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Research Report

Deciding When to Omit Repeat Transurethral Resection of Superficial Bladder Cancer: Do Photodynamic Diagnostics help?

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Abstract.
BACKGROUND: Repeat transurethral resection of bladder tumor is recommended when certain risk constellations are present on initial resection. Current evidence is conflicting, leading to dissenting recommendations in multinational guidelines around the world. Photodynamic diagnostics (PDD) is a tool which has been shown to increase diagnostic accuracy, but evidence is still lacking if this may permit omission of repeat resections in certain cases.
OBJECTIVE: To evaluate whether the use of photodynamic diagnostics has an impact on resection quality and residual tumor rate, and to explore which parameters may have an impact on the necessity of repeat transurethral resections.
METHODS: We retrospectively evaluated 373 patients in the timeframe of ten years, in whom a repeat transurethral resection of bladder tumor has been performed following initial resection at our department. About half of those resections were performed using photodynamic diagnostics.
RESULTS: When PDD was used, more tumor mass was revealed and resected, but the shown trend toward a lower residual tumor rate was non-significant. Muscularis was shown more often on PDD resections. While being a rare occurrence, upstaging on repeat resection happened significantly less often after initial PDD use. Furthermore, tumor size and multifocality significantly influenced residual tumor rate in Ta high-grade stage.
CONCLUSIONS: PDD use may lead to a more accurate initial staging but this may not have an impact on short-term residual tumor rate. Tumor size and multifocality should be granted more weight in the decision-making process as when to perform a repeat resection.

Keywords: Urinary bladder neoplasms, cystoscopy, transurethral resection, photodynamic diagnostics, neoplasms, residual

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ABBREVIATIONS

AUA	American urological association
CIS	Carcinoma *in situ*
CUA	Canadian urological association
EAU	European association of urology
EORTC	European Organisation for Research and Treatment of Cancer
HG	High-grade
iTURBT	Initial transurethral resection of bladder tumor
LG	Low-grade
NCCN	National comprehensive cancer network
PDD	Photodynamic diagnostics
reTURBT	Repeat transurethral resection of bladder tumor
RTR	Residual tumor rate

INTRODUCTION

Urothelial Cancer of the urinary bladder is the fourth most common malignancy in males around the world [1]. Furthermore, its management is one of the most cost-intensive ones of all malignant diseases [2]. The initial transurethral resection of bladder tumor (iTURBT) is paramount in initial staging and therapy of the disease. Further treatment differs greatly depending on invasiveness, so an adequate primary resection is essential for a correct histopathological staging.

An incomplete initial resection can leave residual tumors or carcinoma *in situ* untreated, which also yields incorrect histopathological staging and possibly results in understaging. In a combined analysis of over 2400 patients in seven EORTC Phase III studies, Brausi et al. showed that, in follow-up cystoscopy after three months, recurrence rate following unifocal tumors is up to 20% and up to 45% in multifocal disease [3].

To prevent this, a repeat transurethral resection (reTURBT) may be necessary if certain parameters are met. Current EAU guidelines recommend reTURBT in case of incomplete initial resection, when there is no muscle in the specimen (with the exception of Ta low-grade (LG)/G1 tumors and primary carcinoma *in situ* - CIS) and in T1 tumors) [4].

In this setting, the subgroup of Ta high-grade (HG) tumors represents a peculiarity as they do not necessitate a repeat resection according to current EAU guidelines [4]. Nevertheless, in two retrospective trials, tumor persistence was shown to be as high as up to 41,4% in initial Ta HG [5] resp. 54,6% in initial T1 HG [6]. Current AUA Guidelines leave a repeat resection as optional in case of visually complete primary resection and in small tumors [7].

Multifocality has also been found to be a predictor of tumor persistence and -recurrence, whereas no allowance has been made hereto in current guidelines, even though it has been observed as a significant factor in tumor persistence and recurrence [5, 6]. According to a recent systematic review, the probability of upstaging following reTURBT is between 0,4% in Ta tumors and 8% in T1 tumors [8].

