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CD105-assessed microvessel density and recurrence and progression in non-muscle-invasive bladder cancer: a retrospective cohort study

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Abstract

Purpose.

To determine whether CD105 (endoglin)-assessed microvessel density (MVD) in the initial transurethral resection specimen predicts recurrence or progression in non–muscle-invasive bladder cancer (NMIBC).

Methods.

We retrospectively studied 157 consecutive patients with primary TaT1 urothelial carcinoma resected 2007–2011, with retrievable blocks and ≥ 9 months of follow-up. A single blinded uropathologist re-reviewed all specimens and counted CD105-positive microvessels in the vascular hot spot at ×200. Endpoints followed International Bladder Cancer Group definitions; recurrence was primary, progression secondary and exploratory. CD105-MVD was modelled continuously (per 10 vessels) and dichotomised at a Youden-derived cut-off, internally validated by bootstrap optimism correction, and tested for incremental value over a proxy risk grouping.

Results.

Median follow-up was 24 months (IQR 12–36); 78 patients (49.7%) recurred and 12 (7.6%) progressed. Median CD105-MVD was 47 vessels/×200 field (IQR 28–68) and rose with stage, grade and multifocality (all P ≤ 0.009). For recurrence, 78 events gave a tightly bounded null: adjusted hazard ratio 0.98 per 10 vessels (95% CI 0.91–1.06), AUC 0.552, log-rank P = 0.39, and no gain over the proxy risk grouping. For progression, CD105-MVD discriminated (AUC 0.735; HR 1.18 per 10 vessels, 95% CI 1.02–1.36) and no event occurred below 42 vessels (0/65 vs 12/92; P = 0.001), but did not survive adjustment for grade (HR 1.11, 95% CI 0.95–1.29).

Conclusion.

CD105-MVD does not predict recurrence and adds nothing to clinical risk stratification. The progression signal is not separable from WHO grade at 12 events and is hypothesis-generating.

Introduction

Bladder cancer accounted for approximately 614 000 new cases and 220 000 deaths worldwide in 2022, and roughly three-quarters of patients present with disease confined to the mucosa or lamina propria [1–3]. After complete transurethral resection (TUR), up to 70–80% of patients with non–muscle-invasive bladder cancer (NMIBC) recur and 10–45% eventually progress [4, 5]. Practice rests on the EORTC tables, the CUETO model and the risk groups of the 2021 European Association of Urology update and the AUA/SUO guideline [6–9]. These perform respectably at population level but modestly for the individual:

in 2 211 BCG-treated high-grade NMIBC patients the EORTC progression score and the EAU 2021 stratification achieved concordance indices of only 0.61 and 0.56 [10]. Their principal input, histological grade, is itself only moderately reproducible ($\kappa \approx 0.35$), with prognostic value that differs by pathologist [11, 12].

Angiogenesis is an obvious candidate for a quantitative variable readable from the same slide. Weidner's hot-spot microvessel density (MVD) count has been prognostic in breast and other carcinomas since the early 1990s [13, 14], but in bladder cancer it has behaved erratically: independently prognostic in muscle-invasive disease [15, 16], yet inconsistent in superficial disease, where MVD has correlated with stage and grade but not outcome, shown no independent value, or been outperformed by vessel shape [17–19]. Part of this is technical. CD31, CD34 and factor VIII are pan-endothelial and stain quiescent vessels entrapped within the tumour as readily as newly formed ones [20, 21]. CD105 (endoglin) is different: an accessory transforming growth factor-β receptor largely restricted to proliferating endothelium, upregulated under hypoxia and at the invasive front [22–24]. In lung and colorectal cancer CD105-MVD was prognostic where CD34-MVD was not [20, 25], and a meta-analysis of 30 studies and 3 613 patients linked high CD105-MVD to poor overall and disease-free survival [26]. Endoglin is also a drug target in urothelial carcinoma [27–29].

Despite this rationale, endoglin has been examined in NMIBC only rarely and with divergent conclusions [30–34]; the one substantial dataset outside the bladder, in 99 upper-tract tumours, found endoglin associated with intravesical recurrence yet not with stage, grade or cancer-specific survival [35]. We therefore assessed CD105-MVD in the initial resection specimens of 157 patients with primary TaT1 urothelial carcinoma, asking separately whether it predicts recurrence and whether it predicts progression — separately and deliberately, because a marker of vascular activation might behave differently towards field-effect re-implantation than towards invasive dedifferentiation.

Materials and methods

Study design and population

This single-centre retrospective cohort study was conducted at our department of urology. Consecutive patients undergoing TUR with a histopathological diagnosis of primary TaT1 urothelial carcinoma were screened; eligibility required complete clinical records, at least 9 months of follow-up, and archival blocks with sufficient tumour content. Index resections in the final analysis set were dated 2007–2011. Patients were managed by either of the department's two clinical teams; team was examined as a potential source of clustering. Patients with prior bladder tumours, muscle-invasive disease at first resection, upper-tract or non-urothelial tumours, or previous intravesical therapy were excluded. One hundred and fifty-seven patients met all criteria and all were analysed; the cohort size was determined by the number of eligible archival cases and no a priori sample-size calculation was performed. The number screened could not be recovered from the archive, so a complete patient-flow count is not available. The

study was approved by the institutional review board and conducted in accordance with the Declaration of Helsinki, with a waiver of individual consent. Reporting follows REMARK [36].

Treatment, follow-up and pathology

All patients underwent complete macroscopic TUR with resection of the underlying detrusor. Adjuvant intravesical therapy and re-resection were assigned by the treating urologist according to the risk stratification current at the time [6]. Follow-up comprised cystoscopy and urinary cytology 3-monthly for 2 years, 6-monthly during years 3–5 and annually thereafter. All initial resection specimens were re-reviewed by a single uropathologist blinded to outcome, staged by the 2009 UICC TNM classification and graded by the WHO 2004/2016 system.

Immunohistochemistry and microvessel quantification

Three-micrometre sections were deparaffinised at 60°C and processed on an automated platform (Bond-Max; Leica Biosystems, Wetzlar, Germany). Endogenous peroxidase was blocked with 0.5% hydrogen peroxide for 15 min; sections were incubated for 30 min with a mouse monoclonal anti-endoglin (CD105) antibody (Thermo Fisher Scientific, Fremont, CA, USA), then post-primary reagent, polymer and 3,3'-diaminobenzidine (Leica Bond Polymer Refine Detection) for 10 min each, and counterstained with Mayer's haematoxylin. Placental sections served as positive controls. Microvessels were quantified by the hot-spot method as codified in the second international consensus [13, 14]: the field of most intense CD105 staining was identified at low power and stained endothelial cells or cell clusters counted at ×200. A discernible lumen was not required. Representative staining is shown in Supplementary Fig. S1. Counting was performed by a single observer blinded to outcome; no second observer was available, so interobserver reproducibility could not be estimated.

