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Topographical and stage-related expression of nectin-4 in prostate cancer

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Introduction Nectin-4 is a cell-adhesion molecule overexpressed in several malignancies and is a promising therapeutic target. Its expression profile and clinical relevance in prostate cancer (PCa) remain insufficiently defined.

Material and methods This retrospective study at a single tertiary referral center included 111 surgical specimens: 85 from patients with PCa (53 non-metastatic radical prostatectomy; 32 metastatic transurethral resection of the prostate) and 26 from patients without PCa (19 benign prostatic hyperplasia [BPH] procedures; 7 cystoprostatectomies). Tissue microarrays were constructed. Nectin-4 immunohistochemistry was scored using an H-score (0–300). Comparisons were performed across predefined tissue groups and clinicopathologic strata using non-parametric tests.

Results Adjacent benign prostate showed higher median H-scores than PCa cores (101 vs 88; p = 0.008). Expression declined with pathological stage (≤pT2c vs ≥pT3a: 101 vs 78; p = 0.011) and with nodal involvement (pN0 vs pN1: 94 vs 68; p = 0.004). By subgroup, median H-scores were: BPH 73, tissue distant from PCa 105, tissue adjacent to PCa 116, non-metastatic PCa 96, and metastatic PCa 68 (p <0.0001; BPH vs adjacent p = 0.0001; M0 vs M1 p = 0.005). No difference was observed between hormone-sensitive and castration-resistant metastatic disease (73 vs 68; p = 0.34).

Conclusions Nectin-4 expression in the prostate is heterogeneous and context-dependent, with higher levels in benign glands within cancer-bearing prostates and lower levels with advancing tumor stage and nodal/metastatic spread. These findings provide an expression map of nectin 4 across benign and malignant prostate compartments and disease stages and may inform future exploratory enrichment strategies for nectin-4-targeted therapies.

Key Words: prostate cancer ‹› nectin-4 ‹› enfortumab vedotin ‹› immunohistochemistry ‹› tissue microarray

INTRODUCTION

When diagnosed and treated at a localized stage, prostate cancer (PCa) carries an excellent prognosis, with a 5-year cancer-specific survival rate of approximately 97%. In contrast, survival falls dramatically to about 30% once the disease has metastasized [1–3]. At initial diagnosis, around 5% of patients present with distant metastases and an additional 15% with locoregional spread [3]. Almost all patients with metastatic PCa ultimately progress to castration-resistant prostate cancer (CRPC), a lethal stage of the disease that is refractory to androgen deprivation therapy (ADT).

As in many other malignancies, the development of molecular classifications and targeted therapeutic approaches has become a central focus in PCa

research. Particular attention has been directed toward the identification of cost-effective surrogate biomarkers with diagnostic, prognostic, and predictive value [4]. Immunohistochemistry (IHC) remains a widely applied and versatile technique in this regard. It enables the detection of specific antigens in tissue using monoclonal or polyclonal antibodies and is routinely employed to assess tumor origin, determine cellular differentiation, detect micrometastases, evaluate prognostic factors, and predict therapeutic response [5]. Despite advances in risk stratification, the search for novel IHC-based markers in PCa is ongoing [6]. Of note, expression of nectin-4 has previously been documented in canine prostate tissue [7].

Nectin-4, also known as poliovirus receptor-like 4 (PVRL4), is a member of the immunoglobulin superfamily involved in multiple essential cellular processes, including adhesion, migration, proliferation, differentiation, polarization, and survival. It contributes to the formation and maintenance of cell-cell junctions and regulates cytoskeletal dynamics. Depending on context, nectin-4 can engage in homophilic or heterophilic interactions and activate diverse signaling pathways, including those mediated by ErbB2 and the Rac-1 module [8, 9]. Beyond oncogenic signaling, nectin-4 also acts as a ligand for TIGIT, an immune checkpoint receptor expressed on multiple immune cell subsets, thereby influencing tumor-immune interactions [10].

Physiologically, nectin-4 is only weakly expressed in a limited range of normal adult tissues. In contrast, it is consistently overexpressed in several cancers, where high expression correlates with poor overall survival (OS), particularly in esophageal and gastric cancers [8, 11]. In urothelial carcinoma, strong nectin-4 expression has led to the clinical development of the antibody-drug conjugate (ADC) enfortumab vedotin (EV), now approved for advanced disease [12]. Elevated nectin-4 expression has also been reported in other genitourinary malignancies, including upper tract urothelial carcinoma [12], papillary renal cell carcinoma [13], and penile cancer [14]. However, the therapeutic efficacy of EV in non-urothelial tumors remains uncertain.

