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The Frequency of Recurrence of Superficial Transitional Cell Carcinoma After Turbt

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Abstract

Background:
To determine the frequency of recurrence of superficial tumours on first check cystoscopy i.e. 3 months after complete resection of tumour.

Methods:
In this descriptive study adult male and female patients (n=63) presenting with a superficial transitional cell carcinoma of urinary bladder were included and complete resection of the tumour was done and tissue sent for histopathology. Patients with Superficial T.C.C (confirmed by histopathology) were followed up, after three months by cystoscopy and findings noted. Any tumour growth on the same or new location was resected again and sent to the same histopathologist for examination and confirmation of TCC. All the above information was recorded and entered into a structured proforma.

Results:
Majority (74.6%) were male. The age of patients ranged from 32 to 86 years with a mean of 60 ± 9.04 years. The T-stage at presentation was pTa in 15 (23.8%) patients and pT1 in 480 (76.2%) patients. The histological grade of tumour at presentation was G-I in 15 (38%), G-II in 14 (22.2%) and G-III in 25 (39.6%) patients. First check cystoscopy was done 3 months after TURBT. In which 38 (60.3%) patients showed recurrence of tumour while the rest, i.e. 25 (39.6%) showed disease free status. Out of 38 cases with recurrence of tumour, 1 (2.6%) cases showed pTa and 37 (86.3%) showed pT1. The recurrent histological G-I, G-II and G-II were 4, 13 and 21 respectively.

Conclusion:
Recurrence of superficial transitional cell carcinoma at first check cystoscopy is high and has a predictive value for future recurrence of the disease.

Key Words: Transitional Cell Carcinoma (T.C.C); Transurethral resection of bladder tumour (TURBT); Cystoscopy.

Introduction:

Transitional Cell Carcinoma (T.C.C) is the most common tumour of urinary bladder. White light cystoscopy is the standard tool for diagnosis. Treatment of choice for superficial T.C.C is transurethral resection of bladder tumour (TURBT). Superficial T.C.C has a natural history of recurrence and disease progression. The risk of tumour recurrence can be minimized by using intravesical chemo/immunotherapy. It represents 70%–80% of all bladder neoplasms. [1] More than 90% of urothelial cancers in the bladder TCC. Other important histological types include squamous cell carcinoma and adenocarcinoma. [2] Urinary bladder neoplasm can be grouped into three different categories i.e., superficial, invasive and metastatic. At presentation, 75% of the tumours are superficial, 20% are invasive and up to 5% have de novo metastasis. [3] TCC is the seventh most common cause of death in men and tenth most common cause of death in women. It can occur anywhere along the urinary tract which is lined by transitional cell epithelium (urothelium) but its presence in the bladder, in majority of cases points to a cause related to pooling of urine/mucosal contact with urine. Superficial bladder cancers, which include papillary carcinoma (Ta), Carcinoma in Situ (C.I.S or Tis), which are flat, and on cystoscopy appear as red (hyperemic), raised, velvety areas which bleed readily on touch, and tumors that invade Lamina Propria (T1).2, 3 Superficial TCC is the most common form of transitional cell carcinoma of the bladder, and accounts for 90% of cases. Of the superficial variety, pTa accounts for about 70% of cases and pT1 for 30% of cases. [4] Carcinoma in situ, like T.C.C, can be found anywhere along the urinary tract. It is considered to be a very highly aggressive form of the disease as it has the ability to invade deeper layers of the bladder rapidly and can progress to more invasive

