

Reduced α - and β -catenin Expression Predicts Shortened Survival in Local Prostate Cancer

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Abstract. *The aim of this study was to determine the prognostic value of α - and β -catenin expressions in local prostate cancer (PC). Materials and Methods: One hundred and eighty-one PC patients treated with radical prostatectomy were followed-up for a mean of 7.3 years. The α - and β -catenin expression were analysed by immunohistochemistry TMT (tissue microarray technique) and light microscopy. Results: Strong α -catenin expression was related to low Gleason grade ($p < 0.001$), cancer-free seminal vesicles ($p = 0.04$) and low preoperative PSA ($p = 0.02$). Strong β -catenin expression was related to low Gleason grade ($p < 0.001$) and cancer-free seminal vesicle status ($p = 0.03$). Absence of nuclear β -catenin expression was related to local disease (pT1-T2) ($p = 0.05$). α -catenin ($p = 0.06$), β -catenin ($p = 0.05$), Gleason grade ($p = 0.03$) and capsular invasion ($p = 0.01$) were related to PSA recurrence in patients who reached PSA zero postoperatively. PSA recurrence-free survival (RFS) was significantly related to Gleason grade ($p < 0.001$), capsule invasion ($p = 0.01$), perineural growth ($p = 0.05$) and preoperative PSA ($p = 0.05$). In Cox's analysis, independent predictors of PSA RFS were Gleason grade ($p < 0.001$) and capsular invasion ($p = 0.006$). Low expressions of α - ($p = 0.06$) and β -catenin ($p = 0.05$) were related to shortened PSA RFS. Survival was related to low α - ($p = 0.011$) and β -catenin ($p = 0.016$) expressions. Independent predictors of shortened survival were seminal vesicle invasion ($p = 0.016$) and low α -catenin expression ($p = 0.049$). Conclusion: Reduced α - or β -catenin expressions are related to malignant phenotype in local prostate cancer and predict PSA failure as well as shortened survival.*

Prostate cancer (PC) is the most common malignancy in men in Western countries and is diagnosed more often in its early

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Key Words: α -catenin, β -catenin, prostate neoplasm, prognosis.

stages and in younger men. Radical therapies play a crucial role in the treatment strategy. However, about 30% of patients develop a biochemical relapse after radical therapy within 10 years (1, 2). In practice, 30% of the cases present with capsule penetration at the time of curative therapy despite favourable prognostic signs (3). Since PC is diagnosed at earlier ages, when the patient still has a long life expectancy, it would be very beneficial to recognise those patients who might benefit from adjuvant therapies. Gleason grade, preoperative PSA, PSA doubling time and clinical stage categorise patients into different risk groups, but more accurate methods are needed. For better prediction, different molecular methods, such as suppressor genes, proliferation markers, angiogenesis and cell adhesion molecules have been studied (4-7).

Cadherins are integral transmembrane glycoproteins responsible for calcium-dependent intercellular adhesion. The normal function of E-cadherin depends on binding to the cytoplasmic anchoring proteins α -, β - and γ -catenins (8). β -catenin binds directly to the cytoplasmic part of the E-cadherin molecule, whereas α -catenin connects the E-cadherin-bound β - or γ -catenins to the actin microfilament network of the cellular cytoskeleton (8). β -catenin binds to the transcription factor TCF/LEF and is located in the nucleus, up-regulating transcriptional activity (9). In addition to intercellular adhesion, catenins influence differentiation, maintenance of the architecture of differentiated tissues, cell polarity, migration, proliferation and signal transduction for gene transcription, linking the cell surface to cytoplasmic and nuclear events (10). These interactions are mediated by the association of catenins, not only with E-cadherin, but also with other transmembrane, cytoplasmic and nuclear target proteins (10). The immunohistochemical detection of catenins may reflect intercellular adhesion more directly than that of E-cadherin alone (11). An association between reduced catenin expression and unfavourable prognosis was observed recently in many human malignancies (12-14), and the reduced α -catenin expression has also been linked with unfavourable prognostic factors in PC (6, 15).

The aim of the present study was to relate the expressions of α - and β -catenin to other clinical and histopathological prognostic factors and biochemical relapse in local PC treated by radical prostatectomy in two Finnish hospitals.