Endpoints

Endpoints followed the International Bladder Cancer Group definitions [37]. *Recurrence* was histologically confirmed reappearance of NMIBC at the first 3-month surveillance cystoscopy or later. *Progression* was an increase in stage relative to the index tumour. Recurrence-free (RFS) and progression-free survival (PFS) were measured from initial TUR, with event-free patients censored at last clinical assessment. Recurrence was designated primary because it was the only endpoint accruing an adequate number of events; progression was designated secondary and exploratory. This hierarchy was fixed before modelling but after the event counts were known, and we make no claim that it was pre-registered. Two progression events lacked a recorded date; the date of the patient's first documented recurrence was used, with a sensitivity analysis excluding them.

Statistical analysis

CD105-MVD departed from normality (Shapiro–Wilk W = 0.927, P < 0.001), so non-parametric methods were used: Mann–Whitney U and Kruskal–Wallis tests with Holm-adjusted pairwise comparisons, and Spearman correlation. Discrimination was assessed by the area under the receiver-operating-characteristic curve (AUC) with percentile bootstrap 95% confidence intervals (5 000 resamples). A cut-off was derived by maximising the Youden index, its instability quantified by bootstrapping the cut-off (2 000 resamples). Because data-derived thresholds inflate type I error [38, 39], continuous CD105-MVD (per 10 vessels) was the primary exposure. Survival was estimated by Kaplan–Meier and compared by log-rank test. Hazard ratios were estimated by Cox regression with Efron handling of ties; proportional hazards were tested for every covariate in every model by the Grambsch–Therneau method. The multivariable RFS model included CD105-MVD, stage, grade, focality, age, sex and intravesical therapy (78 events; 11 events per variable). With only 12 progression events the multivariable PFS model was restricted to CD105-MVD and grade (6 events per variable), adequate for demonstrating control of confounding but not for primary inference [40, 41].

EORTC and EAU 2021 scores could not be computed because concomitant carcinoma in situ was not recorded, tumour diameter was available only for solitary tumours and WHO 1973 grade was unavailable. We therefore defined a proxy risk grouping from the available variables (low: Ta, low grade, solitary; high: T1 or high grade; intermediate: all others) and tested the incremental value of CD105-MVD by likelihood-ratio test and change in Harrell's C, with the groups entered as indicator variables. This proxy is not an EORTC or EAU risk group and serves only as an internal comparator. External validation was not possible, so models were validated internally by bootstrap optimism correction (500 resamples; 1 000 for the risk-group comparison). Where separation prevented a finite estimate, a Firth-penalised Cox model was fitted. Precision is reported through confidence intervals rather than post-hoc power. Two-sided P < 0.05 was considered significant; no adjustment was made for multiplicity, the progression analyses being exploratory by design. Full details are given in the Supplementary Methods. Analyses used Python 3.11 with *statsmodels* 0.14, *scikit-learn* 1.8 and *SciPy* 1.17.

Results

Cohort and outcomes

The 157 patients comprised 140 men and 17 women with a median age of 64 years (IQR 55–72). Ninety-four tumours (59.9%) were stage Ta and 63 (40.1%) T1; 95 (60.5%) were low grade and 62 (39.5%) high grade; 85 (54.1%) were solitary. Seventy-one patients (45.2%) received no intravesical therapy, 47 (29.9%) BCG, 28 (17.8%) chemotherapy and 11 (7.0%) both sequentially (Table 1).

Table 1
Baseline characteristics and outcomes of the study cohort (n = 157)

Characteristic	Value
Age, years — median (IQR)	64 (55–72)
Range	23–95
Sex — n (%)	
Male	140 (89.2)
Female	17 (10.8)
Stage — n (%)	
Ta	94 (59.9)
T1	63 (40.1)
Grade (WHO 2004/2016) — n (%)	
Low grade	95 (60.5)
High grade	62 (39.5)
Tumour number — n (%)	
Solitary	85 (54.1)
Multiple	72 (45.9)
Tumour diameter, cm — median (IQR)□	3.0 (2.0–4.0)
≥3 cm — n/N (%)	54/85 (63.5)
Adjuvant intravesical therapy — n (%)	
None	71 (45.2)
BCG	47 (29.9)
Chemotherapy	28 (17.8)
Chemotherapy then BCG	11 (7.0)
CD105-MVD, vessels/×200 field — median (IQR)	47 (28–68)
Range	10–176
Follow-up, months — median (IQR)	24 (12–36)
Range	9–144

IQR, interquartile range; BCG, bacillus Calmette–Guérin; CD105-MVD, CD105 (endoglin)-assessed microvessel density. □ Diameter was recorded only for solitary tumours (n = 85).

Characteristic	Value
Recurrence — n (%)	78 (49.7)
Time to first recurrence, months — median (IQR)	6 (3–12)
Progression — n (%)	12 (7.6)
Time to progression, months — median (range)	9 (3–93)

IQR, interquartile range; BCG, bacillus Calmette–Guérin; CD105-MVD, CD105 (endoglin)-assessed microvessel density. ⍰ Diameter was recorded only for solitary tumours (n = 85).

Median follow-up was 24 months (IQR 12–36; range 9–144), identical by reverse Kaplan–Meier estimation. Seventy-eight patients (49.7%) recurred at a median of 6 months (IQR 3–12) and 12 (7.6%) progressed at a median of 9 months (range 3–93). Progression occurred in 4 of 94 Ta (4.3%) versus 8 of 63 T1 tumours (12.7%), and in 3 of 95 low-grade (3.2%) versus 9 of 62 high-grade tumours (14.5%).

CD105-MVD and clinicopathological features

Median CD105-MVD was 47 vessels per ×200 field (IQR 28–68; range 10–176). It was higher in T1 than Ta tumours (median 64, IQR 42–76 vs 39, IQR 21–58; $P < 0.001$), in high-grade than low-grade tumours (59, IQR 42–78 vs 40, IQR 22–59; $P < 0.001$) and in multifocal than solitary tumours (54, IQR 37–75 vs 42, IQR 22–62; $P = 0.009$) (Fig. 1a–c; Supplementary Table S1). Among solitary tumours it correlated with diameter ($\rho = 0.41$, $P < 0.001$). There was no difference by sex ($P = 0.35$).

