Predicting Recurrence and Progression in Patients with Non-Muscle-Invasive Bladder Cancer : Utility of the EORTC and CUETO Scoring Models

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Gutachter

1. Prof. Dr. med. Marc-Oliver Grimm, Jena
2. Prof. Dr. Iver Petersen, Jena
3. Prof. Dr. med. Michael Fröhner, Dresden

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List of Abbreviations

AUA	American Urological Association
BC	Bladder cancer
BCG	Bacillus Calmette-Guérin
CIS	Carcinoma in situ
CT	Computed tomography
CUETO	Spanish Urological Club for Oncological Treatment
EAU	European Association of Urology
EORTC	European Organization for Research and Treatment of Cancer
IBCG	International Bladder Cancer Group
ICUD	International Consultation on Urological Diseases
MIBC	Muscle invasive bladder cancer
NMIBC	Non-muscle invasive bladder cancer
NCCN	National Comprehensive Cancer Network
PDD	Photodynamic diagnosis
PFS	Progression free survival
PUNLMP	Papillary urothelial neoplasm of low malignant potential
RFS	Recurrence free survival
TNM	Tumor, Node, and Metastasis classification
TUR	Transurethral resection
TURB	Transurethral resection of bladder
TURBT	Transurethral resection of bladder tumor
WHO	World Health Organization
WLC	White light cystoscopy

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Zusammenfassung

Das Harnblasenkarzinom ist der häufigste maligne Tumor der ableitenden Harnwege. Ca. 70% der Patienten kommen initial mit einem nicht-muskel-invasiven Blasenkarzinom (NMIBC) zu Untersuchung. Nach den Leitlinien der European Association of Urology (EAU), werden NMIBC in 3 Risikogruppen eingeteilt: Niedriges, intermediäres und hohes Risiko. Dies ist die Grundlage für eine risikoadaptierte Therapie.

Trotz umfrangreicher molekularbiologischer Forschungen in den vergangenen Jahren gibt es bisher keine geeigneten molekularen Marker für den klinischen Einsatz. Deshalb sind klinische und pathologische Faktoren wichtig, um das Risiko für Tumorrezidiv und -Progression zu bewerten. Auf der Basis einer Metaanalyse haben die EORTC- und die CUETO-Gruppe jeweils einen Risikoscore für NMIBC entwickelt. In der vorliegenden Studie werden potentielle prognostische Faktoren anhand der Daten der Urologischen Klinik der Uni Jena analysiert. Darüber hinaus erfolgt eine Evaluation der EORTC und CUETO Risikotabellen an diesem Patientenkollektiv.

Es wurde eine retrospektive Auswertung aller Patienten mit NMIBC, die sich zwischen Januar 2003 und Dezember 2011 einer transurethralen Resektion unterzogen, vorgenommen.. Zur Datenanalyse wurden die klinischen Befunde, die histopathologischen Ergebnisse des Operationspräparates und die Befunde der Nachsorgeuntersuchungen herangezogen: Geschlecht, Alter, bisherige Rezidivrate, Anzahl der Tumoren, Tumorgröße, Tumorlokalisation, pT-Stadium, Differenzierungsgrad, Vorliegen eines CIS, erste Nachresektion, pathologisches Ergebnis der Nachresektion, intravesikale BCG- oder Chemotherapie, Rezidiv und Progression. Die Patienten wurden drei Risikogruppen nach der EAU Klassifikation eingeteilt..

Non den in die Studie eingeschlossenen 611 Patienten hatten 197 (32%) ein nidriges, 251 (41%) ein intermediäres und 163 (27%) ein hohes Risiko. Bei 535 (87.6%) Patienten wurde eine Nachresektion durchgeführt. Nachbeobachtungsdaten konnten in 528 Fällen erhoben werden. Die mediane Nachbeobachtungszeit lag bei 60 Monaten (1-143Mo) nachbeobachtet Die Gesamtwahrscheinlichkeit für ein Tumorrezidiv zeigten lag nach einem Jahr nach Diagnose bei 18,6%, nach zwei Jahren bei 33.7% und nach fünf Jahren bei 43.9%. Die Progressionsrate lag bei 0.9%, 2.6%, und 6.6% nach ein, zwei und fünf Jahren.

In der Subgruppe der pTaG1/G2 Tumoren führte die sekundäre TUR zu einem signifikant reduzierten Rezidivrisiko. Insgsamt ergibt die statistische Auswertung dass die vorherige Rezidivrate und das pathologische Ergebnis der Nachresektion unabhängige prognosische

Faktoren für ein Tumorrezidiv waren. Alter, vorherige Rezidivrate, pT-Stadium, Differenzierungsgrad, und pathologische Ergebnis der Nachresektion waren unabhängige prognosische Faktoren für eine Tumorprogreession. Im Vergleich zur tatsächlichen Rezidivrate in unserem Patientenkollektiv unterschätzten die CUETO-Risikotabellen das Rezidivrisko. Demgegenüber entsprach die Progressionrate den Vorhersagewerten der EORTC und CUETO Tabellen.

Insgesamt zeigt die Studie eine hohe Bedeutung für die transurethrale Nachresektion beim NMIBC. Die verfügbaren Risikokalkulatoren der EORTC- bzw. CUETO-Gruppe eignen sich vor allem für die Vorhersage des Progressionsrisikos, weniger für die Vorhersage eines Tumorrezidivs. Vor allem bei Patienten mit hohem Risiko ist die Aussagekraft dieser Kalkulatoren in dem vorliegenden Kollektiv mit routinemäßiger Nachresektion allerdings eingeschränkt .

Summary

Bladder cancer is the most common malignancy of the urinary tract. Approximately 70% are non-muscle-invasive tumors at initial diagnosis. Based on the recommendation of EAU guidelines, non-muscle-invasive bladder cancer (NMIBC) is stratified into three categories, including low, intermediate, and high risk groups of recurrence and progression. This allows urologists for better treatment selection.

Molecular research has provided great insight into the biology of bladder cancer. However, no molecular marker has been accepted as a standard diagnostic procedure in clinical practice. Therefore, clinical and pathological variables still play important roles to predict disease recurrence and progression. The currently used risk categories are based on historical data from the EORTC and CUETO groups. However, these models, may not apply to NMIBC patients treated nowadays e.g. if patients undergo routine re-resection and BCG maintenance therapy. Thus, the goal of our study was to distinguish putative important predictive factors and to evaluate the utility of both existing models in our patients.

A retrospective single center study was performed including treated patients with NMIBC between January 2003 and December 2011 at our department. The following clinical and pathologic data were analyzed: gender, age, prior recurrence rate, number of tumors, tumor size, location of tumors, tumor stage, tumor grade, presence of CIS, second TURB, second TUR pathology, intravesical treatment, recurrence and progression of bladder tumor. Patients were stratified into three risk categories according to the EAU guidelines.

Of the 611 patients, 197 (32%), 251 (41%) and 163 (27%) were assigned to the low, intermediate, and high risk category, respectively. Of these patients 535 (87.6%) underwent a second TUR. Overall, 528 patients were included ultimately in our follow-up study. The median follow-up was 60 months (range: 1-143 months). The overall recurrence rates in our cohort was 18.6%, 33.7%, and 43.9% after the 1st, 2nd and 5th year, respectively. The corresponding progression rates were 0.9%, 2.6%, and 6.6%.

A second TUR was associated with a reduced risk of disease recurrence in primary TaG1/G2 patients. Overall, prior recurrence rate and second TUR pathology are independent predictors of disease recurrence, whereas age, prior recurrence rate, tumor stage, tumor grade, second TUR, and second TUR pathology are prognostic factors for disease progression. The CUETO recurrence risk table severely underestimates the risk of disease recurrence in our cohort. However, the EORTC and CUETO risk tables are suitable tools to estimate disease progression in our cohort.

Summary

In summary, second TUR is of paramount importance and should be applied to all NMIBC patients. The EORTC and CUETO risk models are suitable to estimate progression risk. However, both risk calculators do not accurately predict risk of recurrence ,especially in the high risk patients. The latter may be due to the routine use of second TUR in our cohort.

1 Introduction

1.1 Epidemiology and Etiology

Bladder cancer (BC) is the 11th most commonly diagnosed cancer and the 14th leading cause of cancer deaths worldwide, with an estimated 382,700 new cases and 150,300 deaths in 2010 (Ferlay et al. 2010).The world global age standardized mortality rate is 3 per 100,000 for men versus 1 per 100,000 for women. In the European Union, age standardized mortality rate is 8 for men and 3 per 100,000 for women, respectively. At initial diagnosis, approximately 70% of the patients have non-muscle-invasive bladder cancer (NMIBC). Of those patients, 70% are confined to the bladder mucosa (Ta), 25% in the lamina propria (T1) and 5% have carcinoma in situ only (CIS) (Herr et al. 2001).

In Germany, more than 13,000 were diagnosed with non-invasive papillary carcinoma or CIS tumors of the bladder. The majority of BC cases are transitional cell carcinomas. One in 23 men and one in 62 women are identified with BC during their lifetime. The median diagnostic age at diagnosis is 72 years among men and 74 years among women. In the state of Thuringia, incidence and mortality of BC are higher in men and lower in women compared with the average of Germany (Robert Koch-Institute, 2014).

The etiology of BC appears to be multifactorial with exogenous environmental factors, as well as endogenous molecular factors. Firstly, tobacco smoking is the most important risk factor for BC, causing 50-65% of male cases and 20-30% of female cases (Burger et al. 2013, Freedman et al. 2011). However, an association between tobacco consumption and progression or death resulting from BC has never been found (Murta-Nascimento et al. 2007). Occupational exposure is the second most important risk factor for BC. The two groups of chemicals known to cause bladder cancer are aromatic amines and polycyclic aromatic hydrocarbons (Colombel et al. 2008). In 2013, the International Agency for Research on Cancer classified pioglitazone hydrochloride as probably carcinogenic to humans with regard to BC. Chronic inflammatory damage of the bladder mucosa also increases the risk of bladder carcinoma (Burger et al. 2013).

Furthermore, other factors e.g., external-beam radiotherapy and chronic urinary tract infection have been considered related to BC. The links remain, however, controversial.

1.2 Economics

BC is one of the most common malignant diseases worldwide and treatment costs are

substantial. In terms of clinical and economical aspects, it is important to remember that BC is often a chronic disease.

Based on the statistic drawn from USA, BC costs from diagnosis-to-death between $89,287 and $202,203 (Botteman et al. 2003). Another study in UK indicated that transurethral resection of the bladder (TURB) represents the largest BC expenditure, accounting for 71% of treatment costs (Sangar et al. 2005).

NMIBC has an average 60–80% recurrence rate. 40–60% recurrences occur within 2 years, with 10-30% of the patients finally developing muscle-invasive bladder cancer (MIBC) which requires more invasive and costly treatment (Herr 2000). The costs of TURB and cystectomy in Germany are $2,967 and $20,507, respectively. Progression from NMIBC to MIBC obviously increases overall treatment costs.

Based on tumor risk category, the European Association of Urology (EAU) guidelines recommend intravesical chemotherapy or adjuvant immunotherapy using BCG following TURB. Especially in high-risk BC monitoring generates significant on-going costs. About 75% of the post-diagnosis costs relate to preoperative and intraoperative management including postoperative complications, tri-annual examinations and semi-annual diagnostic and laboratory testing (Marchetti et al. 2000).

On the other hand, there is also the enormous financial burden that cancer exerts on patients and their families. Yabro and colleagues showed that the estimated patient's cost for traveling, waiting for appointments and receiving services or procedures during the first 12 months after primary diagnosis was as much as $5605 in USA (YabroV et al. 2007).

The high incidence and long term survival leads to a high prevalence of BC. Lifelong routine monitoring and treatment are often necessary. Therefore, the cost in bladder cancer is the highest of all cancers per patient.

1.3 Staging

The tumor, node and metastasis (TNM) classification of malignant tumors is the method most widely used to classify the extent of cancer spread. Recently, a seventh edition was published (Table 1), effective as of 2010. There are no significant modifications about BC in comparison with the previous 2002 edition.

According to the TNM classification system, a papillary tumor confined to the mucosa is classified as stage Ta. Tumors that have invaded the lamina propria are classified as stage T1. Also CIS are flat, high-grade tumors that are confined to the mucosa. Stage Ta, CIS (mucosa) and stage T1 (submucosa) define the group of NMIBC.

Table 1 2009 TNM classification of urinary bladder cancer

T	**Primary tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*: 'flat tumor'
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle
	T2a Tumor invades superficial muscle (inner half)
	T2b Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue:
	T3a Microscopically
	T3b Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
	T4a Tumor invades prostate, uterus or vagina
	T4b Tumor invades pelvic wall or abdominal wall
N	**Lymph nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis
N2	Metastasis in multiple lymph nodes in the true pelvis
N3	Metastasis in common iliac lymph node(s)
M	**Distant metastasis**
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

1.4 Histological Grading

In 1998, a new classification of non-invasive urothelial tumors was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) (1998 WHO/ISUP classification) and published by the WHO in 2004 (Epstein et al.1998, Sauter et al. 2004).The WHO 2004 classification system is recommended for classification

and grading in urothelial neoplasms (Table 2).

Compared with the old 1973 WHO system,, a new subgroup papillary urothelial neoplasm of low malignant potential (PUNLMP) is described, which is defined as a papillary fibrovascular growth covered with proliferated urothelium, exceeding the normal thickness, this corresponds largely to grade 1 papillary transitional cell carcinoma of the old 1973 WHO system, though not completely.

Table 2 WHO grading of urothelial tumor in 1973 and 2004

1973 WHO grading
Urothelial papilloma
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004 WHO grading
Papillary lesions
Urothelial papilloma (completely benign lesion)
Papillary urothelial neoplasm of low malignant potential
Low-grade papillary urothelial carcinoma
High-grade papillary urothelial carcinoma
Flat lesions
Hyperplasia (flat lesion without atypia or papillary aspects)
Reactive atypia (flat lesion with atypia)
Atypia of unknown significance
Urothelial dysplasia
Urothelial CIS

Urothelial carcinoma in situ (CIS) was firstly reported as a distinct phenomenon by Melicow (Melicow 1952). Despite the non-invasive character of CIS, it was suspected to possess aggressive tumor biology and tendencies towards early progression (Witjes 2004). CIS is malignant neoplasia of the urothelium, which is flat and not protruding into the bladder and which does not invade the lamina propria. While low grade non-invasive lesions are thought to derive from chromosome 9 abnormalities and mutations in the fibroblast growth factor receptor gene, CIS is marked by deletions of 19p13 resulting in TP53 mutations with consecutive prevention of cell cycle arrest and generalized genetic instability (Hartmann et al. 2002).

In terms of tumor distribution, the grading categories of the 2004 WHO system do not directly translate from the 1973 WHO system categories (May et al.2010, Schned et al. 2007). Most clinical trials published so far on bladder cancer have been performed using the 1973 WHO classification. Therefore, until the 2004 WHO classification has been validated by further clinical trials, BC should be graded using both the 1973 and the 2004 WHO classifications.

1.5 Diagnosis

1.5.1 Hematuria

In general, the painless hematuria is a cardinal presenting symptom of NMIBC. However, hematuria may be accompanied by irritative voiding symptoms in patients with CIS. The incidence of BC is 17-18.9% in those macroscopic hematuria and 4.8-6% in patients presenting with microscopic hematuria (Edwards et al. 2006, Datta et al. 2002, Mishriki et al. 2008). It is unknown if early detection of BC associated with asymptomatic microscopic hematuria leads to an improved outcome (Kamat et al. 2013).

1.5.2 Urinary Cytology and Markers

Urine cytology is the morphologic features of urothelial cells, which can be used to screen and evaluate patients at high-risk urothelial tumors and to monitor recurrence, progression, or response to treatment in patients with a known history of NMIBC. Sensitivity and positive predictive value are particularly high in high-grade urothelial tumors as well as in cases of CIS in which sensitivities can exceed 90%. Cytology is less effective for low-grade urothelial tumors and as a qualitative technique is subject to considerable variation in interpretation (Gaston and Pruthi 2004).

The specificity of cytology is superior to that of most of the available bladder tumor markers. Currently, combinations of cytology and urinary biomarkers have also been reported. In a study conducted by Horstmann, 221 patients undergoing cystoscopic surveillance for NMIBC were evaluated with urine cytology, NMP22 testing, fluorescence in situ hybridization (FISH Test) , and ImmunoCyt. Sensitivity increased to over 90% and negative predictive value increased to over 80% with combinations of 2 or 3 biomarkers, although specificity was reduced to an average of 44% with 2 biomarkers and 35% with 3 biomarkers (Horstmann et al. 2009). However, none of the markers has achieved acceptance as a standard diagnostic procedure in clinical practice (Babjuk et al.2011). Those investigated tests and identified markers include the BTA TRAK test, NMP22 BladderChek assay, ImmunoCyt test, FISH test,

BLCA-4, hyaluronic acid, telomerase, microsatellite polymorphism analyses, cytokeratins, and survivin (Konety 2006).

1.5.3 Cystoscopy

The combination of urine cytology and cystoscopy has been considered as the gold standard for the diagnosis and surveillance of BC. White light endoscopic examination of both the urethra and the bladder remains the gold standard for the diagnosis for multiple diseases of the lower urinary tract, including urothelial carcinoma. The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of the resection specimen. A careful description of the urothelial lesions is necessary, including the site, size, number, and appearance of the tumors, as well as a description of mucosal abnormalities.

Photodynamic diagnosis (PDD) is currently recommended for treatment of patients with newly diagnosed lesions suspicious for NMIBC, examination of patients with positive urine cytology but negative findings on white light cystoscopy (WLC), and treatment of multifocal recurrent BC. PDD can improve detection of disease, especially CIS. Improved visualization leads to reduced rates of residual tumor at first-look cystoscopy and perhaps reduced rates of recurrence (Filbeck et al. 2002). The advantage of WLC plus PDD over WLC alone in the visualization and staging of BC is widely accepted. However, there may be artificial fluorescence during PDD examination. Folds of the urothelium will cause such artifact, and therefore the bladder should be sufficiently dilated. Other common sites are along blood vessels, on the trigone, and around the ureteric orifices. Grossman demonstrated a slightly higher false-positive rate due to nonspecific inflammation that can occur after treatment of a urinary tract infection, after TURB, or after intravesical therapy with Bacillus Calmette-Guérin (BCG) (Grossman et al. 2007).

