Original Article

Validation of clinical T stages and of prognostic negative markers in patients with muscle invasive bladder cancer: data in the Swedish National Bladder Cancer Registry *vs.* data from a detailed research database

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Background: A previously published study at Norrland University Hospital, Umeå, Sweden, found that in 29.5% of patients with urinary bladder cancer (UBC) who underwent cystectomy, incorrect cT-stage (clinical T-stage) was registered in the Swedish National Register of Urinary Bladder Cancer (SNRUBC). Tumor in bladder diverticulum (TIBD) and tumor-associated hydronephrosis (TAH) were common causes for misclassification. Our aim was to further investigate cT-staging, as well as pathoanatomical markers, in the SNRUBC, compared to detailed data from medical records in a larger, retrospective multicenter cohort. Our secondary objective was to describe the frequency of pathoanatomical markers in pathology reports (PAD) after transurethral resection of the bladder (TURb): variant histology (VH), concomitant carcinoma in situ (CIS), lymphovascular invasion (LVI) and perineural invasion (PNI).

Methods: Medical records of 630 patients planned for radical cystectomy in the years 2009–2022 in the Northern Healthcare Region, Region of Gävleborg and Region of Västmanland were reviewed. Factors impacting risk of misclassification of cT-staging were identified through logistic regression. In TURb pathology reports, all comments on pathoanatomical markers were identified. For each pathoanatomical marker, respectively, comments were then registered as positive or negative. The absence of a comment on a marker was registered as "not commented".

Results: A total discrepancy rate of 36.5% was found between validated cT-staging and the SNRUBC, of which 13.3% were upstaged from <T2 to ≥T2. The results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Registrations with discrepancy were significantly associated with TIBD (OR: 10.28, 95% CI: 5.20–20.34), TAH (OR: 9.60, 95% CI: 6.12–15.10) and year of cystectomy 2009–2011 (OR: 3.38, 95% CI: 2.13–5.36). Incorrect CIS registration: 134 (35.8%); incorrect histology registration: 98 (25.6%). Total frequencies of recorded pathoanatomical markers in TURb-reports were for VH =23.8%, concomitant CIS =36.9%, LVI =30.4%, PNI =2.3%.

Conclusions: The SNRUBC has a significant prevalence of misclassification of cT-staging with a large

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proportion due to TAH and TIBD. Misclassification of VH and CIS is also common. Improved guidelines could increase consistency. Total rates of recorded pathoanatomical markers in TURb-reports are low.

Keywords: Bladder cancer; tumor staging; national registry; hydronephrosis; diverticulum

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Introduction

Urinary bladder cancer (UBC) is the sixth most common cancer in men, the 17th most common cancer in women, and the tenth most common cancer worldwide [2022] (1). Urothelial bladder cancer is the most common origin, accounting for more than 95% of cases. At less than 5% of cases, non-urothelial bladder cancer such as primary squamous carcinomas, adenocarcinomas and sarcomas are uncommon (2). Twenty-five percent of newly diagnosed bladder cancers are muscle invasive bladder cancer (MIBC), with the rest being non-muscle invasive bladder cancer (NMIBC). The prognosis of MIBC remains poor even after radical cystectomy, with a 5-year overall survival (OS) rate of 50% post cystectomy (3-5). This can be improved with neoadjuvant chemotherapy (NAC), increasing OS greatly with a hazard ratio of 0.82 and showing even better results in chemo-sensitive subgroups (5).

The classification of MIBC serves to select and assess which patients should receive specific treatments and to evaluate prognosis. To achieve this, classification and staging of the tumor is necessary (6,7). Tumor-node-metastasis (TNM) staging is the most widely used when classifying solid tumors. It is updated and maintained by The American Joint Committee on Cancer and the International Union for Cancer Control (7). Stages Ta, Tis and T1 are non-invasive, whilst T2, T3 and T4 are muscle-invasive or beyond. Standard diagnostic procedure for clinical TNM staging (cTNM) of a suspected bladder tumor includes radiological imaging, cystoscopy, bimanual palpation, and transurethral resection of the bladder (TURb) (6). cTNM-staging is the foundation upon which primary treatment choices are made, providing indication for treatments such as cystectomy, NAC, and induction chemotherapy (IC) [chemotherapy for metastasized (cN+) or locally advanced disease (cT4b)]. TURb provides an initial pathological tumor-stage (pT-stage) to aid in cTNM-staging. It provides histological characteristics of the tumor as well, such as grading from low grade (G1) to high grade (G2–G3) (6). Cystoscopy and radiological imaging serves to determine the presence of locally advanced disease (T-stage), lymph node metastasis (N-stage), distant metastasis (M-stage), tumor in bladder diverticulum (TIBD) and tumor-associated hydronephrosis (TAH) (6,8). It is the current consensus that preoperative TAH is associated with advanced disease, reduced OS and reduced cancer specific survival (9).

Bladder diverticulum occurs through a weakening in the detrusor muscle which can cause the mucosal layer to protrude through the muscle wall, creating a thinly walled pocket lacking a muscle layer. This is found most often in adults and males (10). Approximately 1% of cases of UBC are TIBD (11). Due to the lack of a muscle layer it has been

Highlight box

Key findings

- Misclassification of cT-stage was prevalent in 36.5% of cases in the Swedish National Registry of Urinary Bladder Cancer (SNRUBC) when compared to validated data. The misclassification was strongly associated with both tumor-associated hydronephrosis (TAH) and tumor in bladder diverticula (TIBD) and the association remains after adjustments. In the years 2009–2011 misclassification was most prevalent. Incorrect registration of carcinoma in situ (CIS) and variant histology (VH) was also a common issue in the registry, amounting to 35.8% and 25.6% respectively. Total report rates of lymphovascular invasion (LVI), CIS, VH and perineural invasion (PNI) in transurethral resection of bladder pathology reports were low.

