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Clinical-Bladder cancer

Diagnostic accuracy of bimanual palpation in bladder cancer patients undergoing cystectomy: A prospective study

Anna K. Czech, M.D.[a,*], Katarzyna Gronostaj, M.D., Ph.D.[a], Jakub Fronczek, M.D., Ph.D.[b], Jakub Frydrych, M.D.[a], Valentyn Bezshapkin, M.D.[b], Mikolaj Przydacz, M.D., Ph.D.[a], Przemyslaw Dudek, M.D., Ph.D.[a], Lukasz Curylo, M.D.[a], Tomasz Wiatr, M.D.[a], Jerzy Gasowski, M.D., Ph.D., Prof.[c], Piotr L. Chlosta, M.D., Ph.D., Prof.[a]

[a] *Department of Urology, Jagiellonian University Medical College, Krakow, Poland*
[b] *Centre for Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Krakow, Poland*
[c] *Department of Internal Medicine and Gerontology, Jagiellonian University Medical College, Krakow, Poland*

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Abstract

Objectives: To prospectively assess the concordance of examination under anesthesia (EUA)-based clinical T stage with pathological T stage and diagnostic accuracy of EUA in patients with bladder cancer undergoing cystectomy.

Methods: Consecutive patients with bladder cancer undergoing cystectomy between June 2017 and October 2020 in a single academic center were included in a prospective study. Two urologists performed EUA (one blinded to imaging) before patients underwent cystectomy. We assessed the concordance between clinical T stage in bimanual palpation (index test) and pathological T stage in cystectomy specimens (reference test). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with 95% confidence intervals (CIs) to detect or exclude locally advanced bladder cancer (pT3b−T4b) in EUA.

Results: The data of 134 patients were analyzed. Given that stage pT3a cannot be palpated, for the nonblinded examiner, T staging in EUA was concordant with pT in 107 (79.9%) patients, 20 (14.9%) cases being understaged in EUA and 7 (5.2%) overstaged. For the blinded examiner, staging was correct in 106 (79.1%) patients, 20 (14.9%) cases being understaged and 8 (6%) overstaged. For the nonblinded examiner, sensitivity, specificity, PPV, and NPV of EUA were 55.9% (95% CI 39.2%−72.6%), 93% (88%−98%), 73.1% (56%−90.1%), and 86.1% (79.6%−92.6%), respectively; for the blinded examiner, they were 52.9% (36.2%−69.7%), 93% (88%−98%), 72% (54.4%−89.6%) and 85.3% (78.7%−92%), respectively. Awareness of imaging results did not have a major impact on EUA results.

Conclusion: Bimanual palpation should still be used for clinical staging, given its specificity, NPV, and that it could correctly determine bladder cancer T stage in 80% of cases.

Keywords: Bimanual palpation; Bladder cancer; Exam under anesthesia; Muscle-invasive bladder cancer; Staging

1. Introduction

One of the most important prognostic factors in patients with muscle-invasive bladder cancer is tumor stage [1]. Bimanual palpation (examination under anesthesia [EUA]) is an integral part of clinical bladder cancer staging, as recommended by the guidelines [2,3]. Nevertheless, in the era of widespread availability of imaging modalities, clinical staging is most commonly assessed with cross-sectional imaging. EUA is typically performed before and after transurethral resection of bladder tumor (TURBT) [2,3]. Few studies have assessed the accuracy of EUA, but retrospective studies suggest a relatively high rate of understaging (31%) and overstaging (11%) in bimanual palpation [4]. Data regarding EUA utilization in clinical practice is scarce,

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*Corresponding author. Tel.: +48124002500; fax.: +48124002517.
E-mail addresses: aka.czech@uj.edu.pl, anna.czech@gmail.com (A.K. Czech).

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but suggest that EUA might be underused, and increasing availability of imaging might result in a further downward trend in EUA use [5].

