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Clinical role of pathological downgrading after radical prostatectomy in patients with biopsy-proven Gleason score 3+4 prostate cancer

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Abstract

- To identify preoperative factors predicting Gleason score downgrading after radical prostatectomy in patients with biopsy Gleason score 3+4 prostate cancer.
- To determine if prediction of downgrading can identify potential candidates for active surveillance.
- We identified 1317 patients with biopsy Gleason score 3+4 prostate cancer who underwent radical prostatectomy at Memorial Sloan-Kettering Cancer Center between 2005 and 2013.
- Several preoperative and biopsy characteristics were evaluated by forward selection regression, and selected predictors of downgrading were analyzed by multivariable logistic regression.
- Decision curve analysis was performed to evaluate the clinical utility of the multivariate model.
- Gleason score was downgraded after radical prostatectomy in 115 patients (9%).
- We developed a multivariable model using age, prostate specific antigen density, percent of positive cores with Gleason 4 cancer out of all cores taken, and maximum percent of cancer involvement within a positive core with Gleason 4 cancer.
- The area under the curve for this model was 0.75 after ten-fold cross validation.

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Conflicts of Interest
None disclosed.

- However, decision curve analysis revealed that the model was not clinically helpful in identifying patients who will downgrade at radical prostatectomy for the purpose of reassigning them to active surveillance.
- While patients with pathology Gleason score 3+3 with tertiary Gleason pattern 4 or lower at radical prostatectomy in patients with biopsy Gleason score 3+4 prostate cancer may be potential candidates for active surveillance, decision curve analysis showed limited utility of our model to identify such men.
- Future study is needed to identify new predictors to help identify potential candidates for active surveillance among patients with biopsy-proven Gleason score 3+4 prostate cancer.

Keywords

prostate; prostatic neoplasms; prostatectomy; downgrading; active surveillance; decision curve analysis

Introduction

The incidence of indolent prostate cancer has increased substantially over the past two decades due to the widespread use of prostate-specific antigen (PSA) testing for the early detection of prostate cancer. Many of the cases of prostate cancer identified by PSA testing benefit little, if any, from active treatment and thus represent overdiagnosis [1, 2]. Active surveillance evolved as a treatment strategy to prevent overtreatment. Early evidence shows that patients with low risk prostate cancer do not have significantly worse survival when treated with active surveillance compared to surgery or radiation [3, 4]. Recent studies suggest that eligibility for active surveillance might be extended to selected patients with biopsy Gleason score 3+4 prostate cancer. However, there is no concensus regarding how to select candidates for active surveillance among these patients [2, 5–7].

A certain subset of patients will have downgrading at radical prostatectomy [8–11] and these men have been shown to have more favorable outcomes after radical prostatectomy than would have been predicted by the biopsy Gleason score [9]. Furthermore, recent evidence suggests that men with Gleason score 6 prostate cancer in their radical prostatectomy specimen rarely develop distant metastasis or die from prostate cancer [12]. Taken together, these data suggest that most men with Gleason score 6 prostate cancer could be managed with active surveillance [2, 7]. Thus, we hypothesized that prediction of downgrading from Gleason score 3+4 at biopsy to Gleason score 3+3 after radical prostatectomy could help to select potential candidates for active surveillance in patients with biopsy-proven Gleason score 3+4 prostate cancer.

Patients and Methods

We looked at all 1925 men with a biopsy Gleason score of 3+4 who received a radical prostatectomy at Memorial Sloan-Kettering Cancer Center from January 2005 to January 2013. We excluded men for whom more than 6 months passed between biopsy and surgery (n=130) because their disease may have progressed between the time of biopsy and the time

of surgery. We then excluded men who were missing prostate volume information as assessed by magnetic resonance imaging (MRI) (n=104) and men who were missing pathology information from their biopsy such as number of cores (n=42), number of positive cores (n=39), number of cores with Gleason pattern 4 cancer (n=131) and maximum percent of cancer involvement within biopsy cores (n=142). We also excluded men who received less than 12 cores on biopsy (n=298), and men who received neoadjuvant chemotherapy (n=4), neoadjuvant hormone therapy (n=2) or radiation therapy before radical prostatectomy (n=15). This left us with a cohort of 1317 men. We did not find evidence of difference between these 1317 men and the men who were excluded in terms of age, baseline PSA, clinical stage or pathologic stage (all $p > 0.05$). However, we did find that men who were excluded were somewhat less likely to have a pathologic Gleason grade of 6 or lower compared to the men in our cohort (5.8% vs 8.7%, $p < 0.0001$).