What is known and what is new?

- A previous validation study found significant discrepancies between cT-stage in a regional single center cohort associated with TAH and TIBD. There are no previous validation studies including pathoanatomical markers.
- In this study we include a larger national cohort as well as an expansion of validation objectives.

What is the implication, and what should change now?

- To possibly improve the quality of data in the SNRUBC it could be of value to adjust guidelines, or add registration points, for TAH, TIBD, CIS and VH.

suggested that there is no pT2-stage, and that if there is invasion beyond the lamina propria, it is to be regarded as pT3-extravesical disease (11,12). Studies in recent years have shown that pathological upstaging is common (13,14).

In clinical practice not only cTNM-staging is used for decision-making, but also the presence of pathoanatomical markers. These pathoanatomical markers may affect prognosis and/or treatment choices (8). Known markers include lymphovascular invasion (LVI), perineural invasion (PNI), concomitant CIS (concomitant cancer in situ) and variant histology (VH). Many types of VH of urothelial origin show a more aggressive pattern of disease. They are associated with a worse prognosis, and they are overall considered as high-grade tumors (2,8). Higher degree of LVI is also a negative prognostic factor (15-18). The association between concomitant CIS and worse prognosis has been suggested but remains controversial (19). Concomitant CIS is however associated with an increased risk for progression from NMIBC to MIBC (20). According to European guidelines it is recommended to examine and report these findings in pathological analysis (8).

Swedish patient data regarding UBC statistics have been registered in the public Swedish National Register for Urinary Bladder Cancer (SNRUBC) since 1997. Initially it included only an early diagnostical entry-form containing cTNM-stage and limited histological data. This was later expanded on in 2009 with a fillable 5-year follow up form for non-invasive cases, and again in 2011 with a radical cystectomy registry containing fillable forms of detailed pre-, peri- and postoperative data (21). Clinical T-stage as well as histological data is registered after review of TURb-reports exclusively.

One of these forms, referred to as the "cystectomy form", includes preoperative cTNM-staging. This allows cT-stage to be recorded twice, once in the entry form and once in the cystectomy form, allowing for cT-stage to be updated. There are no registration points for TAH, TIBD, LVI or PNI. CIS and VH are recorded only once, in the entry form. The registration point for CIS is not titled specifically as "concomitant". It is currently not possible to record detailed data on VH, such as specific urothelial subtype. Instead, it can only be recorded as either "100% urothelial" or "other than urothelial".

The registration of data in the SNRUBC is generally performed by specialized urology nurses or urologists with access to the registry. This may not always have been the case historically, as experienced nurses or urologists may not always have been available. This could possibly have affected the quality of registered data.

This study is in part a continuation of a previous validation study from Wiberg *et al.*, which exclusively included patients treated at Norrland University Hospital, Umeå, Sweden. The study found a 29.5% discrepancy rate between validated cT-stages and cT-stages in the SNRUBC, with a significant association to TAH and TIBD (22). The primary objectives of this study is: (I) to examine how prevalent misclassification of cT-stage is in the SNRUBC in a larger national cohort; (II) to examine documentation of pathoanatomical markers in TURb reports, and the extent of misclassification of these markers in the SNRUBC. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-454/rc).

Methods

Inclusion criteria

The source population includes patients from all hospitals in the Northern Healthcare-region with a source population of 901,929, the regional hospital of Västmanland with a source population of 280,813, as well as all hospitals in the region of Gävleborg with a source population of 285,642 (23). Medical records from patients between the years 2009–2022 who were planned for cystectomy were reviewed (n=668). Only patients with UBC of urothelial origin with cystectomy as primary treatment were included with a final cohort of 630 patients. Validation of cT-staging included all patients with valid data on cT stage from both medical records and the registry.

The review of pathoanatomical markers and urothelial VH in medical records and TURb pathology reports was performed only in patients with MIBC. TURb reports were labeled diagnostic, decisive or both. Only the pathology report leading to (or in conjunction with) the patient being planned for cystectomy, referred to as the decisive TURb, was reviewed. This was done due to the decisive TURb containing the latest and most relevant information on the characteristics of the tumor foregoing possible cystectomy and/or NAC. The pathology report from the TURb resulting in a bladder cancer diagnosis, regardless of staging, was labeled as the diagnostic TURb. The entry form of the SNRUBC derives from the pathology report of the diagnostic TURb, regardless of later changes in tumor development. Patients having an initial diagnostic TURb date differing substantially in time (≥1 month) from decisive TURb date (MIBC diagnosis) were registered on a separate

list. This time-cut-off for differing diagnostic and decisive TURb date was set as ≥1 month, due to it being deemed unlikely for entry form data to be updated past that time. Patients on this list were excluded from analysis of VH and CIS in the SNRUBC when compared to data from medical records.

Gathering of data

Data from the previous validation study from Wiberg *et al.* were used for patients planned for cystectomy at Norrland University Hospital between years 2009–2020, not including any patients from Sundsvall Hospital (22). In our expanded study the method has been altered slightly due to limited resources, a greater number of patients, and the entailing of additional objectives.

Data regarding patient sex, age, and Charlson Age Comorbidity Index (CACI)-score were recorded for all patients. Type of NAC-treatment and number of cycles was also recorded. Patients were further separated into those who received no NAC, partial NAC (less than 3 cycles), complete NAC (3+ cycles), and those who received IC.

