

Konsultationsfassung: Evidenztabellen der Früherkennung, Diagnose, Therapie und Nachsorge des Harnblasenkarzinoms

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Evidenztabellen

Bitte senden Sie Kommentare, Hinweise und Verbesserungsvorschläge zu dieser Leitlinie unter Verwendung des [Kommentierungsbogens](mailto:harnblasenkarzinom@leitlinienprogramm-onkologie.de) bis zum 15.11.2026 an: harnblasenkarzinom@leitlinienprogramm-onkologie.de

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1 Evidenztabellen

1.1 Primärdiagnostik des Harnblasenkarzinoms

Verknüpfte Empfehlungen:

Empfehlung 5.9: Zur primären Diagnostik des Blasenkarzinoms kann ein multiparametrisches MRT des Beckens durchgeführt werden.

Empfehlung 5.14: Vor der tiefen Resektion eines Harnblasentumors kann ein multiparametrisches MRT des Beckens durchgeführt werden.

Literaturreferenzen: [\[1\]](#), [\[2\]](#), [\[3\]](#), [\[4\]](#)

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
Systematische Reviews*							
Feng, 2022 35181798	Systematic review and meta-analysis 2-	n=19 cohort studies (12 retrospective, 7 prospective) n=2900 patients Mean/Median age: 60.2-76 y Search date: October 2021	VI-RADS based on mpMRI	· TURBT (n=19 studies) · Radical cystectomy (n=13 studies) · Partial cystectomy (n=6 studies)	Diagnostic performance of VI- RADS	Pooled sensitivity Score 3: 0.92 (95%CI 0.89–0.94) Score 4: 0.78 (95%CI 0.72–0.83) Pooled specificity Score 3: 0.82 (95%CI 0.76–0.87) Score 4: 0.96 (95%CI 0.93–0.97) AUC Score 3 and 4: 0.94 (95%CI 0.92– 0.96)	no keywords or search strategy reported serious heterogeneity ($I^2 \geq 75\%$) in the analysis (except sensitivity analysis with score 3 $I^2 = 53.15\%$) The authors declare that they have no conflict of interest. No funding received.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						Proportion of muscle invasive (n=9) Sensitivity: 0.82 (0.76–0.88) p=0.11 specificity: 0.94 (0.90–0.97) p<0.01	
Ye, 2022 35362750	Systematic review with meta-analysis 2++	n=17 cohort studies (11 retrospective, 6 prospective) n=2344 patients Mean age: 57.2- 74 y search date: June 26, 2021	· bpMRI (n=1041 patients) · conventional VI- RADS based on mpMRI (n=1303 patients)	· TURBT (n=17 studies) · re-TURBT (n=11 studies) · radical cystectomy (n=11 studies) · partial cystectomy (n=39 studies)	· Diagnostic performance of the bpMRI and conventional VI-RADS · accuracy of conventional VI-RADS	bpMRI <u>Cutoff score 3</u> (n=6) · Sensitivities: 0.90 (95% CI 0.69– 0.97) · specificities: 0.90 (95% CI 0.81– 0.95) · accuracy: 0.88 (95% CI 0.81– 0.93) · PPV: 0.78 (95% CI 0.65–0.87) · NPV: 0.95 (95% CI 0.86–0.99) · AUC: 0.95 (95% CI: 0.92–0.96) <u>Cutoff score 4</u> (n=6) · Sensitivities: 0.84 (95% CI 0.78– 0.88) · specificities: 0.97 (95% CI 0.87– 0.99)	serious heterogeneity ($I^2 \geq 75\%$) in the analysis (except sensitivity analysis with score 3 $I^2 = 73\%$) The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article. National Science Foundation of China Youth Fund (No. 31801066)

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						· accuracy: 0.92 (95% CI: 0.85–0.96) · PPV: 0.90 (95% CI: 0.65–0.98) · NPV: 0.95 (95% CI: 0.89–0.98) · AUC: 0.89 (95% CI: 0.86–0.91) VI-RADS <u>Cutoff score 3</u> (n=16) · Sensitivities: 0.91 (95% CI 0.87–0.94) · specificities: 0.86 (95% CI 0.77–0.91) · accuracy: 0.87 (95% CI: 0.81–0.91) · PPV: 0.76 (95% CI: 0.66–0.84) · NPV: 0.95 (95% CI: 0.92–0.97) · AUC: 0.95 (95% CI: 0.92–0.96) <u>Cutoff score 4</u> (n=16) · Sensitivities: 0.85 (95% CI 0.77–0.90) · specificities: 0.93 (95% CI 0.89–0.96)	

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						· accuracy: 0.88 (95% CI 0.86–0.90) · PPV: 0.85 (0.76–0.91) · NPV: 0.94 (0.89–0.96) · AUC: 0.95 (95% CI: 0.93–0.97) bpMRI vs mpMRI <u>Cutoff score 3</u> · sensitivities: p=0.15 · specificity: bpMRI was significantly higher than VI-RADS (0.90 [95% CI 0.81–0.95] vs 0.86 [95% CI: 0.77–0.91], p = 0.02) <u>Cutoff score 4</u> · sensitivities: p=0.19 · specificity: bpMRI was significantly higher than VI-RADS (0.97 [95% CI 0.87–0.99] vs 0.93 [95% CI: 0.89–0.96], p = 0.02) hsROC curves showed no difference between the 95% confidence regions with cutoff scores of 3 and 4. T2 thickness (mm)	

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						<u>VI-RADS 3</u> ≤ 4 (n=12) · Sensitivity: 0.89 (95% CI 0.85–0.94) · Specifity: 0.89 (95% CI 0.82–0.95) p=0.35 <u>VI-RADS 4</u> ≤ 4 (n=11) · Sensitivity: 0.85 (95% CI 0.77–0.93) · Specifity: 0.93 (95% CI 0.88–0.98) p=0.94 <u>VI-RADS 3</u> > 4 (n=3) · Sensitivity: 0.92 (95% CI 0.87–0.97) · Specifity: 0.73 (95% CI 0.50–0.97) p=0.35 <u>VI-RADS 4</u>	

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						> 4 (n=3) · Sensitivity: 0.82 (95% CI 0.68–0.97) · Specificity: 0.94 (95% CI 0.87–1.00) p=0.94	
Del Giudice, 2022 35294583	Systematic review with meta-analysis 2-	n=20 cohort studies (16 retrospective, 6 prospective) n=2477 patients Median age: 57-74 y search date: May 26, 2021	VI-RADS based on mpMRI	· TURBT (n=20 studies) · cystectomy (n=10 studies)	Diagnostic performance of VI-RADS	Pooled weighted sensitivity cut-off ≥ 3: 0.87 (95% CI 0.82–0.91) cut-off ≥ 4: 0.78 (95% CI 0.74–0.81) Pooled weighted specificity cut-off ≥ 3: 0.86 (95% CI 0.80–0.90) cut-off ≥ 4: 0.94 (95% CI 0.91–0.96) Area under the hsROC cut-off ≥ 3: 0.93 (95% CI 0.90–0.95) cut-off ≥ 4: 0.91 (95% CI 0.88–0.93)	no search strategy reported, unclear if efforts were made to minimise error in data collection by a second author serious heterogeneity ($I^2 \geq 75\%$) in the analysis (except sensitivity analysis with cut-off ≥ 4 $I^2 = 57\%$) Regarding the content of this paper, the authors declare that they have no conflict of interest to disclose. Open access funding provided by Alma Mater Studiorum – Università di Bologna within the CRUI-CARE Agreement.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
Jazayeri, 2022 34895996	Systematic review with meta-analysis 2++	n=22 cohort studies (14 retrospective, 8 prospective) n=2576 participants Mean age: 57.1-75.3 y search date: 8 March 2021	VI-RADS based on mpMRI	· TURBT (n=3 studies) · TURBT and re-TURBT/ cystectomy (n=18 studies) · Not reported (n=1 studies)	· Diagnostic accuracy of VI-RADS · value for predicting MIBC	Sensitivity Score 2: 82% to 100% Score 3: 77% to 100% Score 4: 36% to 100% Score 5: 0% to 85% Pooled sensitivity VI-RADS ≥ 3: 89% (95%CI: 87%, 91%; I² = 48.4%) VI-RADS ≥ 4: 77% (95%CI: 73%, 82%; I² = 67.7%) Specificity Score 2: 9% to 89% Score 3: 44% to 97% Score 4: 74% to 100% Score 5: 5% to 100% Pooled specificity VI-RADS ≥ 3: 84% (95%CI: 80%, 87%; I² = 90.9%) VI-RADS ≥ 4: 77% (95%CI: 73%, 82%; I² = 67.7%) Accuracy	serious heterogeneity (I²$\geq$75%) in the analysis for pooled sensitivity and specificity ≥ 3 <i>publication bias was noted for VI-RADS ≥ 2 and ≥ 5 (P value = 0.002 with a slope coefficient of -18.49 and P value < 0.001 with a slope coefficient of -25.41</i> The authors confirm that there is no conflict of interest to declare. No information about funding.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						cutoff 3: 0.93 (95%CI: 0.91, 0.95) cutoff 4: 0.93 (95%CI: 0.90, 0.95) AUC Score 3: 0.93 (95%CI: 0.91, 0.95) Score 4: 0.93 (95%CI: 0.90, 0.95) T2WI slice thickness (mm) <u>2&3</u> (n=4) Sensitivity: 0.93 [0.89 – 0.97] p<0.01 Specifity: 0.82 [0.72 – 0.91] p<0.01 <u>4&5</u> (n=9) Sensitivity: 0.88 [0.85 – 0.90] Specifity: 0.85 [0.80 – 0.90]	
Seguier, 2021 34457041	Systematic review 2-	n=20 studies (3 meta-analysis, 12 retrospective studies, 5 prospective studies)	VI-RADS based on mpMRI		evaluate the performance of the VI-RADS score	· Pooled sensitivity ranged from 74.1% to 97.3% · Pooled specificity ranged from 77% to 100% Retrospective studies <u>VI-RADS 2</u> (n=3)	short search period, no search strategy reported, no information if efforts were made to minimise error in data collection and risk of bias assessment, no funnel plot, biases in primary studies were not addressed in the synthesis

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
		n=2144 patients in the cohort studies search date: January 2018- December 2020				· sensitivity was 100% · specificity ranged from 21% to 81% <u>VI-RADS 3</u> (n=12) · sensitivity ranged from 78% to 100% · specificity ranged from 44% to 100% <u>VI-RADS 4</u> (n=7) · sensitivity ranged from 63 to 100% · specificity ranged from 76% to 96% <u>VI-RADS 5</u> (n=7) · sensitivity ranged from 68% to 86% · specificity ranged from 95% to 99% Prospective studies <u>VI-RADS 3</u> (n=3) · sensitivity ranged from 78% to 92%	The authors declare that there is no conflict of interest. The authors received no financial support for the research, authorship, and/or publication of this article.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						· specificity ranged from 88% to 91%	
						<u>VI-RADS 4</u> (n=1) · sensitivity: 85.7% · specificity: 86.9%	
						<u>VI-RADS 5</u> (n=1) · sensitivity: 90.2% · specificity: 98.1%	
						Meta-analyses	
						<u>Woo, 2020</u> (n=6) Overall · sensitivity: 83% · specificity: 90%	
						<u>Luo, 2020</u> (n=5) Overall · sensitivity: 90% · specificity: 86%	
						VI-RADS 4 · sensitivity: 77% · specificity: 97%	

