

Could we safely omit a Repeat Transurethral Resection of the Bladder (re-TURB) after Hexaminolevulinate Photodynamic Diagnostics (PDD)-TURB?

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Summary

Objective: Bladder cancer (BC) is considered one of the malignancies with moderate-high incidence, high rate of recurrence and costly management. Diagnosis and staging are thus important for therapeutic purposes. Considering the risk of residual tumour and understaging, in specific cases, international guidelines recommend performing a second transurethral resection of the bladder (reTURB). Our study aimed to evaluate the impact of hexaminolevulinate Photodynamic Diagnostics (PDD) at first TURB on the rate of residual tumour.

Materials and Methods: We retrospectively analysed patients undergoing TURB in our centre between 2012 and 2020. Eighty-two patients had a re-TURB after a first complete TURB with a delay < 3 months. Patients who had an incomplete first resection were excluded. We compared patients who underwent standard white light cystoscopy/TURB and then hexaminolevulinate PDD-guided reTURB (group A, n = 49) and patients with PDD-cystoscopy/TURB at the first procedure then white light cystoscopy/reTURB (group B, n = 33). The residual tumour rate at reTURB as well as median recurrence-free survival (RFS) were compared between the two groups.

Results: Residual tumour at reTURB was detected in 48.8% of cases in our cohort, with a significant difference between the two groups (71.4% in group A versus 12.5% in group B, $p < 0.001$). After a median follow-up of 22 months, the median RFS was 15 months in Group A and 32 months in Group B, but this difference was not significant ($p = 0.7$).

Conclusions: Using PDD at the time of the initial TURB had a statistically significant impact on the rate of residual tumour at the reTURB. Nevertheless, the percentage of residual tumour even with the use of PDD does not allow for safely omitting second resection. Performing a reTURB with PDD for patients who did not have it initially, provides the same benefit in terms of recurrence-free survival.

KEY WORDS: Bladder cancer; Hexvix; TURB; Second resection; Residual tumor.

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INTRODUCTION

Bladder cancer (BC) represents the seventh most diagnosed cancer in men worldwide, and the tenth one considering both genders. Moreover, Europe is considered one of the countries with the highest incidence with an age-standardized rate of 20 per 100,000 person/years for men (compared to 9.5 worldwide) and 4.6 for women (compared to 2.4 worldwide) (1). Furthermore, it is one of the malignancies with a high economic burden due to its treatments and follow-up (2).

Hence, a correct diagnosis and staging are of utmost importance for correct treatment. *Transurethral resection of the bladder* (TURB) is considered the gold standard to ascertain BC diagnosis, and plan further treatments and can be a curative procedure for early-stage disease (pTa/T1 tumours) (3-5). Nonetheless, guidelines also recommend performing a second TURB in specific clinical scenarios, mainly: after an incomplete first TURB, when there are doubts about the completeness of the first resection, in case of the absence of detrusor muscle in the specimen (except for Ta LG/G1 tumours and primary CIS) and when there is the presence of T1 tumours (6, 7). Second TURB (reTURB) has the intent to eradicate all the tumour burden since there is a consistent risk of leaving residual tumours and consequently of recurrence (1, 8, 9). To improve the correct tumour identification and improve staging and treatment, Hexaminolevulinate *Photodynamic Diagnostics* (PDD)-guided TURB has been proposed and demonstrated to be more sensitive than conventional procedures (10-13). For these reasons, European guidelines propose to use methods to improve tumor visualization including PDD (1). The aim of our study was to evaluate the advantage of using PDD at first TURB on the rate of residual and evaluate if using this technology, we could safely omit a reTURB, without compromising oncological outcomes.

No conflict of interest declared.