Validated cT-category was defined as thorough re-registration of cT-category. Re-registration was evaluated on basis of reviewed medical records including cystoscopy reports, TURb pathology reports with pT-stage, as well as radiological imaging results with assessment of local tumor status, TIBD and preoperative TAH. Decisions at multidisciplinary conferences were also taken into consideration, but the number of patients in which this applied was not documented. TIBD was confirmed by reviewing both cystoscopy and preoperative radiological imaging statements. TAH was confirmed by reviewing preoperative computer tomography or ultrasound imaging statements. Preoperative nephrostomy due to TAH was recorded as TAH. Only clinically significant TAH caused by tumor growth occluding the ureteral orifices was registered as TAH. Patients with cT1 TIBD were registered as cT2 but described as a unique group of T2/T3 due to exact staging sometimes being more difficult. Patients with confirmed TAH and cT1 or cT2 were registered as validated cT3. In cases with both TIBD and TAH, validated cT1/2 was registered as cT3. TaG2 tumors with concomitant CIS were registered as cTis.

As the preoperative cystectomy form was introduced in the year 2011, patients registered pre- or during parts of 2011 only have entry form cT-staging. This was considered a special group. Data on how many patients missed cystectomy forms in other years were not compiled. Regardless of this the unvalidated cT-category was registered as the highest cT-stage available in the registry. Data from the SNRUBC was not blinded to the reviewer, but no analysis was performed before the validation process was completed.

Any type of comment regarding concomitant CIS, LVI or PNI in the decisive TURb was registered for each marker separately. If any marker was commented, it was recorded as either positive or negative, otherwise as "Not commented". In cases of "suspected positive" it was recorded as positive. Histological type was recorded as either urothelial or other (non-urothelial). In patients with urothelial origin histological subtype was recorded. If commented only as urothelial it was recorded as 100% urothelial. Subtype categories were recorded as "Urothelial with … differentiation.". All subtypes mentioned in TURb pathology reports were recorded. If there were multiple tumors, only the muscle-invasive component was considered. If non-muscle-invasive (<pT2) with multiple tumors, only the component most likely associated with TAH or TIBD was considered. If the primary tumor was composed of multiple histological components, it was recorded as multi-differentiated.

The primary outcomes include: (I) the discrepancy between the validated cT category versus the unvalidated cT category from the SNRUBC; (II) the discrepancy between concomitant CIS and VH in TURb reports versus the SNRUBC; (III) the frequency of comments of pathoanatomical markers in TURb reports.

Statistical methods

cT-staging discrepancy between validated and unvalidated categories was compared within groups according to different patient characteristics. Categorical variables were described with frequency tables and groups were compared using Pearson's Chi-squared test. Interval data were presented as the mean with standard deviation, and groups were compared using two independent samples *t*-test. Unadjusted and adjusted logistic regression were used to analyze variable association with cT discrepancy. The results were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). For analysis of VH and CIS compared to the SNRUBC standard descriptive statistics, frequency tables were used. Only complete case data were analyzed. As sensitivity analysis for VH and CIS we used comparative tables including all patients with urothelial UBC with complete case data.