We wanted to predict downgrading preoperatively, so we evaluated the relationship between downgrading and several preoperative variables. Downgrading was defined as any decrease in the pathological Gleason score with the biopsy Gleason score as a total sum of primary and secondary grades. Examined variables were age, body mass index, clinical T stage (T1c vs T2 vs T3 vs T4), preoperative PSA, MRI-measured prostate volume, PSA density, percent of positive cores out of all cores taken, percent of positive cores with Gleason pattern 4 cancer out of all cores taken, and maximum percent of cancer involvement within a positive core with Gleason pattern 4 cancer. Because many of these variables are correlated with one another, we used a forward selection process to choose the best predictors. Variables were added one at a time to a multivariable logistic regression predicting downgrading where the variables that most improve the area under the receiver operating characteristic curve (AUC) were included in the model. This process continued until no remaining variables increased the AUC by more than 1%. We also performed a decision curve analysis to evaluate the clinical utility of our model. We used ten-fold cross validation including the variable selection process to correct estimates of predictive value for optimism. This involved splitting the dataset into ten groups at random, using data from nine of the groups to create a model using the forward selection process described, applying this model to the omitted tenth group and recording the predicted probabilities. This was repeated ten times, omitting each group in turn. The AUC and decision curve were therefore calculated from predictions made for each patient that did not include any data from that patient. Biochemical recurrence (BCR)-free survival probabilities were estimated using Kaplan-Meier methods and differences in BCR-free survival were tested with the log rank test. The definition of BCR included a PSA of ≥ 0.1 ng/ml with confirmatory rise, failure of PSA to fall to undetectable level after radical prostatectomy, or secondary treatment for elevated PSA. All analyses were conducted using Stata 12 (Stat Corp., College Station, TX).

Results

Patient characteristics are given in Table 1. In our cohort of 1317 men, 115 (9%) were downgraded at surgery. Of these 115, 56 (49%) had tertiary Gleason pattern 4 on radical prostatectomy specimens. On the other hand, 205 patients (16%) were upgraded to a Gleason score of 4+3 or higher prostate cancer upon radical prostatectomy specimens.

On univariate analyses, we found that patients who downgraded had a clinical stage of T1c more often than higher stages (78% vs 65%, $p = 0.017$) and had lower total PSA (median 4.8 vs 5.3 ng/mL, $p = 0.004$). Patients who downgraded had less Gleason pattern 4 cancer, both when looking at the maximum amount of high grade cancer within a single biopsy core (median 20% vs 40%, $p < 0.0001$) and when looking at the percent of cores containing Gleason 4 cancer out of all cores taken at biopsy (median 8% vs 16%, $p < 0.0001$).

From our forward selection process, we developed a multivariable model that included age at treatment, PSA density and amount of Gleason pattern 4 cancer out of all biopsy cores as well as the maximum amount found within a single core (Table 2). Lower age at treatment and lower PSA density was associated with downgrading as were lower percent of positive cores with Gleason pattern 4 cancer out of all cores taken and lower maximum percent of cancer involvement within a positive core with Gleason pattern 4 cancer. The AUC of this model after 10-fold cross validation was 0.75.

Prior to our analysis, we had to determine a threshold probability. This is the probability of downgrading at which we are ambivalent about whether to treat with active surveillance or radical prostatectomy. The threshold probability is an implicit measure of how we compare the harms of unnecessarily treating a man who will downgrade with radical prostatectomy compared to the harms of placing on active surveillance a man destined to have Gleason 7 or higher disease on pathologic analysis of the surgical specimen. We used a threshold for downgrading of 50%, that is, we would advise active surveillance for any man with a 50% or greater probability of pathologic Gleason 6. This 50% probability is minimum threshold we would consider based on the basic concept of active surveillance, which includes close monitoring of disease. Given this threshold probability, decision curve analysis did not show that making treatment decisions based on our model was superior to surgery for all patients in our cohort (Figure 1). The prevalence of downgrading is relatively low compared to our threshold probability so our model would have to be exceptionally good in order to be clinically helpful. So while our model does have good discrimination, its ability to help identify patients who could benefit from active surveillance as opposed to immediate radical prostatectomy is limited.

