Prognostication and Risk Assessment

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9.1 Introduction

9.1.1 Prognostic Factors

Prognostication and risk assessment are essential for treatment decision-making, patient counseling, and determination of eligibility for clinical trials. More than most other malignancies, urothelial carcinoma of the bladder cancer (UCB) is a highly aggressive and heterogeneous disease with high prevalence and recurrence rates. In patients with non-muscle invasive bladder cancer (NMIBC), predictors of outcomes could help in the decision-making regarding follow-up scheduling, administration of intravesical instillation therapies (immediate postoperative instillation of chemotherapy (IPOP) and/or adjuvant) [1], and/or early radical cystectomy (RC). In patients with muscle-invasive bladder cancer (MIBC) who underwent RC, an accurate prediction of the presence of lymph node metastasis and the probability of disease recurrence is essential for selecting patients who might benefit from neoadjuvant and/or adjuvant systemic chemotherapy [2].

Anatomical staging systems present the simplest examples of a prediction tool by categorizing the disease based on stage-adjusted outcome. The American Joint Committee on Cancer TNM staging system has been validated and used universally to predict the risk of disease recurrence in patients after RC [3]. These staging systems provide useful estimates of survival outcome; however, the inherent heterogeneity of tumor biology, patient characteristics, and variability in the thoroughness of surgical staging lead to significant variation in outcomes within each stage category. Furthermore, current staging systems for UCB do not incorporate important clinical, pathological, and molecular markers of disease outcome. That said, many patients with UCB are

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elderly and have significant comorbidities, thus competing risks are important in evaluating outcomes and choosing personalized therapies.

9.1.2 Prediction Tools

Recent significant advances have been made in the development of predictive tools including risk stratifications, nomograms, and staging scores, that provide useful risk estimates for patients with UCB [4–8]. Among the available prediction tools, nomograms currently represent the most accurate and widely used tools for prediction of outcomes in patients with cancer [6, 9, 10].

Accuracy represents an important consideration of a prognostic model and should ideally be validated in an external cohort. However, internal validation is a commonly used alternative; the bootstrapping-derived accuracy estimates represent the closest to external validity-derived estimates [11, 12]. That is, no model is perfect and generally accepted accuracy for a model to be clinically useful ranges from 70 to 80 %. While a nomogram may contribute to a better distribution between study arms, a higher accuracy will be achieved when using it for risk stratification within a clinical protocol or to interpret treatment outcomes based on a more accurate description of the patient population under study. It is therefore crucial to assess the performance characteristics of a predictive model, which is also called calibration. Calibration plots demonstrate the relationship between predicted and observed probabilities of the outcome of interest. For clinicians, it is essential to know the performance characteristics of the model they routinely use in clinical practice as some predictive models may perform substantially worse in an external cohort.

The general applicability of a predictive model is important because patient and model characteristics may vary and thereby undermine the performance of the model. The ability to generalize a prediction model may be limited by differences in disease and population characteristics, as well as stage and/or grade migration. For example, a model that has been developed on patients in the pre-PSA era may not be relevant to patients in the post-PSA era due to the biomarker itself, but also due to possible shifts in stage based on changes in care pathways. Thus it is critical to understand the population from which a risk model was developed, as this should then be applied to similar populations for use.

For clinicians the level of complexity represents an important consideration of prediction tools, as excessively complex models are clearly not user-friendly in busy clinical practice. Predictive models that require computational infrastructure might cause problems for general applicability in certain environments [6, 10, 13].

In this chapter, we aimed to give an overview of the prognostic factors and currently available prediction tools associated with UCB recurrence, progression, and mortality. We stratified the chapter by disease states: NMIBC, MIBC, and metastatic UCB. We present the prediction tools by recording predictor variables, the number of patients used for their development, tool-specific features, predictive accuracy estimates, and whether internal and/or external validation has been performed.

9.2 Non-muscle Invasive Bladder Cancer

9.2.1 Prognostic Factors

9.2.1.1 Clinical Factors

9.2.1.1.1 Age

Age at diagnosis has been shown to be associated with disease recurrence, disease progression [14, 15], cancer-specific mortality [15], and response to Bacille Calmette-Guérin (BCG) (Table 9.1) [16–20]. These worse outcomes in elderly patients could be attributed to changes in the biologic potential of the tumor and host as well as to differences in quality of care (i.e., greater reluctance to recommend aggressive treatment in the elderly) [19, 21].

9.2.1.1.2 Race

In a study using the SEER data, 5-year cancer-specific survival was consistently worse in Afro-Americans than in other ethnic groups, even after adjusting for the effect of tumor stage and grade [22]. Moreover, these worse outcomes were persistent over time (1975–2005). To better

Table 9.1 Summary of the preoperative/clinical and pathologic prognostic factors in patients with non-muscle invasive bladder cancer

	Comments	References
Age	Advanced age is an independent predictor of DR, DP, and CSM	[14–21]
Race	Afro-Americans are at higher risk of CSM compared to other racial groups	[22]
Gender	Female gender is an independent predictor of worse DR, DP, and CSM	[14, 23–26]
Obesity	Body mass index ≥ 30 kg/m^2 is an independent predictor of DR, DP, and CSM	[15]
Smoking	Smokers are more likely to be diagnosed with UCB and at higher risk of DR, DP, and CSM	[27–31]
Prior recurrence	Recurrent tumors are at higher risk of DP	[25, 32–35]
Tumor size	Larger tumor size is an independent predictor of DR and DP	[25, 36, 37]
Multifocality	Multifocality is an independent predictor of DR	[25, 36, 37]
Pathologic tumor stage	Advanced pathologic T-stage is an independent predictor of DR, DP, and CSM. The depth of invasion of the muscularis mucosae is also associated with worse outcomes (DR, DP, and CSM)	[14, 25, 37, 39–41]
Pathologic tumor grade	Higher tumor grade (Grade 3 or high grade) is an independent predictor of worse outcomes (DR, DP, and CSM) (both the 1973 and the 2004 World Health Organization classifications)	[38, 42–48]
Concomitant carcinoma in situ	Concomitant carcinoma in situ is associated with advanced tumor stage and grade and is an independent predictor of worse outcomes (DR and DP)	[26, 37, 49, 50]
Lymphovascular invasion	The presence of lymphovascular invasion is an independent predictor of worse outcomes (DP and CSM)	[48, 51–55]
Histologic variants	The presence of a micropapillary variant is an independent predictor of understaging and occurrence of distant metastasis	[56–58]
Delay of cystectomy	Delay of RC >3 months after initial diagnosis is associated with extravesical or node-positive disease, and worse oncologic outcome. Controversial findings	[59–62]

DR disease recurrence, *DP* disease progression, *CSM* cancer-specific mortality

understand these race disparities, as well as the disparities in socioeconomic status and their effect on outcomes of NMIBC, further studies on access to care, quality of care, exposure history, molecular characteristics, and treatment strategies are needed.

9.2.1.1.3 Gender

UCB is more common in men than in women. Data supporting a worse outcome in female patients have been inconsistent. Some studies have demonstrated that female gender is associated with worse oncologic outcomes compared to male gender in NMIBC [14, 23, 24]. However, Sylvester et al. did not find any prognostic value to gender in seven randomized EORTC trials with a total of 2,596 patients with Ta or T1 NMIBC who received different regimens of intravesical therapy after TURB [25]. In a recent retrospective study of 146 patients with primary T1HG UCB [26], female gender was associated with higher risk of disease recurrence in univariable analysis, and disease progression and any-cause mortality in multivariable analyses. In a large multi-institutional cohort of 916 T1HG UCB patients, female gender was an independent predictor of disease recurrence [24]. Additional studies are needed to clarify the gender risk for NMIBC.

9.2.1.1.4 Obesity

In NMIBC, Kluth et al. reported recently that obese patients diagnosed with clinical T1HG were at higher risk of disease recurrence, disease progression, and cancer-specific mortality compared to their non-obese counterparts [15]. In this study, patients with a body mass index ≥30 kg/m^2

were considered as obese. The authors hypothesized that this could be due to change in the underlying biologic potential of the tumor, the host's defense mechanisms, differences in the transurethral resection and intravesical therapy efficacy, comorbidities, as well as possibly socioeconomic factors. Further work is needed to improve our understanding of UCB outcomes in this growing population and to modify its impact on outcomes.

9.2.1.1.5 Smoking

Smoking exposure is the best-established causative agent for UCB [27]. Recently, smoking status (current vs. never) and cumulative exposure have been associated with disease recurrence [28], disease progression and response to BCG, both in primary [29, 30] and recurrent NMIBC [30, 31]. Interestingly, it has been shown that smoking cessation >10 years prior to disease might mitigate this detrimental effect suggesting a potential benefit of smoking cessation on prognosis of NMIBC [30, 31]. These data suggest that smoking cessation could help improve outcomes in patients with NMIBC.

9.2.1.2 Pathologic Factors

9.2.1.2.1 Prior Recurrence

The impact of prior recurrences on outcomes of patients with NMIBC has been assessed by several studies [25]. The CUETO group, in a prospective randomized study comparing the standard 81 mg dose of BCG with 27 mg, reported that prior UCB was a significant factor affecting disease progression in multivariable analysis [32]. In a study comparing primary and recurrent tumors, Alkhateeb et al. have shown that recurrent tumors were at higher risk of disease progression [33]. These findings were confirmed and extended by the association of high-risk patients with cancer-specific mortality [34]. Notably, failure to achieve a complete response to induction BCG therapy resulting in disease recurrence has been shown to be associated with worse cancer-specific mortality [35].

