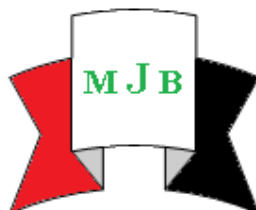


Detrusor Muscle in The First, Apparently Complete TURBT of Resection Quality, Specimen Is A Surrogate Marker “Predicts Risk of Early Recurrence”

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Abstract

Objective To determine whether resection of detrusor muscle (DM) in the first, apparently complete TURBT is a surrogate marker of resection quality.

Patient and method From January 2009 to May 2010, 50 patients with new bladder tumours that were judged to have been completely resected were followed up. Strict exclusion criteria were applied. Prospectively recorded tumour size, tumour multiplicity, DM status, grade and stage of tumour, and findings at first follow-up cystoscopy (at 3 months) and at early re-TURBT were evaluated. Early recurrence (for calculating recurrence rate in the first follow up cystoscopy (RR-FFC) was defined as pathologically confirmed tumour on early re-TURBT or recurrence at the first follow-up cystoscopy.

Results: Of 50 patients, DM was present in 41 patients (82%). Multivariate analyses revealed that large tumours, high-grade tumours, was independently associated with the presence of DM in the resected specimens. The RR-FFCs when DM was absent and present were 55.5% and 21.9%, respectively. The absence of DM independently predicted a higher RR-FFC. This association was also seen in small and low-grade tumours.

Conclusions: DM absence or presence in the first, apparently complete TURBT specimen appears to be a surrogate marker of resection quality by independently predicting the RR-FFC. So the first follow up cystoscopy in those patients with absent detrusor muscle in the first resection should be done within shorter period.

الخلاصة:

لتقرير في ما إذا كان وجود العضلة الدافعة في العينة المأخوذة من الاستئصال الأول الكامل لورم المثانة عن طريق التحليل يمكن استخدامها كعلامة بديلة عن نوعية الاستئصال "توقع خطر التكرار المبكر للورم".

المرضى وطريقة الدراسة:

من يناير/كانون الثاني ٢٠٠٩ إلى مايو/مايس ٢٠١٠، تم اخذ ٥٠ مريض مصاب بأورام المثانة الجديدة و التي حكمت بأنها كانت قد استأصلت بالكامل وتم متابعتها. تم تسجيل حجم و عدد الأورام , حالة العضلة الدافعة , درجة و مرحلة الورم مستقبلياً. كذلك تم تسجيل نتائج ناضور المتابعة الأول (في ثلاثة أشهر) أو نتائج إعادة الاستئصال. تكرار الورم المبكر عرّف بأنه الورم الذي يتم تأكيده بشكل باثولوجي في إعادة الاستئصال أو في تنظير المتابعة الأول.

النتائج: كانت العضلة الدافعة موجودة في ٤١ مريض (٨٢%). كانت نسبة تكرار الورم هي ٥٥.٥ % و ٢١.٩ %، في حالة عدم وجود أو وجود العضلة الدافعة من العينات المأخوذة من الاستئصال الأول للورم على التوالي.

الاستنتاجات:

عدم وجود أو وجود العضلة الدافعة في العينة المأخوذة من الاستئصال الأول الكامل لورم المثانة عن طريق الاحليل يمكن أن تستخدم كعلامة بديلة على نوعية الاستئصال "توقع خطر التكرار المبكر للورم". لذا فإن ناظور المتابعة الأول للمرضى اللذين أظهرت العينات المأخوذة من الاستئصال الأول لهم عدم وجود العضلة الدافعة يجب أن يتم في فترة أقصر.

Introduction

It is estimated that, in 2002, about 357 000 new cases of BC were diagnosed ^[1]. Approximately 75–85% of all patients with BC have disease confined to the mucosa (stage Ta) or submucosa (stage T1) ^[2]. This group of tumours is referred to as non-muscle-invasive or superficial BC as opposed to muscle-invasive disease staged as T2–T4. ^[3] Bladder cancer is more than 2.5 times more common in men than in women ^[4]. In men, it is the fourth most common cancer after prostate, lung, and colorectal cancers, accounting for 6.2% of all cancer cases ^[4]. In women, it is the eighth most common cancer, accounting for 2.5% of all cancers ^[4]. Between 1985 and 2000, the number of bladder cancers diagnosed annually in the United States increased 33%, at roughly the same rate in both sexes ^[5]. Although TURB is a routine urologic procedure, the principles of which have not been changed for decades, the criteria of its quality have never been clearly defined. ^[12] The definition of benchmarks is extremely important, because it could help us to improve the results. There is general acceptance that TURB is successful if there are no missed non-muscle-invasive lesions (ie, the early recurrence rate is low), if the staging of the disease was assessed correctly (ie, there is no tumour understaging), and if the procedure was performed without complications. ^[13] Recurrences after TURB are observed in about 50–80% of patients with