forms of T.C.C. Various etiological/risk factors for T.C.C bladder are identified including environmental factors and genetic factors. The most common environmental factors responsible for T.C.C bladder are the aromatic amines (Arylamies), Benzidine, 4-Aminobiphenyl, Beta- Nephthylamines, found in various industrial products. The occupational hazards include working in paints, petroleum, rubber or leather, coal, printing industries and barbers. [5] Smokers have up to four-fold higher incidence of bladder cancer than nonsmokers. [6] the risk correlates with the number of cigarettes smoked, the duration of smoking and the degree of inhalation of smoke. Causative agents in cigarette smoke are thought to be alpha and beta naphthylamine, which are secreted in the urine of smokers. [7] Various infections, such as Human Papilloma Virus (HPV), are also considered to have an etiological effect. [8] National Cancer Institute Surveillance Epidemiology and End Results (SEER) programme estimates that 89% of bladder carcinoma patients are 55 years of age or older at the time of diagnosis and that the median age at the time of diagnosis for both men and women. [9] Painless, intermittent, gross haematuria with passage of clots is the most common form of presentation of superficial T.C.C. [10] Symptoms such as frequency, urgency, nocturia, supra pubic discomfort and flank pain, are usually not a feature of superficial T.C.C. Their presence at times would indicate a more invasive form or carcinoma in situ (CIS). Intravenous urogram is done to identify a filling defect in the bladder. However, the main aim of intravenous urography is to identify the presence of any synchronous tumour of ureter and renal pelvis on either side. With the availability of more sophisticated ultrasonographic probes and advances in experience, bladder tumours can be fairly picked up by sonography as it is easy to identify any increased vascularity in the bladder mass to differentiate it from a blood clot in a patient with frank haematuria. [11] T.C.C is known to have a varied response to treatment. The disease has a natural course of multiple recurrences and progression in terms of histological grade and T-stage. About 70% of superficial T.C.C recur after T.U.R.B.T and about 25% will progress to more invasive forms. [12] Intravesical chemotherapy is known to be effective in preventing cancer recurrence by suppressing implantation of the postoperative tumor cells wandering in the bladder after the surgery. On the other hand, in the case of non-muscle-invasive bladder cancer patients in the intermediate risk group (TaG1 with multifocal or ＞3 cm diameter, TaG2, T1G1, T1G2). [13] The rates of recurrence and progression can be minimized by intravesical chemo or immunotherapy in the form of Mitomycin-C or BCG respectively. [14] Various factors are considered for the prediction of future recurrence and progression of the disease, according to EORTC risk tables, including tumour diameter, multiplicity, prior recurrence, presence of concomitant C.I.S, T-stage and histological grade. [15] Every patient should have a check cystoscopy three months after the initial T.U.R.B.T. This first check cystoscopy is of utmost importance as it has a predictive value regarding the future recurrences of the disease. Patients who have a recurrence at first check cystoscopy, are at a higher risk of further future recurrences as compared to those with no recurrence at first check cystoscopy. [16]

Patients and Methods:

This descriptive/observational study of total duration of 6 months from September 2012 to March 2013 was carried out at the Institute of Urology, Kiev, Ukraine. The total numbers of patients were 63 of either sex with a clinical suspicion of bladder tumour presenting at OPD and ER Department were included in study. We included all patients who fulfilled our inclusion/exclusion criteria. All patients underwent cystoscopy and if there was papillary growth in bladder it was completely resected (TURBT). If there is any suspicion of concomitant Carcinoma in situ, a biopsy was taken to rule it out. All operations were performed or supervised by single surgeon and the resected tissue was sent to single histopathologsit for examination (To control bias). The exclusion criteria were followed up, after three months with cystoscopy preferably by the same operator and findings were noted. Any tumour growth on the same or new location was resected again and sent to the same histopathologist for examination and confirmation of recurrence of TCC. (Diagnosis Criteria for recurrence was seeing the growth at the same or other sides, resecting the growth and further confirmed on histopathology.

Results:

The total number of patients included in my study were 63 (n=63). Male patients were 47 (74.6%) and females were 16 (25.4%) with a male to female ratio of 2.4:1. The mean age at presentation was 60 years (32-86 years) with majority of patients (42 patients, 75%) falling in the age range of 50-70 years (Table 1). The most common T-stage at presentation was pT1 (76.4%) (Table 2). While the most common histological grade at presentation was G-III (39.6%) followed by G-I (38%) and lastly G-II (22.2%) (Table 3). The frequency of recurrence at first check, 3 months after TURBT, cystoscopy was 60.3% (38) (Table 4). In the group without recurrence 84% (21) of cases belonged to pTa stage and 16% (4) to pT1 stage. Similarly, majority of cases, in no recurrence group, were histologically G-I (72%, 18), while 4 and 3 cases were G-II and G-III respectively. In the group of patients with recurrence, majority belonged to pT1 (97.3%) (Table 5) and histologically in G-III (39.6%) (Table 6). T-stage progression was noted in only one case from pTa to pT1. Progression of histological grade was noted in 2 cases from G-I to G-II, 1 case from G-I to G-III and 2 cases from G-II to G-III. Down grading occurred in 3 cases from G-II to G-I, 1 case from G-III to G-II and one case from G-III to G-I. In recurrence group, there were 13 (34.2%) cases of pT1G-III (T1G3) tumours.