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						<u>Del Guidice, 2020</u> (n=8) · able to confirm an excellent inter-reader agreement of the VI-RADS score to discriminate MIBCs from NMIBCs: mean kappa 0.83 (95% CI 0.78-0.88)	
Carando, 2020 33029409	Systematic review 2-	n=6 cohort studies n=1067 patients search date: December, 2019	VI-RADS based on mpMRI		· The effectiveness of mpMRI in differentiating NMIBC from MIBC · The effectiveness of mpMRI in avoiding second TURBT in high-risk NMIBC · Potential limitations of the VI-RADS score	cut-off VI-RADS score of >2 · sensitivity: 78-91.9% · specificity: 85-91% · PPV: 69-78% · NPV: 88-97.1% cut-off VI-RADS score of >3 · sensitivity: 77-94.6% · specificity: 43.9-96.5% · PPV: 51.6-86% · NPV: 63.7-93% Good interobserver agreement was demonstrated in the evaluated studies with a κ score of 0.73-0.89.	inclusion and exclusion criteria not clearly described, no search strategy reported, no efforts made to minimise error in study selection and data collection, no risk of bias assessment, some study characteristics are missing (e. g. retrospective/ prospective, reference standard), heterogeneity not addressed The authors declare that they have no conflicts of interest. No information about funding.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
Woo, 2020 32199915	Systematic review with meta-analysis 2++	n=6 studies (4 cohort studies, 2 prospective) n=1170 patients Mean age: 57.2- 65.5 y search date: November 10, 2019	VI-RADS based on mpMRI	· TURBT (n=6 studies) · Partial cystectomy (n=2 studies) · Radical cystectomy (n=3 studies)	diagnostic performance of VI- RADS	Pooled sensitivity 0.83 (95% CI 0.70–0.90) Pooled specificity 0.90 (95% CI 0.83–0.95) Area under the HSROC curve 0.94 (95% CI 0.91–0.95) T2WI slice thickness (mm) <u>3</u> (n=3) Sensitivity: 0.90 (0.86–0.95) Specifity: 0.85 (0.78–0.93) p<0.01 <u>4</u> (n=2) Sensitivity: 0.84 (0.77–0.90) Specifity: 0.96 (0.93–1.00) p<0.01	serious heterogeneity ($I^2 \geq 75\%$) for sensitivity and specificity <i>number of patients has been corrected: PMID: 34756363</i> Conflict of interest are reported in detail in the paper. This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748. However, all specific roles were performed only by authors, and NIH/NCI had no direct role or support in those roles.
Cornelissen, 2020 32721515	Systematic review with meta-analysis 2-	n=20 cohort studies (9 prospective, 8 retrospective, 3 unclear)	mpMRI	· TURBT (n=1 studies) · cystectomy or TURBT (n=10 studies)	· What is the overall accuracy of mpMRI in local tumorstaging?	Accuracy · Overall (n=5): 56.0% (95% CI 49.6–62.3)	title screening were performed by 1 author, no information if efforts were made in the data collection, no funnel plot

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
		n=1724 patients Mean age: 52-72 y search date: October 2019		· Cystectomy, cystoscopy+biopsy or TURBT (n=1 studies) · cystectomy (n=5 studies) · unclear (n=3 studies)	· Can mpMRI differentiate stage $\leq T1$ from $\geq T2$? · Can mpMRI differentiate stage $\leq T2$ from $\geq T3$? · What is the sensitivity and specificity of mpMRI per T-stage? · Can mpMRI differentiate stage T-any from pT0 after initial TURBT?	· T2W (n=1): 85.0% (95% CI 62.1-96.8) · DCE (n=1): 64.4% (95% CI 48.8-78.1) · Overstaging was reported more often than understaging: 28.1% (95% CI 22.3-34.4) vs 18.4% (95% CI 13.6-24.1) Stage $\leq T1$ vs stage $\geq T2$ (n=19) Sensitivity: 0.92 (95% CI 0.88-0.95) Specifity: 0.88 (95% CI 0.78-0.94) Stage $\leq T2$ vs stage $\geq T3$ (n=3) Sensitivity: 0.71 (95% CI 0.59-0.82) Specifity: 0.77 (95% CI 0.68-0.84) Stage T0 (n=1) Sensitivity: 0.14 (95% CI 0.02-0.43) Specifity: 0.95 (95% CI 0.90-0.98) Stage T1 (n=7) Sensitivity: 0.75 (95% CI 0.47-0.91)	serious heterogeneity ($I^2 \geq 75\%$) The authors declare that they have no relevant financial interests. No information about funding.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						Specificity: 0.95 (95% CI 0.91-0.97) Stage T2 (n=3) Sensitivity: 0.62 (95% CI 0.49-0.74) Specificity: 0.66 (95% CI 0.57-0.75) Stage T3 (n=3) Sensitivity: 0.59 (95% CI 0.43-0.74) Specificity: 0.80 (95% CI 0.72-0.86) Stage T4 (n=3) Sensitivity: 0.77 (95% CI 0.55-0.92) Specificity: 0.97 (95% CI 0.92-0.99)	
Woo, 2017 28987698	Systematic review with meta-analysis 2-	n=24 cohort studies (13 retrospective, 11 prospective) n=1774 patients Mean age: 52.1-72.1 y	VI-RADS based on mpMRI	· TURBT (n=3 studies) · either cystectomy or TURBR (n=16 studies) · cystectomy (n=4 studies) · not reported (n=1 studies)	· Diagnostic performance of ≥ 1.5 -T MRI	Conventional + ≥ 2 functional (n=5) Sensitivity: 0.94 [0.89 – 1.00] Specificity: 0.95 [0.89 – 0.98] p<0.01 Using multiparametric 3-T MRI seemed to improve both sensitivity and specificity.	no information to heterogeneity in the subgroups, publication bias is present (Fig. 5) There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
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search date:
February 21,
2017

could have influenced its
outcome.

Primärstudien

Aslan, 2022 34919161	Diagnostic study 2+	n=114 patients 2019-2021	· T2-WI · DWI · DCE · bpMRI · mpMRI	TUR-B and/or radical cystectomy	· accuracy and validity of the bpMRI · diagnostic performance and agreement of readers with different experiences	<i>Range: results of both readers</i> T2-WI · Sensitivity: 88.3-37.1% · Specificity: 84.8-90.7% · PPV: 60-71.7% · NPV: 96.1-97.3% · Accuracy: 85.3-90.6% · AUC: 0.86-0.91 DWI · Sensitivity: 90.3% · Specificity: 95.8-99.1% · PPV: 84.3-96.5% · NPV: 96.6-97.5% · Accuracy: 94-97.3% · AUC: 0.91-0.95	consecutive recruitment unclear, unclear if TURBT/cystectomy results were interpreted without knowledge of the results of magnet resonance images No funding was received for this study. The authors declare that they have no conflict of interest.
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Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
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- DCE**
- Sensitivity: 87.1-89.7%
 - Specificity: 90.7-97.4%
 - PPV: 71.7-90.3%
 - NPV: 97.3-97.4%
 - Accuracy: 90.6-96%
 - AUC: 0.91-0.94
- bpMRI**
- Sensitivity: 87.1-90.3%
 - Specificity: 91.6-96.6%
 - PPV: 87.1-96.5%
 - NPV: 97.5-96.6%
 - Accuracy: 91.3-96%
 - AUC: 0.92-0.95
- mpMRI**
- Sensitivity: 90.3-93.5%
 - Specificity: 99.1-96.6%
 - PPV: 73.6-87.8%
 - NPV: 97.3-98.2%

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						· Accuracy: 94.6-97.3% · AUC: 0.92-0.95 No significant differences were shown in diagnostic performance for either reader between both the protocols (p = 0.238 and 0.318).	
Bricio, 2022 35505425	Diagnostic study 2+	n=44 patients Male: 19/44 (43.2%) Mean age: 68.7 y (35-91 y) 2018-2020 Brazil	· biparametric VI-RADS · multiparametric VI-RADS	· TURBT · Radical cystectomy	accuracy and reproducibility of the VI-RADS score	Diagnostic accuracy <u>Small lesions (n=25)</u> Biparametric Vi-RADS · Reader 1: 0.747 +/- 0.12 (0.50-0.99) · Reader 2: 0.800 +/- 0.11 (0.57-1.0) p=0.04 Multiparametric VI-RADS · Reader 1: 0.795 +/- 0.11 (0.57-1.0) · Reader 2: 0.800 +/- 0.11 (0.57-1.0) p=0.56 <u>All cases (n=50)</u>	unclear if TURBT/cystectomy results were interpreted without knowledge of the results of bpMRI and mpMRI The authors declare that they have no competing interests. The study was carried out using the authors' department resources only.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						Biparametric Vi-RADS · Reader 1: 0.879+/-0.05 (0.78-0.95) · Reader 2: 0.885 +/- 0.04 (0.79-0.98) p=0.07 Multiparametric VI-RADS · Reader 1: 0.916 +/- 0.04 (0.85-0.99) · Reader 2: 0.924 +/- 0.04 (0.84-0.99) p=0.24	
Elshetry, 2022 35381566	Diagnostic study 2+	n=54 patients Mean age: 60.1 y (45-76 y) Male: 47/54 (87%) 2019-2021 Egypt	· bpMRI · mpMRI	TURBT	diagnostic accuracy and discriminative power of bpMRI and mpMRI	Reader 1 <u>bpMRI</u> (VI-RADS cut-off values ≥ 3) Sensitivity: 100% (92-100) Specificity: 85.7% (57-98%) PPV: 95.7% (86-98%) NPV: 100% Accuracy: 96.5% (88-99%) <u>mpMRI</u> (VI-RADS cut-off values ≥ 3)	consecutive recruitment unclear, unclear if TURBT results were interpreted without knowledge of the results of bpMRI and mpMRI The authors declare no conflict of interests. This research did not receive any specific grant from funding agencies in the

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						Sensitivity: 100% (92-100) Specificity: 64.3% (35-87%) PPV: 89.8% (81-95%) NPV: 100% Accuracy: 91.3% (81-97%) Reader 2 <u>bpMRI</u> (VI-RADS cut-off values ≥ 3) Sensitivity: 100% (92-100) Specificity: 71.4% (42-92%) PPV: 91.7% (83-96%) NPV: 100% Accuracy: 93.1% (83-98%) <u>mpMRI</u> (VI-RADS cut-off values ≥ 3) Sensitivity: 100% (92-100) Specificity: 64.3% (35-87%) PPV: 89.8% (81-95%) NPV: 100% Accuracy: 91.3% (81-97%) Reader 3	public, commercial, or not-for-profit sectors.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						<u>bpMRI</u> (VI-RADS cut-off values ≥ 3) Sensitivity: 100% (92-100) Specificity: 93.6% (84-97%) PPV: 93.6% (84-97%) NPV: 100% Accuracy: 94.8% (87-99%) <u>mpMRI</u> (VI-RADS cut-off values ≥ 3) Sensitivity: 100% (92-100) Specificity: 71.4% (42-92%) PPV: 91.7% (83-96%) NPV: 100% Accuracy: 93.1% (83-98%) Comparable diagnostic accuracy with insignificant differences for the three readers (P = 0.364, 0.718, 0.702).	
Hagen, 2022 34839167	Diagnostic study 2-	n=33 patient Median age: 70 y (59-81 y)	· VI-RADS based on mpMRI (n=33) · CECT (n=33)	· Radical cystectomy (n=16) · TURBT (n=17)	clinical applicability of local tumor staging with VI-RADS compared to CECT	Radiologist 1 <u>mpMRI</u> (VI-RADS cut-off values ≥ 3) Sensitivity: 80%	unclear if TURBT/cystectomy results were interpreted without knowledge of the results of VI-RADS and CECT results, no time interval between VI-RADS and CECT