9.2.1.2.2 Tumor Size and Multifocality

Tumor size has been shown to be associated with disease recurrence and progression, with the most commonly used cut-off being 3 cm [25, 36, 37]. Multifocality represents a more controversial prognostic factor, which correlates with disease recurrence rather than disease progression [37].

9.2.1.2.3 Tumor Stage

The pathologic stage from TUR specimen has been correlated with outcomes [38]. T1 tumors have higher rates of disease recurrence, disease progression, and cancer-specific mortality compared to Ta tumors [14, 25, 37]. Furthermore, several studies have reported on the prognostic interest of substaging according to invasion in T1 tumors above (T1a), in (T1b), or beyond the muscularis mucosae (T1c) [39, 40]. However, this T1 substage has not been adopted in clinical guidelines due to the lack of consensus among pathologists regarding the identification of the muscularis mucosae and independent prognostic value. Therefore, a new reproducible substaging system in order to discern T1-microinvasive (T1m) and T1-extensive-invasive (T1e) tumors has been proposed and is currently being validated [41].

9.2.1.2.4 Tumor Grade

Historically, the initial grading system of 1973 had a high interobserver variation due to the lack of clear definitions for the three pathologic grades and on increasingly high percentage of tumors classified as grade 2 [38, 42–44]. A new classification was adopted by the World Health Organization and the International Society of Urological Pathology (ISUP) in 1998, and published in 2004. This new grading system introduced detailed histologic criteria to decrease the interobserver variability. Finally, the intermediate grade (grade 2), which was the subject of controversies has been eliminated [38, 42–44]. To date, though the prognostic value of both grading systems has been validated, the published comparisons of these two grading systems, however, have not clearly confirmed that the new one is superior in terms of reproducibility [38, 45, 46]. It has been shown that patients with grade 3 and high-grade tumors are at highest risk of disease recurrence and progression; that said, grade 3 seems to have worse outcomes than high-grade

tumors due to the heterogeneity in the subgroup of high-grade tumors [38, 44, 47]. The EAU guidelines recommend using both grading systems as long as the prognostic role of the WHO 2004 is not validated in prospective trials [48].

9.2.1.2.5 Concomitant Carcinoma In Situ

Concomitant carcinoma in situ (CIS) is a validated prognostic factor for both disease recurrence and disease progression in NMIBC [37, 49]. In 2000, the SWOG has shown that CIS generally responds favorably to BCG [50]. Palou et al. have recently evaluated the incidence of CIS in the prostatic urethra (routinely evaluated by biopsy) in 146 patients with primary T1G3 NMIBC treated with BCG [26]. The authors reported an incidence of 10 % in the prostatic urethra, which was associated with both disease recurrence and progression. These findings suggest that prostatic urethra involvement should be evaluated routinely in all patients suspected of having high-grade tumor or in case of presence of CIS in the bladder.

9.2.1.2.6 Lymphovascular Invasion

Several studies have shown that the presence of lymphovascular invasion (LVI), defined as the presence of carcinoma in the endothelial lining or in the vascular wall, predicts disease progression and cancer-specific mortality [51–54]. The major drawback is the reproducibility among pathologists [55]. However, the EAU guidelines recommend that the presence (or not) of LVI must be reported in pathologic reports [48].

9.2.1.2.7 Histologic Variants

Histologic variants such as micropapillary variant of UCB represent a poor prognostic factor in patients with NMIBC [56–58]. From a pathologic point of view, it remains critical to differentiate whether micropapillary urothelial carcinoma is invasive or non-invasive [57]. While some cases of non-invasive micropapillary UC are not necessarily associated with an adverse outcome, invasive micropapillary UC is an aggressive disease, thereby suggesting it to be an important risk of understaging and occurrence of distant metastasis in these patients [56–58]. In addition, Kamat et al. reported intravesical BCG therapy to be ineffective against micropapillary UC, thus suggesting RC as the optimal treatment strategy for non-muscle invasive micropapillary UC before disease progression [56].

Other sections to consider would be prior response to therapy: progression is exceedingly high in those that recur/do not respond to BCG. Also we could include the data on pathology of the restaging TURBT and outcome. Particular in T1 patients those without invasive changes on the second TUR are more likely to respond to BCG whereas residual T1 on the restaging predicts strongly for progression despite BCG.

9.2.1.3 Surgical Factors

9.2.1.3.1 Delay of Radical Cystectomy

Recently, in several studies the time from diagnosis to treatment has been evaluated and shown that patients who were treated with RC later than 3 months after initial diagnosis were of increased risk of extravesical stage, node-positive disease and worse outcomes compared to those treated within 3 months [59, 60]. However, another recent study could not confirm these findings [61]. Interestingly, the time to RC does not only affect outcomes but also the type of urinary diversion [62], thereby reflecting general health status.

9.2.2 Predictive Tools

9.2.2.1 Prediction of Disease Recurrence and Progression in NMIBC

In the study of 1,529 patients with NMIBC, Millan-Rodriguez et al. assessed predictors of disease recurrence, progression, and mortality and developed a different risk groups based on multifocality, tumor size, intravesical BCG therapy, and presence of concomitant CIS [63]. Tumor grade was the most powerful predictor of disease progression and disease-specific mortality.

In 2006, the European Organization for Research and Treatment of Cancer (EORTC) Genitourinary (GU) group developed a scoring system and risk tables [25], based on data from 2,596 patients diagnosed with Ta/T1 tumors, who were randomized in seven previous EORTC-GU group trials. The scoring system was built on the

six most relevant clinical and pathologic predictors of outcomes such as tumor stage and grade, number of tumors, tumor size, concomitant CIS, and prior recurrence rate (Table 9.2). However, the study was limited by the low number of patients treated with BCG, the high rate of IPOP, and the fact that no Re-TUR was performed.

Therefore, the Club Urológico Español de Tratamiento Oncológico (CUETO) developed a scoring model, which predicts the short- and long-term probability of disease recurrence and progression in 1,062 patients with NMIBC from four CUETO trials that compared the efficacy of different intravesical BCG treatments [14]. These patients received 12 instillations during 5–6 months; however, neither immediate postoperative instillation nor re-TUR was performed. The scoring system was based on seven factors including age, gender, prior recurrence status, number of tumors, tumor stage, tumor grade, and the presence of concomitant CIS.

Though many clinicians are using these scoring systems in daily practice, to date, only few studies have externally validated both these models [64–66]. Furthermore, these validation studies have reported an overestimation of both the risks of disease recurrence and progression, especially in the high-risk group of patients [64–66]. One possible explanation is the high rate of intravesical chemotherapy in the EORTC trials.

Xylinas et al. recently evaluated the discrimination of the EORTC risk tables and the CUETO scoring model in a large retrospective multicenter study of 4,689 NMIBC patients [66]. Therefore, the authors created Cox regression models for time to disease recurrence and progression, thus incorporated the patients' calculated risk score as a predictor into both of these models and then calculated their discrimination. The EORTC risk tables and the CUETO scoring system exhibited a poor discrimination and overestimated the risk for both disease recurrence and progression in NMIBC patients.

The first nomogram in UCB was published in 2005 and estimated the risk of disease recurrence and progression based on a multi-institutional cohort of 2,681 patients with Ta, T1, or Tis UCB [67]. All patients had previous histologically confirmed NMIBC and provided voided urine samples for cytologic and NMP22 analyses before undergoing cystoscopy. In case of suspicious cystoscopy or cytology, patients were further investigated with transurethral biopsies. Overall, 898 patients had a recurrent UCB: 24 % had grade 1, 43 % grade 2, and 33 % grade 3 tumors; 45 % had Ta, 32 % T1 or CIS, and 23 % T2 tumors. In uni- and multivariable analyses, age, urine cytology status, and urinary NMP22 level were associated with outcomes ($p<0.001$). The predictive accuracy of a model based on patient age, gender, and urine cytology significantly increased for all three endpoints when NMP22 level was included as a variable.

Whereas the nomogram from Shariat et al. takes into account age, gender, pre-cystoscopy cytology, and NMP22 to predict recurrence and progression during the follow up of patients with a previous history of NMIBC [67], the EORTC [25] and CUETO [14] tables predict a patient's future short- and long-term probabilities of recurrence and progression at the time of the initial diagnosis or at the time of a recurrence based on the clinical and pathologic characteristics. Thus, these two prediction tools serve different and complimentary purposes.

9.2.2.2 Preoperative Prediction of Pathologic Features and Outcomes at Radical Cystectomy

In the pre-cystectomy setting, the clinical staging is often inaccurate; however, remains a major determinant of treatment decision-making [68]. Accurate preoperative risk-assessment models could help to predict (1) non-organ-confined disease, thus enabling a better selection of patients who may benefit from neoadjuvant chemotherapy; (2) which T1HG patients should undergo early RC; and (3) prediction of lymph node metastasis and thereby provide guidance for the indication and extent of lymph node dissection.

