

MANAGEMENT OF NON-MUSCLE INVASIVE UROTHELIAL CARCINOMA OF BLADDER AND THE NECESSITY FOR ADHERENCE TO STANDARD GUIDELINES: A LOCAL STUDY



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ABSTRACT

Background

Bladder cancer is a very common urological malignancy affecting human being, it is the disease related to environment and aging. The biologic behavior of bladder cancer is unpredictable, but the issue of recurrence, progression in relation to morbidity and mortality are well recognized. NMIBC (Non-Muscle Invasive Bladder Cancer); comprise Ta, T1 and Cis with great difference in their management and prognosis. It is found early recurrence and progression of NMIBC as a clinical marker carries a poor prognosis.

Objectives

To detect the rate of early recurrence, progression, and to evaluate the clinical behavior and final outcome of 44 patients diagnosed with NMIBC.

Materials and Methods

This is a prospective study conducted between June 2013 and December 2014 in Sulaimani Surgical Teaching and Hewa Teaching hospitals. Forty four patients who had been managed for primary NMIBC were reviewed for their medical records, clinical parameters including patients age, gender, physical examination, investigations, the operations, tumor morphology and adjuvant therapy were entered into database. Patients were called back for reviewing their course of the disease and to complete their managements. The outcomes of re-resection, recurrence rate, progression and overall survival were recorded in relation to initial management and follow up.

Results

Of 44 patients with primary NMIBC, male: female ratio is 6:1, the mean age is 55 years. Index TURBT revealed 47.7% was Ta, 45.45% was T1 and 6.8% unknown stage with no CIS detection. Grading showed; 18.1% was PUNLMP, 34.1% G1, 13.6% G2, 27.27% G3, and 6.8% was unknown. Tumor size was; 9.09% < 1 cm, 40.9% size was 1-3 cm, and 50% was > 3 cm. The multiplicity; 36.36% was solitary tumor, 31.8% multiple, and 31.8% the multiplicity was not recorded. Initial treatment was 18.2% TURBT alone, 18.2% second TURBT, 4.5% TURBT and immediate intravesical MMC, 61.36% TURBT and 6 weeks course of MMC, 6.8% underwent TURBT and 6 weeks' course of BCG. Mean time to recurrence was 5.6 months and 7 months for progression. Using multivariate analysis, the P value for tumor size and grade of tumor were 0.001 and 0.008 respectively, which are statistically significant for both recurrence and progression.

Conclusion

The biological behavior of NMIBC remained elusive in term of curability, recurrence, progression and mortality. Lack of documentation and irregular follow up schedules were observed obviously. Deviations from the standard guideline management strategy can threaten the life of patients.

Keywords: *Non-muscle invasive urothelial carcinoma, Bladder cancer.*

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INTRODUCTION

Bladder cancer is the second most common urological malignancy⁽¹⁾. It is strongly related to the environmental factors and advancing age⁽²⁾, can occur in young population, but in general the average spotted is 65 years of age., with highest incidence in 8th decade of life⁽³⁾. It is the ninth most common cancer worldwide with 430000 new cases diagnosed in 2012 .Iraq being ranked as the 19th worldwide for male gender and 16th for female⁽⁴⁾. The biologic behavior of bladder cancer is also elusive; however the magnificent issue of recurrence and progression is well recognized in relation to morbidity and mortality respectively⁽⁵⁾. The mucosal bladder tumors are either benign or malignant⁽⁶⁾. It is further divided to two broad categories ;non muscle invasive (NMIBC) and muscle invasive bladder cancer(MIBC)⁽⁷⁾. Non-muscle invasive (NMI) bladder cancer include the stage Ta (papillary tumors confined to urothelium) and T1 (papillary tumors penetrating lamina propria), accounting for 75-80% of all newly diagnosed bladder cancer. The recent development of the EORTC (European Organisation for the Research and Treatment of Cancer) risk table assist with predicting the recurrence and progression risk of NMI bladder cancer, using simple clinical and pathological factors including tumor grade and stage. In 1973 the world health organization (WHO) proposed a histological classification of urothelial papilloma based on grade ,creating 3 groups; 1 ,well differentiated; 2, moderately differentiated; 3, poorly differentiated tumours, with the distinction based on cyto-pathological features and change in cellular architecture. However an alternative WHO grading system was proposed in 2004 which include 3 groups; urothelial papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade papillary urothelial carcinoma. Despite there being no muscle invasion, this group does encompass a broad disease spectrum ranging from G1 pTa through to G3 PT1with an associated range of behaviors⁽⁸⁾. Many risk factor recognized for bladder cancer ,which are more related to environment. However studies conducted to determine the chromosomal changes related to its occurrence, recurrence and progression with some results^(9, 10). Blue light during cystoscopy with the aid of porphyrin based photosensitizer has a higher ability to detect NMIBC by 20%,also help to reduce the rate of second resection, but still 4.5% of residual tumours may be missed⁽¹¹⁾. Index TURBT is a complete TUR of Ta and T1 macroscopically including under lying

