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## Effects of Pathologic Upstaging or Upgrading on Metastasis and Cancer-Specific Mortality in men with Clinical Low-risk Prostate Cancer

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### Abstract

**Objectives:** To determine if the presence of adverse pathologic features in patients eligible for active surveillance are prognostic of poor oncologic outcomes, independent of pretreatment risk.

**Patients & Methods:** A retrospective analysis was performed on patients who underwent radical prostatectomy at two institutions (CCF, MSKCC) between 1987–2008 and who had subsequent follow-up. Rates of biochemical recurrence, metastasis and death from prostate cancer were compared among patients with adverse pathologic features (Gleason 7, pT3, or lymph node invasion) based on D’Amico clinical risk (low vs. intermediate/high). We also compared survival outcomes between patients with and without pathologic upgrading/upstaging among D’Amico low-risk patients. Univariate and multivariable Cox regression models were used to assess the association between clinical risk, pathologic reclassification and oncologic outcomes.

**Results:** We identified 16,341 patients who underwent radical prostatectomy, of whom 6,371 were clinically low-risk. Adverse outcomes in men with adverse pathologic features were significantly lower in those with low clinical risk, with an approximate 50% and 70% reduction in the risk of metastasis and death, respectively. Only pathologic upgrading/upstaging to Gleason 8, seminal vesicle invasion, and lymph node invasion from clinical low-risk disease were associated with adverse outcomes. However, these types of reclassification were rare.

**Conclusion:** Clinical low-risk patients with pathological upgrading/upstaging have substantially lower rates of important oncologic outcomes compared to those with higher pre-treatment risk and not substantially different than low-risk patients without pathological upgrading/upstaging. These results call into question the use of this endpoint to counsel patients about the merits and risks of surveillance.

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**Conflicts of Interest:** None for all authors.

## Keywords

clinical risk; pathologic upgrading; pathologic upstaging; prostate cancer; radical prostatectomy; survival outcomes

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## Introduction

Clinical risk assessment of prostate cancer (PCa) is imperfect. While adjunctive tools such as genomic classifiers, molecular biomarkers and multiparametric prostate magnetic resonance imaging (mpMRI) have shown promise for improving risk categorization when combined with standard trans-rectal ultrasound (TRUS) biopsy<sup>1,2</sup>, a significant number of patients who undergo radical prostatectomy (RP) will harbor worse disease features (pathologic Gleason upgrading or pathologic upstaging) than clinically predicted<sup>3</sup>. With current guidelines advocating active surveillance (AS) as the standard for patients with National Comprehensive Cancer Network (NCCN) very-low and low-risk PCa<sup>4</sup>, the risk of pathologic upgrading/upstaging after deferred radical therapy is of increasing concern<sup>5</sup>. However, the clinical and prognostic significance of pathologic upgrading/upstaging from clinical very-low and low-risk disease remains controversial<sup>6,7</sup>. In addition, novel molecular biomarkers and genomic classifiers have demonstrated accuracy in predicting adverse pathology and biochemical recurrence (BCR) after RP and help to risk-stratify patients who are candidates for AS<sup>8-11</sup>. Previous work has shown that low-risk patients have improved rates of BCR among those with adverse pathology at RP<sup>12</sup>. However, whether adverse pathology or BCR negatively impacts harder endpoints, such as metastases and survival in clinical low-risk patients remains unclear.

We therefore investigated the role that pre-operative clinical risk plays in estimating the risk of oncologic outcomes including BCR, distant metastases and cancer-specific survival (CSS) in the context of adverse pathologic features, including upstaging and upgrading.

## Patients & Methods

After obtaining institutional review board approval, we identified 11,925 patients who underwent primary radical prostatectomy at Memorial Sloan Kettering Cancer Center (MSKCC) between 1987 and 2015. We also identified 4,868 patients who underwent primary radical prostatectomy at Cleveland Clinic Foundation (CCF) between 1987 and 2008. Patients were excluded if they were unable to be assigned a D'Amico risk classification due to missing data (N=462), leaving 16,341 patients in the final cohort.