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
		Male: 29/33 (88%) 2019-2020 Germany				Specificity: 73.9% Accuracy: 75.6% <u>CECT</u> Sensitivity: 80% Specificity: 60.9% Accuracy: 66.7% p=0.839 Radiologist 2 <u>mpMRI</u> (VI-RADS cut-off values ≥3) Sensitivity: 70% Specificity: 82.6% Accuracy: 78.9% <u>CECT</u> Sensitivity: 90% Specificity: 69.5% Accuracy: 75.6% p=0.307	and TURBT/radical cystectomy reported No information about conflict of interest and funding.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
Kufukihara, 2022 34332846	Diagnostic study 2-	n=61 patients Age: 71.2 (49-88) y Male: 55/61 (90.2%) 2010-2018 Japan	· VI-RADS based on mpMRI · Diagnostic cystoscopy	TURBT	Comparison of the diagnostic performance	VI-RADS (<i>cut-off values</i> ≥ 3) <u>Radiologist 1</u> Sensitivity: 93.8% Specificity: 88.9% <u>Radiologist 2</u> Sensitivity: 87.5% Specificity: 86.7% Cystoscopy <u>Urologist 1</u> Sensitivity: 56.3% Specificity: 68.9% <u>Urologist 2</u> Sensitivity: 68.8% Specificity: 84.4% · sensitivity of cystoscopy was significantly lower than that of VI-RADS scores ($p=0.006$) · specificity of cystoscopy was slightly lower than that of VI-RADS scores ($P = 0.089$)	consecutive recruitment unclear, unclear if TURBT results were interpreted without knowledge of the results of VI-RADS and cystoscopy results, no time interval between bpMRI and mpMRI and TURBT reported No information about conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
Nikulainen, 2021 34448679	Diagnostic study 2+	n=45 patients Mean age: 67.5 y (34-86 y) Male: 39/45 (87%) 2014-2017 Finland	mpMRI · T-category · VI-Rads	TURBT	· performance of mpMRI using a subjective magnetic resonance imaging · performance of VI-RADS	Reader 1 <u>T-category</u> Sensitivity: 100% Specificity: 51% (95% CI 0.37-0.66) AUC: 0.76 (95% CI 0.59-0.85) PPV: 17% (95% CI 0.13-0.22) NPV: 100% <u>VI-Rads</u> Sensitivity: 75% (95% CI 0.75-1.00) Specificity: 51% (95% CI 0.37-0.66) AUC: 0.63 (95% CI 0.51-0.86) PPV: 14% (95% CI 0.05-0.21) NPV: 96% (95% CI 0.87-1.00) Reader 2 <u>T-category</u> Sensitivity: 75% (95% CI 0.75-1.00)	consecutive recruitment unclear Peter J. Boström, is an associate editor of Scandinavian Journal of Urology. The article was partly funded by grants from the Finnish Urology Association and the Turku University Hospital Research Foundation.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						Specificity: 37% (95% CI 0.22–0.51) AUC: 0.56 (95% CI 0.52–0.88) PPV: 10% (95% CI 0.04–0.15) NPV: 94% (95% CI 0.82–1.00) <u>VI-Rads</u> Sensitivity: 75% (95% CI 0.75–1.00) Specificity: 39% (95% CI 0.24–0.54) AUC: 0.57 (95% CI 0.47–0.80) PPV: 11% (95% CI 0.04–0.17) NPV: 94% (95% CI 0.83–1.00) no statistically significant difference between the reporting systems	
Gmeiner, 2021 34252867	Diagnostic study 2+	n=59 patients Mean age: 68.2 y (SD ±13.6 y) Male: 48/59 (81.4%)	· VI-RADS based on mpMRI	· TURBT · cystectomy	Diagnostic performance of overall VI-RADS	<i>Range: results of both readers</i> Cut-off value > 2 <u>T2W</u> Sensitivity: 76.9% Specificity: 92.3–96.2%	consecutive recruitment unclear, unclear if TURBT/ cystectomy results were interpreted without knowledge of the results of VI-RADS results

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
		2012-2014 Austria				<u>DWI</u> Sensitivity: 65.4-69.2% Specificity: 88.5-96.2% <u>DCE</u> Sensitivity: 72% Specificity: 96.15-96.2% Cut-off value > 3 <u>T2W</u> Sensitivity: 92.9-100% Specificity: 97.6% <u>DWI</u> Sensitivity: 78.6-92.9% Specificity: 95-95.1% <u>DCE</u> Sensitivity: 92.9-100% Specificity: 92.5-95% Muscle invasivnesss <u>T2W</u> AUC: 0.976-0.985 <u>DWI</u>	The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. No information about funding.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						AUC: 0.952-0.985 <u>DCE</u> AUC: 0.974-0.979 Tumor grade <u>T2W</u> AUC: 0.911-0.913 <u>DWI</u> AUC: 0.868-0.872 <u>DCE</u> AUC: 0.898-0.902 Upon multivariate logistic regression, only the T2w VI-RADS score contributed independently to the diagnosis of high grade and muscle invasive bladder cancer (P = 0.001 (Reader 1) and P = 0.0022 (Reader 2) for high grade cancer; P = 0.0007 (Reader 1) and P = 0.0019 (Reader 2) for muscle invasiveness).	
Wang, 2015 25615755	Diagnostic study 2+	n=39 patients (6 <i>excluded</i>)	· T2-Weighted Plus DCE-MRI	· radical cystectomy (n=11)	determine an optimal mpMRI protocol for characterizing tumors of low versus high	Reader 1 <u>T2-Weighted Plus DCE-MRI</u>	unclear if surgery results were interpreted without

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
		Mean age: 60.8 ± SD 11.2 y Male: 28/33 (85%) 2011-2013	· T2-Weighted Plus DWI · T2-Weighted Plus DWI Plus DCE-MRI	· partial cystectomy (n=2) · TURBT (n=26)	grade and differentiating tumors as T1 versus T2 for preoperative staging of bladder urothelial carcinoma	AUC: 0.731 (0.587–0.874) <u>T2-Weighted Plus DWI</u> AUC: 0.980 (0.948–1.000) <u>T2-Weighted Plus DWI Plus DCE-MRI</u> AUC: 0.988 (0.966–1.000) p < 0.05 Reader 2 <u>T2-Weighted Plus DCE-MRI</u> AUC: 0.717 (0.571–0.843) <u>T2-Weighted Plus DWI</u> AUC: 0.983 (0.954–1.000) <u>T2-Weighted Plus DWI Plus DCE-MRI</u> AUC: 0.991 (0.974–1.000) p < 0.05 · The combination of T2-weighted imaging, DWI, and DCE-MRI is most accurate for preoperative staging of organ-confined urothelial bladder cancer.	knowledge of the results of mpMRI results No information about conflict of interest or funding.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
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· With a cutoff apparent diffusion coefficient value of $0.899 \times 10^{-3} \text{ mm}^2/\text{s}$, the sensitivity and specificity for differentiating high- and low-grade bladder urothelial carcinoma were 100% and 95%.

1.1.1 Erstbefund eines nicht-muskelinvasiven Harnblasenkarzinoms

1.2 Evidenztabellen ohne Empfehlungsverknüpfung

1.2.1 Perioperative Systemtherapie

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkung
Kubota, 2021	Multicentre retrospective cohort study (matched-pair) 2+	n=261 patients with locally advanced bladder cancer (cT2-4, cN0-2, cM0) 2003-2019 <u>Median age</u>	Optimal neoadjuvant chemotherapy (<i>propensity cohort</i>) n=27 patients with cT3-4	No chemotherapy (<i>propensity cohort</i>) n=27 patients with cT3-4	The purpose of the present multicenter study was to investigate the oncological effect of neoadjuvant chemotherapy on patients with locally advanced bladder cancer stratified by clinical stage T3-4	Neoadjuvant vs. no neoadjuvant treatment cT3-4 cohort <u>5-year OS</u>	Small sample size No conflict of interests declared. No information about funding reported.

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkung
		(<i>propensity cohort</i>) Neoadjuvant: 75 (71–77) y No neoadjuvant: 75 (71–78) y <u>Male</u> (<i>propensity cohort</i>) Neoadjuvant: 74% No neoadjuvant: 89% <u>Median follow-up</u> (<i>propensity cohort</i>) cT3–4 cohort: 23.0 mo (IQR 8.9–42.7 mo) cT2 cohort: 25.5 months (IQR 14.6–45.5 mo)	n= 34 patients with cT2	n=34 patients with cT2	or T2 who underwent laparoscopic radical cystectomy. · OS · CSS · RFS · recurrence site and patterns · postoperative complications	78% vs. 41%; P = 0.014 <u>CSS</u> 81% vs. 44%; P = 0.008 <u>RFS</u> 71% vs. 53%; P = 0.049 cT2 cohort <u>5-year OS</u> 55% vs. 70%; P = 0.77 <u>CSS</u> 64% vs. 81%; P = 0.66 <u>RFS</u> 81 % vs. 67%; P = 0.10	
McCaw, 2021	Systematic review with meta-analysis 1-	n=8 RCTs cT2-4a N0 M0 bladder cancer	NAC + radical cystectomy · Epirubicin (n=1)	cystectomy	We analyzed the survival benefit attributable to NAC in bladder cancer by calculating RMST of previously published clinical trials.	OS (Fixed-effects) <u>NAC vs. cystectomy only</u> (n=6)	Only one database used for search, no number of patients reported, no information if efforts were made to minimise errors in the study selection and data

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkung
		search up to July 2020	· Cyclophosphamide + Doxorubicin + Cisplatin (n=1) · Doxorubicin + Cisplatin (n=1) · Methotrexate + Vinblastine + Cisplatin (n=2) · Methotrexate + Cisplatin (n=1) · Methotrexate + Vinblastine + Doxorubicin + Cisplatin (n=1) · Methotrexate + Vinblastine + Doxorubicin (n=1)		· OS	3.2 mo (95% CI 1.0 to 5.3 mo, P=0.004) OS (random-effects) <u>NAC vs. cystectomy only</u> 3.2 mo (95% CI 0.3 to 6.1 mo, P=0.04)	collection, no risk of bias assessment, unclear if the study from Gad El Mawla was included in the random-effects model No conflict of interest or funding reported.
Soria, 2021	Multicentre retrospective cohort study 2+	n=619 patients with cT2N0M0 bladder cancer without preoperative hydronephrosis 2000-2018	neoadjuvant chemotherapy before radical cystectomy (n=316)	radical cystectomy alone (n=303)	To assess the efficacy of neoadjuvant chemotherapy before radical cystectomy in a retrospective multicentre cohort of patients with cT2N0M0 bladder cancer without preoperative hydronephrosis. · pathological response	cT2N0M0 2-year OS Neoadjuvant: 73% No Neoadjuvant: 60%	Short follow-up time, inverse probability of treatment weighting was used to account for potential selection bias Petros Grivas (all unrelated to this project in the last 3 years):

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkung
		21 centres across Europe, Canada and USA Median age: 66 (59-73) y Male: 496/619 (81%) Follow-up: 18 (7-38) mo			· OS	<u>OS</u> OR 0.78, 95% CI 0.50–1.23, P = 0.3	consulting for AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis Oncology, Driver, EMD Serono, Exelixis, Foundation Medicine, Genentech, Genzyme, GlaxoSmithKline, Heron Therapeutics, Janssen, Merck, Mirati Therapeutics, Pfizer, Roche, Seattle Genetics, QED Therapeutics; prior participation in educational programs for Bristol-Myers Squibb; institutional research funding from AstraZeneca, Bayer, Genentech, Kure It Cancer Research, Merck, Mirati Therapeutics, Oncogenex, Pfizer, Clovis Oncology, Bavarian Nordic, Immunomedics, Debiopharm, Bristol-Myers Squibb, QED Therapeutics. The other authors have no conflict of interest to declare.
Indirekte Evidenz							