Given the established role of nectin-4 as both a biomarker and a therapeutic target, and considering the clinical availability of EV, it is crucial to determine whether PCa expresses this molecule. We therefore investigated nectin-4 expression in surgical tissue specimens across different stages of PCa, aiming to clarify its potential as a predictive biomarker and therapeutic target in metastatic disease.

MATERIAL AND METHODS

Patient cohort and tumor characteristics

Prior to the use of human tissue and clinical data, comprehensive informed consent was obtained from all patients treated at the Department of Urology, University Hospital Tübingen. Patients received both written and verbal information regarding participation in the study. The study was retrospective in design and included a randomly selected cohort of patients who had undergone prostate surgery at the Department of Urology, University Hospital Tübingen, between May 2003 and October 2014.

A total of 111 prostate tissue samples were included. Of these, 85 were derived from patients with PCa. Among these, 53 patients with biopsy-confirmed, non-metastatic PCa underwent radical prostatectomy, while 32 patients with advanced, metastatic disease underwent transurethral resection of the prostate (TURP) as part of palliative treatment. The remaining 26 samples were from patients without PCa. This control group included 19 patients with benign prostatic hyperplasia (BPH)–of whom eight underwent transvesical prostate adenoma nucleation (TVP) and 11 TURP–and seven patients who underwent radical cystoprostatectomy for bladder cancer. Accordingly, all nectin-4 analyses in this study refer to prostate-derived tissue, and metastatic lesions at distant sites were not included. Histopathological examination confirmed the absence of malignancy in all non-PCa specimens. Neuroendocrine carcinoma cases were excluded.

Clinical and pathological data were collected in a dedicated database, including patient age, date of surgery, PSA level, type of surgery, TNM stage, Gleason score, recurrence, ADT treatment status, and nectin-4 expression. Gleason scores were extracted from the original pathology reports. For harmonization and contemporary comparability, all reported Gleason scores were additionally converted to ISUP Grade Groups (GG1–GG5) using the standard mapping (GG1: 3+3; GG2: 3+4; GG3: 4+3; GG4: 4+4; GG5: 4+5, 5+4, or 5+5). Exclusion criteria were unavailability of paraffin-embedded tissue and incomplete pathology reports.

All evaluable samples were classified into six groups according to clinical context and anatomical site:

- normal prostate tissue;
- malignant tissue without metastasis;
- lymph node metastases;
- distant (M1) metastases;
- prostatic tissue distant from PCa;
- prostatic tissue adjacent to PCa.

The "distant from PCa" group comprised benign prostate tissue sampled away from tumor foci in prostates harboring either low- or high-Gleason, non-metastatic tumors. The "adjacent to PCa" group comprised benign prostate tissue sampled immediately adjacent (<5 mm) to tumor foci in prostates with either low- or high-Gleason, non-metastatic tumors.

Immunohistochemical analysis

Nectin-4 expression was evaluated by IHC. All staining procedures were performed in the Department of Urology laboratory at the University Hospital Tübingen, using a polyclonal, rabbit IgG nectin-4 antibody (PA5-50463; Thermo Fisher, Waltham, MA, USA) at 1:1,000 dilution with a ZytoChem HRP One-Step Polymer anti-rabbit/mouse visualization kit (Zytomed, Berlin, Germany) and Dako Liquid DAB as chromogen (Dako – Agilent, Santa Clara, CA, USA).

Tissue microarrays (TMAs) were constructed. For TMA construction, representative areas were selected on H&E slides by a uropathologist. Whenever tissue availability permitted, at least two 1-mm cores per compartment were punched, resulting in multiple cores per patient. After exclusion of non-informative cores (e.g., missing tissue, folding, or absence of evaluable glands), the final analysis comprised 687 evaluable cores in total. To minimize bias, tumor-free samples and metastatic TURP-derived samples were interspersed among high- and low-Gleason tumor specimens. Landmark cores of porcine muscle tissue were incorporated for orientation during evaluation. Benign tissue sources included BPH tissue obtained predominantly by TURP/TVP and benign tissue sampled from tumor-bearing radical prostatectomy specimens as "adjacent" (<5 mm from tumor) or "distant" (non-neoplastic glands away from tumor foci). For radical prostatectomy cases, benign sampling was performed based on HE-guided mapping relative to the index tumor focus. For TURP-derived BPH tissue, which is enriched for transition zone and central gland, exact zonal localization cannot be reconstructed reliably; therefore, BPH/TURP samples were analyzed as a separate benign control category and interpreted with caution regarding anatomical comparability.