	N	Minimum	Maximum	Mean	Std. Deviation
Age (Years)	63	32	86	60	9.04

Table 1: Age distribution with Mean and Standard deviation

	Frequency	Percent	Valid Percent
pTa	23	36.5	36.5
pT1	40	63.5	63.5
Total	63	100.0	100.0

Table 2: Frequencies of T-stage at presentation

Histological grade	No (%)
G-I	39%
G-II	24.4%
G-III	36.6%

Table 3: Frequencies of various histological grades at presentation (n=63)

	No	Percentage
Yes	38	60.3
No	25	39.7

Table 4: Frequency of recurrence on first check cystoscopy after TURBT

	No	Percentage
PTa	9	14.2
pT1	38	60.4

Table 5: Frequencies of recurrent T-stage

Histological grade	No (%)
G-I	38%
G-II	22.2%
G-III	39.6%

Table 6: Recurrent Histological grade

Discussion:

Transitional cell carcinoma of urinary bladder is the second most common cause of death in males. [17] it is considered to be disease of the elderly, with the most common age at presentation being in the 5th and 6th decade. Males being affected in predominance as compared to females, i.e. 2.4:1, it is considered that factors responsible for the disease may be more common in males. The single most important risk factor for the disease is cigarette smoking. Smokers are considered to have ß-naphthylamines in their urine, which usually stagnates in urinary bladder leading to events responsible for cancerous change in the bladder transitional epithelium (urothelium). [18,19] As the whole urinary tract is lined by transitional cell epithelium, TCC can occur anywhere from the calyces down to fossa navicularis of the penile urethra, as the rest is lined by squamous epithelium. Frequency at which the disease affects urinary bladder shows the effect of pooling of urine and its hazardous contents in it as it functions as a reservoir for urine. Other risk factors include chemicals used in industries such as coal, paints, printing, leather, plastic, and many more. Even the artificial sweeteners used in various beverages have been condemned. Infections with Human Papilloma Virus (HPV) have also been reported as the etiological/risk factor. Every patient was followed up every 3 months with cystoscopy in order to detect any recurrence, if so, any progression in T-stage or histological grade. The first check cystoscopy after TURBT is of utmost importance; as a recurrent disease at first check cystoscopy has a bright chance of further future recurrences and progression. Gupta SK et al conducted a research in United Kingdom and their findings have strongly supported these results with a recurrence rate of 68%. [25] Trinchieri et al have further solidified and supported our study by analyzing high grade superficial TCC of bladder and have confirmed recurrence in 69% of cases under TURBT alone. [26] Gudjonsson et al found frequency of recurrence of superficial TCC after TURBT to be 77% in group of patients receiving no intra-vesical chemotherapy supporting our results. [27] YANG et al have contradicted our findings in that their study showed a recurrence in 33.3% of cases. In addition, their patient population was also younger (52.98+/- 11.28 years). [28] The age factor may be responsible for a low recurrence frequency in YANG's work. In addition, a high population of G-3 tumours may be responsible for high recurrence in our study. Larsson et al had findings in their research which also supported our evidence of recurrence more than 60%. Their study showed a 62% recurrence frequency in superficial bladder TCC and also showed that pT1 recur earlier as compared to pTa tumours. [29] Present study showed that pT1 tumours were more common accounting for 73.2% of cases while pTa was found in 26.8%of cases.