Referenz	Studientyp Evidenz- graduierung	Teilnehmer	Intervention	Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkung
Chung, 2021	Systematic review with meta-analysis 2++	n=5 studies (1 RCT, 4 case-control studies) 1206 patients with biopsy-proven MIBC who intended to undergo radical cystectomy and patients who underwent systemic NAC search up to December 2020	NAC using ddMVAC	NAC using gemcitabine and cisplatin	We aimed to provide evidence on the optimal NAC regimen for use in muscle-invasive bladder cancer. · pathologic complete response · pathologic downstaging · OS · CSS	ddMVAC vs. gemcitabine and cisplatin <u>OS</u> (n=2 case-control studies) HR, 2.16; 95% CI, 1.42-3.29; p = 0.0004 <u>CSS</u> (n=1 case-control studies) HR, 2.31; 95% CI, 1.29-4.13; p = 0.005	The authors declare no conflict of interest. This research received no external funding

1.2.2 Biomarker für Diagnostik und Prognose des Urothelkarzinoms

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
Wang, 2022 · 35322590	Systematic review with meta-analysis	n=12 studies n=2456 patients diagnosed with	NMP22	urine cytology	diagnostic efficacy the diagnosis of bladder cancer	Total sensitivity · NMP22: 0.79 (95% CI [0.73, 0.84])	no additional hand search, no complete search strategy reported, no information if efforts were made to minimise

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
	2-	or without bladder tumors search period: 1999-2021				· cytology: 0.55 (95% CI [0.41, 0.69]) Total specificity · NMP22: 0.59 (95% CI [0.46, 0.71]) · cytology: 0.91 (95% CI [0.81, 0.96]) Positive likelihood ratio · NMP22: 1.9 (95% CI [1.4, 2.6]) · cytology: 5.9 (95% CI [3.3, 10.6]) Negative likelihood ratio · NMP22: 0.35 (95% CI [0.27, 0.47]) · cytology: 0.49 (95% CI [0.38, 0.64]) Diagnostic odds ratio · NMP22: 5 (95% CI [3, 9]) · cytology: 12 (95% CI [7, 21]) The area under the summary receiver operating characteristics curve	error in the data extraction and risk of bias assessment <i>There is no heterogeneity caused by the threshold effect, but there is heterogeneity caused by other reasons. The meta-regression found that the heterogeneity is mainly caused by the type of experimental research included in the study and whether the population characteristics are described in detail.</i> The authors declare no conflicts of interest. No information about funding.

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						· NMP22: 0.79 (95% CI [0.75, 0.82]) · cytology: 0.81 (95% CI [0.77, 0.84]) At present, NMP22 cannot replace traditional cystoscopy and urine cytology, but it can be combined to detect bladder tumors. It plays a major role in screening, postoperative monitoring and follow-up.	
Laukhtina, 2021 34753702	Systematic review with network meta-analysis 2++	n=21 studies n=7330 patients with primary detection or were undergoing follow-up for recurrent disease and with detected urothelial carcinoma recurrence	· Xpert bladder cancer · Adxbladder · Bladder EpiCheck · Uromonitor · Cxbladder Monitor	cystoscopy and/or histopathology	To assess the diagnostic estimates of novel commercially available urinary biomarker tests for diagnosis and surveillance of NMIBC	Pooled sensitivity <u>Xpert</u> (n=10 studies) 0.722 (95% CI 0.631; 0.798) <u>EpiCheck</u> (n=3 studies) 0.736 (95% CI 0.570; 0.855) <u>ADXbladder</u> (n=3 studies) 0.571 (95% CI 0.387; 0.737) <u>Uromonitor</u> (n=2 studies) 0.931 (95% CI 0.788; 0.980) <u>Cxbladder</u> (n=2 studies) 0.909 (95% 0.853; 0.945)	no additional hand search, only keyword reported <i>serious heterogeneity ($I^2 \geq 75\%$) in all analysis (expect specificity EpiCheck and Uromonitor; PPV: EpiCheck, Uromonitor and Cxbladder; NPV: Xpert, Uromonitor)</i> Ekaterina Laukhtina is supported by the EUSP Scholarship of the European Association of Urology (EAU). Keiichiro Mori is supported by The Uehara Memorial

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
		search up to April 2021				Pooled specificity <u>Xpert</u> (n=10 studies) 0.763 (95% CI 0.715; 0.805) <u>EpiCheck</u> (n=3 studies) 0.8444 (95% CI 0.801; 0.879) <u>ADXbladder</u> (n=3 studies) 0.618 (95% CI 0.508; 0.717) <u>Uromonitor</u> (n=2 studies) 0.794 (95% CI 0.615; 0.903) <u>Cxbladder</u> (n=2 studies) 0.610 (95% CI 0.209; 0.902) Pooled positive predictive value <u>Xpert</u> (n=10 studies) 0.428 (95% CI 0.318; 0.544) <u>EpiCheck</u> (n=3 studies) 0.479 (95% CI 0.420; 0.539) <u>ADXbladder</u> (n=3 studies) 0.291 (95% CI 0.077; 0.669) <u>Uromonitor</u> (n=2 studies)	Foundation. Funding/Support and role of the sponsor: None.

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						0.673 (95% CI 0.355; 0.885) <u>Cxbladder</u> (n=2 studies) 0.165 (95% CI 0.089; 0.284) Pooled Negative predictive value <u>Xpert</u> (n=10 studies) 0.923 (95% CI 0.901; 0.940) <u>EpiCheck</u> (n=3 studies) 0.942 (95% CI 0.527; 0.969) <u>ADXbladder</u> (n=3 studies) 0.820 (95% CI 0.527; 0.949) <u>Uromonitor</u> (n=2 studies) 0.957 (95% CI 0.863; 0.988) <u>Cxbladder</u> (n=2 studies) 0.987 (95% CI 0.817; 0.999) Network meta-analysis · Sensitivity (OR 68.2, 95% CrI 7.51–1.26e + 03), specificity (OR 0.41, 95% CrI 0.04–4.34), PPV (OR 1.31, 95% CrI 0.15–10.1), and NPV (OR 14.0, 95% CrI 3.28–116) of the Uromonitor test	

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						were significantly higher than those of any other tests for the detection of NMIBC recurrence	
Soorojebally, 2023 36592175	Systematic review 2-	patients at risk of bladder cancer and patients with risk of non-muscle invasive recurrence or progression search period: May 2010-March 2021	· VisioCyt® (n=2) · Xpert® Bladder (n=11) · BTA stat® (n=3) · BTA TRAK™ (n=0) · NMP22 BC® (n=4) · NMP22® BladderChek® Test (n=12) · ImmunoCyt™/uCyt1+™ (n=4) · UroVysion Bladder Cancer Kit® (n=29) · Cxbladder (n=9) · ADXBLADDER (n=9) · Urodiag® (n=2)	· Cytology · Cystoscopy	clinical validity and clinical utility of eleven urinary biomarkers for bladder cancer diagnosis and for non-muscle invasive bladder cancer	VisioCyt® <u>Diagnosis</u> vs. "classical" urinary cytology, · Sensitivity: 84.9% vs. 43% (any grade) · Sensitivity: 92.6% vs. 61.1% (high grade) · Sensitivity: 77.6% vs. 26.3% (low grade) vs. Cytology/Cystoscopy · Specificity: 81.2% vs. 100% Xpert® Bladder <u>Diagnosis</u> vs. cytology · Sensitivity: 78% vs. 44% · Specificity: 84% vs. 97% <u>NMIBC surveillance</u> vs. cytology	inclusion and exclusion criteria not clearly described (e. g. reference status, publication types, outcomes), short search period, only one database used, no information if efforts were made to minimise error in the study selection, data extraction and risk of bias assessment, included study numbers and characteristics not completely reported, no funnel plot The authors declare that they have no conflict of interest. No information about funding.

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						· Sensitivity: 59-84% vs. 5-51% · Sensitivity: 78-100% vs. 11-85% (high grade) · Sensitivity: 40-77% vs. 4-13% (low grade) · Specificity: comparable The test does not have any added value relative to cytology. Cxbladder <u>Diagnosis</u> vs. cytology · Sensitivity: 81% vs. 56% · Specificity: 85% vs. 94% <u>NMIBC surveillance</u> vs. cytology · Cxbladder test was superior to cytology Test seems clinically useful for the follow-up because it can reduce by about 39% the mean number of annual cystoscopies. ADXBLADDER	

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						No study compared this test directly to cystoscopy. <u>Diagnosis</u> · Sensitivity: 73% · Specificity: 68.4% <u>Surveillance</u> vs. cytology · Sensitivity: 75.6% vs. 44.9% (low grade) · Sensitivity: Se: 100% vs 81.8% (MIBC recurrence) Test specificity was lower than that of cytology for the detection of all recurrence types. · The combination of cytology and ADXBLADDER test increases the test value. · It is currently impossible to recommend this test instead of cystoscopy. Urodiag®	

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						We note the absence of comparison with urinary cytology. <u>Diagnosis</u> · Sensitivity: 97.6% · Specificity: 84.8% <u>Recurrence detection</u> · Sensitivity: 94.5% · Specificity: 75.9% Among the 68/72 cancer recurrences, were correctly predicted (93.3% in the low risk, 92.9% in the intermediate risk, and 96.6% in the high-risk group). Overall · sensitivity of the evaluated biomarkers was high, but at the cost of lower specificity compared with urinary cytology · any increase in the false positive rate results in an increase of unnecessary cystoscopies/other tests	

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						· no biomarker can replace urinary cystoscopy or urinary cytology · they might be interesting for the initial diagnosis · Some biomarkers may have a clinical utility in NMIBC surveillance in patients with negative or equivocal cystoscopy or negative or atypical urinary cytology, and also in recurrence prediction, thus contributing to the decision of active surveillance in these patients.	
Aalami, 2021 33997007	Systematic review with meta-analysis 2-	n=4 studies n=656 participants (417 bladder cancer patients, 239 controls) search up to October 2020	angiogenin		diagnostic role of the angiogenin	Pooled sensitivity 0.71 (95% CI: 0.66–0.75) Pooled specificity 0.78 (95% CI: 0.73–0.81) Positive likelihood ratio 3.34 (95% CI: 2.02–5.53) Negative likelihood ratio 0.37 (95% CI: 0.32–0.44) DOR	„gold standard“ of the included studies not reported, no complete search strategy reported, no information if efforts were made to minimise error in the data extraction, risk of bias in the included studies not addressed <i>The I² heterogeneity of sensitivity, specificity, likelihood ratio +, likelihood ratio -, and DOR were 20.8%, 92.1%, 82.7%, 0%, and 77.4%.</i>

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						9.99 (95% CI: 4.69–21.28)	The authors declare that they have no conflicts of interest. No information about funding.
Soputro, 2022 35950042	Systematic review with meta-analysis 2-	n=17 studies patients who presented with primary macroscopic haematuria without prior diagnosis of bladder cancer Median age: 59-69 y search up to September 2020	· AssureMDx (n=1) · CxBladder (n=2) · Bladder Tumour Antigen (n=4) · Immunocyt/uCyt+ (n=4) · NMP22 (n=8) · UroVysion (n=2)	Cystoscopy	diagnostic performance based on their sensitivity, specificity and diagnostic odds ratio, as well as positive and negative likelihood ratios.	AssureMDx (n=1) · Sensitivity: 0.973 (95% CI 0.907–0.993) · Specificity: 0.825 (95% CI 0.727–0.893) · DOR: 169.714 (37.164–775.022) · positive likelihood ratio: 5.560 (3.450–8.961) · negative likelihood ratio: 0.033 (0.008–0.129) CxBladder (n=1) · Sensitivity: 0.818 (95% CI 0.709–0.893) · Specificity: 0.852 (95% CI 0.815–0.883) · DOR: 25.911 (13.112–51.205) · positive likelihood ratio: 5.529 (4.279–7.145)	no additional hand search, no complete search strategy reported, no information if efforts were made to minimise error in the data extraction, heterogeneity and risk of bias of the included studies not addressed, no funnel plot No information about conflict of interest and funding.

