Evolution and prognosis of bladder papillomatosis managed by endoscopic resection and endovesical BCG therapy : About 24 cases

Satâa Sallami*, Anis Gammoudi*, Rym Cherni*, Ines Chelly**, Ali Horchani*.

*: Department of Urology - La Rabta Hospital University - Tunis – Tunisia.
**: Department of pathology - La Rabta Hospital University - Tunis – Tunisia.
Faculty of Medicine of Tunis – University of Tunis - El Manar - Tunis-Tunisia

S. Sallami, A. Gammoudi, R. Cherni, I. Chelly, A. Horchani

Evolution and prognosis of bladder papillomatosis managed by endoscopic resection and endovesical BCG therapy:About 24 cases

LA TUNISIE MEDICALE - 2013 ; Vol 91 (n°10) : 573-576

S. Sallami, A. Gammoudi, R. Cherni, I. Chelly, A. Horchani

Evolution et pronostic de la papillomatose vésicale traitée par résection endoscopique et BCG thérapie endovésicale: A propos de 24 cas

LA TUNISIE MEDICALE - 2013 ; Vol 91 (n°10) : 573-576

R É S U M É

Prérequis : La papillomatose vésicale est une prolifération tumorale diffuse sur la quasi-totalité de la muqueuse vésicale. Nous analysons son pronostic après traitement conservateur.

Méthodes : Nous avons analysé rétrospectivement les données épidémiologiques, cliniques, thérapeutiques et évolutives de 24 patients présentant initialement une papillomtose vésicale. Tous les patients ont eu une résection endoscopique complète (RE) à visée curative suivie d'un « second look » réalisé dans les 30 jours. Une BCG thérapie endovésicale a été instaurée (une instillation endovésicale hebdomadaires pendant 6 semaines, puis mensuelle pendant 6 mois. En cas de récidive sans invasion musculaire, la RE est répétée avec une 2ème cure de BCG-thérapie. Les paramètres étudiés étaient l'âge, le sexe, les facteurs de risque, les données cystoscopiques (aspect, multiplicité et siège de la tumeur), le stade tumoral, le grade tumoral, les délais de récidive et de progression.

Résultats : L'âge moyen des patients lors du diagnostic initial était de 64,9 ± 6,1 ans. Il s'agit de 23 hommes et une seule femme. La tumeur initiale était de stade pta (n = 6) et pT1 (n = 18). La récidive tumorale a été rapportés chez 17 patients (70,8%). Il s'agit d'un stade pta chez 5 patients et d'un stade pt1 chez 12. Le délai de la récidive était de 10,3 mois. La tumeur n'a pas récidivé dans 6 cas. Six patients ont développé une progression, avec une invasion musculaire dans 4 cas. Une cystectomie radicale a été réalisée chez 3 patients et un patient est décédé avant le traitement radical. L'analyse univariée n'a révélé de facteur pronostique: l'âge (p = 0,7), localisation de la tumeur et l'aspect (p = 0,7 et p = 0,5 respectivement), le stade tumoral (p = 0,7) et le grade (p = 0,09).

Conclusion : La papillomatose vésicale est une entité rare. La RE avec BCG thérapie peut être indiquée en première intension à la condition d'un suivi correcte. La cystectomie radicale est réservé aux récidives et aux tumeurs endoscopiquement non contrôlables.

vessie, carcinome à cellules transitionnelles, papillomatose, traitement, pronostic.

M o t s - c l é s

Vessie, carcinome à cellules transitionnelles, papillomatose, traitement, pronostic.

S U M M A R Y

Background: Bladder papillomatosis is a diffuse tumor proliferation even up almost all of the bladder mucosa. We analyzed prognosis of this rare entity after conservative treatment.

