



Is TURBT able to cure high risk recurrent superficial or muscle invasive bladder cancer: Factors resulting in pT0 radical cystectomy specimens

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ABSTRACT

Purpose: In 76% of radical cystectomy patients there is discrepancy between the initial stage at transurethral resection and the final pathological stage of the cystectomy specimen. More specifically in contemporary series the absence of tumor at radical cystectomy specimens (stage pT0) is estimated at 5-25%. Our aim was to determine which factors contributed to the absence of tumor in our series of radical cystectomy patients.

Materials and Methods: Fifty one patients were submitted to radical cystectomy in our department over the last 10 years (January 2002-January 2012). A thorough analysis of the patients' files with no residual tumor on the cystectomy specimen (pT0) was performed. Possible factors contributing to such a result were described and a systematic analysis of the relevant literature was performed.

Results: Five patients had a pT0 stage after radical cystectomy. Four of them had transitional cell carcinoma and one of them had squamous cell carcinoma of the bladder on the initial transurethral resection. None of the tumors presented lymphovascular invasion. Four patients are still alive and one died 45 months postoperatively from a cardiac cause.

Conclusions: Four factors were identified in our study to contribute towards a pT0 cystectomy result. Those included the absence of lymphovascular invasion, the completeness of transurethral resection, the experience of the surgeon and the use of a standardized technique for the transurethral resection. The time to cystectomy in our series did not have a negative effect on pT0 final pathology result.

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INTRODUCTION

Radical cystectomy (RC) with pelvic lymph node dissection is the gold standard for treatment of muscle invasive bladder cancer (MIBC) as well as high risk superficial bladder cancer. In about 76% of patients there is discrepancy between the initial clinical T-stage (cT-stage) at transurethral resection of the bladder tumor (TURBT) and the final pathology (pT-stage) after RC (1). Factors that may be responsible for such discrepancy may be

poor sensitivity of current image exams, incomplete TURBT with undersampling of muscle tissue or a long interval between TURBT and RC (2,3). Clinical understaging of the tumor is reported in 40-49% of RC (1,4) while clinical overstaging occurs in 20-27% of RC (1,5). Up to 30% of patients with MIBC at the time of TURBT have non-MIBC at RC specimen (5).

There are several reports on the effect on prognosis of tumor downstaging from MIBC at TURBT to non-MIBC at RC. Although one study

reported no survival advantage (6) most of them reported excellent long-term survival rates for patients with tumor downstaging (1,5,7-11). The inclusion of patients who have been treated with neoadjuvant chemotherapy (NAC) and/or radiotherapy (5,6,8,10) complicates the interpretation of the results of these studies.

Our aim was to perform an analysis in our series (our center is a regional cancer center covering a population over 2 million) of radical cystectomies in order to determine which factors caused downstaging and particularly the absence of tumor at radical cystectomy. That obviously means that such tumors were in fact cured by just a TURBT from a surgical perspective.

MATERIALS AND METHODS

We retrospectively reviewed the final pathological result of all 51 radical cystectomies performed in our institution over the last 10 years (January 2002 until January 2012). Five pT0 radical cystectomies were discovered while patient and operative notes were thoroughly reviewed by two reviewers. Emphasis was placed when reviewing the notes on the initial TURBT pathology specimen, the surgeon who performed the TURBT and the details of the operation, whether any neo-adjuvant treatment (e.g. chemotherapy) was administered etc. Special attention was placed on the TURBT pathology specimen and thorough re-discussion with an uro-pathologist about all specimens was done. Factors that might have contributed to a pT0 cystectomy specimen were disclosed and a systematic review of the available literature (all articles in PubMed were searched including non-English publications using the keyword 'pT0 radical cystectomy') was performed in order to present possible factors leading to such favorable cystectomy specimens.

RESULTS

Five patients in our series (Table-1) submitted to radical cystectomy for bladder cancer had a final pathological stage of pT0 (no residual tumor). In all patients neither preoperative work-up (chest and computed tomography urogram) nor post-operative full lymph node dissection revealed any

lymph node or metastatic spread. Four TURBT specimens were transitional cell carcinomas (TCC) and one was squamous cell carcinoma (SCC). The estimated macroscopic size of the TURBT tumor ranged from 5 mm to 4 cm. All operative notes from the TURBT reported a complete macroscopic clearance of the tumor with deep resection and additional biopsies from the tumor bed. No lymphovascular invasion was noted in none of the TURBT specimens. All the TURBTs were performed by two experienced senior urologists and the radical cystectomies were performed by 2 urological surgeons. The time from TURBT to radical cystectomy ranged from 120-210 days. Neo-adjuvant chemotherapy was administered to two patients. Follow-up after cystectomy ranged from 6 months to 69 months. Four patients are doing very well on follow-up. One died 45 months after the operation from other cause (cardiac event) and had no cancer recurrence.