The aim of this study was to prospectively assess the concordance between clinical stage in bimanual palpation and pathological stage and to evaluate the diagnostic accuracy of EUA in patients with bladder cancer undergoing cystectomy. To the best of our knowledge, this is the first study to prospectively evaluate the concordance and diagnostic accuracy of bimanual palpation in these patients.

2. Materials and methods

2.1. Patients

Consecutive patients undergoing either elective or emergency cystectomy for bladder cancer between June 2017 and October 2020 in a single tertiary academic center were included in this prospective cohort study. Exclusion criteria included cystectomy for indications other than bladder cancer. This study was performed in agreement with applicable laws and regulations, good clinical practice, and ethical principles, as described in the Declaration of Helsinki of 1964, and revised in 2013. The study was approved by the institution's ethical committee and patients provided informed consent.

Preoperative staging was based on the most recent cross-sectional imaging available (clinical T stage based on imaging "c_iT": c_iT0-T2, c_iT3b, c_iT4a, c_iT4b). All patients had abdominopelvic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), except for three with contraindications who had noncontrast CT. All patients had a chest CT or X-ray.

2.2. Bimanual palpation (index test) and pathological examination (reference test)

Enrolled patients underwent EUA (the index test) in the operating room after bladder emptying and before the start of cystectomy. Bimanual palpation involved palpation of the anesthetized patient with the use of the examiner's two hands: one hand palpated the suprapubic area while the finger of the other hand was inserted into the rectum in a male, or into the vagina in a female, to assess bladder walls, male prostate, bladder neck, and female urethra and vagina. Two urologists performed EUA for the protocol. They were staff members ($n = 16$; 3–24 years' experience in urology) randomly assigned on the day of cystectomy. One of them was blinded to the history and imaging of the patient. The other was the operating surgeon and was never blinded to this information. The examiners separately filled in a prespecified study form and indicated the clinical T stage on the basis of the findings from bimanual palpation (cT0-T2, cT3b, cT4a, cT4b).

The cystectomy specimen was sent for pathological assessment, the gold standard reference test for T stage (pT) determination. Dedicated uropathologists assessed specimens by using the 2009 and 2017 Tumor, Node, Metastasis (TNM) classification [6,7]. Pathologists were blinded to the results of EUA and imaging.

2.3. Statistical analysis

Descriptive statistics were used to characterize the analyzed group. Concordance (correct staging, understaging, overstaging) between clinical T stage in EUA and pathological T stage in the cystectomy specimen was assessed for individual patients and summed for the whole cohort.

Stages cT0-cT2 in EUA were considered to be localized disease, and cT3b, cT4a, and cT4b were considered to be locally advanced disease. Stage pT3a represents bladder cancer with microscopic invasion to the extravesical fat; therefore, it can only be detected based on pathological assessment. For this reason, separate analyses were performed for concordance by assuming that pT3a represents locally advanced disease per TNM classification and that pT3a is not locally advanced disease (because it cannot be determined from bimanual palpation or imaging).

We calculated sensitivities, specificities, positive predictive values (PPVs), and negative predictive values (NPVs) with 95% confidence intervals (CIs) in order to detect or exclude locally advanced bladder cancer, with EUA performed by a nonblinded and a blinded examiner. Weighted kappa with linear weights was computed to assess the agreement between the nonblinded and blinded examiners in clinical T staging [8].

Additionally, we assessed concordance between preoperative imaging (c_iT based on radiology reports) and pathological stage (pT) in patients with imaging during or after neoadjuvant chemotherapy (NAC) and in patients without NAC. Sensitivities, specificities, PPVs, and NPVs with 95% CIs were calculated to detect or exclude locally advanced disease in imaging.

Statistical analyses were performed by using Statistica 13.3, R 4.1.2, and Python 3.8.12.