Methods: We retrospectively analyzed epidemiological, clinical, therapeutic and evolutive data in 24 patients with newly diagnosed bladder transitional cell carcinoma papillomatosis. All patients underwent a complete endoscopic transurethral resection (TUR) with curative intent. A second look was performed within 30 days. The intravesical therapy regimen consisted on weekly instillations for 6 weeks, and then monthly for 6 months. If the tumor recurred without muscle invasion, TUR was repeated with a second intravesical BCG-therapy regimen. Parameters investigated included age, gender, risk factors, cystoscopic findings (aspect, multiplicity and location of bladder lesion), tumor stage, tumor grade, recurrences and progression times from diagnosis to last follow up.

Results: The mean age of the patients at initial diagnosis was 64,9±6,1 years. They were males in 23 cases. Initial cancer staging was as follow: pTa (n=6) and pT1 (n=18). The recurring tumors were reported in 17 patients (70,8%). They were stage Ta in 5 patients and stage T1 in 12. The median interval of time between the initial TUR and the first recurrence was 10,3 months. Six patients remain tumor free. From the 17 recurrences, 6 patients developed progression with muscle invasion in 4 of them. Radical cystectomy with ileal conduit was performed in 3 patients and one patient died before radical treatment. Univariate analysis didn't reveal any prognostic factor: age (p=0,7), tumor location and aspect (p= 0,7 and p= 0,5 respectively), tumor stage (p=0,7) and grade (p=0,09).

Conclusion : TCC bladder papillomatosis is a rare entity. TUR with intravesical BCG therapy may be indicated as a first option despite correct follow up. Radical cystectomy should be considered in cases of recurrent or non-resectable tumours.

K e y - w o r d s

Urinary bladder, transitional cell carcinoma, papillomatosis, treatment, prognosis.

Transitional cell carcinoma (TCC) of the bladder is the first most common malignancy of the genitourinary tract in Tunisia (1). Bladder papillomatosis is a very rare type of these tumours, characterized by a diffuse tumor proliferation even up almost all of the bladder mucosa, leaving only little healthy bladder mucosa (2).

Patients with bladder papillomatosis appear to have a high risk of tumour-related death. Additionally, the risk of developing upper urinary tract disease is higher. Thus, some authors believe that bladder papillomatosis should be grouped with muscle invasive tumours progression with the need for radical treatment (3,4).

The management of bladder TCC papillomatosis is a challenge for urologist. Over-treatment means that many patients may lose bladders sooner with cystectomy, and under-treatment may lead to metastasis and death of the patient.

Through a retrospective study, we analyzed evolution and prognosis of this entity after conservative treatment consisting in endoscopic resection and endovesical BCG therapy.

MATERIAL AND METHODS

From January 1997 to March 2005, 24 patients with newly diagnosed bladder TCC papillomatosis were treated in the department of Urology of the Rabta University-Hospital in Tunis-Tunisia.

We retrospectively analyzed their epidemiological, clinical, therapeutic and evolutive data.

All patients with bladder TCC papillomatosis were included in this study.

Exclusion criteria were concomitant or previous muscle invasive TCC, in situ carcinoma and the presence of another urinary cancer.

All patients were submitted to urinary culture, intravenous urography or ultrasonography and cystoscopy. They underwent a complete endoscopic transurethral resection (TUR) with curative intent (complete TUR of the tumor and the underlying muscular layer).

The pathologic stage of bladder cancer was assessed according to the tumor-node-metastasis (TNM) classification and tumor grade was assessed according to the grading system established by the World Health Organization. Non-muscle-invasive bladder cancer includes pTa and pT1 tumors. The pathologic evaluation was carried out by a referent senior pathologist.

A second look (a second TUR of a potential residual tumour or the base of the previous tumour) was performed within four weeks to exclude any understaging or an incomplete resection. Two to three weeks after TUR, patients were submitted to intravesical adjuvant BCG-therapy. The intravesical therapy regimen consisted on weekly instillations for 6 weeks, and then monthly for 6 months.

