Staging and Staging Errors in Bladder Cancer

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Abstract

Context: The staging of bladder cancer (BCa) is crucial for optimal management of the disease. The staging process is known to be challenging and fraught with errors.
Objective: Our aim was to present current BCa grading and staging systems and to review the crucial steps of the staging process. Sources of errors and pitfalls in the staging process are also discussed.
Evidence acquisition: A comprehensive literature review was performed to identify relevant original articles, review articles, and clinical guidelines in the field of BCa staging.
Evidence synthesis: Staging error is extremely common with reported upstaging in up to 40% of patients. Sadly, little, if any, improvements have been reported during the past two decades. Quality of the transurethral resection of bladder tumor (TURBT) and pathologic evaluation of resected tissue by a specialized uropathologist is the cornerstone of BCa staging. In addition to primary resection, restaging transurethral resection is indicated in high-risk noninvasive cancers and also if incomplete resection is demonstrated or suspected. The accuracy of traditional imaging studies (computed tomography [CT], magnetic resonance imaging [MRI]) is of limited value both in the staging of the primary tumor and nodal status. Novel imaging studies, such as positron emission tomography–CT and USPIO (ultra–small-particle superparamagnetic iron oxide)–MRI are promising modalities and may improve the accuracy of imaging in the future. Nomograms provide some additional information, but novel variables, such as molecular markers, are needed to improve the accuracy of risk-stratification models.
Conclusions: Incorrect clinical staging and especially understaging is a serious problem in BCa, and improvements in all steps of the staging process are needed to achieve more accuracy and improved care for BCa patients.

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1. Introduction

Bladder cancer (BCa) is a heterogeneous disease with a variable natural history. Approximately 70–80% of patients present with noninvasive (pTa) or superficially invasive (pT1) tumors at the time of initial diagnosis; the remaining 20–30% initially present with muscle-invasive tumors (pT2–4) [1]. Correct histologic grading and tumor staging is crucial for proper and optimal patient management. The cornerstone of BCa diagnosis, treatment, and staging is a high-quality transurethral resection of bladder tumor (TURBT). Although staging is quite straightforward in low-grade noninvasive lesions, the staging of high-grade and higher stage lesions is difficult because errors are not uncommon. Upstaging at the time of radical cystectomy (RC) is reported in approximately 40% of clinically localized cases, and the rate of downstaging is approximately 20% [2]. Unfortunately, there has been no evidence of improved staging accuracy during the last 25 yr. In fact, the rate of upstaging has been reported to have even increased [2]. In terms of staging, the most challenging cases are T1 lesions and accurate staging prior to RC for advanced disease, especially if neoadjuvant chemotherapy is considered. Furthermore, the issue of micrometastatic disease to the nodes is also very important because it directly affects patient survival. As such, imaging studies play an important role in the staging of invasive BCa.

The purpose of this review is to present the staging and grading systems and to review the methods used to accurately stage urothelial lesions of the urinary bladder. In addition, the most common pitfalls and sources of staging errors are discussed.

2. Evidence acquisition

Data were acquired by PubMed medical literature research using the following terms: bladder cancer/neoplasm and staging, transurethral resection, TUR, TURBT, restaging TUR, CT, MRI, PET, and/or nomogram. Only publications in English were included in the search, and animal studies were excluded. Relevant original articles and review papers were used to identify missed publications.

3. Evidence synthesis

3.1. Bladder cancer grading and staging systems

3.1.1. Grading systems

Histologic grade is the most important risk factor for progression of non–muscle-invasive tumors [3]. Table 1 presents the World Health Organization (WHO) 1973 and the WHO/International Society of Urological Pathology 2004 histologic classification systems. The new system was developed to avoid the problems clinicians encountered with the WHO 1973 grade 2 tumors because it was associated with a high interobserver variation [4]. Although both systems are three tiered with regard to papillary lesions, it should be emphasized that the two are not directly analogous. WHO 1973 grade 1 will be either an urothelial neoplasm of low malignant potential or low grade, and grade 2 will be either low or high grade [5].

