

HOW ACCURATELY CAN UROLOGISTS PREDICT ELIGIBLE PATIENTS FOR IMMEDIATE POSTOPERATIVE INTRAVESICAL CHEMOTHERAPY IN BLADDER CANCER?

ABSTRACT:

Purpose: To assess the ability of urology residents and experienced urologists to accurately predict pathological features of bladder tumors based solely on cystoscopic appearance, and evaluate how accurately urologists can decide eligible patients for postoperative intravesical chemotherapy.

Methods: 104 patients with bladder mass were included, 7 senior urologists and 4 residents joined the study. Before resection, both specialists and residents were asked to predict the stage, grade of the tumor, and presence of CIS. We obtained resident predictions for 104 patients and senior predictions for 72 of these patients. Based on these predictions, eligibility of the patients for single postoperative immediate chemotherapy were determined according to EAU NMIBC guidelines. After final pathology report, risk scores recalculated and compared with surgeons' predictions.

Results: In correlation analysis, strong agreement with the pathological report could not be demonstrated with any of the stages, grades, and presence of CIS for both senior and resident urologists. Urology residents' predictions were slightly more accurate than the senior urologists'. According to senior urologists' predictions, 14/72 (19,4%) of the patients, and according to residents' predictions, 19/104 (18,2%) of the patients were found to be either overtreated or undertreated.

Conclusions: Cystoscopic visual prediction is not sufficient to decide on immediate postoperative intravesical chemotherapy regardless of the experience, and we need more objective parameters to improve the appropriate patient selection.

What's known: In patients with non-muscle invasive bladder cancer (NMIBC), decision of immediate postoperative chemotherapy instillation is made by urologists according to clinical and "presumed" pathological parameters as definitive pathology is unknown. Therefore, the concordance of this presumption with the final pathology is important.

What's new: In our study, we demonstrated that urologists' predictions on pathological features are not reliable to decide on immediate postoperative intravesical chemotherapy instillation and better criteria for patient selection are needed.

Keywords: bladder cancer, intravesical chemotherapy, prognosis

INTRODUCTION:

Bladder cancer is the 7th most frequently diagnosed cancer in the male population in the world and its incidence decreases to 11th when both sexes are considered [1]. Although there are some imaging techniques such as ultrasonography, CT urography, intravenous urography, and novel techniques like multiparametric MRI that can be used in the initial workup, diagnosis of bladder cancer ultimately depends on cystoscopic examination of the bladder followed by transurethral resection [2–5]. Risk classifications such as the European Organisation for Research and Treatment of Cancer (EORTC) and Spanish Urological Club for Oncological Treatment (CUETO) models are used to predict prognosis and to decide on appropriate treatment [6,7]. Risk classifications are based on cystoscopy findings and pathological features of the tumor and treatment options vary according to these pathological and clinical features. Early prediction of the risk group is important, especially to decide immediate postoperative chemotherapy in low-intermediate risk patients, as it reduces the 5-year recurrence rate by 14% [8]. European Association of Urology Guidelines on non-muscle-invasive bladder cancer (NMIBC), strongly recommend single immediate postoperative chemotherapy instillation (SI) in patients with tumors presumed to be at low risk and in those presumed to be at intermediate risk with previous low recurrence rate (less than one recurrence per year) and expected EORTC recurrence score < 5 [2]. Although tumor size, number of tumors, prior recurrence rate are rather objective parameters; T category, tumor grade, and presence of carcinoma in situ (CIS) are predictions that may vary according to the surgeons' intraoperative evaluation. With this decision, the patient will either receive a single dose of chemotherapy that will benefit the recurrence of the disease or will be exposed to an unnecessary drug administration with a risk of complications. This decision will be made by the urologist during cystoscopy with visual prediction. Therefore, the concordance of this decision with the final pathology is very important. But, how accurately can urologists distinguish low-intermediate risk tumors via cystoscopy without knowing the definitive stage and grade? Although cystoscopy is widely used for diagnosis and staging purposes, there are only a few studies in the literature, investigating the accuracy of urologists' predictions during cystoscopy and effect of clinical experience on these predictions.