Slides were examined using a Carl Zeiss Axioskop (Zeiss, Oberkochen, Germany) microscope under standardized illumination. TMAs were assessed in duplicate sessions. Nectin-4 expression was evaluated using the histological score (H-score), a semi-quantitative scoring system ranging from 0 to 300 [13]. Both tumor and normal tissues were assessed. The H-score was calculated as:

$$\text{H-score} = (1 \times \%1+) + (2 \times \%2+) + (3 \times \%3+)$$

where %1+, %2+, and %3+ represent the percentages of cells showing weak, moderate, or strong staining, respectively, and unstained cells comprise the remainder, summing to 100% of evaluable glandular cells. Staining was recorded irrespective of subcellular localization (membranous and/or cytoplasmic). Separate membranous-only scoring was not performed in this exploratory, topographical mapping study. 'Strong staining' refers to 3+ intensity at the cellular level within the H-score calculation and does not imply a predefined clinical cut-off. For quality control, staining intensities were assigned in 5% increments to account for intratumoral heterogeneity. Reference images for each intensity (0–3) were created using QuPath (v0.6.0) software [14] and applied consistently during scoring (Figure 1).

All cores were scored independently in two microscopy runs. If results differed beyond predefined thresholds (≥10 for scores 0–100, ≥20 for scores 101–200, and ≥30 for scores 201–300), a third evaluation was performed. If the third score matched one of the first two, that score was taken as final. If it was equal to the mean of the first two, the mean was used. Otherwise, the two closest values were averaged, and the outlier discarded. Stromal elements were not included in the quantitative evaluation. H-score assessment was restricted to glandular epithelial cells. Weak cytoplasmic background staining occasionally observed in stromal compartments was interpreted as nonspecific and excluded from scoring.

All results were entered into a dedicated database, linked to patient characteristics, and averaged across multiple evaluable cores per tissue group. The maximum observed staining intensity for each patient was also recorded. For each patient and tissue compartment, the primary quantitative endpoint was the mean H-score across all evaluable cores of that compartment. This patient-level mean was used for all group comparisons and correlation analyses to reduce sampling error and mitigate intratumoral heterogeneity. In addition, the maximum H-score per patient was recorded as a secondary exploratory measure to capture focal high expression; analyses based on maximum values are reported only as supportive analyses and are explicitly indicated where used.

Statistical analysis

Data were extracted into JMP statistical software (version 16, SAS Institute Inc., Cary, NC, USA).

Categorical variables were summarized as frequencies and percentages, and continuous variables as medians with ranges. Distribution of continuous data was evaluated by quantile–quantile (Q–Q) plots and the Shapiro–Wilk test.
Comparisons of nectin-4 expression between tumor and normal tissues, as well as across PCa subgroups, were performed using the Wilcoxon/Kruskal–Wallis test with χ^2 approximation. Correlations were assessed using Spearman's rank correlation. Associations between nectin-4 expression and TNM stage were analyzed using univariate logistic regressions. Multivariate regression analyses were performed to identify independent predictors. A two-sided p-value < 0.05 was considered statistically significant. Given the exploratory nature of this study, p-values were not adjusted for multiple testing.

Bioethical standards

The study was approved by the Ethics Committee of the Eberhard Karls University of Tübingen (approval number: 842/2016BO2).

RESULTS

Patient characteristics

The mean age of 111 patients included in this study at the time of surgery was 68.3 years.

Among the 85 patients with PCa, Gleason scores were available for 81. The distribution was as follows: 12 patients had a Gleason score of 6, 11 of 7a (3+4), 6 of 7b (4+3), 14 of 8, 34 of 9, and 4 had a score of 10. Pathological T stage was available for 70 patients, and lymph node status for 72 patients. Lymph node involvement was documented in 18 cases, 17 of which were in the metastatic cohort. The distribution of patients by T stage and lymph node status, stratified by metastatic status, is summarized in Table 1.
Preoperative PSA values were available for 101/111 patients (overall median 7.8 ng/ml, range 0–4757 ng/ml).
A detailed overview of age and PSA distributions is presented in Table 2.
Of the 32 patients with metastatic PCa, 28 received ADT, with a median treatment duration of 15 months (range 1–180 months).

