The impact of prostate cancer upgrading and upstaging on biochemical recurrence and cancer-specific survival

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Abstract

Significant numbers of prostate cancer (PCa) patients experience tumour upgrading and upstaging between prostate biopsy and radical prostatectomy (RP) specimens. The aim of our study was to investigate the role of grade and stage increase on surgical and oncological outcomes.Methods Upgrading and upstaging rates were analysed in 676 treatment-naïve PCa patients who underwent RP with subsequent follow-up. Positive surgical margin (PSM), biochemical recurrence (BCR), overall (OS) and cancer specific survival (CSS) were analysed according to upgrading and upstaging.Results Upgrading was observed in 29% and upstaging in 22% of PCa patients. Patients undergoing upgrading or upstaging were 1.5-times more likely to have a PSM on RP pathology. Both upgrading and upstaging were associated with increased risk for BCR: 1.8 and 2.1-times, respectively. Mean time to BCR after RP was 2.1 years in upgraded cases and 2.7 years in patients with no upgrading ($p < 0.001$), while mean time to BCR was 1.9 years in upstaged and 2.8 years in non-upstaged cases ($p < 0.001$). Grade and stage increase after RP were associated with inferior ten-year CSS rates: 78% vs. 96% for upgrading ($p = 0.002$) and 77% vs. 95% for upstaging ($p = 0.001$).Conclusions Currently used risk stratification models are associated with a substantial number of misdiagnosis. Pathological upgrading and upstaging have been associated with inferior surgical results, substantial higher risk of BCR and inferior rates of important oncological outcomes, what should be considered when counselling PCa patients at the time of diagnosis or after definitive therapy.

Background

Prostate cancer (PCa) is a heterogeneous disease in various aspects [1]. Up to date, more than 100 DNA biomarkers have been identified in PCa [2] and several grading systems have been proposed for morphological evaluation [3]. While approximately 3 separate tumours are identified in the gland [4] and clinical manifestation varies from indolent localised to aggressive metastatic disease, PCa characterisation is still based on the needle biopsy, where Gleason grading system show the strongest prognostic power. Knowing such heterogeneity of the disease, it is not surprising that a significant number of PCa patients undergoing curative treatment are upgraded and upstaged [5].

The objective of the present study was to characterise the rates of pathological upgrading and upstaging after radical prostatectomy (RP) and investigate their role on surgical so oncological outcomes, including positive surgical margin (PSM), biochemical recurrence (BCR), overall and cancer-specific survival (OS and CSS, respectively).

Methods

Patients and samples

This study is a part of a large-scale PCa biomarker research started in 2008, performed after approval by the Lithuanian Bioethics Committee (2007-11-23 No. 50 and 2011-09-07 No. 6B-11-275). In the present

study 676 treatment-naïve patients with histologically confirmed PCa (at least 10-core random biopsy sampling) who underwent RP at Vilnius University Hospital Santaros Klinikos between January 2008 and December 2014 were included. This subgroup is a part of a large cohort involved in the biomarker-based upgrading and upstaging study [6], with available post-operative follow-up. All patients were followed-up subsequently at the outpatient clinic of the same institution. All data regarding follow-up were collected retrospectively from postoperative medical records up to September 2019. The data regarding survival were obtained from the State Register of Death Cases and Their Causes, by the Institute of Hygiene under the Ministry of Health of The Republic of Lithuania (2019-10-21 No. (9.20) 01-517). Previous androgen-deprivation therapy, active-surveillance and history of urothelial carcinoma were considered as exclusion criteria. Clinico-pathological characteristics of the study cohort are summarized in Table 1.

Gleason score was evaluated according to the 2005 Guidelines of International Society of Urological Pathology (ISUP) and ISUP grade groups were assigned according to ISUP 2014 recommendations [7; 8]. As defined previously [6], upgrading was considered when any increase of ISUP grade group between prostate biopsy (cISUP) and RP pathology (pISUP) was detected, whereas upstaging was confirmed if a patient was pathologically diagnosed with advanced disease (≥pT3) when clinically unsuspected. PSM was defined as the presence of tumour cells at the inked margin on the inspection under microscopy [9]. BCR following RP was defined as a postoperative PSA > 0.2 ng/mL with a subsequent confirmatory value [10]. PCa overall survival (OS) after RP was defined as a time from RP to death from any cause. PCa specific survival (CSS) after RP was defined as a time from RP to death at the time of progressive metastatic disease. Patients who had dead without BCR or with BCR and PSA < 1.0 ng/mL with metastatic-free disease were classified as dying from other causes.