Recently, these grading systems have been compared in two separate papers studying interobserver [6] and both inter- and intraobserver variability [7]. In addition, the outcome of the retrospective patient cohorts was analyzed according to both systems. May et al found that both systems suffer from interobserver variability, but it is less in the WHO 2004 system [6]. In the study by van Rhijn and colleagues, the difference of interobserver variability between the systems was less marked [7]. Interestingly, the “mean grade” of individual pathologists varied significantly and was linked to the risk of progression [7].

Some advocate the simultaneous use of both systems, for example the European Association of Urology (EAU) Guidelines [8]; others have recommended using only the WHO 2004 system [9]. We believe the systems are complementary and it is beneficial for clinicians to receive information based on both classifications, although this may not always be easy to achieve on a practical basis.

3.1.2. Staging systems

The TNM staging system, presented in Table 2, is the most common. Although the system is widely used, there has been an ongoing discussion about some of the categories.

T1 tumors have a markedly variable prognosis and are a constant challenge for clinicians. To aid in clinical decision making, several attempts to improve the T1 category have been carried out. Proposed T1 substaging methods include the following: (1) depth of invasion in relation to the muscularis mucosae layer [10–12], (2) measured depth of invasion (1.5-mm invasion as a cut-off) [13], and (3) extent of invasion (focal vs extensive) [14,15]. Although T1 substaging is obviously needed, and depth and extent of invasion are especially promising methods of substaging, none of the methods has been widely accepted and recognized in the guidelines to date.

Several groups have questioned substaging T2 into T2a (invasion of <50% of the detrusor muscle) and T2b (invasion of >50% of the detrusor muscle) because they found no difference in the prognosis of T2a versus T2b patients when analysis was controlled for nodal status [16–18]. Interestingly, Chen et al found pT2 tumor size (cut-off: 3 cm) to be an independent predictor of disease recurrence [18]. Similarly, T3 substaging into T3a (microscopic perivesical invasion) and

| Table 1 – Histologic classification of urothelial (transitional cell carcinomas) |
|------------------------------------------|-----------------|
| WHO/ISUP 2004 [60]                      | WHO 1973 [61]   |
| Flat lesions with atypia                | In situ carcinoma |
| In situ carcinoma                       | Papilloma       |
| Papillary lesions                       | Papilloma       |
| Papilloma                               | Grade 1, well differentiated |
| UNLMP                                   | Grade 2, intermediate differentiation |
| Papillary carcinoma, low grade          | Grade 3, poorly differentiated |
| Papillary carcinoma, high grade         |                  |

ISUP = International Society of Urological Pathology; UNLMP = urothelial neoplasm of low malignant potential; WHO = World Health Organization.
Indeed, in a study of 248 node-positive patients, Kassouf et al demonstrated that lymph node density (ie, the ratio of positive nodes to total number of removed nodes) has been presented to overcome these problems. Another recently presented nodal staging system is “aggregate metastatic lymph node diameter,” which was an independent prognostic factor for disease recurrence in a single study. Additional studies are needed to confirm this finding [26].

### Table 2 – TNM staging system of bladder cancer [62]

<table>
<thead>
<tr>
<th>Description</th>
<th>T: Primary tumor</th>
<th>N: Lymph nodes</th>
<th>M: Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor cannot be assessed</td>
<td>Lymph nodes cannot be assessed</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td>No regional lymph node metastasis</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>Ta</td>
<td>Noninvasive papillary tumor</td>
<td>Metastasis in single node ≤2 cm</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ, “flat tumor”</td>
<td>Metastasis in single node ≤2 cm</td>
<td>–</td>
</tr>
<tr>
<td>T1</td>
<td>Invades subepithelial connective tissue</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>T2</td>
<td>T2a Invades inner half of muscle layer</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>T2</td>
<td>T2b Invades outer half of muscle layer</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>T3</td>
<td>T3a Invades perivesical tissue microscopically</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>T3</td>
<td>T3b Invades perivesical tissue macroscopically</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>T4</td>
<td>T4a Invades prostate or uterus/vagina</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>T4</td>
<td>T4b Invades pelvic or abdominal wall</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td>Node density [23,24]</td>
<td>–</td>
</tr>
<tr>
<td>N1</td>
<td>Single (≤2 cm) multiple nodes (&lt;2 cm) affected</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>N2</td>
<td>Single (2–5 cm) multiple nodes (&lt;5 cm) affected</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in node &gt;5 cm</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>Nx</td>
<td>Lymph nodes cannot be assessed</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>Mx</td>
<td>Distant metastasis cannot be assessed</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td>Aggregate lymph node metastasis diameter [26]</td>
<td>–</td>
</tr>
</tbody>
</table>

