

TURBT for Treatment of Recurrent High Risk Superficial or Muscle-Invasive Bladder Tumours: Factors Contributing to T0 Radical Cystectomy Specimens

Sz. Lukacs¹, G. Athanasiadis¹, N. Gibbons¹, D. Hrouda¹, E. Mazaris¹

¹Charing Cross Hospital Imperial College Healthcare NHS Trust, FulhamPalace Rd, London W6 8RF, United Kingdom.

evmazaris@yahoo.gr

***Corresponding Author:** Mr. Evangelos Mazaris, Urology Department Hinchingsbrooke Hospital, Hinchingsbrooke Park, Huntingdon PE29 6NT, UK.

Abstract

Objective: To identify factors that could potentially result in a final pathology stage pT0 after radical cystectomy, with the aim to promote bladder preservation techniques for certain patients with recurrent high grade superficial or muscle invasive bladder cancer.

Materials and Methods: 250 patients underwent radical cystectomy in our institution over 7 years (January 2006-December 2012). A thorough analysis of the patients' files with no residual tumour on the cystectomy specimen (pT0) was performed. Possible factors contributing to such a result were described within a detailed literature review context.

Results: Overall fourteen (5.6%) patients had a pT0 stage after radical cystectomy. Twelve patients had transitional cell carcinoma (one with squamous and one with sarcomatoid differentiation). One patient had squamous cell carcinoma and another had adenocarcinoma of the bladder. None of the tumours presented lymphovascular invasion on the transurethral resection specimen. All fourteen patients are still alive with no signs of recurrence. Four factors were predominant in all our T0 cystectomy patients.

Conclusion: We identified four independent factors which potentially could have contributed towards a pT0 cystectomy result. These included the completeness of transurethral resection, the experience of the surgeon, the application of a standardized technique for transurethral resection and the absence of lymphovascular invasion on the TURBT specimen.

Keywords: transurethral resection of bladder; cystectomy; urinary bladder neoplasm.

INTRODUCTION

It is well established and known that radical cystectomy (RC) with pelvic lymph node dissection is the gold standard treatment for muscle invasive bladder cancer (MIBC) as well as recurrent high risk superficial bladder cancer recommended by urological societies around the world [1]. However in about 76% of patients there is discrepancy between the initial clinical stage (cT-stage) at the transurethral resection of the bladder tumour (TURBT) and the final pathology (pT-stage) after RC [2]. Literature shows that clinical overstaging occurs in 20-27% [2, 3] while understaging which is more common as

reported in 40-49% of RC [2, 4]. Factors which may be responsible for such a difference could be the results of poor sensitivity of current imaging techniques, incomplete TURBT with under sampling of muscle tissue or long interval between TURBT and RC [5, 6]. Tumour downstaging from MIBC at TURBT to non-MIBC at RC is reported multiple times, the effect of downstaging on prognosis is considerable and most of the studies reported excellent long-term survival rates [2, 3, 7-10], although one study reported no survival advantage [11]. The inclusion of patients treated with neoadjuvant chemotherapy (NAC) and/or radiotherapy [3,8,10,11] complicates the interpretation of the results of these studies.

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As radical cystectomy is a procedure with considerable amount of mortality and morbidity and an altered quality of life [12], therefore it seems logical that we should continuously aim to identify factors, which could contribute to downstaging the disease. Our aim was to perform a systematic analysis in our RC series (our center covers over 4 million patients as a tertiary referral center of North-West London) to identify factors that could potentially result in a final pathology stage pT0 after radical cystectomy with the aim to promote bladder preservation techniques for certain patients with recurrent high grade superficial or muscle invasive bladder cancer.

MATERIAL AND METHODS

In our retrospective review of the final pathology results of 250 patients who underwent radical cystectomy performed in our institution over seven years (January 2006 until December 2012), fourteen patients were identified with a pT0 radical cystectomy specimen. Case notes including operation notes of the patients were reviewed thoroughly by two independent reviewers. Emphasis was placed during review of the notes on initial and the final TURBT pathology specimen, details of the operation, experience of the surgeon performing it, whether any neo-adjuvant treatment (chemotherapy) was used etc. All the fourteen patients' histology results were re-discussed with the histology department by a senior uro-pathologist different from the ones who performed the initial pathology examination, furthermore all patients were reviewed during a follow-up clinic to assess recurrence and post operative complications.