Regarding pathologic outcomes, the men with downgraded disease were, as expected, significantly less likely to have seminal vesicle invasion, lymph node metastasis, positive surgical margin, and extracapsular extension compared to those without downgrading ($p = 0.008$, 0.029, 0.005, and < 0.0001, respectively). During the follow-up for a median of 22 months, no patients with downgraded disease had BCR. The log-rank test showed that patients who did and did not downgrade had significant differences in BCR-free survival ($p = 0.003$) (Figure 2).

Discussion

Although discrepancies in Gleason score between biopsy and radical prostatectomy are well recognized, few studies have focused on downgrading from the biopsy to the radical prostatectomy specimen [8–11]. A large prostate volume, lower maximum percentage of cancer in any core, more number of biopsy cores obtained, lower serum PSA level, and

lower clinical T stage have been reported as significant predictors of downgrading [9, 10, 13]. However, to our knowledge only one previous study [11] specifically examined patients with biopsy-proven Gleason score 3+4 prostate cancer to identify factors correlated with Gleason score downgrading in the radical prostatectomy specimen. Epstein et al. [11] investigated the predictors of downgrading from Gleason score 3+4 after biopsy to Gleason score 5–6 after radical prostatectomy (n = 943) and found that the PSA level, maximum percentage of cancer, and pathology measured prostate weight were independent predictors of downgrading in the multivariable analyses. However, these investigators were unable to create an accurate prediction model; the c-index of their multivariate model was only 0.629. In addition, as they included pathology weight of the prostate in the model, it might be difficult to use this model in the preoperative prediction of downgrading.

Although downgrading may occur for several reasons [11], one possibility is over-sampling of the very small (less than 5%) amounts of Gleason pattern 4 cancer [11, 14]. Because of its very small proportion, Gleason pattern 4 tumor may be missed by the usual radical prostatectomy pathology examination or might be noted as the presence of a tertiary Gleason pattern if these small tumors are detected. Therefore, we included an estimate of tumor volume in our model, especially for Gleason pattern 4, in an attempt to create a more accurate method of predicting downgrading. In this context, Whitson et al. [8] showed the percentage of cores positive for high-grade (Gleason pattern 4 or 5) cancer to be a useful predictor of downgrading. Although these investigators defined the percentage of positive cores with high-grade cancer as the number of cores with high-grade cancer divided by the total number of positive cores, we defined it instead as the number of cores with Gleason pattern 4 cancer divided by the total number of cores obtained because we would like to know the cancer burden of Gleason pattern 4 cancer in the entire prostate gland. As a result, we confirmed that this novel parameter was an independent predictor of downgrading.

In the present study, we focused on downgrading and did not consider other factors such as extraprostatic disease or tumor volumes, which are usually included in predictions of insignificant cancer. Although it is known that recent International Society of Urological Pathology Gleason grade modifications made in 2005 have led to a Will Rogers effect and the prognosis of the new Gleason score 3 + 4 prostate cancer as well as the new Gleason score 6 prostate cancer should improve [15–17], we currently have little evidence regarding whether the definition of insignificant prostate cancer such as that suggested by the Epstein criteria remains suitable for the management of currently diagnosed prostate cancer.

Zlotta et al. prospectively evaluated the prostate cancer prevalence during autopsy in 320 men and found that overall, 31.6% of cancers had a Gleason score ≥7 and 11.1% of patients had extraprostatic disease [18]. The authors concluded that the definition of clinically insignificant prostate cancer might be worth re-examining. Van der Kwast and Roobol discussed the current pathological criteria for insignificant prostate cancer and noted that more liberal eligibility criteria would be adopted for participation in an active surveillance protocol [17]. The authors also mentioned that, assuming an 8% lifetime risk of clinical prostate cancer (based on pre-PSA-screening-era USA SEER data), essentially all Gleason score 6 prostate cancer would be included in the pathological definition of insignificant prostate cancer, irrespective of their volume, and concluded that we should reassess our