Follow-up was performed by upper urinary tract's ultrasound and cystoscopy (with biopsy of any suspicious bladder lesions) 3 months after the TUR then every 6 months in the first 5-yr and annually thereafter. If the tumor recurred, TUR was repeated. If there was a recurrence without muscle invasion, patients would receive a second intravesical BCG-therapy regimen.

Investigated parameters included: age, gender, risk factors (smoking and professional exposure), cystoscopic findings (aspect, multiplicity and location of bladder tumor), tumor stage, tumor grade, recurrences and progression times from diagnosis to last follow up.

Recurrence-free interval is defined as the period between date of resection and the date of histologically confirmed recurrence. Muscle-invasive bladder cancer was defined as muscularis propria invasion. The interval to progression was defined as the period between the date of the initial diagnosis and the date of proven progression.

Patients without recurrence or progression were censored at the date of their last follow-up.

Statistical analysis:

We investigated the correlations between patient's age, clinical and pathologic data and prognostic features. The Chi-squared test was used to evaluate the statistical significance of difference in the variables with a 95% confidence interval.

Data were analyzed using SPSS version 11.0 (SPSS Inc, Chicago, IL, USA). A p value of less than 0.05 was considered statistically significant.

RESULTS

According to our data, the prevalence of papillomatosis bladder TCC was 24 out of 417 cases of bladder TCC treated during the same period, thus 5,7%.

The mean age of the patients at initial diagnosis was 64,9±6,1 years (range, 44-86 years).

The male to female ratio was 23/1. A history of heavy cigarette smoking was obtained in the majority of cases (83,3%). Two patients had a professional history known to be associated with bladder carcinogenesis (a painter and a welder).

Gross hematuria was the most common presenting symptoms in all cases and lower urinary tract symptoms (LUTS) in only 15 patients (62,5%). Digital rectal examination concluded to a normal posterior bladder wall in all cases.

In cystoscopic exploration, the majority of the lesions (87,5%) was described as papillary and nodular in 3 cases (12,5%). The bladder neck and ureteral meatus were in contact with the tumours in 16 (66.7%) and 17 (70,8%) patients respectively. A complete endoscopic resection was performed in one session in 19 patients and after two sessions in 5 patients. The total TUR duration rages from 47 to 112 min. The initial cancer staging was as follow: pTa (n=6) and pT1 (n=18). There were 12 grad I tumour and 12 grad II.

One patient died 5 months after the first TUR due to a metastatic pulmonary cancer.

The observation period ranged from 9 to 106 months with a median of 37 months. Ninety patients had a minimum follow-up of 24 months. The recurring tumors were reported in 17 patients (70,8%). They were stage Ta in 5 patients and stage T1 in 12. The median interval of time between the initial TUR and the first recurrence was 10,3 months (range: 3-61 months).

From the 17 recurrences, 6 patients developed progression with muscle invasion in 4 of them. Treatment consisted on a new TUR in all recurrences without bladder muscle invasion (n=13). With a median follow up of 27 months (16-50), the remaining 6 patients remain tumor free.
Patients developed only one recurrence in 7 cases with median follow up of 51,1 months (10-106). Three patients developed two recurrences (26-65). Three patients developed multiple recurrences without progression which were managed by TUR since they refused radical treatment. No patient experienced serious adverse effects requiring the stop of BCG-therapy.
Six patients progressed with a median time interval of 5,3 months (range 3-12 months). Initial bladder tumours were Ta in 2 cases and T1 in 4 cases. A second endoscopic resection was performed in 2 patients, radical cystectomy with ileal conduit replacement in 3 patients and one patient died before radical treatment due to rapid tumor progression with metastatic bladder tumor.
Finally and during the observation period, about 7 out of 8 patients maintained their bladder.
Univariate analysis didn't reveal any prognostic factor to predict evolution: age (p=0,7), smoking (p=1), tumor location and aspect (p= 0,7 and p= 0,5 respectively), bladder stage (p=0,7) and grade (p=0,09).