The purpose of this study was to assess the ability of urology residents and experienced urologists to accurately predict pathological features of the tumor based solely on cystoscopic appearance, and evaluate how accurately urologists can decide eligible patients for SI.

METHODS:

One hundred and four consecutive patients who admitted to our clinic with a newly diagnosed bladder mass were included in our study. Patients who had been diagnosed with bladder cancer priorly were excluded. White light rigid cystoscopy was performed on all patients before transurethral resection of bladder (TURB). All procedures were performed by a senior urologist or a resident. Seven senior urologists (who had 7 to 25 years of experience with endourology and TURB) and 4 residents (who had 6 to 18 months of continuous experience in operation room) joined the study. Before resection, both senior urologists and residents were asked to predict the stage, grade of the tumor, and presence of concomitant CIS without hearing each other. We obtained resident predictions for 104 patients and senior predictions for 72 of these patients. Predictions of the surgeons were compared with pathological findings. Pathology specimens were evaluated by uropathologists who are blinded to predictions of surgeons. 2017 TNM classification of urinary bladder cancer for staging and 2004/2016 WHO classification was used for grading purposes [9,10].

The Cohen Kappa (κ)co-efficient was used to describe the agreement between surgeons' predictions and pathological grade and stage. Kappa results interpreted as follows; values ≤ 0 as indicating no agreement and 0.01-0.20 as poor, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial, and 0.81-1.00 as almost perfect agreement [11]. Positive and negative predictive values were calculated for both senior and resident urologists.

EAU risk scores and EORTC recurrence scores are calculated for all of the patients who were predicted to have NMIBC. Patients who were predicted to be low-intermediate risk group and to have an EORTC recurrence score <5 were considered as eligible patients for SI. After pathological examination, risk scores and EORTC recurrence scores were recalculated according to the final pathological report and compared with surgeons' predictions.

RESULTS:

Mean age of the patients was 67.6 ± 10.7 , 84,6% were male, 15.5% were female. 16 (15.3%) patients were diagnosed with muscle-invasive bladder cancer (MIBC), 88 (84.6%) with NMIBC on pathological analysis. 59 (56.7%) patients were evaluated as high grade and 45 (43.2%) patients as low grade on pathological analysis.

When we analyzed the agreement between senior urologists' predictions and pathological assessment, there was a fair correlation for stage, moderate correlation for grade, and poor correlation for presence of CIS (kappa: 0.333, 0.528, 0.180 respectively) (Table 1). As we look at the agreement between residents' predictions and pathological assessment, there was a fair correlation for stage, moderate correlation for grade, and fair correlation for presence of CIS (kappa: 0.393, 0.574, 0.228 respectively) (Table 2). Urology residents' predictions were slightly more accurate than the senior urologists' for stage, grade, and presence of CIS (Table 3).

All surgeons were more likely to overstage and overgrade bladder cancer. Likelihood of predicting NMIBC as MIBC was 68,4% (13/19) and 64,2% (18/28) for seniors and residents respectively. Conversely, likelihood of predicting MIBC as NMIBC was 9,4% (5/53) and 7,8% (6/76). Likelihood of predicting low grade tumors as high grade was 25,4%(13/51) and 27,4%(17/62). Whereas likelihood of predicting high grade tumors as low grade was 14,2% (3/21) and 12,5% (4/32) for seniors and residents respectively.

When tumor grade, stage, and presence of CIS were predicted together, 30/72 (41.6%) cases were in full agreement with pathological evaluation for senior urologists and 46/104 (%44.2) for resident urologists.

Both seniors and residents could predict low stage and grade tumors more accurately than the tumors with higher stage and grade (Table 3).

According to senior urologists' predictions, 20 of 72 patients were considered eligible for SI. 3/20 (15%) of eligible patients were determined to be ineligible after pathological report. 52 patients were considered to be ineligible for SI. 11/52 (21,1%) of these patients were determined to be eligible after pathological report. Cumulatively 14/72 (19,4%) of the patients were found to be either overtreated or undertreated based on surgeons' predictions.