eligibility criteria for enrollment in active surveillance and develop less restrictive criteria that would enable more men to enroll and participate in active surveillance programs [17]. Ross et al. demonstrated that Gleason score 6 prostate cancer rarely caused distant metastases and/or compromised patients' lives following a pathology review conducted according to the International Society of Urological Pathology 2005 modified criteria [12]. Mullins et al. studied a total of 4478 patients who underwent radical prostatectomy before 2005 with a median follow-up of 10 years; subgroup analyses revealed that only 1 out of 2185 patients with Gleason score 6 prostate cancer died of cancer, although 309 patients with pT3a disease who had undergone radical prostatectomy were included [19]. Ellis et al. [20] studied 6156 consecutive men with Gleason score 6 prostate cancer in terms of the relationship between prostate cancer -specific outcomes and multiple positive cores. The authors found that the Gleason score of the biopsy was a powerful prognostic factor and that a favorable outcome was maintained even in cases exhibiting multiple positive cores with Gleason score 6 prostate cancer. In the studies conducted by the Johns Hopkins group, whereas Tosoian et al. reported a favorable prostate cancer-specific mortality outcome for patients with very-low-risk active surveillance-treated prostate cancer [21], a recent study by the same authors reported that in another population that met the same criteria (very-low-risk prostate cancer), 8.5% of the patients had non-organ confined disease [22]. In addition, a recent study by Adam et al. reported the lack of a significant difference in biochemical-recurrence-free survival outcomes in patients with Gleason score 6 prostate cancer, who were diagnosed between 2007 and 2013, with and without tertiary Gleason patterns [23]. Based on these findings, it is possible that patients with downgraded disease in the present study could be managed with active surveillance if we could preoperatively and accurately predict downgrading; therefore, focusing on downgrading would be a reasonable option for the selection of potential candidates for active surveillance among patients with biopsy-proven Gleason score 3+4 prostate cancer.

The present study showed that no patient with downgraded disease had seminal vesicle invasion or lymph nodes metastasis at radical prostatectomy. In addition, none experienced BCR during follow-up of median 22 months. Thus, patients with pathology Gleason score 3+3 with tertiary Gleason pattern 4 or lower in the radical prostatectomy specimen appear to have favorable prostate cancer outcomes despite having biopsy Gleason 3+4 cancer. So patients with Gleason score 3+3 and tertiary Gleason pattern 4 or lower at radical prostatectomy would be potential active surveillance candidates if we were able to identify them preoperatively. However, determining whether the downgraded patients could be managed via active surveillance would require prospective confirmation and a long-term follow-up study.

Our study has several limitations. First, it is a retrospective single institutional study with the associated limitations of such a study design, including selection bias such that we only included the patients who underwent radical prostatectomy when treatment was not randomized. Since patients who received other treatments may have different disease characteristics that affect the relationship between preoperative characteristics and downgrading, it is unclear whether our model would predict downgrading in these other patient populations; although, it is unlikely that it would. In addition, we only included patients with complete biopsy information. Missing biopsy information may indicate more

extensive disease as we did find that excluded patients had higher Gleason grades on radical prostatectomy pathologic examination. This supports the robustness of our decision curve analysis as the rate of downgrading among the full population would have been lower than we observed in our study cohort, making it even more difficult to reach the predetermined threshold probability to predict downgrading. Second, biopsy technique heterogeneity occurred because a proportion of the cases in our cohort were biopsied at outside hospitals. In fact, not all institutions had introduced the same prostate needle biopsy protocol, which might have introduced some bias. We did attempt to address this somewhat by including only patients from whom a minimum of 12 cores were collected during their prostate biopsy sessions, a criterion that was recommended in a recent paper [24] in order to reduce the potential effect of biopsy specimen under-sampling as much as possible. Third, the pathology examinations were performed by several pathologists, allowing some variety in the interpretation/reporting of the pathology findings. One particular concern is the interpretation of maximum percent of high grade disease within a single core. If there were 2 or more foci of prostate cancer in a single biopsy core separated by benign intervening stroma, maximum percent of cancer involvement within a positive core could be measured i) as if they were one single continuous focus, or ii) by adding up the separate percentages of tumor involvement. We could not distinguish which methods were used. Fourth, follow-up in the current study was relatively short. Further evaluations with longer follow-up time is necessary to determine the extent of downgrading's impact on oncologic outcomes. Finally, although our multivariable model does have good discrimination, the results of decision curve analysis showed limited utility of the model to predict downgrading. Given the difference between our threshold probability and the prevalence of downgrading, the decision curve analysis showed that a model would need exceptional discrimination in order to be clinically useful. Recent studies suggest that the MRI or genomics can distinguish between high grade (Gleason pattern 4 or higher) and low-grade (Gleason pattern 3 or lower) prostate cancer [25, 26]. We believe that incorporating information from MRI imaging and/or genomics are needed to identify new predictors that improve our ability to identify potential candidates for active surveillance among these patients.