Statistical analysis

Statistical analyses as well as reporting and interpretation of the results were conducted according to the established guidelines [11]. Continuous variables are expressed as means with standard error of mean (SEM). Data for categorical variables are presented as frequencies and percentages. Continuous variables were checked for normal distribution by Shapiro-Wilk statistics and compared them by the *t* test when normally distributed or the Mann-Whitney U test for non-normally distributed variables. Pearson's c^2 and Fisher exact tests were used for comparison of categorical variables, as appropriate. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using multivariate Cox proportional hazards analysis. Kaplan-Meier curves were depicted and Log Rank (Mantel-Cox) test was applied to support the survival analyses. All statistical tests were performed using SPSS software (IBM Corp., Armonk, NY, USA). P-value of < 0.050 was considered significant.

Results

Upgrading, upstaging and surgical margin

Overall, upgrading was observed in 29.1% (197/676) and upstaging in 22.0% (149/676) of PCa patients undergoing RP. The total misclassification rate, when at least upgrading or upstaging was detected, was 41.7% (282/676). Among the upgraded cases 85.3% (168/197), 10.2% (20/197), 2.0% (4/197) and 2.5% (5/197) of PCa patients were initially diagnosed with cISUP 1, 2, 3 and 4 disease, respectively. The majority of patients (73.6%, 145/197) were upgraded to pISUP grade group 2. Patients initially diagnosed with cT1c cancer dominated among the upstaged cases (47.0%; 70/149).

Positive surgical margin was detected in 32.1% (217/676) of PCa patients undergoing RP. According to prostate anatomy, apex was the most common site for PSM – 56.0% (108/193), followed by postero-lateral position – 48.2% (93/193), base – 15.0% (29/193) and seminal vesicles – 4.7% (9/193).

The patients, whose cancer was upgraded post RP, more commonly had PSM (41.6%, 82/197) as compared to patients with no upgrading (28.2%, 135/479; $p = 0.001$). Upstaging after RP was also associated with PSM, where 44.3% (66/149) of PCa patients with upstaging and 28.7% (151/527) with no upstaging had been reported with PSM ($p < 0.001$).

Biochemical recurrence

BCR-only was diagnosed to 25.7% (174/676) of PCa patients after RP. At the time of BCR detection 77.3% (126/163) of the patients presented with PSA value < 0.5 ng/mL, 12.3% (20/163) – with PSA 0.5-2.0 ng/mL and 10.4% (17/163) – with PSA > 2.0 ng/mL. The mean follow-up time of patients without BCR was 46.8 months (SEM: 1.6).

BCR was diagnosed to 37.6% (74/197) of PCa patients whose cancer was upgraded post RP, while only to 20.9% (100/479) of patients with no upgrading ($p < 0.001$). Mean time to BCR after RP was 2.1 years (SEM: 0.2) in upgraded cases and 2.7 years (SEM: 0.3) in patients with no upgrading (Fig. 1A; $p < 0.001$). Patients who were upgraded from clinically low risk (cISUP 1) disease showed more favourable BCR rates as compared to patients with clinically diagnosed intermediate or high risk (cISUP 2-4) PCa (Fig. 1B; $p < 0.001$).

Upstaging after RP was also associated with BCR, where 43.6% (65/149) of PCa patients undergoing upstaging in contrast to 20.7% (109/527) of patients without upstaging were diagnosed with BCR ($p < 0.001$). Mean time to BCR after RP was 1.9 years (SEM: 0.3) in upstaged and 2.8 years (SEM: 0.2) in non-upstaged cases (Fig. 1C; $p < 0.001$).

In Cox proportional hazards analysis PSM showed the highest OR for BCR (2.29 [1.55-3.40], $p < 0.001$). According to this model, the ORs for upgrading and upstaging were 1.92 [1.29-2.86] and 2.14 [1.39-3.27], respectively (Table 2; all $p < 0.001$).