Materials and Methods

Patients. Two hundred and eleven (211) consecutive PC patients were treated with radical prostatectomy in Kuopio University Hospital and in Päijät-Häme Central Hospital, Finland, between 1987 and 1999. The mean (SD) age of the patients was 64.2 (5.5) years, and the mean follow-up was 7.3 (2.4) years. All the patients had a clinically local tumour, according to digital rectal examination and/or transrectal ultrasonography. The clinical TNM-classification was done according to UICC guidelines. Distant metastases were excluded by bone scans. The follow-up reviews were done at 3-month intervals during the first year, at 6-month intervals during the next year and annually thereafter. Recurrences were screened by laboratory tests (PSA, ALP), digital rectal examination and by different image analysis methods when required. An elevation of the PSA concentration 0.2 ng/ml or more was considered as a PSA failure. The causes of death were verified from the patient records.

Adequate and sufficient histopathological samples for immunohistochemistry were available in 184 cases, of which 3 patients had lymph node metastases in the final histological analysis and were therefore excluded. One hundred and forty-two patients (79%) had not received hormone ablation prior to radical prostatectomy.

Histological methods. Radical prostatectomy specimens were used for histological analyses. The specimens were fixed in buffered formalin (pH 7.0), embedded in paraffin, sectioned at 5 μ m and stained with haematoxylin and eosin (HE). The specimens were reanalysed by two consultant cellular pathologists unaware of the clinical data. The pT classification was done according to the 2002 guidelines (16), while the histological grading was done according to Gleason (17). Capsule invasion, surgical resection margin status, seminal vesicle invasion and perineural infiltration were recorded as absent (0) or present (1).

Tissue microarray (TMA) construction. Three representative tumour regions of each case were marked to HE-stained sections. From these regions, tissue cylinders with diameter of 0.6 mm were obtained and arrayed into a recipient block using the tissue chip microarrayer (Beecher Instruments, Silver Spring, MD, USA). The recipient block was subsequently cut into 5- μ m sections on pretreated slides to support adhesion of the tissue samples.

Immunohistochemistry. Paraffin wax-embedded sections from TMA blocks were washed twice in phosphate-buffered saline (PBS) and heated in a microwave oven at 600 W for 3 cycles of 5 minutes each in 0.005 mol/l Tris-HCl buffer (pH 9.7) for α -catenin, and 0.05 mol/l citrate buffer (pH 9.7) for β -catenin. Endogenous peroxidase activity was blocked with 5% H₂O₂ in distilled water for 5 minutes and washed 3 times for 5 minutes in distilled water and twice for 5 minutes in PBS. After treatment with 1.5% normal horse serum (Vectastain Elite ABC kit; Vector Laboratories, Burlingame, California, USA), mouse anti- α - and anti- β monoclonal antibodies (Transduction Laboratories, Lexington, Kentucky, USA) were applied to the sections at a dilution of 1/200 and 1/1000, and 1/200 respectively, in PBS with 1% bovine serum albumin and incubated for 24 hours at 4°C. Thereafter, the

sections were washed and biotinylated secondary antibody and avidin-biotin peroxidase reagent (Vectastain Elite ABC kit; Vector Laboratories) were applied to detect bound primary antibody. Diaminobenzidine tetrahydrochloride (DAB; Sigma, St Louis, Missouri, USA) was used to demonstrate peroxidase activity. The slides were counterstained with Mayer's haematoxylin, dehydrated, cleared and mounted with DePex (BDH, Poole, Dorset, UK). Normal epithelium and glandular tissue served as internal positive controls when they were seen. In addition, strongly positive samples for each catenin from other series (intestine, colon) were used as positive controls in each staining batch. Samples from the same series without the use of primary antibody served as negative controls.

The scoring of nuclei and cell membranes were separately analysed. The intensity of membranous staining of both catenins was primarily graded into 5 different groups: 0=negative, 1=<10%, 2=10-90% and 3=>90% positive cells. For survival analyses 2 different categories, 0-90% and >90%, were used. The nuclear β -catenin staining was analysed and scored: 0=negative, 1=weak, 2=moderate and 3=strong. In survival analyses groups 1-3 were considered as one group.