As it is a disease of the elderly and male population, my study has shown that our community shares similarities with other regions of the world with the most common presenting age group being 50-70 years of age and a male to female ratio of 2.4:1. Fritsche HM, Germany, studied superficial bladder tumours (T1G3) and his study population had a median age of 66.6 years (29.3-94.2) with male-to-female ratio of 4:1.51 The mean age in my study was 60 years (SD: +/- 9.04) and 74.6 % were males while the mean age was 65.8 years (SD: +/- 11.8) and 82.8 % were males in a study conducted in Iran by Karimianpour N et al. [30] My study also has some similarity to another Iranian research conducted by Halimi M et al which showed a mean age of 64.69 +/- 12.99 years and a study population having 71% males and 29% females. [31] Our study has revealed that at initial presentation, superficial bladder TCC shows a predominance of stage pT1. 76.4% of the primary tumours when resected were found to be in stage pT1 at initial diagnosis and the remaining 23.6% were stage pTa in my study. These findings are supported by a research done by Akagashi K et al in Japan which showed abundance of pT1 tumours i.e. pTa and pT1 tumours were found in 25.4% and 74.6% of cases respectively. [32] The histological grades of primary tumours in my study were G-I, G-II and G-III in 38%, 22.2% and 39.6% of cases showing G-I and G-III to be in abundance followed by G-II which is in contrast to the findings of Andres Rodreguez Alonso et al whose research showed an abundance of G-II and G-III tumours i.e. G-I, G-II and G-III were present in 13.7%, 39.2% and 45.1% of cases respectively. [33] This may be due to the fact that they actually followed cases of upper urinary tract TCC which later on developed bladder TCC. In such cases, of course, high grade tumours are more common. The frequency of recurrence of superficial TCC after TURBT on first check cystoscopy in my study was 60.3%. Gupta SK et al conducted a research in United Kingdom and their findings have strongly supported my results with a recurrence rate of 68%. [34] Trinchieri A et al have further solidified and supported my study by analyzing high grade superficial TCC of bladder and have confirmed recurrence in 69% of cases under TURBT alone. [35] Gudjonsson S et al found frequency of recurrence of superficial TCC after TURBT to be 77% in group of patients receiving no intra-vesical chemotherapy supporting my evidence. [36] YANG Tu-bao et al have contradicted my findings in that their study showed a recurrence in 33.3% of cases. In addition, their patient population was also younger (52.98+/- 11.28 years). [37] The age factor may be responsible for a low recurrence frequency in

YANG's work. In addition, a high population of G-III tumours may be responsible for high recurrence in my study. Our studies were, however, similar in having predominantly pT1 group and male population. Larsson et al had findings in their research which also supported my evidence of recurrence more than 60%. Their study showed a 62% recurrence frequency in superficial bladder TCC and also showed that pT1 recur earlier as compared to pTa tumours. [38] My study showed that pT1 tumours were more common accounting for 73.2% of cases while pTa was found in 26.8%of cases. In my study the additional findings were that no-recurrence group had 8 pTa tumours and 5 pT1 tumours. In no-recurrence group there were 18 G-I tumours, 4 G-II tumours and 3 G-III tumours. It is important to note here that in no-recurrence group pTa tumours are in abundance and G-I tumours are in abundance. These are considered to be low risk tumours and usually have low potential for recurrence and progression. Thus their management needs less aggressive therapy. This debate in my study is supported by Gofrit and colleagues in their study which concluded the low-grade pTa tumours to be minimal risk for the patient after resection and approved conservative management. [39] In my study, the group with recurrence had majority of the patients in pT1 variety and G-III variety. pTa was found in 3 cases (n=38) while pT1 in 4 cases (n=38). G-I, G-II and G-III were found in 13, 9 and 16 cases respectively. My study has shown that recurrence is more common in patients with pT1G-III (T1G3) tumors. This evidence is supported by Kulkarni et al by recommending a more aggressive treatment regimen for T1G3 tumours. [40] Shinohara et al also recognized a virulent nature of G-III tumors and confirmed that G-III was more aggressive in recurrence and progression as compared to G-I and G-II tumors, in support of my findings. [41] In order to reduce the frequencies of recurrence and, especially, progression, these high risk groups should receive intra-vesical BCG according to Irani J. [42] In addition, primary T1G3 tumors have a more significant risk of recurrence and progression as compared to non-primary T1G3 despite multifocality of the latter. [43] Despite the above discussion, Dangle et al has reported a case of recurrence even in low grade tumor after radical cystectomy. [44] According to Gunlusoy et al, BCG is effective treatment for T1G3 tumours but radical cystectomy should be performed early if a failure of immunotherapy is suspected. [45] My study has additionally highlighted the evidence of disease progression in the recurrent tumours. There was only 2 case (n=3) which progressed from pTa to pT1. However, 2 cases progressed from G-I to G-II and 2 cases from G-I to G-III (n=4). Progression from G-II to G-III was noted in 6 cases (n=8). Downgrading was also noted in some cases from G-III to G-II (6/15) and to G-I (2/15). Only 2 cases (n=9) downgraded from G-II to G-I in the recurrent tumour. It is noteworthy here that, after TURBT alone, there are chances of T-stage and histological grade progression in some cases and hence such patients are prone to further recurrences in future. Such cases are high risk cases and will need some adjuvant therapy for the reduction of tumor recurrence and more importantly progression. Several different tests are increasingly being used, on experimental basis though, to predict recurrence or progression of the disease. Li et al have tested the presence of XIAP as a predictor. They have shown that expression of XIAP was more on recurrent cases and also that the expression was present in all the cases which have progressed to invasive form. [46] In addition, expression of Bmi-I has also been studied recently by Zi-Ke Qin et al who noted that not only is the expression stronger in invasive form as compared to superficial form but also it is stronger for G-III against G-II and G-I.69 Another agent is cellular fibronectin (cFN) which also correlates well with the disease recurrence and progression in the follow up of patients with TCC bladder. [47] Keeping in view the above findings and suggesting a more aggressive therapy for T1 and high grade tumours, BCG is the best. [48] But these aggressive therapies are not without side effects with the most common ones for intravesical instillations being urgency, frequency, dysuria, haematuria and fever etc. [49] Radical cystectomy is the treatment of choice in patients with failed intra-vesical therapy and localized disease. However, significant changes in body composition, muscle function and energy expenditure occur after radical cystectomy and the nutritional status of patients should be assessed and corrected before embarking upon such an invasive treatment. [50]

