Results of Repeat Transurethral Resection of Bladder Tumor After Macroscopically Complete Primary Resection

Resultado de Segunda Ressecção Transuretral de Neoplasia Vesical Após Ressecção Primária Macroscopicamente Completa

Miguel Eliseu*, Vera Marques, Hugo Antunes, Mário Lourenço, Edgar Tavares-da-Silva, Paulo Temido, Arnaldo Figueiredo

Abstract

Introduction: Non-muscle invasive (NMI) bladder cancers (BC) account for 75% of BC cases, and most are initially diagnosed and treated with transurethral resection of bladder tumor (TURB). After primary TURB, a repeat resection (rTURB) should be carried out in cases of incomplete resection; however, rTURB is recommended by EAU guidelines in pT1 tumors even when the completeness of the original resection is believed by the surgeon, with reported rates of residual tumor in up to 33%-55% and upstaging in up to 25%. Since the quality of initial resection impacts in the result of a rTURB, these rates are largely dependent on the primary treatment and accurate prediction of completeness, with a probable high variability between surgeons and Centres.

Our objectives to determine whether rTURB after initial perceived complete resection would frequently identify residual tumor and if this procedure would improve outcomes in NMIBC patients.

Methods: Patients submitted to TURB from 2015 to 2017 were analysed, identifying which underwent rTURB after initial resection without follow-up cystoscopy in between. Primary perception of completeness, stage and grade were correlated with the eventual presence, stage and grade of residual tumor.

Results: We analyzed 546 TURB procedures; of these, 275 (50.4%) were for primary bladder cancer. pT1 lesions were found in 85 (30.9%) of primary TURBs; 12 of these were selected for rTURB due to incomplete resection. Of the remaining 73 macroscopically completely resected primary pT1 tumors, 26 (30.6%) underwent elective rTURB.

Repeat TURB after complete resection of primary pT1 tumors yielded residual tumor in 11.5% of patients (n= 3). All patients with residual tumor had primary pT1 high grade lesions; no upstaging or upgrading was observed. Patients had similar recurrence rates at 1-year regardless of rTURB.

Discussion/Conclusion: Standard practice in primary TURB procedures varies across surgeons and centers and will reflect on residual tumor rates. Indications for rTURB might not be suitable for all patients, and single Centre results should be taken in consideration when selecting patients for rTURB.

Keywords: Neoplasm Recurrence, Local Reoperation; Urinary Bladder Neoplasms/surgery

Resumo

Introdução: *O cancro da bexiga não músculo-invasivo corresponde a 75% dos casos de cancro da bexiga, sendo que a maioria são inicialmente diagnosticados e tratados com ressecção transuretral (RTU). Depois de uma RTU primária macroscopicamente incompleta, uma segunda ressecção (reRTU); no entanto, a reRTU é recomendada pelas linhas de orientação da EAU mesmo quando a ressecção inicial é macroscopicamente completa, com taxas de neoplasia residual entre 33%-55% e* upstaging *em até 25% dos casos. Dado que a qualidade da RTU primária tem impacto significativo no resultado anatomopatológico de uma reRTU, estas taxas são largamente dependentes do tratamento primário e da acuidade de determinação intraoperatória de ressecção macroscopicamente completa, com uma provável variabilidade grande entre Centros e cirurgiões.*

Os objectivos foram averiguar se a reRTU após RTU primária macroscopicamente completa mostraria taxas de neoplasia residual significativas e se a realização deste procedimento melhoraria os resultados do tratamento do cancro da bexiga não músculo-invasivo.

Métodos: *Doentes submetidos a RTU entre 2015 e 2017 foram analisados, identificando quais realizaram reRTU planeada sem controlo cistoscópico entre as intervenções. Foi realizada correlação da percepção de RTU primária completa, estadio e grau com a presença, estadio e grau de neoplasia residual.*

Resultados: *Foram analisadas 546 RTUs; destas, 275 (50,4%) foram por neoplasia primária. Oitenta cinco doentes (30,9%) tinham pT1; destes, 12 foram seleccionados para reRTU por ressecção incompleta. Dos restantes 73 casos de pT1 primário com ressecção completa, 26 (30,6%) foram submetidos a reRTU.*

A reRTU após ressecção completa de pT1 primário mostrou neoplasia residual em 11,5% dos doentes (n=3). Todos os doentes com tumor residual tinham neoplasia primária de alto grau; não se verificou upstaging ou upgrading. A taxa de recorrência ao 1º ano foi semelhante nos doentes submetidos ou não a reRTU.