We aimed to assess the association between pre-operative risk and the risk of BCR and distant metastases among men found to have adverse pathology. D'Amico risk classifications were used to identify clinically low, intermediate and high-risk PCa. We addressed the problem in both directions, that is, we asked both "For men with high-risk surgical pathology, is preoperative risk associated with outcome?" and "For men with low preoperative risk, is high-risk surgical pathology associated with outcome?"

For the first set of analyses, we examined the role of pre-operative risk among four cohorts of men who were identified based on the presence of four adverse pathologic features: men with extracapsular extension (ECE), seminal vesicle invasion (SVI), lymph node involvement (LNI) and pathologic Gleason grade  $\geq 7$ . In each cohort, we calculated Kaplan Meier (KM) estimates and used log rank tests to test for differences in BCR-free survival, metastasis-free survival and CSS between men with adverse pathologic features who had clinical low-risk disease and men who did not have clinical low-risk disease. To assess whether the association between pre-operative risk and oncologic outcomes for men with adverse pathology persist when controlling for other pathologic features, we created a multivariable Cox proportional hazards model that was adjusted for pre-operative PSA, pathologic Gleason grade ( $\leq 6$ , 7 or  $\geq 8$ ), and the presence of ECE, SVI and LNI (N0, N1, or Nx), and applied this model separately to each cohort. To investigate whether clinical risk affected the risk of BCR, distant metastasis, or CSS differently between the two cohorts, the analyses were repeated separately in each cohort, and heterogeneity Chi squared tests using Cochran's Q were performed. Since data was available for Cleveland Clinic patients to 2008, and for MSKCC patients to 2015, we repeated the analyses excluding MSKCC patients from 2009 to 2015 as sensitivity analyses.

For the second set of analyses, we included D'Amico low-risk, androgen deprivation naïve patients who underwent RP at CCF between 1987 and 2008 and who had subsequent follow-up. Upgrading and upstaging were categorized in several ways: Gleason 3+4 upgrading; Gleason 4+3 upgrading; Gleason  $\geq 8$  upgrading; pT3a upstaging; SVI or LNI upstaging; and Gleason  $\geq 8$  or SVI or LNI. Analyses were performed using Stata 13.1 (StataCorp, College Station, TX) and SPSS version 22 (IBM, Chicago, IL).

## Results

Patient and disease characteristics stratified by site and by D'Amico risk are reported in Table 1a and 1b, respectively. In the combined cohort, 6,371 (39%) men had D'Amico clinically low-risk PCa, while 9,970 (61%) had D'Amico intermediate or high-risk PCa. Among the 16,341 men in this cohort, 2,827 men had biochemical recurrence, 679 men developed distant metastases, and 295 men died of PCa. Median follow-up for survivors was 4.3 years (interquartile range 1.8, 8.0). There were 5,596 and 2,124 men followed for 5 and 10 years without BCR, respectively. Meanwhile, 7,028 and 2,900 men were followed for 5 and 10 years without distant metastasis, respectively. A total of 2,121 men were followed for 10 years without BCR, distant metastasis, or death from PCa.

Oncologic outcomes were assessed in four cohorts of men. The ECE cohort included 5,557 men, of whom 1,016 (18%) had low-risk disease. The SVI cohort included 1,406 men, with 70 of those men having low-risk disease (5%). The LNI cohort included 970 men, with 23 men having low-risk disease (2.4%). 2163 (45%) of the CCF patients did not undergo lymphadenectomy and was mainly due to the low nomogram-predicted risk of LNI based on clinical features and non-suspicious nodes at the time of RP. The largest cohort included 10,836 men with pathologic Gleason scores  $\geq 7$ , of whom 2,955 had low-risk disease (27%) preoperatively.

The results of our first set of analyses are shown in table 2a, 2b, 2c. Amongst men with adverse features on surgical pathology, preoperative low-risk status was associated with an approximate 50% and 70% reduction in the risk of PCa death and metastasis respectively. The results for LNI differ slightly, but these analyses are based on very small numbers of patients and are associated with very wide confidence intervals. KM rates of BCR-free survival, metastasis-free survival and CSS of patients with pathologic ECE, SVI, Gleason 7 and LNI and stratified by clinical risk are shown in supplementary figures 1, 2 and 3, respectively.