muscle. While second TURBT is usually undertaken within 2-6 weeks after first TURBT. Combination of thermotherapy and intra vesical chemotherapy is called thermos chemotherapy which showed in some studies lesser rate of recurrence even in BCG failed cases^(12, 13) Intra vesical BCG is another additional post TURBT treatment which is superior to intra-vesical chemotherapy in both preventing recurrence and progression but with added serious side effects and list of contraindications^(14, 15). Despite its toxicity, the risk benefit ratio favors the use of BCG inpatients who have moderate to high risk tumours⁽¹⁶⁻¹⁸⁾. BCG with Alfa interferon or BCG with electromotive ,both methods show promising results⁽¹⁹⁾. Partial cystectomy offered for patients with single T1 tumor located in posterior ,lateral wall or dome of bladder after rolling wide spread disease⁽²⁰⁾. Recurrence is common in NMIBC and range for 60-70%.(21)and overall progression range from 20-30%⁽²²⁾. NMIBC is a great challenge in urologic oncology, which reflects itself as a significant economic burden on health care system⁽²³⁾.

METHODS

All patients who had been treated for bladder cancer between June 2013 and December 2104 were included in this study. Patients medical records and hospital database were reviewed for demographic information including history, physical examination, investigations, diagnosis and treatment used of intra vesical chemotherapy or BCG. Patients recall with telephone to visit for reviewing their course of disease.

The histo-pathological reports were identified for each patient from the pathology department or from report the patient had. Type of cancer, recurrence, progression and follow up for each patient were notified and recorded.

All patients with history of benign tumors and muscle invasion were exclude from the study. Initially the patients were asked to have cystoscopy with or without TURBT by his surgeon to identify the disease status including size, numbers, shape, location operative procedures and to be recorded in the paper sheet. The tissue specimens were examined by two consultant pathologist. The patients were asked to come back to see and record the results. Those who had intra-vesical chemotherapy or immunotherapy at Hewa hospital were recorded. The patients were seen at 3, 6, 9 and 12 months for follow up progress with history, physical examination, investigations and cystoscopy with or without TURBT for diagnosis of recurrence and

progression according to a paper diagram containing all the fields which asked to be full by the unit doctors. Recurrence was defined as biopsy show recurrence and progression if there was change in grade or stage of the cancer. The data were entered into a Microsoft Excel Spreadsheet after data cleaning and then were transported into SPSS version 18.0 (IBM, IL, USA) for statistical analysis. Descriptive statistics (mean, standard deviation, minimum, maximum, numbers and percentage) were calculated for variables. Probability measure were used; the analytical statistics was done to find the relations between variables with p value < 0.05 considered as significant.

RESULTS

Forty-four patients were identified for inclusion in the study of which 38 were male and 6 were female. The average patient age was 55years with a range of 25-85 years, see Fig.1.

39 patients (88%) had basic study, 3 (6%) had high school diploma and 2 patients (4%) had university degree. 10

patients (22.7%) were still smokers with mean duration of smoking was 15 years, 24 patients (54.6%) were nonsmoker and 10 patients (22.7%) ex- smoker with mean duration of 14 years, the duration after quitting smoking to development of bladder cancer was 15± 9 years. One patient (2%) was alcoholic, 2 patients (4.5%) had family history of bladder cancer, 2 patients (4.5%) had history of vesical stone and non-had history of catheterization, bilharzias, urinary tract infection, radiation, trauma or cyclophosphamide therapy.

After that all patients underwent index TURBT, the tumor characteristics were revised, the pathological stage data shoven in table 2. No CIS detection recorded in any patient.

Tumor grading showed; 8 patients (18%) had PUNLMP, 15 patients (34%) had G1, 6 patients (13%) had G2, 12 patients (27%) had G3, and 3 patients (6%) tumor grade were unknown see Fig. 2.

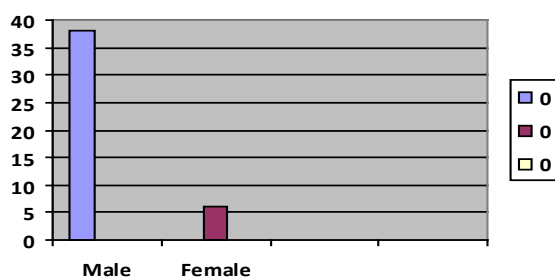


Figure 1. Male to female ratio.

Table 1. Patients characteristics and risk factors.