1.5.4 Imaging

If hematuria is the initial symptom, imaging will be performed to evaluate the upper urinary tract especially with regard to the putative presence of upper tract tumors. These occur in less than 5% of patients with a known history of lower tract cancer (Messing EM and Catalona W. 1998). Options for imaging are ultrasonography, intravenous urography, computed tomography (CT), magnetic resonance imaging, or a combination of these examinations. Ultrasonography is primarily used to evaluate the renal parenchyma.

Improvements in the technical quality of ultrasonography have also resulted in improved

performance of this imaging modality in detecting BC. The reported sensitivities are 63-98% and specificity is 99% with respect to BC (Datta et al. 2002). CT urography permits evaluation of both the renal parenchyma and other pathologic conditions within the genitourinary tract. A meta-analyses of 5 studies of CT urography indicated a pooled sensitivity of 96% and a pooled specificity of 99% in identifying upper urinary tract malignancy (Chlapoutakis et al. 2010). In imaging of the bladder, ultrasonography and CT urography have similar specificities in the diagnosis of BC. However, CT urography has higher sensitivity (89.7% vs 69%) (Knox et al. 2008). Furthermore, CT urography demonstrates the size of lesions within the bladder, extravesical spread, and pelvic lymph node status whereas ultrasonography may not. On the other hand, the disadvantages of CT urography are relatively high radiation doses, need for intravenous contrast medium, limited availability, and relatively high cost.

1.5.5 Diagnostic Transurethral Resection of Bladder Tumors

Ultimately, the diagnosis of urothelial carcinoma is made upon excision of the vesical lesion by TURB (Shelfo et al. 1997). The diagnostic purpose of TURB is to obtain a specimen sufficient to permit proper estimation of the tumor, which is based largely on stage, grade, histological subtype and the presence of lymphovascular invasion.

The bladder should be examined perfectly with both a 30-degree and a 70-degree lens. Visualization of the anterior bladder neck may be improved by using a 120-degree scope or by using retroflexion with a flexible cystoscopy. The dome and anterior bladder are examined by applying gentle suprapubic pressure to move the bladder mucosa down and closer to the lens. It is critical to maintain optimal bladder distention during cystoscopy and TURB. Finally, prostatic urethral biopsy may be performed in selected cases using electrocautery loop resection including the 5 o'clock and 7 o'clock positions of the verumontanum.

1.6 Treatment Strategy

The major goals in treating patients with NMIBC are to reduce recurrence frequency and to prevent progression to muscle-invasive disease. The optimal management of NMIBC is based on three criteria: complete first TUR, effective intravesical treatment and optimal time intervention with radical cystectomy in high-risk patients (Kulkarni et al. 2010).

In most cases of NMIBC, tumors are treated initially with TURB. A precise documentation of the cystoscopic examination is necessary. Generally, the site of tumor(s), tumor configuration, (papillary or sessile), estimates of the number of tumors and their sizes should be noted to

assist evaluation during second TUR and follow-up. After resection of all visible tumors, adjuvant intravesical immunotherapy or chemotherapy can be used (Messing EM and Catalona W. 1998). Urologists must always weight the risks and benefits of aggressive versus conservative treatment of NMIBC.

1.6.1 TURB and Second Resection

TURB is the first-line treatment for patients with NMIBC. The goal of TURB is to make the correct diagnosis and remove all visible lesions. It is a crucial procedure in the diagnosis and treatment of BC. A careful cystoscopic evaluation and eradication of tumor is an important therapeutic intervention at primary diagnosis.

TURB not only establishes staging of the tumor, but it also serves as the basis for adjuvant treatment decisions and follow-up intervals. The strategy of resection depends on the size of the lesion. Small tumors (< 1 cm) can be resected en bloc, which includes the entire tumor and part of the underlying bladder wall. Larger tumors (＞1 cm) should be resected separately in fractions, including the exophytic part of the tumor, the underlying bladder wall associated with the detrusor muscle, and the edges of the resection area. This approach provides enough information about the vertical and horizontal extent of the tumor and helps to improve resection completeness (Richterstetter et al. 2012).

The significant risk of residual tumor after initial TURB of Ta, T1 lesions has been demonstrated (Miladi et al. 2003). Therefore, a second TUR (second TUR) is recommended in the following situations (Babjuk et al. 2011):

- After incomplete initial TUR;
- If there was no muscle in the specimen after initial resection, with exception of Ta G1 tumors and primary CIS;
- In all T1 tumors;
- In all G3 tumors, except primary CIS.

In summary, a second TUR has to be performed in the case of high-grade malignancy or incomplete resection according to the EAU guidelines.

1.6.2 Intravesical Chemotherapy

In view of the relatively high rates of recurrence, adjuvant intravesical therapy can be considered. The goals of intravesical treatment are to: reduce the implantation of tumor cells after TURBT, eradicate any residual tumors, reduce tumor recurrence and prevent tumor progression.

The EAU guidelines recommend one immediate postoperative dose of intravesical chemotherapy at the initial resection of suspected BC with low-risk NMIBC. However, those of intermediate risk require additional intravesical chemo- or immunotherapy. Oosterlinck and associates found one single instillation with a chemotherapeutic agent within 24 h can decrease the recurrence rate by almost 50% (Oosterlinck et al. 1993). For other patients with multiple tumors, a single immediate instillation is considered as an incomplete treatment because of the potential likelihood of recurrence and/or progression. In order to reduce the number of recurrences, a series of intravesical instillations is given postoperatively. The recurrence rate of NMIBC after intravesical chemotherapy decreases in the short term, but this benefit disappears in the long term (van der Heijden et al. 2009).

It is still controversial how long and how frequently chemotherapy instillations should be given. Therefore, the optimal regimen, frequency and duration of intravesical chemotherapy are not yet consent, although the EAU recommendation is treatment for no more than 1 year (Babjuk et al. 2011). Generally, Mitomycin C, Doxorubicin, Epirubicin, and Gemcitabine are used in clinical practice.

1.6.3 Intravesical Bacillus Calmette-Guérin Immunotherapy

Bacillus Calmette-Guérin, first indicated as a tuberculosis vaccine, has had widespread use in intravesical immunotherapy since the 1970s (Morales et al. 1976). Intravesical BCG is considered the most effective intravesical therapy for high-risk NMIBC and thus the recommended adjuvant non-surgical treatment (Herr 2008).

Initiation of intravesical BCG therapy is usually delayed for two to three weeks following TURB to allow for healing of the urothelium thereby reducing the risk of systemic side effects. Most patients develop an inflammatory immunologic response to BCG during a typical induction course of six weekly instillations. It has been suggested that BCG reduces the risk of progression of intermediate- and high-risk tumors if it is applied including a maintenance schedule. Optimal dosing and instillation schedules have not yet been established but some trials have demonstrated that a reduced dosing regimen (one-third dose) may be as effective as the standard dose but has fewer side effects (Martinez-Pineiro et al. 2005).

Unfortunately, BCG instillation is associated with a considerable number of local and systemic side effects. Of the 1316 intermediate- and high-risk patients treated with BCG, Brausi et al reported 30.6% with systemic side effects, whereas 69.5% with local or systemic side effects (Brausi et al. 2014). Therefore, the use of BCG is usually restricted to patients with intermediate and high risk of recurrence and progression.

1.6.4 Radical Cystectomy

High-risk NMIBC must be handled with the most effective treatment to prevent progression to muscle-invasive disease. However, if progression occurs or if patients are at high risk for progression radical cystectomy is the choice of treatment.

The only proven method to prevent progressive disease is to do an early cystectomy (Skinner 2007). Moreover, early cystectomy has three advantages. The first is good pathological staging through precise assessment with adequate lymph node status. The second is an early stage of the disease, which makes a nerve-sparing cystectomy possible. The third is a great reduction in the risk of subsequent recurrences and mortality.

Potential benefit must be outweighed against the risks, morbidity, and impact on quality of life of radical cystectomy. It is crucial to propose immediate radical cystectomy to those patients with non-muscle-invasive tumor who are at highest risk of progression. It is also recommended in BCG failures (e.g. persistence of high-risk disease at 6 months) and an option in patients with a higher risk for progression based on adverse prognostic factors.

Open radical cystectomy is the gold-standard treatment for MIBC and for high-risk recurrent NMIBC. Recently, laparoscopic radical cystectomy and robot-assisted radical cystectomy have been explored. The advantages include decreased blood loss, reduced postoperative pain, early healing of bowel function and shorter hospital stay.

2 Aims of the Study

The appropriate assignment of risk is the first principle in the management of NMIBC. The decision about when to treat, how to treat, and the optimal combination of treatment modalities is ultimately based on an understanding of the risk of disease recurrence and progression. Because NMIBC is considered a heterogeneous disease, an accurate prognostic estimate for each individual patient is important. In terms of defining a set of routinely assessed clinical and pathological factors, the European Organization for Research and Treatment of Cancer (EORTC) and the Spanish Urological Club for Oncological Treatment (CUETO), respectively, proposed a scoring system and risk tables to calculate the probability of recurrence and progression in individual patients with NMIBC. However, these nomograms were derived from historical clinical trials and may not apply to patients treated nowadays (e.g. using routine second TUR and maintenance BCG-schedules). Therefore, the following aims of this study were defined:

- Retrospective analyses of clinical and pathological results in patients suffering from NMIBC at the Jena University Hospital.
- Determine the utility of EAU risk stratification in patients with NMIBC
- Evaluation of second-look transurethral resection in patients with NMIBC.
- Estimate the value of second TUR pathology on disease recurrence and progression
- Investigation of independent prognostic factors on risks of recurrence and progression in patients with NMIBC
- Provide long term follow-up of primary TaG1/G2 NMIBC in our cohort
- External validation of EORTC and CUETO scoring models to predict recurrence and progression in patients with NMIBC in our institution

3 Patients and Methods

3.1 Study Design

A single retrospective study of NMIBC was conducted by the department of urology, Jena University Hospital, Germany. We retrospectively analyzed the patients with a histology-proven diagnosis of NMIBC between January 2003 and December 2011. The medical records were collected through the SAP system of the Jena University Hospital, the oncological center of the Jena University and family doctors of the patients, respectively. The following clinical and pathologic data were analyzed: gender, age, prior recurrence rate, number of tumors, tumor size, location of tumors, tumor stage, tumor grade, presence of CIS, second TURB, second TUR pathology, intravesical treatment, recurrence and progression of bladder tumors. The data associated with disease recurrence and progression after the initial TURB were documented from medical records until April 2015. All patients had histologically confirmed NMIBC and were treated according to the EAU guidelines and current standard.

The total information were recorded in a database (Access; Microsoft®). Thus, a Microsoft® Excel table was subsequently generated that included the clinicopathologic factors and follow-up information. Patients with concomitant upper urinary tract tumor, ureteral tumor, or other cancers at first TUR were excluded from the study. In addition, all patients with primary CIS or at least T1G3 in diagnostic TURB, who underwent subsequently radical cystectomy within 6 months after initial TURB , were also excluded in follow-up analyses. Remaining NMIBC, including Ta, T1 and concurrent CIS, were included in the present study. All data were anonymized before being used .

3.2 Study Population

Between 01.01.2003 and 31.12.2011, a total of 611 patients of NMIBC underwent TURBT at the department of urology, Jena University Hospital.

In the analyses of follow-up, 83 patients who were lost at follow-up were excluded . Ultimately, 528 patients were available for investigation of follow-up. The study was performed in accordance with the principles of the Declaration of Helsinki, and was approved by the institutional review board of the Jena University Hospital.

3.3 Pathological Data

Pathological assessment of specimens obtained by TURB is an essential step in making decision of the diagnosis and treatment for bladder cancer. Tumor stage and grade of TURB specimens were diagnosed by pathologists in our university hospital, according to the 2002 TNM classification and the 1973 World Health Organization system, respectively (Greene et al. 1973).

Pathologists must report accurately and with minimal variability the key pathologic parameters using terminologies that are well understood by clinicians. Generally, The pathological data should include (Lopez-Beltran et al. 2004):

• Location of the evaluated sample
• Grade of each lesion;
• Depth of tumor invasion (stage);
• Presence of CIS;
• Presence of detrusor muscle in the specimen;
• Presence of lymphovascular invasion;
• Presence of aberrant histology.

Meanwhile, adequate clinical information is also important to pathologists in judging the best approach in handling and processing the surgical specimens.

3.4 EAU Risk Stratification in TaT1 Bladder Cancer

The risk definitions proposed by the EAU, AUA, ICUD, NCCN and IBCG vary and in some instances are cumbersome for use in routine clinical practice. In our institution, risk stratification recommended by the EAU Guidelines Panel will facilitate treatment modalities, including low, intermediate and high risk category, in patients suffering from NMIBC (Table 3).

Table 3 Risk stratification recommended by EAU guidelines

Risk category	Definition
Low-risk tumors	Primary, solitary, Ta, G1, < 3 cm, no CIS
Intermediate-risk tumors	All cases between categories of low and high risk
High-risk tumors	Any of the following: • T1 tumors • G3 tumors • CIS • Multiple and recurrent and large (> 3 cm) Ta G1G2 tumors (all these conditions must be presented)

3.5 Treatment Regimen

The EAU recommend the high-risk patients to undergo second TUR in 2-6 weeks after initial resection, however, in our clinical practice, the majority of low-risk and intermediate-risk patients were also treated with a second TUR. For intravesical therapy, the types of adjuvant intravesical chemotherapies were divided into three groups:1)The low-risk group was recommended with single immediate postoperative instillation of doxorubicin or mitomycin-C; 2) The intermediate-risk group was recommended with one immediate instillation of chemotherapy followed by further instillations, either chemotherapy for a maximum of 1 year or 1 year full-dose BCG, which depended on each surgeon's decision; 3) The high-risk group was recommended with intravesical full-dose BCG instillations, including 6 to 8 weekly instillation and maintenance for 1-3 years, or cystectomy. All therapies are adapted according to personal and subjective conditions. For the elderly patients (more than 80 years), less aggressive treatments are usually performed, e.g. palliative TUR.

3.6 Recurrence and Progression

About 50-70% patients with NMIBC develop recurrence within 5 years, and 25% eventually develop muscle-invasive disease. Lifelong surveillance is therefore mandatory in the management of NMIBC (Fritsche et al. 2010). Clinical prognostic factors for tumor recurrence and progression are multiplicity, tumor stage, tumor grade, and tumor size.

Recurrence was defined as a new histology-proven tumor appearing in the bladder after initial TURB. Disease progression is recognized as one of the most relevant clinical outcomes in patients with NMIBC (Ta/T1/CIS). The commonly used definition of progression is from Ta,

T1 or CIS to stage T2 or higher disease in the bladder. Both recurrence and progression were diagnosed by cystoscopy and/or cytology and were further confirmed by histological examination after TUR.

The following were the endpoints of this study:

Time to first recurrence (Recurrence-free interval): time from cancer diagnosis to the date of the first bladder recurrence. Patients who were still alive and without recurrence were censored at the date of the last available follow-up cystoscopy.

Time to progression to muscle invasive disease (Progression-free survival): time from cancer diagnosis to the date of first increase to stage T2 or higher disease on pathological examination in the bladder. Patients who were still alive and without muscle invasion were censored at the date of the last available follow-up cystoscopy.

Currently, the IBCG proposes the definition of NMIBC progression as an increase in T stage from CIS or Ta to T1 (lamina propria invasion), development of T2 or greater or lymph node (N+) disease or distant metastasis (M1), or an increase in grade from low to high (Lamm et al. 2014).

Patients known to have died from causes unrelated to bladder cancer were censored in the recurrence and progression analyses. Patients who underwent radical cystectomy in the staging of NMIBC and were not upstaged to muscle invasive disease were censored because they were no longer at risk of local progression.

3.7 Follow Up

The follow-up of NMIBC patients was calculated from the first TURB to the last cystoscopy procedure or the last TURB in the medical records. According to the EAU guidelines and our usual procedure , a subsequent cystoscopy was advised every 3 months for a period of 2 years subsequently every 6 months in the third, forth and fifth year and yearly thereafter. Patients with intermediate and high risks of progression should undergo cystoscopy and supplementary urinary cytology. The follow-up of the upper urinary tract (CT or intravenous urography) is recommended yearly in NMIBC patients at high risk of progression (Babjuk et al. 2011). The potential risk for disease recurrence and progression even in the long term typically requires lifelong follow-up (Leblanc et al.1999, Messing EM and Catalona W. 1998) .

Clinical follow-up involves an appropriate patient history including voiding symptoms and hematuria, urinalysis, cystoscopy, and urine cytology. Although many urine-based tumor markers have been developed, their role in surveillance has not been sufficiently validated,

and their use is not recommended in the current guidelines（van Rhijn et al. 2005）.

3.8 EORTC and CUETO Models

In order to estimate risk of recurrence and progression, the European Organization for Research and Treatment of Cancer (EORTC) proposed a scoring system and risk tables (Table 4 and Table 5)(Sylvester et al.2006) .For individual prediction of the risk of disease recurrence and progression at different intervals after TURB, application of EORTC risk tables and calculator (http://www.eortc.be/tools/bladdercalculator/) is strongly recommended.