The literature review resulted in 11 articles (Table-2) after excluding case reports and small series as well as irrelevant publications and duplicates.

DISCUSSION

Our series of pT0 radical cystectomies indicated a few factors that may be contributing to such a result (no tumor found on final cystectomy specimen). Obviously it would be very important to know if there are factors after a TURBT that should prompt treatment with bladder preservation strategies for muscle invasive or recurrent high risk superficial bladder cancer. This would obviously prevent patients from having a major operation like a radical cystectomy with urinary diversion, which have high morbidity and a deterioration in the quality of life. Herr (12) 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. Although initially an older study (6) found no advantage in cancer-specific survival for pT0 cystectomy patients (the study had low number of patients to draw statistically valid results) all subsequent studies (Table-2) have shown an advantage in recurrence-free survival or cancer-specific survival.

Table 1 - Our series of pT0 radical cystectomies.

Patient (Male/Female)	Age at cystectomy	Co-morbidities/ Smoking	TURBT pathology/size	Neoadjuvant chemotherapy	Time to cystectomy (days)	Follow-up / Recurrence
1-Male	65	Hypertension	G2-3 cT2 TCC with no lymphovascular invasion (41 gm resected tissue)/4cm on MRI scan	Yes	162	9 months doing well
2-Female	71	Abdominal aortic aneurysm, myocardial infarction/Heavy smoker	G2 cT2 SCC with no lymphovascular invasion/3cm on cystoscopy calcified lesion	No	120	45 months post-op died from other cause (cardiac)
3-Male	76	Non-smoker	G2-3 cT2a at least with no lymphovascular invasion and tumour necrosis/3.5cm on CT scan	No	100	6 months doing well
4-Male	69	Hypertension	Recurrent G3 cT1 and CIS (no lymphovascular invasion)/ Failed intravesical therapy	No	125	68 months doing well
5-Male	80	Atrial flutter ablated, poor performance status	G3 cT2 (no lymphovascular invasion)/ quite small on cystoscopy 5mm	Yes	210	24 months doing well

It seems that a macroscopic complete resection as reported by the surgeon in the operative notes was a factor contributing to a pT0 specimen. It has been suggested in other studies (11,13) that a thorough and complete TURBT may be warranted in most patients who have even got an appearance of invasive tumor as when re-evaluating with a re-TURBT they may be candidates for bladder preservation especially if no residual tumor is present. Furthermore, a study (9) confirmed that patients with a cT2a tumor stage on TURBT had significantly better cancer-specific survival when a pT0 stage was achieved at RC (with the use of

neo-adjuvant chemotherapy) compared with those who had residual cancer on RC. As others (14) have suggested a radical TURBT is probably not causative of the improved cancer-specific survival in pT0 cystectomy patients but rather individual tumor characteristics allow for complete tumor eradication, including small tumor size, unifocality and stage T2a.

Another factor that was evident, even in large tumors measuring 3-4 cm, was the absence of lymphovascular invasion which seemed to consistently produce final pT0 radical cystectomy specimens in our series. Another study (15) has

Table 2 - Series pT0 cystectomy patients.

Author	No. of pT0	Total No. of cystectomy patients	Neoadjuvant Chemotherapy (NAC)	Neoadjuvant Radiotherapy	Staging TURBT Pathology	Median Follow Up (months)	CSS / DSS	OS	RFS
Van Dijk PR et al. (13)	62	375	--	--	--	92	93.9% (5-year)	--	91.9% (5-year)
Kassouf W et al. (15)	120	1104	Yes(77)	--	cT1 (21), cT2 (65), cT3b (20), cT4a (11), cT4b (3)	32	88% (5-year)	84% (5-year)	84% (5-year)
Chromecki TF et al. (17)	433	5018	Yes(41)	--	--	46 (TUR-alone) 34 (NAC)	--	--	87.2% (TUR-alone) 75.6% (NAC)
May M et al. (14)	132	2403	--	--	cTa (5), cTis (9), cT1 (39), cT2 (79)	53 (mean)	92% (5-year)	75% (5-year)	--
Iriarte AL et al. (11)	20	153	--	--	T2 G3 (80%), T2G2 (10%), T1G3 (5%), Tis (5%)	24 (mean)	75%	--	65%
Kaag MG et al. (23)	24	1905	Yes (24)	--	--	27	--	--	100%
Palapattu GS et al. (10)	59	888	Yes (8)	Yes (2)	cTis (9%), cTa (4%), cT1 (32%), cT2 (52%), cT3 (4%)	56	95% (5-year)	88%	90%
Tilki D et al. (19)	228	4430	--	--	cTa-is (13.6%), cT1 (29.8%), cT2-4a (56.2%)	48.2	93.1% (5-year)	--	89.7% (5-year)
Volkmer BG et al. (24)	181	900	--	--	Ta/Tis/ T1 (43.1%), T2a/ T2b (56.9%)	120	86.5%	65.9%	85.2%
Mateo EM et al. (25)	43	420	--	--	T1 (23.3%), T2 (72%), T3 (4.7%)/ G2 (55.8%), G3 (44.2%)	89.3	88.4%	--	83.7%
Cho KS et al. (26)		197	--	--	--	60	84.1%	--	--