Data	Number	Percentage
Age		
≤ 60	16	36.4
61-70	12	27.3
71-80	9	20.5
>80	7	15.9
Family history		
Yes	2	4.5
No	42	95.5
Smoking		
Smoker	10	22.7
Non-smoker	24	54.6
Former smoker	10	22.7
Bladder stone		
Present	2	4.5
Absent	42	95.5
Education		
Primary school	39	88.6
High school	3	6.8
University	2	4.5

Table 2. Tumor characteristic after initial index TURBT.

Tumor stage	Number of patients	Percentage
Ta	21	47.7%
T1	20	45.5%
Unknown stage	3	6.8%

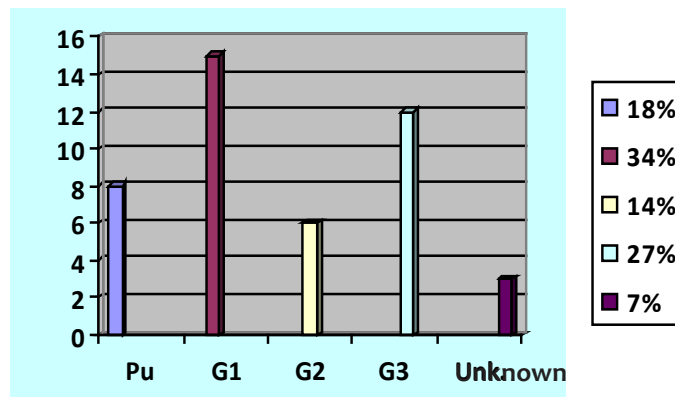


Figure 2 Tumors grade after first TURBT.

Urine cytology in 10 patients (22.7%) were negative for malignancy, the rest 34 patients (77.3%) had no urine for cytology. The bladder biopsies were positive for 4 patients (9.1%), while 23 patients (52.3%) were unknown whether biopsies were taken or not, 17 patients (38.6%) had no bladder biopsy with TURBT at all. The size of the tumor recorded by ultrasound; 4 patients (9%) the tumor size was < 1 cm, 18 patients (40%) had tumor size of 1-3 cm, and 22 patients (52.3%) had tumor size of > 3 cm. In 22 patients (50 %) the tumor arose from the lateral walls, 1 patient (2.3%) the tumor occurred in the dome, 2 patients (4.5%) in the trigone, 1 patient (2.3%) in the base, and 18 patients (40.9 %) the site were not recorded.

The multiplicity of the tumor in bladder recorded as follow; 16 patients (36.4%) had solitary tumor, 14 patients (31.8%) had multiple tumor, and 14 patients (31.8%) the multiplicity was unknown. Among the multiple tumors, 6 patients (13.6%) had 2 tumors, 2 patients (4.5%) had 3 tumors, and 20 patients (45.5%) the number was unknown. See table 3.

Nineteen patients (43.2%) presented with hematuria, 16 patients (36.4%), presented with lower urinary tract

symptoms, and 9 patients (20.5%) were incidentally diagnosed. See table 4.

In the first 3 month follow up (Table 5); the urinalysis in 2 patients (4.5%) showed hematuria, 16 patients (36.4%) had no hematuria, and 26 patients (59.1%) were unknown to have urinalysis. The urine for cytology in 18 patients (40.9%) was negative, and 26 patients (59.1%) had no urine for cytology. Ultrasound done for 32 patients (72%) of which 26 patients (59.1%) had normal result, 6 patients (13.6%) had recurrent tumor; and 12 patients (26.3%) had no ultrasound. The cystoscopy were done for 23 patients (52%), of which 4 patients (9.1%) had recurrent tumor, and 19 patients (43.2%) were tumor free, and 21 patients (47.7%) had no cystoscopy check. The first 3 month tumor were evaluated for pattern of recurrence, and the results were as follow; 1 patient (2.3%) had solitary tumor, 5 patients (11%) had multiple tumors, and 38 patients (86%) the multiplicity were not determined. The tumor size was < 1cm in 1 patient (2.3%), 1-3cm in 1 patient (2.3%), in 4 patients (9.1%) it was > 3 cm, and in 38 patients (86.3%) the size was not determined. The pathological stages were noted as follows; 1 patient (2.3%) had Ta recurrence, 5 patients (11.4%) had T1 recurrence, and 38 patients

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(86.3%) the stage of recurrence were not recorded. The grade of recurrence showed; 1 patient (2.3%) had G 1 recurrence, 3 patients (6.8%) had G3 recurrence, and 40 patients (90.9%) the grade of recurrence were

not recorded. The site of recurrence was as follow; 2 patients (4.5%) had recurrent away from the index tumor, and 42 patients (95.5%) the recurrent site was not determined. See table 5.

Table 3. Tumor characteristics.