MATERIALS AND METHODS

We retrospectively analysed patients undergoing TURB in our centre between 2012 and 2020. Eighty-two patients had a reTURB after a first complete TURB with a delay < 3 months. Patients who had an incomplete first resection were excluded. We compared patients who underwent standard white light cystoscopy/TURB and then hexaminolévulinate PDD-guided reTURB (Group A, n = 49) and patients with PDD-cystoscopy/TURB at the first procedure then white light cystoscopy/reTURB (Group B, n = 33). The residual tumour rate at reTURB as well as median recurrence-free survival were compared. Comparisons of the proportions were done by the χ^2 test. Kaplan-Meier

Table 1.
Baseline characteristic and postoperative variable statistics of patient (n = 82).

Blue Light Cystoscopy at First TURB					P value	
		No-Group A (n = 49)		Yes-Group B (n = 33)		
		N	%	N	%	
Age (years), median (SD)		69 (9)	-	71 (9)	-	0.7 ^a
Sex	F	8	47	9	52	0.23 ^b
	M	41	63	24	36	
Stage	Ta	11	73	4	26	0.23 ^b
	T1	38	56	29	43	
Presence of CIS	Yes	32	64	18	36	0.32 ^b
	No	17	53	15	46	
Presence of muscle	Yes	9	69	4	30	0.44 ^b
	No	40	58	29	42	
Multifocality	Yes	29	60	19	39	0.8 ^b
	No	20	58	14	41	
R+	Yes	14	33	28	66.7	< 0.001 ^b
	No	35	87	5	12.5	
Recidive	Yes	36	61	23	39	0.7 ^b
	No	13	56	10	43	
RFS		15		32		0.7 ^c

F: Female; M: Male; CIS: Carcinoma in situ; R+: Residual tumor; RFS: Recurrence free survival; ^a Student t Test; ^b Chi Test; ^c Log-rank Test.

curves were used to analyze time to recurrence and to compare the two groups. The statistical analysis was done with SPSS version 25 (SPSS Inc., Chicago, IL, USA).

RESULTS

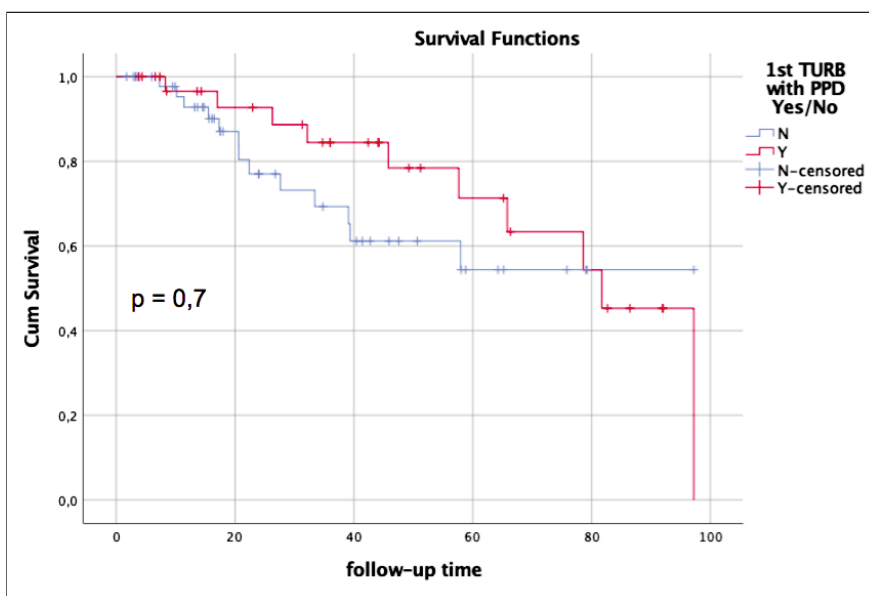
No statistically significant differences were observed between the two groups in terms of age, sex, history of bladder cancer, stage, grade, presence of CIS, presence of muscle and multifocality (Table 1). Residual tumour at reTURB was detected in 48.8% of cases in our cohort, with a significant difference between the two groups (71.4% in group A versus 12.5% in group B, $p < 0.001$). After a median follow-up of 22 months, the median recurrence-free survival (RFS) was 15 months in group A and 32 months in group B (Figure 1), but this difference was not significant ($p = 0.7$).

