

Superficial Urinary Bladder Cancer: Histopathological Findings, Recurrence Rate after Transurethral Resection and Association with Upper Urinary Tract Urothelial Cancer; a Retrospective Analysis

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ABSTRACT

Objective: To assess different histopathological types of superficial urinary bladder cancer, their recurrence incidence and correlation with upper urinary tract urothelial cancer.

Methods: This retrospective study included 84 patients, of both genders; of different age groups and with histopathological diagnosis of superficial urothelial carcinoma at Prince Hussein bin Abdullah the second center for urology and organ transplant and at Prince Iman center for laboratory research, King Hussein medical centre, Amman, Jordan, during the period March 2010-May 2014. Transurethral resection of tumor was performed in all subjects with tumor grading and staging. Cystoscopic follow up was performed to record incidence of recurrence in all subjects.

Results: The mean age of patients was 61 years; with male percentage (84.5%). Successful transurethral resection of tumor in first trial was achievable in 68 patients (80.95%). Multiple tumors were recorded in 35 patients (41.7%). Total recurrence incidence was recorded in 75% of patients. Subjects with TaG3 experienced delayed recurrence frequency of 22.2% with good recurrence-free period, while T1G3 subjects had less and early recurrence incidence of 15.9%.

Conclusion: Early recurrence was recorded with tumor limited to sub epithelium (T1), while late recurrence was recorded with urothelium confined disease (Ta).

Key words: Superficial urinary bladder cancer, Recurrence, Urothelial carcinoma.

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Introduction

Urinary bladder cancer is the fourth and eighth most frequent cancer in males and females, respectively.⁽¹⁾ urothelial carcinoma is the most frequent tumor of it and accounts for more than 90% of total bladder cancer, while adenocarcinoma accounts for 2% and squamous cell carcinoma accounts for less than 1 %.⁽²⁾ Urothelium can differentiate greatly into spindle cells, squamous and adenocarcinoma. Superficial bladder tumor (a

non-muscle invasive tumor) is staged as Ta, T1 and carcinoma in situ with different grades. Superficial bladder tumor accounts for 70-80% of primary bladder cancer. Ta disease is urothelium confined and accounts for 70%, while T1 disease is when the sub-epithelium is penetrated while muscles spared and accounts for 20 %.⁽³⁾ The carcinoma in-situ accounts for 10 %.⁽³⁾ Secondary carcinoma in situ is more frequent than primary carcinoma in situ and is correlated with high-grade T1 superficial cancer

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or muscle-invasive type.

Recurrence is the re-showing of tumor after successful resection. There are two types of recurrence after TURT. Early (true) recurrence can occur during 500 days after-TURT, which can be reduced by intra-vesical management. Delayed recurrence may occur during the period of more than 500 days postoperatively with no response to any local treatment.⁽⁴⁾ Fifty to seventy percent of superficial bladder cancer shows recurrence during 5 years and 5-20% develops invasive carcinoma.⁽⁵⁾

The aim of this investigation was to assess different histopathological types of superficial urinary bladder cancer, its recurrence incidence and correlation with upper urinary tract urothelial cancer among Jordanian population.

Methods

This retrospective investigation included 84 patients, of both genders, of different age groups and with diagnosed histopathological superficial urothelial carcinoma with successful surgical treatment using TransUrethral Resection of Tumor (TURT) at Prince Hussein bin Abdullah the second center for urology and organ transplant and at Prince Eman center for laboratory research, King Hussein medical centre, Amman, Jordan, during the period March 2010-May 2014, after obtaining written informed consent from all patients for the purpose of the study and approval from the ethics and research board review committee of royal Jordanian medical services. Cystoscopic follow up was performed to record recurrence incidence in all subjects.

Patients with muscle invasive Urothelial carcinoma, simultaneous carcinoma in situ, synchronous upper tract or urethral disease and non-transitional cell tumors were ruled out. In addition, patients who received any form of intravesical treatment were excluded. Successful TURT was performed in all subjects. TURT is considered successful when all the tumors are resected transurethrally whether in one or two sessions (the so called second look TURT, usually within 4 weeks) without need for open resection of part of urinary bladder as when perforation occurs. Growth patterns as location, size and numbers

of papillary or nodular lesions were registered. Pathological staging was based on the TNM classification (Ta/T1). Tumor grading was performed according to the new WHO classification (G1: low grade and G3: high grade) which cancelled the intermediate grade (G2) used in old WHO classification. Check cystoscopy was performed to evaluate recurrences, according to the American urology association protocol for the management of non-muscle invasive bladder cancer. Follow-up cystoscopy, according to American Urology Association (AUA) was carried out every 3 months for the first year, then every 6 months for the second year and then annually.