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						· negative likelihood ratio: 0.213 (0.128–0.357) Bladder Tumour Antigen (n=4) · Sensitivity: 0.659 (95% CI 0.572–0.736) · Specificity: 0.7 (95% CI 0.636–0.756) · DOR: 4.494 (2.819–7.165) · positive likelihood ratio: 2.192 (1.731–2.777) · negative likelihood ratio: 0.488 (0.377–0.631) Immunocyt (n=4) · Sensitivity: 0.844 (95% CI 0.805–0.876) · Specificity: 0.833 (95% CI 0.815–0.850) · DOR: 26.923 (19.969–36.299) · positive likelihood ratio: 5.048 (4.509–5.653) · negative likelihood ratio: 0.188 (0.149–0.236)	

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						NMP22 (n=8) · Sensitivity: 0.718 (95% CI 0.670–0.761) · Specificity: 0.577 (95% CI 0.542–0.611) · DOR: 3.465 (2.657–4.520) · positive likelihood ratio: 1.696 (1.530–1.880) · negative likelihood ratio: 0.489 (0.412–0.582) Urovysion (n=2) · Sensitivity: 0.712 (95% CI 0.624–0.786) · Specificity: 0.818 (95% CI 0.790–0.844) · DOR: 11.135 (7.193–17.235) · positive likelihood ratio: 3.920 (3.254–4.723) · negative likelihood ratio: 0.352 (0.265–0.468)	
Dong, 2021 34585369	Systematic review with	n=58 studies	· BTA stat	cytology	To identify effective urine biomarkers for	Sensitivity	no complete search strategy reported, no information if efforts were made to minimise

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
	network meta-analysis 2-	n=12038 participants search date: September 30, 2020	· BTA trak · fluorescence in situ hybridization · NMP-22 · Hyaluronidase 1 · ImmunoCyt · Survivin · urothelial carcinoma associated-1		bladder cancer diagnosis.	· HYAL-1, UCA1, and survivin were the most sensitive group · urine cytology was the least sensitive group Specificity · Urine cytology, FISH, and HYAL-1 were the highest · UCA1 was the lowest Positive predictive value · Urine cytology, FISH, and HYAL-1 had the highest positive predictive value · BTA group had the lowest positive predictive value Negative predictive indicators · HYAL-1, UCA1, and survivin had the highest negative predictive value · Urine cytology had the lowest negative predictive value Accuracy indicators · HYAL-1, UCA1, and survivin had the highest accuracy	error in the study selection, no risk of bias assessment The authors declare that they have no competing financial interests. No information about funding.

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						- Urine cytology had the lowest accuracy - HYAL-1 and survivin were found to be the two most suitable urine biomarkers for bladder cancer diagnosis.	
Dardeer, 2021 34465950	Systematic review with meta-analysis 2-	n=4 studies n=771 participants (417 bladder cancer patients, 254 controls) search date: up to March 2020	Apolipoprotein A1	- Cystoscopy - cytology	diagnostic accuracy	Pooled sensitivity 90.7% (95% CI, 87.5%–93.3%) Pooled specificity 90% (95% CI, 86.1%–93%) DOR 99.424 (95% CI, 29.6–333.96) Positive likelihood ratio 9.478 (95% CI, 4.178–21.502) Negative likelihood ratio 0.100 (95% CI, 0.073–0.138)	no additional hand search, no complete search strategy reported, no information if efforts were made to minimise error in the risk of bias assessment <i>serious heterogeneity ($I^2 \geq 75\%$) in the specificity analysis</i> Conflicts of interest: There are no conflicts of interest. Financial support and sponsorship: Nil.
Hentschel, 2021 32539176	Systematic review 2++	n=25 studies patient with a risk of bladder cancer and	- single mutation markers - marker panels	- cystoscopy - histology	diagnostic accuracy of urinary mutation analysis is separately assessed for	Diagnosis <u>Single-mutation markers</u> - sensitivity: 1–85% - specificity: 84–100%	no funnel plot <i>As studies were too heterogeneous, no quantitative analysis could be performed.</i>

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
		bladder cancer patients search date: October 2019			primary bladder cancer diagnosis and for follow-up of bladder cancer patients	<u>Marker panels</u> · sensitivity: 50–94% · specificity: 43–97% Follow-up <u>Single-mutation markers</u> · sensitivity: 0–85% · specificity: 66–100% <u>Marker panels</u> · sensitivity: 51–84% · specificity: 66–96%	supported by the Weijerhorst Foundation R.D.M. Steenbergen has a minority share in Self-screen BV, a spin-off company of Amsterdam UMC, location VUmc. J. Bosschieter, R.D.M. Steenbergen and J.A. Nieuwenhuijzen are inventors on patent(s) related to the work.
Sciarra, 2021 34084118	Systematic review 2-	n=35 studies n=16691 patients at risk of bladder cancer search period: 2000-2019 Mean age varied between 30.8-72.4 y America, (n=8), Asia (n=10),	· Cytology · MCM5 · Microsatellite · UroVysion · BTA stat · ImmunoCyt · NMP-22	· cystoscopy · transurethral bladder biopsy or resection	critically analyze and compare results in the literature of promising molecular urinary tests for the initial diagnosis of bladder cancer	Cytology (n=25 studies, 14375 patients) · Mean Sensitivity: 45.5±23.1 % · Mean Specificity: 89.7±13.2 % · Mean Negative Predictive Value: 82.6±16.1 % · Mean Positive Predictive Value: 64.9±28.5 % MCM5 (n=3 studies, 2147 patients)	no complete search strategy reported, no information if efforts were made to minimise error in the risk of bias assessment, heterogeneity and risk of bias of the included studies not addressed, no funnel plot The authors declare that they have no financial conflict of interest with regard to the content of this report.

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
		Europe (n=15), Oceania (n=2)				· Mean Sensitivity: 72.8±12.7 % · Mean Specificity: 74.0±11.4 % · Mean Negative Predictive Value: 83.0±20.0 % · Mean Positive Predictive Value: 52.7±23.2 % Microsatellite (n=3 studies, 592 patients) · Mean Sensitivity: 61.5±11.1 % · Mean Specificity: 90.1±2.6 % · Mean Negative Predictive Value: 86.9±22.2 % · Mean Positive Predictive Value: 53.7±43.9 % UroVysion (n=12 studies, 5033 patients) · Mean Sensitivity: 64.3±19.0 % · Mean Specificity: 88.4±14.2 % · Mean Negative Predictive Value: 72.4±24.6 % · Mean Positive Predictive Value: 67.7±26.8 %	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. <i>wrong search period in the abstract reported</i>

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						BTA stat (n=6 studies, 999 patients) · Mean Sensitivity: 70.2±5.8 % · Mean Specificity: 77.2±6.5 % · Mean Negative Predictive Value: 67.9±17.1 % · Mean Positive Predictive Value: 74.8±13.1 % ImmunoCyt (n=7 studies, 4976 patients) · Mean Sensitivity: 76.4±8.9 % · Mean Specificity: 79.0±5.6 % · Mean Negative Predictive Value: 83.4±21.4 % · Mean Positive Predictive Value: 57.7±26.7 % NMP-22 (n=19 studies, 8988 patients) · Mean Sensitivity: 60.1±21.0 % · Mean Specificity: 80.6±13.6 % · Mean Negative Predictive Value: 82.1±16.6 %	

Referenz*	Studientyp Evidenz- graduierung	Teilnehmer	Marker	Referenztest	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						· Mean Positive Predictive Value: 48.0±29.5 %	

1.2.3 Leitliniensynopse Urinzytologie

Leitlinie	Empfehlung	Empfehlungsgrad/LoE
AUA/ASCO/ASTRO/ SUO 2020	Multi-modal Bladder Preserving Therapy Following completion of bladder preserving therapy, clinicians should perform regular surveillance with CT scans, cystoscopy, and urine cytology. Laboratory Values and Urine Markers Following therapy for muscle-invasive bladder cancer, patients should undergo laboratory assessment at three to six month intervals for two to three years and then annually thereafter. (Expert Opinion)	Strong Recommendation; LoE: Grade C Expert Opinion
AUA/SUO 2020	Diagnosis In a patient with a history of NMIBC with normal cystoscopy and positive cytology, a clinician should consider prostatic urethral biopsies and upper tract imaging, as well as enhanced cystoscopic techniques (blue light cystoscopy, when available), ureteroscopy, or random bladder biopsies. Urine Markers after Diagnosis of Bladder Cancer In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation. In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance.	Expert Opinion Strong Recommendation; Evidence Strength: Grade B Expert Opinion Expert Opinion Conditional Recommendation; Evidence Strength: Grade C

Leitlinie	Empfehlung	Empfehlungsgrad/LoE
	In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). BCG Relapse and Salvage Regimens In an intermediate- or high-risk patient with persistent or recurrent disease or positive cytology following intravesical therapy, a clinician should consider performing prostatic urethral biopsy and an upper tract evaluation prior to administration of additional intravesical therapy. Risk Adjusted Surveillance and Follow-up Strategies For an intermediate-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every 3-6 months for 2 years, then 6-12 months for years 3 and 4, and then annually thereafter. For a high-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every three to four months for two years, then six months for years three and four, and then annually thereafter.	Expert Opinion Expert Opinion
EAU 2022a	Summary of evidence and guidelines for the primary assessment of non-muscle-invasive bladder cancer <u>Summary of Evidence</u> Urinary cytology has high sensitivity in high-grade tumours including carcinoma <i>in situ</i>. <u>Recommendations</u> Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test. Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour. Perform cytology on at least 25 mL fresh urine or urine with adequate fixation. Morning	2b Strong Strong Strong Strong Strong Strong Strong Weak

Leitlinie	Empfehlung	Empfehlungsgrad/LoE
	urine is not suitable because of the frequent presence of cytolysis. Use the Paris System for cytology reporting. Summary of evidence and guidelines for transurethral resection of the bladder, biopsies and pathology report <u>Recommendations</u> Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended if cytology or urinary molecular marker test is positive. If the equipment is available, perform fluorescence-guided (PDD) biopsies. Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if bladder carcinoma <i>in situ</i> is present or suspected, if there is positive cytology or urinary molecular marker test without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection. In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy). Summary of evidence and guidelines for follow-up of patients after transurethral resection of the bladder for non-muscle-invasive bladder cancer <u>Recommendations</u> Patients with high-risk and those with very high-risk tumours treated conservatively should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy	Strong Strong

Leitlinie	Empfehlung	Empfehlungsgrad/LoE
	and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly. Perform endoscopy under anaesthesia and bladder biopsies when office cystoscopy shows suspicious findings or if urinary cytology is positive. During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	
EAU 2022b	Summary of evidence and guidelines for the primary assessment of presumably invasive bladder tumours <u>Summary of Evidence</u> Urinary cytology has high sensitivity in high-grade tumours including carcinoma <i>in situ</i>. <u>Recommendations</u> Take a biopsy of the prostatic urethra in cases of bladder neck tumour, when bladder carcinoma <i>in situ</i> is present or suspected, when there is positive cytology without evidence of tumour in the bladder, or when abnormalities of the prostatic urethra are visible.	2b Strong
EAU/ESMO 2019	After radical cystectomy with curative intent, follow-up of the urethra with cytology and/or cystoscopy is recommended in selected patients (e.g. multifocality, carcinoma in situ and tumour in the prostatic urethra).	Level of consensus: 88% Agree, 6% disagree, 6% equivocal (33 voters)
JUA 2019	Follow-up strategy for NMIBC <u>Low risk:</u>	<i>LoE and recommendation level not clearly described.</i>