In conclusion, while patients with pathology Gleason score 3+3 with tertiary Gleason pattern 4 or lower at radical prostatectomy had very favorable pathologic and BCR-free survival outcomes and as such may be potential candidates for active surveillance, decision curve analysis showed limited utility of this model in the context of assigning patients with Gleason score 3+4 at biopsy to active surveillance or radical prostatectomy. Future studies including imaging and/or genomics may improve our ability to identify potential candidates for active surveillance among these patients.

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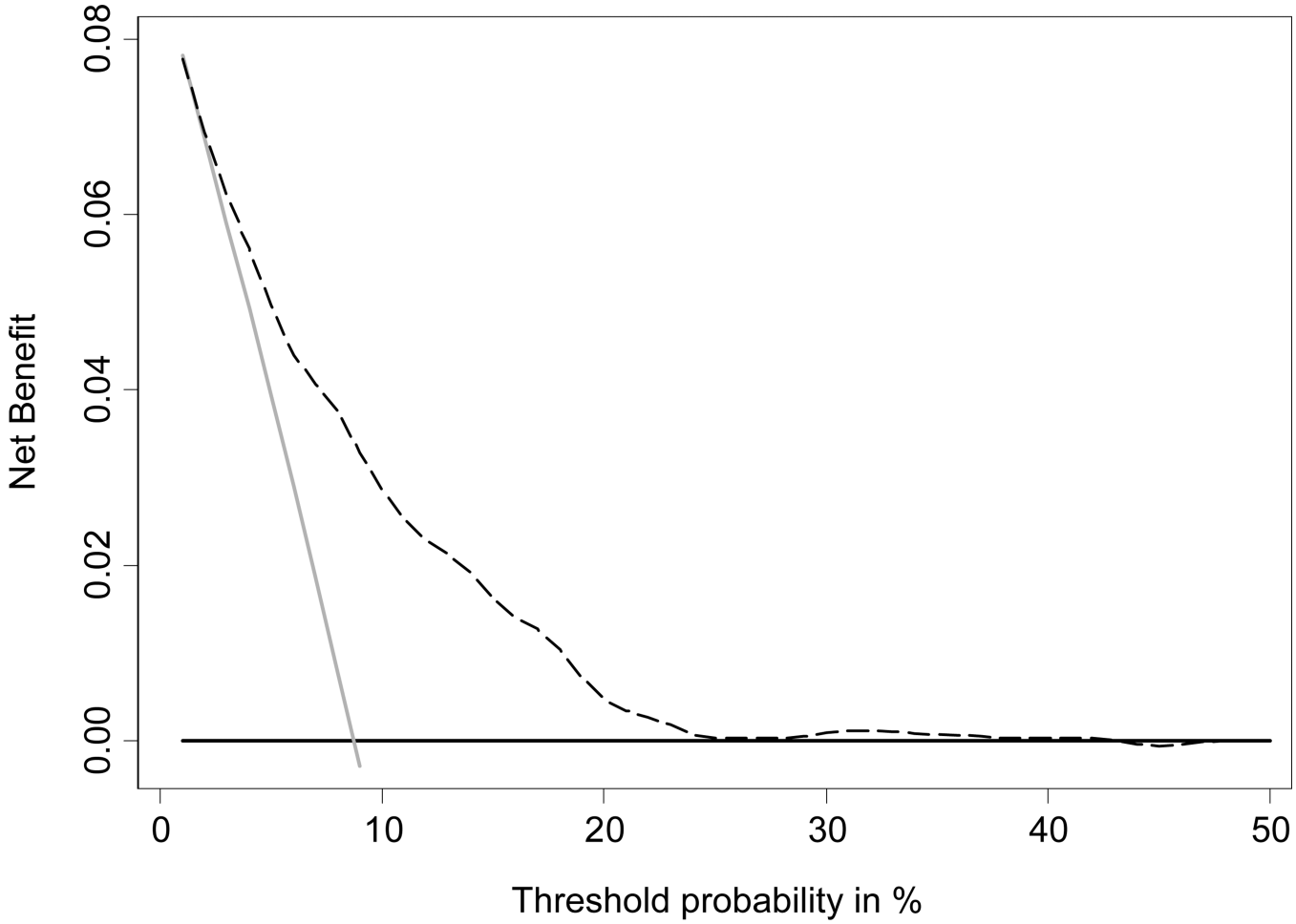