Karakiewicz et al. developed a preoperative nomogram which can predict advanced pathologic stage (pT3–4) and presence of lymph node metastasis based on a multicenter cohort of 731 patients with available clinical and pathologic staging data [69]. When patient age, clinical tumor stage and grade, and presence of carcinoma in situ were integrated within the nomogram, a 76 % accuracy

Table 9.2 Available predictive models in bladder cancer before radical cystectomy

Pre-cystectomy tools							
Reference	Prediction form	Patient population	Outcome	No. of pts.	Variables	Accuracy	Validation
Qureshi et al. [193]	Artificial neural network	Ta T1	Recurrence-free survival (RFS) within 6 months	56	EGFR, c-erbB2, p53, tumor stage, tumor grade, tumor size, number of tumors, gender, smoking status, histology of mucosal biopsies, carcinoma in situ (CIS), metaplasia, architecture, tumor location	75 % (RFS)	Internal
		Ta T1	Progression-free survival (PFS) within 1 year	105		80 % (PFS)	
		T2–T4	Cancer-specific free survival (CSS)	56		82 % (CSS)	
Catto et al. [192]	Neuro-fuzzy modeling	Ta-T4	RFS	109	P53, mismatch repair proteins, tumor stage, tumor grade, age, smoking, previous cancer	88–95 %	Internal
Millan-Rodriguez et al. [63]	Risk stratification	NMIBC	RFS, PFS, and CCS	1,529	Number of tumors, tumor size, tumor stage, tumor grade, CIS, intravesical Bacillus Calmette-Guerrin (BCG)	Not reported	Not performed
Sylvester et al. [25]	Look-up table	NMIBC	RFS and PFS	2,596	Number of tumors, tumor size, prior recurrence rate, tumor stage, tumor grade, concomitant CIS	Not reported	Internal and external
Fernandez-Gomez [14]	Look-up table	NMIBC	RFS and PFS	1,062	Age, gender, tumor stage, tumor grade, prior recurrence rate, multiplicity and concomitant CIS	CCI: 0.69	Internal
Shariat et al. [67]	Probability nomogram	NMIBC	RFS and PFS	2,681	Age, gender, urine cytology, dichotomized NMP22 level (and institution)	84 % for RFS of any UCB 87 % for RFS of high-grade UCB or T1 and higher stage 86 % for RFS of stage ≥ T2 UCB	Internal
Karakiewicz et al. [69]	Probability nomogram	NMIBC and MIBC	Cystectomy T and N stage	731	Age, TUR stage, TUR grade, CIS	76 % T stage 63 % N stage	Internal
Green et al. [55]	Probability nomogram	NMIBC and MIBC	Non-organ-confined disease at radical cystectomy (pT3/Nany or pTany/N+)	201	Tumor stage, presence of LVI, radiographic evidence of non-organ-confined UCB or hydronephrosis	83 %	Internal
Shariat et al. [70]	Nodal Staging Score	NMIBC and MIBC	Lymph node metastasis at radical cystectomy	4,335	Tumor stage, number of lymph nodes removed, number of positive lymph nodes		Internal

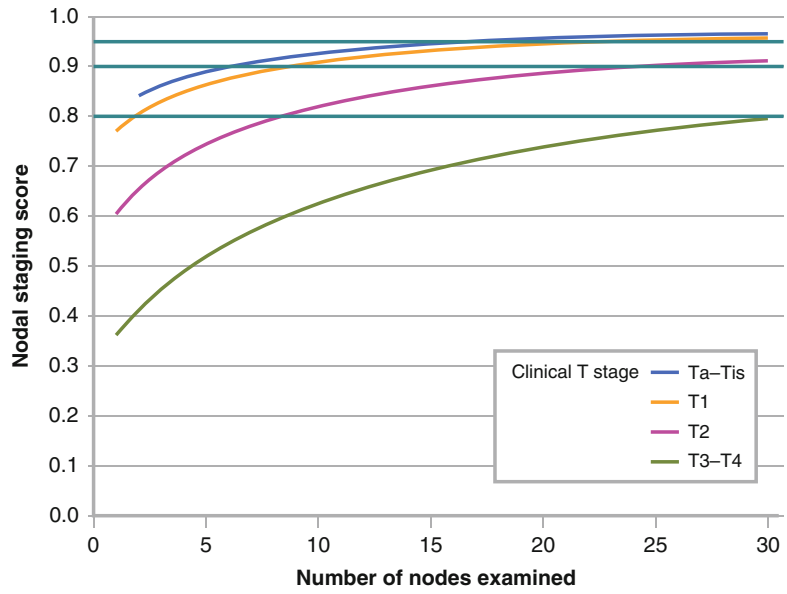

Fig. 9.1 Sensitivity of the pathologic evaluation of nodal disease stratified by clinical tumor stage in 4,335 patients who were treated with radical cystectomy with pelvic lymphadenectomy. Vertical axis is the probability of missing nodal disease (1 – sensitivity) and horizontal axis is the number of examined nodes. Adapted from Shariat et al. Eur Urol 2012;61:237–242

was recorded in predicting advance pathologic stage vs. 71 % when TUR stage alone was used. In predicting lymph node metastasis, the nomogram showed an accuracy of 63 % when TUR stage and grade were used compared to 61 % of patients using TUR stage alone. Heterogeneity in lymph node staging in this multicenter series likely contributed to the lower accuracy of the model.

In a similar fashion and a more contemporary cohort, Green et al. developed a nomogram which predicts non-organ confined UCB based on a single-institution cohort of 201 patients with clinically organ-confined disease who underwent RC with pelvic lymph node dissection without neoadjuvant chemotherapy [55]. The authors found that clinical tumor stage, presence of LVI, and radiographic evidence of non-organ-confined UCB or hydronephrosis were independently associated with pT3/Nany UCB. Furthermore, clinical tumor stage and presence of LVI remained independent predictors of pT3/Nany or pTany/N+UCB, for which the final nomogram showed a predictive accuracy of 83 %.

Recently, Shariat et al. developed a preoperative clinical Nodal Staging Score, which estimates the number of lymph nodes needed to be removed to ensure that a node-negative patient is indeed without lymph node metastasis, based on the numbers of lymph nodes examined and clinical tumor stage (Fig. 9.1) [70].

Pre-cystectomy nomograms provide only a modest increase in accuracy and reasons for this may include differences in TUR technique, non-standardized use of restaging biopsies, inaccuracy and variable use of preoperative imaging, and variability in the pathologic evaluation. The integration of other pathologic prognostic markers, for example LVI in addition to molecular markers of disease, possibly will enhance predictive accuracy of pre-cystectomy nomograms [71]. Nevertheless, they demonstrate that the combined use of clinical and pathologic variables, which cannot always be integrated within look-up tables, results in more accurate predictions than the use of a single variable.

9.3 Muscle-Invasive Bladder Cancer

9.3.1 Prognostic Factors

9.3.1.1 Preoperative/Clinical Factors

9.3.1.1.1 Age

The extent to which advanced chronologic age impacts the indications for and outcomes of RC is controversial. Though it has been reported in small surgical series that older patients fare well compared to their younger counterparts in terms of complications and perioperative outcomes [72, 73],

Nielsen et al. have shown in a study of 888 patients who underwent RC for UCB, that higher age at RC is associated with extravesical disease, pathologic upstaging, and higher cancer-specific mortality. These findings have been subsequently validated in several studies [74, 75]. The impact of age on treatment tolerability and tumor biology may relate to cancer outcomes but remains to be clarified.

9.3.1.1.2 Gender

The influence of gender on the incidence, staging, prognosis, and survival in UCB has been poorly investigated and understood [76]. Recent epidemiologic [77–80] and translational research [81, 82] has shed some light on the complex relationship between gender and UCB. A growing body of evidence has shown that despite UCB being more common in men, women with bladder cancer have worse survival than men in both non-muscle invasive [14, 24] and muscle-invasive bladder cancer [83, 84].

Hormonal differences have been discussed as a possible explanation for discrepancy in UCB biology [81, 82, 85]. Another reason for gender-specific discrepancies in UCB outcomes may be inequalities in health care and treatment delay. That is, for example, among patients treated with RC for UCB, female patients have been found to have significantly longer operative times, higher blood loss, higher transfusion rates, and a greater rate of perioperative complications than males [86–88]. Interestingly, it has been reported that women were more likely to present with more advanced bladder cancer than men in a retrospective study of the Netherlands Cancer Registry between 1989 and 1994 which provided data of more than 20,000 UCB patients [89]. One reason for this might be that women who present with initial macrohematuria are treated for urinary tract infection by their gynecologist or general practitioner, thus primary treatment is delayed [90]. Finally, differences in stage distribution have been suggested to be an alternative etiology for the disproportionally higher cancer-specific mortality among female UCB patients [91, 92]. However, large collaborative studies have demonstrated that even after adjustment for the effect of tumor stage, female patients experience worse outcomes after RC [93, 94]. Kluth et al. recently reported in a multi-institutional study of 8,102 (6,497 (80%) males and 1,605 (20%) females) patients treated with RC for UCB, that female gender was associated with disease recurrence in univariable, but not multivariable analysis [211]. Interestingly, although female gender was an independent predictor for cancer-specific mortality, there was no significant interaction between gender and either stage, nodal metastasis or LVI.