Statistical analysis. For statistical analysis, the SPSS-X program package was used. The Chi-square test was used to analyse the relationships between the groups. Survival analyses (log rank analysis) were based on the Kaplan-Meier method and used positive cancer deaths as events. Multivariate survival analyses were done according to Cox's methods. In PSA RFS analysis, a PSA elevation of 0.2 ng/ml or over was used as an event.

Results

The clinical data of the patients are shown in Table I, and the results of α - and β -catenin immunohistochemistry are presented in Figures 1 and 2 and in Table II.

The expressions of α - and β -catenin were highly significantly interrelated ($p<0.0001$) and nuclear expression of β -catenin was more common in tumours showing strong expression of α -catenin ($p=0.01$). Strong α -catenin expression was related to low Gleason grade ($p=0.001$), low pT category ($p=0.021$), cancer-free seminal vesicles ($p=0.017$) and low preoperative PSA level ($p=0.011$). The expression of α -catenin was not linked with perineural invasion, surgical margin status or capsule invasion. Strong β -catenin expression was related to low Gleason grade ($p<0.001$) and cancer-free seminal vesicle status ($p=0.03$). Tumours with absent nuclear β -catenin staining were usually confined to the prostate gland (pT1-2) ($p=0.05$).

The expressions of neither α - nor β -catenin were linked with postoperative PSA elevation in the entire series. A subgroup analysis of patients who had reached PSA zero after the operation showed that α - and β -catenin, Gleason grade and capsular invasion were able to predict PSA failure (Table III).

In patients with postoperative PSA zero, the PSA RFS was about 9 years longer in low Gleason score-patients as compared to the patients with poorly-differentiated tumours. Patients without capsule invasion of the tumour had nearly 5 years longer PSA RFS than patients with

invasion of the prostate capsule (Table IV). The PSA RFS in the entire series is also shown in Table IV. Cox's hazards analysis revealed that Gleason score and capsule invasion were the only independent predictors of biochemical failure after radical operation (Table V).

In survival analysis, low expressions of α -catenin ($p=0.0071$, Figure 3) and β -catenin ($p=0.0016$, Figure 4) predicted shortened survival. In Cox's multivariate analyses, independent predictors of survival were seminal vesicle status and α -catenin expression, Table V.

Discussion

For PC, the most important preoperatively available prognostic parameter is the Gleason score, although the Gleason score in biopsy is under- or overgraded in 30% of cases as compared to radical prostatectomy specimen analysis (18). Therefore, new clinically relevant prognostic markers are urgently needed for more accurate clinical decisions. Although the prognostic significance of adhesion factors, including catenins, has been previously studied (6, 7), their clinical significance is unclear. To further verify the potential clinical application, we analysed the prognostic value of α - and β -catenin expressions in a uniformly treated cohort of PC patients.

Membranous α -catenin expression was high in about 70% of specimens, and high expression was related to low Gleason grade and PSA under 20 ng/ml. In line with our results, previous studies had also shown that low-grade tumours expressed α -catenin more frequently than high-grade tumours (6, 15). Indeed, α -catenin expression had prognostic value in terms of PSA RFS. Similarly, in our previous study (19) including all stages of prostate cancer, the high expression of α -catenin was not related to survival in advanced stages, but was a powerful predictor of recurrence-free survival in M0 tumours. Our present cohort was larger than that previously reported and was also more homogeneous, since only radically-treated patients were included. The expression of α -catenin was a predictor of PC survival and also reached significance as an independent predictor. This is the first report indicating the independent prognostic value for loss of α -catenin expression and confirms the initial findings by Umbas *et al.* (6).