CD105-MVD does not predict recurrence

CD105-MVD showed no relation to recurrence by any analysis. Median CD105-MVD was 52 (IQR 31–72) in patients who recurred and 46 (IQR 22–67) in those who did not ($P = 0.26$), and discrimination was essentially absent (AUC 0.552, 95% CI 0.461–0.639; Fig. 2a). Kaplan–Meier RFS did not differ across the cut-off of 42 vessels (12-month RFS 55.5%, 95% CI 44.6–65.1 at or above the threshold versus 70.5%, 95% CI 57.7–80.1 below it, converging thereafter; log-rank $P = 0.39$; Fig. 3), across tertiles ($P = 0.70$), or across the cohort median ($P = 0.74$). Each 10-vessel increment carried a univariable hazard ratio of 1.01 (95% CI 0.95–1.09; $P = 0.70$) and an adjusted 0.98 (95% CI 0.91–1.06; $P = 0.59$) (Table 2; Fig. 4b). CD105-MVD was unrelated to the number of recurrences ($\rho = 0.06$, $P = 0.42$), and the null persisted when restricted to patients with ≥ 12 months (n = 138; $P = 0.36$) or ≥ 24 months of follow-up (n = 79; $P = 0.68$).

Table 2
Cox proportional-hazards models for recurrence-free survival (78 events among 157 patients)

Variable	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
CD105-MVD, per 10 vessels	1.01 (0.95–1.09)	0.698	0.98 (0.91–1.06)	0.588
Stage T1 (vs Ta)	1.13 (0.71–1.78)	0.612	0.99 (0.54–1.81)	0.963
High grade (vs low grade)	1.11 (0.70–1.75)	0.662	0.99 (0.53–1.85)	0.986
Multiple tumours (vs solitary)	1.74 (1.11–2.74)	0.016	1.89 (1.17–3.05)	0.010
Age, per 10 years	0.89 (0.73–1.08)	0.234	0.86 (0.70–1.06)	0.151
Male sex (vs female)	1.10 (0.53–2.29)	0.800	1.54 (0.72–3.29)	0.262
Any intravesical therapy (vs none)	1.77 (1.11–2.83)	0.017	1.81 (1.09–3.03)	0.023

Multivariable model contains all listed covariates (11 events per variable); Harrell's C = 0.641, falling to 0.592 after bootstrap optimism correction. The association between intravesical therapy and recurrence is most likely explained by confounding by indication; the observational design cannot separate treatment from its indication. HR, hazard ratio; CI, confidence interval; CD105-MVD, CD105 (endoglin)-assessed microvessel density.

Two variables did predict recurrence: multifocality (adjusted HR 1.89, 95% CI 1.17–3.05; P = 0.010) and receipt of any intravesical therapy (adjusted HR 1.81, 95% CI 1.09–3.03; P = 0.023). The latter most likely reflects confounding by indication — intravesical therapy was concentrated in patients with adverse pathology (37 of 48 T1 high-grade patients received it, versus 30 of 80 Ta low-grade patients).

CD105-MVD, progression, and its dependence on grade

Patients who progressed had a markedly higher CD105-MVD (median 67, IQR 52–89 vs 46, IQR 26–68; P = 0.007), with an AUC of 0.735 (95% CI 0.608–0.849; Fig. 2a). Comparison across the three outcome groups was significant (Kruskal–Wallis P = 0.022), driven entirely by the progression group: median CD105-MVD was 45 with no event, 47 with recurrence alone and 67 with progression (Holm-adjusted P = 0.019 progression vs no event, P = 0.029 progression vs recurrence, P = 0.54 recurrence vs no event) (Fig. 1d).

The Youden-optimal cut-off was 42 vessels. Below this threshold no patient progressed: 0 of 65 versus 12 of 92 above it (13.0%, 95% CI 7.6–21.4; Fisher exact P = 0.001), giving a sensitivity of 100% (95% CI 75.8–100), specificity 44.8% and negative predictive value 100% (95% CI 94.4–100). Kaplan–Meier PFS separated accordingly (36-month PFS 100% vs 82.3%, 95% CI 68.1–90.6; log-rank P = 0.006; Fig. 5), and the same gradient appeared across tertiles, with 0 of 56, 4 of 50 and 8 of 51 patients progressing (log-rank P = 0.024; Fig. 2b). Modelled continuously, each 10-vessel increment was associated with an 18% higher progression hazard (HR 1.18, 95% CI 1.02–1.36; P = 0.024) (Table 3; Fig. 4a).

Table 3
Cox proportional-hazards models for progression-free survival (12 events among 157 patients)

Variable	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
CD105-MVD, per 10 vessels	1.18 (1.02–1.36)	0.024	1.11 (0.95–1.29)	0.199
Stage T1 (vs Ta)	3.68 (1.10–12.30)	0.034	—	—
High grade (vs low grade)	5.24 (1.42–19.40)	0.013	4.13 (1.05–16.32)	0.043
Multiple tumours (vs solitary)	2.64 (0.79–8.80)	0.114	—	—
Age, per 10 years	1.56 (0.93–2.62)	0.089	—	—
Any intravesical therapy (vs none)	0.51 (0.16–1.62)	0.252	—	—

Multivariable model contains CD105-MVD and grade only (6 events per variable); Harrell's C = 0.811 (0.791 after bootstrap optimism correction). Adding CD105-MVD to a grade-only model did not improve fit (likelihood-ratio $\chi^2 = 1.49$, P = 0.22). Sex was not estimable because all 12 progression events occurred in men. For the dichotomised marker (CD105-MVD ≥ 42 vs < 42 vessels) the maximum-likelihood hazard ratio is not finite because no event occurred below the threshold; a Firth-penalised model gives HR 15.6 (profile-likelihood 95% CI 2.0–1998) and the likelihood-ratio test $\chi^2 = 11.4$ (P < 0.001). HR, hazard ratio; CI, confidence interval; CD105-MVD, CD105 (endoglin)-assessed microvessel density.

This association did not survive adjustment. In the bivariable model with WHO grade, grade retained significance (HR 4.13, 95% CI 1.05–16.32; P = 0.043) whereas CD105-MVD did not (HR 1.11, 95% CI 0.95–1.29; P = 0.20), and adding CD105-MVD to a grade-only model did not improve fit (likelihood-ratio $\chi^2 = 1.49$, P = 0.22). Substituting stage for grade gave the same pattern. Cross-classification makes the interdependence concrete: no progression occurred in either the 15 high-grade or the 50 low-grade patients with CD105-MVD below 42, whereas 9 of 47 high-grade and 3 of 45 low-grade patients above the threshold progressed.