Tissue microarray analysis

When comparing normal prostate tissue with PCa tissue, the median H-score was significantly higher in normal tissue (101 vs 88, p = 0.008; Figure 2A). Similarly, patients with ≤pT2c tumors exhibited higher median expression compared with those with ≥pT3a tumors (101 vs 78, p = 0.011; Figure 2B). Lymph node-negative cases also showed higher expression than node-positive cases (94 vs 68,

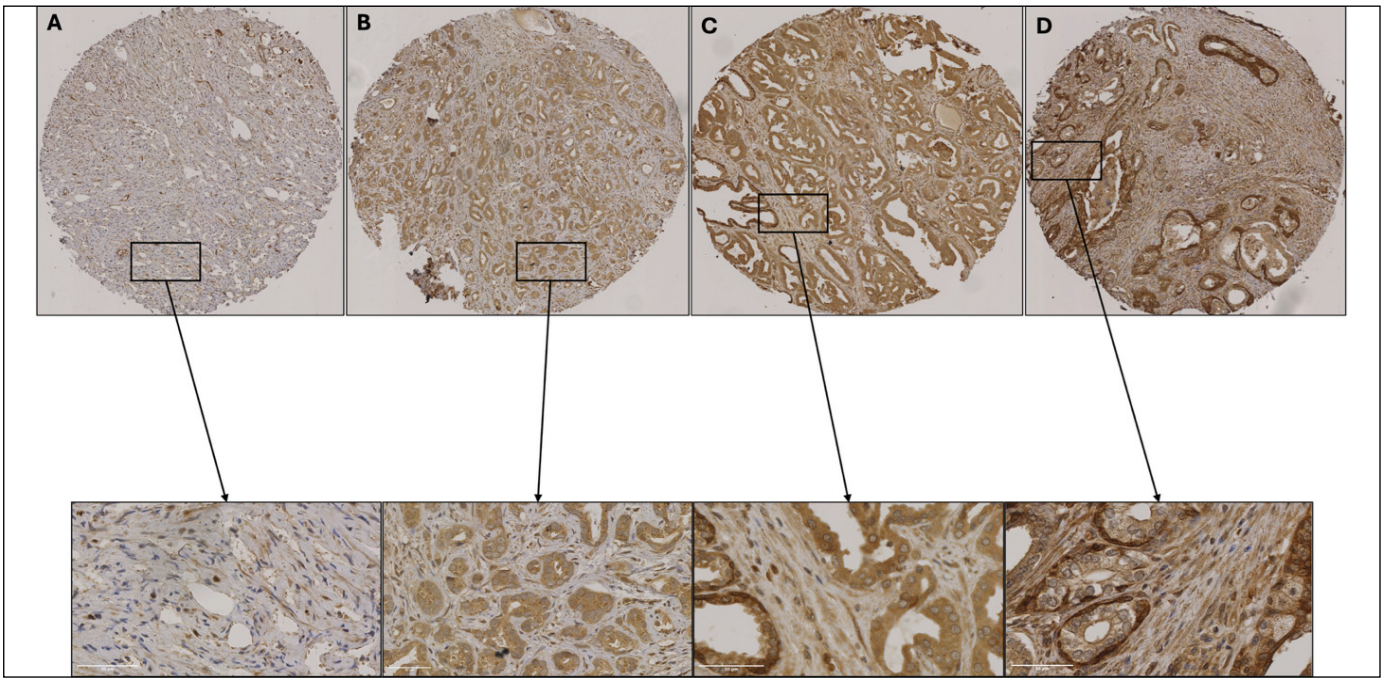

Figure 1. *Representative images of nectin-4 expression in prostate cancer tissue microarrays (100× magnification). Staining intensity was scored as follows:* **A)** *0 = absent;* **B)** *1 = low;* **C)** *2 = moderate;* **D)** *3 = strong.*

p = 0.004; Figure 2C). No significant difference was observed between hormone-sensitive and castration-resistant PCa (73 vs 68, p = 0.34).