Leitlinie	Empfehlung	Empfehlungsgrad/LoE
	· Cystoscopy after 3 months. After that, cystoscopy every 6 months for 2 years. Then every year with cystoscope up to 5 years. After that, by clinical decision <u>Intermediate risk:</u> · Cystoscopy + cytology 3 months later. After that, cystoscopy + cytology every 6 months for 3 years. Thereafter, cystoscopy and cytology every year until 5 years. After that, by clinical decision <u>High risk:</u> · Cystoscopy + cytology every 3 months for 2 years. Cystoscopy + cytology every 6 months for 3–5 years. Cystoscopy + cytology every year until the 10th year. After that, by clinical decision. Urinary molecular markers are considered as appropriate. CT + CT urography every year up to 3 years, thereafter every 2 years for a total of 10 years observation Follow-up strategy after radical cystectomy for MIBC <u>pT2 or less and N0</u> Cytology: · 1 year: Post 3, 6, and 12 months · 2-3 years: every 6 months · 4 years: every 12 months · 5 years: every 12 months · After 5 years (60 months): Cytology is used for urinary tract recurrence <u>pT3 or high or any pT N1-3</u> Cytology: · 1 year: every 3 months · 2-3 years: every 6 months · 4 years: every 6 months · 5 years: every 6 months	

Leitlinie	Empfehlung	Empfehlungsgrad/LoE
NCCN 2021	Suspicion of bladder cancer Initial Evaluation: H&P; Office cystoscopy, enhanced if available consider cytology, Abdominal/pelvic imagingb that includes imaging of upper urinary tract collecting system before transurethral resection of bladder tumor, Screen for smoking Recurrent or persistent disease-follow-up Cytology positive: · If initial positive cytology, consider repeating cytology test within 3 months or If repeated positive cytology: · Consider selected mapping biopsies including transurethral biopsy of prostatec and · Cytology of upper tract and · Consider ureteroscopy and · Consider enhanced cystoscopyc (if available) Follow-up <u>Intermediate Risk, Non-Muscle Invasive Bladder Cancer</u> · Year 1: Urine cytology (3, 6, 12 mo) · Year 2: Urine cytology (every 6 mo) · Year 4-5: Urine tests annually · Year 5-10 & >10 Year: as clinically indicated <u>High-Risk, Non-Muscle Invasive Bladder Cancer</u> · Year 1-2: Urine cytology (every 3 mo); Consider urinary urothelial tumor markers · Year 3-5: Urine cytology (every 6 mo) · Year 5-10: Urine tests annually · >10 Year: as clinically indicated	All recommendations are category 2A unless otherwise indicated.

Leitlinie	Empfehlung	Empfehlungsgrad/LoE
	<u>Post-Cystectomy Non-Muscle Invasive Bladder Cancer</u> · Year 1-2: Urine cytology (every 6-12 mo), consider urethral wash cytology every 6-12 mo · 3->10 Year: Urine cytology as clinically indicated, Urethral wash cytology as clinically indicated <u>Post-Cystectomy Muscle Invasive Bladder Cancer</u> · Year 1-2: Urine cytology (every 6-12 mo), consider urethral wash cytology every 6-12 mo · 3->10 Year: Urine cytology as clinically indicated, Urethral wash cytology as clinically indicated <u>Post-Bladder Sparing</u> · Year 1-2: Urine cytology (every 6-12 mo) · 3->10 Year: Urine cytology as clinically indicated <u>Metastatic Disease: Observation</u> · urine cytology as clinically indicated	
NICE 2015	Do not offer routine urinary cytology or prolonged cystoscopic follow-up after 12 months for people with low-risk non-muscle-invasive bladder cancer. After radical cystectomy consider using a follow-up protocol that consists of: · monitoring of the upper tracts for hydronephrosis, stones and cancer using imaging and glomerular filtration rate (GFR) estimation at least annually and · monitoring for local and distant recurrence using CT of the abdomen, pelvis and chest, carried out together with other planned CT imaging if possible, 6, 12 and 24 months after radical cystectomy and · monitoring for metabolic acidosis and B12 and folate deficiency at least annually and · for men with a defunctioned urethra, urethral washing for cytology and/or urethroscopy annually for 5 years to detect urethral recurrence.	The evidence was assessed as being of low to moderate quality using GRADE The overall quality of the evidence for each outcome was low to very low as assessed with GRADE.

1.2.4 Leitliniensynopse Biomarker

Leitlinie	Empfehlung	Empfehlungsgrad/LoE
AUA/ASCO/ASTRO/SUO 2020	Laboratory values and urine markers · Following therapy for muscle-invasive bladder cancer, patients should undergo laboratory assessment at three to six month intervals for two to three years and then annually thereafter.	Expert Opinion
AUA/SUO 2020	Urine Markers after Diagnosis of Bladder Cancer · In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation. · In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance.	Strong Recommendation; Evidence Strength: Grade B Expert Opinion
	· In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™).	Expert Opinion
EAU 2022a	Follow-up of patients after transurethral resection of the bladder for non-muscle-invasive bladder cancer <u>Recommendations</u> · In patients initially diagnosed with Ta LG/G1–2 bladder cancer, use ultrasound of the bladder, and/or a urinary marker during surveillance in case cystoscopy is not possible or refused by the patient.	Weak
	Transurethral resection of the bladder, biopsies and pathology report <u>Recommendations</u> · Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended if cytology or	Strong Strong

Leitlinie	Empfehlung	Empfehlungsgrad/LoE
	urinary molecular marker test is positive. If the equipment is available, perform fluorescence-guided (PDD) biopsies. · Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if bladder carcinoma <i>in situ</i> is present or suspected, if there is positive cytology or urinary molecular marker test without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	
EAU 2022b	Urothelial markers <u>Summary of evidence</u> · There is insufficient evidence to use tumour mutational burden, molecular subtypes, immune or other gene expression signatures for the management of patients with urothelial cancer. Neoadjuvant therapy <u>Summary of evidence</u> · There are still no tools available to select patients who have a higher probability of benefitting from neoadjuvant chemotherapy. In the future, genetic markers in a personalised medicine setting might facilitate the selection of patients for neoadjuvant chemotherapy and differentiate responders from non-responders. Adjuvant therapy · Circulating tumour DNA holds promise as both a prognostic and predictive biomarker to guide the use of adjuvant IO for UC in patients who are at a high risk of recurrence and positive for ctDNA treated with adjuvant atezolizumab demonstrating improved outcomes compared with observation.	LoE: - LoE: - 2b
EAU/ESMO 2019	· In patients with metastatic disease, genetic profiling should never be done. · In patients with metastatic disease, always measure the LDH and/or serum albumin as general prognostic markers of patient outcome.	A priori consensus a threshold met across all three stakeholder groups.

Leitlinie	Empfehlung	Empfehlungsgrad/LoE
	· Before radical cystectomy or chemotherapy, the neutrophil-to-lymphocyte ratio does NOT need to be assessed. · Before prescribing a checkpoint inhibitor, tumour mutation burden always needs to be assessed. · In contrast to the first-line setting, the PDL1 biomarker is not useful for selecting patients for immunotherapy in platinum-refractory metastatic urothelial cancer. · Levels of lactate dehydrogenase and Carcinoembryonic antigen are NOT essential in the follow-up of patient with urothelial cancer to detect recurrence.	Level of consensus: 65% Agree, 16% disagree, 19% equivocal (31 voters). Level of consensus: 97% Agree, 4% disagree, 0% equivocal (31 voters). A priori consensus a threshold met across all three stakeholder groups. Level of consensus: 81% Agree, 4% disagree, 15% equivocal (28 voters). Level of consensus: 100% Agree (34 voters).
JUA 2019	Follow-up strategy for NMIBC <u>Low risk:</u> · Cystoscopy after 3 months. After that, cystoscopy every 6 months for 2 years. Then every year with cystoscope up to 5 years. After that, by clinical decision <u>Intermediate risk:</u> · Cystoscopy + cytology 3 months later. After that, cystoscopy + cytology every 6 months for 3 years. Thereafter, cystoscopy and cytology every year until 5 years. After that, by clinical decision <u>High risk:</u>	<i>LoE and recommendation level not clearly described.</i>

Leitlinie	Empfehlung	Empfehlungsgrad/LoE
	· Cystoscopy + cytology every 3 months for 2 years. Cystoscopy + cytology every 6 months for 3–5 years. Cystoscopy + cytology every year until the 10th year. After that, by clinical decision. Urinary molecular markers are considered as appropriate. CT + CT urography every year up to 3 years, thereafter every 2 years for a total of 10 years observation	
NCCN 2021	Follow-up <u>High-Risk, Non-Muscle Invasive Bladder Cancer</u> · Year 1-2: Urine cytology (every 3 mo); Consider urinary urothelial tumor markers · Year 3-5: Urine cytology (every 6 mo) · Year 5-10: Urine tests annually · >10 Year: as clinically indicated	All recommendations are category 2A unless otherwise indicated.
NICE 2015	Diagnosing and staging bladder cancer · Offer white-light-guided TURBT with one of photodynamic diagnosis, narrow-band imaging, cytology or a urinary biomarker test (such as UroVysion using fluorescence in-situ hybridization [FISH], ImmunoCyt or a nuclear matrix protein 22 [NMP22] test) to people with suspected bladder cancer. This should be carried out or supervised by a urologist experienced in TURBT. · Do not substitute urinary biomarkers for cystoscopy to investigate suspected bladder cancer or for follow-up after treatment for bladder cancer, except in the context of a clinical research study. · Do not use urinary biomarkers or cytology in addition to cystoscopy for follow-up after treatment for low-risk bladder cancer.	Moderate to high quality evidence good quality good quality

1.2.5 AG 2 SF 5

5. Hat eine Subklassifikation von pT1-Tumorstadien eine diagnostische und therapeutische Bedeutung?

Referenz	Studientyp Evidenz- graduierung	Patienten-charakteristika	Fälle/Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkung
Budina, 2022 34871364	Prognostic study 2+	n=73 patients with the confirmed first-time diagnosis of pT1 urothelial carcinoma 2004-2014 USA Male: 61/73 (84%) Mean age: 70 y (39-94 y) Mean follow-up: 46 mo (1-157 mo)	T1 cancer with luminal phenotypes n=48 vs. T1 cancer with non-luminal phenotypes n=19 (3 basal, 16 double-positive)	Prognostic value	Recurrence luminal phenotypes: 26/48 (54%) non-luminal phenotypes: 9/19 (47%) p=0.37 Progression luminal phenotypes: 13/48 (27%) non-luminal phenotypes: 2/19 (11%) p=0.14	patient characteristics for the subgroups not described The authors have no relevant financial interest in the products or companies described in this article. No funding reported.
Grobet-Jeandin, 2022 33965961	Prognostic study 2+	n=217 patients diagnosed with pT1 urothelial bladder carcinoma at TURB · pT1a (n=124) · pT1b (n=59) · pT1c (n=34) 2001-2015 Switzerland	patients with pT1a, pT1b and pT1c	· disease recurrence · progression · OS	Recurrence · pT1a: Reference · pT1b: HR 1.28 (95% CI 0.67-2.44) p=0.45 · pT1c: HR 0.99 (95% CI 0.44-2.20) p=0.98 Progression · pT1a: Reference	The authors have no conflicts of interest to declare. The authors report no funding.