CD105-MVD adds nothing to a proxy risk grouping

Against a stage-, grade- and focality-based proxy grouping (Supplementary Table S2), CD105-MVD rose steeply across groups (median 28, 47 and 56 vessels; Kruskal–Wallis P < 0.001). Adding it to the risk group raised Harrell's C for progression from 0.713 to 0.780 — 0.693 to 0.740 after bootstrap optimism correction — but the improvement was not significant (likelihood-ratio P = 0.19). For recurrence there was no gain, and after optimism correction the marker made discrimination slightly worse (C 0.580 to 0.587 apparent, 0.562 to 0.555 corrected; P = 0.98).

Precision, internal validation and sensitivity

Bootstrap optimism correction showed negligible overfitting in the simple progression models (C 0.733 → 0.728 for CD105-MVD alone; 0.742 → 0.742 for grade alone) and modest overfitting in the two-variable model (0.811 → 0.791). The multivariable recurrence model was the most optimistic, falling from 0.641 to 0.592. After correction, CD105-MVD alone and grade alone discriminate progression almost identically, consistent with the two carrying largely the same information. For the dichotomised marker, complete separation makes the maximum-likelihood hazard ratio infinite; a Firth-penalised model gives 15.6 (profile-likelihood 95% CI 2.0–1998), informative about direction but not magnitude.

The two endpoints differ in precision. For recurrence, 78 events gave a 95% confidence interval for the adjusted per-10-vessel hazard ratio of 0.91–1.06; compounded across the interquartile span of 40 vessels the upper limit corresponds to a hazard ratio of 1.25. For progression the binding limitation is the inability of 12 events to support adjustment, the grade-adjusted interval running from 0.95 to 1.29. Findings were robust to sensitivity analyses, and proportional hazards held for CD105-MVD in every model (Grambsch–Therneau $P \geq 0.31$), the single exception being stage for progression; full details are given in the Supplementary Results.

Discussion

In 157 patients with primary TaT1 urothelial carcinoma we found a dissociation between two endpoints that are often reported together — and, just as importantly, a dissociation in how much the study is entitled to say about each. CD105-assessed microvessel density carried no detectable information about recurrence, and the result held across three ways of categorising the marker, two restrictions on follow-up, and comparison against a clinical risk grouping. It did discriminate progression, and not one of the 65 patients with fewer than 42 CD105-positive vessels per ×200 field progressed. Yet once WHO grade entered the model, the marker's independent contribution disappeared.

The dissociation is biologically coherent. Recurrence in NMIBC is substantially a field phenomenon — incomplete resection, tumour cell re-implantation, and transformation of a urothelium exposed to the same carcinogens — and there is little reason to expect the vascular density of the index lesion to govern it. Progression is invasion, and invasion is the process for which a tumour must recruit new vessels [42, 43]. Read in this light our data are consistent with most of the bladder literature (Table 4). Reiher and colleagues, in the only other series confined to primary resection specimens — a design choice that matters, because re-resection specimens contain granulation-tissue neovascularisation that is not tumour-driven — found MVD correlated with stage and grade but not with outcome [17]; Stavropoulos and colleagues found no independent prognostic significance [18]; Korkolopoulou and colleagues found vessel area and compactness, not density, predicted outcome in T1 disease [19]; and Agrawal and colleagues found CD105 significant only in combination with VEGF or p53 [31].

Table 4

Present findings in the context of published angiogenesis and endoglin studies in urothelial carcinoma

Study	Population	Method	Recurrence	Progression / survival
Present study	157 NMIBC (TaT1), primary resections	CD105 IHC, hot-spot ×200	No association (adj. HR 0.98, 0.91–1.06)	Univariable HR 1.18 (1.02–1.36); lost after adjustment for grade
Siddhartha 2025 (Biomarkers)	90 UCB (60 NMIBC, 30 MIBC)	CD105-MVD IHC + RT-qPCR	High CD105-MVD predicted poor RFS in NMIBC	Correlated with stage, grade and size
Siddhartha 2025 (Biochem Genet)	110 UCB; survival in 52 NMIBC, 36 MIBC	CD105-MVD with MMP-2/9, VEGF, bFGF	Independent predictor of poor RFS	Independent for OS, PFS and CSS
Wang 2021	Bladder TCC, superficial and invasive	CD31/CD34/CD105/ α-SMA on TMA	MVD differed by tumour-free vs recurrence group	MVD related to grade and invasive depth; vessel type independent
Agrawal 2011	90 NMIBC	CD105 with VEGF and p53, confocal	Not significant alone; significant combined with VEGF or p53	Not assessed separately
Reiher 2002	84 primary superficial tumours	CD31/CD34 MVD	No association	No association; MVD correlated with stage and grade
Stavropoulos 2004	127 superficial tumours	MVD and VEGF	No association	No independent significance; signal limited to grade 3
Korkolopoulou 2001	115 TCC (35 T1)	CD31 morphometry	Vessel compactness predicted DFS in superficial disease	MVD predicted survival only in muscle-invasive disease

Studies are ordered by proximity of design to the present one. IHC, immunohistochemistry; MVD, microvessel density; NMIBC, non–muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer; TCC, transitional cell carcinoma; UTUC, upper urinary tract urothelial carcinoma; TMA, tissue microarray; RFS, recurrence-free survival; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; CSS, cancer-specific survival.

Study	Population	Method	Recurrence	Progression / survival
Santos 2003	66 superficial papillary tumours	CD31/CD34/factor VIII/endoglin	Microvessel clusters predicted early recurrence in T1/G2	Not assessed
Fujita 2015	99 UTUC after nephroureterectomy	Endoglin IHC on TMA	Associated with intravesical recurrence (P = 0.015)	Not associated with stage, grade, metastasis or CSS
Laukhtina 2022	1 036 radical cystectomy	Plasma (soluble) endoglin	Not applicable	Independently predicted ≥pT3, nodal disease, CSS and OS

Studies are ordered by proximity of design to the present one. IHC, immunohistochemistry; MVD, microvessel density; NMIBC, non–muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer; TCC, transitional cell carcinoma; UTUC, upper urinary tract urothelial carcinoma; TMA, tissue microarray; RFS, recurrence-free survival; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; CSS, cancer-specific survival.

The clearest disagreement is with the two recent series from Siddhartha and colleagues, who report CD105-MVD to be an independent predictor of recurrence-free survival in NMIBC cohorts of 60 and 52 patients [32, 33]. Their cohorts are a third the size of ours, and the discrepancy may reflect case mix, antibody clone, counting protocol or the number of events available; it may equally reflect the optimism of small biomarker series. A null result in 157 patients with 78 recurrence events carries more information about the absence of a large effect than a positive result in 52 patients carries about its presence. Wang and colleagues likewise found MVD related to grade and invasive depth, but their independent signal came from a classification of vessel *type* rather than total density [34]. The most instructive contrast is Fujita and colleagues' study of 99 upper-tract tumours, where endoglin was associated with subsequent intravesical recurrence but not with stage, grade, metastasis or cancer-specific survival [35] — the mirror image of our result. The inversion is informative: intravesical recurrence after nephroureterectomy is largely a seeding phenomenon, whereas recurrence in an intact bladder is a field phenomenon.