Table 4 Weights used to calculate recurrence and progression scores (EORTC)

Factor	Recurrence score	Progression score
No. of tumors		
Single	0	0
2-7	3	3
≥8	6	3
Tumor diameter		
＜3cm	0	0
≥3cm	3	3
Prior recurrence rate		
Primary	0	0
≤1 recurrence per year	2	2
≥1 recurrence per year	4	2
Category		
Ta	0	0
T1	1	4
Concomitant CIS		
No	0	0
Yes	1	6
Grade(1973 WHO)		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

Table 5 Recurrence and progression probabilities at 1 and 5 years (EORTC)

	Probabilities at 1 y (95% CI)	Probabilities at 5 y (95% CI)
Recurrence score		
0	15(10-19)	31(24-37)
1-4	24(21-26)	46(42-49)
5-9	38(35-41)	62(58-65)
10-17	61(55-67)	78(73-84)
Progression score		
0	0.2(0-0.7)	0.8(0-1.7)
2-6	1(0.4-1.6)	6(5-8)
7-13	5(4-7)	17(14-20)
14-23	17(10-24)	45(35-55)

The main limitation of the EORTC risk tables is that small patients were treated with BCG therapy. To overcome this limitation, the Spanish Urological Club for Oncological Treatment (CUETO) developed a modified model using gender, age, prior recurrence rate, number of tumors, cancer stage, CIS, and WHO grade, which predicts the short- and long-term probability of disease recurrence and progression at the basis of data from 1,062 patients treated by BCG instillation (Table 6 and Table 7) (Fernandez- Gomez et al. 2009).

Table 6 Recurrence and progression probabilities at 1, 2 and 5 years (CUETO)

	Probabilities at 1 y (95% CI)	Probabilities at 2 y (95% CI)	Probabilities at 5 y (95% CI)
Recurrence score			
0-4	8.24 (5.91–10.57)	12.6 (9.76–15.44)	20.98 (17.33–24.63)
5-6	12.07 (7.95–16.19)	22.28 (16.93–27.63)	35.57 (29.18–41.96
7-9	25.36 (19.56–31.16)	39.61 (32.93–46.29)	47.65 (40.55–54.75)
10-16	41.79 (28.05–55.53	52.55 (38.48–66.62)	67.61 (53.67–81.55)
Progression score			
0-4	1.17 (0.15–2.19)	2.16 (0.77–3.55)	3.76 (1.9–5.62)
5-6	3 (0.82–5.18)	4.97 (2.34–7.6)	11.69 (7.57–15.81)
7-9	5.55 (2.73–8.37)	11.95 (7.93–15.97)	21.26 (15.85–26.67)
10-14	13.97 (6.64–21.3)	24.81 (15.6–34.02)	33.57 (23.06–44.08)

Table 7 Weights used to calculate recurrence and progression scores (CUETO)

Factor	Recurrence score	Progression score
Gender		
Male	0	0
Female	3	0
Age(y)		
＜60	0	0
60-70	1	0
≥70	2	2
Prior recurrence rate		
No	0	0
Yes	4	2
Number of tumors		
＜3	0	0
≥3	2	1
T Category		
Ta	0	0
T1	0	2
Associated Tis		
No	0	0
Yes	2	1
Grade		
G1	0	0
G2	1	2
G3	3	6
Total score	0-16	0-14

3.9 Statistics

Differences in characteristics of patients in different risk groups were tested using chi-square, Fisher-exact and Mann-Whitney-Wilcoxon tests where appropriate. No imputation of missing data was performed. Logistic regression analyses was used to identify categorical variables associated with residual tumor after second TUR. The scores for risk of progression and recurrence were estimated by using the EORTC and CUETO models. The Kaplan-Meier survival analyses was used to assess recurrence and progression curves in both models. The recurrence-free survival (RFS) and progression-free survival (PFS) were estimated by the

Kaplan–Meier method, and three EAU risk groups were compared using the log–rank test. Univariate and multivariate Cox proportional hazards regression analyses were used to identify the prognostic factors for recurrence and progression. A backward stepwise elimination procedure was performed to identify factors associated with survival at the 0.05 significance level. The discriminative ability of the two models was assessed using Harrell's c-index, where 1.0 and 0.5 reflected perfect prediction and agreement by chance, respectively. A p-value of less than 0.05 was considered statistically significant for all tests. All statistical analyses were conducted by using IBM SPSS version. 19.0 (IBM Co., Armonk, NY, USA) and R 3.1.2 (R Project, www.r-project.org).

4 Results

4.1. Patients Characteristics

4.1.1 Demograpic and Clinical Data

Between January 2003 and December 2011, 611 patients with histology-proven NMIBC were included in our study. Of the 611 patients, 83 (13.5%) were lost to follow-up and 525 (85.9%) were diagnosed firstly with primary tumor in our institution. The median follow-up was 60 months (range: 1-143 months). According to the EAU classification of NMIBC, all patients were divided into the low, intermediate and high risk groups in the present study. Of the total patients, 197 (32%) had low, 251 (41%) intermediate and 163 (27%) high-risk, respectively (Figure 1).

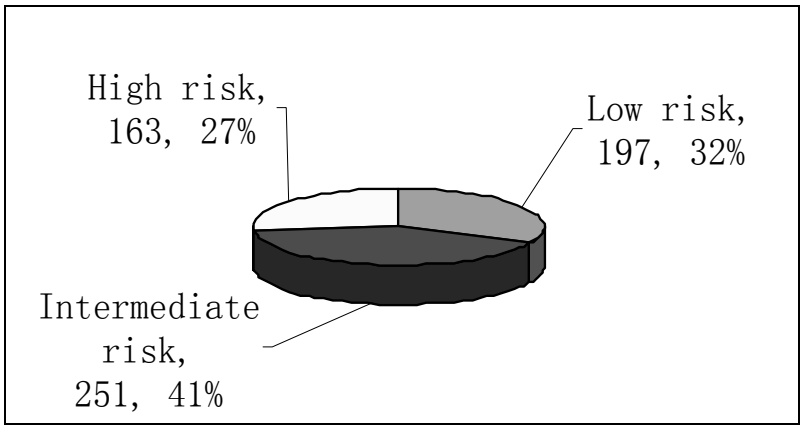


Figure 1 The proportion of NMIBC according EAU classification

Overall, 65 patients (10.6%) underwent radical cystectomy during follow-up, and the postoperative histological examination indicated heterogeneous outcomes. 4 of these patients were diagnosed without tumor after radical cystectomy. Another 29 patients were reported with pTis, Ta and T1 disease. The remaining 32 patients (49.2%) progressed to stage T2 or higher based on the pathological reports.

The distribution of age is indicated in Figure 2. Median age of the patients was 71 years (range: 28-98 years) and the male to female ratio was 3.4:1 (471 men and 140 women). In our cohort, 77.1% were men with a median age of 70 years (range: 28-98 years) as opposed to women with 74 years (range: 29-91 years) (Figure 3).

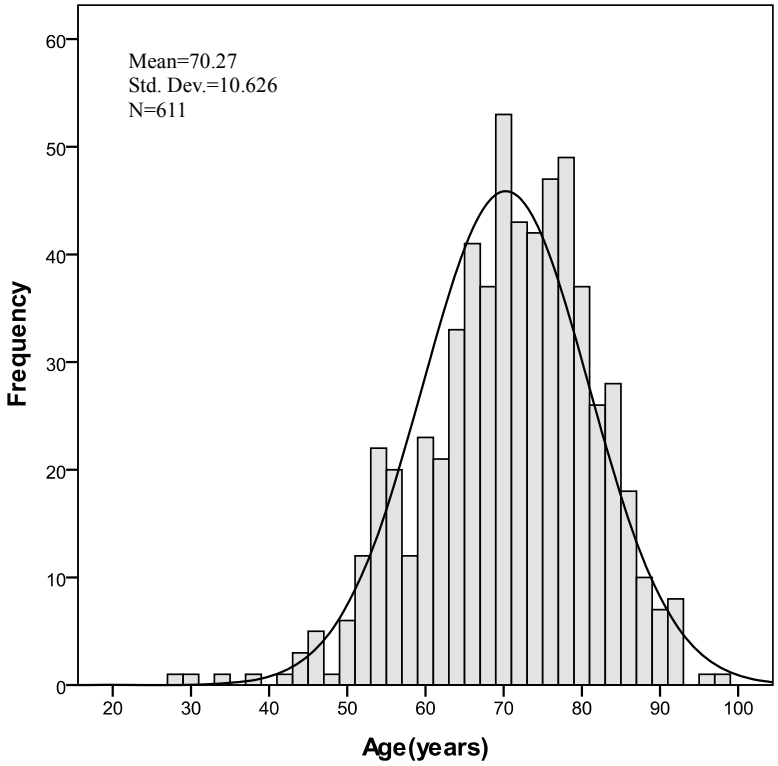


Figure 2 Distribution of age in patients with NMIBC (N=611)

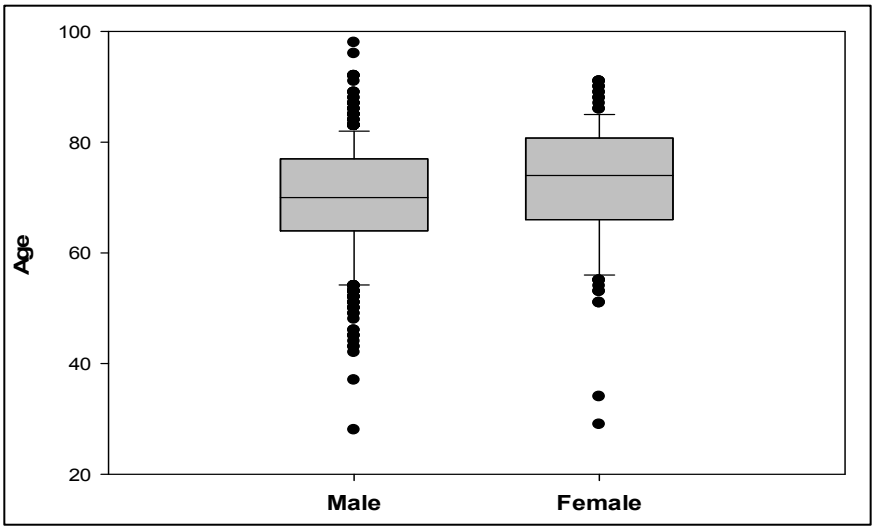


Figure 3 Age characteristics between male and female patients

In both male and female patients, the age group 61-80 years included approximately 2/3 of all patients, but the proportion of women older than 80 years was significantly higher than in men (25.0 % vs. 13.6%) (Figure 4).

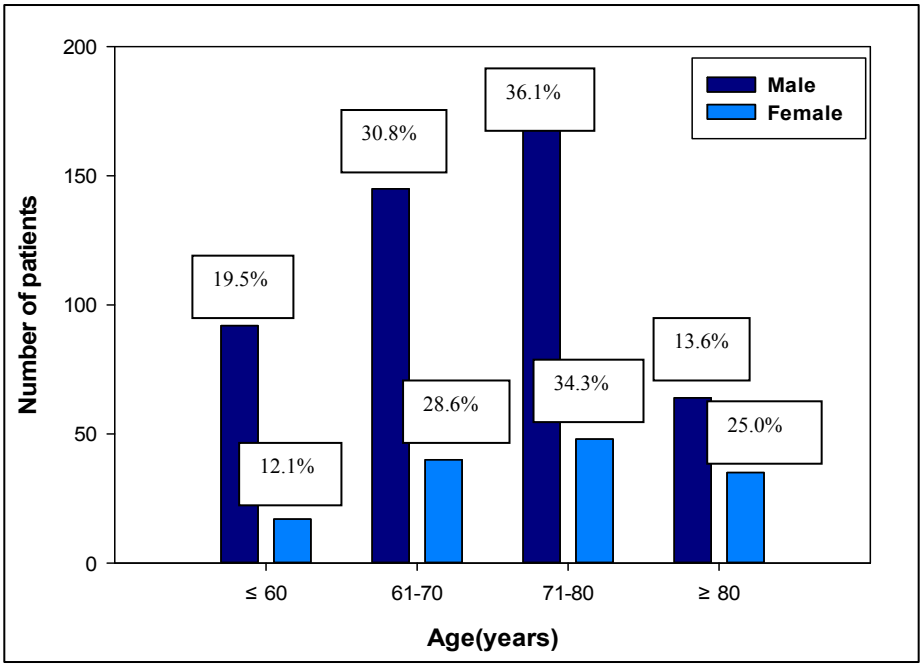


Figure 4 Distribution of age in male patients compared with female patients

In the low, intermediate and high-risk group, the male to female ratios were 3.3:1, 3.2:1, and 3.4:1, respectively. The gender among three EAU risk groups was not statistically significant different (*P*=0.972) (Figure 5).

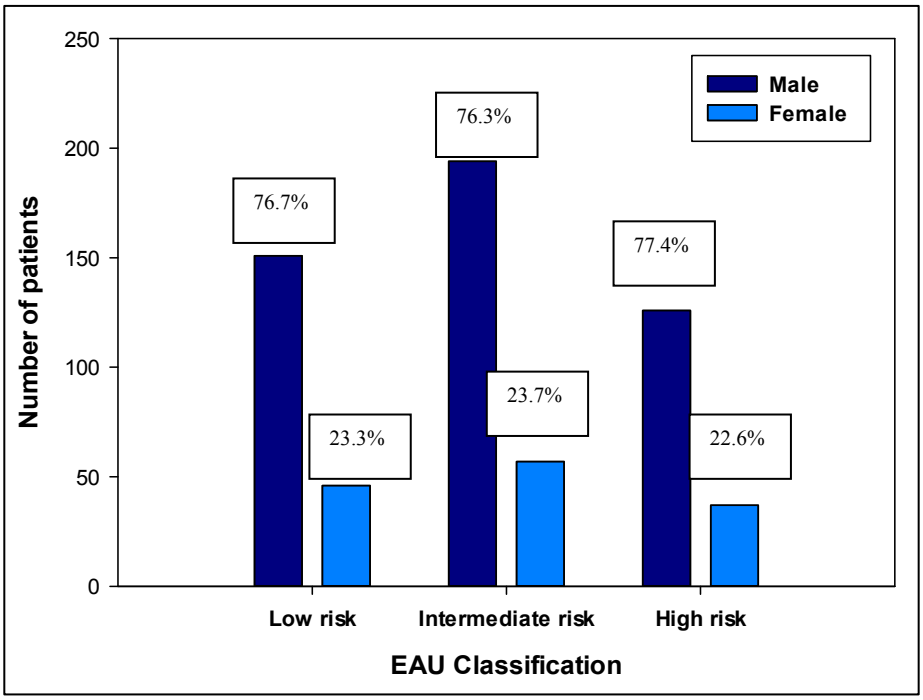


Figure 5 Distribution of gender according to EAU classification

4.1.2 Operative Data

According to the operative records, number of tumors, tumor size, and tumor location were collected and analyzed in the study.

Of the patients, 456 (74.6%) had one, 124 (20.3%) 2 or 3 and 31 (5.1%) more than 3 tumors, respectively. Figure 6 shows the number of tumors among three EAU risk groups. There were only 8 patients with more than 3 tumors in the high-risk group.

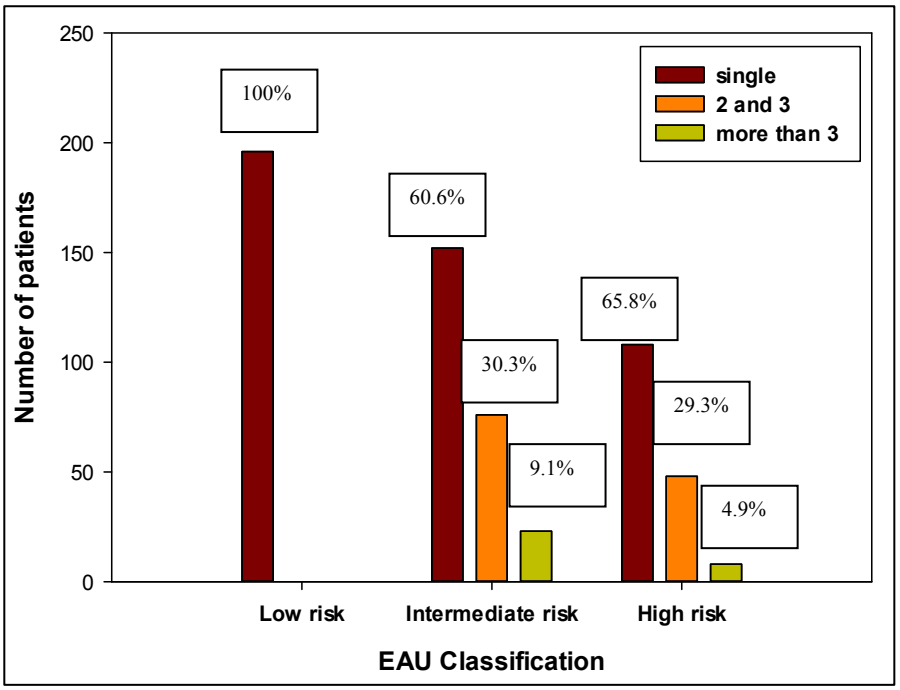


Figure 6 Distribution of number of tumors according to EAU classification

Overall, only 39 (6.4%) patients had a tumor with a diameter of at least 3cm. In the high risk group, 14.3% of the patients had a tumor diameter more than 3 cm (Figure 7).

Based on the bladder anatomy, the locations of bladder tumor were divided generally into left wall, right wall, posterior wall, dome, trigone, neck, left ureteral orifice and right ureteral orifice. Overall, there were 163 (26.7%) patients with multifocal tumors and 33 patients (5.4%) with missing data regarding location (Table 8). Of the patients with unifocal location, the majority of tumors (74.4%) were located on side wall as well as posterior wall of the bladder (Figure 8).