Overall and cancer specific survival

Mean OS for patients with and without upgrading was 10.2 (SEM: 0.4) and 9.7 (SEM: 0.2) years, while five and ten-year OS rates were comparable in both groups: 88.6%, 66.7% and 90.1%, 67.7%, respectively (Fig. 2A, p = 0.746). Similar OS results were observed in upstaged and non-upstaged PCa cases, where mean overall survival was 9.3 (SEM: 0.4) and 10.0 (SEM: 0.2) years, while five and ten-year OS did not differ significantly: 91.2%, 56.4% and 89.5%, 69.9%, respectively (Fig. 2B, p = 0.567).

For patients with and without PCa upgrading mean CSS was 11.3 (SEM: 0.4) and 11.7 (SEM: 0.1) years. Five-year CSS didn't differ between both cohorts (97.0% vs. 98.4%), while ten-year CSS rate was significantly lower (77.9% vs. 95.6%) in patients who underwent pathological upgrading after RP (Fig. 3A; p = 0.002). Mean CSS for upstaged and non-upstaged PCa was 10.6 (SEM: 0.4) and 12.2 (SEM: 0.1) years. No differences were also observed at five year (95.9% vs. 98.6%), while upstaging was associated with inferior ten-year CSS rates after RP (76.9% vs. 95.0%; Fig. 3B; p = 0.001).

Discussion

PCa with high-levels of molecular and morphological diversity is an extremely heterogeneous neoplasm, ranging from clinically indolent to metastatic and life-threatening disease [1]. Therefore, accurate assessment of tumour characteristics at diagnosis is essential for optimal disease management. The D'Amico classification is the most commonly used criterion for the definition of PCa [12], however high rates of upgrading (24-41%) and upstaging (29-34%) have been reported after RP so far [5; 13-15]. Discrepancies between prostate biopsy results and final pathological assessment of prostatectomy specimens may be attributed to diagnostic problems, especially when higher Gleason grade tumour is missed on the needle biopsy or insufficient biopsy material is available for pathological examination [16]. In the present study, as in our previous research with a larger cohort [6], upgrading and upstaging have been observed in 29% and 22% of PCa patients, respectively.

The clinical and prognostic significance of PCa upgrading and upstaging remains controversial. According to our data, patients undergoing upgrading or upstaging after RP are 1.5-times more likely to have a PSM on pathological specimen. It is generally known that PSM occur due to the biology of PCa and are associated with RP for high-risk disease [17]. Adverse cancer-specific features definitely increase the risk for PSM [18], especially in upgrading and upstaging settings when surgeons are facing the disease clinically suspected to have low-risk of progression [19].

It has been shown that downgrading is associated with better BCR-free survival [20], while upgrading increases the risk for BCR, which dramatically varies depending on PCa clinical characteristics [13]. According to our data, both upgrading and upstaging significantly increase the risk for BCR (1.8 and 2.1-times, respectively), while patients with clinically diagnosed intermediate and high-risk disease carry the highest risk. Different risk for BCR could be explained by different upgrading categories, i.e. the vast majority of low-risk patients (cISUP 1) are upgraded to intermediate-risk disease (pISUP 2; in the present

study 86.3% (145/168)), while intermediate-risk PCa cases (cISUP 2) are upgraded to an even higher-risk disease, i.e. pISUP 3 and higher.

The association between BCR and progression to metastatic disease so death of PCa is well documented in the literature [21], so as the endpoints of our study OS and CSS were analysed. According to our data upgrading and upstaging did not reveal any impact on OS, while grade and stage increase after RP were associated with inferior ten-year CSS results: 78% vs. 96% for upgrading, while 77% vs. 95% for upstaging. Our findings are consistent with other investigators, where inferior CSS results have been reported for patients undergoing upstaging [22] and upgrading to more aggressive (pISUP $\geq$ 4) disease [23].

Disease upgrading and upstaging after radical treatment are raising the issue about serious diagnostic problems in PCa and are often the rationale for costly imaging or genomic studies, especially when active surveillance is considered. Several nomograms have been suggested to predict the probability of pathologic upgrading in patients with low-risk disease [24-26], however most of them are based on randomised biopsies and have limited value in counselling patients who are candidates for definitive therapy. Novel molecular biomarkers and genomic classifiers, containing molecular information from all tumour foci and reflecting PCa heterogeneity, have shown accuracy in predicting PCa aggressiveness and may provide valuable information for improved diagnostics [6; 27-29].