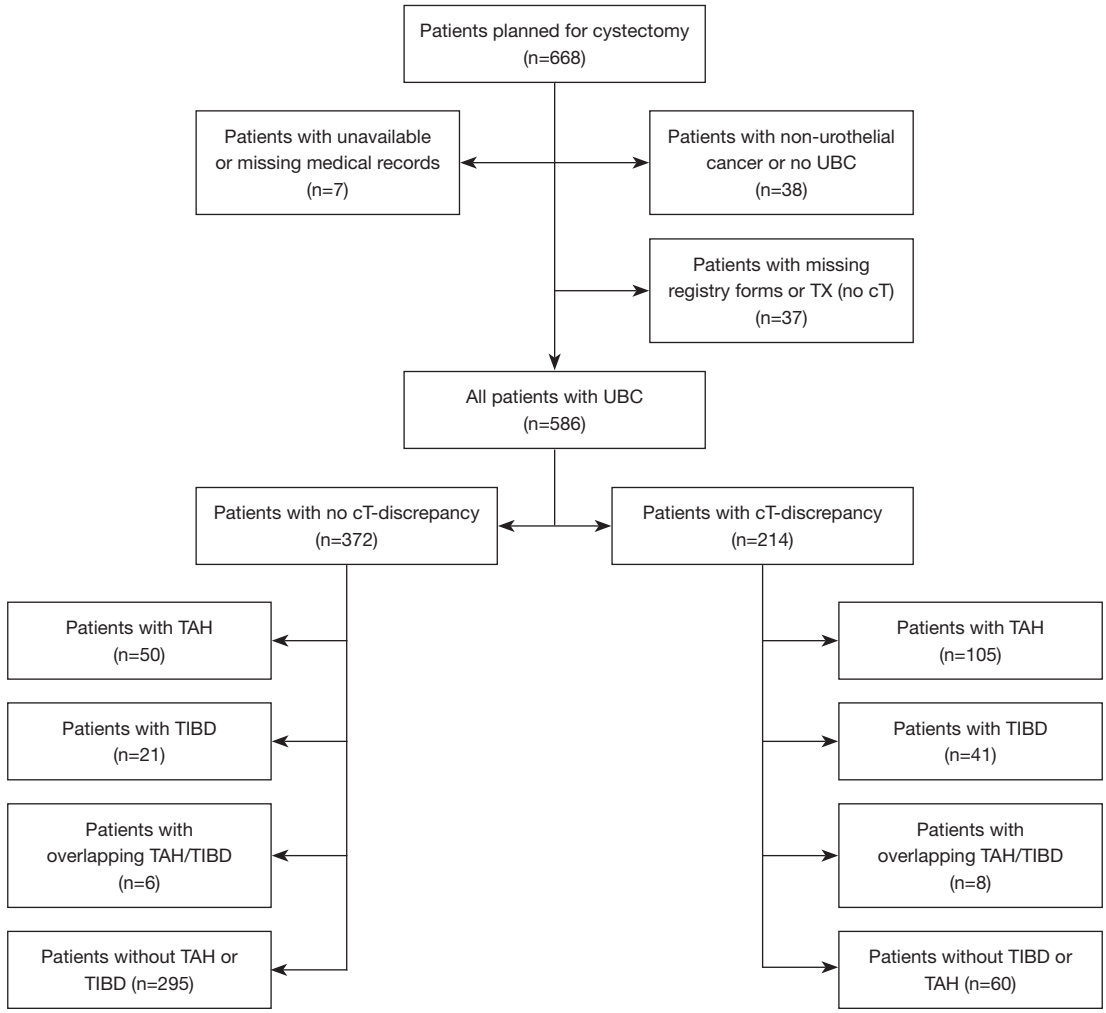

Figure 1 Flowchart of inclusion process for patients included for cT-validation. UBC, urinary bladder cancer; Tx, there is insufficient information for stage classification; cT, clinical classification of the primary tumor; TAH, tumor-associated hydronephrosis; TIBD, tumor in bladder diverticulum.

Statistical analysis was performed using IBM SPSS Statistics, Version 29 (IBM Corporation, Armonk, NY, USA).

Ethical statement

The study was approved by the regional ethics committee (Umeå) on behalf of The Swedish Ethical Review Authority (EPM) with approval number: 2013/463-31M (date of decision 140603), and EPM-amendment with approval number: 2023-06497-02 (date of decision 231106). The study was retrospective and therefore no informed consent was required according to the EPM. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

cT-discrepancy

In patients planned for cystectomy during years 2009–2022 with urothelial bladder cancer (n=630), 37 patients were excluded due to being registered as Tx or having missing registry forms, and 7 patients were excluded due to missing data in the validated cT-category (missing or unavailable medical record data), resulting in a final cohort of 586 patients (*Figure 1*). Discrepancy between the unvalidated cT-category from the SNRUBC and the validated cT-category was found in 214 cases (36.5%). A higher cT in the validated cT-category was found in 187 cases (31.9%).

A lower cT in the validated category was found in 27 cases (4.6%). Upstaging from <T2 to ≥T2 was found in 13.3% of patients. Discrepancy was found in 105 patients with TAH and 41 patients with TIBD. Nine patients had overlapping TAH/TIBD. One hundred and eighty-nine patients received complete NAC, 31 partial NAC and 30 received IC. Results regarding association to discrepancy for factors: age, sex, CACI, and chemotherapy, were inconclusive (*Table 1*).

cT-stages varied widely between the validated and the unvalidated category (*Table 2*). Discrepancy was most common in years 2009–2012, during which detailed cystectomy data did not exist (2009–2011) or had just been introduced (2011–2012) (*Figure 2*). Analysis of factors affecting probability was performed using logistical regression (*Table 3*). TAH, TIBD and cystectomy year of 2009–2011 showed statistically significant association with cT-discrepancy in both adjusted and unadjusted analysis. TAH had an unadjusted OR: 6.56 with 95% CI (4.40–9.80), P<0.001, TIBD unadjusted OR: 3.96, 95% CI (2.27–6.91), P<0.001 and cystectomy year 2009–2011 unadjusted OR: 2.98, 95% CI (2.00–4.45), P<0.001. Results for overlapping TAH/TIBD in unadjusted analysis were inconclusive; OR: 2.68, 95% CI (0.94–7.63), P=0.06, and in adjusted analysis there was only a slight risk increase for cT-discrepancy; OR: 0.06, 95% CI (0.02–0.23), P<0.001 (*Table 3*).

VH, SNRUBC registry versus decisive TURb report

Three hundred and eighty-three patients were included for comparison between VH in TURb pathology reports and histology type in the SNRUBC (*Figure 3*). Misclassification in the SNRUBC was prevalent in 98 patients total (25.6%). Ninety-five patients with VH in TURb were registered as 100% urothelial in the SNRUBC. One patient verified as 100% urothelial in TURb was registered as "other than urothelial" (*Table 4*). In the sensitivity analysis, 467 cases were included for comparison. Misclassification in the SNRUBC was prevalent in 114 patients in total (24.4%). One hundred and eight patients with VH were registered as 100% urothelial in the SNRUBC. Six patients verified as 100% urothelial in TURb were registered as "other than urothelial" in the SNRUBC (Table S1).

VH, CIS, LVI and PNI in TURb reports

474 patients with MIBC were initially included for analysis of VH in TURb pathology reports (*Figure 3*). One hundred and thirteen patients (23.8%) had any type of VH while 361 were 100% urothelial (76.2%). Urothelial carcinoma with squamous differentiation was most common amongst the different types of VH (*Table 5*). An additional 3 patients were excluded in analysis of CIS, LVI and PNI due to mis-registration during the reviewing process, resulting in a final cohort of 471 patients (*Table 6*). All markers had low report rates. Concomitant CIS was reported in 174 cases (36.9%), LVI was reported in 143 cases (30.4%) and PNI was reported in 11 cases (2.3%) (*Table 6*).