9.3.1.1.3 Performance Status and Comorbidity

Patients with poor performance status and higher comorbidity have been shown to have a higher mortality. In a single-center experience, Boorjian et al. evaluated five different comorbidity indices of 891 patients who underwent RC: the American Society of Anesthesiologists (ASA) score, Charlson comorbidity index (CCI), Elixhauser index (EI), and Eastern Cooperative Oncology Group performance status (ECOG) [95]. The authors found that EI, ASA, and ECOG were significantly associated with 90-day perioperative mortality. Moreover, within a median follow-up of 10 years, CCI, EI, ASA, and ECOG were independent predictors of 5-year cancer-specific survival. These findings are in line with recent studies that reported a higher comorbidity to be associated with a higher risk of postoperative and any-cause mortality [96].

9.3.1.1.4 Laboratory Values

Several studies suggest that different laboratory markers assessed at the time of RC are associated with oncologic outcomes. In a recent published single-center study of 246 consecutive patients who underwent RC for UCB, it has been found that CRP evaluated at the time of RC was independently associated with a higher risk of cancer-specific mortality [97]. These findings are in line with a recent screening study among healthy individuals in which elevated CRP concentrations indicated a higher risk of developing UCB [98]. Furthermore, Yoshida et al. found in a study of 88 MIBC patients treated with chemoradiotherapy only, an association of elevated CRP and adverse outcome [99]. Leukocytosis (higher WBC) is a sensitive, non-specific marker of inflammation associated with systemic progress

such as cancer metastasis [100]. Elevated platelet count is frequently observed in patients with cancer and has been reported as a prognostic factor in several tumors such as renal cancer [101]. In a recent published retrospective study of 258 patients who underwent RC, the presence of thrombocytosis at RC was associated with higher cancer-specific mortality [102]. Hypoalbuminemia is controversial as a nutritional marker due to its long half-time and the potential impact of systemic factors such as inflammation and stress on serum albumin [103]. However, it has been shown that preoperative albumin is associated with a higher risk of overall survival in UCB patients after RC [104].

9.3.1.1.5 Obesity

In MIBC, Chromecki et al. have recently shown that obesity (defined as BMI ≥30 kg/m^2) is associated with a higher risk of disease recurrence, cancer-specific mortality, and overall mortality in a study cohort of 4,118 patients who underwent RC and lymphadenectomy for UCB [105]. These findings suggest that metabolic syndrome is an important area of investigation and therapy in patients with UCB. In contrast, Hafron et al. reported no significant association between higher BMI and disease-specific survival in RC patients [106]. However, this study was limited by its small sample size and a high rate of preoperative therapies.

9.3.1.1.6 Smoking

Recently, Rink et al. found that current smokers were at a significantly higher risk of experiencing disease recurrence after RC compared with former and never smokers, who had a similar risk [107]. These findings are in line with previous studies in NMIBC [29–31] and MIBC, in which smoking duration and quantity have been shown to be associated with higher tumor stage and grade in patients with newly diagnosed UCB [108, 109]. Similarly to previous studies in NMIBC [110], patients who stopped smoking more than 10 years before RC had less aggressive tumor stages and improved prognosis compared to those who stopped less than 10 years before RC or were current smokers at RC.

9.3.1.2 Intraoperative/Surgical Factors

9.3.1.2.1 Lymph Node Dissection and Invasion

Recently, several localization studies in UCB patients with regards to lymph node dissection demonstrated that no metastatic lymph nodes are found outside the pelvis if the pelvic lymph nodes are negative [111, 112]. In contrast, a multicenter study by Leissner et al. has shown that there may be a low rate of "skip" metastases to higher lymph nodes [113]. However, the extent and impact on survival of lymph node dissection in UCB is highly controversial [113–122].

Therefore, many studies have tried to establish a minimum number of lymph nodes needed to be taken at the time of RC in an effort to reduce understaging and maximize survival [121, 123]. In node-positive patients, one of the largest single-center reports of patients treated with RC, the recurrence-free survival at 10 years for patients with eight or fewer positive lymph nodes was significantly higher than in those with more than eight positive lymph nodes (40 % vs 10 %, respectively) [124]. In pathologic node-negative patients, increasing the number of LNs has also been suggested to result in better survival [115, 119]. In a recent multi-institutional study of 4,188 pN0 patients after RC, a lymph node removal over 20 nodes resulted in a survival benefit [125]. Many of these retrospective studies may however represent stage migration with more thorough pelvic lymph node dissections and not a therapeutic effect.

9.3.1.3 Postoperative/Pathologic Factors

9.3.1.3.1 Pathologic Tumor Stage

Tumor stage has been clearly established as one of the most important predictors of cancer-specific and overall mortality in patients after RC (Table 9.3) [124, 126]. The clinical TNM staging system combines a pathologic evaluation of the TUR specimen with findings from an examination under anesthesia and preoperative radiographic imaging. Unfortunately, inaccuracies in clinical staging are highlighted in that up to 40 % of patients are up-staged and about 25 % are down-

Table 9.3 Summary of the preoperative/clinical, intraoperative, and pathologic prognostic factors in patients with muscle invasive bladder cancer

	Comments	References
Age	Advanced age is an independent predictor of extravesical disease, pathologic upstaging, and CSM	[1–4]
Gender	Female gender is an independent predictor of worse DR and CSM	[5–25]
Performance status and comorbidity	Poor performance status and higher comorbidity are independent predictor of 90-day perioperative mortality, CSM, and any-cause mortality	[26, 27, 211]
Laboratory values	Elevated CRP, leukocytosis (higher WBC), thrombocytosis (elevated platelet count) are independent predictors of CSM. Hypoalbuminemia is associated with perioperative and overall mortality	[28–35]
Obesity	Body mass index ≥ 30 kg/m^2 is an independent predictor of DR, CSM, and overall mortality	[36, 37]
Smoking	Smokers are more likely to experience DR. Smoking cessation >10 years is associated with improved diagnosis	[38–44]
Lymph node dissection/invasion	Lymph node metastasis is an independent predictor of DR and CSM	[45–59]
Pathologic tumor stage	Advanced pathologic T-stage is an independent predictor of CSM and overall mortality	[58, 60–62]
Pathologic tumor grade	While tumor grade is one of the most important predictors of disease recurrence and progression after TUR and/or intravesical immunotherapy, the predictive power after RC is limited	[58, 60, 63, 64]
Lymph node invasion	Lymph node metastasis is the most important pathologic prognostic factor after RC and is associated with higher risk of DR and survival	[50, 51, 60, 65–67]
Soft tissue surgical margin	Soft tissue surgical margin is an independent predictor of DR and CSM	[68, 69]
Tumor size	Larger tumor size is an independent predictor of CSM	[69–71]
Lymphovascular invasion	The presence of lymphovascular invasion is an independent predictor of DP and CSM. That is also true in lymph node negative patients	[72–79]
Histologic variants	Studies have failed to show significant differences in outcomes between UC and squamous histology. Non-UC/non-squamous histology is an independent predictor of DP and CSM. Previous studies failed to show significant association between histologic variants and outcomes	[80–84]

DR disease recurrence, *DP* disease progression, *CSM* cancer-specific mortality

staged after pathologic assessment of the RC specimen, thus limiting the prognostic accuracy of clinical staging system [68]. The problem of understaging has significant implications such as in counseling patients for neoadjuvant chemotherapy [2]. After RC and lymph node dissection, the pathologic evaluation of the specimen provides a more accurate stratification of cancer-specific outcome. The 5-year bladder cancer-specific survival in patients with ≤pT1, pT2, pT3, and pT4 is reported as 80–90 %, 50–70 %, 30–45 % and 20–35 %, respectively [124, 126].

9.3.1.3.2 Pathologic Tumor Grade

Tumor grading systems are designed to reflect the degree of tumor cell anaplasia. Recently, members of the WHO and the International Society of Urological Pathologists (ISUP) published the WHO/ISUP consensus classification of urothelial neoplasms of the urinary bladder. That is, there is no uniformly accepted grading system for UCB. The WHO/ISUP system classifies bladder tumors into papillary urothelial neoplasms of low malignant potential, or papillary carcinomas of low or high grade [127]. While tumor grade is one of the most important predictors of disease recurrence and progression after TUR and/or intravesical immunotherapy, the predictive power after RC is limited [128]. One of the reasons may be because most patients undergoing RC have high-grade disease [124, 126].

9.3.1.3.3 Lymph Node Invasion

The presence of lymph node metastasis is the most important pathologic prognostic factor after RC, with associated 15–30 % 5-year survival rates [4, 116, 117]. Multi-institutional series of patients treated with RC have shown that approximately 70–80 % of patients with pathologic node-positive disease experience disease recurrence compared to 30–40 % of patients with extravesical disease and pathologically negative lymph nodes within 5 years of surgery [4, 5, 126]. Tarin et al. have recently investigated impact of lymph node involvement by location on disease outcomes using the 2010 TNM staging system [129]. Of 591 patients treated with radical cystectomy with mapping pelvic lymph node dissection, 114 patients (19 %) had lymph node involvement and 42 patients (7 %) had pN3 disease. The authors could demonstrate that lymph node location was not associated with outcomes; however, the number of positive lymph nodes was associated with worse oncologic outcomes. Interestingly, a similar disease recurrence-free survival for patients with pN3 disease compared to pN1 or pN2 tumors has been shown.

