When taking the history of a patient with non-muscle-invasive urothelial carcinoma, the physician should inquire about changes of urinary function, including hematuria, dysuria, and urinary urgency and frequency. Risk factors should also be asked about, including cigarette smoking and occupational exposure to carcinogens (diagram 1).

Cystoscopy and fractionated tissue biopsy
Cystoscopy is standard for the diagnosis and treatment of bladder tumors, with a sensitivity greater than 90% (1). Nonetheless, white-light endoscopy alone is inadequate for the detection of carcinoma in situ. Zaak et al. have shown that about 50% of these flat urothelial lesions escape detection by white-light endoscopy (2). This tumor entity can be detected much more sensitively with the aid of photodynamic diagnostic techniques, i.e., the intravesical application of dyes that are taken up selectively by tumor tissue (3, e1, e2). The diagnosis is then established histopathologically with a fractionated tissue biopsy.

About 95% of all bladder tumors arise from the urothelium. The manner of tumor growth is generally classified as either papillary or solid. There are two types of urothelial carcinoma of the bladder with regard to tumor biology and rate of progression: 80% of urothelial tumors display non-invasive, papillary growth at the time of diagnosis. 10% to 15% of these progress to invade the vesical muscle (diagram 2).

The term ”superficial urothelial carcinoma” has been used to designate all urothelial tumors without muscle invasion, including not only non-invasive papillary tumors, but also urothelial tumors invading the stroma. As it seems contradictory to describe a tumor that is, by definition, invasive as ”superficial,” and also in view of the genetic heterogeneity of tumors that invade the stroma, it is better to differentiate explicitly between non-invasive (Ta, Cis) and invasive (T1) tumors and to characterize the tumor further by its growth pattern (papillary) and depth of invasion.
Histopathological grading

The new WHO classification makes clear that the various stages of urothelial carcinoma contain subclasses of tumors that have a higher degree of malignancy and a greater likelihood of progression. These subclasses are increasingly being genetically classified. Genetically stable tumors are called "low-grade malignant," while genetically unstable tumors are called "high-grade malignant."

Papillary, well-differentiated tumors are no longer classified as malignant and are now called "papillary urothelial neoplasia with low malignant potential," or PUNLMP. A urothelial tumor with a mild disturbance of stratification and a correspondingly disorganized appearance is called a low-grade non-invasive urothelial carcinoma and is thus classified as a low-grade malignancy.

A papillary tumor displaying cellular and nuclear polymorphism and a more pronounced disturbance of stratification resembling that of an invasive tumor is called a high-grade non-invasive papillary carcinoma and is thus considered a highly malignant tumor. The polymorphism is due to aneuploidy. Apart from their histological picture, a further indication of the high-grade malignancy of these lesions comes from genetic analyses – expression and mutation analyses of, e.g., p53 and the retinoblastoma protein pRB – and from the accompanying immunohistochemical tests (Ki 67 and CK 20).

A particular challenge is posed by patients with pT1 urothelial carcinoma, a type of lesion that accounts for 10% to 20% of all urothelial carcinomas and is usually treated conservatively with transurethral resection. 20% to 30% of these patients develop local progression with muscle invasion; thus, after a pT1 tumor is resected, secondary resection is indicated 4 to 6 weeks later. The genetic findings confirm that the histopathologically defined tumor entities are indeed prognostically relevant subtypes. When these tumors are histologically diagnosed, however, it is crucial to obtain a large number of sections of the tumor for processing and study. This is a prerequisite for the reliable differentiation of non-invasive from invasive tumors, as it ensures that a less well-differentiated component of the tumor will not be missed when a benign tumor such as PUNLMP is diagnosed.

Carcinoma in situ is a flat, non-papillary, intraepithelial lesion. Evidence suggests that carcinoma in situ is a precursor of invasive urothelial carcinoma (figure). Tyrkus et al. showed that carcinoma in situ possesses chromosomal aberrations resembling those of invasive carcinoma (4). The new WHO classification differentiates between carcinoma in situ,
a high-grade lesion, and dysplasia, a low-grade lesion. A small focus of highly abnormal cells surrounded by normal urothelium must be designated as carcinoma in situ, because, regardless of the small number of cells, such lesions have a high potential for local progression.

**Prognostic factors**

The important prognostic factors for urothelial carcinoma are its depth of invasion and degree of differentiation. These two factors are closely associated with each other: non-invasive urothelial carcinomas, unlike those that invade muscle, are well differentiated in more than 60% of cases (table). Patients with non-invasive tumors (pTa) develop metastases in 0.7% of cases, independently of the degree of differentiation. If the lamina propria is infiltrated, metastasis is to be expected in 14% to 23% of cases. The risk of recurrence increases if there are multiple tumors, if the tumor is more than 3 cm in diameter, if it is poorly differentiated, if there is accompanying carcinoma in situ, or if its stage is pT1.