Concomitant CIS, registry versus decisive TURb pathology report

A total of 374 patients were included for comparison of concomitant CIS in TURb pathology reports versus in the SNRUBC (*Figure 3*). A few patients were registered in the SNRUBC as "not examined", these were excluded from analysis. In 134 patients there was discrepancy between the SNRUBC-category and the TURb-category resulting in a total discrepancy rate of 35.8%. Out of 52 true negatives (TURb commented as negative), 21 were not commented and 4 were registered as positive (48.1% discrepancy) (*Table 4*). Out of 80 true positives (TURb commented as positive), 35 were not commented and 17 registered as negative (65.0% discrepancy). Out of 242 TURb reports with no comment on CIS, 49 were registered as negative, and 8 were registered as positive (19.4% discrepancy) (*Table 7*, *Figure 3*). In 40 SNRUBC forms (10.7%) CIS was registered as positive. In the sensitivity analysis, 444 patients were included and showed a similar distribution. In 157 patients there was discrepancy between the SNRUBC-category and the TURb-category with a total discrepancy rate of 35.3% (Table S2).

Discussion

The general results indicate a high prevalence of misclassification of cT-stage, VH and CIS in the SNRUBC, as well as low report rates for pathoanatomical markers in TURb reports. Sensitivity analysis of VH and CIS with less strict inclusion criteria gave similar results differing only 1.2% (VH) and 0.5% (CIS) in total discrepancy rates to the main analyses. It should be stated that maintaining the quality of registries through updated guidelines is a constantly ongoing process, of which retrospective analyses not always account for. The results of this study should be viewed with this taken into consideration.

Table 1 Discrepancy between cT-stages

Characteristic	Yes (n=214)	No (n=372)	Total (n=586)	P value (test)
Age (years), mean (SD)	69.8 (7.44)	70.6 (7.96)	70 (7.79)	0.22 (*t*-test)
Sex, n (%)				0.77 (Chi²)
Male	165 (77.1)	282 (75.8)	447 (76.2)	
Female	49 (22.9)	90 (24.2)	139 (23.8)	
Detailed cystectomy data (no form 2009–2011), n (%)				<0.001 (Chi²)
Yes	140 (65.4)	316 (84.9)	456 (77.8)	
No	74 (34.6)	56 (15.1)	130 (22.2)	
Unvalidated cT-category, n (%)				<0.001 (Chi²)
Ta	22 (10.3)	17 (4.5)	39 (6.7)	
Tis	9 (4.2)	16 (4.3)	25 (4.3)	
T1	65 (30.4)	48 (12.9)	113 (19.3)	
T2	93 (43.5)	231 (62.0)	324 (55.3)	
T3	19 (8.9)	43 (11.6)	62 (10.6)	
T4	6 (2.8)	17 (4.6)	23 (3.9)	
CACI, mean (SD)	5.16 (1.23)	5.10 (1.27)	5.12 (1.3)	0.52 (*t*-test)
Chemotherapy, n (%)			(3 missing NAC data)	0.06 (Chi²)
None	132 (61.7)	201 (54.0)	333 (56.8)	
Partial NAC	12 (5.6)	19 (5.1)	31 (5.3)	
Complete NAC	55 (25.7)	134 (36.0)	189 (32.2)	
IC	14 (6.5)	16 (4.3)	30 (5.1)	
TIBD, n (%)				<0.001 (Chi²)
No	173 (80.8)	351 (94.4)	524 (89.4)	
Yes	41 (19.2)	21 (5.6)	62 (10.6)	
TAH, n (%)				<0.001 (Chi²)
No	106 (49.5)	322 (86.6)	428 (73.0)	
Yes	108 (50.5)	50 (13.4)	158 (27.0)	
Overlapping TAH/TIBD, n (%)				0.06 (Chi²)
No	205 (95.8)	366 (98.4)	571 (97.4)	
Yes	9 (4.2)	6 (1.6)	15 (2.6)	

Patient characteristics, distribution and comparison between groups with or without cT discrepancy (yes or no). cT, clinical T-stage; SD, standard deviation; CACI, Charlson Age Comorbidity Index; NAC, neoadjuvant chemotherapy; IC, induction chemotherapy; TIBD, tumor in bladder diverticulum; TAH, tumor-associated hydronephrosis.

cT-validation

As was expected our results show great similarities with Wiberg *et al.* regarding the quality of the SNRUBC (22). The discrepancy rate in our study was higher (36.5%) compared to Wiberg *et al.* (29.5%). The similar discrepancy rate between the validated and unvalidated cT-categories in the larger cohort indicates that the issues with cT-staging in the SNRUBC are not limited to Norrland University

Table 2 Frequency and distribution of cT-stages

cT-stage distribution	Validated cT-stage frequencies						Total
	Ta	Tis	T1	T2	T3	T4	
Unvalidated cT-stage frequencies							
Ta	17	4	5	7	6	0	39
Tis	2	16	5	1	1	0	25
T1	2	0	48	39	22	2	113
T2	0	0	2	231	82	9	324
T3	0	1	1	13	43	4	62
T4	0	0	0	1	5	17	23
Total	21	21	61	292	159	32	586

The distribution of number of cases of each cT-stage in the re-reviewed validated and the unvalidated cT-category (SNRUBC). cT, clinical T-stage of primary tumor; SNRUBC, Swedish National Registry of Urinary Bladder Cancer.