Further subgroup analysis revealed median H-score values of 73 for BPH tissue, 105 for tissue distant from PCa, 116 for tissue adjacent to PCa, 96 for non-metastatic PCa, and 68 for metastatic PCa (p < 0.0001; Figures 3 and 4). Significant differences were observed between BPH and adjacent tissue (p = 0.0001) and between non-metastatic and metastatic PCa (p = 0.005).

Table 1. *Distribution of patients according to pathological T stage and lymph node status, stratified by non-metastatic vs metastatic prostate cancer*

	Non-metastatic PCa	Metastatic PCa
T2a	5	0
T2c	32	2
T3a	12	1
T3b	4	3
T4	0	11
N+	1	17

PCa – prostate cancer

DISCUSSION

Immunohistochemistry remains central to PCa diagnostics, particularly in challenging cases in which basal cell markers are interpreted alongside α-methylacyl-CoA racemase expression [5]. Against the background of increasing clinical interest in nectin-4 as a therapeutic target – most notably through the antibody–drug conjugate enfortumab vedotin (EV) in urothelial carcinoma (UC) – we sought to define nectin-4 expression across benign and malignant prostate compartments and across disease stages. Because no PCa-specific, clin-

Table 2. *Age at surgery and PSA at the earliest available preoperative time point, stratified by patient subgroup*

	Patients with PCa	Patients without PCa
n	85	26
Median age at surgery (years)	66 (range 51–95)	71 (range 55–82)
PSA prior to tissue acquisition (ng/ml)	Median 8.6 (n = 81)	Median 9.7 (n = 20)

	Non-metastatic PCa (M0)	Metastatic PCa (M1)
n	53	32
Median age at surgery (years)	65 (range 51–78)	72 (range 54–95)
PSA prior to tissue acquisition (ng/ml)	Median 6.8 (n = 51)	53 (n = 30)

	Low-Gleason, non-metastatic	High-Gleason, non-metastatic	Metastatic, hormone-sensitive	Metastatic, castration-resistant
n	28	25	14	18
Median age at surgery (years)	63 (range 51–72)	66 (range 57–78)	73.5 (range 54–95)	71.5 (range 56–84)
PSA prior to tissue acquisition (ng/ml)	Median 6.3 (n = 28)	Median 6.9 (n = 23)	Mean 15.6 (n = 14)	Median 125 (n = 16)

Low-grade disease was defined as ISUP Grade Group 1–2 (Gleason 3+3 and 3+4), while high-grade disease was defined as ISUP Grade Group 3–5 (Gleason 4+3, 4+4, 4+5, 5+4, or 5+5).
PCa – prostate cancer; PSA – prostate-specific antigen

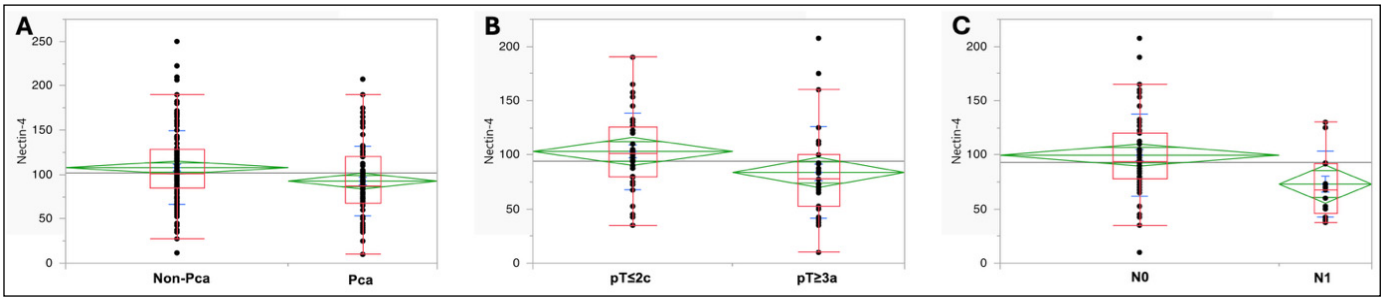

Figure 2. A) *Nectin-4 expression in normal vs PCa tissue.* **B)** *Nectin-4 expression stratified by pathological T-stage (≤pT2c vs ≥pT3a).* **C)** *Nectin-4 expression patterns in node-negative (pN0) and node-positive (pN1) PCa.*
PCa – prostate cancer