For recurrence, 78 events produced an adjusted hazard ratio of 0.98 with a 95% confidence interval of 0.91–1.06. No equivalence margin was pre-specified, so we do not claim formal equivalence; what we can say is that the upper limit corresponds to a hazard ratio of 1.25 across the interquartile span of the marker, which is not the magnitude a clinically useful prognostic factor would show. Progression is a different matter, and the limitation there is more specific than low power: the crude association is estimated with reasonable precision, but 12 events cannot separate the marker from grade, and the grade-adjusted interval (0.95–1.29) is compatible with both no effect and a meaningful one. The

bootstrapped threshold ranged from 42 to 86 vessels, and data-derived cut-points are notorious for inflating type I error and shrinking on validation [38, 39]. We would regard any reader who took the 42-vessel threshold into practice on this evidence as having over-read us.

The most consequential result is the multivariable one. CD105-MVD rose monotonically with stage, grade, multifocality and size, and once grade was accounted for it added nothing. This is not a failure of the assay but a statement about what it measures: in NMIBC, endothelial activation appears to be a downstream correlate of dedifferentiation rather than an independent driver — the pattern also reported for endoglin-defined vascular density in prostate cancer [44] and the conclusion of systematic appraisals of MVD methodology [45, 21]. The implication is not that angiogenesis is irrelevant but that *total* vessel count is the wrong summary of it: larger, higher-grade tumours simply contain more vessels. A normalised measure — the proportion of vessels that are CD105-positive relative to a pan-endothelial marker — would be structurally less collinear with grade, and both Korkolopoulou's and Wang's results suggest vascular architecture carries information density does not.

Two other lines of evidence keep endoglin interesting. In 1 036 patients undergoing radical cystectomy, higher preoperative *plasma* endoglin independently predicted ≥pT3 disease, nodal metastasis and cancer-specific survival [46], suggesting the soluble compartment may carry information the tissue compartment does not. Therapeutically, TRC105 showed CD105 expression in half of urothelial tumours but did not improve 6-month progression-free survival [28], consistent with the broader failure of anti-angiogenic strategies in this cancer [47]. Our finding that CD105-MVD marks the progression-prone phenotype without being independent of grade fits that frame: a candidate enrichment variable, not a candidate prognostic factor.

The limitations are substantial. First and above all, there were only 12 progression events, which forces a two-variable model at 6 events per variable, makes the threshold unstable and leaves the Firth-penalised hazard ratio with an upper limit two orders of magnitude above its point estimate. Second, median follow-up was 24 months, short for an endpoint that accrues for a decade [48]; progression will be under-ascertained. Third, concomitant carcinoma in situ was not recorded, tumour diameter was documented only for solitary tumours and WHO 1973 grade was unavailable, so EORTC and EAU 2021 scores could not be computed; the proxy grouping is only an approximation and the definitive comparison with guideline models remains untested. Fourth, counting was performed by a single observer, so interobserver reproducibility could not be estimated — a real weakness, since reproducibility is the principal published objection to MVD [14, 21]. Fifth, a single hot-spot field cannot capture intratumoural heterogeneity. Sixth, the study is retrospective and single-institution, and eligibility required retrievable blocks, so selection bias cannot be excluded. Finally, no external validation cohort was available; bootstrap optimism correction quantifies overfitting but cannot substitute for it. The index resections also date from 2007 to 2011, before pembrolizumab, nadofaragene firadenovec and N-803 became available for BCG-unresponsive disease [49–51], so the absolute event rates are not contemporary benchmarks — although endoglin biology, WHO grading and hot-spot counting are unchanged.

What a definitive study would require is not primarily power for a crude hazard ratio but events enough to adjust: a five-covariate model at ten events per variable needs 50 progression events, roughly 420 patients at a 12% progression rate or 250 if enriched for high-risk disease. Such a study should be prospective with at least five years of follow-up, should record carcinoma in situ, size for all tumours and both grading systems so that EORTC and EAU 2021 scores can be computed, should have every specimen counted independently by two pathologists with reproducibility reported, should pre-specify the threshold, and — on the evidence assembled here — should test a pan-endothelial-normalised measure of vascular activation rather than total microvessel density.

Conclusion

CD105 (endoglin)-assessed microvessel density in the initial resection specimen did not predict recurrence in 157 patients with primary TaT1 urothelial carcinoma. With 78 events and an adjusted hazard ratio of 0.98 (95% CI 0.91–1.06) this is a tightly bounded null, and the marker added nothing to a proxy clinical risk grouping. CD105-MVD was associated with progression and no progression occurred below 42 vessels per ×200 field, but that analysis rests on 12 events and does not survive adjustment for WHO grade; it is hypothesis-generating. Taken together, the results place CD105-MVD as a quantitative correlate of the high-grade, high-stage phenotype rather than an independent prognostic factor.

Declarations

Funding

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Conflicts of interest / competing interests

The authors declare that they have no competing interests.

Ethics approval

The study was approved by the institutional review board of Dr. Lütfi Kırdar Kartal Training and Research Hospital, University of Health Sciences, Istanbul, Türkiye (approval number [2012/514/235/2], date [12.10.2012]), the centre at which the resections were performed and the archival material is held, and was conducted in accordance with the Declaration of Helsinki.

Consent to participate

A waiver of individual informed consent was granted by the institutional review board for the retrospective analysis of anonymised records and archival tissue.

Consent for publication

Not applicable. No individually identifiable data are reported.

Availability of data and material

The de-identified patient-level dataset supporting the conclusions of this article is available from the corresponding author on reasonable request.

Code availability

The complete analysis code is available from the corresponding author on reasonable request.