non-muscle-invasive disease, most of which occur during the first year ^[17]. The source can be found in incomplete TURB, in tumour cell implantation, or in aggressive tumour biology. The analysis of 2410 patients from seven phase 3 trials by the EORTC showed substantial variations in early recurrence rates among different institutions. The frequency of 3- months recurrence ranged from 0% to 46%. These differences are not the result of the clinical features of the tumour but probably of the quality of TURB performed by individual surgeons ^[13]. The risk of tumour understaging by initial TURB was discovered by investigation of cystectomy specimens. It is known that as much as 40% of clinically T1 tumours are upstaged to pathologic muscle-invasive disease ^[18]. The most important risk factor of T1 tumour understaging is absence of muscle in the tissue obtained by TURBT ^[14,16,17]. Unfortunately, the muscularis propria is missing in 30–50% of submitted specimens ^[37–39]. The presence of detrusor muscle in resected tissue is today considered the most important surrogate marker indicating a complete TURBT ^[15,20].

Patients and Methods

From January 2009 to May 2010, 50 patients with newly diagnosed ca bladder, of theme 36 male and 14 female, their age ranging between 47 to 80 years with a mean of 63.5 years. Forty four (88 %) patients presented with intermittent

haematuria which was painless in 38 patients (76 %) and painful in 6 patients (12 %) . Irritative voiding symptoms was the presenting complaint in 6 patients (12 %) . On examination the most common finding was pallor which was presented in 10 patients (20 %) All patients underwent the following investigations: 1-GUE. 2- abdominal us.3- Hb. 4- blood urea and serum creatinine.5-CXR and6-ECG. **The inclusion criteria were:** (a) new tumors that were diagnosed.(b) tumors determined to have been completely resected by the operating surgeon. After TURBT all patients received a 6-wk course of an intravesical instillation of Mitomycin C (40 mg) started after the result of the histopathology usually within the first week of operation. All patients had a cystoscopy at 3 months following first TURBT, with recurrences confirmed by subsequent biopsy and/or resection. **The following exclusion criteria were used:** patients for whom the surgeon documented “incomplete resection” or felt that biopsy alone was adequate.patients with tumours that were histologically considered to be muscle invasive patients who not received postoperative Mitomycin C. patients who did not have follow-up cystoscopy by 3 months.

Operative technique : Anesthesia.

All of our patients underwent the surgery under general anesthesia with muscle relaxant.**Bimanual palpation.** Bimanual palpation of the bladder under anesthesia before and after TURBT done in all patients.

Urethrocystoscopy The procedure begins with a careful urethrocystoscopic examination of the entire urethra during insertion of the cystoscope. Subsequently, all areas of the bladder are inspected using 30 degree lens. The size (by comparison with the diameter of the resection

loop), number, and location of tumours as well as regions of erythema and mucosal abnormalities suggestive of CIS, all these findings were documented in a diagram immediately after the procedure. **Irrigant fluid.** We use a 10 % mannitol as an irrigant fluid (Glycine not available in our center) at a height of about 65 cm and continuous irrigation. **Tumour resection.** After perfect cystoscopic evaluation of the entire urinary bladder a we insert 24 Fr. Storz resectoscope with 30 degree lens. The resection started from the top of the tumour toward its base in an antegrade direction. After complete resection of the macroscopic tumor we try to resect piece from the base of the tumour separately and sent the 2 sample in a separate container for histopathological study.**Completion of transurethral resection of the bladder** Careful haemostasis is obtained by fulguration of resected areas using a roller ball electrode. The procedure is finished by doing bimanual examination of the bladder and finally insertion of 22 or 24 Fr. 3 ways Folly's catheter. One pathologist reviewed our pathology database and obtained information on tumour grade, tumour stage, and DM status (i.e. absent or present). We used a combination of the 1973 World Health Organization (WHO) and 2004 WHO–International Society of Urological Pathology grading systems on all reports in our institution, and for description and/or analysis in this study, we used the 1973 WHO grading system. Pathologic T stage was defined using the 2002 TNM classification.