I studied superficial TCC of bladder and followed my patients for 6 months. For a more informative research and to draw certain recommendations regarding treatment of the condition, a larger population should be studied for a longer period of time. Similarly, different treatment regimens, including Mitomycin-C, BCG, second look TURBT and radical cystectomy should be compared regarding their efficacy and safety, especially in pT1 and G-III tumours.

Conclusions:

1. Superficial TCC of the bladder is a common condition affecting elderly male population. Recurrence is common after TURBT and is more so in T1 G-III tumours. Progression was also noted in certain cases of recurrence.
2. TURBT alone is the preferred mode of treatment for patients with pTa and G-I tumours whereas tumours of pT1 stage and higher grades require immediate instillation of Mitomycin-C and then 6 weekly intravesical BCG course.
3. Radical cystectomy should be considered early if the disease is organ confined and there is failure of BCG.

References:

1. Li NC, Xiao YX, Song Y, Zhang K, Yuan JF. Intravesical instillation of pirarubicin for preventing postoperativerecurrence of superficial bladder cancer. Chin J Clin Oncol (Chin) 2005; 32: 1245-47.
2. Marston LW, Zbar B, Leach F, Cordon-Cardo C. Cancer of the genitourinary system. In Cancer: Principles & practice of oncology. Edited by: VTDeVita, SHellman, SARosenberg. Philadelppia: Lippincott Williams 2001:13431489.
3. Shelley MD, Mason MD, Kynaston H. Intravesical therapy for superficial bladder cancer: a systematic review of randomised trials. Cancer Treat Rev. 2010;36(3):195–205
4. Babjuk M. What is the optimal treatment strategy for T1 bladder tumours? Eur Urol 2010; 57:32-34.
5. Pashos CL, Botteman MF, Laskin BL, Redaelli A. Bladder cancer: epidemiology, diagnosis and management. Cancer Pract 2002; 10:311-22.
6. Burch RD, Rohan TE, Howe CR, Risch HA, Hill GB, Steele R. Risk of bladder cancer by source and type of tobacco exposure. Int J Caner. 1989; 44:622–28.
7. Carroll PR. Urolthelial carcinoma: cancers of bladder, ureter and renal pelvis. In: "Tanagho EA, McAninch JW, editor. eds Smith General Urology. 15. McGraw Hill publishers. USA;