Our research has important clinical implication, demonstrating the limitations of current preoperative assessment of PCa, resulting in inaccurate treatment, subsequent BCR and worse CSS in substantial number of patients. However, we must acknowledge several limitations of the present study. Firstly, this is a single-institution experience, therefore, external validation is mandatory. Secondly, although the clinical data were maintained prospectively, the patients' follow-up and survival were analysed in a retrospective way. Thirdly, prostate multiparametric MRI so MRI-fusion biopsies were not routinely performed on our present patient population, therefore, were not available for the analysis.

Conclusions

Our results indicate that the currently used modified D'Amico criteria are associated with a substantial number of misdiagnosis in the light of PCa heterogeneity. Upgrading and upstaging after RP are associated with inferior surgical results, substantial higher risk of BCR and inferior rates of important oncological outcomes. This suggest that clinical risk is an important factor and all these findings should be considered when counselling PCa patients in order to focus efforts on improving oncologic surgical care with the goal to improve patient outcomes.

Abbreviations

BCR – biochemical recurrence

CI – confidence intervals

cISUP – clinical ISUP grade group

CSS – cancer-specific survival

cT – clinical tumour stage

DNA – deoxyribonucleic acid

ISUP – International Society of Urological Pathology

MRI – magnetic resonance imaging

RP – radical prostatectomy

OR – odds ratios

OS – overall survival

PCa – prostate cancer

pISUP – pathological ISUP grade group

PSA – prostate-specific antigen

PSM – positive surgical margin

SEM – standard error of mean

Declarations

Ethics approval and consent to participate

The study was approved by the Lithuanian Bioethics Committee (2007-11-23 Nr.:50 and 2011-09-07 Nr.:6B-11-275) and written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and material

All data supporting the results reported in the article is available from the corresponding author upon a reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

AB collected and analysed the data, drafted the manuscript. MD collected the data and revised the manuscript. KD analysed the data and revised the manuscript. MB collected the data and revised the manuscript. FJ and SJ designed the research, supervised the analysis, revised the manuscript critically for important intellectual content. All authors read and approved the manuscript.

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Tables

Table 1. Clinico-pathological characteristics of prostate cancer patients

Variable	PCa patients (N = 676)
Age at surgery, years	
Mean (±SEM)	62.1 (0.3)
Median	62
Preoperative PSA, ng/mL[a]	
Mean (±SEM)	8.2 (0.3)
Median	5.9
Prostate size, g [b]	
Mean (±SEM)	52 (0.9)
Median	47
cISUP grade group, n (%)	
1	459 (67.9)
2	152 (22.5)
3	40 (5.9)
4	23 (3.4)
5	2 (0.3)
pISUP grade group, n (%)	
1	312 (46.1)
2	284 (42.0)
3	58 (8.6)
4	8 (1.2)
5	14 (2.1)
cT stage, n (%)	
≤cT1c	406 (60.1)
cT2a	7 (1.0)
cT2b	84 (12.4)
cT2c	120 (17.8)
cT3a	50 (7.4)
cT3b	9 (1.3)
cT4	0 (0.0)
pT stage, n (%)	
pT2a	41 (6.1)
pT2b	6 (0.9)
pT2c	448 (66.3)
pT3a	105 (15.5)
pT3b	74 (10.9)
pT4	2 (0.3)
Time from biopsy to RP, days [c]	
Mean (±SEM)	114.7 (7.5)
Median	63

Abbreviations: cISUP = clinical ISUP grading; cT = clinical T-staging; ISUP = International Society for Urological Pathology; pISUP = pathological ISUP grading; RP = radical prostatectomy; pT = pathological T-staging; PCa = prostate cancer; PSA = prostate-specific antigen; SEM = standard error of mean; T = local tumour staging according to TNM classification.

[a] PSA missing in 4 patients. [b] Prostate size missing in 6 patients. [c] Time from biopsy to RP missing in 51 patients.

Table 2. Univariate and multivariate Cox regression analysis of the associations between clinico-pathological characteristics and biochemical recurrence.