Tumors	Number	Percentage
Grade		
PUNLMP	8	18.2
I	15	34.1
II	6	13.6
III	12	27.3
Unknown	3	6.8
Urinary cytology		
Positive	0	0.0
Negative	10	22.7
Unknown	34	77.3
Bladder Biopsy		
Positive	4	9.1
Negative	0	0.0
Unknown	23	52.3
Not done	17	38.6
Size		
<1 cm	4	9.1
1-3 cm	18	40.0
> 3 cm	22	52.3
Site		
Lateral wall	22	50.0
Dome	1	2.3
Trigon	2	4.5
Neck	0	0.0
Anterior	0	0.0
Base	1	2.3
Unknown	18	40.9
Multiplicity		
Solitary	16	36.4
Multiple	14	31.8
Unknown	14	31.8
Number of tumors		
1	16	36.7
2	6	13.6
3	2	4.5
Unknown	20	45.5

Table 4. Patients presentation data.

Presentation	Number of patients	%
Hematuria	19	43.2
LUTS	16	36.4
Incidental	9	20.5

Table 5. First follow up at 3 months.

Patient information	Number	Percentage
Urinalysis		
Hematuria	2	4.5
No hematuria	16	36.4
Unknown	26	59.1
Urine cytology		
Negative	18	40.9
Positive	0	0.0
Unknown	26	59.1
UltraSound		
Normal	26	59.1
Recurrent	6	13.6
Unknown	12	26.3
Cystoscopy		
Recurrent	4	9.1
None	19	43.2
Unknown	21	47.7
Character of recurrence number		
Solitary	1	2.3
Multiple	5	11.4
Unknown	38	86.3
Size		
< 1 cm	1	2.3
1-3 cm	1	2.3
>3 cm	4	9.1
Unknown	38	86.3
Stage		
Ta	1	2.3
T1	5	11.4
CIS	0	0.0
Unknown	38	86.3
Grade		
I	1	2.3
II	0	0.0
III	3	6.8
Unknown	40	90.9
Site		
Same site	0	0.0
Other site	2	4.5
Unknown	42	95.5

Table 6. Follow up at 6 months.

	Number	Percentage
GUE		
Hematuria	4	9.1
No hematuria	14	31.9
Unknown	26	59.0
Urine cytology		
Negative	20	45.5
Positive	0	0.0
Unknown	24	54.5
US		
Normal	17	38.6
Recurrent	11	25.0
None	16	36.4
Cystoscopy		
Recurrent	14	31.8
None	18	40.9
Unknown	12	27.3
Character of Recurrence Number		
Solitary	4	9.1
Multiple	6	13.6
Unknown	34	77.3
Size		
< 1 cm	5	11.4
1-3 cm	0	0.0
> 3 cm	2	4.5
Unknown	37	84.1
Stage		
Ta	3	6.8
T1	5	11.4
CIS	0	0.0
Unknown	36	81.8
Grade		
I	5	11.4
II	0	0.0
III	3	6.8
Unknown	36	81.8
Site		
Same Site	3	6.8
Other Site	4	9.1
Unknown	37	84.1

Table 7. Follow up at 9 months.

	Number	Percentage
GUE		
Hematuria	4	9.1
No hematuria	8	18.2
Unknown	32	72.7
Urine cytology		
Negative	14	31.8
Positive	0	0.0
Unknown	30	68.2
US		
Normal	17	38.6
Recurrent	5	11.4
None	22	50.0
Cystoscopy		
Recurrent	4	9.1
None	18	40.9
Unknown	22	50.0
Character of Recurrence Number		
Solitary	0	0.0
Multiple	2	4.5
Unknown	42	95.5
Size		
< 1 cm	0	0.0
1-3 cm	0	0.0
> 3 cm	2	4.5
Unknown	44	95.5
Stage		
Ta	0	0.0
T1	0	0.0
CIS	0	0.0
Unknown	44	100.0
Grade		
I	2	4.5
II	0	0.0
III	0	0.0
Unknown	44	95.5
Site		
Same Site	2	4.5
Other Site	0	0.0
Unknown	44	95.5

Table 8. Follow up at 1 year.

	Number	Percentage
GUE		
Hematuria	3	6.8
No hematuria	19	43.2
Unknown	22	50.0
Urine cytology		
Negative	22	50.0
Positive	2	4.5
Unknown	20	45.5
US		
Normal	25	56.8
Recurrent	6	13.6
None	13	29.5
Cystoscopy		
Recurrent	6	13.6
None	20	45.5
Unknown	18	40.9
Character of Recurrence Number		
Solitary	2	4.5
Multiple	2	4.5
Unknown	40	91.0
Size		
< 1 cm	0	0.0
1-3 cm	2	4.5
> 3 cm	2	4.5
Unknown	40	91.0
Stage		
Ta	2	4.5
T1	0	0.0
CIS	0	0.0
Unknown	42	95.5
Grade		
I	0	0.0
II	0	0.0
III	2	4.5
Unknown	42	95.5
Site		
Same Site	2	4.5
Other Site	2	4.5
Unknown	40	91.0

The overall recurrence, progression and survival rates recognized and showed in Table 9; total number of recurrences in one year proved by cystoscopies were 28 patients (63%), of which 4 patients (9%) occurred during first 3 months, 14 patients (31%) occurred during 9 months, 6 patients (13%) occurred during 12 months; and 16 patients (36%) recurrence were free within one year.