Department of Urology and Renal Transplantation, Coimbra Hospital and University Centre, Coimbra, Portugal
Serviço de Urologia e Transplantação Renal do Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

Discussão / Conclusão: *Os padrões de técnica e profundidade de RTU variam entre Centros e cirurgiões, e vão invariavelmente reflectir-se na taxa de neoplasia residual. A reRTU pode não ser benéfica para todos os casos, e dados de cada centro devem ser considerados na selecção.*

Palavras-Chave: *Neoplasias da Bexiga Urinária/cirurgia; Recidiva Local de Neoplasia; Reoperação*

Introduction

Bladder cancer (BC) is the eleventh most common malignancy worldwide (seventh in the male population).[1] Non-muscle invasive (NMI) BC accounts for 75% of BC cases,[2] and most are initially diagnosed and treated with transurethral resection (TURB). After primary TURB, depending on operative and histopathological factors, a repeat resection (rTURB) may be performed to detect and treat residual tumor, optimizing adjuvant treatments[3] and decreasing recurrence rates in some patients.[4]

Repeat TURB should clearly be carried out in cases where primary resection was perceived as incomplete; however, when the completeness of the original resection is believed by the surgeon, opinions diverge as to whether rTURB would add value as opposed to adjuvant intravesical treatment and follow-up as indicated.[4-6] The decision in these cases is based largely on tumor macro- and microscopical characteristics.

In patients undergoing rTURB, literature reports describe rates of microscopically detectable residual tumor in up to 33%--55% of primary pT1 tumors, with upstaging in up to 25% of patients.[6-10] Since the quality of initial resection is directly reflected in the result of a rTURB, these rates are largely dependent on the primary treatment and accurate prediction of completeness, with a probable high variability between surgeons and Centres.[11]

TURB procedures carry significant morbidity and costs. Complication rates, including prolonged hematuria, urinary tract infection or bladder perforation, range from 8%-16% of cases,[12] warranting unplanned hospital return and even readmission as inpatient in 4.2% of patients.[13] This burden could be lessened if unnecessary rTURBs were to be avoided.[6] Better predicting which patients bene?t from this procedure would optimize disease and resource management.

Our objectives were to retrospective analysis of population and tumor characteristics in patients undergoing rTURB after initial perceived complete resection. To determine rates of residual tumor in rTURB in different disease stages. To evaluate if submitting patients to this procedure improves outcomes in NMIBC.

Methods

We performed a cross-sectional analysis, reviewing the files of all patients submitted to TURB in our Centre from January 2015 to January 2017. All procedures were performed with similar surgical equipment. All pathology reports were done by the same team and lab throughout the period studied.

To comply with the purpose of the study, we identified which patients underwent rTURB after initial primary resection (direct decision of rTURB after pathology report, without follow-up cystoscopy); only those who underwent rTURB after a perceived complete resection were selected. Further stratification was conducted according to tumor stage, tumor grade and associated carcinoma in situ (CIS) in the primary specimen. Correlation of these factors with presence, stage and grade of residual tumor was evaluated. Recurrence rates at first cystoscopy and 1-year follow-up were analyzed for all patients. Statistical analysis was performed using SPSS 23®.

Results

We reviewed 546 TURB procedures performed in the defined period. The average age of patients was 71.21 years (SD +/- 11.92 years); 86.1% were males. Most patients had a prior history of smoking (74.4%); 1.2% of patients had a history of exposure to occupational risk factors (paint industry).

Review of tumor characteristics showed the presence of single tumor in 65.8% of cases, between two and seven tumors in 32.2% and eight or more tumors in 2%; tumor size was under 3 cm in 65.6% of cases, and over 3 cm in 34.4%; tumor morphology was more frequently papillary, occurring in 62.3% of cases; sessile tumors were found in 31.5% and both morphologies were simultaneously present in 6.2%. Associated or primary CIS was present in 12.8% of cases. Table 1 describes relevant patient and disease characteristics for the overall population.

Of all the TURB procedures, 275 (50.4%) were done as diagnosis and treatment for primary (non-recurrent) bladder cancer. pT1 lesions were found in 85 (30.9%) of primary TURBs, 12 of these (14.2%) being immediately elected for rTURB due to macroscopically incomplete resection. No patients with completely resected pTa of any tumor grade were selected for rTURB.

Of the 73 patients with primary pT1 tumors for which the surgeon had perception of complete resection, 26 (30.6%) underwent elective rTURB. This selection was not systematic or randomized, and reflects the surgeon's choice for each case (Fig. 1). Tumor characteristics of these last two groups are shown on Table 2; these show a higher number of tumors and tumor size in the patients selected for rTURB, although not statistically significant.