Figure 1.

Decision curve of the final model predicting downgrading after radical prostatectomy in patients with biopsy-proven Gleason score 3+4 prostate cancer with the net benefit of assigning patients to active surveillance based on model (dashed line) compared to treating all patients with radical prostatectomy (solid black line) and treating all patients with active surveillance rather than radical prostatectomy (solid grey line).

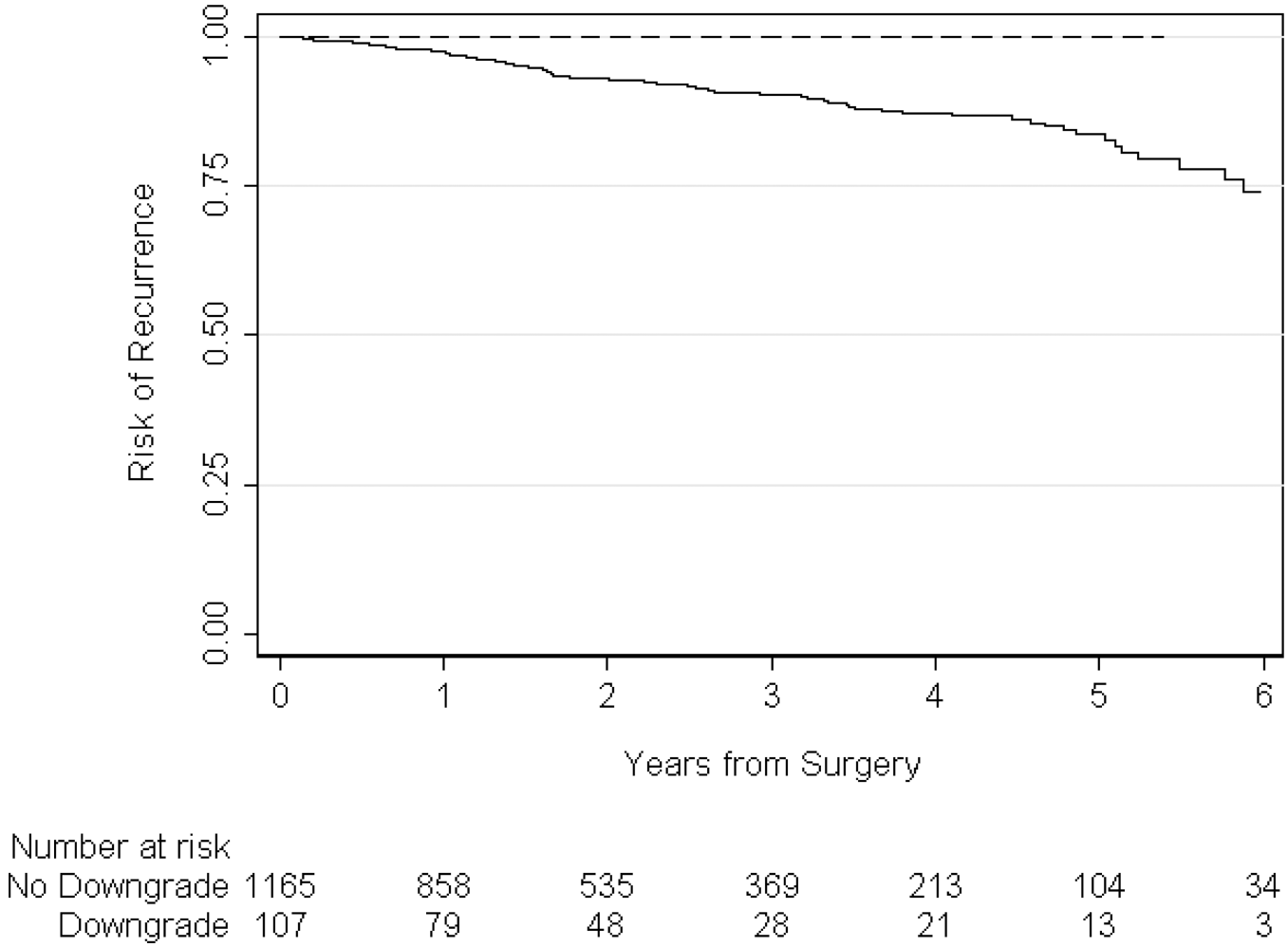

Figure 2.

Kaplan-Meier curves of biochemical recurrence-free survival for patients who downgraded (dashed line) and did not downgrade (solid line).

Table 1

Patient characteristics. Data presented as medians with interquartile ranges in parentheses or frequency with percentages in parentheses, using Fisher's exact test or Wilcoxon rank sum test, respectively.

Characteristics	**No Downgrade n=1202 (91%)**	**Downgrade n=115 (9%)**	**p-value**
Age at Treatment (years)	61 (56, 66)	60 (55, 64)	0.11
Body Mass Index (kg/m^2) (n=1316)	28 (26, 31)	27 (25, 30)	0.007
Clinical Stage (n=1314)			0.017
T1c	784 (65%)	90 (78%)	
T2	387 (32%)	22 (19%)	
T3	27 (2.3%)	3 (2.6%)	
T4	1 (0.1%)	0 (0%)	
Total PSA (ng/mL)	5.3 (4.0, 7.3)	4.8 (3.1, 6.2)	0.004
Prostate Volume (cm^3)	32.3 (24.9, 44.6)	34.4 (27.7, 51.8)	0.014
PSA Density (ng/mL per cm^3)	0.16 (0.11, 0.24)	0.12 (0.09, 0.16)	<0.0001