T3b (macroscopic perivesical invasion) is questioned because there seems to be no difference in the prognosis if node status is controlled in the analysis [19–21]. Although one may speculate that when analyzing larger cohorts of patients, studies would be powered to detect significant differences between T2 and T3 substaging, according to available reports, it would seem reasonable to simplify the T staging by abandoning the T2/T3 substaging.

The TNM nodal staging takes the number and size of the affected nodes into account, but this substaging is rarely used in the BCa literature, and in most publications, only node positivity/negativity rate is reported. Another problem with the TNM staging is the fact that it does not take the extent of node dissection into account, a factor that has been demonstrated to be of great importance [22]. The concept of node density (ie, the ratio of positive nodes to total number of removed nodes) has been presented to overcome these issues [23,24]. Indeed, in a study of 248 node-positive patients, Kassouf et al demonstrated that lymph node density of 20% is superior to TNM nodal staging in predicting disease recurrence [25]. Another recently presented nodal staging system is “aggregate metastatic lymph node diameter,” which was an independent prognostic factor for disease recurrence in a single study. Additional studies are needed to confirm this finding [26].

### 3.2. Primary tumor and upper urinary tract staging

#### 3.2.1. Transurethral resection of bladder tumor

The two ultimate goals of TURBT are (1) removal of all cancerous tissue (if technically feasible) and (2) obtaining good quality tissue to allow accurate pathologic grading and staging [27]. For the procedure, the patient needs to be under adequate anesthesia, and a meticulous inspection of the urethra and bladder should be done prior to resection to identify all suspicious lesions. Small (up to 1 cm) lesions may be resected en bloc, but larger lesions are resected in sections, and the bulk of the tumor and tumor base including margin of normal-appearing tissue are sent to the pathologist in separate containers [8,28,29]. If multiple tumors are resected, the pathologist should also analyze them separately. Apart from tiny, obviously noninvasive lesions, muscle should be included in the resection specimen. Electrocautery should be kept at a minimum to avoid tissue artifacts. All suspicious areas should be biopsied, but random biopsies of normal-appearing urothelium are of limited value [27]. Prostate sampling (resection loop biopsy) should be obtained if the prostatic urethra appears suspicious or if the bladder tumor seems macroscopically invasive and RC is the likely next step (also at the time of the re-resection of a high-grade lesion) [27,30]. Although modern imaging has diminished its importance, bimanual palpation should be done after the resection. If the tumor is palpable after TURBT, the tumor is staged as cT3 (or as cT4 if the bladder is fixed).

Several novel techniques have been introduced to improve cystoscopy and TURBT. Photodynamic diagnosis (fluorescence cystoscopy) uses fluorescence within tumor cells to improve detection of bladder lesions. The most widely used fluorescence agents include 5-aminolevulinic acid and, most recently and successfully, hexyl ester hexaminolevulinate [31]. Photodynamic diagnosis (PDD) is demonstrated to aid in the detection of bladder lesions, especially carcinoma in situ (CIS) lesions, and to aid in achieving complete TURBT [32,33]. Apart from these advantages, the value of PDD in BCa staging is most likely limited because invasive tumors are rarely missed with normal white light. Other novel techniques in the field...
of bladder tumor detection include optical coherence tomography, narrow band imaging, and confocal laser endomicroscopy [34–36]. Although promising, these techniques need further studies and should be considered experimental for the time being.