Author contributions

Conceptualisation: AS, MU. Methodology: MU. Formal analysis: MU. Investigation and clinical data curation: AS, AT, AK. Resources (archival retrieval and pathology liaison): AS. Visualisation: MU. Writing — original draft: AS, MU. Writing — review and editing: all authors. Supervision: MYB. Project administration and correspondence: MU. The blinded histological review and microvessel counts were performed by a uropathologist who is not an author and who is thanked in the Acknowledgements. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.***Acknowledgements***

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Clinical trial number

Not applicable

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Figures

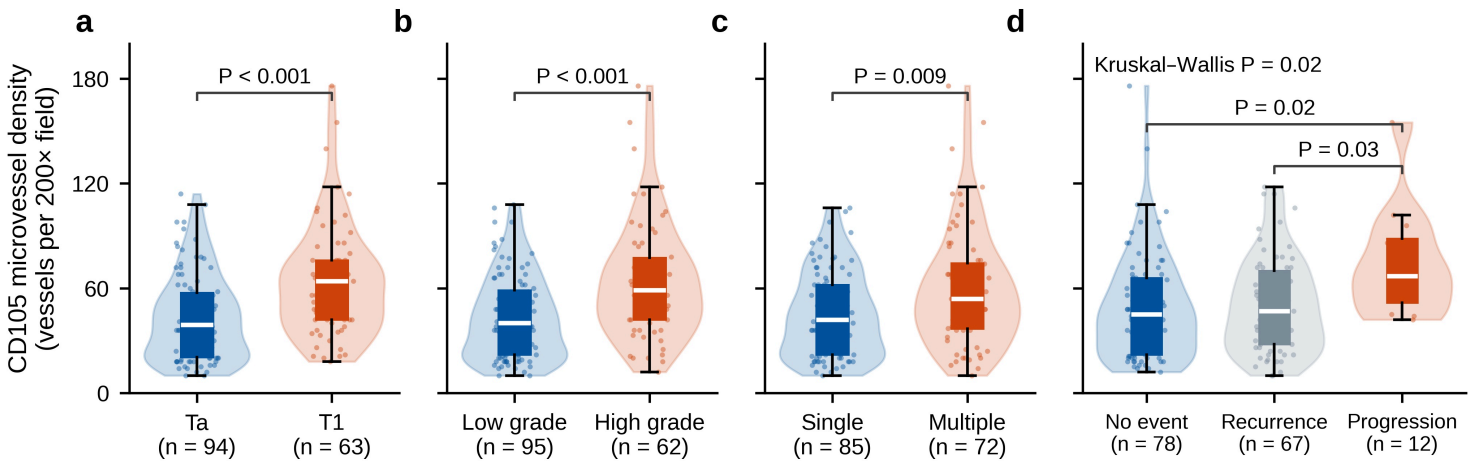


Figure 1

Distribution of CD105-assessed microvessel density by clinicopathological category and by outcome. Violin plots show the kernel density of the full distribution; boxes span the interquartile range with the median in white; whiskers extend to 1.5 × IQR; individual patients are shown as jittered points. **a** Stage. **b**WHO 2004/2016 grade. **c** Focality. **d** Outcome group. P values are from Mann–Whitney U tests (**a**–**c**) and from Kruskal–Wallis with Holm-adjusted pairwise comparisons (**d**). Within panel **d** the elevation is confined to the progression group: patients who recurred without progressing are indistinguishable from patients with no event (P = 0.54)

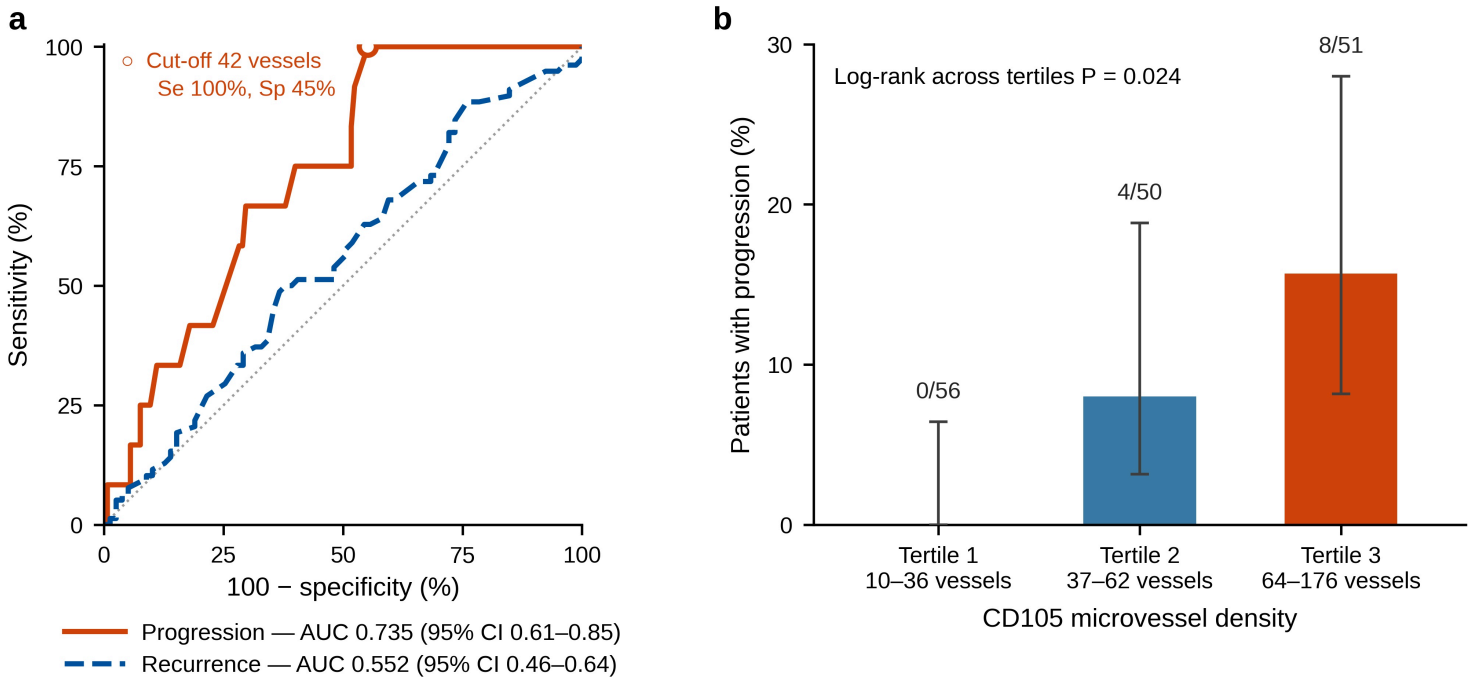


Figure 2

Discrimination and progression risk gradient. **a** Receiver-operating-characteristic curves for CD105-assessed microvessel density as a classifier of progression (solid) and of recurrence (dashed). The open circle marks the Youden-optimal operating point for progression (42 vessels per ×200 field). **b**Proportion of patients progressing within tertiles of CD105-assessed microvessel density, with Wilson 95% confidence intervals; fractions above each bar are events/patients. No patient in the lowest tertile progressed