For purposes of data and/or statistical analysis, the following assumptions and principles were used: large tumour was defined as tumour size >30 mm or specified as “large” by the surgeon; small tumour was defined as tumour size ≤30 mm or specified as “small” or “moderate”

by the surgeon; multiple tumours was defined as more than one tumour at presentation; recurrence was defined as a pathologically confirmed tumour and/or lesion; RR-FFC included recurrence at the first follow-up cystoscopy; and absence of early recurrence defined a good-quality resection.

Results

From January 2009 to May 2010, 50 patients with newly diagnosed bladder tumour of theme 36 male(72%) and 14 female(28%) , their age ranging between 47 to 80 years with a mean of 63.5 years. Table No. (1) By ultrasound tumour size was less than 3 cm in 38 pt (74%). and more than 3 cm in 12 patients. (26 %), the tumour was single in 42 patients (84 %), and multiple (more than 1) in 8 patients (16 %).Table No. (2.) DM was present in TURBT specimens in 41 patients (82 %) while it was absent in 9 patients (18 %) Table No (3) . Of those deemed suitable for FFC analysis, 36 patients (72 %) had first follow-up cystoscopy at 3 months and were negative(no recurrence) , while the remaining 14 patients(28 %) had re-TURBT. Table No. (4) The absence and presence of DM were associated with RR-FFC of 55.5% and 21.9 %, respectively . Table No.(4) In large tumours (> 3 cm), the absence and presence of DM were associated

with early recurrence rates of 50 % and 30 %, respectively, while in small to moderate tumour ($\leq 3\text{cm}$) the absence and presence of DM were associated with early recurrence rates of 57.1 % and 19.3 % respectively . Sub analyses by tumour grade and stage revealed that, in patients with G1 the absence and presence of DM were associated with early recurrence rates of 50 % and 25 % respectively and in G3 tumours, the risk of early recurrence was 75 % in the absence of DM, compared with 33.3 % when DM was present. Table No.(4) In patient with stage Ta the recurrence rate was 50 % in the absence of detrusor muscle compared with 16 % when it is present . The recurrence rate was 66.6 % versus 25 % in absence and presence of DM respectively . Table No.(4) In patients with single tumour the recurrence rate was clearly higher when DM absent than when it is present and this is also true for patient with multiple tumours . Table No (4) The present study had 3 extraperitoneal bladder perforation. All perforations were managed conservatively by leaving an indwelling catheter in place a little longer (10 days) , with few detrimental consequences. We also reported 5 patients of excessive bleeding but all of these patient controlled intraoperatively and no patient require blood transfusion. Table No.(5)

(Table No. 1) Patient characteristics, at the time of first transurethral resection of bladder tumors (TURBT).

Variable	No.	(%)
Total patients No.	50	100
Patients average age	63.5 years	
Gender		
male	36	72
Female	14	28

Presentation Haematuria		
Painless	38	76
Painful	6	12
Irritative voiding symptoms	6	12

(Table No. 2) tumor characteristics, at the time of first transurethral resection of bladder tumors

Variable	No.	(%)
Tumor size		
Small to moderate ($\leq 3\text{cm}$)	38	74
Large ($> 3\text{ cm}$)	12	26
Tumor multiplicity		
Single	42	84
Multiple	8	16
Primary Grade (WHO. 1973)		
G1	12	24
G2	13	26
G3	25	50
Primary stage		
Ta	35	70
T1	15	30

(Table No.3) Presence and absence of detrusror muscle in relation to tumor size , number , grade and stage.

Variable	Detrusor Present (No. 41)		Detrusor Absent (No. 9)	
	No.	(%)	No.	(%)
Tumor size				
Small to moderate (≤ 3cm)	31	62	7	14
Large (> 3 cm)	10	20	2	4
Tumor multiplicity				
Single	38	76	4	8
Multiple	3	6	5	10
Primary Grade (WHO. 1973)				
G1	8	16	4	8
G2	12	24	1	2
G3	21	42	4	8
Primary stage				
Ta	25	50	6	12
T1	16	32	3	6