Six patients (13%) had progression, and 38 patients (86%) had no progression. Thirty eight patients (86%) are still live, 6 patients (13%) were died. Of those who died; 4 patients the death was cancer- related and 2 patients were non cancer- related. See table 9.

Table 9. Recurrence, Progression and survival Rates.

	Number	Percentage
Recurrence		
At 3 months	4	9.0
At 6 months	14	31.0
At 9 months	4	9.0
At 12 months	6	13.0
No Recurrence	16	36.0
Progression		
At 6 Months	4	9.1
At 9 months	2	4.5
No Progression	38	86.3
Survival		
Alive	38	86.4
Died	6	13%
Cause of Death		
Non-Cancer-related	2	33.3
Cancer-Related	4	66.7

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We observed the impact of initial treatment in relation to recurrence and progression, as shown in figure 3, eight patients (20%) were treated with TURBT alone, in this group of patients 4 of them (50%) had no recurrence or progression, the rest 4 patients (50%) had progression and none of them had recurrence.

Eight patients (20%) were treated with second TURBT, in this 4 patients (50%) had no recurrence or progression and 4 patients (50%) had recurrence, and none of them had progression.

Two patients (5%) were treated with TURBT and Immediate intravesical MMC; none of the patients had recurrence or progression.

Twenty seven patients (67.5%) were treated with TURBT and 6 weeks course of intravesical MMC; in this group 15 patients (55%) had no recurrence or progression, 10 patients (37%) had recurrence, and 2 patients (7%) had progression.

Three patients (7.5%) were treated with TURBT and 6 weeks course of intravesical BCG; in this group 2 patients (66.6%) had no recurrence or progression. 1 patient (33.3%) had recurrence, and none of them had progression.

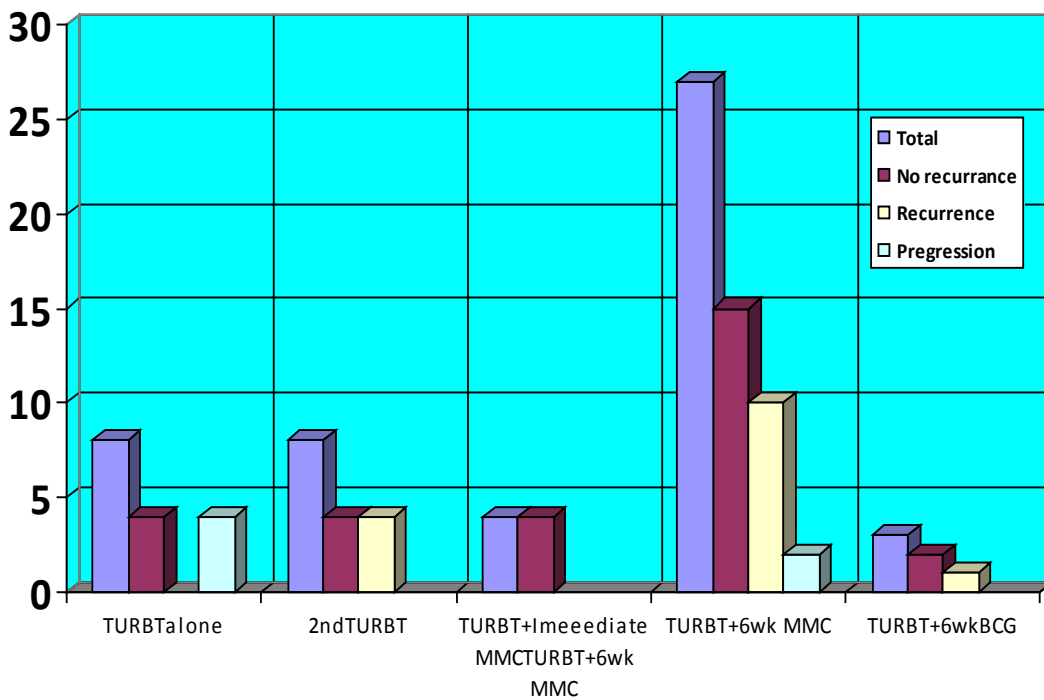


Figure 3. Shows Pattern of treatment in different groups of patients.

We compared our study results to the probability of recurrence and progression calculated by EORTC table; were shown in Table 10.

For our study those with score zero had 30 % recurrence rate, those with score 1-4 had 35 % recurrence rate, and those with score 5-9 had 35 % recurrence rate. For progression analysis; there were no patients with score 0 and score 2-6, but those with 7-13 had 9% progression rate and those with score 14-23 had 4% progression rate.