Repeat TURB after complete resection of primary pT1 tumors yielded residual tumor in 11.5% of patients (n= 3) (Table 3). All patients with residual tumor had initial primary pT1 high grade lesions, and no upstaging or upgrading was observed: of the three patients with residual tumor, one (3.8%) had persistent high grade pT1 and two (7.7%) had persistent CIS (Table 4).

No residual tumor was found in rTURB specimens after complete resection of low-grade pT1.

Table 1 Overall characteristics of patients and tumors subjected to TURB; frequencies represented in percentage of valid results and absolute number of cases in brackets.

Overall patient / tumor characteristics		Frequency in % (n)
Sex	Female	13.9% (76)
	Male	86.1% (470)
Number of episodes	Primary	50.4% (275)
	Recurrent disease	49.6% (271)
Number of tumors	Single	65.8% (359)
	2-7 lesions	32.2% (176)
	8 or more	2.0% (11)
Tumor size	= 3 cm	65.6% (358)
	> 3 cm	34.4% (188)
Macroscopic characteristics	Papillary	62.3% (340)
	Sessile	31.5% (172)
	Both	6.2% (34)
Tumor stage	pT0	19.2% (105)
	pTa	36.1% (197)
	pT1	26.6% (145)
	pT2	14.3% (78)
	pTis (only)	3.3% (18)
	pTx	0.5% (3)
Tumor Grade	Low grade	45.4% (199)
	High grade	54.6% (239)
CIS	Exclusively	3.3% (18)
	Associated	3.8% (21)
History of smoking	(identified)	74.4% (406)
Occupational risk factor	(identified)	1.2% (4)

Patients were counselled and offered adjuvant intravesical treatment according to the standard of care. A total of 59 (69.4%) patients with primary pT1 disease underwent induction with BCG (weekly for 6 weeks); 25.9% (n=22) completed the first year of BCG maintenance.

Follow-up was conducted throughout the first postoperative year with cystoscopy every 3 months for all pT1 patients, as well as evaluation of the upper tract with contrast-enhanced computed tomography. Four patients (5.5%) out of the 73 completely resected primary pT1 BCs did not complete the first year of follow-up (three non-cancer related deaths, one abandoned; none having been submitted to rTURB). Among the patients who completed the first year of follow-up, bladder recurrence was detected in 5 of the 26 (19.2%) patients who underwent rTURBT and in 8 of the 43 (18.6%) patients who did not ($p = 0.471$).

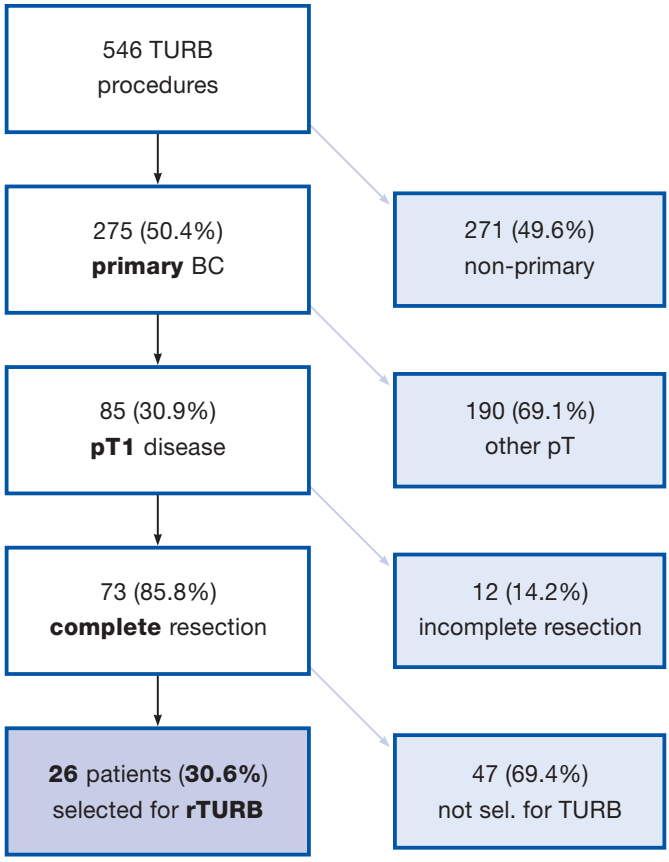

Figure 1: Selection process for analysis of primary, completely (macroscopical perception) resected pT1 tumors in planned TURB

Discussion / Conclusion

While managing NMIBC, residual tumor rates after primary TURB were significantly lower in our Centre than generally described (33%-55%), with persistent disease found in 11.5% of the cases. If we exclude the two cases of persistent CIS (both previously identified in association with pT1 disease) only 1 in 26 (3.8%) patients with primary pT1 had persistent papillary tumor after initial complete resection. While only about one-third of our patients with primary pT1 disease underwent rTURB, the ones who were selected for a second surgery presented more adverse features when compared to the ones who did not undergo rTURBT, making the possibility of a selection bias being the reason for the findings very unlikely. In fact, it was the perceived higher tumor risk that prompted the performance of the rTURBT in each case.