Variable	Univariate			Multivariate		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
PSA, ng/mL	1.10	[1.07-1.13]	**<0.001**	1.09	[1.05-1.13]	**<0.001**
Prostate size, g	0.99	[0.99-1.00]	0.182	0.99	[0.98-1.00]	0.057
PSM	3.27	[2.28-4.69]	**<0.001**	2.29	[1.55-3.40]	**<0.001**
Upgrading*	2.28	[1.59-3.28]	**<0.001**	1.92	[1.29-2.86]	**0.001**
Upstaging	2.97	[2.02-4.37]	**<0.001**	2.14	[1.39-3.27]	**<0.001**

* All cISUP grade groups were included.

Abbreviations: CI = confidence interval; cISUP = clinical International Society of Urological Pathology (ISUP) group; PSA = prostate-specific antigen; PSM = positive surgical margin.

Statistically significant p-values ($p < 0.050$) of the logistic regression models are marked in bold.

Figures

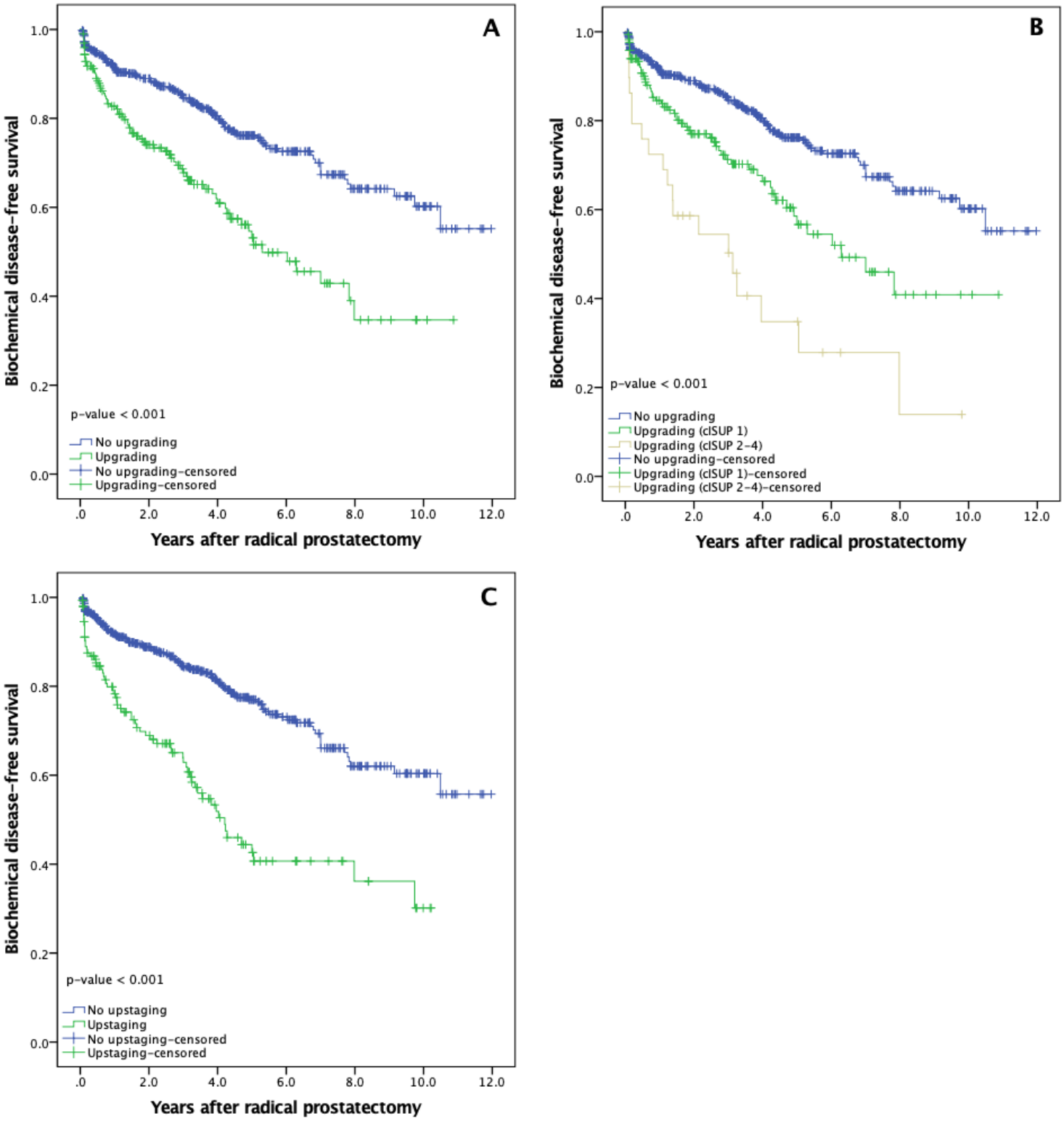

Figure 1

Prostate cancer biochemical disease-free survival rates after radical prostatectomy. A. Biochemical disease-free survival according to upgrading (all cISUP grade groups); B. Biochemical disease-free survival for patients with no upgrading (blue line), upgrading from cISUP grade group 1 (green line) and upgrading from cISUP grade group 2-4 (yellow line); C. Biochemical disease-free survival according to upstaging.

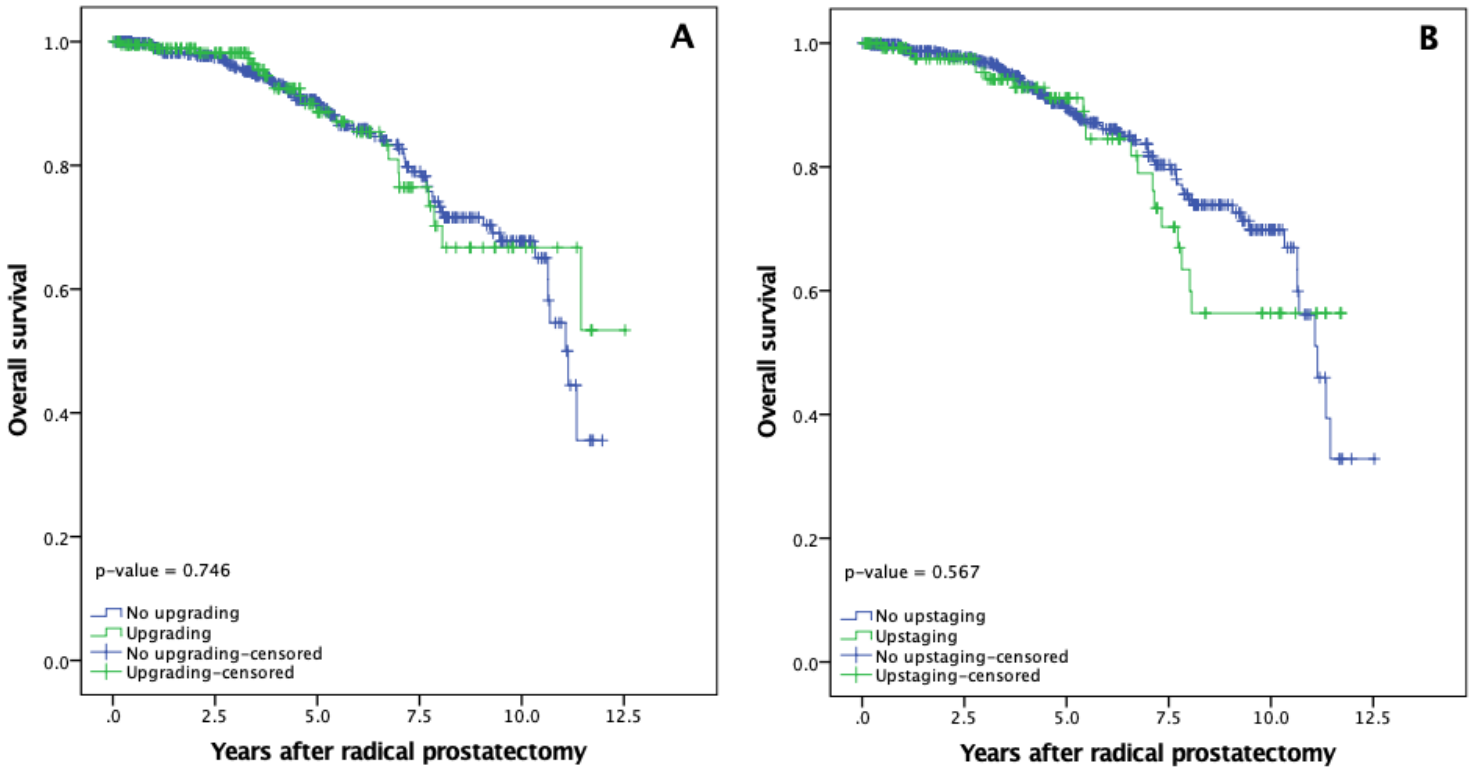

Figure 2

Prostate cancer overall survival rates after radical prostatectomy. A. Overall survival according to upgrading; B. Overall survival according to upstaging.