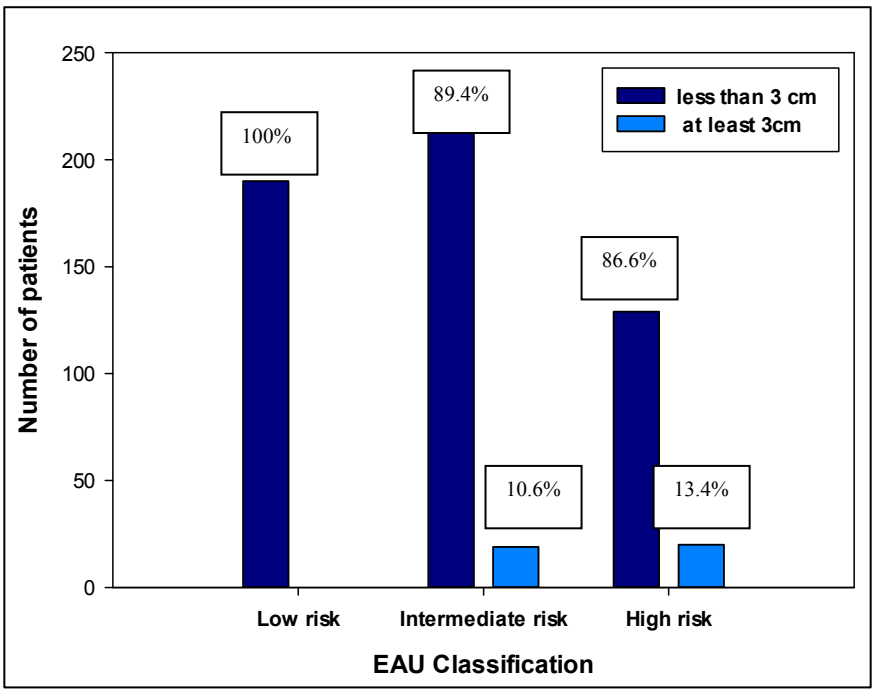


Figure 7 Distribution of tumor size according to EAU classification

Table 8 Distribution of tumor locations in cystoscopy

Locations of bladder tumor	Number of patients	Percent(%)
Left wall	118	19.3%
Right wall	139	22.7%
Posterior wall	52	8.6%
Dome	18	2.9%
Trigone	31	5.1%
Bladder neck	28	4.6%
Left ureteral orifice	10	1.6%
Right ureteral orifice	19	3.1%
Not sepcified	33	5.4%
Multifocal	163	26.7%
Toatl	**611**	**100%**

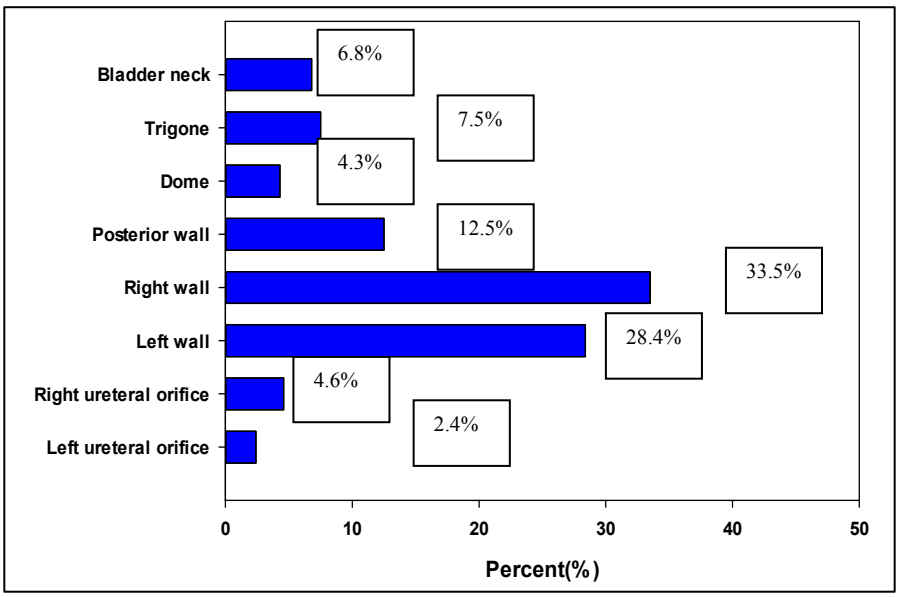


Figure 8 Distribution of location in patients with single bladder tumor

4.1.3 Pathological Data

Of the 611 patients, 462 (75.6%) had stage Ta, 143 (23.4%) stage T1 and 6 (1.0%) isolated pTis at first resection. Histological diagnosis was grade 1 in 312 (51.1%), grade 2 in 226 （36.9%) and grade 3 in 73 (12.0%) of the patients, respectively. Of the 304 patients with pTaG1, 259 (85.2%) were documented with a primary tumor (Table 9).

Table 9 The characteristic of tumor stage and grade

Stage	Grade 1	Grade 2	Grade 3	Total
pTa	304(65.7%)	145(31.4%)	13(2.9%)	462
pT1	8(5.6%)	81(56.6%)	54(37.8%)	143
CIS	-	-	6(100%)	6
Total	312	226	73	**611**

4.2 Treatment Strategy

4.2.1 Second TURB

Overall, there were 535 patients (87.6%) undergoing a second TURB after the initial resection while 76 did not. Of those patients who underwent second TURB the pathological results showed tumor in 107 (20.0%) of the cases. According to the risk classification of EAU, the rate of residual tumor was 13.2% in the low-risk, 19.5% in the intermediate-risk, and 29.8%

in the high-risk group, respectively. Of the 107 patients with residual tumor 24 were at low-, 44 at intermediate- and 39 at high-risk, respectively (Figure 9). Thus, a significant difference was found in residual tumor rate among three EAU risk groups (P=0.001).

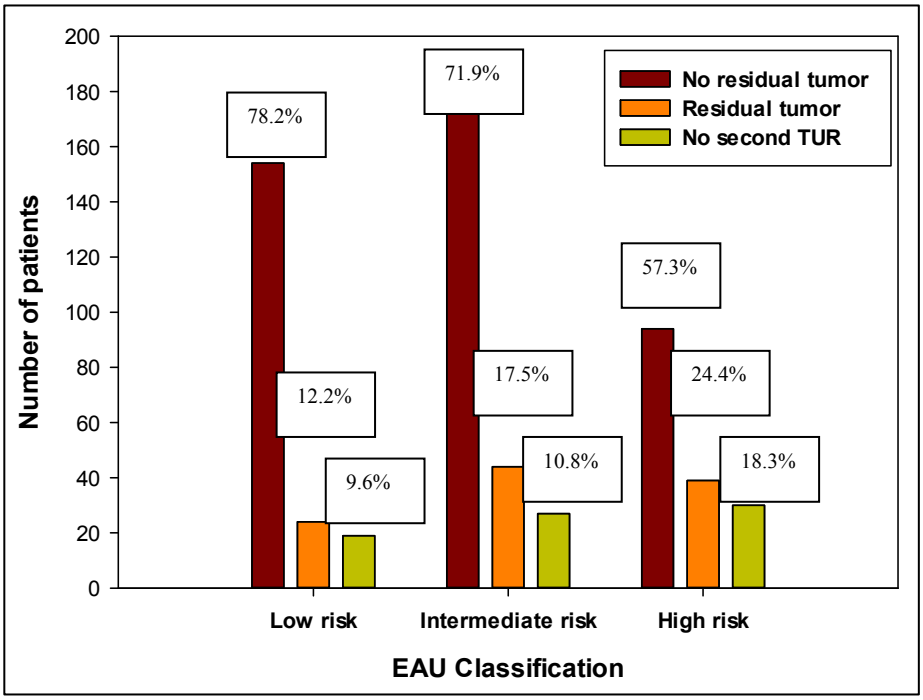


Figure 9 Distribution of second resection according to EAU classification

The results showed that 16.9% of pTa BC had residual tumor at second TUR compared to 31.1% of pT1 BC. The main features, including age, gender, prior recurrence rate, number of tumors, tumor size, stage and grade, were analyzed between the residual and no residual tumor groups. There were a significant difference in variables of age, number of tumors, stage, and grade (P <0.05, respectively). In addition, the residual rate was associated with the EAU risk classification (Table 10). Moreover, the logistic regression results showed that number of tumors and tumor grade were independent variables for predicting residual tumor (Wald statistic P<0.001 and P=0.002, respectively) .

Table 10 Patients characteristics of residual tumor group compared with no residual tumor group after second TURB

Variable	Residual tumor Group	No residual tumor Group	*P*-value
Age (years)			**0.009**
≤70	41	224	
＞70	66	204	
Gender			0.337
Male	85	321	
Female	22	107	
Prior recurrence rate			0.900
Primary	92	370	
Recurrence	15	58	
Number of tumors			**＜0.001**
1	66	330	
2-3	27	84	
＞3	14	14	
Tumor size			0.681
＜3cm	100	395	
≥3cm	7	33	
T category			**0.001**
Ta	70	344	
T1	37	82	
Grade			**0.002**
G1	42	247	
G2	48	139	
G3	17	42	
EAU Classification			**0.001**
Low risk	24	157	
Intermediate risk	43	177	
High risk	40	94	

According to the 2002 TNM classification and the 1973 World Health Organization (WHO) system, the percentage of residual tumor was 16.9% in pTa and 31.1% in pT1 group, respectively. 2 pTis patients had also residual tumor at second TUR. The residual tumor rate based on stage and grade is shown in Table 11.

Table 11 Distribution of residual tumor rates at second TURB

Stage	Grade 1	Grade 2	Grade 3	Total
pTa	41/281 (14.6%)	28/122(22.9%)	1/11(9.1%)	70/414(16.9%)
pT1	1/8 (12.5%)	20/65(30.8%)	16/46(34.7%)	37/119(31.1%)
Total	42/289(14.5%)	48/187(25.7%)	17/57(29.8%)	**523**

Analyzing the change of histology at second TURB, of the 67 low and intermediate risk patients, only 6 had a higher stage at second resection. In contrast, of the high risk patients 8 tumors were upstaged. However, of theses cases 7 had a lower staged in the second TURB (Figure 10).

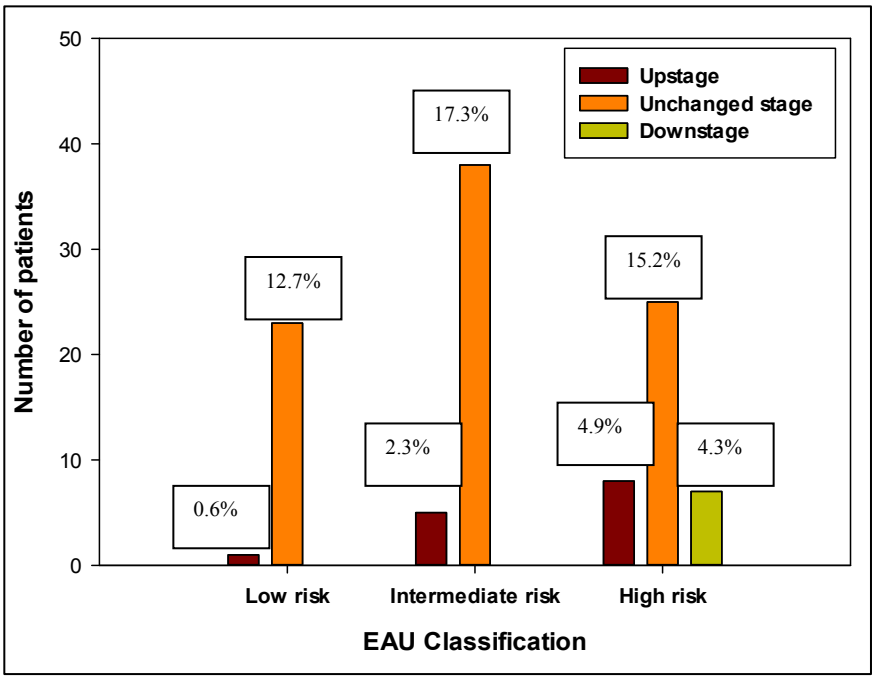


Figure10 Upstaging and downstaging of histology after second TURB

Of the 107 patients with residual tumor at second TURB, 80 underwent a third section. Figure 12 shows that there were still 29 patients (36.2%) with persistent tumor, including 1 with downstaging, 2 with upstaging and 26 at the same stage.

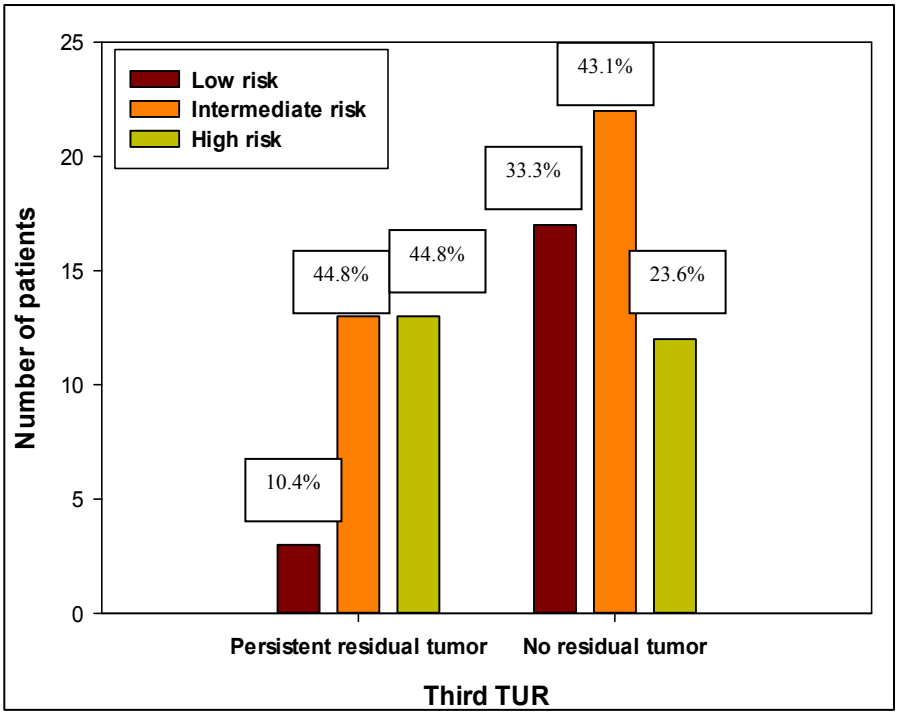


Figure 11 Distribution of risk in persistent tumor group undergoing third TURB compared with no residual tumor

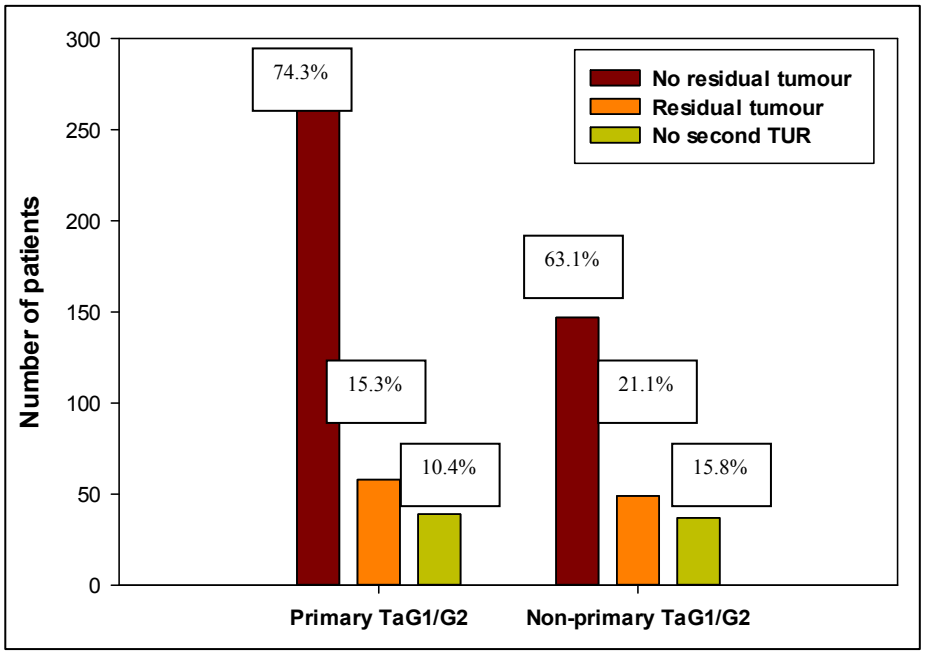


Figure 12 Residual tumor in primary TaG1/G2 bladder tumor compared with non-primary TaG1/G2 bladder tumor group

In the subgroup analyses, there were 378 (61.9%) patients with primary TaG1 (307) and TaG2 (71) bladder cancer in our cohort. Of these patients, 199 (52.6%) were low-risk tumors and 179 (47.4%) had intermediate-risk. Furthermore, of the 339 TaG1/G2 (89.6%) patients who underwent a second TURB, 58 (17.1%) had residual tumor detected by second TURB, and the

negative to positive ratio was 4.8:1 and 3.0:1, in primary TaG1/G2 and non-primary TaG1/G2, respectively (*P*=0.028) (Figure 12).

The interval between first and second resection ranged normally from 2 weeks to 8 weeks in our study. Of the 535 patients who underwent a second TURB, the majority (40.3%) had this procedure between 36 days and 42 days after the initial TURB. The remaining groups were ≤28 days, 29-35 days, 43-49 days, and 50-56 days in 22 (5.4%), 97 (22.3%), 94 (22.5%), and 35 (8.4%) patients, respectively (Figure 13). Thus, the time interval in 40.9% of the patients treated with second TUR was more than 2-6 weeks, which is recommended in the EAU guidelines.