3. Results

From June 2017 to October 2020, 137 patients were enrolled in the study and underwent EUA by two examiners in the operating room before cystectomy. Three patients were excluded from the final analysis because the pathology report revealed histology other than bladder cancer in the absence of bladder carcinoma (patients with pT0 bladder cancer with localized prostate cancer were not excluded). Demographic, clinical, and preoperative staging data are presented in Table 1 and Supplementary Table 1.

3.1. Bimanual palpation and pathology results

The results of bimanual palpation performed by the nonblinded and the blinded examiners and the details of pathological results are presented in Table 2. The overview of

Table 1
Patients' baseline characteristics ($n = 134$)

Demographic and surgical/radiotherapy history		
Gender, *n* (%)	Male	106 (79.1)
Age, y	Median (IQR)	67 (62−71)
BMI	Median (IQR)	26 (24.1−29)
History of (abdomino) pelvic surgery, *n* (%)	Yes	55 (41)
History of pelvic radiotherapy*, *n* (%)	Yes	9 (6.7)
	Bladder cancer history	
Indication for RC, *n* (%)	Pathologically confirmed MIBC	95 (70.9)
	Suspicion of MIBC (imaging suggesting MIBC)	28 (20.9)
	NMIBC	11 (8.2)
History of BCG therapy, *n* (%)	Yes	16 (11.9)
Neoadjuvant chemotherapy (NAC), *n* (%)	Underwent NAC	92 (68.7)
	Complete NAC	81 (60.5)
	Incomplete NAC	11 (8.2)
	No NAC	40 (29.9)
	History of radiochemotherapy	2 (1.5)
Preoperative staging based on the most recent imaging (abdominopelvic CECT or MRI and chest CT or X-ray)		
T staging, *n* (%)	c_iT0-T2 (tumor not visible/tumor visible)	57 (42.5)
	c_iT3b (extravesical invasion)	26 (19.4)
	c_iT4a (invasion of the prostate/uterus/vagina)	13 (9.7)
	c_iT4b (invasion of pelvic/abdominal wall)	4 (3)
	c_iTx (no imaging after NAC or noncontrast CT)	34 (25.4)
N staging, *n* (%)	cN0	90 (67.2)
	cN+	10 (7.5)
	cNx	34 (25.4)
M staging, *n* (%)	cM0	93 (69.4)
	cM+	5 (3.7)
	cMx	36 (26.9)

* Includes neoadjuvant radiotherapy ($n = 1$) and radiochemotherapy for bladder cancer ($n = 2$).BCG = Bacillus Calmette-Guérin; BMI = body mass index; CECT = contrast enhanced computed tomography; CT = computed tomography; IQR = interquartile range; MIBC = muscle invasive bladder cancer; MRI = magnetic resonance imaging; NAC = neoadjuvant chemotherapy; NMIBC = nonmuscle invasive bladder cancer; RC = radical cystectomy.

the results of clinical EUA-based and pathological T staging is illustrated in Supplementary Figure 1. Differences between pathological results and results of cT assessment by bimanual palpation by the nonblinded and blinded examiners are shown in Fig. 1.

3.2. Concordance between bimanual palpation (cT; index test) and pathology (pT; reference test) and diagnostic accuracy of bimanual palpation to detect or exclude locally advanced disease

The cross-tabulation of EUA results and pathological results is presented in Fig. 2A for the nonblinded examiner and in Fig. 2B for the blinded examiner. Concordance between clinical stage from EUA and pathological stage (assuming that pT3a does not represent a typical locally advanced disease because it cannot be palpated) is detailed in Table 3. The results of parallel analyses (assuming that pT3a represents locally advanced disease per TNM classification) are presented in Supplementary Table 2.

3.3. Concordance between nonblinded and blinded examiners

The cross-tabulation of the results of bimanual palpation performed by the nonblinded and blinded examiners is presented in Supplementary Figure 2. In 111 (82.8%) patients, both examiners indicated the same cT stage. In 13 (9.7%) patients, the nonblinded examiner indicated a lower stage than the blinded examiner did, whereas in 10 (7.5%) patients, the nonblinded examiner indicated a higher stage than the blinded examiner did. There was a moderate agreement between the 2 examiners (weighted kappa = 0.61, 95% CI 0.46−0.78, $p < 0.0001$) [9].