DISCUSSION

Bladder papillomatosis is characterized by a diffuse tumor proliferation even up almost all of the bladder mucosa, leaving little healthy bladder mucosa. Its appearance is usually papillary with a fringed appearance (5,6). As in the other bladder TCC, the male is a predisposing factor, especially if he is a heavy smoker and over fifty years (4).
It is very difficult to determine the prognosis of papillomatosis; it may recur or progress and have a high propensity for malignant transformation and extension. If the trend is not halted by appropriate treatment, these bladder cancers may invade pelvic organs and produce metastasis. In our study we didn't find any predictive factor of recurrence or progression.
The goal of the TUR in bladder tumours is to make the correct diagnosis and remove all visible lesions. Large tumours as papillomatosis should be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle and the edges of the resection area. The specimens from different fractions must be referred to the pathologist in separate containers to enable him to make a correct diagnosis.

Place of the second-look TUR:
The significant risk of residual tumour after the initial TUR of lesions has been demonstrated (5,6) (level of evidence:1). Persistent disease after resection of T1 tumours was observed in up to 33-53% of patients (3,7-9). Moreover, the tumour may be understaged by the initial resection. The likelihood that a Ta-T1, high grade tumours has been understaged and is therefore muscle invasive is 10% of cases (7,8).
According to the European Organization for Research and treatment of cancer (4), one of the six most significant clinical and pathological factors (recurrence and progression) was tumour size (> 3 cm). It has been demonstrated that a second TUR can increase recurrence-free survival (3,9) (level evidence: 2). Thus, when the initial diagnosis is bladder papillomatosis, we believe that it is a safe and reasonable practice to have a second-look cystoscopy and perform TUR of the residual tumour or the base of the previous tumour between two and six weeks after the first TUR (10).

Treatment of bladder papillomatosis:
As far as the bladder TCC papillomatosis is concerned, two options are available to the urologist. They include conservative treatment with TUR of the tumour and intravesical therapy or immediate cystectomy. A proportion of the bladder papillomatosis are destined not to progress following conservative treatment (11) and whilst immediate cystectomy has the highest cure rates (12), it will be substantial over-treatment for many patients. The dilemma in the management is therefore to try and identify those tumours that will progress and are potentially lethal and offer them cystectomy, while not over-treating those tumours which do not progress (13). With the present available data, it was not possible to satisfactorily predict which of the tumours will progress, and so the decisions and advice have to be based on available literature and clinical judgment. Ideally, there should be a prospective randomized trial between upfront cystectomy at presentation for bladder papillomatosis and endoscopic resection with intravesical therapy. Such a study is unlikely to be done and we have to extrapolate data from literature.

Conservative treatment:
There are no doubts that conservative treatments with a combination of TUR and intravesical BCG are of immediate efficacy as shown by the reduction in recurrence rates and risks of progression. The data from meta-analysis (14) indicated that the tumour recurrence was significantly reduced with intravesical BCG especially in patients at high risk for tumour recurrence. Sylvester et al (15), in a review of meta-analysis of randomized clinical trials, concluded that BCG significantly decreased the risk of progression after TUR of bladder tumour in patients who receive maintenance treatment. They studied 24 trials, based on a median follow-up of 30 months. They found a 27% reduction in the odds progression.
Moreover, intravesical chemotherapy with Gemcitabine showed interesting results (16).
The presence or absence of tumour at initial cystoscopy (three months after TUR and BCG adjuvant therapy) is crucial for determining further treatment. When there is no recurrence the patient enters a maintenance intravesical BCG program. However, the identification of recurrence of the same grade and stage TCC or new onset CIS, leads to the recommendation of radical cystectomy (4).
Cystectomy: for whom, why and when?
Radical surgery should be considered in high-risk tumors

(papillomatosis) with early recurrence despite a correct endoscopic treatment and intravesical instillations. It may also be considered in exceptionally non-resectable (rare bladder tumors can not be removed completely by endoscopic resection) (17). There was great emphasis on upfront radical cystectomy as curative treatment. The timing for cystectomy was considered controversial. Amling (18) et al recommended radical cystectomy only when conservative measures failed to eradicate bladder cancer. Their survival rates were 77%-84% for early radical cystectomy or radical cystectomy after failed bladder-sparing treatment.