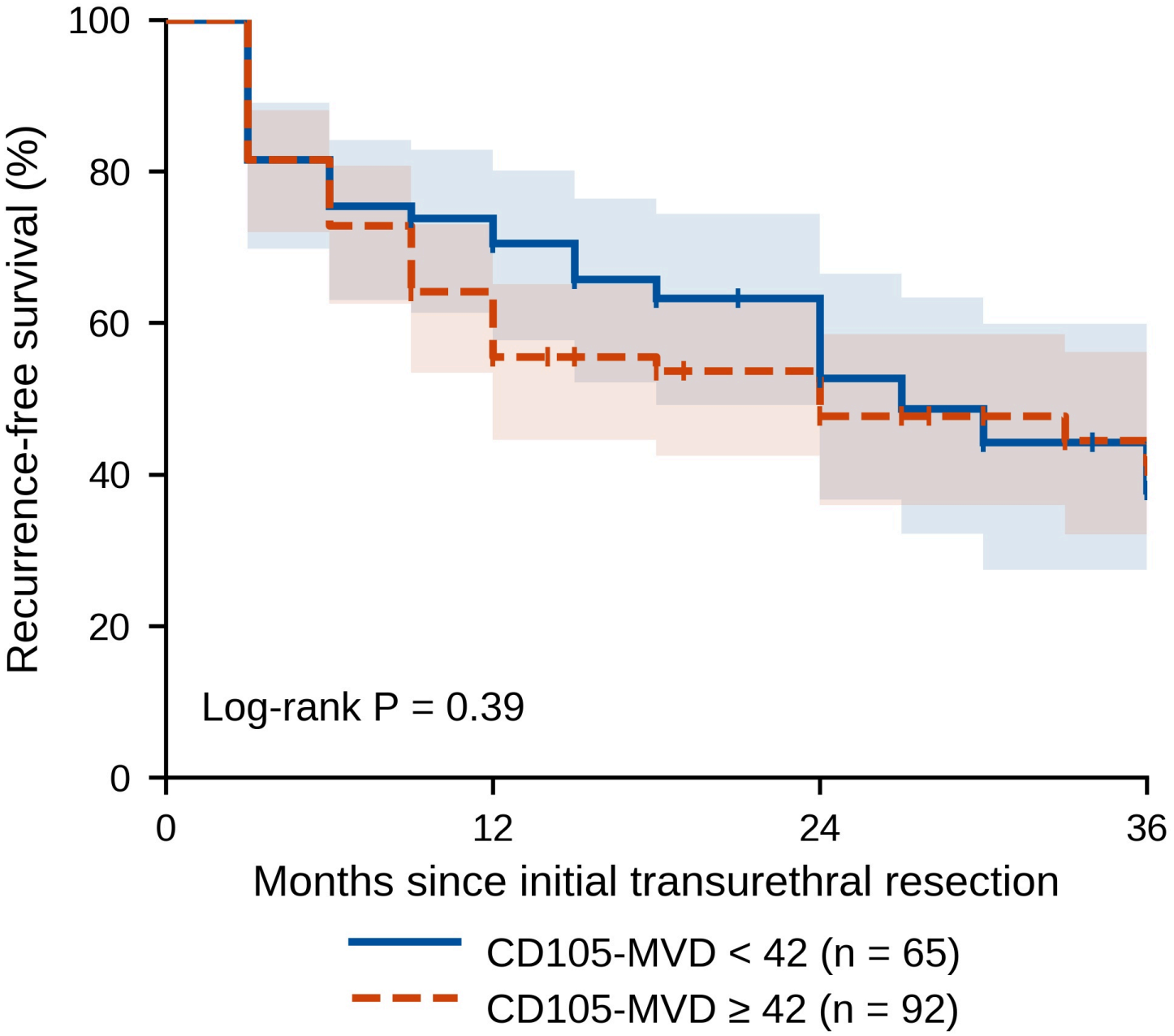


Figure 3

Recurrence-free survival according to CD105-assessed microvessel density, below and at or above the cut-off of 42 vessels per ×200 field. The curves converge after the first year and the log-rank test is non-significant (P = 0.39). Shaded bands are 95% confidence intervals (log–log transformation); vertical ticks denote censored observations. Curves are truncated at 36 months, at which point 7 patients below and 13 at or above the threshold remained at risk (65 and 92 at baseline; 44 and 52 at 12 months; 18 and 27 at 24 months)