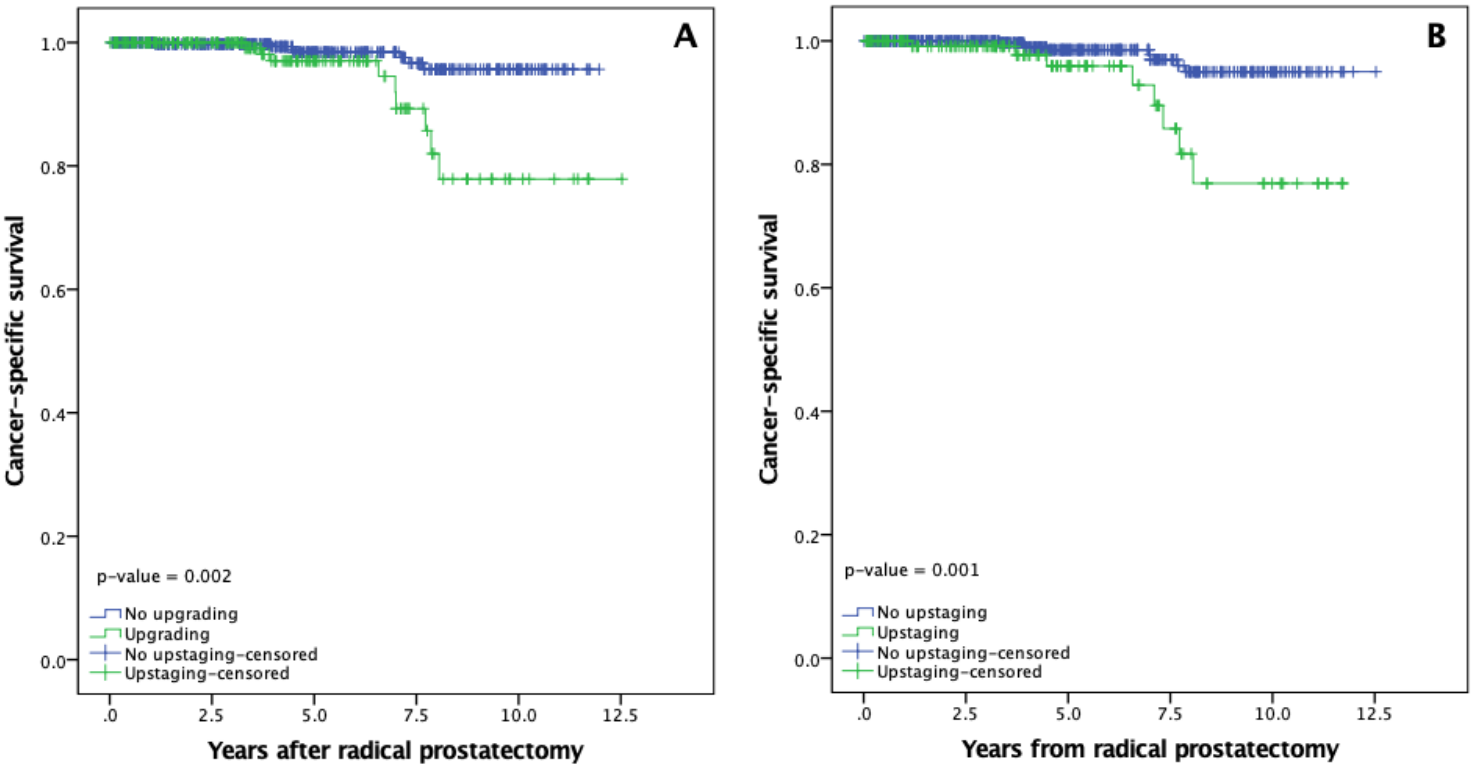

Figure 3

Prostate cancer-specific survival rates after radical prostatectomy. A. Cancer-specific survival according to upgrading; B. Cancer-specific survival according to upstaging.