Detailed literature review was performed (all articles in PubMed were searched including non-English publications using key words such as 'pT0 radical cystectomy' 'stage pT0 bladder cancer') etc. to identify possible contributing factors which might lead to such favourable cystectomy result.

RESULTS

In our series fourteen patients (5.6%) out of 250 who underwent a radical cystectomy for bladder cancer had a final pathology stage of pT0, virtually no residual cancer reported in the specimen. Demographically

eight men and six women with a mean age of 68.42 years (Table 1). In all patients neither preoperative radiological assessment (CT chest and CT urogram), nor post-operative bilateral lymph node dissection revealed signs of metastasis. Twelve patients (85%) had transitional cell carcinoma (TCC) (one with squamous and the other with sarcomatoid differentiation) (Table 2). One patient had squamous cell carcinoma (SCC) on a background of schistosomiasis proven on histology and one had adenocarcinoma of the bladder. Documented macroscopic size of the TURBT tumour ranged from 5mm to 34 mm. One patient had lymphovascular invasion on the initial resection however none of the bladder tumours presented lymphovascular invasion on the pre-cystectomy transurethral resection specimen. Four patients (28.6%) had multiple TURBTs (range for example 2 to 3 resections) before cystectomy and ten patients (71.4%) had only one transurethral resection of their bladder tumour. Operative notes revealed that all final TURBTs before cystectomy were performed by a Consultant with a high level of experience and they all reported complete tumour resection macroscopically with additional deep muscle biopsies from the tumour bed. The time from the final TURBT to radical cystectomy ranged from 30 to 60 days, except one patient (150 days) as a result of 3 cycles of neoadjuvant chemotherapy. Two patients had neoadjuvant chemotherapy (3 cycles) and one patient has undergone an induction course of BCG and one instillation of maintenance BCG before opting for cystectomy. Follow up after cystectomy ranged from 8 months to 79 months. All fourteen patients are still alive with no cancer recurrence clinically and radiologically on follow up CT scans.

In terms of the number of bladder lesions per patient, 5 patients had multifocal, 9 patients had a single tumour. There was no correlation whether the tumour was unifocal or multifocal with the final pT0 histology results, however most of the multifocal tumours underwent multiple TURBTs before cystectomy (3 of the 5 multifocal and only 1 of the 9 unifocal underwent multiple TURBTs).

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Table 1. Demographic details of the T0 Radical cystectomy patients

Gender	Age at cystectomy	Co-morbidities	Timescale of follow up (months)	Post operative complications
F	62	Hypertension	10	Nephrostomy and JJ stent on the left post op 3/52 and UTI
F	63	Total knee replacement, rectopexy, arthroscopies	10	No complication
M	77	COPD, hypercholesterimaemia, Hypertension, 3.4cm AAA	11	No complication
M	57	Type 2 diabetes mellitus, hypertension Hypercholesterinaemia,	11	Laparotomy, reimplation of both ureters-6months post-op due to uretero-ileal stenosis
M	69	Myocardial infarction, Sciatica, 3X cardiac stents, COPD, atrial fibrillation	13	Incisional hernia repair 6 months, and aspiration of lymphocele
F	75	Hypothyroidism, hypertension, Hyperchloesterianemia	15	No complication
F	73	Hypertension, Left open nephrectomy 1978 open cystolithotomyfor bladder stones 1978	27	Mild wound dehiscence
M	65	Hypercholesterineamia	42	Wound infection treated with antibiotics
M	57	Hypertension, Asthma	52	Wound infection and small leak from neobaldder
M	78	Hypercholesterineamia, Hypertension, Gout	51	No complication
M	73	Hypercholesterineamia, Hypertension, IHD	55	No complication
F	80	Hypertension, previous appendicitis	68	Wound infection
M	69	Type 2 diabetes mellitus, Hypercholesterineamia	67	Bowel adhesions, conservative management
F	60	Asthma, Type 2 diabetes mellitus, Hypertension, Hypercholesterianaia, Ischemic heart disease, TCC G2Pta 2 years	79	No complication

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Table 2. *Initial and pre-cystectomy TURBT histology results of our series*