Standard practice in performing a primary TURB procedure varies across surgeons and Centers and it will inevitably impact on residual tumor rates.[14] Recurrences in patients not submitted to rTURB are strongly influenced by high residual tumor rates.[3,5]

Table 2 Tumor characteristics in primary pT1 tumors for which the surgeon had perception of complete resection.

Initial tumor characteristics in macroscopically complete resection of primary pT1 tumors		Selected for rTURB in % (n)	Not selected for rTURB in % (n)
Number of tumors	Single	19.2% (5)	53.2% (25)
	2-7 lesions	73.1% (19)	40.4% (19)
	8 or more	7.7% (2)	6.4% (3)
Tumor size	= 3 cm	26.9% (7)	42.6% (20)
	> 3 cm	73.1% (19)	57.4% (27)
Macroscopic characteristics	Papillary	61.5% (16)	59.6% (28)
	Sessile	30.8% (8)	38.3% (18)
	Both	7.7% (2)	2.1% (1)
Tumor Grade	Low grade	23.1% (6)	29.8% (14)
	High grade	76.9% (20)	70.2% (33)
CIS	Associated	15.4% (4)	12.8% (6)

Table 3 Tumor stage prevalence in analysis of rTURB specimens after apparent complete resection of a primary pT1 tumor.

Histology of residual tumor (rTURB)	
pT0	88.5% (23)
pTa	none
pT1	3.8% (1)
pT2	none
pTis (only)	7.7% (2)

Table 4 Synthesis of the primary and re-resection pathology results of the 3 positive cases for residual tumor

Summary of residual tumor cases	
Primary ⟶	rTURB
pT1 high grade	pT1 high grade
pT1 + CIS	CIS
pT1 + CIS	CIS

The need to perform rTURB after initial macroscopically incomplete resection of a pT1 tumor or pT1 histology with no detrusor muscle representation in the specimen is undisputable.[4,5,15] However, the assumption that all patients with primary pT1 disease should undergo rTURB merits more consideration.[5,6,10,16] Analysis of one of the largest cohorts of patients treated with BCG suggests that rTURB may only benefit pT1G3 patients without muscle in the primary specimen.[16]

Several other factors could be considered when selecting patients for different treatment modalities, namely multifocality, size and lymphovascular invasion. Substaging of pT1 disease is a promising strategy, as it seems to be feasible and a significant predictor of poor oncological outcomes in retrospective analysis; studies have proposed different substaging classification systems, either based on depth or extent of invasion,[17-19] with none proving to be definitively more accurate. Lack of orientability in pathology analysis is an important caveat of substaging pT1 BC;[17] two-layer resection or en bloc TURB could provide additional pathological information to aid in patient selection for planned rTURB,[5] possibly reducing the need for repeat surgery.[17]

In conclusion, the indication for rTURB in all primary pT1 lesions might not be advisable in all cases, and single Centre results should be evaluated and taken into account when selecting patients for this procedure, to avoid unnecessary morbidity and costs.[11]

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Provenance and Peer Review: Not commissioned; externally peer reviewed.

***Autor Correspondente/Corresponding Author:**
Miguel Eliseu
mgl.nobre@gmail.com
Rua José Marques Dias Ferreira, Lote 25A; 3030-792 Coimbra, Portugal

Recebido/Received: 2020-10-28
Aceite/Accepted: 2021-02-07
Publicado / Published: 2022-01-25