also underlined the role of lymphovascular invasion as an independent factor of advanced tumor stage, grade and shorter overall and recurrence-free survival.

There was a source of bias for two of our patients who received neo-adjuvant chemotherapy and that might have contributed to a favorable 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 has been demonstrated in one study (16) that the prognostic significance of a pT0 stage is independent of whether this was achieved by means of TURBT or neo-adjuvant chemotherapy. In the same study TURBT achieved a 15% pT0 rate at radical cystectomy, while neoadjuvant chemotherapy and TURBT achieved a 38% pT0 rate respectively. Others (7) claimed that neoadjuvant chemotherapy is not necessary or beneficial for downstaged cT2 tumors to pT0 by TURBT. On the contrary, another study (17) 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 rate of non-organ confined clinical stage was selected for chemotherapy in the study).

Furthermore, it has been found from studies that delay > 90 days for cystectomy is unfavorable (18) regarding prognosis. That was not confirmed in our study since even extreme delay up to 210 days did not affect the outcome. It seems that in three of our patients the TURBT cleared the tumor and in two more the addition of neo-adjuvant chemotherapy either consolidated such a result or eradicated any residual tumor. Other factors that have been mentioned in a study (19) which are associated with a worse outcome for pT0 cystectomy patients were females and patients with nodal spread, however, these could not be assessed in our series. Also, the presence of concomitant carcinoma in situ is associated with disease progression but could be treated with intravesical BCG and closer follow-up (20).

Experience of the surgeon performing the TURBT might also play a role. All our patients were operated by experienced surgeons

(> 50 procedures) and a standardized procedure was performed with the aim of completely removing the whole tumor including deep resection and also biopsy of its base. The base was then thoroughly diathermised with a rolleyball. It has been suggested that a 'radical' transurethral resection is justified when the tumor is clinically limited to the muscular layer and when all biopsies of the periphery and the base of the tumor are negative for further muscular invasion (20). This offered an 80.5% cancer-specific survival in 5 years with a bladder preservation rate of 82.7% (20).

Bladder sparing techniques have included re-TURBTs (12), the use of chemotherapy and/or radiotherapy and also the use of re-TURBT with adjuvant radiotherapy and laparoscopic lymphadenectomy for high risk tumors (Grade 2 or 3) (21). One very important multi-institutional trial (SPARE trial) comparing selective bladder preservation versus radical excision was abandoned in 2010 due to poor accrual (22). The urological community has to learn by these mistakes and conduct relevant trials that will answer the important issue of bladder preservation.

The limitations of the study are that the number of patients is obviously small to extract valid statistical results but our aim was to identify in our series factors that would be worth investigating in a multi-institutional setting in order to increase validity. More than one surgeon performed the procedures but a standard operative technique was used as described earlier.

CONCLUSIONS

Four factors were identified in our study and could be investigated further: the absence of lymphovascular invasion and a complete resection which do have a favorable role, surgical experience and adherence to standardized techniques according to guidelines also contribute to such results. On the contrary, the time to cystectomy did not seem to have affected outcomes in our case series and that also remains to be confirmed. All these issues need to be clarified by the urologic community by designing and conducting multi-institutional randomized studies.

ACKNOWLEDGMENTS

RC = radical cystectomy
 MIBC = muscle-invasive bladder cancer
 TURBT = transurethral resection of bladder tumor
 TCC = transitional cell carcinoma
 SCC = squamous cell carcinoma
 NAC = neo-adjuvant chemotherapy

CONFLICT OF INTEREST

None declared.

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