Results

Mean age of patients at diagnosis was 61 years (ranging from 33-84 years) (Table I). There were 71 males (84.5%) and 13 females (15.5%), with a male to female ratio of almost 6:1. Successful TURT in first trial was achievable in 68 subjects (80.95%), while 16 subjects (19.05%) with very big or multiple lesions require second TURT for successful removal of tumor. Multiple tumors were seen in 35 patients (41.7%), while single growth was recorded in 49 patients (58.3%). Various sites of single tumor were right lateral wall in 21, left lateral wall in 14, neck in 5, posterior wall in 4, dome in 3 and trig one in 2 patients. Table II shows the distribution of patients in terms of stage and grade. Regarding stage; 70 patients had Ta disease 83%, 13 patients had T1 disease (15.4%) and one patient had CIS (1.2%). For grade; 53 patients had G1 disease (63.1%) while 30 patients had G3 disease (35.7%).

Follow-up period ranged from 540 to 2050 days (mean 1120 days). All patients continue surveillance as scheduled and no patient lost follow-up. Total recurrence incidence was recorded in 75% of patients (63/84). Subjects with TaG1-3 experienced delayed recurrence frequency of 53.96% (34/63) with good recurrence free period (78%), while T1G3 subjects had less and early recurrence incidence of 46.04 % (29/63).

Regarding the correlation of tumor recurrence rate to specific stage and grade (Table III).

Table I: Age with Urothelial Carcinoma.

Demographic	Urothelial carcinoma Stage(no)		Urothelial carcinoma Grade(no)		CIS
	Ta	T1	G1	G3	
Age(years)					
30-40	4		2	2	
41-50	11	1	9	3	1
51-60	18	5	14	9	
61-70	21	1	15	7	
71-80	14	5	12	7	
81-90	2	1	1	2	
Total no.	70	13	53	30	1

CIS: carcinoma in situ

Ta: non invasive papillary carcinoma

T1: tumor invading sub epithelial connective tissue.

G1: low grade

G3: high grade

Table II: Distribution of Urothelial Carcinoma.

Urothelial Carcinoma	Number
TaG1	53
TaG3	17
T1G3	13
CIS	1

CIS: carcinoma in situ

Ta: non invasive papillary carcinoma

T1: tumor invading sub epithelial connective tissue

G1: low grade

G3: high grade

Table III: Recurrence Incidence.

Urothelial Carcinoma	Numbers of patients with recurrence	Number of patients without recurrence	Upper tract involvement
TaG1	37	16	1
TaG3	15	2	2
T1G3	10	3	1
CIS	1		

CIS: carcinoma in situ

Ta: non invasive papillary carcinoma

T1: tumor invading sub epithelial connective tissue

G1: low grade

G3: high grade

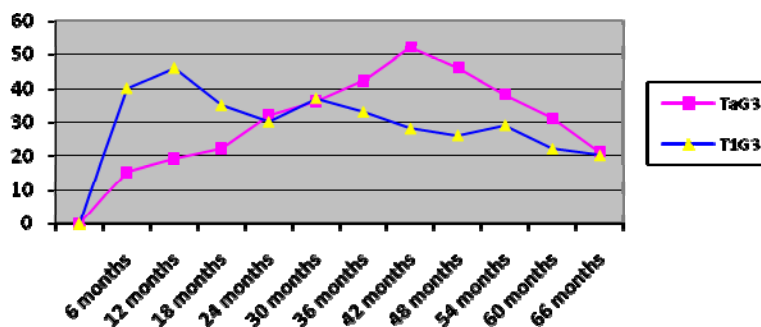


Fig. 1: Recurrence Rate against Time for Patients with Tag3 and Patients with T1G3 Disease

TaG1 patients had 69.8% recurrence rate (37/53), while TaG3 patients had a recurrence

rate of 88% (15/17). In comparison, patients with T1G3 disease had 77% recurrence rate

(10/13). The recurrence rate for G3 disease was 83% (25/30) while for G1 disease it was 69.8% (37/53). TaG3 patients demonstrated a delayed recurrence incidence of 53.96%. The patients with T1G3 disease experienced violent model, with early recurrence frequency of 46.04%, seen in 70% at first postoperative check cystoscopy (fig. 1). Most recurrences were intravesical (93.7%). Early recurrence was within 500 days of post-tumor resection while delayed (late) recurrence was within more than 500 days of post-tumor resection. Good recurrence free period was within more than 6 months to 18 months.

Upper urinary tract involvement was recorded in 4 patients, 3 with recurrences and one without recurrence. The 3 patients had T1G3 and TaG3 grading while the one patient without recurrence had TaG1 grading.

One patient with carcinoma in situ had recurrence but without upper tract involvement. He continued his scheduled surveillance and had frequent recurrences which were always amenable for fulguration alone as his medical condition did not permit major surgery (i.e. cystectomy) to be done for him.