3.2.2. Restaging transurethral resection of bladder tumor

Numerous papers have highlighted the importance of restaging TURBT in selected patients. The rationale for restaging TURBT derives from studies demonstrating residual tumor in 20–78% of patients with Ta/T1 tumors [37–39]. In addition, upstaging and significant change in the treatment paradigm is common. Upstaging Ta to T1 or higher lesions has been reported in 8–33% of cases, and upstaging of T1 lesions to muscle-invasive cancer has been reported in 2–28% of cases [38,39]. In T1 lesions, upstaging is more prevalent if the primary resection did not include muscle in the specimen [40]. In addition to more accurate staging, patients undergoing re-TURBT have been reported to have a lower risk of recurrence and to have a better response to bacillus Calmette-Guérin [39,40]. According to the EAU guidelines, re-TURBT should be considered (1) in all T1 lesions, (2) if muscle layer is not identified in the specimen, (3) if primary resection was incomplete, or (4) in bulky or multiple tumors [8]. Re-TURBT is usually performed 2–6 wk after primary resection, and it should include resection of the primary tumor site and biopsy of all suspicious areas. Prostatic biopsy should also be considered [8].

3.2.3. Imaging

Proper TURBT (and restaging TURBT in selected cases) allows differentiation between Ta versus T1 versus muscle-invasive tumors. Further staging of muscle-invasive lesions before definitive treatment is important, albeit challenging. Abdominal and pelvic CT is the most commonly used imaging modality. Unfortunately, CT (and also MRI) is unable to differentiate the different layers (lamina propria, superficial and deep muscle) of the bladder, and clinical staging of T1 versus T2a versus T2b is rarely possible [41]. Differentiation between T2 and T3a tumors is also not possible in most cases because modern imaging technology is unable to detect the microscopic extravesical extension [41]. In contrast, T3b (macroscopic extravesical invasion) may be detected as irregularity, stranding, or nodularity of the bladder wall [41]. Invasion to adjacent organs (T4a/b) may be detected easily in bulky tumors, but local extension into prostate/semenal vesicles/vagina/uterus may be missed because normal anatomic planes are not always appreciated. Also, if imaging is done after TURBT, postoperative reactions are difficult to differentiate from residual cancer [42]. Table 3 summarizes the staging accuracy of CT and MRI.

### Table 3 – Accuracy of different imaging modalities in bladder cancer staging

<table>
<thead>
<tr>
<th>Modality</th>
<th>Overall accuracy, %</th>
<th>Understaging, %</th>
<th>Overstaging, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary tumor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>55</td>
<td>39</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
<td>[63]</td>
</tr>
<tr>
<td>MRI</td>
<td>83</td>
<td>NR</td>
<td>16</td>
<td>87</td>
<td>91</td>
<td>-</td>
<td>[67]</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>25</td>
<td>26</td>
<td>100</td>
<td>76</td>
<td>-</td>
<td>[65]</td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>NR</td>
<td>32</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
<td>[68]</td>
</tr>
<tr>
<td></td>
<td>68</td>
<td>26</td>
<td>5</td>
<td>80</td>
<td>79</td>
<td>-</td>
<td>[69]</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>NR</td>
<td>7</td>
<td>NR</td>
<td>NR</td>
<td>-</td>
<td>[66]</td>
</tr>
<tr>
<td><strong>Nodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>70–97</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>[70–72]</td>
</tr>
<tr>
<td>MRI</td>
<td>73–98</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MRI-USPIO</td>
<td>95</td>
<td>2</td>
<td>11</td>
<td>96</td>
<td>95</td>
<td>-</td>
<td>[48]</td>
</tr>
<tr>
<td>PET</td>
<td>90</td>
<td>NR</td>
<td>NR</td>
<td>50</td>
<td>100</td>
<td>-</td>
<td>[73]</td>
</tr>
<tr>
<td>PET</td>
<td>89</td>
<td>11</td>
<td>0</td>
<td>63</td>
<td>100</td>
<td>-</td>
<td>[74]</td>
</tr>
<tr>
<td>PET</td>
<td>88</td>
<td>9</td>
<td>29</td>
<td>70</td>
<td>94</td>
<td>-</td>
<td>[47]</td>
</tr>
<tr>
<td>PET</td>
<td>84</td>
<td>16</td>
<td>15</td>
<td>46</td>
<td>97</td>
<td>-</td>
<td>[46]</td>
</tr>
</tbody>
</table>