Since patients from two cohorts were included, we also investigated whether there was heterogeneity between institutions in the effect of clinical low-risk disease on oncologic outcomes. We found significant heterogeneity between sites for the outcome of BCR-free survival when comparing patients among patients with ECE or LNI, and for the outcomes of BCR-free and metastasis-free survival among patients with pathologic Gleason grade 7. For cases where significant heterogeneity in effect size was found, having clinical low-risk was associated with a reduction in risk of BCR or distant metastasis at both institutions, with one exception. The multivariable model for BCR-free survival among CCF patients with LNI showed a non-significant increase in risk of BCR for low-risk patients (HR 1.64, 95% CI 0.58, 4.66,  $p=0.4$ ). However, there were only 5 patients from the CCF cohort who were clinically low-risk and had LNI.

As a sensitivity analysis, we dropped 4,428 MSKCC patients treated between 2009 and 2015 to restrict the cohort to the same years for both sites. No appreciable changes in the results were seen when excluding these patients.

Our second set of analyses examined whether pathologic upstaging or upgrading influenced survival outcomes in men with low-risk disease. Baseline characteristics for this group are described in table 3. Of the 2297 CCF D'Amico low-risk patients identified, 1,305 (57%) experienced any pathologic upgrading or upstaging, while 992 (43%) did not experience any pathologic upgrading or upstaging (Table 4). When isolating pT3a upstaging only, regardless of pathologic Gleason score, 402 (18%) patients experienced such reclassification, while 1858 (82%) did not. Kaplan-Meier estimates of 10 year CSS are presented in Table 4. Of all types of pathologic reclassification, only upgrading to Gleason 8 and upstaging to SVI or LNI were associated with worse CSS. However, reclassification on the basis of Gleason 8 or SVI or LNI was observed in only 62 (3%) patients. As there were only 8 deaths from PCa in the CCF cohort, a multivariable analysis was not performed.

## Discussion

AS in patients with low-risk PCa is underutilized<sup>13</sup>, and may be attributed, in part, to the perceived risk of upgrading or upstaging at RP. Our analysis of patients from MSKCC and CCF who underwent RP between 1987 and 2015 suggests that in patients who are candidates for AS based on clinical features, pathologic upgrading or upstaging from clinical low-risk PCa has limited long-term effects on BCR, metastasis-free survival and CSS rates among patients with adverse pathologic features. Intuitively, we believe that when matched for adverse pathologic findings, clinically low-risk patients will have superior outcomes

when compared to clinically intermediate or high-risk patients. We therefore sought to describe the magnitude of this difference in outcome. We found that clinically low-risk patients with adverse pathologic features exhibited significantly better outcomes than patients with clinically intermediate or high-risk features. In addition, our analysis of 2297 CCF patients with clinical low-risk PCa who underwent RP suggests that the deleterious effects of adverse pathologic reclassification on CSS are of questionable significance. While patients with arguably the most severe forms of adverse pathologic reclassification (Gleason score 8, SVI and/or LNI) did exhibit significantly worse CSS rates, these forms of reclassification from low-risk disease were rare. Our results suggest that the risk of upgrading/upstaging from low-risk disease should not deter clinicians from offering AS to clinical low-risk patients.

Our results beg the question: why do patients with adverse pathological features have differing outcomes based on clinical features? We believe that the overall clinical picture of low-risk patients should be considered, regardless of final pathology. Clinically low-risk patients present not only with Gleason scores  $\leq 6$ , but also with low serum PSA levels ( $<10$  ng/ml) and clinically undetectable or minimally detectable disease volume (T1c or T2a). While we did not perform tumor volumetric analysis on our cohorts, we suspect that we would observe smaller tumor volumes in clinically low-risk patients. We also believe that the biology of clinical low-risk PCa that exhibit adverse pathologic features is different than those that present clinically with adverse features, even if the final pathologic specimens are categorized similarly. There is strong evidence to suggest that there is considerable biologic heterogeneity among clinical risk groups and we believe that these prior findings help to explain our results <sup>10</sup>.