Most patients with "low-risk" tumors (pTa G1) do not develop metastases primarily, but rather as a sequel to local tumor progression. Local tumor progression is a poor prognostic factor mainly for patients with pT1 G3 tumors. It is firmly established that tumor recurrence in a patient with pT1 G3 urothelial carcinoma adversely affects survival. Data from the Essen Bladder Tumor Registry provide evidence of a clear difference in tumor biology between patients with non-invasive pTa G1–2 urothelial carcinoma and those with pT1 G3 carcinoma. The former patients have a lower rate of metastasis and a lower rate of progression of the local recurrence (5).

**Urine cytology and urine-associated marker systems**

The main purpose of urine cytology is the detection of "high-risk" urothelial carcinoma. The sensitivity in this spectrum of tumors is 75% to 95% for tumors previously classified as G2 and G3 (6, e3, e4). An excellent sensitivity of 95% is obtained in the case of carcinoma in situ. The method is also highly specific (17, e5).

The "bladder tumor antigen" (BTA) attracted much attention when it was found to be demonstrable with a rapid urinary test. The BTA stat test is 95% specific for bladder tumors; its sensitivity is 57% for G1 tumors, 56% for G2 tumors, and 95% for G3 tumors. The rate
of positive findings in a control group of patients with urinary tract infections, urolithiasis, or benign prostatic hyperplasia was 33% (e5, e6).

The NMP-22 test is based on the detection of nuclear matrix protein, a component of the mitotic apparatus. The team of Poulakis et al. documented the high sensitivity of this test: 82% for G1 tumors, 89% for G2 tumors, and 94% for G3 tumors. Its specificity was 68% (8). A new option for the detection of urothelial carcinoma by urinary testing is fluorescent in situ hybridization (FISH) and microsatellite analysis (9, e7). In this technique, fluorescent centromeric and locus-specific DNA fragments are used to detect urothelial cells with chromosomal anomalies. Halling et al. demonstrated sensitivities of 36% for G1 tumors, 76% for G2 tumors, and 96% for G3 tumors, with 96% specificity (10). Another marker is the anti-apoptosis protein survivin (e8). The two studies on this marker that have been performed to date included only a small number of patients; its sensitivity was 100% in both studies, while its specificity was 100% in one study and 87% in the other (11, e9).

Cytokeratins are the main cytoskeletal proteins of epithelial cells. Many studies have been performed to investigate the expression of cytokeratins 8, 18, 19, and 20 in urothelial carcinoma. The UBC test and Cyfra 21–1 are urinary tests for the detection of cytokeratins 8 and 18 and a fragment of cytokeratin 19. Cytokeratin 20 can be detected only by immunohistochemistry and RT-PCR. In the studies published to date, the sensitivity stratified by degree of tumor differentiation has been reported to be 13% to 60% for G1 tumors, 42% to 79% for G2 tumors, and 35% to 75% for G3 tumors (12, e10). At present, no urine-based marker system can take the place of cystoscopy for the detection of non-invasive urothelial carcinoma. Their use for primary diagnosis cannot be unequivocally recommended at present, because the rate of false-positive findings is still high.

i.v. Urography and ultrasound
Further techniques for the diagnostic assessment of bladder tumors include i.v. urography and ultrasonography for the detection of exophytic bladder tumors, lymphadenopathy (enlargement to 2.5 cm or more), or hepatic metastases. The need for intravenous urography as part of the primary work-up is debated, however, because of the rare occurrence of synchronous tumors within the upper urinary tract.

Treatment of non-invasive urothelial carcinoma
Patients with non-invasive bladder tumors constitute a heterogeneous group: the corrected survival rates of patients with non-muscle-invasive tumors (Ta G1–3, T1 G1–2) five years after transurethral resection (TUR) range from 81% to 96%. Patients with T1G3 carcinomas
have a poorer prognosis. Non-invasive tumors (pTa) metastasize in fewer than 1% of cases; 99.3% of these patients survive at least 5 years without metastasis.

**Indications for re-resection**

A repeated TUR is indicated in all patients with pT1 tumors or pTa tumors that were incompletely resected at the first procedure (13). Re-resection should also be performed if pathological study of the specimens from the first resection revealed no muscle tissue or if a Ta/T1 high-grade carcinoma was found at the first resection. 10% of all Ta/T1 G3 urothelial tumors invade muscle (13) and a tumor of this type should therefore be re-resected as well.

**Radical cystectomy**

Patients with pT1G3 tumors have a high rate of tumor progression: 36% die of this form of cancer within 5 years (5, 14). Stöckle et al. and Herr et al. compared the survival rates after cystectomy upon initial diagnosis of pT1 urothelial carcinoma with those after delayed cystectomy upon recurrence of a pT1 tumor. The corrected 5-year survival rates in the two studies were 89% and 92% for cystectomy upon initial diagnosis, but only 60% and 56% for delayed cystectomy after recurrence (15, 16). BCG treatment (see below), however, is another useful option in T1G3 urothelial carcinoma, achieving five-year survival rates up to 88%. It is thus unclear at present which patients with T1G3 tumors need to undergo early cystectomy.