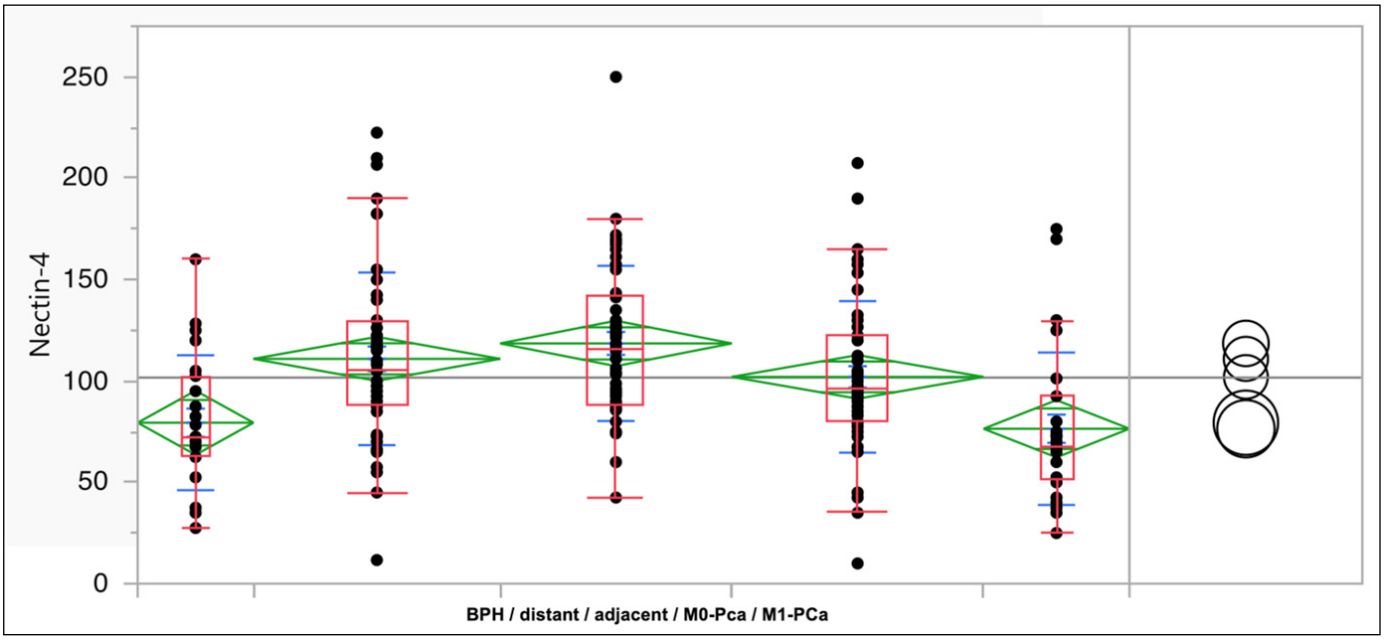

Figure 3. *Nectin-4 expression across subgroups: 1) BPH, 2) distant from PCa, 3) adjacent to PCa, 4) non-metastatic PCa, 5) metastatic PCa.*

BPH – benign prostatic hyperplasia; PCa – prostate cancer

ically validated nectin-4 scoring system or H-score threshold exists, cut-offs proposed in other tumor entities should not be extrapolated to prostate tissue. Accordingly, we report nectin-4 expression as a continuous variable and interpret our findings primarily as relative differences across compartments and stages, rather than as a binary 'positive/negative' classification. Our scoring approach captured the overall epithelial nectin-4 signal (membranous and/or cytoplasmic). While membranous expression is likely most relevant for ADC binding and internalization, cytoplasmic staining has been described in prostate tissue and may reflect receptor trafficking, altered junctional localization, or assay-related factors. Future translational work aimed at informing ADC eligibility should incorporate standardized membranous-focused scoring and correlate localization with treatment response.

Elevated nectin-4 expression has been identified as a prognostic biomarker in multiple malignancies [8, 9, 11]. In bladder cancer, reduced nectin-4 expression disrupts cell adhesion, enhancing apoptosis and metastatic potential via the β4/SHP-2/c-Src signaling axis [15], whereas overexpression promotes angiogenesis through endothelial integrin-β4 [16]. In lung cancer, the expression of exogenous nectin-4 enhances invasiveness by activating Rac1 signaling [17]. In gastric and gallbladder cancers, nectin-4 overexpression promotes proliferation, migration, and invasion via the PI3K/AKT pathway [11, 18]. Additional evidence suggests roles in modulating afadin expression and the AKT–NF-κB pathway [19], as well as promoting epithelial–mesenchymal transition (EMT) through alterations in adhesion proteins, including E-cadherin, N-cadherin, and vimentin [16, 20]. Beyond its tissue expression, the ectodomain of nectin-4 can be cleaved by ADAM-17, allowing its detection in serum [9].