We believe that our results confirm the utility of standard TRUS biopsy alone as a risk-assessment tool for low-risk patients who are candidates for AS. While prostate mpMRI, molecular-based biomarkers and genomic classifiers aim to identify patients who potentially harbor more adverse pathologic features than clinically detected using traditional techniques, we question the value of identifying those that potentially harbor ECE or Gleason 3+4 disease, as their BCR, metastasis and survival rates do not seem to be adversely affected when compared to those without such pathologic features. Furthermore, we observed that the absolute rate of the most severe forms of pathologic reclassification is very low. Whether adjunctive tools are both sufficiently accurate and cost effective for identifying the most severe adverse pathologic features in a clinically low-risk population remains to be seen.

Additionally, we observed that among low-risk patients with adverse pathologic features and who developed BCR, the risk of subsequent PCa-related metastases or death was approximately half the risk of BCR, suggesting that BCR does not necessarily lead to morbidity from metastases or death. These findings are consistent with previous reports <sup>12</sup>.

Our study results reflect those of previous analyses. In a recent study, similar BCR rates were seen among AS candidates who were pathologically upgraded from Gleason 3+3 to 3+4 <sup>14</sup>. Meanwhile, Muralidhar et al. demonstrated that patients with occult T3 disease exhibit better CSS than patients with clinical T3 disease <sup>15</sup>. However, we believe our study is the first to analyze BCR, metastasis-free and survival rates from the viewpoint of both

adverse pathologic features, stratified by D'Amico clinical risk and from the viewpoint of pathologic upstaging from clinical D'Amico low-risk disease. Our analyses from both vantage points reached similar conclusions. In addition, we believe our analysis of 2297 CCF patients with clinical low-risk disease and who were pathologically upgraded and/or upstaged at RP is the first to study various definitions of pathologic reclassification with such granularity.

Our study carries several limitations. Firstly, the retrospective nature of our study lends itself to inherent biases. For example, our cohorts likely carry a selection bias, since many patients diagnosed with clinically very-low or low-risk disease at our respective institutions pursue AS rather than curative treatments such as surgery or radiation. However, AS for low-risk disease as the accepted standard is relatively novel and was not widely employed at our respective institutions until the latter part of the study period, thus limiting the selection bias in our study population. Furthermore, previous reports have found no difference in pathologic outcomes between low-risk, AS patients who underwent deferred RP versus clinically similar patients who underwent immediate RP<sup>16</sup>. Secondly, prostate mpMRI and other adjunctive classifying tools were not routinely performed on our patient population. However, in current contemporary practice, only 6.5% of biopsy-naïve men undergo prostate MRI prior to biopsy<sup>17</sup>. Our study is therefore germane to the current state of urologic practice. Moreover, although a recent randomized trial concluded that MRI with MRI-fusion biopsy identifies more significant (Gleason 3+4) PCa than standard TRUS biopsy in biopsy-naïve men<sup>18</sup>, only 3% of patients in the CCF cohort experienced significantly adverse pathologic upgrading/upstaging. This calls into question the need for such adjunctive tools in a clinically low-risk population. Thirdly, while both cohorts were similar in most respects, heterogeneity analysis revealed that certain clinical characteristics of the MSKCC and CCF cohorts had different and statistically significant effects on BCR, metastases-free and CSS. Finally, our study period was long (1988–2015) and the Gleason scoring system changed over the course of this period. Of note, many patients who were graded as Gleason 3+3 in the pre-2005 system would have been scored as Gleason 3+4 in the 2005 International Society of Urological Pathology (ISUP) update. The 2005 update has led to a “Will Rogers Effect”: because more aggressive Gleason 6 tumors were reclassified, the Gleason reclassification lowered the risk of both Gleason 6 and Gleason 7 patients. As a result, any bias introduced by including pre-2005 patients is in the opposite direction to our hypothesis, in that contemporary (post-2005) low-risk patients are at lower risk than historical (pre-2005) patients and it is thus even less likely that upstaging or upgrading would lead to poor clinical outcome.

Despite these limitations, we believe our study contributes significant understanding regarding the long-term outcomes of clinical low-risk PCa patients regardless of adverse reclassification at RP. We believe that patients who exhibit either upgrading or upstaging at RP should be counseled that their long-term risk of adverse outcome is not necessarily worse than patients without pathologic reclassification. In particular, predicted risk of upstaging or upgrading should not be used to recommend immediate treatment in low-risk PCa patients who are eligible for AS.