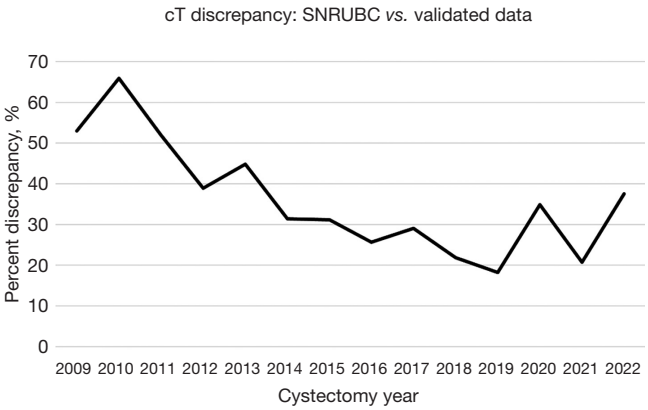

Figure 2 The discrepancy rate between the SNRUBC unvalidated cT and validated cT in each year. cT, clinical classification of the primary tumor; SNRUBC, Swedish National Register of Urinary Bladder Cancer.

Table 3 Factors impacting misclassification of cT-stage in SNRUBC

Factors impacting misclassification	Unadjusted		Adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value
TIBD	3.96 (2.27–6.91)	<0.001	10.28 (5.20–20.34)	<0.001
TAH	6.56 (4.40–9.80)	<0.001	9.60 (6.12–15.10)	<0.001
Overlapping TAH/TIBD	2.68 (0.94–7.63)	0.06	0.06 (0.02–0.23)	<0.001
Registered in 2009–2011 (no detailed cystectomy data)	2.98 (2.00–4.45)	<0.001	3.38 (2.13–5.36)	<0.001

Factors associated with discrepancy analyzed with logistical regression. Individually as unadjusted and with all factors as adjusted. cT, clinical T-stage; SNRUBC, Swedish National Registry of Urinary Bladder Cancer; TIBD, tumor in bladder diverticulum; TAH, tumor-associated hydronephrosis; OR, odds ratio; CI, confidence interval.

Hospital. This points toward possible systematic flaws in the registration process. The increase in discrepancy could be attributed to possible overemphasis on TIBD and TAH, as no radiologist was available to re-review uncertain cases.

TAH was found in 26.3% of patients. It is associated with locally advanced disease, reduced OS and reduced cancer-specific survival (CSS) as shown in a 2019 meta-analysis (9). A 2023 study found preoperative TAH to be an independent negative prognostic factor for OS (24). Due to this it is cause for upstaging in accordance with common urology practice. Preoperative TAH often led to upstaging from cT1/T2 to T3 in the validated cT-category. This led to significant discrepancies compared to the unvalidated cT-category and is in line with Wiberg *et al.* (22), further proving that TAH is often not considered.

TIBD was found in 10% of cases, which is remarkably high in comparison to a prevalence of 1–4% in other studies and published literature (11,13). One possible explanation could be the extensive reviewing process resulting in the finding of less available information and confirmation of more cases. Another possible explanation is a higher incidence of TIBD in the study population. As TIBD is rare there are few studies on its implications. This in combination with the unique anatomical properties of lacking a muscle layer, makes staging of TIBD a diagnostic challenge. This could be reason as to why TIBD is commonly associated with pathological upstaging (11,13,14). Pathological upstaging could in turn indicate tendency to under stage TIBD. In this study, we categorized cT1 cystoscopically and radiologically verified as TIBD as cT2 in the validated category. Discrepancies between validated and unvalidated cT-categories owing to this upstaging were