The morbidity and mortality associated with radical treatment remain relatively high and are 20% and 1-4% respectively (15). Notwithstanding techniques of orthotopic bladder reconstruction, the quality of life is still altered after radical cystectomy.

CONCLUSION

TCC bladder papillomatosis is a rare entity. TUR with intravesical BCG therapy may be indicated as a first option despite correct follow up. Radical cystectomy should be considered in cases of recurrent or non-resectable tumours.

References

1. Ben Abdallah M, Zehani S, Hizem Ben Yakoub W, Hsairi M, Achour N. Registre des cancers Nord-Tunisie données1999-2003, evolution 1994-2003 et projections à l'horizon 2024. 1ère édition. Tunis: ISBN, 2009: 25-31.
2. Wetzel O, Glemain P, Bouchot O et al. Prévention des récidives des tumeurs de vessie de stade pTa par instillation endovésicale de BCG. Prog Urol. 1993;3: 595-607.
3. Grimm MO, Steinhoff C, Simon X, Spiegelhalder P, Ackermann R, Vogeli TA. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. J Urol. 2003;170:433-7.
4. Sylvester RJ, van der Meijden AP, Oosterlinck W et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006;49: 466-5.
5. Brausi M, Collette L, Kurth K et al. Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. Eur Urol. 2002;41: 523-31.
6. Miladi M, Peyromaure M, Zerbib M, Saïghi D, Debré B. The value of a second transurethral resection in evaluating patients with bladder tumours. Eur Urol. 2003; 43: 241-5.
7. Jakse G, Algaba F, Malmström PU, Oosterlinck W. A second-look TUR in T1 transitional cell carcinoma: why? Eur Urol. 2004;45: 539-46.
8. Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? J Urol. 2001;165: 808-10.
9. Divrik RT, Yildirim U, Zorlu F, Ozen H. The effect of repeat transurethral resection on recurrence and progression rates in patients with T1 tumors of the bladder who received intravesical mitomycin: a prospective, randomized clinical trial. J Urol. 2006;175: 1641-4.
10. Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. J Urol. 1999;162:74-6.
11. Heney NM, Ahmed S, Flanagan MJ et al. Superficial bladder cancer: progression and recurrence. J Urol. 1983;130:1083-6.
12. Malavaud B. T1G3 bladder tumours: the case for radical cystectomy. Eur Urol. 2004; 45:406-10.
13. Soloway MS, Sofer M, Vaidya A. Contemporary management of stage T1 transitional cell carcinoma of the bladder. J Urol. 2002;167:1573-83.
14. Shelley MD, Court JB, Kynaston H, Wilt TJ, Coles B, Mason M. Intravesical bacillus Calmette-Guerin versus mitomycin C for Ta and T1 bladder cancer. Cochrane Database Syst Rev. 2003;(3):CD003231.
15. Sylvester RJ, Van der meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol. 2002; 168:1964-70.
16. Horinaga M, Fukuyama R, Iida M et al. Enhanced antitumor effect of coincident intravesical gemcitabine plus BCG therapy in an orthotopic bladder cancer model. Urology. 2010;76:1267.e1-6.
17. Rischmann P, Bittard H, Chopin D et al. Recommandation: tumeurs urothéliales. Comité de cancérologie (CCAFU). Prog Urol. 1998; 8: 27-50.
18. Amling CL, Thrasher JB, Frazier HA, Dodge RK, Robertson JE, Paulson DF. Radical cystectomy for stages Ta, Tis and T1 transitional cell carcinoma of the bladder. J Urol. 1994;151:31-5.