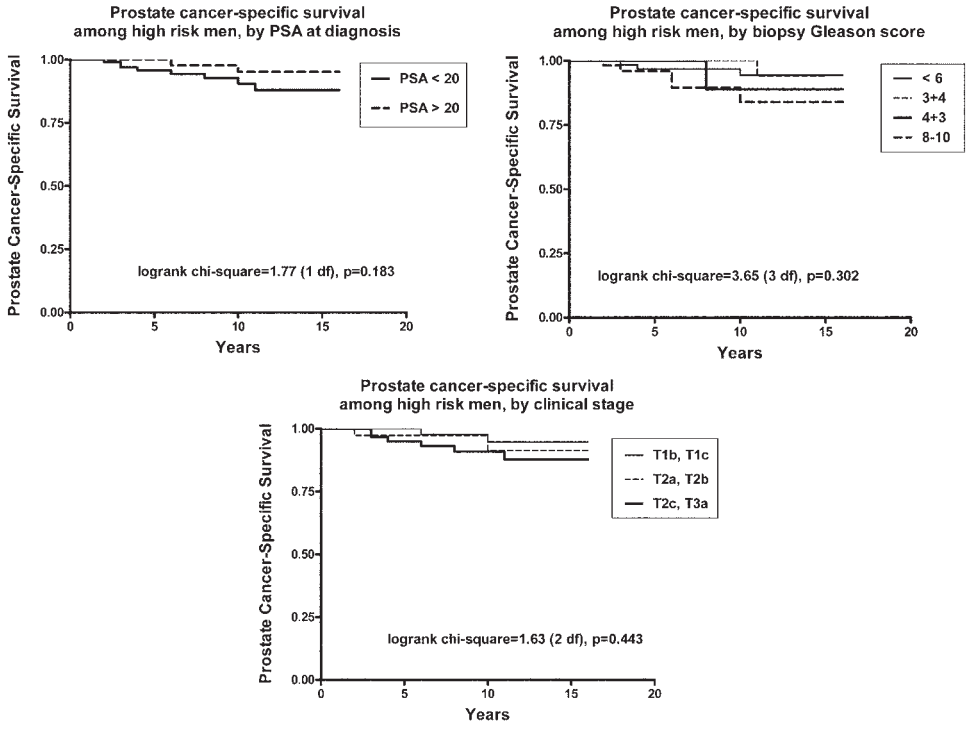

Figure 3. Prostate cancer-specific survival after radical retropubic prostatectomy in men with D'Amico high-risk prostate cancer, by preoperative prostate-specific antigen, biopsy Gleason score, and clinical stage.

COMMENT

The optimal management for patients with high-risk prostate cancer remains controversial. An increasing proportion of high-risk patients are treated with combined radiation and hormonal therapy, in light of evidence from randomized controlled trials demonstrating an advantage over radiation alone. In 1997, Bolla et al[6] reported on this issue in a total of 415 men with clinical stage T3 or poorly differentiated clinical stage T1-T2. At 5 years, overall survival was 62% with

Table 1. Cox proportional hazards models to predict biochemical progression, metastasis, and cancer-specific mortality among men with D'Amico high-risk characteristics who were treated by radical prostatectomy

	HR	95% CI	*P*
Biochemical progression			
PSA (>20 vs. ≤20)	2.2	0.8-5.9	.142
Gleason score (8-10 vs. <8)	3.2	1.2-8.9	.025
Clinical stage (T2c/T3 vs. <T2c)	1.1	0.4-2.7	.876
Metastasis			
PSA	2.1	0.6-6.7	.229
Gleason score	4.2	1.3-13.4	.014
Clinical stage	1.6	0.5-4.6	.399
Cancer-specific mortality			
PSA	1.3	0.3-7.2	.727
Gleason score	6.6	1.5-28.3	.011
Clinical stage	4.9	1.1-21.0	.035

radiation monotherapy, vs 79% for radiation therapy with hormonal therapy (P <.001). Subsequently, D'Amico et al[7] validated these findings in 206 patients with clinically localized intermediate to high-risk prostate cancer randomized to EBRT alone vs EBRT plus 6 months of hormonal therapy. Prostate cancer-specific mortality was significantly higher with EBRT alone, and the 5-year overall survival rates were 78% and 88% in the EBRT and combination therapy groups, respectively.

Currently, however, many men wish to avoid the side effects associated with long-term hormonal therapy, including osteopenia, impaired cognitive function, hot flashes, impotence, loss of libido, gynecomastia, and potential increased risk of cardiovascular events.[9,10] Therefore, for many patients, especially young men, the alternative option of primary surgical therapy for high-risk patients is attractive.