Referenz	Studientyp Evidenz- graduierung	Patienten-charakteristika	Fälle/Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkung
		Male: 176/217 (81%) Median age: 75 y (IQR 67-81 y) Median follow-up: 3.1 y (IQR 0.7-6.1 y)			· pT1b: HR 2.9 (95% CI 1.45-5.67) p=0.002 · pT1c: HR 3.1 (95% CI 1.29-7.23) p=0.011 OS · pT1a: Reference · pT1b: HR 2.1 (95% CI 1.33-3.37) p=0.001 · pT1c: HR 1.8 (95% CI 1.04-3.16) p=0.035	
Yanagisawa, 2021 33502235	Prognostic study 2+	n=123 patients diagnosed with pT1 bladder cancer 2013-2018 Japan Male: 92/123 (75%) Median age: 72 y (43-92 y) Median follow-up: 23 mo	patients with pT1a (n=53) or pT1b (n=50) or patients with pT1m (n=20) or pT1e (n=103)	Prognostic value	3-y RFS · pT1a: 67.6% (95% CI: 50.1-80.1) · pT1b: 63.4% (95% CI: 45-77.4) · pT1m: 56.5% (95% CI: 29-76.9) · pT1e: 69.8% (95% CI: 57.4-79.2) 3-y PFS · pT1a: 97.3% (95% CI: 82.3-99.6) · pT1b: 72.8% (95% CI: 53.4-85.1) · pT1m: 94.1% (95% CI: 65-99.1) · pT1e: 83.8% (95% CI: 71.5-91.1)	patient characteristics not described <i>Owing to the limited number of progressions, we were unable to include a sufficient number of variables in multivariate analysis for PFS.</i> Financial interest and/or other relationship with Takeda, Astellas, AstraZeneca, Sanofi, Janssen and Pfizer. Funded by the National Institutes of Health.

Referenz	Studientyp Evidenz- graduierung	Patienten-charakteristika	Fälle/Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkung
					Impact of possible prognostic factors on PFS <i>Univariate analysis</i> · pT1a/b: 7.63 (1.71-34.0) p=0.02 · pT1m/e: 2.18 (0.46-10.3) p=0.32 <i>Multivariate analysis</i> · pT1a/b: 3.62 (0.7-18.83) p=0.13	
Yasui, 2021 33387223	Prognostic study 2-	n=61 bladder cancer specimens · pT1a (n=39) · pT1b (n=6) · pT1c (n=16) 2020-2018 Japan Male: 51/64 (83.6%) Median age: 76 y (47-88 y) Median follow-up: 44.1 mo (1.7-118.8 mo)	patients with pT1a, pT1b and pT1c	Prognosis	Recurrence · pT1a: 2/39 (5.1%) · pT1b: 1/6 (16.7%) · pT1c: 6/16 (37.5%) Cancer death · pT1a: 1/39 (2.6%) · pT1b: 0 · pT1c: 3/16 (18.8%) PFS+CSS the cohort of patients with pT1a or pT1b cancer had a significantly better prognosis than those with pT1c cancer (p < 0.001; p = 0.010, respectively).	patient characteristics not described, recurrence not defined No conflict of interest or funding reported.

Referenz	Studientyp Evidenz- graduierung	Patienten-charakteristika	Fälle/Kontrolle	Zielgrößen	Hauptergebnis	Methodische Bemerkung
					pT1c vs pT1a + pT1b <i>Multivariate analyses</i> HR: 13.28 (95% CI 2.10-84.16) p=0.006	

1.2.6 AG SF 6

6. Hat die Diagnostik von histopathologischen Subtypen und -sonderformen eine klinische bzw. prognostische Bedeutung?

Referenz	Studientyp Evidenz- graduierung	Studien- charakteristika	Patienten- charakteristika	Intervention/Kontrollen	Zielgrößen	Hauptergebnis	Methodische Bemerkung
Variant Histology							
Systematische Reviews							
Zhu, 2022	Systematic	n=22 observational studies	bladder	neoadjuvant chemotherapy or	· RFS	Neoadjuvant chemotherapy vs. radical cystectomy	no additional hand search,
	review and	· neoadjuvant chemotherapy (n=14)	cancer patients with	adjuvant chemotherapy on the	· CSS	<u>RFS</u> (n=2) HR: 1.15 (95% CI 0.56-2.33) p=0.706	no information if efforts

Referenz	Studientyp Evidenz- graduierung	Studien- charakteristika	Patienten- charakteristika	Intervention/Kontrollen	Zielgrößen	Hauptergebnis	Methodische Bemerkung
35912201	meta-analysis	· adjuvant chemotherapy (n=4) · both (n=4) Search date: December 2021	variant histology	basis of radical cystectomy	· OS	<u>CSS</u> (n=4) HR: 0.74 (95% CI 0.55-0.99) p=0.044 <u>OS</u> (n=10) HR: 0.74 (95% CI 0.66-0.84) p=0.000 <u>Subgroup analyses (only significant results reported) CSS</u> · neuroendocrine variant history (n=1): HR 0.37 (95% CI 0.17- 0.79) p=0.011 <u>OS</u> · sarcomatoid variant history (n=4): HR 0.67 (95% CI 0.54- 0.83) p=0.000 · neuroendocrine variant history (n=2): HR 0.54 (95% CI 0.43- 0.68) p=0.000 Adjuvant chemotherapy vs. radical cystectomy <u>RFS</u> (n=2) HR: 0.82 (95% CI 0.55-1.2) p=0.304	were made to minimise error
							in the study selection,
	2-			vs.			endpoints differ from study
							protocol (missing: pathologic
				only radical			complete response, pDS)
				cystectomy			
							P-values and conclusion for
							adjuvant chemotherapy
							unclear:

Referenz	Studientyp Evidenz- graduierung	Studien- charackteristika	Patienten- charackteristika	Intervention/Kontrollen	Zielgrößen	Hauptergebnis	Methodische Bemerkung
							„Receiving adjuvant
							chemotherapy was not
							associated with RFS (HR 0.60,
							95% CI 0.22–1.61, p=0.314)
							or OS (HR 0.48, 95% CI 0.17–
							1.38, p=0.004), but was
							associated with better CSS
							(HR 0.29, 95% CI 0.13–0.67,
							p=0.174) in this pooled

Referenz	Studientyp Evidenz- graduierung	Studien- charackteristika	Patienten- charackteristika	Intervention/Kontrollen	Zielgrößen	Hauptergebnis	Methodische Bemerkung
							analysis.“
							The authors declare that the
							research was conducted in
							the absence of any
							commercial or financial
							relationships that could be
							construed as a potential
							conflict of interest.

1.2.7 AG 2 SF 1

SF 1: Welche immunhistochemischen Marker eignen sich zur Differenzialdiagnose des Urothelkarzinom bei der Frage der Abgrenzung anderer Primärtumoren (z.B. Colon, Prostata, Ovar/Genital)?

Referenz	Studientyp Evidenz- graduierung	Studienziel	Studien- und Patienten- charakteristika	Marker	Methode	Hauptergebnis	Methodische Bemerkung
Lennartz, 2023 36269681	Immuno- histochemical analysis 3	To comprehensively determine CK13 expression in normal and neoplastic tissues.	n=10439 samples from 131 different tumor types and subtypes n=608 samples of 76 different normal tissue types Germany	Cytokeratin 13	immunohistochemistry	CK13 in cancer tissues · 1,563(17.1%) of the 9,156 analyzable tumors: 665 (7.3%) weak, 258 (2.8%) moderate, 640 (7.0%) strong immunostaining · The highest rate of positive staining was found in various categories of urothelial neoplasms (52.1–92.3%) including Brenner tumor of the ovary (86.8%) and in squamous cell carcinomas from various sites of origin (39.1– 77.6%), Warthin tumors of salivary glands (66.7%), adenosquamous carcinomas of the cervix (33.3%), thymomas (16.0%), and endometroid carcinomas of the ovary (15.3%). · In squamous cell carcinoma of the cervix, reduced CK13 immunostaining was linked to high grade($p = 0.0295$) as well as shortened recurrence-free ($p = 0.0094$) and overall survival ($p = 0.0274$). · combined analysis of 1,151 squamous cell carcinomas from 11 different sites of origin, reduced CK13 staining was linked to high grade ($p = 0.0050$) and absence of HPV infection ($p = 0.0002$) · separate analysis of 9 different squamous cell carcinoma entities did not show significant	consecutive tissue inclusion unclear, no patient information Open Access funding enabled and organized by Projekt DEAL. no information about conflict of interest.

Referenz	Studientyp Evidenz- graduierung	Studienziel	Studien- und Patienten- charakteristika	Marker	Methode	Hauptergebnis	Methodische Bemerkung
						differences in the HPV status between tumors with high and low CK13 expression CK13 expression predominates in urothelial neoplasms and in squamous cell carcinomas of different organs, and a loss of CK13 expression is associated with aggressive disease in these tumors.	
Dum, 2022 35390310	Immuno- histochemical analysis 3	To better understand the combined diagnostic utility of cytokeratin 7 and 20 expression.	n=15424 tumor samples from 120 different tumor types	· CK7 (n=14110) · CK20 (n=13140)	immunohistochemistry	Tumor analysis <u>positivity</u> · CK7 in 52% (8.7% weak, 5.9% moderate, 37% strong)	consecutive tissue inclusion unclear, no patient information No funding was received.

1.2.8

AG 2 SF 2

2. Welche immunhistochemischen Marker eignen sich bei der Differenzialdiagnose von Metastasen zur Sicherung eines urothelialen Ursprungs, insbesondere, wenn andere Primärtumoren wie Plattenepithelkarzinome aus Lunge, Kopf/Hals- oder des genitalen Bereichs zur Diskussion stehen?

Referenz	Studientyp Evidenz- graduierung	Studienziel	Studien- und Patienten- charakteristika	Marker	Methode	Hauptergebnis	Methodische Bemerkung
Dum, 2022 35390310	Immuno- histochemical analysis 3	To better understand the combined diagnostic utility of cytokeratin 7 and 20 expression.	n=15424 tumor samples from 120 different tumor types n=606 samples of 76 normal tissue types 2005-2020 Germany	· CK7 (n=14110) · CK20 (n=13140)	immunohistochemistry	Tumor analysis <u>positivity</u> · CK7 in 52% (8.7% weak, 5.9% moderate, 37% strong) · CK20 in 23% (5.1% weak, 3.4% moderate, 15% strong) CK20 · primarily seen in tumors derived from the gastrointestinal tract, urothelial carcinomas and Merkel cell cancers · upregulation was linked to high grade in non-invasive urothelial carcinoma (pTa) ($p < 0.0001$) and lymph node metastasis in invasive urothelial carcinoma ($p < 0.0001$) · Downregulation was unrelated to tumor phenotype in colorectal and gastric cancer but linked to mismatch repair deficiency in both cancers ($p < 0.0001$; $p = 0.0291$). CK7 · usually negative in adenocarcinomas of the colorectum and the prostate	consecutive tissue inclusion unclear, no patient information No funding was received. The CK7 antibody (rabbit recombinant, MSVA-607R) and the CK20 antibody (rabbit recombinant, MSVA-620R) was provided from MS Validated Antibodies GmbH (owned by a family member of GS).

Referenz	Studientyp Evidenz- graduierung	Studienziel	Studien- und Patienten- charakteristika	Marker	Methode	Hauptergebnis	Methodische Bemerkung
						· upregulation was associated with high pT in high-grade serous ovarian cancer ($p = 0.0411$) and nodal metastasis in gastric cancer ($p = 0.0210$) and invasive bladder cancer (0.0205) · Downregulation was associated with advanced pT ($p = 0.0151$) high grade tumor ($p = 0.0002$) and loss of ER expression ($p < 0.0001$) in breast cancer, no special type as well as with high grade in non-invasive urothelial carcinoma (pTa) ($p = 0.0388$) · only exception: link between low CK7 expression levels and unfavorable stage and grade, and prognosis in papillary and clear cell renal cell carcinomas in univariate	

1.2.9

AG 2 SF 4

4. Welche histomorphologischen Kriterien von Läsionen der Harnblase haben eine prognostische Bedeutung für die Diagnose von TUR-Präparaten der Harnblase?