9.3.1.3.4 Soft Tissue Surgical Margin

The positive soft tissue surgical margin rate (STSM) is usually rare after RC (2–10 %); however, it is a strong independent predictor of local disease recurrence and cancer-specific mortality. The finding of a positive STSM correlates with tumor stage, previous pelvic radiation, extent of lymph node dissection, and surgeon experience [130]. The Southwest Oncology Group 8710 trial reported a 100 % local disease recurrence, and 0 % 5-year cancer-specific rate among 25 patients with a positive STSM after RC [130].

Xylinas et al. identified 231 patients with positive STSM of a multi-institutional cohort of 4,335 patients (5.3 %) treated with RC and lymphadenectomy. Actuarial cancer-specific survival estimates at 2 and 5 years after RC were 33 ± 3 and 25 ± 4 %, respectively [131]. Moreover, it has been shown that higher body mass index, higher tumor stage, presence of grade 3 disease, lymphovascular invasion (LVI), and lymph node involvement were all independently associated with disease recurrence (all p values <0.05). Furthermore, higher tumor stage, LVI, and lymph node involvement were independently associated with cancer specific mortality, while location and multifocality of STSM were not associated with outcomes.

9.3.1.3.5 Tumor Size

The current pathologic TNM classification of bladder cancer relies on the depth of tissue invasion, but does not consider the size of the index tumor. However, in several recent reports, tumor size was identified as an independent predictor of cancer-specific mortality [131, 132]. It has been shown that the 10-year cancer-specific mortality was 94 % for patients with pT2 tumors of ≤3 cm and only 68 % for pT2 tumors of >3 cm ($p < 0.001$) [133] While published proposed size threshold criteria have varied, there is a strong rationale to include tumor size as an important risk stratification variable for patients treated with RC.

9.3.1.3.6 Lymphovascular Invasion

LVI is an important step in systemic cancer cell dissemination [134, 135]. LVI is an established independent predictor of disease recurrence and cancer-specific mortality, thus help identifying patients without lymph node metastasis who are at increased risk of disease recurrence and mortality despite RC [136–138]. LVI has been identified in 30–50 % of RC specimens, and positively correlates with adverse pathologic features. Several previous studies found that LVI is an independent predictor of disease recurrence and cancer-specific mortality in lymph node-negative, non-metastatic patients treated with RC [139–141]. This is an important distinction, as node-positive patients are usually recommended to receive adjuvant chemotherapy regardless of LVI status. Knowing that patients with negative nodes and positive LVI are at higher risk of recurrence might change the treatment in these patients.

9.3.1.3.7 Histologic Subtype/Variants

In Western countries, the most common histologic subtype of bladder cancer is UC, comprising >90 % of cases [142]. Histologic subtypes of non-UC of the bladder include mesenchymal and epithelial tumors of other histologic types. Epithelial

cancers include squamous cell, adenocarcinoma, and small cell/neuroendocrine carcinoma.

Several previous studies failed to show a significant difference in cancer-specific mortality when comparing squamous and UC histology [142–144]. Conversely, non-UC/non-squamous histology (i.e. adenocarcinoma, small cell carcinoma, carcinosarcoma, etc.) was identified as an independent predictor of disease recurrence and cancer-specific mortality [142].

Recently, Xylinas et al. analyzed differences between pure UCB and UCB with variant histology in 1,984 treated with RC [145]. The authors reported one-fourth of UCB patients treated with RC harbored histologic UCB variants, which were associated with features of biologically aggressive disease. While variant UCB histology was associated with worse outcomes in univariable analyses, this effect did not remain significant in multivariable analyses.

The nested variant of UC has recently shown to be associated with a high rate of locally advanced disease at RC [146]. However, when stage was matched in this analysis with a median follow up of 10.8 years, no significant differences on disease recurrence or survival were observed between patients with pure UC and those with the nested variant.

9.3.1.4 Tissue-Based Molecular Markers

9.3.1.4.1 Cell Cycle

p53 (gene and protein) is known as the "guardian of the genome," because it plays important roles in the regulation of the cell cycle, DNA repair, and apoptosis (Table 9.4) [147, 148]. It presents one of the most commonly mutated genes in humans; its expression reflects chromosome 17p abnormalities. Previous studies support the view that p53 nuclear accumulation is predictive of the outcome in patients treated with RC [149–152]. In these studies it has been shown that the proportion of specimens with altered p53 expression progressively increases from normal urothelium to NMIBC, to MIBC and finally to metastatic lymph node UCB. Moreover, retrospective studies demonstrate that p53 is associated with a greater risk of disease recurrence and cancer-specific mortality [147, 153–156]. There is evidence however for and against the prognostic role of p53. A prospective randomized study demonstrated no prognostic significance to p53 status in a series of muscle invasive lesions. Reasons for the discrepancies between studies may be related to the choice of antibody used in p53 assays, variability in interpretation and stratification criteria, and inconsistencies in specimen handling and other technical procedures [157]. Recent meta-analysis found that immunohistochemistry was the most commonly (96 % of the 117 studies) used approach to assess p53 status, with molecular analysis being used in the other five studies [150]. Interestingly, the p53 status was a stronger predictor of UCB outcomes in patients treated with RC than chromosomal alterations or expression patterns of p21, pRB, p27, p16, cyclin E1, or cyclin D1 [158].

The retinoblastoma gene is the prototype tumor-suppressor gene that encodes a nuclear protein (pRb) which is an important cell cycle regulator [147]. Recent evidence suggests that the predictive power of pRB may be inferior to that of other cell cycle regulators in both NMIBC and MIBC [147, 155, 159, 160]. However, pRb as part of a biomarker panel improved the predictive accuracy of a base model for disease recurrence and cancer-specific mortality after RC in MIBC [155]. Nevertheless, to date, the clinical utility of pRB in UCB prognostication seems limited and remains to be validated.

Ki-67 is a nuclear protein expressed by proliferating cells that regulates all phases of the cell cycle. Ki-67 overexpression has been shown to be independently associated with disease recurrence and stage-adjusted cancer-specific mortality in RC patients [161, 162]. Though Ki67 seems to be the most convincing biomarker for prognostication in MIBC, its impact in NMIBC is still controversial [158, 159, 163].

p21 binds to and inhibits the activity of cyclin-dependent kinase complexes, and thus functions as a regulator of cell cycle progression at G1 [164]. In MIBC patients, p21 was an independent predictor of both disease recurrence and cancer-specific mortality [155, 165]. In patients with organ-confined disease, p21 remained independently associated with outcomes when combined in a multivariable model with p27 and p53 [153].

Table 9.4 Selection of tissue-based biomarkers for staging and prognostication of bladder cancer

Biomarker	Function	Relevant studies (year of publication)	*N*	Findings
Cell-cycle				
p53	Inhibits G1-S progression	Schrier et al. (2006)	80	Altered expression of p53 associated with DR and CSM in pT1N0
		Esuvaranthan et al. (2007)	80	Altered p53 not associated with response to intravesical BCG, DR, DP, and CSM in NMIBC
		Moonen et al. (2007)	105	No additional value for p53 mutation analysis for high-risk NMIBC
		Shariat et al. (2009)	324	Incorporating p53 expression into clinico-pathologic predictive model improved accuracy in RC patients with organ-confined disease
		Shariat et al. (2010)	692	p53 as part of biomarker panel improved predictive accuracy for DR and CSM in patients with locally advanced disease after RC
		Shariat et al. (2010)	692	Incorporating p53 expression into clinico-pathologic predictive model does not improve accuracy in RC patients with locally advanced disease
		Goebell et al. (2011)	3,421	Altered p53 associated with DP in patients with ≥T1 disease
		Stadler et al. (2011)	499	p53 status has no association to DR, OS, or adjuvant chemotherapy benefit in Phase III trial of targeted chemotherapy for pT1/T2 patients based on p53 positivity
		Mitra et al. (2013)	212	p53 associated with DR and CSM after RC p53 as part of 9 biomarker panel with smoking intensity improved predictive accuracy for DR and CSM after RC
pRB	Cell cycle regulator Sequesters E2F Inhibitor of cell-cycle progression	Shariat et al. (2010)	692	pRB as part of biomarker panel improved predictive accuracy for DR and CSM in patients with locally advanced disease
		Park et al. (2011)	61	No predictive value for pRb expression on IVR or DP in BCG-treated high-grade T1 NMIBC
Ki-67	Marker of cell proliferation	Margulis et al. (2009)	713	High Ki-67 labeling index independently associated with DR and CSM in RC patients and improved predictive model for these outcomes
		Shariat et al. (2009)	80	Altered Ki-67 predictive of DR and CSM in pT1 UCB patients at RC
		Behnsawy et al. (2009)	161	No predictive value for Ki-67 expression on IVR in newly diagnosed NMIBC
		Park et al. (2011)	61	No predictive value for Ki-67 expression on IVR and DP in BCG-treated high-grade T1 patients