Several independent studies have examined the results of RP among men meeting 1 of the 3 original D'Amico high-risk criteria. For example, our group has previously reported on the outcomes after RP among 62 men with clinical stage T3 disease, who were diagnosed between 1987 and 2003.[11] At a median follow-up of 10.3 years, 50% had biochemical progression, 21% had metastases, and 13% died of prostate cancer. The corresponding 15 year metastasis-free rates and CSS rates were 73% and 84%, respectively.

Magheli et al[12] specifically examined the results of 265 men with a preoperative PSA level >20 ng/mL who underwent RP at our institution. Of these men, 50 (19%) had anterior tumors. The 5- and 10 year biochemical PFS rates were 47% and 33%, respectively. Of note, patients with anteriorly located tumors were significantly less likely to experience biochemical progression.

With respect to high-grade disease, Bastian et al[13] previously reported on the outcomes of RP in 369 men with a biopsy Gleason score of 8-10 from the Johns Hopkins and SEARCH databases. Overall, they reported organ-confined disease with negative surgical margins in 21% and 41%, with 10-year progression-free survival rates of 27% (18%-36%) and 28% (18%-36%) in the 2 populations, respectively. The metastases-free and CSS rates were not reported in this study.

Boorjian et al[14] reported on 1513 men with D'Amico high-risk disease who underwent RP at the Mayo Clinic. The 10-year biochemical progression-free, systemic progression-free, and CSS rates were 55%, 89%, and 95%, respectively. Loeb et al[15] similarly reported the outcomes of RP in 288 men with clinical stage T3 or high-risk T2b (PSA >15 ng/mL or Gleason 8-10) prostate cancer. In this series, the actuarial PFS rate was 35% and CSS rate was 88% at 10 years.

Herein, we expand upon these findings to report on the outcomes of all men with high-risk prostate cancer treated by the same surgeon (P.C.W.). Although only one-third of this cohort had organ-confined disease in the RP specimen, 68% had no evidence of biochemical recurrence at 10 years. Moreover, the metastasis-free and CSS rates were impressive at 84% and 92%, respectively. Finally, the majority of men avoided hormonal therapy, with its significant associated side effects.

Several limitations of our study deserve mention. First, our population represents a carefully selected surgical population, who may not be representative of all men with high-risk prostate cancer. In addition, all men were treated by a single high-volume surgeon, and several studies have shown a relationship between surgeon experience with treatment-related outcomes.[16] By contrast, we chose to focus on a single-surgeon experience to ensure that all patients were managed using the same follow-up protocol. Of note, very few men in our series received postoperative radiation therapy. Accumulating evidence from randomized trials suggests a survival advantage associated with adjuvant radiation therapy in specific pathological subgroups.[17-19] Additional study is, therefore, warranted to compare the long-term outcomes between adjuvant and early salvage radiation therapy in this setting.

Another limitation of our study is the relatively small sample size, limiting the power to define subgroups with varying risk of recurrence, metastasis, or death. However, our rates of PFS, MFS, and CSS, as well as the occurrence of pathological stage ≥T3 and lymph node metastases were comparable to those reported at the Mayo Clinic.[14] Because men with multiple high-risk features are infrequently managed at our institution with surgery alone, only 6% of the men in our series had multiple high-risk features. Prior studies have shown worse treatment outcomes among men with multiple high-risk features.[20] Nevertheless, it is unlikely that our results represent a high degree of selection for better prognosis patients, given the similarity of our outcomes to those of high-risk patients reported by Boorjian et al.[14]

Another limitation is that the D'Amico classification is one of many criteria for high-risk prostate cancer,[21] and

some prior studies have shown heterogeneity in outcomes depending upon the definition of high-risk disease.[22] Thus, additional study of long-term RP outcomes is warranted using alternate criteria.

In addition, our Kaplan–Meier analyses suggested worse outcomes for clinical stage T2b compared with T2c/T3. However, we believe this is an artifact of the definition for high-risk prostate cancer, in that men with T2b tumors must have either a biopsy Gleason score of 8-10 or PSA >20 ng/mL to be considered high risk. Because most of our patients had only 1 high-risk characteristic, a comparison of men with lower vs higher clinical stage is necessarily a comparison of Gleason 8-10 vs <8, or PSA >20 vs ≤20 ng/mL.

Finally, 11 men treated during the study period did not undergo RP because of a finding of positive lymph nodes during staging lymphadenectomy or intraoperatively. Thus, it is unknown what their results would have been had they undergone RP. However, we did perform separate "intent-to-treat" Cox proportional hazards models including these men, and the results did not change.

CONCLUSIONS

Our results and those of others suggest that RP is a viable treatment option for selected high-risk men. Although some patients ultimately required a multimodality approach, a considerable proportion was free from progression at 10 years with surgical monotherapy. Nevertheless, high-risk patients considering RP should be counseled on the possibility of multimodality therapy, depending on their pathology features and postoperative PSA levels. Additional prospective studies are needed to directly compare the results of RP to external beam radiation therapy with hormonal therapy in high-risk men.

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