The expression pattern of β -catenin was similar to that of α -catenin and in about 70% of tumours expression was present in over 90% of cells. Membranous staining of β -catenin was observed in 88% prostatic adenocarcinomas (20). High levels of Wnt-1 and β -catenin expression were associated with advanced, metastatic, hormone-refractory prostate carcinoma, in which they can serve as markers of disease progression (21). However, in our series, in patients who reached PSA zero postoperatively, high β -catenin expression was linked with long PSA RFS and in survival analysis strong expression was protective against death from PC. High β -catenin expression was also linked with other

Table I. Clinical data of the patients.

| | |
|------------------------------------|-------------|
| Mean age, years (SD) | 64.2 (5.5) |
| Mean follow-up, years (SD) | 7.3 (2.4) |
| Mean PSA at diagnosis, ng/ml (SD) | 15.7 (14.6) |
| PSA μ g/ml, n (%) | |
| <10 | 69 (40) |
| 10-20 | 67 (39) |
| >20 | 37 (21) |
| pT category, n (%) | |
| 1-2 | 121 (67) |
| 3 | 57 (32) |
| 4 | 2 (1) |
| Gleason grade, n (%) | |
| 2-6 | 137 (76) |
| 7 | 34 (19) |
| 8-10 | 10 (5) |
| Capsule invasion, n (%) | |
| No | 116 (64) |
| Yes | 62 (34) |
| Surgical margin status, n (%) | |
| Negative | 113 (62) |
| Positive | 67 (37) |
| Seminal vesicle involvement, n (%) | |
| Negative | 143 (79) |
| Positive | 35 (19) |
| Postoperative PSA <0.1 ng/ml | |
| Yes | 140 |
| No | 41 |
| Survival, n (%) | |
| Alive | 164 (91) |
| Died | 17 (9) |

favourable prognostic features. In line with these results, in oral carcinoma (22), in ovarian cancer (23) and in renal cell cancer (24) reduced β -catenin expression has been related to poor clinical outcome. In contrast, in small cell lung cancer β -catenin overexpression has been related to short recurrence-free survival (25). These variable results suggest that β -catenin may have different roles in different types and phases of tumour development.

β -catenin binds to the transcription factor TCF/LEF, which is located in the nucleus, up-regulating transcriptional activity and wnt cell signaling pathway is associated with malignant cell transformation (9). It is also evident that nuclear expression of β -catenin correlates with mutation of the β -catenin gene (26). Most of the tumours (82%) do not express nuclear β -catenin, and this absence of nuclear

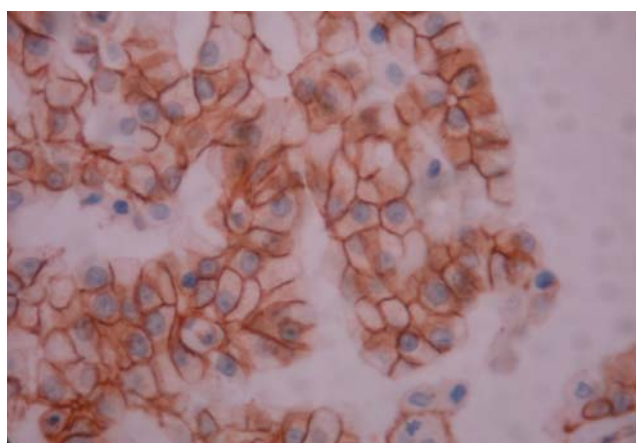


Figure 1. Strong membranous expression of α -catenin in prostate adenocarcinoma. Magnification 250x.

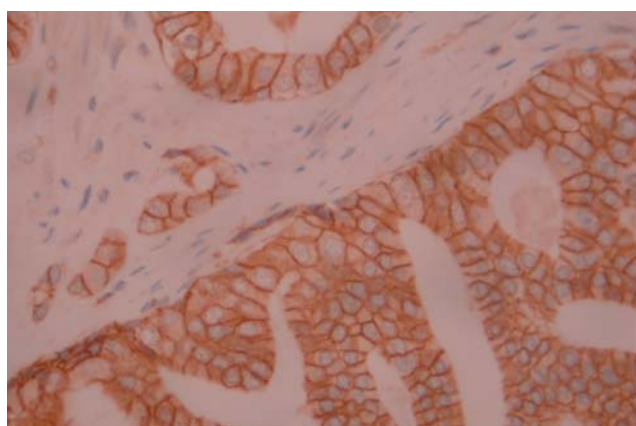


Figure 2. Strong membranous expression of β -catenin in prostate adenocarcinoma. Magnification 250x.