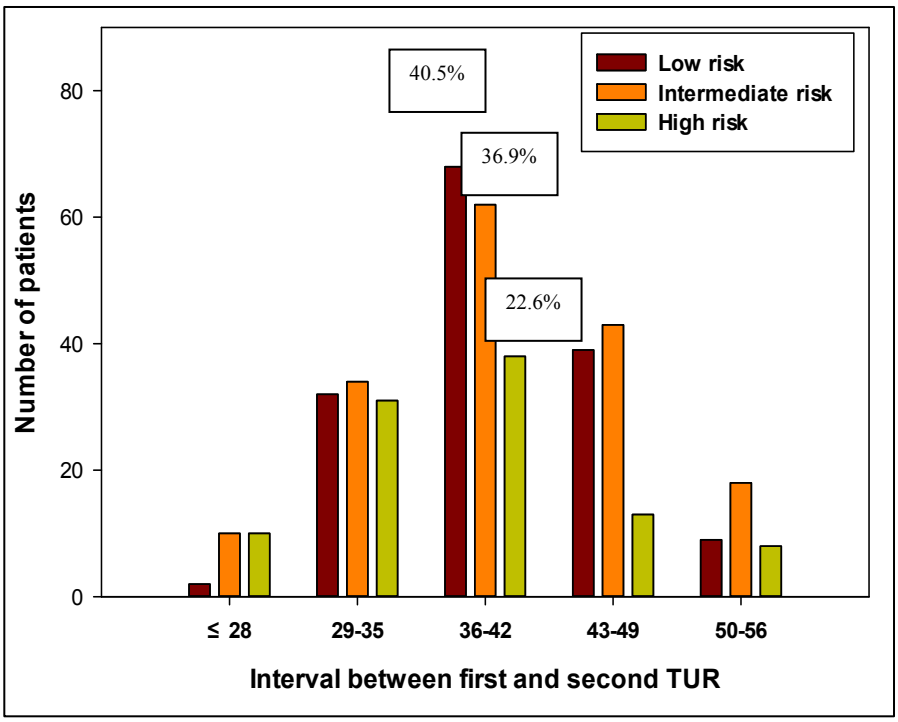


Figure 13 Interval between first and second TURB (range : 2-8 weeks)

4.2.2 Adjuvant Intravesical Treatment

According to the EAU guidelines local adjuvant intravesical treatment was recommended to the NMIBC patients. Of 285 patients who were documented with intravesical treatment, 237 underwent either one immediate instillation of doxorubicin after initial TURB or metaphylaxis with one or more instillation-cycles (Doxorubicin or Mitomycin-C) , and 48 high-risk patients received BCG immunotherapy with or without maintenance scheme .

Of these patients with doxorubicin or Mitomycin-C instillation, 139(58.6%) had recurrence during follow-up. Furthermore, the result indicated that high-risk patients were preferentially selected for adjuvant treatment. In fact, higher recurrence rate resolved in higher instillation

chance. Meanwhile, 20 (8.4%) advanced into MIBC during follow-up. In the group with BCG immunotherapy, 24(50.0%) patients had recurrence, and 6 (12.5%) patients advanced further to stage T2 or higher during follow-up.

4.3 Predicting Disease Recurrence and Progression

4.3.1 Recurrence and Progression

Between January 2003 and December 2011, 528 patients with histology-proven NMIBC were included in our follow-up study. Two hundred and fifty-nine patients (49.1%) recurred during follow-up, and forty-six (8.7%) advanced into muscle-invasive BC. Median follow-up for patients who did not experience disease recurrence was 56 months and 61 months for those who did not experience disease progression. The overall recurrence rates of our series were 18.6%, 33.7%, and 43.9% at the first, second, and fifth year, respectively. The overall progression rates were 0.9% at first, 2.6% at second, and 6.6% at the fifth year.

Of the patients who had at least 1 recurrence during follow-up, the median time of recurrence-free survival (RFS) was 16 months (range: 3-123months). The average number of recurrences was 1.9 (range: 1-14 recurrences). The mean time of RFS was 21.6 months (range: 3-86 months) for patients at high-risk, 27.4 months (range: 3-123months) at intermediate-risk, and 64.9 months (range: 3-103 months) at low-risk, respectively. The recurrence rate was 34.1%, 56.5% and 57.1% in the low, intermediate and high risk group, respectively (Figure14; $P < 0.001$).

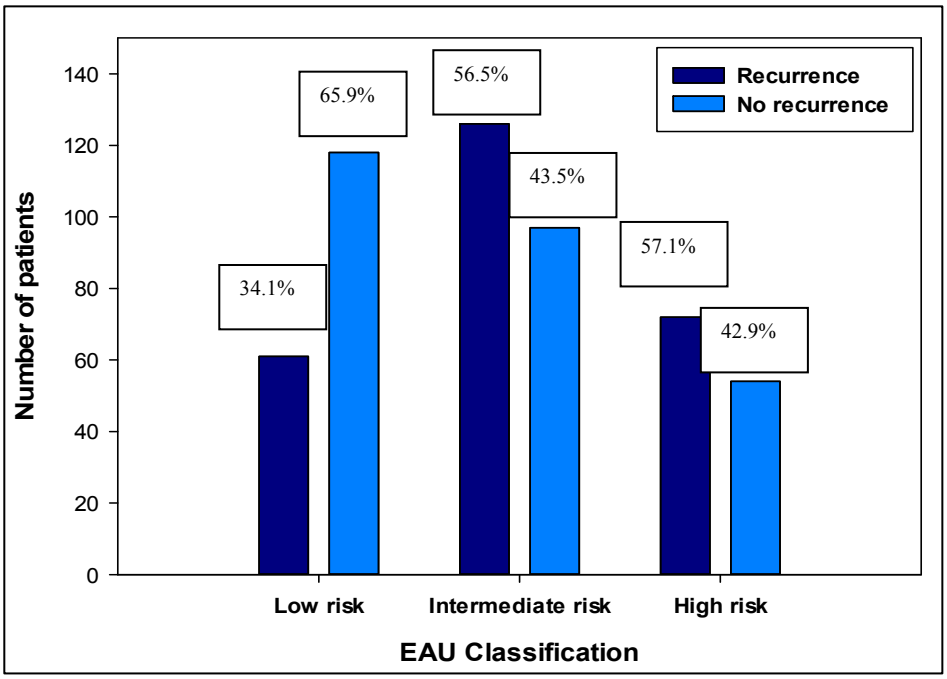


Figure 14 Distribution of recurrence according to EAU risk classification

In the anlayses of disease progression, an invasive carcinoma of stage T2 or higher were found in 49 patients. The median time of progression-free survival (PFS) was 40 months (range: 5-123 months). Of 415 Ta patients at initial diagnosis, 23 (5.5%) developed directly into stage T2 or higher during follow-up, whereas 26 (6.3%) advanced from stage Ta to stage T1. Of the 108 T1 patients, 26 (24.1%) progressed directly into muscle-invasive stage. The higher stage was related to higher progression risk to MIBC ($P<0.001$).

Figure 15 shows the disease progression among three EAU risk groups. Of the patients in the low risk group according to the EAU classification 3 and 2 patients progressed from stage Ta to T1 and stage Ta to T2 or higher, respectively. Of the intermediate and high risk group 38 (17.0%) and 32 (25.4%) progressed. The patients with higher risk had a greater probability to develop MIBC or to progress from lower to higher stage ($P<0.001$).

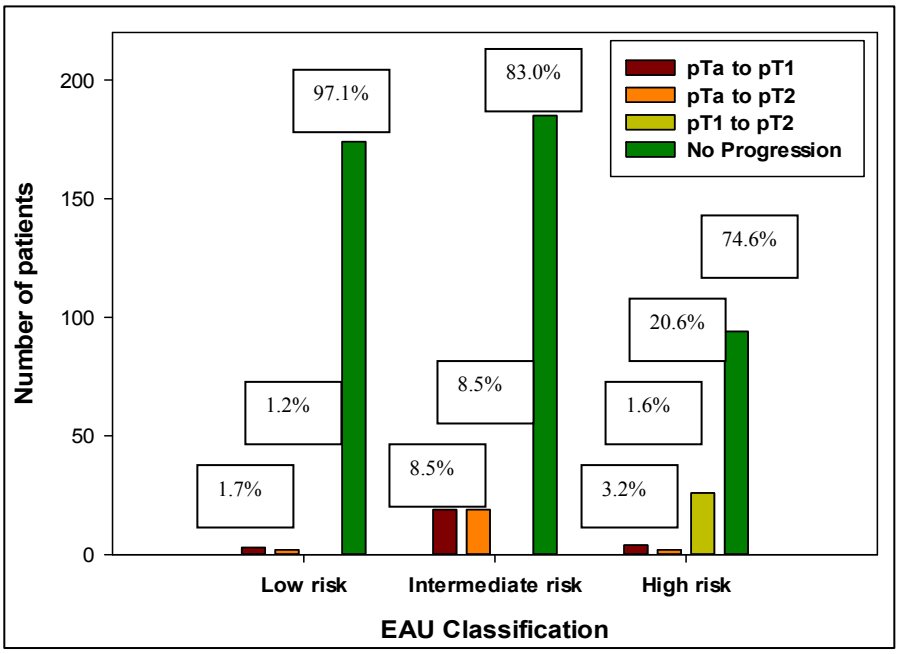


Figure 15 Distribution of progression according to EAU risk classification

4.3.2 Prognostic Factors of RFS and PFS

In order to predict the short-term and long-term risks of disease recurrence and progression, all clinical and pathological factors including age, gender, prior recurrence rate, stage, grade, tumor size, number of tumors, second TURB and interval between first and second resection were analyzed concerning RFS and PFS,.

4.3.2.1 Prognostic Factors of RFS

The results of univariate and multivariate Cox regression analyses for recurrence risk based on clinical and pathological factors are shown in Table 12. Univariate analyses revealed that

prior recurrence rate, T category, second TURB and second TUR pathology were significantly associated with RFS.

Furthermore, prior recurrence rate and second TUR pathology were independent risk factors for RFS according to multivariate analyses. Compared with patients with recurrent tumors, the RFS rate of patients with primary bladder tumors was significantly higher (*P*=0.001) (Figure16 A). The recurrence risk associated with positive pathology at second TUR was significantly higher compared with those with negative pathology (*P*=0.010) (Figure 16 D).

Table 12 Univariate and multivariate Cox regression analyses for RFS

Variable	Univariate			Multivariate		
	HR	**95% CI**	***P*-Value**	**HR**	**95% CI**	***P*-value**
Age(years):						
≤70 vs ＞70	1.005	0.890-1.136	0.931			NS
Gender:						
Male vs Female	0.847	0.631-1.138	0.271			NS
Prior recurrence rate:						
Primary vs Recurrence	1.805	1.339-2.433	**<0.001**	1.728	1.253-2.382	**0.001**
Number of tumors:						
Single vs Multifocal	1.174	0.885-1.558	0.266			NS
Tumor size:						
＜3cm vs ≥3cm	0.966	0.582-1.602	0.893			NS
T category:						
Ta vs T1	1.378	1.033-1.838	**0.029**			NS
Grade:						
G1, G2, G3	1.186	0.996-1.412	0.056			
G1/2 vs G3	0.891	0.712-1.113	0.309			NS
Second TURB:						
Yes vs No	1.592	1.066-2.377	**0.023**			NS
Second TUR pathology:						
Negative vs Posiitive	1.519	1.108-2.084	**0.009**	1.514	1.104-2.078	**0.010**
Interval(days):						
≤42, ≥43	1.078	0.798-1.458	0.624			NS

*NS: No significant.

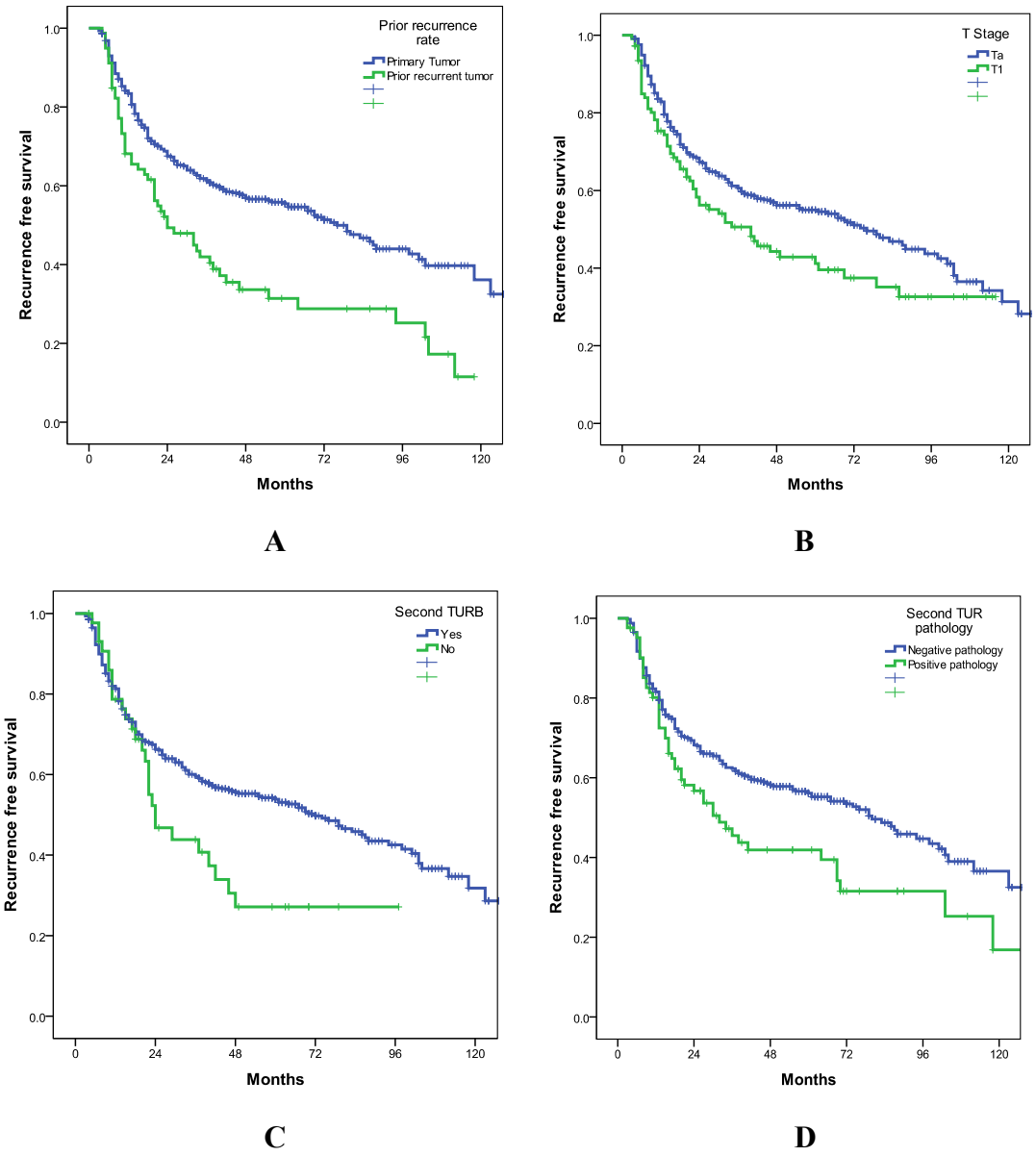


Figure 16 Kaplan-Meier survival curves of recurrence free survival (RFS) in patients with NMIBC according to prior recurrence rate（A），T stage (B), second TURB (C) and second TUR pathology (D)

4.3.2.2 Prognostic Factors of PFS

Regarding the analyses of prognostic factors associated with disease progression, only progression to stage T2 or higher was considered. The relationships between clinical parameters and PFS are shown in Table 13.

Using univariate analyses, age, prior recurrence rate, tumor stage, tumor grade, second TURB and second TUR pathology were significantly associated with PFS.

Multivariate analyses identified age, prior recurrence rate, tumor stage, tumor grade, and

second TUR pathology as independent prognostic factors associated with the risk of tumor progression (Table 13 and Figure 17). Compared with predicting the risk of recurrence, more variables were associated with predicting progression.

Table 13 Univariate and multivariate Cox regression analyses for PFS

Variable	Univariate			Multivariate		
	HR	95% CI	*P*-Value	HR	95% CI	*P*-value
Age (years):						
≤70 vs ＞70	1.761	1.291-2.403	**<0.001**	1.575	1.085-2.288	**0.017**
Gender:						
Male vs Female	1.164	0.671-2.198	0.638			NS
Prior recurrence rate:						
Primary vs Recurrence	2.072	1.095-3.924	**0.025**	2.568	1.193-5.527	**0.016**
Number of tumors:						
Single vs Multifocal	1.740	0.957-3.163	0.069			NS
Tumor size:						
＜3cm vs ≥ 3cm	0.622	0.151-2.561	0.510			NS
T category:						
Ta vs T1	4.690	2.639-8.336	**<0.001**	2.460	1.116-5.422	**0.026**
Grade:						
G1, G2, G3	2.687	1.824-3.959	**<0.001**	1.887	1.082-3.289	**0.025**
G1/2 vs G3	1.609	1.118-2.316	**0.010**			
Second TURB:						
Yes vs No	5.257	2.733-10.112	**<0.001**			**0.015**
Second TUR pathology:						
Negative vs Positive	2.599	1.304-5.177	**0.007**	2.381	1.187-4.775	**0.015**
Interval(days):						
≤42, ≥43	0.810	0.358-1.831	0.612			NS

*NS: No significant.