## Conclusion

Clinical low-risk patients with adverse pathologic findings at radical prostatectomy have substantially lower rates of important oncologic outcomes compared to those with higher clinical risk and not substantially different than low-risk patients with without upgrading or upstaging. These results call into question the risk of adverse pathologic reclassification as an endpoint to counsel patients about the merits and risks of AS.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## References

1. Radtke JP, Schwab C, Wolf MB, et al. Multiparametric Magnetic Resonance Imaging (MRI) and MRI-Transrectal Ultrasound Fusion Biopsy for Index Tumor Detection: Correlation with Radical Prostatectomy Specimen. *Eur Urol* 2016.
2. Tomlins SA, Alshalalfa M, Davicioni E, et al. Characterization of 1577 primary prostate cancers reveals novel biological and clinicopathologic insights into molecular subtypes. *Eur Urol* 2015;68:555–67. [PubMed: 25964175]
3. Epstein JI, Feng Z, Trock BJ, Pierorazio PM. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. *Eur Urol* 2012;61:1019–24. [PubMed: 22336380]
4. Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate Cancer, Version 1.2016. *J Natl Compr Canc Netw* 2016;14:19–30. [PubMed: 26733552]
5. Busch J, Magheli A, Leva N, et al. Higher rates of upgrading and upstaging in older patients undergoing radical prostatectomy and qualifying for active surveillance. *BJU international* 2014;114:517–21. [PubMed: 24112652]
6. Richstone L, Bianco FJ, Shah HH, et al. Radical prostatectomy in men aged  $\geq 70$  years: effect of age on upgrading, upstaging, and the accuracy of a preoperative nomogram. *BJU international* 2008;101:541–6. [PubMed: 18257855]
7. Moussa AS, Li J, Soriano M, Klein EA, Dong F, Jones JS. Prostate biopsy clinical and pathological variables that predict significant grading changes in patients with intermediate and high grade prostate cancer. *BJU international* 2009;103:43–8. [PubMed: 18782303]
8. Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. *J Clin Oncol* 2013;31:1428–34. [PubMed: 23460710]
9. Karnes RJ, Bergstralh EJ, Davicioni E, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. *J Urol* 2013;190:2047–53. [PubMed: 23770138]
10. Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur Urol* 2014;66:550–60. [PubMed: 24836057]
11. Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. *Eur Urol* 2015;68:464–70. [PubMed: 25454615]
12. Innadze M, Sjoberg DD, Vickers AJ. Adverse Pathologic Features at Radical Prostatectomy: Effect of Preoperative Risk on Oncologic Outcomes. *Eur Urol* 2016;69:143–8. [PubMed: 25913389]
13. Bechis SK, Carroll PR, Cooperberg MR. Impact of age at diagnosis on prostate cancer treatment and survival. *J Clin Oncol* 2011;29:235–41. [PubMed: 21135285]
14. Jo JK, Hong SK, Byun SS, Lee SE, Lee S, Oh JJ. Prognostic Significance of the Disparity Between Biopsy and Pathologic Gleason Score After Radical Prostatectomy in Clinical Candidates for

Active Surveillance According to the Royal Marsden Criteria. *Clinical genitourinary cancer* 2016;14:e329–33. [PubMed: 26935997]

15. Muralidhar V, Dinh KT, Mahal BA, et al. Differential post-prostatectomy cancer-specific survival of occult T3 vs. clinical T3 prostate cancer: Implications for managing patients upstaged on prostate magnetic resonance imaging. *Urol Oncol* 2015;33:330 e19–25.
16. Dall’Era MA, Cowan JE, Simko J, et al. Surgical management after active surveillance for low-risk prostate cancer: pathological outcomes compared with men undergoing immediate treatment. *BJU international* 2011;107:1232–7. [PubMed: 20804478]
17. Liu W, Patil D, Howard DH, et al. Adoption of Pre-Biopsy Magnetic Resonance Imaging for Men Undergoing Prostate Biopsy in the United States. *Urology* 2018.
18. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med* 2018;378:1767–77. [PubMed: 29552975]

**Table 1a.**

Patient and disease characteristics for the combined cohort analysis (N=16341).