According to residents' predictions, 31 of 104 patients were considered eligible for SI. 4/31 (12,9%) of eligible patients were determined to be ineligible after pathological report. 73 patients were considered to be ineligible for SI. 15/73 (20,5%) of these patients were determined to be eligible after pathological report. Cumulatively 19/104 (18,2%) of the patients were found to be either overtreated or undertreated based on surgeons' predictions.

DISCUSSION:

Predicting stage and grade early may be useful to inform patients about the prognosis of the disease and prepare for the possible treatments. It is also essential for deciding immediate postoperative chemotherapy. Several meta-analyses have shown the benefits of SI in NMIBC [12–14]. The prediction of urologists during cystoscopy are important to decide eligible patients, as the definitive stage and grade of the tumor are unknown at this time.

In examining our results according to pathological parameters separately, urologists were able to predict low stage and low grade tumors better than pT1, pT2, and high grade cancers. However, in correlation analysis, strong agreement with the pathological report could not be demonstrated with any of the stages, grades, and presence of CIS.

We hypothesized that more experienced surgeons would be more accurate in predicting pathological features. But on the contrary, we found that residents were slightly more accurate. In our clinic, residents who are assigned to operation room participate in every operation performed during their assignment. Whereas, senior urologists only perform or supervise the operations consulted with them. Therefore, we speculate that recent experience might be more important than lifelong experience in predicting the histopathological features of the tumor.

It has been previously shown that urologists can distinguish malignant lesions from benign lesions quite accurately [15]. Also, there are several studies with conflicting results investigating accuracy of cystoscopy regarding prediction of the histological features of the tumor [15–18]. In a study conducted by Cina et al., it is reported that urologists discriminated between benign and malignant lesions with positive and negative predictive values of 100%, however, cystoscopy could not accurately predict the invasion of lamina propria or muscle tissue or the stage of the urothelial carcinoma [15]. In a multicentre study by Steffens et al, they suggest that cystoscopy is not a reliable tool for predicting stage of the bladder cancer, with a PPV of 52%, and an NPV of 95% for MIBC, regardless of the educational degree of the urologists [17].

Contrary to our result During et al. suggests that visual assessment is accurate in predicting the presence of MIBC with a PPV of 78.4% (95% CI 65.4%– 87.5%) and an NPV of 95.7% (95% CI 90.3%–98.1%) [19]. Likewise in a recent study, it is reported that positive predictive values for low- and high- grade cancers were 85.8% and 71.3%, respectively; and non-muscle-invasive and muscle-invasive cancers were predicted accurately in 93.4% and 85.2% patients, respectively [20].

Nevertheless, none of these studies investigated appropriate patient selection for immediate postoperative chemotherapy.

Our study shows that, based on urologists' predictions, a significant percentage of patients who do not benefit from early postoperative chemotherapy may be over-treated, leading to unjustifiable morbidities and cost loss. On the other hand, patients who may benefit from the treatment can be overlooked.

EORTC trials have demonstrated that tumor size and number of tumors are predictors of recurrence of the disease [21]. However, while deciding on SI; tumor stage, grade, and presence of CIS depends on urologists' estimation. Our findings show that these predictions are not accurate enough and better criteria are needed to avoid unnecessary treatments and improve cost-effectiveness.

Our study has a number of limitations. We could not obtain predictions of senior urologists for 32 of the patients before resection as they were not present in the operation room to supervise, due to the high volume of our clinic. In literature, T1 tumors have been shown to have an 8-49% risk of misstaging and repeated TURB is recommended [22,23]. We included the first pathological reports in our study and did not evaluate repeat TURB reports. Therefore, there may be pathological understaging in some cases. However, on the subject of SI, it is not a limitation since T1 patients were not our target.

CONCLUSION:

Although cystoscopy is known to be a good diagnostic tool for bladder urothelial carcinoma, it is not accurate in predicting stage and grade of the tumors, regardless of experience of the surgeon. Cystoscopy findings cannot replace histopathology in managing the disease or predicting the prognosis of the patient. Cystoscopic visual prediction is not sufficient to decide on immediate postoperative intravesical chemotherapy instillation, and we need more objective parameters to improve the appropriate patient selection.