3.4. Concordance between imaging clinical stage (c_iT) and pathology (pT) and diagnostic accuracy of imaging to detect locally advanced disease

Fig. 3 shows cross-tabulation of the results of imaging and pathology in 100 patients, after excluding 34 patients without contrast-enhanced CT or MRI after NAC or

Table 2
Results of bimanual palpation performed by the nonblinded and blinded examiners and details of pathological assessment of cystectomy specimens ($n = 134$)

Results of bimanual palpation performed by the nonblinded and blinded examiners			
Nonblinded examiner ($n = 134$)		Blinded examiner ($n = 134$)	
Clinical T stage	*n* (%)	Clinical T stage	*n* (%)
c_{nb}T0-T2	108 (80.6)	c_bT0-T2	109 (81.3)
c_{nb}T3b	14 (10.4)	c_bT3b	9 (6.7)
c_{nb}T4a	8 (6)	c_bT4a	10 (7.5)
c_{nb}T4b	4 (3)	c_bT4b	6 (4.5)
Tumor or bladder fixed in bimanual palpation	21 (15.7)	Tumor or bladder fixed in bimanual palpation	23 (17.2)

Details of pathological assessment of cystectomy specimens ($n = 134$)		
Pathological assessment		*n* (%)
pT staging	pT0	27 (20.1)
	pTa	1 (0.7)
	pTis	10 (7.5)
	pT1	19 (14.2)
	pT2a	6 (4.5)
	pT2b	17 (12.7)
	pT3a	20 (14.9)
	pT3b	6 (4.5)
	pT4a	23 (17.2)
	pT4b	5 (3.7)
pN staging	pN0	94 (70.1)
	pN+	34 (25.4)
	pNx	6 (4.5)
Surgical margins	Negative	112 (83.6)
	Positive	22 (16.4)

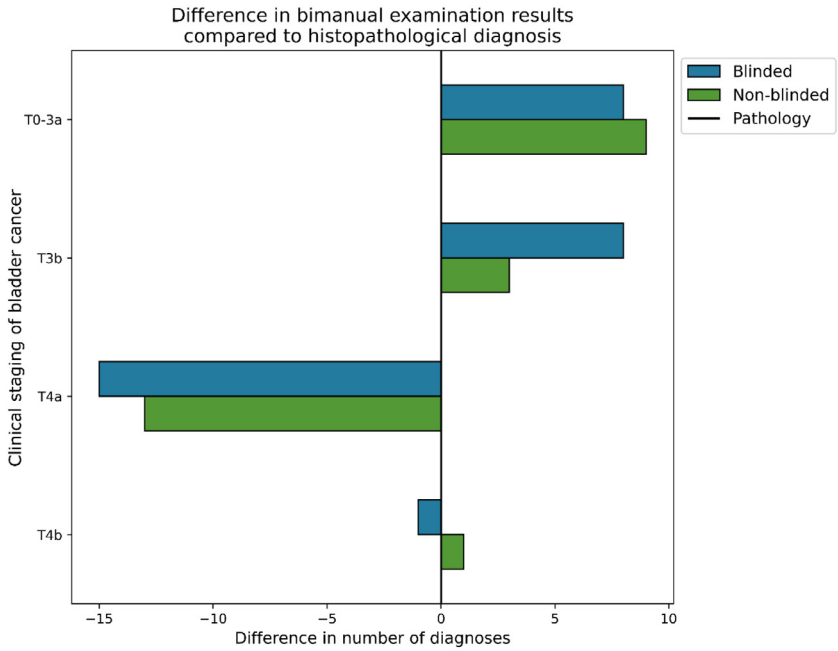

Fig. 1. Differences between clinical EUA-based and pathological staging.