Partial cystectomy may be indicated in cases of easily accessible, solitary tumors (e.g., in the dome of the bladder), in diverticular carcinoma, or in solitary T1G3 carcinoma without accompanying carcinoma in situ.

**Radiotherapy**

Randomized studies have shown that radiotherapy alone is inferior to combined radio- and chemotherapy as definitive treatment. Radiochemotherapy is a multimodal concept aiming at the maintenance of organ structure and function; its results with respect to survival are

### TABLE

<table>
<thead>
<tr>
<th>Tumor stage</th>
<th>G0/1</th>
<th>G2</th>
<th>G3</th>
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</thead>
<tbody>
<tr>
<td>pTa</td>
<td>65%</td>
<td>32%</td>
<td>3%</td>
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<tr>
<td>pT1</td>
<td>13%</td>
<td>48%</td>
<td>39%</td>
</tr>
<tr>
<td>pT2/3a</td>
<td>2%</td>
<td>34%</td>
<td>64%</td>
</tr>
<tr>
<td>pT3b–4</td>
<td>–</td>
<td>15%</td>
<td>85%</td>
</tr>
</tbody>
</table>

by Rutt (5)
generally 10% to 15% worse than those of cystectomy in non-randomized comparative studies. Larger series have shown five-year survival rates of 48% to 63% (17). The most common side effects are radiation cystitis and proctitis shortly after treatment. The major late complications are fistulae and radiogenic shrinking of the bladder.

**Adjuvant therapy**

Adjuvant therapy is performed after TUR to prevent tumor recurrence and progression, if possible. Either chemotherapy or immunotherapy can be used for adjuvant treatment.

**Intravesical chemotherapy**

The efficacy of intravesically applied chemotherapeutic drugs in preventing tumor recurrences has been demonstrated for the topical use of thiotepa, mitomycin, doxorubicin, and epodyl against incompletely resected urothelial tumors without muscle invasion. A metaanalysis performed by the European Organisation for Research and Treatment of Cancer and the British Medical Research Council revealed that topical therapy provides no advantage to TUR alone with respect to tumor progression, distant metastases, survival, or death. The immediate postoperative application of cytostatic agents (early instillation) has been recommended (18, e11). Further induction or maintenance therapy is given weekly or every two weeks at first, and once a month thereafter. If early instillation has been performed, the overall duration of treatment should not exceed 6 months. Without early instillation, maintenance therapy over a period of 12 months seems reasonable.

**Immunotherapy**

The immunotherapeutic agents bacillus Calmette-Guérin (BCG) and α-interferon are comparable in their effects to intravesical chemotherapy. Interferon has immune-modulating and anti-proliferative effects. The possible efficacy of these agents when instilled into the bladder in the presence of incompletely resected tumor has been investigated. Controlled studies of intravesiculat treatment with BCG showed a lower rate of recurrence compared to TUR alone. The recurrence rate can be reduced by up to 56% through the use of BCG (19). Immunotherapy with BCG is more effective when given as maintenance therapy. A prospective, randomized study by the Southwestern Oncology Group (Lamm) showed that maintenance therapy with BCG significantly lowers the recurrence rate, but not the rate of progression or the tumor-associated mortality. Moreover, BCG maintenance therapy had serious adverse effects in 26% of patients (20).

A meta-analysis by the EORTC concerned the possible effect of BCG on tumor progression (21). 260 of 2 658 patients treated with BCG had progressive disease (9.8%), in comparison with 304 of 2 205 control patients (13.8%). The difference was significant, but it was restricted to patients who underwent BCG maintenance therapy.

**Treatment of carcinoma in situ**

The current treatment concept for Ta involves initial intravesicular treatment with BCG. If a complete remission is not achieved within 3 months, the instillation should be repeated, or a cystectomy performed.

Current data show that intravesical immunotherapy with BCG can prolong time to progression of high-grade carcinoma or carcinoma in situ. Different BCG strains were used: they were applied weekly for 6 weeks, after which maintenance treatment was given for up to 36 months (22). In view of the high rate of later development of muscle-invasive carcinoma, it seems reasonable to recommend early radical cystectomy for the treatment of carcinoma in situ that has not responded to nonsurgical treatment (23). Nonetheless, because markers and prospective comparative studies are currently lacking, it remains unclear which patients stand to benefit most from radical cystectomy.
REFERENCES
For e-references please refer to the additional references listed below.

ADDITIONAL REFERENCES

Corresponding author
Dr. med. Frank vom Dorp
Department of Urology, Pediatric Urology, and Urologic Oncology
Essen University Clinic
Hufelandstr. 55
D-45122 Essen, Germany
frankvomDorp@web.de