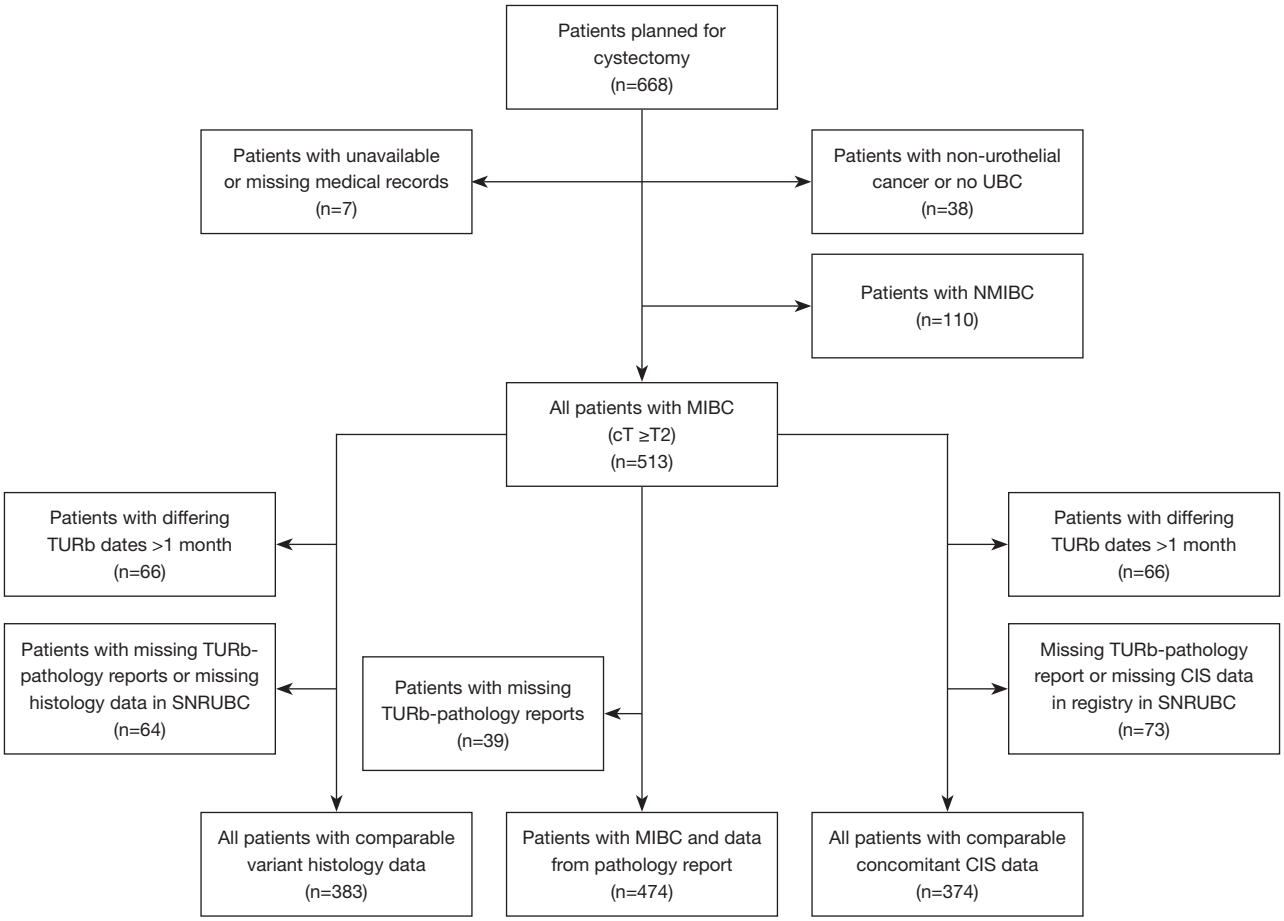

Figure 3 Flowchart of inclusion process for patients included for analysis of pathoanatomical markers. Comparable data refers to the patient having valid data from both TURb and the SNRUBC. CIS, carcinoma in situ; UBC, urinary bladder cancer; NMIBC, non-muscle invasive bladder cancer; MIBC, muscle invasive bladder cancer; cT, clinical classification of the primary tumor; TURb, transurethral resection of bladder; SNRUBC, Swedish National Register of Urinary Bladder Cancer.

Table 4 Variant histology in TURb *vs.* SNRUBC

Variant histology comparison	"100% urothelial" in SNRUBC	"Other than urothelial" in SNRUBC	Total
100% urothelial in TURb	283 (73.9)	3 (0.8)	286 (74.7)
Any type of VH in TURb	95 (24.8)	2 (0.5)	97 (25.3)
Total	378 (98.7)	5 (1.3)	383 (100.0)

Data are presented as n (%). Distribution of urothelial variant histology, in TURb compared to the SNRUBC. Includes only MIBC patients. TURb, transurethral resection of bladder; SNRUBC, Swedish National Registry of Urinary Bladder Cancer; VH, variant histology; MIBC, muscle invasive bladder cancer.

found in 38 cases. A limitation of this method is that it is possible that our upstaging was overestimated. Voskuilen *et al.* found that 55% of patients with TIBD staged as cTa/Tis/T1 had upstaging to ≥pT2 (14), and Hu *et al.* found upstaging in 48% of TIBD (13). The significant association between discrepancy in validated and unvalidated cT found in this study does still indicate an inclination towards understaging in the registry.

In this study we were also able to highlight how classification and registration of cT-stage improved in the SNRUBC after year 2011, when the cystectomy form was introduced, allowing for the preoperative cT-staging to be registered (21).

Table 5 Variant histology of urothelial carcinoma

Subtype	Frequency	Percent
100% urothelial	361	76.2
Squamous	49	10.3
Nested	17	3.6
Glandular	13	2.7
Sarcomatoid	6	1.3
Plasmacytoid	6	1.3
Small cell/neuroendocrine	6	1.3
Micropapillary	4	0.8
Pleomorphic	1	0.2
Microcystic	1	0.2
Clear cell	1	0.2
Sebaceous	1	0.2
Not specified	2	0.4
Multi-differentiated	6	1.3
Total	474	100.0

The distribution of cases with different urothelial histological variations. Includes only MIBC patients. MIBC, muscle invasive bladder cancer.

Table 6 Pathoanatomical markers in TURb reports

Comments on pathoanatomical markers	Frequency (N=471)
LVI at TURb	
Negative	82
Positive	61
Not commented	328
PNI at TURb	
Negative	5
Positive	6
Not commented	460
CIS at TURb	
Negative	72
Positive	102
Not commented	297

Distribution of comments on CIS, LVI and PNI in TURb reports. Includes only MIBC patients. TURb, transurethral resection of bladder; LVI, lymphovascular invasion; PNI, perineural invasion; CIS, carcinoma in situ.

VH

In patients with validated MIBC VH was found in 113 (23.8%) of cases. This is a relatively high incidence in comparison to Cai *et al.*, who found uncommon subtypes of urothelial cancer in 262 (6.4%) of TURb specimens (25), but more in line with Abufaraj *et al.* who found histological subtypes, other than squamous or glandular, in 30 TURb specimens (11.2%) (26). It should be stated that under-reporting has been shown in 18–44% of pathology reports (27,28). Some types of VH are associated with reduced OS, less response to NAC, increased risk of pathological upstaging, advanced disease and/or muscle invasiveness in TURb (25,26,29). Because of this, tumors presenting with VH can require different treatment strategies, and are therefore important to keep recording. The registry only allows for classification of the tumor as either "100% urothelial" or "Other than urothelial". This means it contains no reliable data on specific urothelial histological subtypes. But as was found in this study, VH was commonly present even if registered as 100% urothelial in the SNRUBC. Whether or not it should be included in the SNRUBC is debatable. It would require more knowledge from the registrator, but it remains an important prognostic factor (2,25,26) and is stated by pathology guidelines to be documented in standard pathology practice (8). Our results provide a limited insight into the incidence of VH and show that it is commonly reported in TURb-specimens.