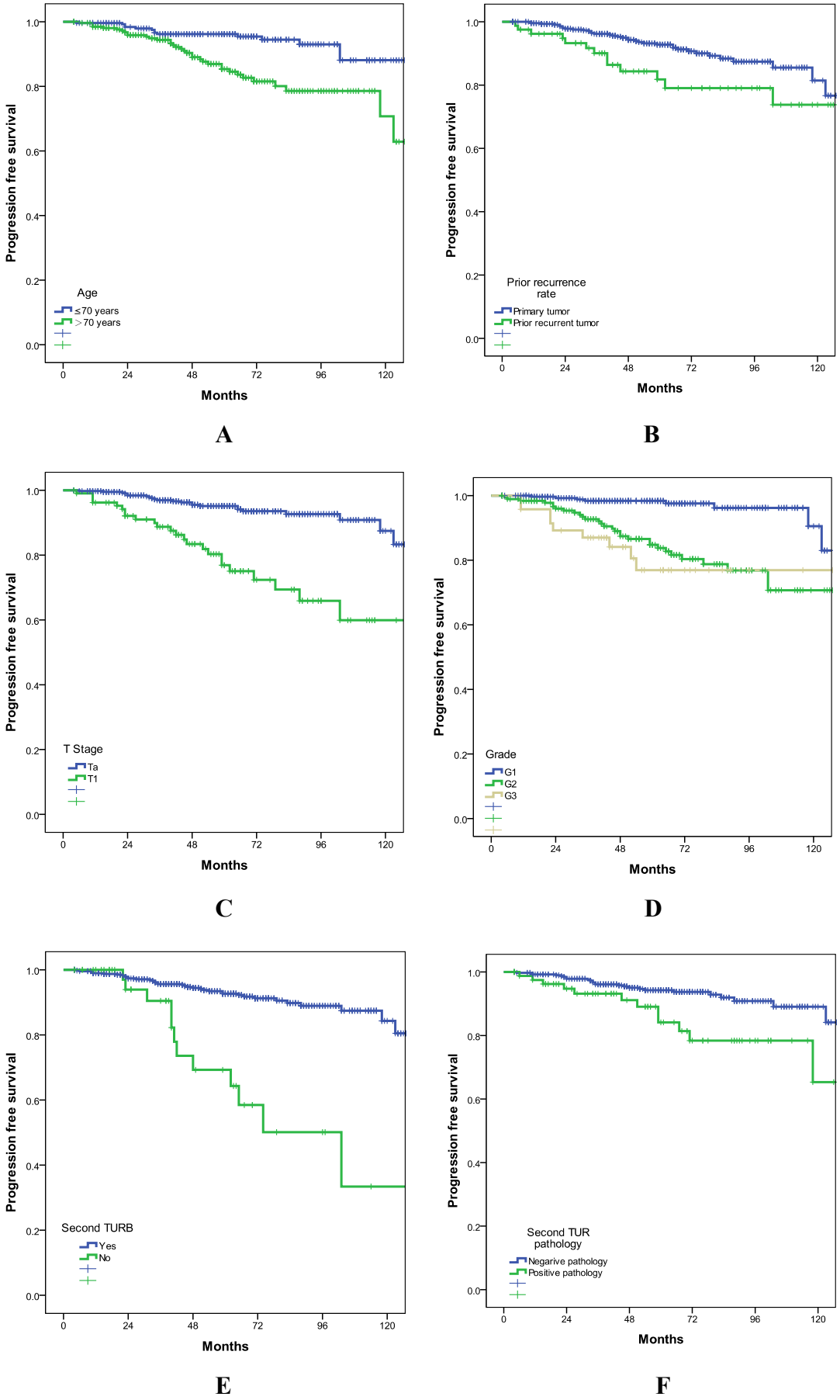


Figure 17 Kaplan-Meier survival curves of PFS(Progression to MIBC) in patients with NMIBC

according to age（A），prior recurrence rate (B), T Stage (C), Grade (D), second TURB (E) and second TUR pathology (F)

4.3.2.3 Prognostic Factors of RFS and PFS in Patients with Primary TaG1 and TaG2 Bladder Tumor- A Subgroup Analyses

In a subgroup analyses, 336 patients with primary TaG1 and TaG2 were analyzed to identify the relative predictive variables in RFS and PFS. Age, gender, number of tumors, tumor size, second TURB, second TUR pathology, and interval between first and second TURB were taken into account in the univariate analyses. In the RFS analyses, only second TUR pathology was significantly associated with RFS (*P*=0.030) (Figure 18), whereas other factors were not correlated to RFS. Similarly, all mentioned variables were analyzed with regard to PFS in the univariate analyses. Age (*P*=0.007) and second TURB (*P*<0.001) were found to be associated with PFS (Figure 19).

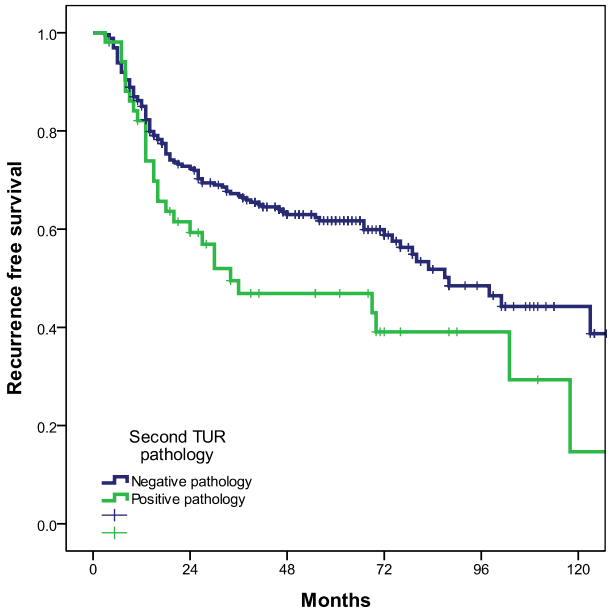


Figure 18 Kaplan-Meier survival curves of RFS in patients with primary TaG1 and TaG2 bladder tumor according to second TUR pathology

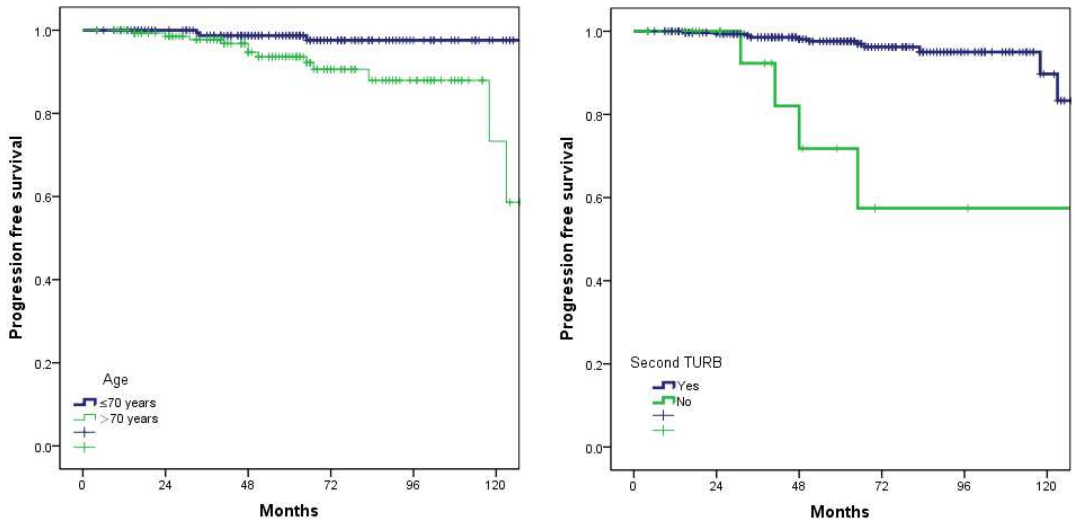


Figure 19 Kaplan-Meier survival curves of PFS in patients with primary TaG1 and TaG2 bladder tumor according to age（A）and second TURB (B)

4.3.2.4 EAU Classification System in TaT1 Bladder Cancer

According to the EAU guidelines, patients were divided into low, intermediate and high risk categories. Overall, the risk stratification was significantly associated with disease recurrence ($P<0.001$). According to the Log Rank test, there was a statistical difference between the low and intermediate risk group ($P<0.001$). However, no difference between the intermediate and the high risk group was observed ($P=0.606$). A significant difference was found for progression risk between three EAU risk groups ($P<0.001$), low risk versus intermediate risk ($P<0.001$) and intermediate risk versus high risk ($P<0.001$), respectively (Figure 20).

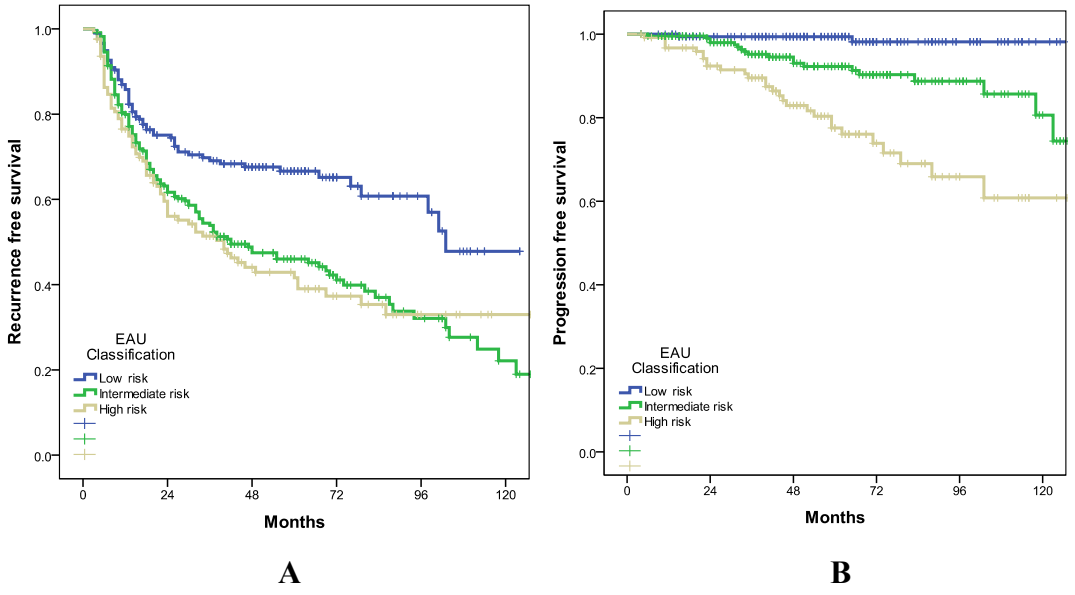


Figure 20 Kaplan-Meier survival curves of recurrence free survival (A) and progression free survival (B) according to EAU risk classification

4.4 Dimcriminative Abilities for the EORTC and CUETO Models

Table 14 shows the distribution of basic clinical and pathological parameters in our cohort compared with the similar studies of the EORTC and CUETO group. The major differences include: (1) the proportion of patients older than 70 years was approximately 50% and thus much higher than in the EORTC and CUETO studies (31%); (2) the percentage of patients with recurrent tumors was much lower than the EORTC study (15.2% vs 44.5%); (3) the proportion of patients with more than 3 tumors, tumor size more than 3cm in diameter and stage T1 in our cohort were 23% vs 42-50%, 7% vs 18-45%, and 21% vs 42-77% as opposed to the both EORTC and CUETO cohorts, respectively.

The recurrence and progression probabilities at 1 and 5 years and the corresponding reference probabilities as determined by the EORTC risk tables for each risk group are listed in Table 15. The EORTC recurrence score was 0 in 175 patients, 1 or 4 in 273 patients and 5 to 9 in 79 patients. There was only 1 patient with a score in the 10 to 16 range. Thus, there was no analyses of this highest score group.

The actual recurrence rates in our cohort were summarized and compared with the EORTC recurrence prediction (Table 15). In the group of score 0, there were 25 patients (14.3%) with recurrence at the 1st year and 54 patients (30.9%) at 5 years. In patients with the lower intermediate risk (score 1-4 group), recurrence rates of 19.1% at the 1st year and of 49.4% at 5 years were noted. In the score 5-9 group with higher intermediate risk, recurrence rates of 25.3% at the 1st year and of 53.2% at 5 years were documented. The recurrence rates in those patients were overestimated at 1 and 5-year applying the EORTC scoring system (25% vs 38%; 53% vs 62%, respectively).

The same analyses were carried out with regard to progression. All patients were divided into four groups of progression risk: the score 0 group with a low risk, the score 2-6 with an intermediate risk, the score 7-13 group with an lower high risk, and the score 14-23 group with a very high risk of progression. The EORTC progression score was 0 in 248 patients, 2 to 6 in 206 patients, 7 to 13 in 74 patients. No patients was found in the score 10 to 16 . In the score 0 group, there was no progression at 1 year but 9 patients had progressed (3.6%) at 5 years. In those patients with an intermediate risk disease (Score 2-6), progression rates of 1.4% at the 1st year and of 7.8% at 5 years were found. In the score 7-13 group with a lower high risk, progression rates of 2.7% at the 1st year and 17.5% at 5 years were documented. In

contrast to 5% progression in 1 year according the EORTC risk tables, our result had a lower probability (2.5%) to muscle-invasive stage. However, there was not patient with the score 14-23 in our study.

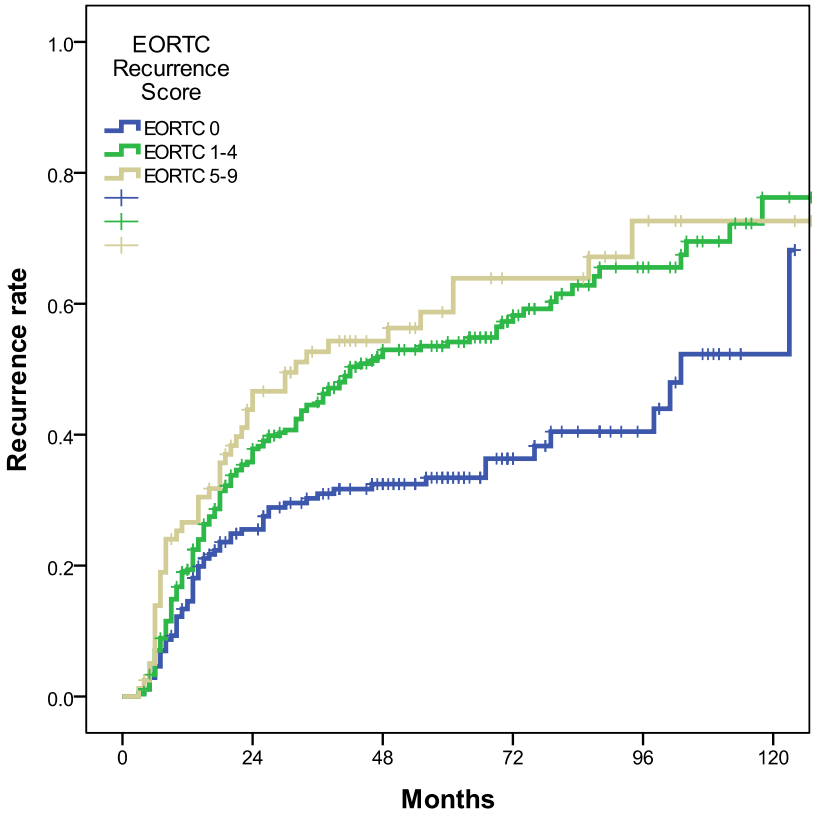
Table 14 Differences of patient characteristics among Jena ,EORTC and CUETO studies

Variable	Jena(%)	EORTC(%)	CUETO(%)
Age(years)			
≤60	96 (18.2)	33.1	31.2
61-70	170 (32.2)	34.3	37.6
71-80	184 (34.8)	26.6	28.3
＞80	78 (14.8)	4.5	2.9
Gender			
Male	403 (76.3)	78.7	-
Female	125 (23.7)	19.8	-
Prior recurrence rate			
Primary	448 (84.8)	54.1	66.7
≤1 recurrence/y	80 (15.2)	19.5	33.3
＞1 recurrence/y		24.8	
Number of tumors			
1	407 (77.1)	56.4	49.2
2-3	96 (18.2)	32.2	26.9
＞3	25 (4.7)	9.8	23.9
Tumor size(cm)			
＜3	493 (93.4)	80.4	54.2
≥3	35 (6.6)	17.9	45.8
T category			
Ta	415 (78.6)	55.9	19.4
T1	108 (20.5)	42.7	77.2
Grade			
G1	288 (54.5)	43.2	15.2
G2	189 (35.8)	43.9	57.9
G3	47 (8.9)	10.4	23.5
Concomitant CIS			
No	516（97.7）	94.0	89.7
Yes	12（2.3）	4.4	10.3

Table 15 Probability of recurrence and progression at 1 and 5 years based on the weighted variables according to the EORTC score

Variable	Patients(n)	Probabilities at 1 y (%)		Probabilities at 5 y (%)	
		Jena(%)	EORTC(%)	Jena(%)	EORTC(%)
Recurrence score					
0	175	14.3	15 (10-19)	30.9	31 (24-37)
1-4	273	19.1	24 (21-26)	49.4	46 (42-49)
5-9	79	25.3	38 (35-41)	53.2	62 (58-65)
10-17	1	-	61 (55-67)	-	78 (73-84)
Progression score					
0	248	0	0.2 (0-0.7)	3.6	0.8 (0-1.7)
2-6	206	1.4	1 (0.4-1.6)	7.8	6 (5-8)
7-13	74	2.7	5 (4-7)	17.5	17 (14-20)
14-23	0	-	17 (10-24)	-	45 (35-55)

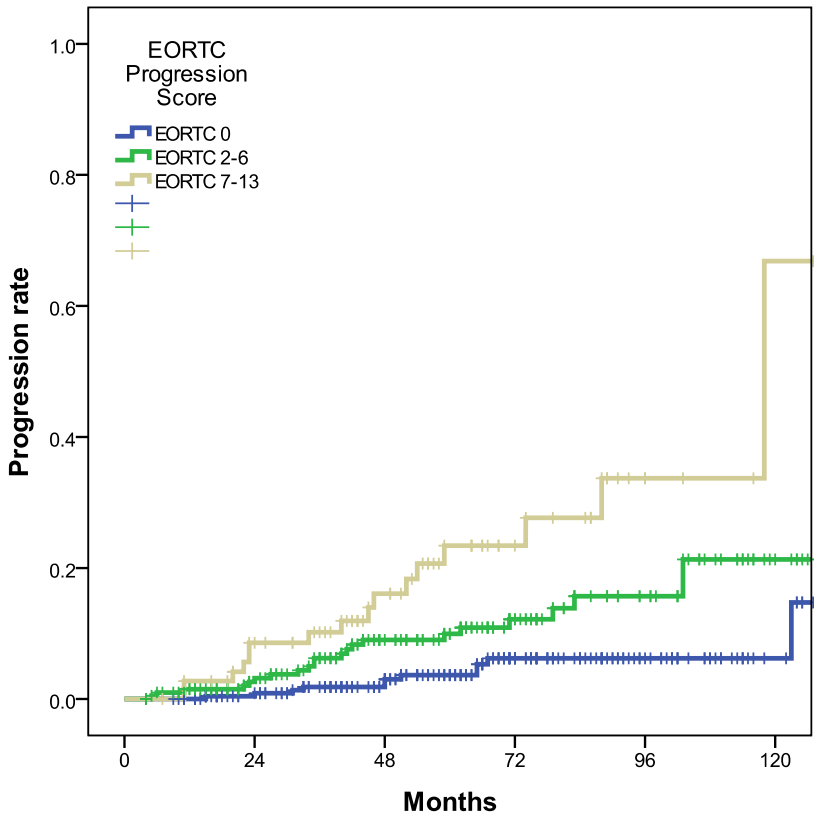
Kaplan-Meier survival curves for the 3 risk groups were plotted for recurrence and progression in Figure 21 and 22, and a statistically significant difference were found among different score groups (Log-rank $P<0.001$). To assess discriminative abilities of the EORTC models, concordance index of the EORTC models was 0.567 for recurrence and 0.675 for progression, respectively.