Percent of Positive Cancer Cores out of all Biopsy Cores (%)	31 (17, 46)	25 (13, 42)	0.003
Percent of Positive Cancer Cores with Gleason Pattern 4 Cancer out of all Biopsy Cores (%)	16 (8, 25)	8 (7, 15)	<0.0001
Maximum Percent of Cancer involvement within a Positive Core with Gleason Pattern 4 Cancer (%)	40 (20, 65)	20 (10, 35)	<0.0001
Seminal Vesical Invasion	57 (4.7%)	0 (0%)	0.008
Lymph Node Invasion (n=1279)	46 (3.9%)	0 (0%)	0.029
Positive Surgical Margin (n=1316)	185 (15%)	7 (6.1%)	0.005
Extracapsular Extension	478 (40%)	15 (13%)	<0.0001
Pathologic Stage			<0.0001
pT0	0 (0%)	1 (0.9%)	
pT2	711 (59%)	99 (86%)	
pT3	485 (40%)	15 (13%)	
pT4	6 (0.5%)	0 (0%)	

PSA indicates prostate-specific antigen.

Table 2

Multivariable models for the prediction of Gleason score downgrading after radical prostatectomy in patients with biopsy Gleason 3+4 prostate cancer.

Variable	Odds Ratio	95% C.I.	p-value
Age at Treatment (years)	0.96	0.93, 0.99	0.003
PSA Density (per 0.1 ng/mL/cm^3)	0.61	0.48, 0.79	0.0001
Percent of Positive Cancer Cores with Gleason Pattern 4 Cancer out of all Biopsy Cores (per 5%)	0.83	0.73, 0.95	0.006
Maximum Percent of Cancer involvement within a Positive Core with Gleason Pattern 4 Cancer (per 5%)	0.88	0.84, 0.93	<0.0001

PSA indicates prostate-specific antigen; C.I., confidence interval.