The mean time to recurrence in month calculated and it was 5.6 months (starting from 3 month to 12 months) as shown in Figure 4. While the mean time to progression

was 7 months (6 month- 9 month), as shown in Figure 5.

In Univariate analysis, the Hazard Ratio and P value were statistically not significant for age, gender, T category, tumor size, number of tumor, and grade for time to first recurrence and progression as shown in Table 11.

In Univariate analysis, the Hazard Ratio and P value were statistically not significant for age, gender, T category, Tumor size, number of tumor, and grade for time to first recurrence and progression as shown in Table 11.

Table 10. Comparison of EORTC probability for recurrence and progression and our

Recurrence scor	Probability Recurrence Standard 1 year (95% CI)	Probability Recurrence This study 1 year (95% CI)
0	15%(10%,19%)	30%
1-4	24% (21%, 26%)	35%
5-9	38% (35%, 41%)	35%
10-17	61% (55%, 67%)	0%
Progression score	Probability Progression Standard 1 year (95% CI)	Probability Progression This study 1 year (95% CI)
0	.2%(0%, 7%)	0%
2-6	1%(.4%-,1.6%)	0%
7-13	5%(4%,7%)	9%
14-23	17%(10%, 24%)	4%

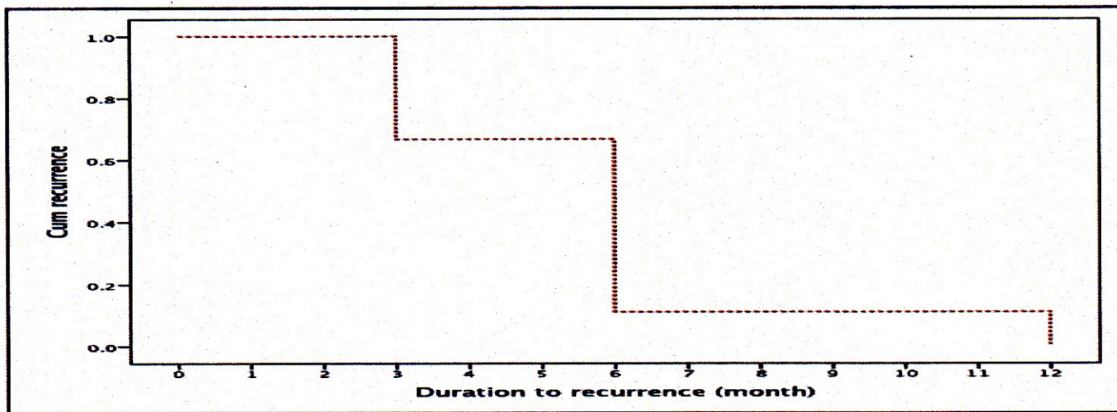


Figure 4. Duration to recurrent of baldder cancer.
 Mean (95%CI) recurrence time = 5.66 (4.41,6.91) months

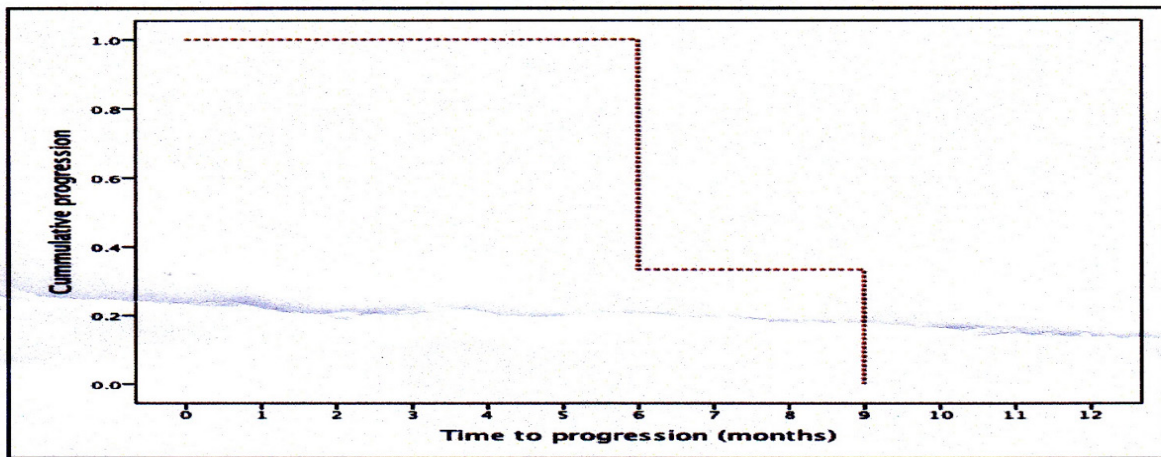


Figure 5. Duration to progression of baldder cancer.
 Mean (95%CI) progression time = 7.0 (5.76,8.24) months

Table 11. Univariate analysis of time to first recurrence and time to progression.