	Total	12m	24m	36m	48m	60m	72m	84m	Recurrence
O	175	145	114	98	80	58	33	24	**EORTC 0**
R	62	25	43	51	53	54	56	58	
O	273	210	153	129	89	71	43	28	**EORTC 1-4**
R	150	52	99	116	133	135	140	144	
O	79	57	38	29	23	16	12	12	**EORTC 5-9**
R	46	20	35	39	40	42	44	44	

*O = Observed number of recurrence; R= Number of cumulative recurrence

Figure 21 Kaplan-Meier survival curves of risk of recurrence using EORTC recurrence score



	Total	12m	24m	36m	48m	60m	72m	84m	Progression
O	248	240	217	198	160	124	83	59	**EORTC 0**
P	11	0	2	4	6	9	10	10	
O	206	190	168	148	114	93	62	43	**EORTC 2-6**
P	22	3	6	11	15	16	18	20	
O	74	70	60	54	40	27	18	15	**EORTC 7-13**
P	16	2	6	7	10	13	13	14	

*O = Observed number of progression; P= Number of cumulative progression

Figure 22 Kaplan-Meier survival curves of risk of progression using EORTC progression score

Using the same method, the recurrence and progression probabilities at 1, 2 and 5 years and the corresponding reference probabilities based on the CUETO risk tables for each risk group are shown in Table 16.

The CUETO recurrence score was 0 to 4 in 378 patients, 5 or 6 in 103 patients, 7 to 9 in 41 patients, and 10 to 16 in 3 patients. We compared our actual recurrence rates with the CUETO predictions among the four groups. There was not a statistical value in the forth group because of only 3 patients enrolled in our cohort.

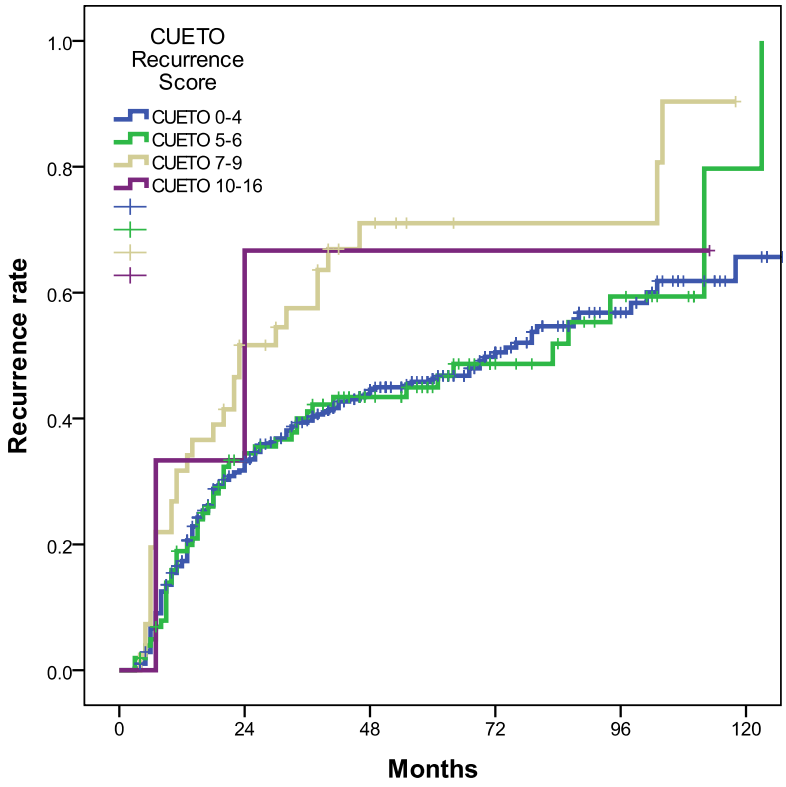
In contrast to the corresponding reference probabilities in the CUETO risk table the recurrence rates in our series were generally higher in the 4 groups regardless of the time point (1,2 and 5 years; Table 16).

For the progression risks, patients were divided into four groups based on the progression score: the first group with score 0-4, the second group with score 5-6 , the third group with score 7-9, and the forth group with score 10-14. The CUETO progression score was 0 to 4 in 412 patients, 5 or 6 in 62 patients, 7 to 9 in 29 patients, and 10 to 14 in 25 patients. In the first group, there were a progression incidence of 0% at the 1st year , 4 patients (0.9%) at 2 years and 16 patients (3.9%) at 5 years. In the second group, progression rates of 1.6% at the 1st year, 4.3% at 2 years and of 11.3 % at 5 years were reported. In the third group, progression rates of 6.9% at the 1st year, 13.8% at 2 years and 31.0% at 5 years were documented. The progression rates in the forth group were 8.0% at the 1st year, 12.0% at 2 years, and 24.0% at 5 years, respectively.

Figure 23 and Figure 24 present the Kaplan-Meier survival curves in the four groups for recurrence and progression. The curves reveal a significant difference among the 4 categories based on the CUETO score (Log-rank $P<0.001$). To assess discriminative abilities of the CUETO models, concordance index of the CUETO models was 0.526 for recurrence and 0.705 for progression, respectively.

Table 16 Probability of recurrence and progression at 1, 2, and 5 years based on the weighted variables according to the CUETO score

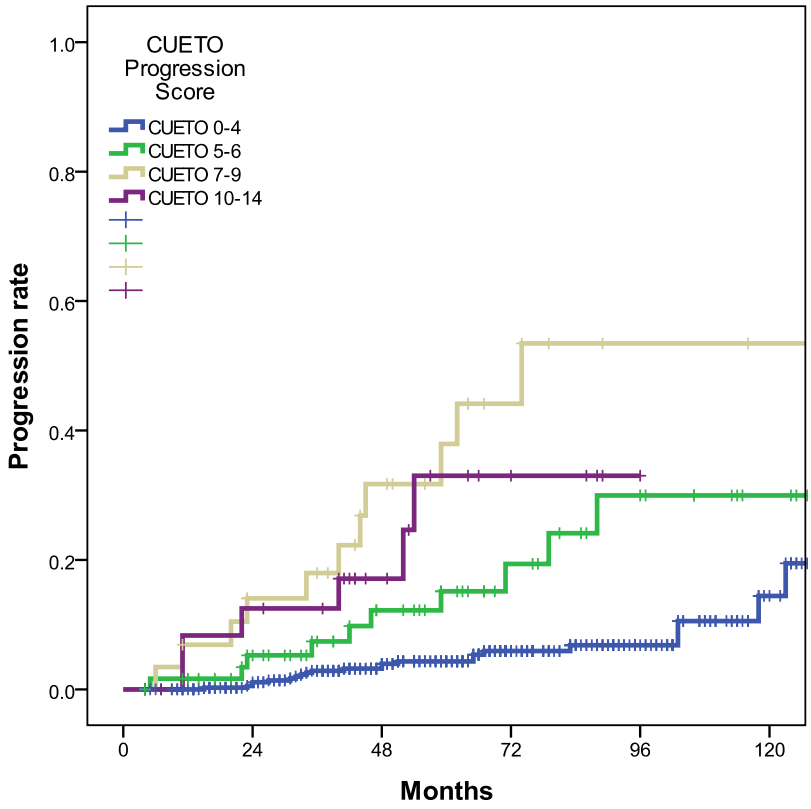
Variable	Patients (n)	Probabilities at 1 y (%)		Probabilities at 2 y (%)		Probabilities at 5 y (%)	
		Jena(%)	CUETO(%)	Jena(%)	CUETO(%)	Jena(%)	CUETO(%)
Recurrence score							
0-4	378	17.2	8 (6-11)	31.7	13 (10–15)	41.9	21 (17-25)
5-6	103	18.4	12 (8-16)	33.0	22 (17–28)	41.7	36 (29-42)
7-9	41	31.7	25 (20-31)	48.7	40 (33–46)	65.8	48 (41-55)
10-16	3	33.3	42 (28-56)	66.7	53 (38–67)	66.7	68 (54-82)
Progression score							
0-4	412	0	1.2 (0.2-2.2)	0.9	2.2 (0.8–3.5)	3.9	3.8 (1.9-5.6)
5-6	62	1.6	3 (0.8-5.2)	4.8	5 (2.3–7.6)	11.3	12 (7.6-16)
7-9	29	6.9	5.6 (2.7-8.4)	13.8	12 (8–16)	31.0	21 (16-27)
10-14	25	8.0	14 (6.6-21)	12.0	25(16–34)	24.0	34 (23-44)



	Total	12m	24m	36m	48m	60m	72m	84m	Recurrence
O	381	302	226	188	141	111	76	46	**CUETO 0-4**
R	178	65	121	142	156	160	167	172	
O	103	80	60	53	40	29	18	14	**CUETO 5-6**
R	50	19	34	40	42	43	45	46	
O	41	28	18	14	7	4	3	3	**CUETO 7-9**
R	29	13	21	23	27	27	27	27	
O	3	2	1	1	1	1	1	1	**CUETO 10-16**
R	2	1	2	0	0	0	0	0	

*O = Observed number of recurrence; R= Number of cumulative recurrence

Figure 23 Kaplan-Meier survival curves of risk of recurrence using CUETO recurrence score



	Total	12m	24m	36m	48m	60m	72m	84m	Progression
O	412	394	352	319	254	200	134	95	**CUETO 0-4**
P	22	0	4	10	13	16	17	18	
O	62	58	50	41	34	27	19	15	**CUETO 5-6**
P	10	1	3	4	6	7	8	9	
O	29	26	22	20	14	10	6	3	**CUETO 7-9**
P	11	2	4	5	8	9	10	11	
O	25	22	21	20	12	7	4	4	**CUETO 10-14**
P	6	2	3	3	4	6	6	6	

*O = Observed number of progressions; P= Number of cumulative progression

Figure 24 Kaplan-Meier survival curves of risk of progression using CUETO progression score

5 Discussion

5.1 Clinical and Pathological Characteristics

To identify the important variables associated with disease recurrence and progression, a retrospective NMIBC study was performed in our institution. Overall, 611 patients with NMIBC were identified between January 1, 2003 and December 31, 2011, including 471 men and 140 women which equals a male to female ratio of 3.4:1. The median age of 74 years in women was greater than 70 years in men. Thus, our cohort resembles a typical bladder cancer population. Of the patients 528 were followed up excluding those undergoing cystectomy directly and with incomplete data after initial TUR etc. The median follow-up duration was 60 months (range: 1-143 months), and 448 (84.8%) were diagnosed with primary BC disease.

In general, clinical characteristics of NMIBC patients vary in different regions and countries, which have been reported in several investigations (Rianne et al.2014, Kohjimoto et al. 2014). Schulze and colleagues assessed 251 german NMIBC patients with a mean follow-up of 69 months in 2007, which showed 2.6:1 of male to female ratio, and 85% patients with primary BC (Schulze et al. 2007). Other studies also showed slight differences of clinical characteristics based on local demographic data (Lazica et al.2014, Grimm et al. 2003).

According to the EORTC and CUETO scoring systems and risk tables (Sylvester et al. 2006, Fernandez-Gomez et al. 2009), all clinical and pathological data were collected to predict disease recurrence and progression, including gender, age, prior recurrence rate, number of tumors, tumor size, tumor stage, tumor grade, and presence of CIS. However, the risk scoring of the EORTC is exclusively based on studies, in which no second TUR and no BCG maintenance therapy was applied.

Meanwhile, some studies have demonstrated that second TUR plays an important role to determine the therapeutic strategy and reduce disease recurrence rates (Dobruch et al. 2014, Kim et al.2012). Therefore, location of the tumors at initial TUR, second TUR, and second TUR pathology are further included in the present study.

Compared to the patient characteristics of the EORTC and CUETO studies, there is some variation in our cohort. Firstly, the proportion of elderly patients more than 70 years was higher (50% in our study vs. 31% according to EORTC and CUETO studies) in our institution. Secondly, the percentage of recurrent tumors was lower (15% vs. 33-45%). Thirdly, the proportion of stage T1 tumors was significantly reduced (21% vs. 42-77%). Thus, the number of high-risk patients was relatively smaller than in both large scale studies.

In the past, the majority of studies focused on NMIBC using the classification based on stage and grade only (Soloway et al.2006, Lazica et al. 2014, Takaoka et al.2013). In the present study, NMIBC patients were stratified into low, intermediate and high risk category according to the EAU guidelines subsequently facilitating to define an accurate therapeutic scheme. Of these patients 197 (32%) had low-risk, 251(42%) intermediate-risk and 163 (26%) high-risk, respectively.

With respect to the distribution of tumor locations, there were 26.7% patients with multifocal and 42% single tumors of the side walls. This result was quite similar with previous findings from another german hospital reporting multiple tumors in 33% patients and single tumor of the side walls in 47% patients (Schulze et al. 2007).

5.2 Second TURB

A second TURB should be performed generally within 2-6 weeks if incomplete resection tumors, no muscle in original specimen for high grade tumors, multifocal tumors and any T1 in NMIBC patients (Babjuk et al. 2011), which have been recommended by EAU guidelines. Moreover, the residual tumor rate detected by a second TUR varies between 27% and 78% (Babjuk et al. 2011).

Some authors focused only on second TURB in stage Ta or T1 high-grade NMIBC. A randomized trial performed by Divirik and associates demonstrated that second TURB after complete first TURB could significantly decrease the recurrence and progression rates in patients with primary diagnosed T1 BC (Divrik et al. 2010). Likewise, Sfakianos et al. suggested that second TURB should be performed before initial BCG therapy for NMIBC, which was drawn from the analyses of 1,021 patients (Sfakianos et al.2014).

Generally, second resection is not recommended in low-grade bladder tumors, because it does not alter treatment strategy (Herr 2011). However, a 5-year observational study performed by Grimm and coworkers indicated that recurrence-free rate was 63% in patients undergoing second TUR compared with 40% of patients after TUR alone (Grimm et al. 2003). Furthermore, there were residual tumors in 27% of pTa and 53% of pT1 patients. In our present study, 16.9% of pTa patients had residual tumor after second TUR, but only 31.1% in pT1 patients. However, patients in the study by Grimm et al. were treated between 1993 and 1995 while the present cohort underwent TUR after 2003. Thus, improvements in camera-systems used during TUR might have contributed to the lower tumor rate detected by second TURB.

According to the EAU classification the rate of residual tumor after second TUR was 13.2%

in low-risk , 19.5% in intermediate-risk and 29.6% in high-risk patients, respectively. Thus, the residual tumor rate was significantly associated with EAU risk categories. In order to better understand the features of primary TaG1 and TaG2 tumors, we performed a subgroup analyses and compared primary TaG1/G2 cases with the remaining NMIBC patients. The results indicated that the residual tumor rate was significantly reduced in primary TaG1/G2 group.

We analyzed further downstaging and upstaging after second TUR compared with first pathological diagnosis. Of the 67 patients with low and intermediate risk at primary TUR, 6(8.9%) had a higher stage at second resection. In the high-risk cases, 8(20%) were found upstaged and 7 (17.5%) had however a lower stage after second TUR. A prospective study published by Ali et al also showed that 20% of pTa patients developed into pT1 at second TUR, and 26.2% of pT1 cases progressed into muscle-invasive disease. In that study 14.8% of the pT1 patients were downstaged to stage pTa (Ali et al. 2010). The authors concluded that second TUR was recommended for T1, high grade, nodular tumors with a diameter of at least 3cm tumors. However, considering the present study the risk of understaged NMIBC is significant and, considering its impact on subsequent treatment modalities in the upstaged patients, should be carefully considered based on risk category.

Of the 107 patients with residual tumor detected by second TUR, 80 (74.8%) even underwent a third TUR. The results showed that of the patients 36.2% still had persistent tumor including 1 with lower, 2 with higher and 26 with the same stage, respectively. The rate of persistent tumor was significantly correlated to the EAU risk groups ($P<0.05$). Those patients might need close observation or to undergo an aggressive therapeutic strategy. Thus, third TURB might further help clinicians to distinguish between immediate radical cystectomy and intravesical therapy, as the majority of patients with residual T1 disease at second TUR developed probably into muscle-invasive disease.

Süer and colleagues showed that a prolonged interval between first and second TURBT was an independent predictor for residual tumor detection in high-grade T1 cases (Süer et al. 2013). Furthermore, Baltaci et al. reported that time interval between first and second TUR should to be less than 42 days in patients with high-risk NMIBC treated with BCG maintenance instillation, in order to obtain lower recurrence and progression rates (Baltaci et al. 2014). Therefore, we considered the time interval as a potential prognostic factor for disease recurrence and progression in our study. However, we could not confirm these observations in our high-risk cases. To our knowledge, most authors recommend the second TUR at 2-6 weeks after initial TUR (Babjuk et al. 2011). However, our results indicate that

this is difficult in clinical practice as only 68 % of our patients stayed within the 42 days time frame (69%) while 31% of our patients underwent second TUR between days 43-56.

5.3 Recurrence and Progression in Follow up

Of the NMIBC patients, recurrence is the main problem for stage pTa patients, whereas progression is the main potential life-threatening aspect in pT1 and CIS cases (van Rhijn et al. 2009). Recurrence and progression was reported in 49.1% and 8.7% of our cases, respectively. Similarly, Choi et al. reported that 33.0% patients had recurrence within a mean follow-up of 19.0 months, and 9.0% cases advanced into MIBC with 33.6 months (Choi et al. 2014). In addition, Linton and coauthors also published their finding in a large sample with primary pTaG1 bladder cancer. The author's observed that 28.5% of the patients recurred and 4.5% progressed after a median period at 13.5 months and 35.7 months, respectively (Linton et al. 2013). Based on the similar median follow-up (58-61 months vs 60 months), the greater rate of disease recurrence and progression in our study could be explained by the higher proportion of high-risk patients. However, the median RFS and PFS are comparable (16-19moths vs 13.5 moths; 33.6-40 moths vs 35.7months; respectively).