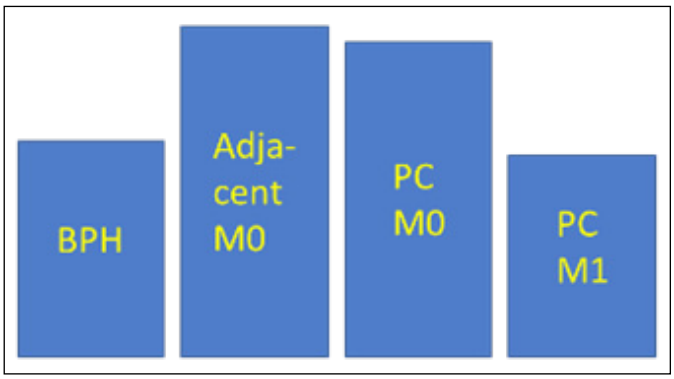

Figure 4. *Schematic summary of nectin-4 expression in BPH, tissue adjacent to PCa, non-metastatic PCa (M0), and metastatic PCa (M1).*

BPH – benign prostatic hyperplasia

Our findings show that prostatic adenocarcinomas may be either positive or negative for nectin-4. In the metastatic cohort, the median H-score was 68 (range 25–175). In a canine comparative study,

Della Salda et al. [7] reported prominent membranous and moderate cytoplasmic nectin-4 staining in metastatic PCa, with higher cytoplasmic expression in malignant tissue than in BPH ($p < 0.0001$) and with particularly strong membranous staining in metastatic deposits. Such patterns may be consistent with dynamic regulation of adhesion molecules during tumor cell dissemination and subsequent metastatic clustering.

In the present study, median H-score values were significantly higher in adjacent benign tissue compared to tumor tissue (101 vs 88). Ordu et al. [21] reported nectin-4 staining in atypical small acinar proliferation and benign glands, but not in malignant PCa cores. While our dataset includes a substantial number of prostatectomy specimens and shows measurable nectin-4 expression across both benign and malignant compartments, both studies highlight that benign glands may express nectin-4 and that tumor expression can be absent or lower in a subset of cases. Differences in case mix (e.g., limited prostatectomy material), antibodies, fixation, and scoring criteria may contribute to variability. Baraban et al. [22] reported nectin-4 expression in both benign tissue (86% of cases, mean H-score 40) and prostatic adenocarcinoma (91% of cases, mean H-score 90), without significant variation across ISUP GG. Our findings are compatible with this heterogeneity and further suggest that expression may decline in advanced/metastatic disease, although this requires confirmation in larger, prospectively collected cohorts.

Such patterns may be consistent with dynamic regulation of adhesion molecules during tumor cell dissemination and subsequent metastatic clustering. Weiten et al. [23] demonstrated greater EV sensitivity in nectin-4-expressing PCa cell lines and reported a small subset of metastatic human specimens with high expression despite low or absent staining in primary tumor cohorts. Although our metastatic cases showed lower median expression overall, both datasets support substantial intra-disease and inter-study heterogeneity and underscore the importance of assay harmonization and sampling considerations, particularly in metastatic disease, where expression may be spatially variable.

Immune checkpoint inhibitors targeting CTLA-4, PD-1, and PD-L1 have revolutionized therapy in several cancers, yet their role in PCa remains limited. While pembrolizumab has been FDA-approved for microsatellite instability-high/dMMR PCa, EMA approval is lacking, and PD-L1 expression has not proven to be a reliable predictive biomarker in PCa [3, 4, 24]. Immunotherapy trials in PCa have been disappointing, potentially due to unique immune resistance mechanisms. Recent data suggest that androgen receptor (AR) signaling within T cells suppresses IFN-γ production, leading to T-cell exhaustion. Blocking AR can enhance CD8+ T-cell function and sensitize tumors to checkpoint blockade [3, 25], providing new insights into resistance mechanisms in mCRPC.