DISCUSSION

In this retrospective study, we compared patients who underwent standard white light cystoscopy/TURB then PDD-guided reTURB and patients with PDD-cystoscopy/TURB at the first procedure then white light cystoscopy/reTURB. After the first resection, there was a risk of disease recurrence due to a regrowth of undetected lesions. We found that PDD cystoscopy at the time of the initial TURB had a statistically significant impact on the rate of residual tumor at the reTURB. In fact, we found that residual tumor rates at reTURB were 71.4% and 12.5% in Group A and B respectively. Our result corroborated data from previously published studies. Since its first use in 1994, the benefits of fluorescent light cystoscopy with hexaminolevulinate (HAL) in non-muscle-invasive bladder cancer (NMIBC) have been reported in many trials. Nowadays PDD is widely used for the diagnosis and treatment of superficial bladder cancer. In NMIBC the possible benefits of using PDD-guided TURB were higher detection rates, a higher rate of complete resection, and fewer residual tumors (14). Several studies reported an increased tumor detection rate by HAL-PDD with a most pronounced benefit for CIS lesions (15).

Riedel *et al.* found lower residual tumor rates for Ta and T1 tumors using PDD, while Filbeck *et al.* found a statistically significant reduction of residual tumors only in Ta tumors (16, 17). Albarghouth *et al.* showed that the use of PDD significantly reduces the risk of residual tumors compared with conventional TURB. In the same study, they have also shown that PDD can significantly improve 3 and 12-month recurrence-free survival especially in low and intermediate-risk tumors, and 1-year progression-free survival in high-risk tumors (18). Burger *et al.* conduct-

Figure 1.
Kaplan-Meier curves for recurrence-free survival time.



ed a meta-analysis confirming that HAL-PDD cystoscopy significantly improves the detection of bladder tumours leading to a reduction of recurrence at 9-12 month (19). *Mariappan et al.* found that HAL-PDD-assisted TURB was associated with a significantly lower risk of early recurrence compared to white light TURB. Moreover, recurrence rate at the first follow-up cystoscopy in the study cohort was 13.6% and 30.9% in the two settings respectively (20). *Gakis et al.* systematically reviewed literature reporting a significantly lower rate of progression in patients treated with PDD compared to white light TURB (21). In a recent meta-analysis *Sun et al.* reported that cystoscopy with aminolevulinic acid (ALA) or HAL was associated to a reduced residual tumor rate compared with standard cystoscopy in NMIBC and RFS was higher in the first case at the 12- to 24-month follow-up (22).

Even if we confirmed that the use of PDD allows reducing residual tumour rate, we did not find a statistically significant difference in terms of RFS. This can be explained by the design of our study which establishes the use of PDD in both groups but at different times. Probably the difference in terms of RFS favouring the group who perform PDD initially, which is also marked at the beginning of follow-up, tends to be mitigated later by the delayed use of PDD in the other group as shown by the Kaplan-Meier curves.

We also conceived this study to question if the use of PDD at the initial TURB would allow for the omission of a re-resection that, meaning a second surgical procedure, can have an impact not only for the patient (psychological, surgical or medical-related complications) but also for the healthcare systems in terms of costs. However, despite the advantages of the PDD technique, considering the biological characteristic of bladder cancer and the percentage of the residual tumour even after PDD cystoscopy we do not consider it safe to spare a second resection.

Our study is not devoid of limitations: mainly its retrospective nature and the small sample size.

Concluding, reTURB even with the aid of PDD technology seems to be necessary. Even if all studies showed a reduced risk of residual tumour, none of them suggested to avoid a reTURB.

CONCLUSIONS

The quality of the initial TURB, when performed by using PDD, had a statistically significant impact on the rate of residual tumour at the reTURB. Nevertheless, the percentage of residual tumour even after PDD cystoscopy is not negligible and cannot allow to safely avoid a second resection. Performing a reTURB with PDD for patients who did not have it initially, provides the same benefit in terms of recurrence free survival.

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