p21	Cyclin-dependent kinase inhibitor Regulator at G1 checkpoint	Stein et al. (1998)	242	p21 status was an independent predictor of DR and CSM after RC
		Shariat et al. (2003)	49	Altered p21 expression independently associated with DR and DP in patient with Cis
		Shariat et al. (2007)	74	Combination of p21 with p53, pRB, and p27 stratified patients into statistically significantly different risk groups for DR and DP in patients with NMIBC
		Shariat et al. (2007)	300	p21 has cooperative/synergistic action with p53, p27, and pRB
		Shariat et al. (2009)	80	Altered p21 not predictive of DR and CSM in pT1 UCB patients at RC
		Shariat et al. (2010)	692	p21 as part of biomarker panel improved predictive accuracy for DR and CSM in patients with locally advanced disease
p27	Cyclin-dependent kinase inhibitor	Shariat et al. (2009)	80	Altered p27 predictive of DR and CSM in pT1 UCB patients at RC
Cyclins	Deregulation of the G1/S transition	Del Pizzo et al. (1999)	50	Decreased expression of cyclin E1 significantly associated with advanced pathologic stage, LVI, LNM, and CSM
		Shariat et al. (2006)	235	Cyclin D1 immunoreactivity elevated in UCB patients compared to controls, but not associated with clinical or pathologic characteristics
Apoptosis				
Caspase-3	Protease that acts as an apoptosis effector	Karam et al. (2007)	226	49 % of the patients had loss of caspase-3 expression, which was associated with higher pathologic grade and stage, and presence of LNM Loss of caspase-3 independent predictor of CSM after RC
		Karam et al. (2007)	226	Overexpression of bcl-2 found in 32 % of RC specimens, and correlated with higher pathologic stage, DR and CSM
Survivin	Acts as inhibitor of apoptosis by blocking downstream caspase activity	Shultz et al. (2004)	37	Protein and mRNA level associated with cancer presence, higher tumor grade, and advanced pathologic stage
		Karam et al. (2007)	226	Survivin overexpression present in 63 % of UCB specimens, and associated with higher pathologic stage, presence of LVI, LNM, DR and CSM in 219 patients treated with RC
		Shariat et al. (2007)	231	The proportion of specimens with survivin overexpression increased gradually from NMIBC to advanced bladder cancer and to LNM
		Shariat et al. (2009)	726	Altered survivin status added to standard clinico-pathologic predictive model improved accuracy for prediction of DR and CSM in T1-3 N0 subgroup
		Xi et al. (2012)	72	Survivin overexpression associated with DR in NMIBC

(continued)

Table 9.4 (continued)

Biomarker	Function	Relevant studies (year of publication)	*N*	Findings
Angiogenesis				
MVD	Traditional histologic marker of angiogenesis	Bochner et al. (1995)	164	Patients with high microvessel density (>100 microvessels per hpf) were at highest risk of DR and CSM
		Jaeger et al. (1995)	41	Higher MVD in the primary tumor if LNM
		Shariat et al. (2010)	204	Failed to detect an association between MVD and prognosis, but MVD higher in patients with LNM Higher relative MVD in LNM
		Ajili et al. (2012)	28	MVD associated with DR in patients with T1HG NMIBC treated with BCG
Thrombospondin-1	Component of the extracellular matrix Implicated in the regulation of cell growth and proliferation Inhibitor of angiogenesis	Grossfeld et al. (1997)	163	Altered thrombospondin-1 expression independently associated with increased risk of DR and CSM in 163 patients treated with RC
		Shariat et al. (2010)	204	Decreased thrombospondin-1 independently associated with DR and CSM Loss of thrombospondin-1 expression associated with alterations in other cell cycle regulators such as p21 and p27

N number of patients, *MVD* microvessel density, *RC* radical cystectomy, *DR* disease recurrence, *DP* disease progression, *OM* overall mortality, *CSM* cancer-specific mortality, *NMIBC* non-muscle invasive bladder cancer, *MIBC* muscle invasive bladder cancer, *UCB* urothelial carcinoma of bladder, *LNM* lymph node metastasis

Conversely, p21 expression alone was not an independent predictor of outcomes in the subgroup of patients with pT1 disease [158], suggesting that p21 does not predict outcomes in NMIBC.

The product of the p27, a member of the Cip/Kip family of Cdk inhibitors, prolongs cell cycle arrest in the G1 phase. Though in NMIBC, p27 has been found to have only limited predictive value, in patients with MIBC treated with RC, p27 significantly improved prediction of disease recurrence and cancer-specific mortality [158]. No prospective validation however has confirmed the ability of this marker to improve prediction of disease status after RC.

Cyclin E1 is the predominant regulatory protein determining rates of cell-cycle transition from the G1 to S phase, thereby thus affecting oncogenesis [166, 167]. Cyclin E1 expression was significantly decreased in patients with advanced pathologic stage, LVI, metastases to regional lymph nodes, and cancer-specific mortality in both TUR and RC specimens. The role of cyclins is currently evaluated in prospective multicenter studies.

9.3.1.4.2 Apoptosis

Apoptosis, or programmed cell death, is a complex and highly regulated process comprising a series of coordinated steps resulting in cell death [168].

Activated caspase-3 is a protease that constitutes an important downstream step in both the intrinsic and extrinsic apoptotic pathways and promotes apoptosis by cleaving multiple cellular components [169]. The prognostic value of this biomarker is controversial [170–172]. In a most recent study evaluating the combined effect of apoptotic markers on oncologic outcomes in 226 patients treated with RC, Karam et al. demonstrated that altered caspase-3 expression was associated with features of biologically and clinically aggressive disease and independently predicted cancer-specific mortality after RC [172].

Survivin is a member of the Inhibitor of Apoptosis family, and its overexpression inhibits extrinsic and intrinsic pathways of apoptosis, by blocking downstream caspase activity [173]. Survivin represents a promising marker in UCB outcome prediction since it has been shown that overexpression is associated with cancer presence and features of aggressive disease [174–176], as well as disease recurrence and cancer-specific mortality [177, 178]. Survivin is an attractive target for therapy in UCB [168], because of its selective and substantial upregulation in UCB and its causal role in cancer progression [179]. In addition, recently, survivin expression has been associated with disease recurrence in NMIBC [180].

9.3.1.4.3 Angiogenesis

Angiogenesis is a critical event in the initiation and progression of solid malignancies. Traditionally, angiogenesis has been quantified by microvessel density (MVD: >100 microvessels per hpf) [181]. Bochner et al. reported that high MVD were associated with higher disease recurrence and cancer-specific mortality after RC [182]; however, others did not confirm these results [183–185]. Reasons for that may be found in differences in staining and scoring protocols as well as variability in MVD due to tumor heterogeneity.

Thrombospondin-1 is a glycoprotein of the extracellular matrix that has been implicated in the regulation of cell growth and proliferation, thus a potent inhibitor of angiogenesis. Altered thrombospondin-1 expression was independently associated with an increased risk of disease recurrence and all-cause mortality [186]. However, the prognostic value of thrombospondin-1 was not independent of p53 expression status [185].

Due to the complexity of the molecular abnormalities in UCB, it is unlikely that a single biomarker can accurately differentiate tumors of similar clinicopathologic phenotypes into precise prognostic categories. Therefore, combinations of independent, complementary biomarkers may provide a more accurate prediction of outcome compared to any single biomarker [155, 158, 187, 188]. Recently, Lotan et al. investigated prospectively a panel of biomarkers in 216 patients with high-grade UCB treated with RC between 2007 and 2012 [189]. Expression of p53, p21, p27, cyclin E1, and Ki-67 was altered in 54 %, 26 %, 46 %, 15 %, and 75 % patients, respectively. In a multivariable analysis, the number of altered biomarkers remained an independent predictor of disease recurrence and cancer-specific mortality. Future investigations should focus on

promising biomarker combinations that encompass a variety of different pathways in order to increase the predictive value and possibility for targeted therapy. Critical to the adoption of any marker/marker panel will be prospective validation that clarifies the clinical usefulness in predicting postoperative behavior.

9.3.2 Prediction Tools

9.3.2.1 Postoperative Prediction Tools for Disease Recurrence and Survival After Radical Cystectomy

9.3.2.1.1 Nomograms

Several nomograms after RC have been developed to predict the natural history of surgically treated UCB and thus to help in the decision-making process regarding the use of adjuvant therapy (Table 9.5) [4–6]. The Bladder Cancer Research Consortium (BCRC) developed three nomograms to determine the probabilities of disease recurrence, cancer-specific and all-cause mortality at 2, 5 and 8 years after RC (Fig. 9.2; available at www.nomogram.org) [5, 6]. The disease recurrence nomogram showed a 78 % accuracy and comprised pathologic features such as T and N stages, pathologic grade, presence of LVI and CIS at RC, as well as the administration of chemotherapy (either neoadjuvant, adjuvant or both), and/or radiation. The predictive accuracy of the nomograms for cancer-specific and all-cause mortality nomogram were 78 % in 73 %, respectively.

In the same year, the International Bladder Cancer Nomogram Consortium (IBCNC) published a postoperative nomogram predicting the 5-year risk of disease recurrence following RC and pelvic lymph node dissection (available at www.nomograms.org) based on the data of more than 9,000 patients from 12 centers (including the BCRC) [4]. The nomogram included significant features such as age, gender, grade, pathologic stage, histologic type, lymph node status, and time from diagnosis to surgery. The predictive accuracy of the nomogram was 75 % and statistically superior to the AJCC TNM staging (68 %) or the standard pathologic grouping models (62 %). Interestingly, based on the same patient data, Vickers et al. have demonstrated in a decision analysis approach that a nomogram cutoff outperformed pathologic stage for decision-making regarding chemotherapy. Thus the authors concluded that referring patients to adjuvant chemotherapy on the basis of a multivariate model is likely to lead to better patient outcomes than the use of pathologic groups.