A

Pathology / Non-blinded examiner	pT0-T2	pT3a*	pT3b	pT4a	pT4b**
c_{nb}T0-T2	76	17	1	14	-
c_{nb}T3b	3	3	5	3	-
c_{nb}T4a	1	-	-	5	2
c_{nb}T4b	-	-	-	-	4

* pT3a represents microscopic extravesical extension and cannot be palpated

** If bimanual palpation examiner indicated c_{nb}T4b and final pathology showed pT4a with multiple positive soft tissue margins, bimanual palpation was considered concordant (n=1)

B

Pathology / Blinded examiner	pT0-T2	pT3a*	pT3b	pT4a	pT4b**
c_{b}T0-T2	76	17	2	14	-
c_{b}T3b	2	2	3	2	-
c_{b}T4a	1	1	1	5	2
c_{b}T4b	1	-	-	-	5

* pT3a represents microscopic extravesical extension and cannot be palpated

** If bimanual palpation examiner indicated c_{b}T4b and final pathology showed pT4a with multiple positive soft tissue margins, bimanual palpation was considered concordant (n=2)

Fig. 2. Cross-tabulation of the results of bimanual palpation (index test) performed by the nonblinded examiner (c_{nb}T) and pathological T stage (pT) from pathological assessment (reference test) of cystectomy specimen (n = 134) (A) and cross-tabulation of the results of bimanual palpation (index test) performed by the blinded examiner (c_{b}T) and pathological T stage (pT) from pathological assessment (reference test) of cystectomy specimen (n = 134) (B).

Pathology / Imaging	pT0-T2	pT3a*	pT3b	pT4a	pT4b**
c_{i}T0-T2	41	6	1	9	--
c_{i}T3b	15	6	1	4	-
c_{i}T4a	2	3	3	4	1
c_{i}T4b	-	-	-	-	4

* pT3a represents microscopic extravesical extension and cannot be visualized in imaging

** If imaging indicated c_{i}T4b and final pathology showed pT4a with multiple positive soft tissue margins, imaging was considered concordant (n=1)

Fig. 3. Cross-tabulation of the results of clinical T staging from the most recent imaging (c_{i}T) and pathological T staging (pT) of cystectomy specimen in 100 patients with imaging after neoadjuvant chemotherapy or without neoadjuvant chemotherapy.

radiotherapy, or with NCCT only. Given that pT3a cannot be determined from imaging, T staging in imaging was correct in 56 (56%) cases, with 15 (15%) cases understaged and 29 (29%) overstaged (Supplementary Table 3). Sensitivity, specificity, PPV, and NPV of imaging to detect or exclude locally advanced disease (pT3b-T4b) was 63% (95% CI 44.7%−81.2%), 64.4% (95% CI 53.4%−75.4%), 39.5 (95% CI 24.9%−54.1%), and 82.8% (95% CI 72.6% −92.3%), respectively (Supplementary Table 3). The results of parallel analyses (assuming that pT3a represents locally advanced disease per TNM classification) are presented in Supplementary Table 4.

4. Discussion

This study showed that an examiner who was aware of the patient's history and imaging results was able to correctly determine clinical T stage in bimanual palpation in 80% of cases. The concordance rate of EUA performed by the examiner blinded to history and imaging was comparable. Almost 15% cases were understaged, whereas 5.2% were overstaged, which is less than that reported in the literature. To date, only retrospective studies regarding bimanual palpation have been published [4,10,11]. Ploeg et al. [4] assessed concordance between clinical stage in EUA and pathological stage, showing correct staging in 57.6% of cases, understaging in 31.1%, and overstaging in 11.3%. However, in their study, bimanual palpation findings before and after TURBT were compared with pathological results from a cystectomy performed later, and a different stratification of T stages was used. The improved concordance rate in our study could be due to different methodology.