Patient Number	First TURBT pathology result	Neoadjuvant chemotherapy	Time to cystectomy from last resection (months)	Size of TURBT final tumour (mm)	unifocal	Number of resection before RC	Last histology before RC
1	G3 pT2 at least	Nil	2	34X1.6 on CT	Y	1	G3 pT2
2	G3 pT2 at least TCC with glandular and sarcomatoid differentiation involving left UO resected	Nil	1	26 on MRI	Y	1	G3 pT2
3	G3 pT2	Nil	2	Dome 18 on CT	Y	1	G3 pT2
4	G3 pT1 and CIS	Nil	1	15 on cystoscopy	N	2	G3 pT1+CIS
5	G2/3 pT2 with squamous differentiation	Nil	1	14 and 2 on cystoscopy	N	2	G2/3 T2 with squamous differentiation Nil Lymphovascular invasion
6	G3 pTa multifocal	induction BCG and 1 maintenance	2	12 and 7 on cystoscopy	N	2	G3 pTa multifocal
7	G3 pT2a multifocal and CIS	Nil	1	7 and 4 on cystoscopy	N	1	
8	G3 pT2 re-resection G1 Pt1	SPARE trial neoadjuvantchemo +radiotherapy)	2	7mm and 4mm on cystoscopy	Y	3	(1st resection G3PT2 re-resection G1 pT1,SPARE trial T0, biopsy failed 3rd re-resection G3pT1c+CIS)
9	G3 pT2	3 cycles of neoadjuvant chemotherapy	5	28 on CT	Y	1	last biopsy T0 after Chemo
10	G3 pt2 and CIS	Nil	1	15 on cystoscopy	Y	1	G3 pT2 and CIS
11	G2 pT2	Nil	2	2.5 on CT	Y	1	G2 pT2
12	Sarcomatoid bladder TCC	Nil	1	3.2 on CT	Y	1	Sarcomatoid bladder TCC
13	G2 pT2 adenocarcinoma	Nil	2	22 and small 3mm on CT	N	1	G2 pT2
14	G3pT1 Keratinizing Squamous cell	Nil	1	12 on cystoscopy	Y	1	Keratinizing Squamous cell

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Abbreviations

RC: radical cystectomy

MIBC: muscle-invasive bladder cancer

TURBT: transurethral resection of bladder tumour

TCC: transition cell carcinoma

SCC: squamous cell carcinoma

NAC: Neo-adjuvant chemotherapy

DISCUSSION

There is an increased demand in society towards the development of new techniques to improve cancer prognosis and increase cancer free and overall survival. Radical cystectomy is so far the best option to achieve these goals however it involves a major operation with urinary diversion which has high mortality and morbidity and deterioration in quality of life [12]. Our aim was to investigate those patients who underwent a cystectomy with favourable histological results of pT0 to try to identify possible factors which might be the cornerstone of a new bladder preservation strategy for muscle invasive or recurrent high risk superficial bladder cancer.

Our series of pT0 cystectomies indicated a few factors, which might have contributed to these results. Herr [13] found a 10-year disease-specific survival of cT2 patients who were treated with re-TURBT of 76% (57% had eventually their bladder preserved) compared with 71% for those who had immediate radical cystectomy.

One of the factors which was present in all patients and possibly contributed to pT0 specimen was the macroscopically reported complete resection reported by the surgeon. It has been suggested in other studies [14-16] that a thorough and complete TURBT may be warranted in most patients who have even got an appearance of invasive tumour as when re-evaluating with a re-TURBT they may be candidates for bladder preservation especially if no residual tumour is present. As others [17] have suggested a radical TURBT is probably not causative of the improved cancer-specific survival in pT0 cystectomy patients but rather individual tumour characteristics allow for complete tumour eradication like small tumour size, unifocality and stage T2a.

Another factor is the absence of lymphovascular invasion on the TURBT - even in a relatively large 2-3cm tumour - specimen which seemed to be consistently associated with a final pT0 radical cystectomy results in our series. Previously the role of lymphovascular invasion was described as an independent factor of advanced tumour stage, grade and shorter overall and recurrence-free survival [18].