Recently, Xylinas et al. developed competing-risk, probability nomograms that predict disease recurrence and cancer-specific survival of chemotherapy-naive pT1-3 N0 UCB patients ($n=2{,}145$). With a median follow-up of 45 months, the 5-year disease recurrence-free and cancer-specific survival estimates were 68 and 73 %, respectively.

In contrast, Rink et al. developed two nomograms predicting disease recurrence and cancer-specific mortality based on 381 patients with nodal metastases from a multi-institutional cohort of 4,335 patients with UCB treated with RC and lymphadenectomy without preoperative chemo- or radiotherapy. Including gender, tumor stage, STSM, lymph node density, and administration of adjuvant chemotherapy, the model showed a predictive accuracy for disease recurrence-free and cancer-specific survival of 63 and 66 %, respectively.

9.3.2.1.2 Other Prediction Tools

Bassi et al. developed an ANN utilizing gender, several pathologic features, and history of upper tract UC as input variables for prediction of 5-year all-cause survival after RC [190]. In a single institution cohort of 369 patients, the prognostic accuracy of the ANN (76 %; based on 12 variables) was slightly superior to the logistic regression model that was based on only two statistically significant variables (75 %; stage and grade). Unfortunately, the comparison of the accuracy of both models was performed on the same population.

A promising Artificial Intelligence model, a neurofuzzymodel (NFM), to predict disease recurrence following RC and PLND was elegantly developed by Catto et al. Therefore, 609 patients with organ-confined disease and no lymph node metastases were identified. Two NFM were trained, tested, and validated to predict the risk of

Table 9.5 Available prediction tools in bladder cancer after radical cystectomy

Post-cystectomy tools							
Reference	Prediction form	Patient population	Endpoint/Outcome	No. of pts.	Variables	Accuracy	Validation
Karakiewicz et al. [5]	Probability nomogram	Radical cystectomy	2, 5 and 8 year RFS	731	Age, T-stage, N-stage, pathologic grade, LVI, CIS, adjuvant radiotherapy, adjuvant chemotherapy, neoadjuvant chemotherapy	78 %	External
Shariat et al. [126]	Probability nomogram	Radical cystectomy	2, 5, 8 year CSM and overall survival	731	Age, T-stage, N-stage, pathologic grade, LVI, adjuvant radiotherapy, adjuvant chemotherapy, neoadjuvant chemotherapy	79 % (ACS) 73 % (CSS)	External
Bochner et al. [4]	Probability nomogram	Radical Cystectomy	5 year RFS	9,064	Age, gender, tumor stage, Nodal status, grade, histology, time from diagnosis to surgery	75 %	External
Shariat et al. [188]	Probability nomogram	Radical cystectomy pTa-3N0M0	2, 5, 8 year RFS and CSM	191	p53, p21, pRB, p27, cyclin E1, gender, age, pathologic stage, grade, LVI, concomitant carcinoma in situ	83.4 % (RFS) 86.9 % (CSS)	Internal
Xylinas et al. [7]	Probability nomogram	Radical cystectomy pT1-3 pN0	2, 5 and 7 year RFS and CSM	2,145	T-stage, STSM, and LVI	2, 5 and 7-year RFS: 67 %, 65 % and 64 %, respectively 2, 5 and 7-year CSS: 69 %, 66 % and 66 %, respectively	External
Rink et al. [195]	Probability nomogram	Radical cystectomy with pN1.	2 year RFS and CSM	381	Gender, tumor stage, STSM, lymph node density, adjuvant chemotherapy	63 % (RFS) 66 % (CSS)	Internal
Bassi et al. [190]	Artificial neural network	Radical cystectomy	5 year all cause survival	369	Age, gender, T stage, N stage, grade, LVI, grade, concomitant prostate cancer, history of upper tract UC	76 %	Internal
Catto et al. [191]	Neuro-fuzzy modeling	Radical cystectomy	2 and 5 year RFS	609	Gender, tumor stage, tumor grade, concomitant CIS, lymphovascular invasion (LVI), margin status, administration of chemotherapy	84 %	Internal
Sonpavde et al. [212]	Risk stratification	Radical cystectomy	5 year RFS and all cause survival	707	Gender, grade, LVI, number of lymph nodes, age	68 %	Internal
Sonpavde et al. [213]	Risk stratification	Radical cystectomy	5 year RFS and all cause survival	578	Age, grade, gender, LVI, STSM, number of lymph nodes, decade	66 %	External

(continued)

Table 9.5 (continued)

Post-cystectomy tools							
Reference	Prediction form	Patient population	Endpoint/Outcome	No. of pts.	Variables	Accuracy	Validation
Gakis et al. [97]	Risk stratification	Radical cystectomy	3 year CSM	246	T-stage, lymph node density, STSM, CRP level	79 %	Internal
Todenhoefer et al. [199]	Risk stratification	Radical cystectomy	3 year CSM	258	T-stage, STSM, thrombocytosis	75 % (CSS)	Internal
Shariat et al. [70]	Nodal Staging Score	Radical cystectomy	Lymph node metastasis at radical cystectomy	4,335	Number of lymph nodes removed, number of positive lymph nodes, T-stage, LVI		Internal

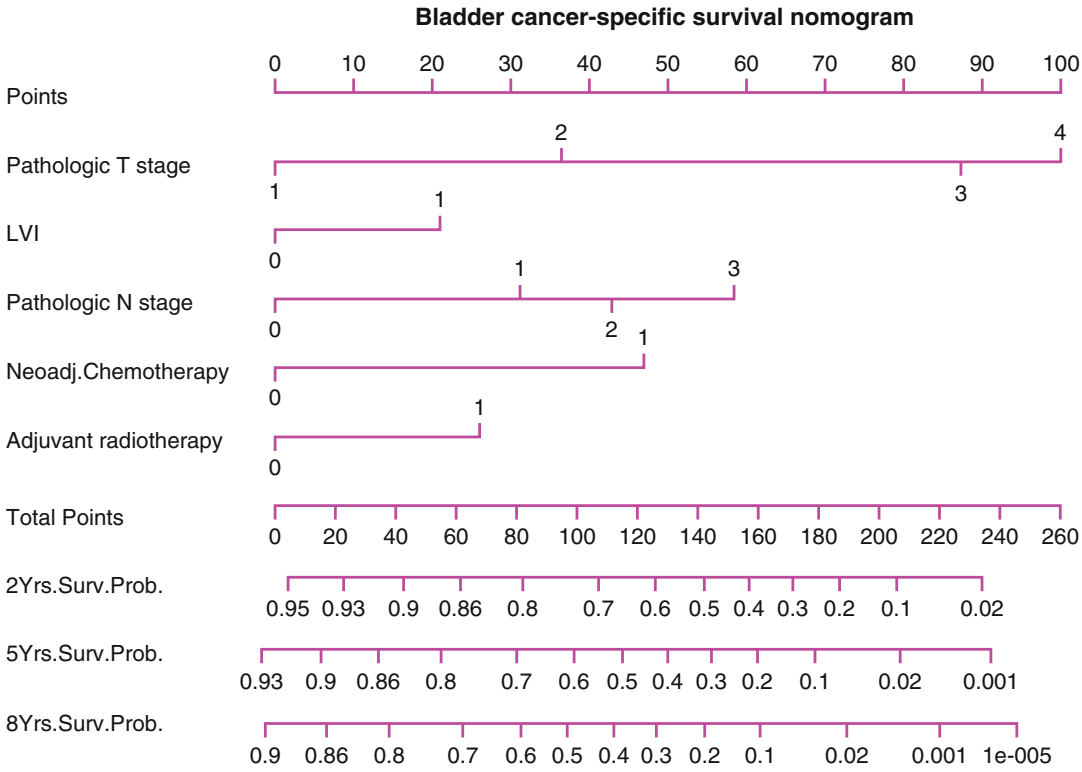

Fig. 9.2 Bladder cancer-specific survival nomogram in 731 patients treated with radical cystectomy and bilateral lymphadenectomy for urothelial carcinoma of the bladder. Instructions for nomogram use: Locate patient values at each axis. Draw a vertical line to the "Point" axis to determine how many points are attributed for each variable value. Sum the points for all variables. Locate the sum on the "Total Points" line. Draw a vertical line toward the "2Yrs.Surv.Prob.," "5Yrs.Surv.Prob.," and "8Yrs.Surv.Prob." axes to determine, respectively, the 2-year, 5-year, and 8-year survival probabilities. Adapted from Shariat et al. Clin Cancer Res 2006;12:6663

disease recurrence after RC, thus the model showed a predictive accuracy of 84 % [191].

Gakis et al. developed a risk-score model predicting the 3-year cancer-specific survival by including significant pathologic features such as higher tumor stage, positive STSM, higher lymph node density, and elevated CRP levels [97]. The accuracy of this model was 79 %. The same study group developed a similar risk-score predicting the 3-year cancer-specific survival based on pathologic features (tumor stage, STSM) and thrombocytosis with a 75 % accuracy [102].