Concomitant CIS

Concomitant CIS has previously been treated as a negative prognostic factor if found in cystectomy specimens. A 2019 meta-analysis found that the presence of concomitant carcinoma in situ (CIS) in organ-confined disease is associated with an increased risk of urethral cancer recurrence, reduced recurrence-free survival (RFS), and higher cancer-specific mortality (CSM) (30). A more recent 2024 meta-analysis and systematic review found no significant association between concomitant CIS in cystectomy specimens and reduced CSS, OS or RFS (19). However, in TURb specimens, it was found to be associated with an increased risk of progression to invasive disease (20). As such concomitant CIS is still an important prognostic factor to be reported in TURb reports and in the SNRUBC. In our study we found that CIS was recorded in 132 (35.3%) TURb reports and in 133 (35.3%) SNRUBC forms. CIS was positive in 80 (21.4%) of TURb

Table 7 CIS in TURb compared to SNRUBC

Comments on CIS	Frequency of CIS-comments in SNRUBC			Total
	Negative	Positive	Not commented	
Frequency of CIS-comments in TURb				
Negative	27 (7.2)	4 (1.1)	21 (5.6)	52 (13.9)
Positive	17 (4.5)	28 (7.5)	35 (9.4)	80 (21.4)
Not commented	49 (13.1)	8 (2.1)	185 (49.5)	242 (64.7)
Total	93 (24.9)	40 (10.7)	241 (64.4)	374 (100.0)

The distribution of CIS comments in TURb reports and the SNRUBC. Showcases varying types of discrepancy. Includes only MIBC patients. CIS, carcinoma in situ; TURb, transurethral resection of bladder; SNRUBC, Swedish National Registry of Urinary Bladder Cancer.

reports and 40 (10.6%) of SNRUBC forms, which can be compared to a 39.4% prevalence in post-cystectomy specimens according to Kimura *et al.* (30). Due to the limitations of the TURb procedure, not encompassing the entire lumen of the bladder, we expectedly found a lower incidence when compared to cystectomy data. For the same reason mentioned it is not possible to completely rule out concomitant CIS with a TURb. This is a likely explanation as to why it is less often commented as negative. This could highlight the importance of random biopsies.

Discrepancy between the SNRUBC and pathology reports was found in 134 cases (35.8%). This high of a prevalence of varying types of errors, indicate that there is uncertainty regarding CIS registration in the registry. This could be due to lack of clear guidelines, difficulty in interpretation of pathology reports or various other reasons. In the registry CIS is not specifically labeled as "concomitant", which could account for some of the discrepancy.

LVI and PNI

LVI was reported in 61 (12.9%) patients, which is lower compared to a meta-analysis from 2014 that found LVI in 18.6% of TURb specimens (17) and 17.3% in meta-analysis from 2019 (18). This indicates possible underreporting in this cohort. In most reports, it was not commented upon at all which makes interpretation of incidence difficult. As LVI in TURb has been associated with pathology upstaging and decreased RFS, it is something which needs further studying (17,18).

PNI was not reliably documented in TURb pathology reports. No current studies have analyzed the prognostic significance of PNI in TURb specimens. In studies on PNI in cystectomy specimens no independent association with worse outcomes has been found (16,31). If PNI in TURb specimens is underreported or rare to find remains unknown. This could be a possible subject for future studies, which would require centralized pathology review.

Strengths and limitations

There are many limitations in this study. The review of medical records was performed by junior doctors and not urologists, but with support from senior urologists and urology nurses. No radiologists were included in the re-review of radiological imaging other than patients between years 2009–2020 at Norrland University Hospital included in Wiberg *et al.* (22). In patients other than those included from Wiberg *et al.* only radiological statements and cystoscopy reports were reviewed.

Due to time constraints only patients with validated MIBC were included in analysis of pathoanatomical markers, resulting in a smaller cohort. Pathology reports were in many cases unattainable or missing, resulting in exclusion. Mistakes in the registration process, such as not entering data in the correct format, were also prevalent in a few cases, resulting in exclusion from some of the analyses. These mistakes were not possible to correct in retrospect due to limited access to medical records.

Guidelines regarding pathoanatomical markers may have been updated or renewed both for pathologists and for the SNRUBC, which has not been adjusted for. Another weakness is that the study does not investigate whether the mistakes in the SNRUBC were due to mistakes in medical records or mistakes in the registration process. The strengths of the study include a relatively large cohort as well as data from multiple medical centers, improving

external validity. This is the first published validation study of the national registry that includes both histological data and cT-staging.

Conclusions

In conclusion, we found that the SNRUBC is subject to misclassification of cT-staging, histological subtype and CIS. Studies using data from the register should consider the current limitations imposed by misclassification of these factors. The misclassification of these factors in the registry could negatively affect the reliability of any conclusions drawn in studies using registry data. We have several suggestions as to how the registry can be improved. As cT-discrepancy was significantly associated with TAH and TIBD, the implementation of registration points for these factors could reduce the risk of misclassification. More detailed data of VH could be implemented in registration to avoid misclassification of urothelial VH as purely urothelial. CIS could be specified more clearly as either the primary tumor constituting of CIS itself, or CIS as concomitant to the primary tumor. We suggest education and training of staff responsible for the registration process. This could aid in proper tumor classification and help improve the general quality of the registry. The role of LVI and PNI in clinical practice remains uncertain, but improved documentation through standardized pathology reporting in TURb reports could be of importance to gain further knowledge about their possible impact.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the regional ethics committee (Umeå) on behalf of The Swedish Ethical Review Authority (EPM) with approval number: 2013/463-31M (date of decision 140603), and EPM-amendment with approval number: 2023-06497-02 (date of decision 231106). The study was retrospective and therefore no informed consent was required according to the EPM. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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