Stage pT3a represents microscopic extravesical invasion and posed a challenge to the methodology, as it cannot be palpated or visualized in imaging. Studies show conflicting results regarding the importance of the differentiation between microscopic and macroscopic perivesical fat extension for prognosis [12−14]. In a study by Bastian et al. [12], microscopic perivesical extension (pT3a) was not associated with a higher recurrence or mortality rate in comparison with pT2, whereas the presence of deep perivesical extension (pT3b) was associated with a higher recurrence rate and twice the death rate in comparison with pT2. In contrary, Maas et al. [14] did not observe significant differences in overall survival or recurrence-free survival between patients with pT3a and with pT3b N0 bladder cancer. Whether stages pT2, pT3a, and pT3b carry significantly different prognoses remains unclear. Given that stage pT3a is impossible to be palpated or visualized in imaging, pT3b −T4b represented locally advanced disease in our study, as it was clinically more valid.

Stage pT4a seemed to be the most difficult stage to be recognized from bimanual palpation in our study (Fig. 1). One possible explanation is that urologists may be prone to interpret bimanual palpation as they do a digital rectal examination and may suspect concomitant prostate cancer rather than bladder cancer invasion to the prostate.

Bimanual palpation can yield different information depending on gender. Assessment of urethra and vagina in females might be particularly helpful in determining the ability to perform organ-sparing cystectomy. Moreover, examination involving vagina and urethra can further help in surgery planning, e.g. palpable urethral and/or vaginal infiltration would guide the operating team to secure proper surgical instruments and to appropriately position the patient.

The study group included 11 nonmuscle invasive bladder cancer (NMIBC) patients who had NMIBC in TURBT and

Table 3
Concordance between bimanual palpation clinical T stage (cT) and pathological T stage (pT) and diagnostic accuracy parameters of bimanual palpation to detect or exclude locally advanced disease (pT3b−-T4b; taking into consideration that pT3a is impossible to be palpated)

Concordance between bimanual palpation cT and pT (n = 134)		
	Nonblinded examiner	Blinded examiner
Correct staging, n (%)	107 (79.9)	106 (79.1)
Understaging, n (%)	20 (14.9)	20 (14.9)
Overstaging, n (%)	7 (5.2)	8 (6)
Concordance between bimanual palpation clinically organ confined vs. locally advanced (cT3b−T4b) and pathologically organ confined vs. locally advanced (pT3b−T4b)		
	Nonblinded examiner	Blinded examiner
Correct staging, n (%)	112 (83.6)	111 (82.8)
Understaging, n (%)	15 (11.2)	16 (11.9)
Overstaging, n (%)	7 (5.2)	7 (5.2)
Diagnostic accuracy parameters of bimanual palpation to detect or exclude locally advanced disease (pT3b−T4b)		
	Nonblinded examiner	Blinded examiner
Sensitivity, % (95% CI)	55.9 (39.2-72.6)	52.9 (36.2−69.7)
Specificity, % (95% CI)	93 (88-98)	93 (88−98)
Positive predictive value, % (95% CI)	73.1 (56-90.1)	72 (54.4−89.6)
Negative predictive value, % (95% CI)	86.1 (79.6-92.6)	85.3 (78.7−92)

CI = confidence interval.

who had no suspicion of MIBC in imaging. In these 11 patients EUA did not suggest locally advanced disease, and in all of them final pathology showed either no signs of disease, NMIBC, or localized muscle invasive disease.

Sensitivity, specificity, PPV, and NPV of EUA to detect or exclude locally advanced (pT3b−T4b) bladder cancer were higher in our study than in the study by Rozanski et al.[10], who retrospectively assessed the diagnostic accuracy of EUA, imaging, and a combination of these methods to detect clinically advanced disease (T3, T4). However, different methodologies make direct comparison of their results and ours impossible. Nonetheless, the satisfactory diagnostic parameters of EUA in our study underline the clinical value of EUA.