Variable	Recurrence		Progression	
	HR	P value	HR	P value
Age: <65, >65 years	1.13	0.779	1.14	0.506
Gender: female, male	0.37	0.845	0.84	0.378
T category: Ta, T1	1.22	0.639	1.22	0.639
Tumor size: <3 cm, >3 cm	0.83	0.407	0.83	0.409
Number of tumors: single, multiple	1.44	0.472	1.44	0.472
Grade: G1, G2, G3	1.16	0.492	1.61	0.492

In multivariate analysis, the tumor size has a P value of 0.001 which is statistically significant for both time to first recurrence and progression. Also tumor grade has p value of 0.008 which is statistically significant for time to first recurrence and progression as shown in Table 12.

The post management follow up results revealed; 10 patients (22%) developed urethral stricture, 2 patients (4%) developed lower urinary tract symptoms, and 32 patients (72%) developed no complications (Table 13). No patient has maintenance BCG therapy, optimized MMC, or BCG with interferon usage.

Table 12. Multivariate analysis of time to first recurrence and time to progression.

Variable	Recurrence		Progression	
	HR (95%CI)	P value	HR (95%CI)	P value
T category: Ta, T1	0.5 (0.1, 1.7)	0.287	0.51 (0.1, 1.8)	0.277
Tumor size: <3 cm, >3 cm	16.1 (5.0, 34.4)	0.001	16.3 (5.2, 34.6)	0.001
Number of tumors: single, multiple	0.7 (0.2, 1.8)	0.443	0.6 (0.24, 1.9)	0.443
Grade: G1, G2, G3	2.11 (1.2, 3.6)	0.008	2.12 (1.1, 3.7)	0.008

Table 13. Post management course.

	Number	Percentage
Post-Operative Course		
Stricture	10	22.7
LUTS	2	4.5
Nothing	32	72.7
Maintenance BCG		
Yes	0	0.0
No	44	100.0
Optimized MMC		
Yes	0	0.0
No	44	100.0
BCG + Interferon		
Yes	0	0.0
No	44	100.0

DISCUSSION

NMIBC is well known for its recurrence and progression⁽²⁴⁾. In this study male: female ratio is 6:1, however in Europe this ratio is 3:1 except for Spain which is 7:1⁽¹⁰⁾. This indicates that gender plays a significant role in the incidence of bladder tumor⁽²⁵⁾. Our mean age is 55 years which is indicating much earlier age of developing NMIBC by 15 year compared to the results of European studies^(26,27). 36% of our patients were below age of 60 years, fewer than 15 % are above the age of 80 years. The majority of the patients (88%) are illiterate or have basic education, due to lower socioeconomic status and this directly proportional to the occurrence of the disease⁽²⁸⁾. 22 % still smoker, and 22% former smoker.

The very high percentage of T1 tumor 45.5% as shown in table 3 indicate a more aggressive behavior of NMIBC in our population, despite that only 18% underwent second TURBT, which in many literature the second TURBT is highly recommended and even it is absolutely indicated for T1 tumor, to avoid under staging, leaving residual tumor and to search for concomitant CIS, because these groups of patients need more radical treatment. Why higher percentage of patients have G2 and G3? We can link it to environment alone; or genetic predisposition. Tumor grade has stronger correlation to progression than recurrence.^(29,30)

The tumor size by ultrasound were 52.3% had size > 3cm. Ultrasound showed 50 % developed from the lateral walls and 40.9 % the site was not recorded.

Multiplicity of the tumor is linked to the rate of recurrence, progression, incomplete TURBT and residual tumor^(31,32), which all gives the idea to the urologists to be more alert in recognizing this tumor characteristics in the management of NMIBC, 36.4 % of our patients had single tumor, 31.8% had multiple tumors, and 31 % of them the multiplicity was unknown. In our study hematuria is accounting for 43 % of the patients, 36 % of them presented with lower urinary tract symptoms and 20 % of the patient diagnosed with bladder growth incidentally. A proper TURBT should be performed to get maximum response from adjuvant therapy⁽³³⁾.

Recently there is no TURBT alone managements, because it carries the risk of recurrence up to 90 %⁽³⁶⁾. It is proved that immediate postoperative instillation of chemotherapy within 6-24 hours reduce the rate of recurrence by 50% within 2 years^(35,36). Our results

showed 22% of the patient managed with TUR alone. On the other hand, only 5 % of patients received immediate post TURBT intravesical chemotherapy and 67.5% of patients received 6 course of intravesical MMC, which started after the histopathology exam confirmed the diagnosis of NMIBC, this delay in instillation of MMC resulted in higher cost on the hospital and significantly higher rate of recurrence⁽³⁷⁾. Maintenance MMC is recommended for cases with multiple or recurrent low grade Ta this is to reduce the recurrence rate but not the progression⁽³⁸⁾. At 3 months follow up 40% of patients had negative urine cytology for malignancy, 59% of patients had follow up without urine for cytology.