expression is linked with intracapsular carcinoma, as confirmed by Bismar *et al.* (20). Horvath *et al.* reported that low nuclear β -catenin expression was related to poor prognosis in localised PC (27). In our analysis, nuclear expression was unable to predict PSA RFS or survival. Bondi *et al.* (28) reported that nuclear expression predicts poor survival in colon cancer, whereas Wang *et al.* found that nuclear expression was an indicator of long RFS in hepatocellular carcinomas (29). Controversial results have also been reported regarding the relationship between nuclear β -catenin, prognostic factors and survival in other tumours (13, 30, 31). These data suggest that the nuclear and β -catenin signaling pathways act differently in different carcinomas and even in different stages.

In Cox's analysis of the prognostic factors, the PSA RFS was predicted by Gleason grade and capsular invasion. Similar results have been reported by Arakawa *et al.*, in a smaller series of PC (32). So it seems that the tissue microarray technique

Table II. Description of α - and β -catenin expressions.

| Variable | Number (%) |
|------------------------------------|------------|
| α -catenin | |
| negative | 2 (1) |
| <10% | 17 (9) |
| 10-90% | 42 (23) |
| >90% | 120 (66) |
| β -catenin | |
| negative | 0 (0) |
| <10% | 12 (6) |
| 10-90% | 43 (24) |
| >90% | 126 (69) |
| β -catenin nuclear intensity | |
| negative | 147 (82) |
| weak | 16 (9) |
| moderate | 13 (7) |
| strong | 4 (2) |

Table III. Parameters related to PSA recurrence in patients (n=140) who reached PSA value zero postoperatively.

| Variable | PSA elevation ≥ 0.2 $\mu\text{g/l}$ | | p-value |
|------------------------------|--|-----------|---------|
| | No, n=87 | Yes, n=53 | |
| α -catenin expression | | | |
| 0 | 0 | 2 | 0.06 |
| <10 | 5 | 8 | |
| 10-90 | 20 | 12 | |
| >90 | 62 | 31 | |
| β -catenin expression | | | |
| 0 | 0 | 0 | 0.05 |
| <10 | 2 | 6 | |
| 10-90 | 21 | 15 | |
| >90 | 64 | 32 | |
| Gleason grade | | | |
| 6 | 74 | 33 | 0.03 |
| 7 | 12 | 14 | |
| 8-10 | 1 | 6 | |
| Capsule invasion | | | |
| Negative | 67 | 30 | 0.01 |
| Positive | 19 | 22 | |
| Chi-square test | | | |

(TMA) and immunohistochemistry in current use can not overcome the prognostic potential of the Gleason score. The intratumour heterogeneity of catenin expression may interfere with the final prognostic power of these new parameters. In TMA, the sample selection is crucially important, and a small sample size easily omits the intratumour heterogeneity of the analysed parameters. An advantage of this new technique is

Table IV. The PSA RFS time categorised according to prognostic factors in patients with PSA zero post operatively and in the entire series (Kaplan-Meier).

| PSA zero | Mean time (SE) | 95% CI | p-value |
|-------------------------|----------------|-----------|---------|
| Gleason grade | | | |
| 2-6 (n=107) | 12.3(.70) | 10.9-13.7 | <0.0001 |
| 7 (n=26) | 5.5 (.78) | 3.9-7.0 | |
| 8-10 (n=7) | 1.9 (.67) | 0.6-3.2 | |
| Capsule invasion | | | |
| No (p=99) | 12.1 (.75) | 10.6-13.6 | 0.0114 |
| Yes (n=41) | 7.3 (.87) | 5.6-9.0 | |
| Entire series | | | |
| Gleason grade | | | |
| 2-6 (n=136) | 10.9(.66) | 9.6-12.1 | <0.001 |
| 7 (n=34) | 4.6 (.70) | 3.2-6.0 | |
| 8-10 (n=10) | 1.4 (.52) | 0.41-2.5 | |
| Capsule invasion | | | |
| No (n=118) | 10.8 (.73) | 9.4-12.2 | 0.01 |
| Yes (n=61) | 6.1 (.73) | 4.7-7.5 | |
| PNI | | | |
| No (N=77) | 10.7 (.88) | 9.0-12.5 | 0.05 |
| Yes (n=102) | 8.7 (.74) | 7.3-10.2 | |
| PSA ng/ml | | | |
| <10 (n=69) | 8.2 (.60) | 7.1-9.4 | 0.05 |
| 10-20 (n=67) | 4.8 (.47) | 3.9-5.7 | |
| >20 (n=36) | 7.4 (.99) | 5.5-9.3 | |