Author Contributions

All of the authors have contributed in conception and design. H.A. YILDIZ and M. D. DEĞER did data acquisition. H.A. YILDIZ and G. ASLAN analysed and interpreted the data. H.A. YILDIZ drafted the manuscript. Study was supervised by G. ASLAN. All authors reviewed the final manuscript.

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The authors have no conflicts of interest to declare.

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925–933.

TABLES:

Table 1: Assosiaciton between pathological and predicted tumor features by senior urologists.

| | | | |
|---|--------------------|-----------------|---------|
| | Pathological stage | | |
| | Ta (29) | T1 (32) | T2 (11) |
| Predicted stage | | | |
| Ta (22) | 19 | 3 | 0 |
| T1 (31) | 10 | 16 | 5 |
| T2 (19) | 0 | 13 | 6 |
| <i>Kappa 0,333 (fair correlation)</i> | | | |
| | Pathological grade | | |
| | Low grade (31) | High grade (41) | |
| Predicted grade | | | |
| Low grade (21) | 18 | 3 | |
| High grade (51) | 13 | 38 | |
| <i>Kappa 0,528 (moderate correlation)</i> | | | |
| | Pathological CIS | | |
| | Positive (14) | Negative (58) | |
| Preticted CIS | | | |
| Positive (11) | 4 | 7 | |
| Negative (61) | 10 | 51 | |
| <i>Kappa 0,180 (poor correlation)</i> | | | |

Table 2: Assosiaciton between pathological and predicted tumor features by resident urologists.

| | | | |
|---|--------------------|-----------------|---------|
| | Pathological stage | | |
| | Ta (44) | T1 (44) | T2 (16) |
| Predicted stage | | | |
| Ta (33) | 29 | 4 | 0 |
| T1 (43) | 13 | 24 | 6 |
| T2 (28) | 2 | 16 | 10 |
| <i>Kappa 0,393 (fair correlation)</i> | | | |
| | Pathological grade | | |
| | Low grade (45) | High grade (59) | |
| Predicted grade | | | |
| Low grade (32) | 28 | 4 | |
| High grade (72) | 17 | 55 | |
| <i>Kappa 0,574 (moderate correlation)</i> | | | |
| | Pathological CIS | | |
| | Positive (20) | Negative (84) | |
| Preticted CIS | | | |
| Positive (18) | 7 | 11 | |
| Negative (86) | 13 | 73 | |
| <i>Kappa 0,228 (fair correlation)</i> | | | |

Table 3: Positive predictive values for urology specialists and residents.

| | Specialists | | Residents | |
|--------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| | PPV (95% CI) | NPV (95% CI) | PPV (95% CI) | NPV (95% CI) |
| Ta | 86.36% (67.33% - 95.11%) | 80% (70,64% - 86,93%) | 87.88% (73.32% - 95.03%) | 78,87% (71,11% - 84,99%) |
| T1 | 51.61% (38.59% - 64.42%) | 60,98% (50,62% - 70,43%) | 55.81% (44.38% - 66.66%) | 67,21% (58,69% - 74,73%) |
| T2 (MIBC) | 31.58% (18.29% - 48.76%) | 90,57% (83,22% - 94,89%) | 35.71% (24.09% - 49.31%) | 92,11% (86% - 95,68%) |
| Ta/T1 (NMIBC) | 90.57% (83.22% - 94.89%) | 31,58% (18,29% - 48,76%) | 92.11% (86.00% - 95.68%) | 35,71% (24,09% - 49,31%) |
| High Grade | 74.51% (65.69% - 81.69%) | 85,71% (65,97% - 94,89%) | 76.39% (68.85% - 82.57%) | 87,5% (72,57% - 94,88%) |
| Low grade | 85.71% (65.97% - 94.89%) | 74,51% (65,69% - 81,69%) | 87.50% (72.57% - 94.88%) | 76,39% (68,85% - 82,57%) |
| CIS | 36.36% (16.24% - 62.75%) | 83,61% (78,32% - 87,8%) | 38.89% (22.02% - 58.92%) | 84,88% (80,11% - 88,67%) |