Recently, Shariat et al. developed a model (pathologic Nodal Staging Score) to estimate the probability that a pathologic node-negative UCB patient is indeed free of lymph node metastasis. To this end, the authors analyzed data of 4,335 patients treated with RC and bilateral lymph node dissection. Based on the number of lymph nodes examined and pathologic features, they demonstrated that the probability of missing a positive node decreases with the increasing number of nodes examined. Furthermore, the probability of having a positive node increased proportionally with advancing pathologic T stage and LVI.

9.3.2.1.3 Nomograms Including Novel Biomarkers

Only few studies have demonstrated a significant improvement in predictive accuracy, when biomarkers were added to established predictors in the predictive tool setting [172, 188, 192, 193]. One of these studies, for example, demonstrated in 191 pTa-3N0M0 patients following RC that the addition of a panel of five well-established cell

cycle regulatory biomarkers (p53, pRB, p21, p27, and cyclin E1) improved the predictive accuracy of competing-risk nomograms and survival in these patients. In comparison, two smaller studies have added biomarkers to standard clinicopathologic features using pre-cystectomy prediction tools (ANN and neuro-fuzzy modeling) [192, 193]. Prediction tools such as these that incorporate pathologic and molecular information could form the basis for counseling patients regarding their risk of disease recurrence following surgery and for designing clinical trials to test adjuvant treatment strategies in high-risk patients.

Several limitations of nomograms and other prediction tools to patient risk stratification should be noted. First, and foremost, their retrospective nature of data accrual and the fact that all currently available predictive tools in UCB are not perfectly accurate. Furthermore, all available nomograms and predictive tools were derived and are applicable to centers of excellence for bladder surgery, thus the general applicability requires additional validation. The fundamental issue raised by opponents of predictive tools is regarding their utility. Indeed, to date, there are no prospective randomized studies that clearly demonstrate improving patient care by using prediction tools. However, despite these limitations, nomograms and prediction tools provide optimum accuracy for individualized evidence-based decision-making process of UCB.

9.3.2.1.4 Prediction models using genomic data

Recently, there have been published studies on using genomic data sets. It is likely that future prediction models will rely on biology from these types of cellular interrogations.

Developed a gene expression model predicting the response to M-VAC chemotherapy based on TUR tumor biopsy materials from 27 patients with T2a-T3bN0M0 UCB who were expected to undergo RC as a primary treatment using a cDNA microarray comprising of 27,648 genes [212] .

The authors found 14 genes that were expressed differently between nine responder (downstaging after 2 courses of MVAC, ≤pT1 or ≤T1) and 9 non-responders (upstaging after 2 courses of MVAC, ≥pT2 or ≥T2). Based on these gene expression profiles a prediction scoring system for chemosensitivity was established. The study is limited by the small dataset and needs to be prospectively validated. Further refinement is needed in the clinical laboratory setting to bring this test to routine clinical use.

Smith et al. developed a 20-genes model based on the expression of TUR- tumor tissue to predict the risk of lymph node invasion in clinically lymph node negative MIBC patients prior to RC [213]. A training dataset of 156 patients from two independent centers was used to develop the gene expression model and determine cutoffs for lymph node metastasis. External validation was performed on 185 patients from a prospective randomized phase 3 trial evaluating two different adjuvant chemotherapy regimens. The gene expression model demonstrated 67% (AUC) discrimination for discriminating lymph node negative and positive patients in the validation cohort. Although the gene model was externally validated on a prospective cohort, the clinical assay has not undergone analytic validation yet.

9.4 Metastatic and Recurrent Bladder Cancer

9.4.1 Prognostic Factors

Patients with UCB who experience disease recurrence after RC and those with metastatic disease have very poor outcomes. Despite advances in surgical techniques and systemic chemotherapies [124, 126, 194], the majority of patients will die from UCB within 1 year after disease recurrence and only few patients survive beyond 2 years after disease recurrence [195]. Modern salvage chemotherapies may prolong survival if a patient responds; however, cure is very rare [196, 197], thus underscoring the lethal nature of UCB once the disease recurs and becomes systemic [124, 126, 194]. While the natural history of UCB from RC to disease recurrence has been intensively investigated [4–6], that of patients who experience disease recurrence after RC and/or have metastatic disease is still poorly understood. Accurate prediction of clinical outcomes after disease recurrence could help in patient counseling

and clinical trial design and analysis. There are only a few studies that analyzed prognostic factors for outcomes in UCB patients with disease recurrence after RC and/or metastatic disease.

9.4.1.1 Time from Radical Cystectomy to Disease Recurrence

Recently, several study groups found that in patients who experience disease recurrence, the median time from RC to disease recurrence was less than 12 months [198–200]. Mitra et al. reported that a time to disease recurrence <12 months is associated with worse outcomes in patients with UCB [198]. Rink et al. confirmed that time from RC to disease recurrence is a strong predictor of survival after disease recurrence [195]. The shorter the time from surgery to disease recurrence, the shorter is the survival time. Interestingly, the 1-year risk of cancer-specific mortality after disease recurrence disproportionately improved in patients experiencing disease recurrence after 12 months. In other words, while even after 12 months it remained true that the shorter the time to disease recurrence the faster the mortality, the change in rate becomes less significant if the time to disease recurrence is more than 12 months.

The time to disease recurrence may be considered as a surrogate for the burden of disease thus suggesting that patients with a shorter time to disease recurrence had occult metastatic disease that became clinically evident faster. Therefore, the time to recurrence should be considered as a valuable predictor for outcome prognostication in patients treated with RC and experienced disease recurrence.

9.4.1.2 Pathologic Factors

Several established pathologic characteristics such as non-organ-confined pathologic stage, lymph node metastasis and positive soft tissue surgical margin as well as the clinical factors such as advanced age and female gender have previously been shown to be significantly associated with survival outcomes in patients treated with RC and LND [4, 76, 124, 126, 131, 194, 201]. Moreover, a recent study has found these factors to predict cancer-specific mortality even after disease recurrence [195]. That said, it seems reasonable that the more biologically aggressive the disease, the faster the disease may recur.

Pathologic stage and nodal status are still the most well established independent predictors for outcomes [202, 203]. Notably, these factors cannot only help in outcome prediction after RC, but should also be taken into consideration for decision-making in regards of patient counseling and risk stratification after disease recurrence. Unfortunately, most studies investigating metastatic UC patients [204–207], fail to evaluate pathologic factors and/or are unable to assess time to disease recurrence. They are inherent to the multicenter and retrospective design including a lack of data regarding a possible delay between diagnosis and surgery due to patient preferences and comorbidities.

9.4.2 Prediction Tools

Bajorin et al. reported that two risk factors, a poor Karnofsky performance status (KPS) and the presence of visceral metastases (Bajorin criteria), can stratify patients with non-resectable or metastatic urothelial carcinoma into separate risk groups with regards to overall mortality [204]. This and other studies [96, 205] suggest that comorbidities are important and should be taken into account for predicting survival in both localized and metastatic UCB. Recent studies confirmed that not only the presence, but the number [199, 200] and location [199] of visceral metastasis can predict outcomes in patients who experienced disease recurrence after RC.

Though the Bajorin risk grouping has been validated in the setting of prospective randomized trials [205, 206], since then in 1999, this risk stratification has been the only prediction model available for patients with metastatic UCB. In addition, Bajorin et al.'s and the following studies included a selected group of patients who were eligible for inclusion in these trials (i.e., receiving chemotherapy), possibly introducing a selection bias. Moreover, the patients included in these studies present a heterogeneous cohort with unresectable and/or metastatic UC at presentation of both the lower and upper urinary tract.

Recently, Apolo et al. developed a model that predicts overall survival in 308 metastatic UC patients receiving a cisplatin-based chemotherapy on seven prospective phase II trials and compared this model with the Bajorin risk model [207]. The final model included four variables, namely the presence of visceral metastases, KPS, albumin, and hemoglobin. Comparison of both models to the patient cohort resulted in a favorable discrimination for the new developed model with four variables (c-index: 0.67 vs. 0.63). The objective of the developed nomogram was to predict the 1-, 2-, and 5-year overall survival and to improve accuracy over the prognostic MSKCC (Bajorin) prediction model. That said, the two additional markers are controversially discussed. Hypoalbuminemia is controversial due to its long half-time and the potential impact of systemic factors such as inflammation and stress on serum albumin [103]. However, preoperative albumin is associated with a higher risk of overall survival in UCB patients after RC [104]. Though anemia is a variable associated with cancer-specific survival [208], hemoglobin levels of cancer patients may be confounded by administration of blood transfusions or erythropoietin substitution [209]. However, the authors could not control for these factors due to the study's retrospective character. Galsky et al. recently published a similar pretreatment nomogram based on 399 UC patients who received a first-line cisplatin-based chemotherapy [210]. However, in both studies, all patients were receiving a cisplatin-based chemotherapy and had a larger burden of metastasis compared to our study.

Nakagawa et al. have recently developed a risk model to predict survival in patients with disease recurrence after RC which was based on four factors: time to recurrence, symptoms of recurrence, number of metastatic organs, and CRP level. However, this study was clearly limited by its small number of patients ($n = 114$) and single-center character. The 1-year cancer-specific free survival of this cohort was 89 %, 30 %, and 12 % for patients with favorable (0–1 risk factors), intermediate (2 risk factors) and poor risk (3–4 risk factors). The clinical benefit of this risk stratification needs to be assessed using c-index and longer datasets.

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