With respect to recurrence, the overall recurrence rates were 18.6% and 43.9% at the first and fifth year. Likewise, a retrospective study conducted by Kikuchi et al based on the Japanese National Bladder Cancer Registry, indicated that the 1-year, 2-year, and 5-year overall recurrence rates were 33.0%, 38.7%, and 47.2%, respectively (Kikuchi et al. 2009). The lower recurrence rate in the short term in our cohort may be due to second TUR or the consistent use of early instillation therapy. Our results showed that the recurrence rate was significantly associated with the risk category of NMIBC ($P<0.001$). In this setting, the mean time of RFS were 64.9 months, 27.4 months and 21.6 months in the low, intermediate and high risk group, respectively. Therefore, high risk patients should undergo close follow up within the 24 months after initial diagnosis.

Currently, the IBCG defines progression of NMIBC as an increase in the T stage not only as development of T2 or greater, but also as an increase in the T stage from CIS or Ta to T1 (Lamm et al. 2014). In our institution the results indicated that 6.3% patients were found with progression from stage Ta to T1 and 5.5% pTa patients developed directly into muscle-invasive disease. However, the rate of progression in pT1 stage was 24.1%. In the subgroup analyses among different risk groups, the patients with higher risk had a greater probability to develop into MIBC or from pTa to pT1 ($P<0.001$). Thus, a close follow up to detect progression early should mainly focus on stage T1 patients.

5.4 Prognostic Factors in Disease Recurrence and Progression

Sylvester and colleagues proposed that the EORTC scoring system was applied to calculate an individual probability of recurrence and progression (Sylvester et al. 2006). Consequently, this method was recommended by the EAU guidelines for NMIBC. The important prognostic variables are prior recurrence rate, multiplicity, tumor size, tumor stage, tumor grade and concomitant CIS. Several investigators have reported also that second TUR played an important role to decrease the risk of recurrence and progression (Herr HW and Donat SM 2006, Divrik et al. 2010). Therefore, second TUR and second TUR pathology were also considered as potential prognostic factors in our study. Furthermore, the time interval between first and second TUR was analyzed in recurrence and progression models according to the study of Baltaci and coworkers (Baltaci et al.2014).

As discussed above, univariate Cox proportional hazards regression analyses revealed prior recurrence rate, T category, second TURB and second TUR pathology were significant predictors for tumor recurrence. Compared to other studies (Xu et al.2013, Sylvester et al. 2006, Kikuchi et al. 2009), we found that number of tumors, tumor size and tumor grade were not associated with tumor recurrence in our cohort. This difference may be attributed to a possible bias in the low proportion of at least 3cm tumors and the number of tumors (more than 3). Of note, our patients were not enrolled in a clinical trial and documentation of tumor diameter and number of tumors relies on retrospective chart review. Only prior recurrence rate and second TUR pathology were independent risk factors for disease recurrence in multivariate analyses.

With regard to progression, age, prior recurrence rate, T category, tumor grade, second TURB and second TUR pathology were identified as significant predictors for tumor progression. In the subsequent multivariate analyses, age, prior recurrence rate, tumor stage, tumor grade and second TUR pathology were found as independent risk factors for tumor progression. These results indicate that most variables were significant associated with tumor progression. The Kaplan–Meier curve showed the significant differences among three EAU risk groups (P <0.05). Nevertheless, time interval between first and second TUR was not related to risk of recurrence and progression which may, however, play an important role in stage pT1 or high-risk patients (Baltaci et al.2014).

In the subgroup analyses with primary TaG1/G2 bladder tumors, the results indicate that only second TUR pathology is associated significantly with RFS, whereas age and second TUR are predictors in PFS. In a 10-year study of TaG1 NMIBC, Bosset and colleagues found that

tumor size and number of lesions were prognostic factors for disease recurrence (Bosset et al. 2014). Moreover, Rieken et al. retrospectively analyzed 1447 patients with TaG1 BC and demonstrated that advancing age, tumor >3cm, multiple tumors and recurrent tumors were associated with increased recurrence risk. In the same study, advanced age and multiple tumors were independent predictors of disease progression (Rieken et al. 2014). Linton et al reported that low-grade dysplasia at initial resection and tumor weight were related to disease specific mortality (Linton et al. 2013). In contrast to these other investigations, out cohort contains a higher proportion of low and intermediate risk patients (Olivier et al. 2015, Linton et al. 2013, Rieken et al. 2014).

5.5 EAU Classification System in TaT1 Bladder Cancer

The EAU panel recommends urologists to stratify patients with three EAU risk categories based on the clinical prognostic factors and EORTC risk tables, in order to facilitate subsequent treatment selection. We found that the EAU risk stratification was significantly associated with disease progression ($P < 0.001$). However, it is difficult to distinguish recurrence risk between intermediate and high risk. In fact, the definition and management for intermediate risk NMIBC varies between EAU, AUA, and ICUD recommendations (Konety et al. 2012, Hall et al. 2007, Babjuk et al. 2013). Therefore, the IBCG recently recommended that multiple and at least 3 cm in size tumors, recurrence within 1 year and frequency (more than 1 per year) of recurrences as well as previous treatment are prediction factors to facilitate clinical decisions in intermediate risk NMIBC. The number of these factors was stratified into different therapeutic scheme (Kamat et al. 2014). The risk category should be calculated again at each tumor recurrence.

5.6 Discriminative Abilities of the EORTC and CUETO Models

Numerous studies were reported to identify prognostic factors for recurrence and progression of NMIBC (Sylvester et al. 2006, Fernandez-Gomez et al. 2009). Generally, the important prognostic factors are clinical and pathological variables, including the number of tumors, tumor size, prior recurrence rate, tumor stage, tumor grade, and the presence of CIS. Up to now, the EORTC and CUETO scoring system and risk tables are considered the most reliable systems.

In 2006, Sylvester et al. developed the EORTC scoring system, which was derived from the data obtained from studies between 1979 and 1989 comprising 2596 NMIBC patients enrolled

in seven EORTC-trials. According to the mentioned six clinicopathologic variables, weighting scores for each factor differed depending on the severity of the specific parameter and the total score from all factors predicts the probability of recurrence and progression at 1-year and 5-years. The main limitation of the EORTC model is that just 171 patients (6.6%) were treated with BCG instillation therapy and none of the patients received a maintenance schedule. Furthermore, second TUR was not part of the treatment strategy in these trials.

To overcome this deficiency (only 6.6% with BCG therapy), a new scoring system was described by the CUETO group (Fernandez-Gomez et al. 2009). They reviewed data from four CUETO trials involving a total of 1062 patients with BCG therapy treated between 1990 and 1999. This scoring model includes seven clinicopathologic factors, adding both age and gender compared to the EORTC model. In the same way, the probability of 1-year, 2-year and 5-year recurrence and progression rates were calculated from sum scores of each factor. Their results demonstrated the overestimated risks of recurrence and progression in NMIBC patients with BCG therapy using the EORTC model.

In order to evaluate the applicable ability of EORTC and CUETO in different countries, several external validation studies (Table 17) have been performed with controversial results (Kohjimoto et al. 2014). Although the majority of authors recommend the EORTC or CUETO scoring systems to manage NMIBC patients, the largest cohort study (4689 patients) conducted by Xylinas et al. demonstrated that both EORTC and CUETO scoring systems had a poor discrimination for recurrence and progression in NMIBC patients. The main finding was overestimated risk of disease recurrence and progression in high-risk patients, especially in BCG-treated patients (Xylinas et al. 2013). Therefore, EORTC and CUETO models may not apply to NMIBC patients treated nowadays e.g. if patients undergo routine re-resection and BCG maintenance therapy. In order to analyze the discriminative abilities, we calculated the 1- and 5-year risk of disease recurrence and progression in our cohort and compared it with EORTC and CUETO risk tables.

Overall, our cohort is similar to that of the EORTC but not to that of the CUETO cohort. In conclusions, 79 patients with EORTC recurrence score 5-9 were overestimated at 1 and 5 years (25% vs 38%; 53% vs 62%, repectively) and the patients with EORTC progression score 7-13 also exhibited a lower progression rate at 1 year (2.3% vs 5%). Thus, our results are similar to the conclusions of Xylinas (Xylinas et al.2013). On the other hand, our recurrence rates (Table 16) showed an overestimated probabilty in all patients at the same time point (1,2 and 5 years) compared with the expected probabilities according to the CUETO risk tables. This poor discriminative ability of the CUETO recurrence risk table is not

surprising, considering that only 8.4% of our patients were treated with BCG therapy. However, the CUETO progression risk table results in a good prediction in our cohort regardless of the time point considered (c-index: 0.702).

Table 17 External validation studies for the EORTC and CUETO models

Author	Country	Period	No. patients	BCG%	EORTC	CUETO
Altieri	UK	2002-2011	259	23%	＋	NA
Pillal	UK	1983-1985	109	0%	＋	NA
Hernandez	Spain	1998-2008	417	8.2%	＋	NA
Ajili	Tunisia	2002-2011	112	NA	＋	NA
Ding	China	2000-2009	301	0%	＋	NA
Seo	Korea	1993-2007	251	100%	＋	NA
Fernandez-Gomez	Spain	1990-1999	1062	100%	－	NA
Borkowska	Poland	2006-2009	91	NA	－	NA
Rosevear	USA	1999-2001	718	100%	NA	＋
Lammers	Netherland	1987-2010	728	0%	＋	－
Xu	China	2003-2010	363	0%	＋＋	＋
Choi	Korea	1985-2011	531	NA	＋	＋＋
Kohjimoto	Japan	1985-2007	366	100%	－	＋
Xylinas	International	2000-2007	4689	11%	－	－
Vedder	International	1979-2012	1892	23.7%	Progression	Progression
Our present study	**Germany**	**2003-2011**	**528**	**8.9%**	**Progression**	**Progression**

*:＋:Recommendation; －:No recommendation; NA : Not Applicable.

Those conclusions could be reflected through the Harrell's concordance index. Our results are similar with the findings of Vedder et al (0.57 vs. 0.55 in EORTC recurrence prediction, 0.68 vs. 0.72 in EORTC progression prediction; 0.53 vs. 0.61 in CUETO recurrence prediction, 0.71 vs. 0.82 in CUETO progression prediction) (Vedder et al. 2014). In contrast to Xylinas' conclusions, our C-indexes in recurrence prediction are 0.57 vs. 0.60 compared to EORTC and 0.53 vs. 0.52 compared to CUETO. Regarding disease progression C-indexes of disease progression are 0.68 vs. 0.66 compared to EORTC and 0.71 vs. 0.62 copmpared to CUETO (Xylinas et al.2013). However, other investigators have shown a higher C-index in recurrence (range: 0.62-0.75) and a comparable progression C-index (range: 0.65-0.77) regardless of the used models (Kohjimoto et al. 2014, Pillai et al.2011, Xu et al.2013) .

In contrast to the recurrence models, the progression models of both, EORTC and CUETO,

appeared to be more applicable to our cohort. Furthermore, the CUETO models overestimate generally recurrence probabilities in our institution. Because age is an independent predictor in disease progression, EORTC plus the variable age maybe have a better utility for predicting disease recurrence and progression.

5.7 Limitations

There are some limitations in the present study. Given the retrospective nature of this analyses and long term follow-up period, not all patients were treated subsequently by the standard regimen or the same clinician, which might influence the treatment effect. We could not assess thoroughly intravesical chemotherapy or dosage and discontinuation of BCG instillation due to incomplete medical records. On the other hand, the quality of TUR between WLC and PDD period and the old classification of stage and grade might influence our results. Another limitation is the size of the sample, especially in the high-risk category in which the number of patients is relatively smaller than in other investigations.

Even with these limitations, our results indicate the true characteristics of NMIBC patients as far as possible based on our cohort, which may facilitate better therapeutic strategy in our institution.

6 Conclusion

Optimal management of NMIBC requires accurate and individual prediction of the risk for recurrence and progression. To date, clinical and pathological variables still are the optimized prognostic factors to facilitate clinicians to choose optimal therapeutic modalities. In the setting, age, gender, prior recurrence rate, tumor size, number of tumors, tumor stage, tumor grade, second TURB, second TUR pathology, and interval between first and second TUR were analyzed to distinguish independent prognostic factors in our cohort. The main conclusions are:

In our institution, EAU risk stratification is a good tool to define the therapeutic strategy in patients with NMIBC.

In subgroup analyses of primary pTaG1/G2 patients, second TUR is associated with a reduced risk of disease recurrence. However, advanced age and residual tumor after second TUR increase the progression risk in this subgroup

In terms of the univariate analyses, prior recurrence rate, any T1, second TUR and positive pathology after second TUR are related to increased risk of disease recurrence, whereas age, prior recurrence rate, T1, high grade, second TUR, and positive pathology after second TUR are also significantly associated with increased risk of disease progression.

In terms of the multivariate analyses, prior recurrence rate and second TUR pathology are the independent predictors in disease recurrence. Likewise, age, prior recurrence rate, tumor stage, tumor grade, and second TUR pathology are the prognostic factors in disease progression.

In view of the statistical results obtained, we suggest that EORTC and CUETO progression risk tables are included into our clinical practice to estimate individual progression risk in patients suffering from NMIBC.

In contrast to the EORTC recurrence risk table, the CUETO recurrence risk table underestimates completely the risk of disease recurrence in our cohort. On the other hand, EORTC recurrence risk table overestimates the risk in patients with higher intermediate-risk (recurrence score: 5-9).

In conclusion, we propose that second TUR is of paramount importance and should be applied to all NMIBC patients, CUETO progression risk table is the best choice in our NMIBC population. Our therapeutic strategy is appropriate in the management of NMIBC patients, especially in high-risk patients resulting in a relatively low recurrence risk.

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8 Appendix

Curriculum Vitae

Personal Data

Name : Guoxian Zhang

Gender : Male

Date of Birth : 18. 12. 1981

Place of Birth : Henan Province, P. R. China

Nationality: Chinese

Address : Westendstr. 2, 07743, Jena, Germany

Education

February 2013-June 2015 : MD. Student, Urologie, Friedrich-Schiller-University, Jena, Germany

September 2005-July 2008: Master of Medicine, Zhengzhou University,
Henan Province, P.R.China

September 2000-July 2005: Bachelor of Medicine, Zhengzhou University,
Henan Province, P.R.China

September 1996-July 2000 : Senior high school

September 1993-July 1996 : Junior high school

September 1988-July 1993 : Primary school

Work experience

June 2012-January 2013: Resident doctor, Hannover ,Germany

September 2008-October 2011: Resident doctor, Zhengzhou , P.R.China

Publications

1. **Guoxian Zhang**, Daniel Steinbach, Marcus Horstmann, Marc-Oliver Grimm. Predicting Recurrence and Progression in Patients with Primary Non-muscle-Invasive Bladder Cancer Undergone Second Transurethral Resection: Utility of the EORTC and CUETO Scoring Models. (Submission preparation)
2. **Guoxian Zhang**, Daniel Steinbach, Miezcyslaw Gajda, Tobias Franiel, Marc- Oliver Grimm, Marcus Horstmann. High-grade Carcinoma of the Proximal Ureter With Negative

Nephroureteroscopy Detected by a positive FISH Test : A Case Report. Urology Case reports. 2015(3):167-169.

3. **Guoxian Zhang**, Daniel Steinbach, Marcus Horstmann, Marc-Oliver Grimm. Prognostische Faktoren für das Rezidiv- und Progressionsrisiko beim nicht muskelinvasiven Urothelkarzinom der Harnblase (NMIBC). 67. Kongress der Deutschen Gesellschaft für Urologie , Hamburg , September 23-26, 2015.

4. **Guoxian Zhang**, Daniel Steinbach, Marcus Horstmann, Marc-Oliver Grimm. Validierung der EORTC und CUETO Rezidiv- und Progressionsscores anhand eigener Patientendaten beim NMIBC. 67. Kongress der Deutschen Gesellschaft für Urologie , Hamburg , September 23-26, 2015.

5. Marcus Horstmann, Astrid Enkelmann, **Guoxian Zhang**, Ihab Ali Mohammad Abutabanjeh, Lars Twelker, Marc-Oliver Grimm. Outcome nach weiteren transurethralen Resektionen bei Patienten mit persistierender Malignität in der Nachresektion bei nicht muskelinvasiven Blasenkarzinomen (NMIBC). 66. Kongress der Deutschen Gesellschaft für Urologie , Dusseldorf , October 01-04, 2014.

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This dissertation is dedicated to my wife, my little daughter, and all my family.

Ehrenwörtliche Erklärung

Hiermit erkläre ich, dass mir die Promotionsordnung der Medizinischen Fakultät der Friedrich-Schiller-Universität bekannt ist,

ich die Dissertation selbst angefertigt habe und alle von mir benutzten Hilfsmittel, persönlichen Mitteilungen und Quellen in meiner Arbeit angegeben sind,

mich folgende Personen bei der Auswahl und Auswertung des Materials sowie bei der Herstellung des Manuskripts unterstürzt haben:
- Prof. Dr. Marc-Oliver Grimm
- PD. Dr. Marcus Horstmann

die Hilfe eines Promotionsberaters nicht in Anspruch genommen wurde und dass Dritte weder unmittelbar noch mittelbar geldwerte Leistungen von mir für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen,

dass ich die Dissertation noch nicht als Püfungsarbeit für eine staatliche oder andere wissenschaftliche Prüfung eingereicht habe und

dass ich die gleiche, eine in wesentlichen Teilen ähnliche oder eine andere Abhandlung nicht bei einer anderen Hochschule als Dissertation eingereicht habe.

Jena,den 30.06.2015 Guoxian Zhang