BCa = bladder cancer; CT = computed tomography; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; NR = not reported; PET = positron emission tomography; USPIO = ultrasmall particle superparamagnetic iron oxide.
MRI. When comparing CT with MRI techniques, MRI seems clinically better with a reported staging accuracy of 62–85% compared with 35–55% in CT studies [41]. It is the modality of choice when staging patients destined to be treated with bladder-sparing modalities. Nevertheless, both overstaging and especially understaging are major problems with both imaging modalities. Because most of the studies were done years ago, it is possible that modern scanners (multi-detector CT scanners, 3-T MRI) might have better staging accuracy, but the data are limited to support this assumption.

Along with the primary tumor, the upper urinary tract (UUT) needs to be evaluated. Because the risk of UUT carcinoma in low-risk noninvasive BCa patients is low (up to 2%), UUT imaging is not considered mandatory [8]. In contrast, the risk of UUT is significantly higher in high-grade and invasive tumors, and imaging is recommended [8]. Although excretory urography is the classic imaging modality, in the case of invasive tumors, it is reasonable to combine the staging of primary tumor and UUT imaging by CT or MRI urography [43]. It is also important to detect possible hydronephrosis because it may have an impact on treatment paradigm and is also known to be a poor prognostic factor [44].

3.3. Staging of lymph nodes

Because in traditional serial imaging (CT, MRI), possible nodal metastasis is evaluated by the nodal size and shape criteria, it is not surprising that these methods are far from perfect in nodal staging, especially in the case of minimal nodal burden (metastasis of <5–8 mm). Using MRI size criteria of 10 mm for oval nodes and 8 mm for round nodes, Jager et al reported a sensitivity of 83% and a specificity of 98% [45]. The sensitivity may be slightly overoptimistic because most of the modern RC series report nodal metastasis in 20–25% of cases with negative clinical staging [22]. The accuracy of nodal staging has been reported in 70–97% of CT studies and 73–98% in MRI studies. The results are directly related to patient selection (eg, incidence of nodal metastasis in study population, rate of bulky nodal metastasis in study population) (Table 3).

To improve the nodal staging accuracy, a few interesting novel techniques have recently been introduced. Positron emission tomography (PET) uses radiolabeled tracers such as fluorodeoxyglucose (FDG) to image tissue metabolic activity. Combined FDG-PET and CT imaging (FDG-PET/CT) is a method to detect both glucose metabolism and anatomic information, and it is a relatively widely accepted novel modality in cancer staging [46]. Reported accuracy for PET staging seems improved when compared with conventional CT and MRI studies, but the risk of understaging is still evident (Table 3). However, the results are also conflicting. Recently, Swinnen et al reported FDG-PET/CT nodal staging accuracy of 84% in 51 patients but failed to demonstrate significant improvement in accuracy compared with CT alone [46]. In contrast, Kibel et al recently published results of 43 BCa patients, and they reported 70% sensitivity and 94% specificity, with PET/CT missing only 3 of 10 patients with nodal metastasis [47]. It should be emphasized that all these patients had negative conventional CT imaging [47].

Ultra–small-particle superparamagnetic iron oxide (USPIO–MRI) uses particles that are ingested by macrophages in normal lymph nodes resulting in low nodal signal intensity. In metastatic node (or metastatic part of node), particles are not concentrated, resulting in high signal intensity and thus allowing, theoretically, the detection of metastasis in normal-size nodes [48]. Several studies have evaluated the value of USPIO-MRI in nodal staging of pelvic malignancies, and encouraging results are reported [48,49]. In BCa, only a few studies are available. In these studies, results are markedly improved when compared with conventional imaging (Table 3). Because USPIO-MRI is more complicated to perform (two MRI imaging studies per patient before and after USPIO injection with a 24–36-h interval), more time consuming, and expertise interpretation is required, further studies are mandatory to validate this interesting and promising imaging modality [50].