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86. doi: 10.1002/ijc.29210
2. Burger M, Catto J, Dalbagni G, Grossman B, Herr H, Karakiewicz P, et al. Epidemiology and Risk Factors of Urothelial Bladder Cancer. Eur Urol. 2013;63:234-41. doi: 10.1016/j.eururo.2012.07.033
3. Divrik R, Yildirim U, Zorlu F, Özen H. The Effect of Repeat Transurethral Resection on Recurrence and Progression Rates in Patients With T1 Tumors of the Bladder Who Received Intravesical Mitomycin: A Prospective, Randomized Clinical Trial. J Urol. 2006;175:1641-4. doi:10.1016/S0022-5347(05)01002-5
4. Cumberbatch M, Foerster B, Catto J, Kamat A, Kassouf W, Jubber I, et al. Repeat Transurethral Resection in Nonmuscle-invasive Bladder Cancer: A Systematic Review. Eur Urol. 2018;73:92533. doi:10.1016/j.eururo.2018.02.014
5. Soria F, Marra G, D'Andrea D, Gontero P, Shariat S. The rational and benefits of the second look transurethral resection of the bladder for T1 high grade bladder cancer. Transl Androl Urol. 2019;8:4653. doi:10.21037/tau.2018.10.19
6. Calò B Chirico M, Fortunato F, Sanguedolce F, Carvalho-Dias E, Autorino R, et al. Is Repeat Transurethral Resection Always Needed in High-Grade T1 Bladder Cancer? Front Oncol. 2019;9:465. doi: 10.3389/fonc.2019.00465
7. Cao M, Yang G, Pan J, Sun J, Chen Q, Chen Y, et al. Repeated transurethral resection for non-muscle invasive bladder cancer. Int J Clin Exp Med. 2015;8:14169.
8. Hashine K, Ide T, Nakashima T, Hosokawa T, Ninomiya I, Teramoto N. Results of second transurethral resection for high-grade T1 bladder cancer. Urol Ann. 2016;8:10-15. doi:10.4103%2F0974-7796.163798
9. Grimm M, Steinhoff C, Simon X, Spiegelhalder P, Ackermann R, Vogeli T. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. J Urol. 2003;170:433-7. doi:10.1097/01.ju.0000070437.14275.e0
10. Angulo J, Palou J, García-Tello A, de Fata F, Rodríguez O, Villavicencio H. Second transurethral resection and prognosis of high-grade non-muscle invasive bladder cancer in patients not receiving bacillus Calmette-Guerin. Actas Urol Esp. 2014;38:164-71. doi:10.1016/j.acuroe.2014.03.004
11. Yuk H, Kim J, Jeong C, Kwak C, Kim H, Ku J. Differences in Pathologic Results of Repeat Transurethral Resection of Bladder Tumor (TURBT) according to Institution Performing the Initial TURBT: Comparative Analyses between Referred and Nonreferred Group. Biomed Res Int. 2018; 9432606. doi:10.1155%2F2018%2F9432606
12. Gregg J, McCormick B, Wang L, Cohen P, Sun D, Penson D, et al. Short term complications from transurethral resection of bladder tumor. Can J Urol. 2016;23:8198-203.
13. Marques V, Eliseu M, Tavares-da-Silva E, Rolo F, Figueiredo A. Fatores preditivos de retorno hospitalar inesperado após ressecção transuretral de tumor vesical. Acta Urol Port. 2018;35:18-24. doi:10.24915/aup.35.3-4.89
14. Mariappan P, Zachou A, Grigor K. Detrusor muscle in the first, apparently complete transurethral resection of bladder tumour specimen is a surrogate marker of resection quality, predicts risk of early recurrence, and is dependent on operator experience. Eur Urol. 2010;57:8439. doi:10.1016/j.eururo.2009.05.047
15. Sfakianos J, Kim P, Hakimi A, Herr H. The Effect of Restaging Transurethral Resection on Recurrence and Progression Rates in Patients with Nonmuscle Invasive Bladder Cancer Treated with Intravesical Bacillus Calmette-Guérin. J Urol. 2014;191:341-5. doi:10.1016/j.juro.2013.08.022
16. Gontero P, Sylvester R, Pisano F, Joniau S, Oderda M, Serretta V, et al. The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of patients with T1 high-grade/Grade 3 bladder cancer treated with bacille CalmetteGuérin. BJU Int. 2016;118:44-52. doi:10.1111/bju.13354
17. Patriarca C, Hurle R, Moschini M, Freschi M, Colombo P, Colecchia M, et al. Usefulness of pT1 substaging in papillary urothelial bladder carcinoma. Diagn Pathol. 2016;11:6. Doi:10.1186/s13000-016-0466-6
18. Colombo R, Hurle R, Moschini M, Freschi M, Colombo P, Colecchia M, et al. Feasibility and Clinical Roles of Different Substaging Systems at First and Second Transurethral Resection in Patients with T1 High-Grade Bladder Cancer. Eur Urol Focus. 2018;4:87-93. doi:10.1016/j.euf.2016.06.004
19. Martin-Doyle W, Leow J, Orsola A, Chang S, Bellmunt J. Improving selection criteria for early cystectomy in high-grade t1 bladder cancer: a meta-analysis of 15,215 patients. J Clin Oncol. 2015;33:643-50