A possible source of bias for two of our patients who received neo-adjuvant chemotherapy as part of the SPARE trial might have contributed to a final pT0 cystectomy result however, we have to take into account that chemotherapy is a non-invasive treatment and may consist part of a multimodality approach for bladder-preserving techniques. It was demonstrated in a previous study [19] that the prognostic significance achieving a pT0 stage on final RC specimen is independent of whether this was achieved by means of TURBT or neo-adjuvant chemotherapy. Also in this study they achieved a 15% pT0 rate at radical cystectomy with only TURBT, while neoadjuvant chemotherapy and TURBT achieved a 38% pT0 rate respectively. Others [7] claimed that neoadjuvant chemotherapy is not beneficial or necessary for downstaged cT2 tumours to pT0 by previous TURBT. Interestingly another study [20] supported that patients who are pT0 after neoadjuvant chemotherapy are at higher risk of disease recurrence compared with those who achieve pT0 with TURBT alone (the explanation was that an increased number of non-organ confined clinical stage was selected for chemotherapy in the study).

In terms of the optimal timing of the cystectomy it has been found from studies that delay >90 days for cystectomy is unfavourable [21] regarding prognosis. This was confirmed in our series as the time from the final TURBT to radical cystectomy ranged from 30 days to 60 days in 93% of the patients, except in one patient (150 days) as a result of 3 cycles of neoadjuvant chemotherapy. It seems that in twelve of our patients the TURBT cleared the tumour and in two more the addition of neo-adjuvant chemotherapy either consolidated such a result or eradicated any residual tumour.

Other factors that have been mentioned in a study [22] which are associated with a worse outcome for pT0 cystectomy patients were female gender and

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patients with nodal spread, however, these could not be assessed in our series. We have 2 patients who had initial concomitant CIS with TCC which was treated with cystodiathermy and loop resection, and one of these patients received BCG treatment. A study suggests that the presence of concomitant carcinoma in situ is associated with disease progression but could be treated with intravesical BCG and closer follow-up [23].

Another factor which might play a role is the experience of the surgeon performing the TURBT. All our patients were operated by experienced surgeons (>100 procedures) and a standardized procedure was performed with the aim of completely removing the whole tumour including deep resection and also biopsy of its base with muscle included. The base was then thoroughly diathermised with a roleyball. It has been suggested that a 'radical' transurethral resection is justified when the tumour is clinically limited to the muscular layer and when all biopsies of the periphery and the base of the tumour are negative of further muscular invasion [23]. In a study this offered an 80.5% cancer-specific survival in 5 years with a bladder preservation rate of 82.7% [23].

There are a number of options already available for bladder sparing techniques including re-TURBTs [13], the use of chemotherapy and/or radiotherapy and also the use of re-TURBT with adjuvant radiotherapy and laparoscopic lymphadenectomy for high risk tumours (Grade 2 or 3) [24]. Interesting and very important multi-institutional trial (SPARE trial) comparing selective bladder preservation versus radical excision was abandoned in 2010 due to poor accrual [25]. However other trials such as RTOG (TURBT followed by induction and consolidation chemoradiotherapy) showed a more than 65% 5-year survival rates for those who had their bladder preserved [26].

The limitations of our study are that the number of patients representing a single institution is obviously small to extract valid statistical results but our aim was to identify in our series possible factors that would be worth investigating in a multi-institutional setting in order to increase validity. With the SPARE trial stopped the urologic community is in urgent need of similar large scale prospective trials.

CONCLUSION

Four factors were identified in our study, which potentially may contribute to final pT0 histology. Complete resection of the tumour on TRUBT, absence of lymphovascular invasion on the final TURBT specimen, surgeon experience and adherence to standardized techniques according to guidelines. We are hoping that with this article we would be able to trigger a constructive debate and further research toward bladder preservation technique to improve patient care and quality of life. All these issues need to be clarified by the urologic community by designing and conducting multi-institutional randomized studies.

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Citation: Sz. Lukacs, G. Athanasiadis, N. Gibbons, D. Hrouda, E. Mazaris. *TURBT for Treatment of Recurrent High Risk Superficial or Muscle-Invasive Bladder Tumours: Factors Contributing to T0 Radical Cystectomy Specimens. Archives of Urology. 2018; 1(1): 9-16.*

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