(Table No. 4) Early recurrence in the first follow-upCystoscopy

Variable	Early recurrence Detrusor Present		Early recurrence Detrusor Absent	
	No.	(%)	No.	(%)
Tumor size				
Small to moderate (≤ 3cm)	6	19.3	4	57.1
Large (> 3 cm)	3	30	1	50
Tumor multiplicity				
Single	8	21	2	50
Multiple	1	33.3	3	60
Primary Grade (WHO. 1973)				
G1	2	25	2	50
G2
G3	7	33.3	3	75
Primary stage				
Ta	4	16	3	50
T1	5	31.25	2	66.6
Overall Recurrence	21.9		55.5	
Total Recurrence	28%			

Table No. 5 Complications of TURBT

Complications	No.	(%)
Bleeding	5	10
Perforation	3	6

Discussion

Recurrence rate in the first follow up cystoscopy, an important prognostic marker for subsequent recurrence, has been suggested to vary according to the quality of the resection [5]. Findings from the current study reveal that this hitherto subjective quality can possibly be measured by the ability or inability to resect DM at the first TURBT when the tumour otherwise appears to be completely resected Herr and Donat have recently found that the quality of TURBT can be measured by determining completeness of resection, ability to obtain DM in the resection specimen, and recurrence at the resection site [9]. The ability to resect DM in the first TURBT specimen cannot be overemphasized in terms of establishing accurate pathologic staging to determine prognosis and plan subsequent management. Our pathologists prefer to report the stage as pTx when DM is absent, especially when the tumour extends to the lamina propria (ie, at least pT1), stressing the need for a further staging resection. Herr [14] documented an overall rate of absence of DM in 15.3% of initial resections. Similarly, the series by Dutta et al [15] identified absence of DM. in 25 % of his specimens . The

overall absence of DM. in our study was about 18 % Regardless of DM status, re-resection after initial TURBT is becoming established as the standard of care when high grade tumours or T1 tumours are identified [16,17] to ensure complete clearance and to establish accurate pathologic stage.

In a retrospective analysis, Herr [14] found recurrent disease in 31.6% and 51.7%, of Ta tumours and in 54 % and 71 % in T1 tumours with DM absent and present respectively The present study demonstrate 16 % recurrence rate for Ta and 31.25 % for T1 disease when DM. present . When DM. absent the recurrence rate were 50 % and 66.6 % for Ta and T1 disease respectively. The lower recurrence rate in our study can be due to smaller total number of patients in addition to higher percent of patients with small size tumour i.e. $\leq 3\text{cm}$. Grimm et al [6] retrospectively identified overall recurrent disease at re-TURBT in 21% of their patients with G1 tumour; this rate increased to 67 % in G3 tumours when DM. is present . In the present study the recurrence rate was 25 % when DM. present and 50 % when it was absent in G1 tumour; this rate increase to 33.3 % and 75 % for G3 tumour .

Grimm et al ^[6] also demonstrated on univariate analysis that stage and grade of tumour predicted residual disease, a feature we identified as well. Although deep resection in T1 tumours is essential to reducing the risk of residual disease, our study confirms the importance of resecting DM even in the lower to moderate-grade noninvasive disease. We found that the presence of DM in smaller tumour resections was associated with a lower risk of early recurrence. Deliberate deep resections can potentially result in bladder perforations. Our study had 3 extraperitoneal bladder perforation. All perforations were managed conservatively by leaving an indwelling catheter in place a little longer (10 days) , with few detrimental consequences. We also reported 5 patients of excessive bleeding but all of these patients controlled intraoperatively and no patient require blood transfusion. Despite our department's policy to obtain DM by resecting the tumour base in all resections regardless of size, there is a possibility that this may not have been the case in some of the smaller bladder tumours.

Conclusions

This study demonstrates that absence of DM in the first apparently complete, TURBT appear to be independently associated with an increased risk of early recurrence. This finding suggests that DM in the specimen can be used as a surrogate marker of TURBT quality, also the first follow up cystoscopy in those patients with absent Detrusor muscle in the first resection should be done within shorter period .

Recommendations

The number of patients in this study appears to be small and larger number is needed for validation of the results.

The ability to stage tumours accurately and to clear all macroscopic disease depends on the surgeon's experience and the surgeon's confidence in resecting widely enough and deeply enough to obtain DM (muscularis propria) whilst ensuring technical safety . So a study comparing the result of a consultant surgeon and registrar or resident surgeon is essential to be included in a similar study. Other factors that may affect the quality and safety of resection are the sex of the patient and the site of the tumour which need to be included in the future studies. The first follow up cystoscopy in those patients with absent detrusor muscle in the first resection should be done within shorter period , this period need to be evaluated in a future study.

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