Table V. The independent predictors of PSA RFS time and prostate cancer-specific survival.

| PSA recurrence-free survival | | | | |
|------------------------------|---------|--------|--------|-------------------|
| | p-value | B | exp(B) | 95%CI for Exp (B) |
| Gleason grade | 0.000 | 0.148 | 1.160 | 1.081-1.244 |
| Capsule invasion | 0.006 | 0.592 | 1.808 | 1.186-2.756 |
| PC-specific survival | | | | |
| Vesicle invasion | 0.016 | 2.654 | 14.216 | 1.656-122.044 |
| α -catenin expression | 0.049 | -2.174 | 0.114 | 0.013-0.987 |

the more standardised staining results. In spite of these potentially important methodological problems, the ability of the analysed parameters to predict PSA recurrence and survival indicates that these cellular features are relevant to assessing prognosis in PC.

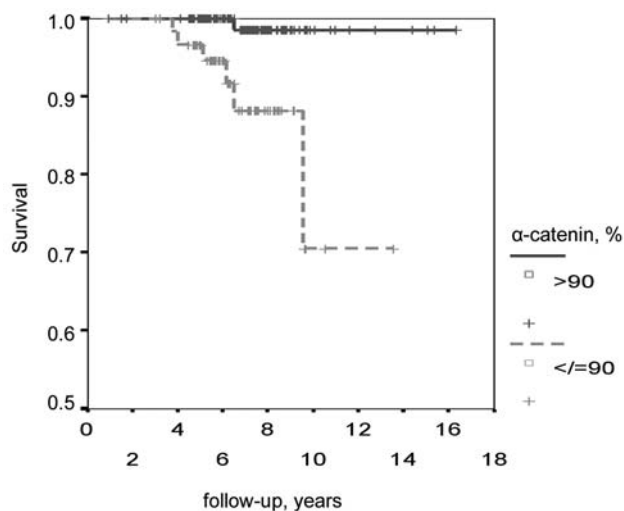


Figure 3. The expression of α -catenin ($p=0.0071$) predicted survival. α -catenin expression >90%, n=120; α -catenin expression $\leq 90\%$, n=61.

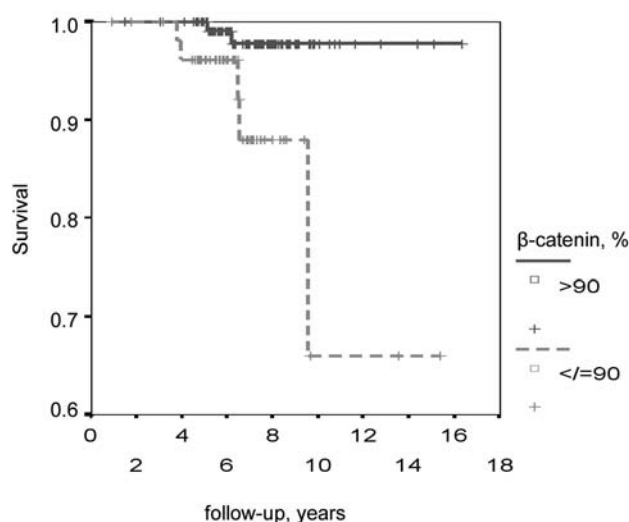


Figure 4. The expression of β -catenin ($p=0.0016$) predicted survival. β -catenin expression >90%, n=126 and β catenin expression $\leq 90\%$, n=55.

Acknowledgements

This study was financially supported by a research grant (EVO funding) from the Kuopio University Hospital and Päijät Häme Central Hospital, Finland. The technical assistance of Mrs Helena Kemiläinen is gratefully acknowledged.

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Received May 31, 2005
Accepted August 30, 2005