2000;55–77.
8. Barghi MR and Arbab MM, Moghaddam HM, Kazemi B. Correlation between human papillomavirus infection and bladder transitional cell carcinoma. BMC Infectious Diseases 2005; 5:102. 98.
9. Ries LAG, Eisner MP, Kosary CL. SEER Cancer Statistics Review, 1973–1999. Bethesda: National Cancer Institute;2002.
10. Al-Bazzaz PH. Stage of urinary bladder cancer at first presentation. Saudi J Kidney Dis Transplant 2009; 20:62831.
11. Abascal JJM, Hevia SM, Abascal GJM, Estebanez C. Experience in diagnosis and treatment of superficial bladder tumors with Hexvix. Arch Esp Urol 2008; 61:475-83.
12. Amling CL. Diagnosis and management of superficial bladder cancer. Curr Probl Cancer 2001; 25:219-78.
13. Barghi MR, Rahmani MR, Hosseini Moghaddam SM. Immediate intravesical instillation of mitomycin C after transurethral resection of bladder tumor in patients with low-risk superficial transitional cell carcinoma of bladder. Urol J 2006; 3:220-24.
14. van der Meijden AP. Optimal treatment for intermediate- and high-risk, nonmuscleinvasive bladder cancer. ScientificWorldJournal 2006; 6:2611-16.
15. Sylvester RJ, van der Meijden AP, Oosterlinck W. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables. EORTC trials. Eur Urol 2006; 49:466-77.
16. Guney S, Guney N, Canogullari Z, Ergenekon E. Ta T1 low and intermediate transitional cell carcinoma of the bladder: 90 recurrence rates and the timing of check cystoscopies within first year. Urol Int 2008; 80:124-28.
17. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010 CA Cancer J Clin 2010; 5:277-300.
18. Satbbert R, Scharfer KH, Biefel C. Analysis of aromatic amines in cigarette smoke. Rapid Commun Mass Spectrom 2003; 17:2125-32.
19. Samanic C, Kogevinas M, Dosemeci M. Smoking and bladder cancer in spain: effects of tobacco type, timming, environmental tobacco smoke, and gender. Cancer Epidemiol Bolmarkers Prev 2006; 15:1348-54.
20. Fritsche HM, Burger M, Svatek RS, Jeldres C. Characteristics and outcomes of patients with clinical T1 Grade 3 urothelial carcinoma treated with radical cystectomy: results from an international cohort. Eur Urol 2010; 57:300-09.
21. Karimianpour N, Ziaee AA, Akbari MT, Pourmand G. Mutations of RAS gene family in specimens of bladder cancer. Urol J 2008; 5:237-42.
22. Halimi M, Salehi A, Baybordi H, Nezami N. Immunohistochemical positive stained p53 in bladder transitional cell carcinoma. Indian J Pathol Microbiol 2009; 52:155-58.
23. Akagashi K, Tanda H, Kato S, Ohnishi S, Nakajima H. Recurrence pattern for superficial bladder cancer. Int J Urol 2006; 13:686-91.
24. Rodríguez Alonso A, González Blanco A, Barbagelata López A. Predictive factors of metachronous bladder neoplasm after nephroureterctomy. Actas Urol Esp 2009; 33:258-69.
25. Gupta SK and Parr NJ. Outcome of very large superficial bladder tumours: a 10-year experience. Scand J Urol Nephrol 2008; 42:243-48.
26. Trinchieri A, Bonacina P, Butti A, Cappoli S, Esposito N. Conservative treatment of high grade superficial bladder tumours. Arch Ital Urol Androl 2005; 77:215-18.
27. Gudjonsson S, Adell L, Merdasa F, Olsson R. Should all patients with non-muscle-invasive bladder cancer receive early intravesical chemotherapy after transurethral resection? The results of a prospective randomized multicentre study. Eur Urol 2009; 55:773-80.
28. Yang TB, Zeng FH, Sun ZQ. Prognostic factors for primary superficial transitional cell carcinoma of the bladder: a retrospective cohort study. Chin Med J 2006; 119:1821-28.
29. Larsson P, Wijkstrom H, Thorstenson A, Adolfsson J. A population-based study of 538 patients with newly detected urinary bladder neoplasm followed during 5 years. Scand J Urol Nephrol 2003; 37:195-201.
30. Hegele A, Kosche B, Schrader AJ, Sevinc S, Olbert PJ, Hofmann R et al. Transitional cell carcinoma of the bladder: evaluation of plasma levels of cellular fibronectin as a stage-dependent marker. UrologeA 2008; 47:1137-40.
31. Andius P, Fehrling M, Holmang S. Intrvesical bacillus Calmette-Guerin therapy: experience with a reduced dwell-time in patients with pronounced side-effects. BJU Int 2005; 96:1290-93.
32. Mathur S, Plank LD, Hill AG, Rice MA, Hill GL. Changes in body composition, muscle function and energy expenditure after radical cystectomy. BJU Int 2007; 101:973-977.
33. Sauter G, Algaba F, Amin M, Busch C, Cheville J, Gasser T et al. Tumours of the urinary system: non-invasive urothelial neoplasias. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, eds. WHO classification of tumors of the urinary system and male genital organs. Lyon: IARCC Press, 2004, pp. 29-34.
34. Jakse G, Algaba F, Malmstorm PU, Oosterlinck W. A second-look TUR in T1 transitional cell carcinoma: why? Eur Urol 2004; 45:539-46.
35. Daniltschenko DI, Riedl CR, Sachs MD, Koenig F, Daha KL, Pflueger H et al. Longterm benefit of 5-aminolevulinic acid fluorescence assisted transurethral resection of superficial bladder cancer: 5-year results of a prospective randomized study. J Urol 2005; 174:2129-33.
36. Babjuk M, Soukup V, Petrik R, Jirsa M, Dvoracek J. 5-aminolaevulinic acid-induced fluorescence cystoscopy during transurethral resection reduces the risk of recurrence in stage Ta/T1 bladder cancer. BJUI 2005; 96:798-802.
37. Denziger S, Burger M, Walter B, Knuechel R, Roessier W, Wieland WF et al. Clinically relevant risk of reduction in risk of recurrence of superficial bladder cancer using 5-aminolevulinic acid-induced fluorescence diagnosis: 8-years results of prospective randomized study. Urology 2007; 69:675-9.
38. Schumacher MC, Holmang S, Davidsson T, Friedrich B, Pedersen J, Wiklund NP. Transurethral resection of non-muscle invasive bladder transitional cell cancers with or without 5-aminolevulinic acid under visible and fluorescent light: results of a prospective, randomized, multicentre study. Eur Urol 2010; 57:293-299.
39. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage TaT1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 2004; 171:2186-90.
40. Shah S, Tarar KD, Bhatti SU, Suhaib S. Our experience with