Ultrasound exam in 72% of the patients, of which; 59.1% were free of recurrence, 13.6 % had recurrent tumor and 26.3 % had no ultrasound. During this period 52 % of patients underwent cystoscopy, of which; 9% had definite recurrence and 47.7% of patient had no cystoscopy. According to EUA guideline the first 3 month cystoscopies follow up is mandatory, because high grade tumor recurrence is critical and can alter the prognosis further, our study shows 11.4 % had T1 recurrence, and 6.8% of them the grade is G3.

In table 9 we showed the overall recurrence, progression and survival rate in one year; 63 % of patients developed tumor recurrence of which 9 % of them were during the first 3 months, 31 % during 6 month, 9% during 9 month, 13 % during 12 month and 36 % of them were recurrence free within one year. This high recurrence rate can be related to aggressiveness in the biologic behavior of bladder tumor among Kurdish population, heterogeneous non-standard way of managing bladder tumor, lesser rate of performing second TURBT, lesser rate of immediate intravesical MMC, and follow up schedule flexibility. Again lower rate of second TURBT and taking lower rate of bladder biopsy along with fewer uses of intravesical BCG is well recognized outcome of these group of patients.

These types of tumors have great impact on cancer specific mortality; 6 patients in our study were died during the first year follow up, 4 of them were died of cancer related. We can conclude from fig. 3 the impact of treatment the best result was from those group who received TURBT and immediate MMC and group of TURBT plus 6 week course of BCG. None of our patients received maintenance BCG or MMC. We compared our results with the probabilities determined by EORTC calculator. The recurrence rate for score zero is 30 % in our study, while in EORTC

calculator it is 15 %, this double risk probability can be explained by either the tumor were not resected completely, or missed tumor in multiple tumors, or no immediate post-operative MMC given, or higher grade of tumor not received BCG intravesically, or T1 disease without second TURBT, or due to the natural and biological aggressiveness of these tumor among kurdish population.

The higher percentage of occurrence observed for score 1-4, again we recorded 35 % recurrence if compared with 24 % probability by EORTC calculator; and score 5-9, observed to have the recurrence of 35 % which pretty similar to EORTC table. We do not have score 10-17, because firstly we didn't diagnosed any case of CIS and secondly from the start we excluded cases of prior tumor, prior recurrence and prior treatment for the same disease, and this makes the score to fall below 10-17. The rate of progression is quite lower if compared to recurrence, but in our study we found we don't have score zero and score 2-6, but for score 7-13 we found 9% had progression, which is higher than what is mentioned in EORTC, and for score 14-23 we have 4 % progression rate, this is lower than the EORTC result, but we have to be careful here because our study sample is small, and this number may not exactly reflect the reality. By this depending on these probability data clinicians can provide options to the patients with most appropriate treatment ⁽³⁹⁾. Figure 4 and 5 should alert the urologists and oncologists for having early recurrences and progression of NMIBC, which carry poorer prognosis. and needs more earlier radical treatment. Statistical analysis using the Univariate and multivariate analysis of time to first recurrence and progression, shown in table 11 and 12; The hazard ratio and P value in Univariate has no statistically significant relations; but for multivariate we found that the tumor size and grade is statistically significant; by this we can say these two parameters should be taken in consideration in treating and following up patients in terms of both early recurrence and early progression ⁽³⁹⁾.

Deviation from the standards of managements were observed in our study; lack of documentation or non performing the necessary investigation, imaging, bladder biopsy with proper index TURBT and postoperative management in high percentage of patients were noted; for example 77 % of patients have no urine for cytology, 38 % of them have no bladder biopsy with TURBT, and 52 % were unknown whether biopsy taken or not; for this reason we can say however CIS is an uncommon tumor, but the lower the rate of

taking urine for cytology and bladder biopsy can be attributed to lower detection of CIS in our study.

Conclusion

True incidence of NMIBC among kurdish population is unknown. The biological behavior looks to more aggressively than what have been reported in other literatures. Male to female ration is higher than other communities. Incidental finding of bladder growth is rising. TURBT plus neoadjuvant therapy is the standard initial treatment, and subsequent treatment depends on the histopathological exam. Second TURBT is strongly recommended. Patients should be managed according to the risk groups rather than stage and grade of tumor. Tumor size and grade of tumor statistically significant in relation to time to first recurrence and progressions. Higher rate of recurrence and progression noted among the low and intermediate risk groups. Failure of grouping patients according to risk groups, lesser rate of intravesical BCG were all observed very common in our practice.

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