Discussion

Schulze M, *et al*, found that 73% of males with median age of 67 years had transitional superficial cell carcinoma.⁽⁶⁾ Ahmed Z, *et al*, demonstrated male preponderance (79.8%), with median age of 59.1 years in patients with superficial transitional bladder carcinoma.⁽⁷⁾ In our study, male preponderance was 84.5% with mean age of 61 years. Superficial urinary bladder cancer (non-muscle invasive) is classified into two stages: Ta (tumor is confined to urothelium and T1 (with invasion to lamina propria). Regarding classification of superficial urinary bladder in terms of grades, it has low and high grades. In Schulze M, *et al*, investigation, after TURT, 55% of patients experienced a Ta tumor, while 45% experienced a T1 tumor.⁽⁶⁾ In our investigation, Ta disease was recorded in 83% while T1 was in 15.4% of patients. Carcinoma in situ was recorded in 1.2% of patients. Grading in Schulze M, *et al*, study was as follows: grade 1=23%, grade 2=47% and grade 3=30%.⁽⁶⁾ In our study, grade 1 was in 63.1% and grade 3

was in 35.7% of patients. Multiple tumors were found in 41.7% of patients in our investigation, while 33% was shown in Schulze *et al*, investigation.⁽⁶⁾ Successful TURT was curative in 80.95% of patients at first attempt, but second TURT within 4 weeks was needed in 19.05% of patients. Causes for second TURT were huge tumor size, reduced visibility and shortage of surgical time. In these cases second TURT removes residual tumors that otherwise would be considered as early recurrence. Herr HW, *et al*, demonstrated the existence of muscle invasive cancer on second TURT of patients previously diagnosed on first TURT as superficial bladder tumor (T1G3).⁽⁸⁾ The number of patients with T1 disease was 14.3% in this study.

There are two theories implemented for recurrence of urothelial carcinoma; the "field defect" theory shows that carcinogens cause genetic modifications of cells in the bladder at various sites, developing synchronous and metachronous cancer. The "re-implantation theory" shows that intra-vesical seeding of tumor cells may float on bladder urothelium and proliferate into full cancer.^(9,10) Risk factors for recurrence of superficial bladder carcinoma are stage of disease (Ta/T1), grade of tumor (G1/G3), number of primary tumor (single/multiple), size of tumor (< 3 cm / > 3 cm), growth model (papillary/solid) and existence of simultaneous carcinoma in situ, duration of symptoms (< 6 months / > 6 months), blood transfusion preoperatively, presence of hydronephrosis, intra-vesical treatment, number of recurrences, number of reexamination and duration of recurrence free interval.⁽¹¹⁾ In our investigation, tumor recurrence frequency was 75%. Oosterlinck W, *et al*, showed that the frequency of tumor recurrence after TURT 30-80%.⁽¹²⁾ Sakai *et al*, demonstrated that the intravesical recurrence was 41%.⁽¹³⁾ Herr HW, *et al*, found a recurrence incidence of 52%.⁽¹⁴⁾ Pasin, *et al*, demonstrated that previous recurrence rate predicts future recurrences, and for patients with low-grade Ta tumors, a previous recurrence rate of more than 1 per year has an increased risk of future recurrences.⁽¹⁵⁾ Factors contributing to this pattern are duration of surveillance and incidence of recurrence. Frequent recurrences are a risk factor for tumor

progression.⁽¹⁶⁾ Disease progression was found in 53% of patients with high risk recurrent tumor in one study.⁽¹⁷⁾ Progression was not measured in our study because in many patients the recurrences were dealt by using fulguration without resection and pathologic examination and so it was outside the scope of the study. Correlated bladder outflow obstruction of enlarged prostate was managed using transurethral resection of prostate in 5% patients. Incidence of prostatic fossa recurrence was not seen in our patients.

There are discrepancies regarding the interval of surveillance of patients with superficial bladder carcinoma. Some advice to stop surveillance cystoscopy 5-10 years after last recurrence in patients with single, low grade tumors.⁽¹⁶⁾ Invasive cancer may appear in patients with superficial bladder tumor after tumor free for more than 5 years.⁽¹⁸⁾

From the discussion above, it appears that superficial urinary cancer in Jordan behaves very similar to that of other parts of the world. Superficial bladder cancer had to be followed for as long as possible, as late recurrences may occur even after long recurrence-free periods. Accordingly, our patients should be counseled clearly about the importance of their commitment to the cystoscopy follow up even if it was prolonged. One of the most important limitations of our study is that patients need more follow up than in our study.

Finally there is about a subset (17%) of patients with TaG1 disease who were free of recurrence at initial 3 month cystoscopy but then had recurrences at 6 and 9 months Cystoscopic follow-up. While these recurrences are normally detected using the AUA protocol (cystoscopy every 3 months in the first year for all stages and grades), in other protocols that advocate follow-up at 3, 12 and 24 months for TaG1 they would otherwise be missed.

Conclusion

Early recurrence was recorded with T1 disease, while late recurrence was seen with Ta disease.

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