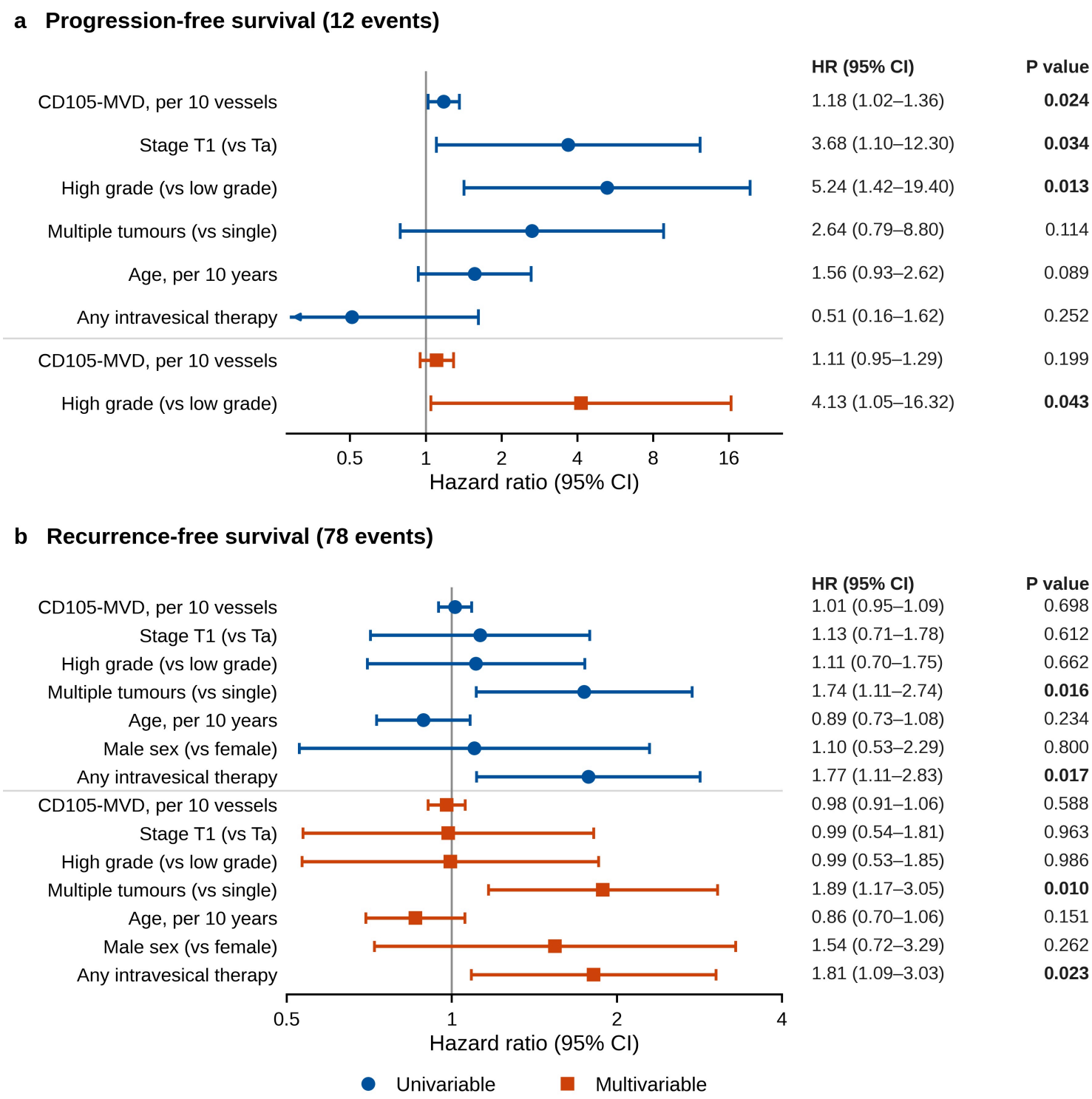


Figure 4

Cox proportional-hazards models. Hazard ratios with 95% confidence intervals on a logarithmic scale. **a** Progression-free survival (12 events); circles are univariable estimates, squares the bivariable model containing CD105-assessed microvessel density and grade. Sex was not estimable because all progression events occurred in men. **b** Recurrence-free survival (78 events); the multivariable model contains all listed covariates. Arrowheads indicate confidence limits extending beyond the plotted range

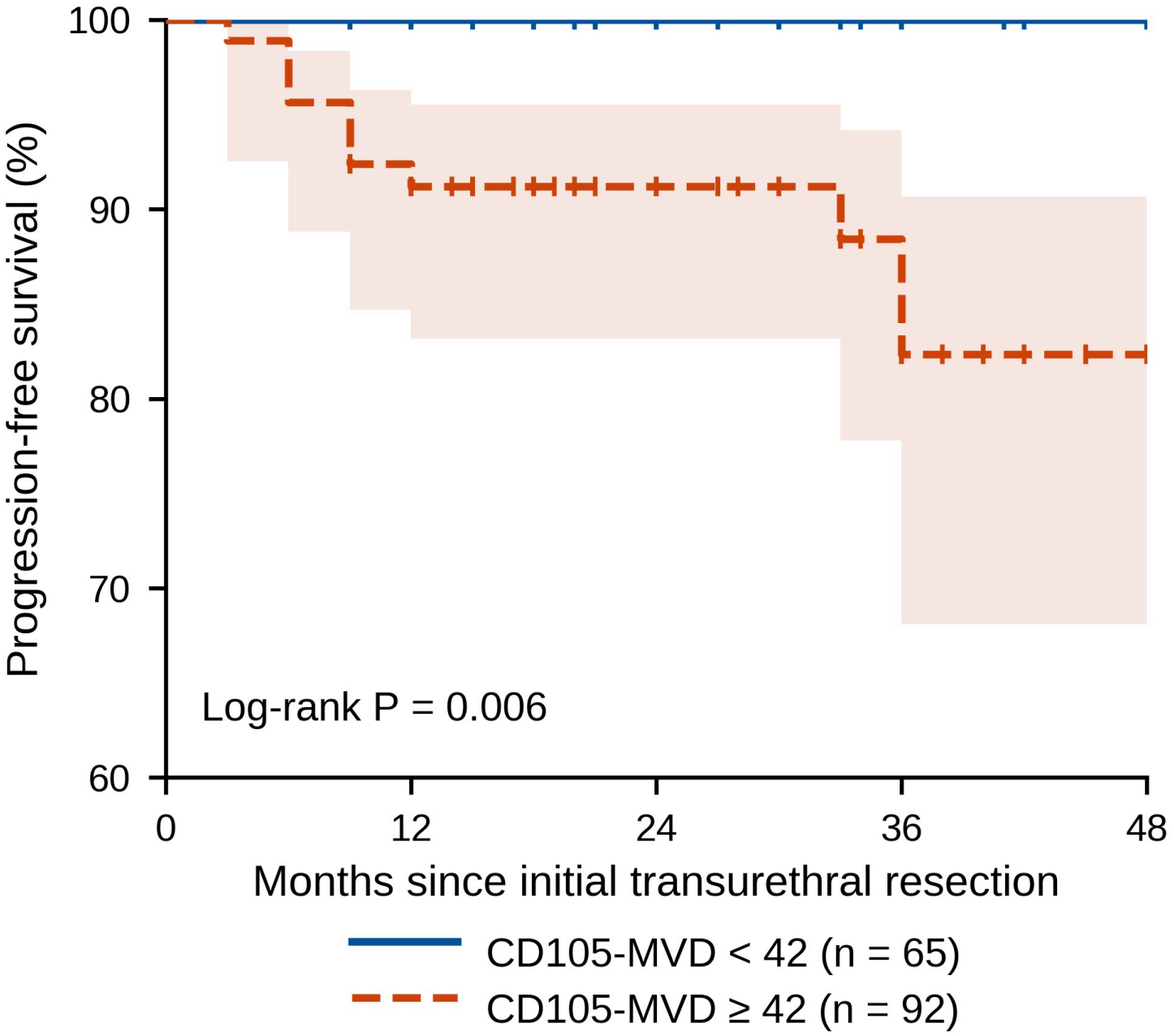


Figure 5

Progression-free survival according to CD105-assessed microvessel density, below and at or above the cut-off of 42 vessels per ×200 field. No progression event occurred in the low-CD105 group (0/65) compared with 12 of 92 in the high-CD105 group; 36-month progression-free survival was 100% versus 82.3% (95% CI 68.1–90.6). Shaded bands are 95% confidence intervals (log–log transformation); vertical ticks denote censored observations. Curves are truncated at 48 months, at which point 10 patients below and 14 at or above the threshold remained at risk (65 and 92 at baseline; 58 and 78 at 12 months; 32 and 47 at 24 months; 16 and 29 at 36 months)

Supplementary Files

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