the management of superficial bladder cancer (Transitional Cell Ca), the role of adjuvant intravesical BCG therapy. Ann King Edward med Coll 2006; 12:550-2.

41. Sylvester RJ van der Meijden A, Witjes JA, Jakse G, Nonomura N, Cheng C et al. High grade Ta urothelial carcinoma and carcinoma in situ of the bladder. Urology 2005; 66:90-107.
42. Duchek M, Johansson R, Jahnson S, Mestad O, Hellström P, Hellsten S et al. Bacillus Calmette-Guérin is superior to a combination of epirubicin and interferon-α2b in the intravesical treatment of patients with stage T1 urinary bladder cancer: a prospective randomized, Nordic study. Eur Urol 2010; 57:25-31.
43. Witjes JA, Hendricksen K. Intravesical pharmacotherapy for non-muscle-invasive bladder cancer: a critical analysis of currently available drugs, treatment schedules, and long-term results. Eur Urol 2008; 53:45-52.
44. Hendricksen K, Gleason D, Young JM, Saltzstein D, Gershman A, Lerner S et al. Safety and side effects of immediate instillation of apaziquone following transurethral resection in patients with nonmuscle invasive bladder cancer. J Urol 2008; 180:116-20.
45. Hendricksen K, Witjes JA. Current strategies for first and second line intravesical therapy for nonmuscle invasive bladder cancer. Curr Opin Urol 2007; 17:352-7.
46. Naito S, Koga H, Yamaguchi A, Fujimoto N, Hasui Y, Kuramoto H et al. Prevention of recurrence with epirubicin and lactobacillus casei after transurethral resection of bladder tumour. J Urol 2008; 179:485-90.
47. Akcetin Z, Todorov J, Tuzel E, Engehausen DG, Krause FS, Sauer R et al. Radiochemotherapy after transurethral resection is an effective treatment method in T1G3 bladder cancer. Anticancer Res 2005; 25:1623-8.
48. Mariappan P, Smith G. A surveillance schedule for G1Ta bladder cancer allowing efficient use of check cystoscopy and safe discharge at 5 years on a 25-year prospective database. J Urol 2005; 173:008-11.
49. Weiss C, Wittlinger M, Engehausen DG, Krause FS, Otto OJ, Dunst J et al. Management of superficial recurrences in irradiated bladder after combined-modality organ-preserving therapy. Int J Radiat Oncol Biol Phys 2008; 70:1502-6.
50. Iida S, Kondo T, Kobayashi H, Hashimoto Y, Goya N, Tanabe K. Clinical outcome of high-grade non-muscle-invasive bladder cancer: a long-term single center experience. Int J Urol 2009; 16:287-92.