	<b>CCF (N=4756)</b>	<b>MSKCC (N=11585)</b>
Median age at surgery (IQR)	61 (56, 65)	61 (56, 66)
Median pre-operative PSA (N=16153) (IQR)	5.9 (4.5, 8.7)	5.4 (3.9, 8.0)
Biopsy Gleason score (N=15941)		
6	3000 (63%)	4988 (45%)
7	1379 (29%)	4950 (44%)
8–10	368 (7.8%)	1256 (11%)
Clinical T stage (N=16092)		
T0	0 (0%)	11 (0.1%)
T1	3192 (68%)	6769 (59%)
T2	1458 (31%)	4109 (36%)
T3	47 (1.0%)	502 (4.4%)
T4	0 (0%)	4 (<0.1%)
Clinical D'Amico risk classification		
Low	2441 (51%)	3930 (34%)
Intermediate	1691 (36%)	5354 (46%)
High	624 (13%)	2301 (20%)
Pathologic Gleason Score (N=15159)		
6	1392 (33%)	2931 (27%)
7	2545 (60%)	6943 (64%)
8–10	295 (7.0%)	1053 (10%)
ECE (N=16282)	1578 (33%)	3979 (34%)
Seminal vesicle invasion (N=16287)	406 (8.6%)	1000 (8.7%)
Lymph node invasion (N=16329)		
Positive	123 (2.6%)	847 (7.3%)
Negative	2470 (52%)	9736 (84%)
No LND performed	2163 (45%)	990 (8.6%)
Positive surgical margins (N=16298)	1372 (29%)	2164 (19%)
Year of surgery		
1987–1990	201 (4.2%)	125 (1.1%)
1991–1995	532 (11%)	744 (6.4%)
1996–2000	1037 (22%)	1439 (12%)
2001–2005	2001 (42%)	2831 (24%)
2006–2010	985 (21%)	3621 (31%)
2011–2015	0 (0%)	2825 (24%)

**Table 1b.**

Patient and disease characteristics for both MSKCC and CCF patients (N=16,341) stratified by clinical D'Amico risk.

	<b>Low Risk (N=6371)</b>	<b>Intermediate or High Risk (N=9970)</b>
Median at age surgery (IQR)	59 (55, 64)	62 (57, 66)
Median pre-operative PSA (IQR) (N=16153)	5.0 (3.8, 6.4)	6.2 (4.4, 10.5)
Biopsy Gleason score (N=15941)		
6	6371 (100%)	1617 (17%)
7	0 (0%)	6329 (66%)
8–10	0 (0%)	1624 (17%)
Clinical T stage (N=16092)		
T0	0 (0%)	11 (0.1%)
T1	5098 (80%)	4863 (50%)
T2	1273 (20%)	4294 (44%)
T3	0 (0%)	549 (5.6%)
T4	0 (0%)	4 (<0.1%)
Clinical D'Amico risk classification		
Low	6371 (100%)	0 (0%)
Intermediate	0 (0%)	7045 (71%)
High	0 (0%)	2925 (29%)
Pathologic Gleason Score (N=15159)		
6	3176 (52%)	1147 (13%)
7	2895 (47%)	6593 (73%)
8–10	60 (1.0%)	1288 (14%)
ECE (N=16287)	1016 (16%)	4541 (46%)
Seminal vesicle invasion (N=16282)	70 (1.1%)	1336 (13%)
Lymph node invasion (N=16329)		
Positive	23 (0.4%)	947 (10%)
Negative	3712 (58%)	8494 (85%)
No LND performed	2632 (41%)	521 (5.2%)
Positive surgical margins (N=16298)	1027 (16%)	2509 (25%)
Year of surgery		
1987–1990	68 (1.1%)	258 (2.6%)
1991–1995	389 (6.1%)	887 (8.9%)
1996–2000	1146 (18%)	1330 (13%)
2001–2005	2515 (39%)	2317 (23%)
2006–2010	1717 (27%)	2889 (29%)
2011–2015	536 (8.4%)	2289 (23%)

**Table 2a.**

Univariable and multivariable analysis of the association between preoperative risk and biochemical recurrence in patients with adverse pathology. For example, the hazard ratio (HR) of 0.26 for extracapsular extension means that, amongst men with extracapsular extension, the hazard of recurrence was about two-thirds lower in men who had preoperative low-risk features in comparison to men with preoperative intermediate or high-risk disease.