By contrast, ADC therapy with EV has demonstrated efficacy in metastatic UC, where approximately 60% of tumors exhibit moderate to strong nectin-4 expression [10]. A practical challenge for nectin-4-directed ADC strategies in PCa is the absence of a validated, PCa-specific IHC threshold defining clinical benefit. In biomarker-unselected mCRPC studies, such as the ENCORE trial (NCT04754191), EV monotherapy was explored [26]. Despite the lack of nectin-4 stratification, responses were observed, with 64% of patients achieving protocol-defined responses and a median radiographic progression-free survival of 5.5 months. Responses despite heterogeneous nectin-4 levels may be explained by spatial heterogeneity with focal high-expression subclones, sampling constraints of small biopsies, and potential bystander killing from ADC payload release. These considerations suggest that future trials should evaluate both mean and maximum expression metrics, require standardized staining, and consider metastatic-site sampling when feasible.

A key finding of our study is that nectin-4 is not uniformly tumor-restricted in the prostate. Benign glands – particularly in cancer-bearing prostates – can show measurable expression. This observation constrains the interpretation of nectin-4 as a diagnostic or prognostic biomarker and suggests that any future ADC-selection strategy will require careful definition of clinically meaningful thresholds, standardized assays, and consideration of sampling location (tumor vs adjacent benign glands). We do not propose nectin-4 as a validated prognostic marker. Given the absence of outcome data, the present study cannot evaluate prognostic associations or predictive treatment benefit and should be interpreted as an expression-mapping study across compartments and disease stages. Potential scenarios where nectin-4 assessment could be informative include: (i) trial enrichment for nectin-4-directed ADCs in advanced PCa, where confirmation of target expression may be required; (ii) exploring whether earlier disease states (e.g., localized high-grade tumors) harbor higher expression than end-stage metastatic tissue, which may influence timing of target-directed approaches; and (iii) supporting future studies comparing expression across primary vs metastatic sites to understand spatial heterogeneity relevant to biopsy-based selection.

This study is limited by its retrospective, single-center design and modest cohort size. Because the follow-up was incomplete and heterogeneous–particularly in the metastatic TURP cohort treated across different systemic therapy eras–we could not assess associations with long-term outcomes or treatment response. Immunohistochemistry is subject to technical variability, and we evaluated nectin-4 as a combined epithelial signal (membranous and/or cytoplasmic) without separate membranous-only scoring, which limits direct therapeutic extrapolation for ADC targeting. In addition, benign TURP specimens are enriched for transition-zone tissue and cannot be reliably assigned to prostatic zones; although our key topographical comparisons (adjacent vs distant benign tissue) were derived from internally controlled prostatectomy specimens, residual anatomical heterogeneity cannot be excluded. Metastatic cases were represented by palliative TURP specimens, sampling periurethral tissue, which may underestimate expression if higher-expressing tumor foci were located outside the resection field. Finally, nodal involvement was rare in localized prostatectomy cases (pN1 in 1/53), and pN0 vs pN1 comparisons are therefore exploratory and largely reflect advanced-stage biology. Owing to collinearity between metastatic status, pathological stage, and nodal involvement, and incomplete annotation across specimen types, robust multivariable modeling was not feasible. Accordingly, the findings should be interpreted as hypothesis-generating and warrant validation in prospectively collected, clinically annotated cohorts with standardized sampling and, when feasible, metastatic-site tissue.

CONCLUSIONS

Nectin-4 expression in prostate tissue is heterogeneous and decreases with advancing PCa disease. Median H-score values were higher in adjacent benign tissue than in tumor cores, and expression declined with stage progression. Non-metastatic PCa showed moderate expression, while metastatic PCa displayed the lowest levels. No difference was observed between hormone-sensitive and castration-resistant disease. These findings suggest that nectin-4 is not uniformly tumor-restricted in PCa but may have value as a stratification biomarker, particularly in earlier disease stages or in subsets with higher peritumoral expression; however, due to the absence of outcome and treatment-response correlations, no prognostic or predictive conclusions can be drawn. Prospective studies with larger cohorts and outcome correlations are warranted to determine its clinical relevance and therapeutic potential as a target for antibody-drug conjugates.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The study was approved by the Ethics Committee of the Eberhard Karls University of Tübingen (approval number: 842/2016BO2).

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