The combination of lymphoscintigraphy with CT-enhanced preoperative anatomic localization of sentinel nodes in BCa may aid in the identification of sentinel nodes during surgery. Sherif et al showed that the yield of detected sentinel nodes, both metastatic and nonmetastatic, was markedly increased using the combined method compared with conventional planar lymphoscintigraphy. Six consecutive patients scheduled for RC underwent lymphoscintigraphy after transurethral injection of Albures–technetium 99m in the detrusor muscle peritumorally both with planar imaging and with single-photon emission computed tomography (SPECT)/CT. CT for anatomic fusion was performed directly after the SPECT/CT, and both investigations were combined to a fused image. However this technique is still investigational at this stage [51].

3.4. Staging of distant sites

The most common sites for distant metastasis in BCa are nonregional nodes, liver, and lungs. These sites are examined with abdominal and pelvic MRI or CT and chest imaging with x-ray or CT. EAU guidelines recommend multidetector CT of thorax, abdomen, and pelvis as the optimal staging for confirmed muscle-invasive BCa [52]. Because metastasis to brain and bone is rare at initial presentation, imaging of these sites is not recommended routinely. Routine bone scintigraphy is reported to alter the decision of surgery only in approximately 1% of cases [53].

If clinically indicated (pain, elevated alkaline phosphatase), MRI is recommended over bone scintigraphy [54].

3.5. Other prognostic factors and nomograms

In addition to traditional TNM staging, other important factors should be evaluated at the time of BCa staging. As mentioned earlier, hydronephrosis is an independent prognostic factor for poorer survival in patients treated with RC [44]. Lymphovascular invasion (LVI) is another prognostic factor with importance that has been recently
demonstrated. It has been shown to be a robust prognostic factor for poorer survival after RC [55]. Importantly for clinical staging, detection of LVI in TURBT specimens seems reliable [56]. In addition, LVI in a TURBT specimen increases the risk of nodal metastasis [56].

Because clinical staging is quite inaccurate with traditional clinicopathologic means, nomograms and other risk-stratification models are designed to improve staging accuracy. Karakiewicz et al presented their precystectomy nomogram to aid in the prediction of extravesical disease [57]. By including patient age, TUR stage, grade, and presence of CIS, the model had a 76% accuracy of predicting locally advanced disease [57]. A 63% accuracy was achieved in the prediction of lymph node metastasis. Recently, Margel et al presented their principal component analysis (PCA) model to predict organ-confined disease [58]. In addition to clinical stage, presence of hydrenephrosis, CIS, tumor size, three laboratory tests (carcinoembryonic antigen, cancer antigen 125, and carbohydrate antigen 19-9 levels) were included in the model. After internal validation, 85% accuracy was reported for the model [58]. It is possible that a risk-stratification model combining classic clinicopathologic variables, other prognostic factors (LVI, hydrenephrosis), imaging, and also molecular markers would increase the predictive accuracy.

4. Conclusions

The outcome of patients with high-risk BCa has not improved significantly during the last few decades [59]. One important reason for the lack of improvement is the accuracy of clinical staging, even if modern imaging is used. To select appropriately among various therapy options (radical surgery, chemotherapy, bladder preservation), staging accuracy needs to be improved, and urologists, together with radiologists, should work on that aspect. The staging process starts at the time of initial TURBT. Urologists need to appreciate the challenge of this apparently simple operation, and dedicated uropathologists are needed to analyze the specimens. Challenging cases should be reviewed in uropathologic meetings. Restaging TURBT in selected cases decreases delays in the diagnosis of invasive tumors and may improve responses to intravesical therapy. Current imaging modalities, although widely performed, are of limited value, and understaging is a very significant problem. Hopefully, novel imaging modalities may improve results, but further studies are needed to validate these new imaging techniques. We also urgently need other novel tools to improve staging, such as molecular markers and risk-stratification models.

Conflicts of interest

The authors have nothing to disclose.

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