Adverse Feature (Low-risk vs. Intermediate/High Risk)	Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value
Extracapsular extension	0.26 (0.22, 0.31)	<0.0001	0.49 (0.40, 0.59)	<0.0001
Seminal vesicle invasion	0.44 (0.30, 0.64)	<0.0001	0.65 (0.44, 0.96)	0.029
Pathologic Gleason 7+	0.25 (0.22, 0.29)	<0.0001	0.46 (0.39, 0.53)	<0.0001
Lymph node invasion	0.46 (0.25, 0.87)	0.016	0.47 (0.23, 0.95)	0.036

**Table 2b.**

Univariable and multivariable analysis of the association between preoperative risk and distant metastasis in patients with adverse pathology.

Adverse Feature (Low-risk vs. Intermediate/High Risk)	Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value
Extracapsular extension	0.14 (0.09, 0.22)	<0.0001	0.32 (0.19, 0.51)	<0.0001
Seminal vesicle invasion	0.24 (0.10, 0.57)	0.001	0.30 (0.12, 0.73)	0.008
Pathologic Gleason 7+	0.12 (0.08, 0.18)	<0.0001	0.30 (0.20, 0.47)	<0.0001
Lymph node invasion	0.10 (0.01, 0.70)	0.020	0.09 (0.01, 0.69)	0.020

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**Table 2c.**

Univariable and multivariable analysis of the association between preoperative risk and death from prostate cancer in patients with adverse pathology.

Adverse Feature (Low-risk vs. Intermediate/High Risk)	Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value
Extracapsular extension	0.15 (0.07, 0.29)	<0.0001	0.40 (0.19, 0.84)	0.015
Seminal vesicle invasion	0.37 (0.14, 0.99)	0.047	0.47 (0.17, 1.28)	0.14
Pathologic Gleason 7+	0.19 (0.11, 0.33)	<0.0001	0.48 (0.26, 0.87)	0.016
Lymph node invasion	0.20 (0.03, 1.42)	0.11	0.19 (0.03, 1.35)	0.10

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**Table 3.**

Patient characteristics for the CCF cohort analysis (N=2297)

Median age at surgery (IQR)	60 (55, 64)
Median pre-operative PSA (IQR)	5.2 (4.2, 6.5)
Biopsy Gleason score (%)	
6	2297 (100%)
Clinical T stage	
T1a	7 (0.3%)
T1b	15 (0.7%)
T1c	1,807 (78.7%)
T2a	468 (20.3%)
D'Amico risk classification	
Low	2297 (100%)
Year of surgery	
1987–1990	63 (3%)
1991–1995	218 (9%)
1996–2000	489 (21%)
2001–2005	1,090 (48%)
2006–2008	437 (19%)

**Table 4.**

10-year Kaplan-Meier unadjusted estimates with 95% confidence intervals for cancer-specific survival among D'Amico low-risk CCF patients who underwent RP between 1987 and 2008 (N=2297) and stratified by type of pathologic reclassification.

Type of Reclassification	N	10-Year CSS	p value
<b>Upgrade to Gleason 3+4</b>			0.9
Yes	952 (49%)	100% (95% CI N/A)	
No	992 (51%)	100% (95% CI N/A)	
Missing Gleason Breakdown	127		
<b>Upgrade to Gleason 4+3</b>			0.9
Yes	74 (7%)	100% (95% CI N/A)	
No	992 (93%)	100% (95% CI N/A)	
Missing Gleason Breakdown	127		
<b>Upgrade to Gleason 8</b>			<0.001
Yes	28 (3%)	94% (95% CI 83–100)	
No	992 (97%)	100% (95% CI N/A)	
<b>Upstage to pT3a</b>			0.7
Yes	402 (18%)	99% (95% CI 97–100)	
No	1858 (82%)	99% (95% CI 99–100)	
<b>Upstage to SVI or LNI</b>			<0.001
Yes	37 (3%)	96% (95% CI 89–100)	
No	992 (97%)	100% (95% CI N/A)	
<b>SVI, LNI or Gleason 8</b>			0.001
Yes	62 (6%)	97% (95% CI 93–100)	
No	992 (94%)	100% (95% CI N/A)	