Referenz	Studientyp Evidenz- graduierung	Studien- und Patienten- charakteristika	Fälle	Kontrollen	Zielgrößen	Hauptergebnis	Methodische Bemerkung
Culpan, 2022 36449779	Prognostic study 2-	n=287 patients with pTa and pT1 NMIBC 2016-2021 Turkey Male: 244/287 (85%) Mean age: 66.2 y (SD 10.3 y) Mean follow-up: 27.9 y (SD 13.6 y)	patients with tumor necrosis n=33	patients without tumor necrosis n=254	Recurrence Progression	Mean RFS with tumor necrosis: 42.3 mo (SD 4.6 mo) without tumor necrosis: 43.5 mo (SD 1.8 mo) p=0.72 Mean PFS with tumor necrosis: 43.1 mo (SD 4.6 mo) without tumor necrosis: 58.4 mo (SD 0.9 mo) p<0.001 <i>Univariate Analyses</i> Recurrence <u>Tumor number (multiple vs. single)</u> HR: 1.651 (1.071–2.545) p=0.023 <u>Tumor size (>3 cm vs. ≤3 cm)</u> HR: 1.518 (0.99–2.326) p=0.055 <u>Tumor necrosis (yes vs. no)</u>	Patient characteristics not reported for subgroups, unclear why multivariate analyses were only performed for T stage, Mitomycin and Bacillus Calmette-Guerin Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Referenz	Studientyp Evidenz- graduierung	Studien- und Patienten- charakteristika	Fälle	Kontrollen	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						HR: 1.127 (0.581–2.184) p=0.724 Progression <u>Tumor number (multiple vs. single)</u> HR: 2.100 (0.889–4.96) p=0.091 <u>Tumor size (>3 cm vs. ≤3 cm)</u> HR: 2.562 (1.107–5.932) p=0.028 <u>Tumor necrosis (yes vs. no)</u> HR: 5.828 (2.513–13.515) p<0.001	
Eckstein, 2021 34504238	Prognostic study 2-	n= 141 patients with pT1 NMIBC 2007-2015 Germany Male: 76/92 (82.6%) Median age: 72 (IQR 66-81 y)	patients with tumor budding	patients without tumor budding	Survival	Tumor budding is associated with worse RFS (p=0.005), PFS (p=0.017) and CSS (0.002). Discontinuous invasion pattern was statistically significantly associated with worse RFS (p = 0.001) and CSS (p=0.039) but not PFS. A discohesive growth pattern (p < 0.001) and extensive lamina propria invasion	Patient characteristics not reported for patient with or without tumor budding, recurrence and progression not clearly defined, potential confounder not named The authors declare no competing interests. Open Access funding enabled and organized by Projekt DEAL.

Referenz	Studientyp Evidenz- graduierung	Studien- und Patienten- charakteristika	Fälle	Kontrollen	Zielgrößen	Hauptergebnis	Methodische Bemerkung
						(p=0.008) were only associated with worse RFS. Focality was the only statistically significant parameter (RFS: p=0.014; PFS: p=0.023; CSS: p=0.037).	
Mastroianni, 2020 32900676	Prognostic study 2-	n=521 patients with Ta low-grade urothelial carcinoma of the bladder 1996-2018 Male: 422 (81%) Median age: 66 y (IQR 59-74 y) Minimum follow-up of 1 y	absence of detrusor muscle n=66	presence of detrusor muscle n=401	RFS	1-RFS Absence of detrusor muscle: 82% Presence of detrusor muscle: 80% p=0.125 Predictors of recurrence <i>Univariable Analysis</i> <u>Absence of detrusor muscle</u> HR: 1.284 (95% CI 0.929-1.774) p=0.13	Patient characteristics not reported for the detrusor muscle subgroup, place of recruitment not described, follow-up time not reported, recurrence not clearly defined, only univariable analysis performed for the absence/presence comparison The authors declare no conflict of interests and funding.

1.2.10 AG 2 SF 7

SF 7: Welche immunhistochemischen Marker haben einen prädiktiven Wert bezüglich einer Immun- oder ADC-Therapie?

Referenz	Studientyp Evidenz- graduierung	Studien- und Patientencharakteristika	Pathologische Faktoren und immunhistochemische Marker	Hauptergebnis	Methodische Bemerkung
Liu 2022, 35039625	Immuno- histochemical analysis 3	N=1076 MIBC patients from 5 cohorts (TCGA cohort: n=391; IMvigor210 cohort: n=348; ZSHS cohort: n=141; FUSCC cohort: n=118; FCM cohort n=25) <u>Male</u> ZSHS: n=117/141 (83%) FUSCC: n=86/102 (86.4%) IMvigor210: n=272/348 (78.3%) <u>Median age at surgery</u> ZSHS: 62 y FUSCC: 62 y China	· combination of TIGIT and PD-1 expression · patients were divided into three clusters: cluster I (TIGIT+ cells_{low} & PD-1+ cells_{low}), cluster II (TIGIT+ cells_{low} & PD-1+ cells_{high}), and cluster III (TIGIT+ cells_{high})	Prognosis of MIBC patients could be predicted according to the levels of TIGIT and PD-1 expression We found that PD-1+ cells infiltration had no prognostic value in patients with high TIGIT+ cells infiltration. Thus, we trichotomized the patients based on TIGIT+ cells and PD-1+ cells infiltration into three clusters. We found patients from Cluster II aired the best prognosis while patients from Cluster III possessed the worst prognosis (ZSHS: OS: p = 0.006, RFS: p = 0.010; FUSCC: OS: p = 0.003, RFS: p = 0.024). In multivariate and univariate models with classical prognostic factors, the novel stratification was found to be significantly associated with OS and RFS, independent of other clinical parameters, such as AJCC stage, pathological N stage, grade and lymphovascular invasion in both ZSHS and FUSCC cohorts. Therefore, our findings illustrated that this new combined classification based on TIGIT and PD-1 expression was proved to be an independent prognostic factor of MIBC patients. TIGIT expression may guide the application of anti-PD-L1 therapy in MIBC patients	Reasons for the exclusion of certain patients were given and presented in a flow chart. Detailed patient information was presented for the ZSHS cohort, the FUSCC cohort IMvigor210 cohort <u>Conflict of interest</u> The authors declare no competing interests. <u>Funding</u> This study was funded by grants from National Natural Science Foundation of China (31770851, 81872082, 81972279, 82002670, 82103408), Shanghai Municipal Natural Science Foundation (19ZR1431800), Shanghai Sailing Program (18YF1404500, 21YF1407000), Shanghai Municipal Commission of Health and Family Planning Program (201840168) and Fudan University Shanghai Cancer Center for Outstanding Youth Scholars Foundation (YJYQ201802).

Referenz	Studientyp Evidenz- graduierung	Studien- und Patientencharakteristika	Pathologische Faktoren und immunhistochemische Marker	Hauptergebnis	Methodische Bemerkung
				In both TCGA and IMvigor210 cohorts, Cluster I patients, characterised by high level of FGFR3-coexpressed gene signature score (TCGA: $p = 0.001$; IMvigor210: $p < 0.001$), might be sensitive to FGFR3-targeted therapy. In comparison, the EGFR signatures were found stagewise elevated among Cluster I, II and III (TCGA: EGFR signalling: $p < 0.001$, EGFR ligands: $p < 0.001$; IMvigor210: EGFR signalling: $p < 0.001$, EGFR ligands: $p < 0.001$), suggesting the promising prospect of EGFR-targeted drugs for Cluster III patients.	

1.2.11 AG 4 SF 1.2

1.2 Welchen Einfluss hat eine bildunterstützte TURBT gegenüber einer konventionellen Weisslicht-TURBT auf die Rezidiv- und Progressionsrate?

Patient	Nichtmuskelinvasive Blasenkrebs-Patienten
Intervention	bildunterstützte TURBT
Kontrolle	Weisslicht-TURBT
Endpunkte	Rezidiv- und Progressionsrate

1.2.12 AG 4 SF 1.21

1.2.1 Welchen Einfluss hat die fluoreszenzassistierte TURBT mit Hexylaminolaevulinat gegenüber einer konventionellen Weisslicht-TURBT auf die Rezidiv- und Progressionsrate?

Patient	Nichtmuskelinvasive Blasenkrebs-Patienten
Intervention	fluoreszenzassistierte TURBT mit Hexylaminolaevulinat
Kontrolle	konventionellen Weisslicht-TURBT
Endpunkte	Rezidiv- und Progressionsrate

1.2.13 AG 4 SF 1.2.2

1.2.2 Welchen Einfluss hat eine durch narrow-band-imaging unterstützte Zystoskopie gegenüber einer konventionellen Weisslicht-TUR-BT auf die Rezidiv- und Progressionsrate?

Patient	Nichtmuskelinvasive Blasenkrebs-Patienten
Intervention	narrow-band-imaging unterstützte Zystoskopie
Kontrolle	konventionellen Weisslicht-TUR-BT
Endpunkte	Rezidiv- und Progressionsrate

1.2.14

AG 4 SF 4.3

4.3. Welchen Einfluss hat die Frühzystektomie auf die Lebensqualität der Patienten?

Patient	Nichtmuskelinvasive Blasenkrebs-Patienten
Intervention	Frühzystektomie
Kontrolle	Keine Frühzystektomie
Endpunkte	QoL

Abbreviation

CI Confidence Interval

CrI Credible Interval

HAL Hexaminolevulinate Hydrochloride HR Hazard Ratio

mo months

NBI Narrow Band Imaging

NBI-BPV Narrow Band Imaging-associated Bipolar Plasma Vaporization NBI-ETUR Narrow Band Imaging-assisted Electro-Transurethral Resection NBI-HLR Narrow Band Imaging-associated Holmium Laser Resection NMIBC Non-Muscle Invasive Bladder Cancer

OR Odds Ratio

PDD Photodynamic Diagnosis PFS Progressions-Free Survival RCT Randomized Clinical Trials RFS Recurrence-Free Survival RR Risk Ratio

SIIC Single Immediate Intravesical Chemotherapy SUCRA Surface Under the Cumulative Ranking curve TUR Transurethral Resection

TURBT Transurethral resection of Bladder Tumor WL White Light

WLC White-light cystoscopy WLI White Light Imaging

y year

Abbreviation

5-ALA 5-Aminolevulinic CI Confidence Interval

CSS Cancerspecific survival HAL Hexyl-Aminolaevulinate

HR Hazard Ratio

EORTC European Organisation for Research and Treatment of Cancer mo months

MIBC Muscle-Invasive Bladder Cancer NBI Narrow-Band Imaging

NMIBC Non-Muscle Invasive Bladder Cancer OR Odds Ratio

OS Overall survival

PDD Photodynamic Diagnosis PFS Progression-Free Survival RCT Randomized Controlled Trial RD Risk Difference

RFS Recurrence-Free Survival RR Risk Ratio

SIIC Single Immediate Intravesical Chemotherapy SUCRA Surface Under the Cumulative Ranking Curve TUR Transurethral Resection

TURBT Transurethral Bladder Tumor Resection WL White-Light

WLC White-Light Cystoscopy Y year

Abbreviation

5-ALA 5-aminolaevulinic acid CI Confidence Interval

CrI Credible Interval

FL Fluorescent Light

HAL Hexyl-Aminolaevulinate

HR Hazard ratio

MIBC Muscle-invasive bladder cancer NBI Narrow band imaging

NMIBC Non-Muscle Invasive Bladder Cancer PDD Photodynamic diagnosis

PFS Progression-free survival

RCT Randomized clinical trial

RFS Recurrence-free survival

SIIC Single immediate intravesical chemotherapy SUCRA Surface under the cumulative ranking curve TUR Transurethral resection

TURBT Transurethral resection of bladder tumour WL White light

WLC White-light cystoscopy

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