To explore the impact of imaging on staging in bimanual palpation, we blinded one of the examiners to the patients' imaging and history. Sensitivity, specificity, PPV, and NPV of EUA to detect locally advanced disease were comparable between the blinded and the nonblinded examiner, which suggests that awareness of imaging results did not have a major impact on EUA results.

Analysis of imaging for staging was considered an adjunct to the main study analyses, given that the imaging protocols and reports were not standardized, and staging was based on the imaging performed in various centers. The reason for the surprisingly high overstaging rate in imaging could be that radiologists might be prone to assess oncological cases overcautiously.

Direct comparison of EUA (assessed prospectively per protocol) and imaging (obtained from nonstandardized radiology reports) in T staging is not possible. Rozanski et al. [10], in the aforementioned study that retrospectively compared EUA, imaging, and other clinical factors, suggested that a combination of EUA and imaging was more accurate than any of these methods used alone. Studies prospectively comparing EUA and imaging are lacking.

To the best of our knowledge, this is the first study to prospectively assess the concordance and diagnostic accuracy of bimanual palpation in patients with bladder cancer. Additionally, we included settings of a nonblinded vs. blinded examiner. This approach gives further insight into the role of EUA in the era of widespread availability of imaging techniques.

The limitations of our study include the fact that the guidelines recommends bimanual palpation during TURBT [2,3], while in our study EUA was performed just before cystectomy. Nevertheless, in a diagnostic accuracy study, we wanted to ensure a close assessment time between the index and the reference test. Moreover, prospective comparison of EUA performed during TURBT, with cystectomy performed weeks later, in majority of cases preceded by NAC, could result in staging migration, and significantly change the index test findings. Another limitation is that cT staging in imaging was not standardized, and some reports were inconclusive, which makes a direct comparison of staging in EUA (assessed prospectively per protocol) and imaging impossible.

Despite these limitations, this is the first prospective assessment of diagnostic accuracy of a EUA as a diagnostic test, and 80% cT/pT concordance rate, which is higher than reported in retrospective studies, showed that it should not

be abandoned, and a downward trend in EUA use is not warranted.

The ability to correctly determine bladder cancer stage at the time of TURBT yields important information that can help in further treatment planning, e.g. decision regarding implementation of NAC vs. proceeding directly to cystectomy. Moreover, a strong suspicion of locally advanced disease in EUA performed during TURBT and/or before cystectomy, particularly when accompanied by limited mobility of the bladder, aids in planning surgical approach (open vs. minimally invasive) and can guide the operating surgeon towards more extensive resection.

Interestingly, in our study, among 23 patients with suspicion of locally advanced disease and fixed tumor or bladder in bimanual palpation performed by the blinded examiner, 11 (48%) had positive surgical margins in the final cystectomy specimen compared with 11 (10%) out of 111 patients without limited mobility of the tumor or bladder in EUA (with similar rate distribution for the nonblinded examiner). These findings suggest that preoperative EUA could yield prognostic information regarding surgical margins status, and that EUA demonstrating fixed tumor or bladder should prompt reconsideration of radical cystectomy given poor prognosis associated with positive surgical margins.

Large prospective comparison of EUA and imaging for clinical staging, taking into consideration also staging migration after NAC, could draw definite conclusions, but such data is lacking.

5. Conclusions

In this prospective study, bladder cancer T stage was correctly determined in bimanual palpation in 80% of cases if EUA was performed by an examiner who was aware of patient history and imaging results. Nearly 15% cases were understaged in EUA, whereas 5.2% were overstaged. The results of EUA performed by the blinded examiner were comparable, which suggests that awareness of imaging results did not have a major impact on EUA results.

Although a direct comparison of the diagnostic performance of EUA and imaging for T staging was not possible in this study, the results suggest that bimanual palpation should not be abandoned, as both methods of clinical stage assessment continue to be of value and should be used until proven otherwise.

Declaration of Competing Interest

None to declare

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Supplementary materials

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