To enhance tumor visualization and, in turn, resection quality of the initial resection, photodynamic diagnostics (PDD) is a viable approach. Here, hexaminolevulinate is instilled into the bladder preoperatively, which enriches especially in tissue which has a high rate of cell turnover, such as in tumor cells or cystitis. When exposed to light of a certain wavelength, suspicious tissue is highlighted during cystoscopy. Multiple systematic reviews highlighted a positive correlation of PDD usage with tumor detection [9–12], residual tumor rate and recurrence, as well as longer recurrence-free survival, whereas a more recent work by Neuzillet et al. showed no significant difference in these regards [13].

While several publications reported a decrease in overall tumor recurrence following reTURBT in Ta tumors [14] and a more pronounced decrease in tumor recurrence and progression in T1 tumors [15], a recent systemic review by Cumberbatch et al. only showed a non-significant trend toward lower progession [8]. A significant influence on overall mortality or recurrence risk was not seen.

MATERIALS AND METHODS

We retrospectively evaluated 373 patients in the timeframe of 2007-2017, in whom a repeat transurethral resection has been performed following initial resection of bladder tumor at our department. Parameters were, among others, residual tumor rate, histopathological staging, multifocality, tumor size and completeness of initial resection, as well as PDD use. During the mentioned timeframe, PDD was gradually introduced in our department as standard procedure in initial bladder tumor resections or in cases of late (>5 years) recurrence.

We evaluated in how far objective clinical parameters (T-stage, grading, muscularis, tumor size and

multifocality) as well as surgeon reported completeness of resection had an influence on residual tumor rate, as well as the influence of PDD. Special attention was granted to those histopathologic constellations in which a clear recommendation for or against routine repeat resection is lacking in current guidelines.

This study was reviewed by the Upper Austrian Ethics Committee (approval number: J-1–15).

Informed consent has been obtained by all participants. The study was performed in compliance with the Declaration of Helsinki in its most recent form. (Adopted in 1964 by the 18th World Medical Assembly in Helsinki, Finland, and revised by the 64th World Medical Assembly in Fortaleza in 2013).

STATISTICS

Subgroup data sets of the only continuous variable (age) were checked for normal distribution (test of normality: Kolmogorov-Smirnov with Lilliefors significance correction, type I error = 10%). Accordingly, subgroup comparisons were performed either by the *t*-test (test for variance homogeneity: Levene test, type I error = 5%) for independent samples or by the Mann-Whitney U test. The latter was also used for subgroup comparisons of ordinal variables. Categorical variables were compared by the exact Chi-square test or by the Fisher's exact test.

Logistic regression analysis (including stepwise forward approach) was used to investigate the influence of the following variables on tumor on reTURBT [no residual tumor vs. residual tumor]; muscularis [present vs. not present in histopathological staging]; sex [male vs. female]; T-stage on initial resection [pTa vs. pT1]; PDD [not performed vs. performed] as well as age [years]

Since the type I error was not adjusted for multiple testing, the results of inferential statistics are descriptive only and the use of the term "significant" in the description of the study results always reflects only a local $p < 0:05$ but no error probability below 5%.

Statistical analysis was performed using the open-source R statistical software package, version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

General (See Table 1)

In 285 of the 373 patients (76,4%), bladder tumor was a de-novo diagnosis, whereas it constituted a recurrence of disease in 88 patients. 312 Patients were male (83,6%), 61 female. Median age was 70,34 years (27,81–91,96). Complete resection (cR0) in iTURBT was reported by the surgeon in 350 of 373 (93,8%) cases (reTURBT outcome parameters were henceforth evaluated in these cases).

Residual tumor rate (See Table 1)

In case of surgeon reported complete resection, residual tumor was found in 15,1%.

Several factors evaluated in the initial resection had a significant impact on residual tumor rate found in repeat resection:

In high-grade disease, residual tumor was found in 26,1% and only in 2,5% in low-grade disease ($p < 0{,}001$). In Ta tumors, residual tumor rate was 8,8%, in T1 tumors 31,6% ($p < 0{,}001$).

In 35,8% of cases which had residual tumor on reTURBT, CIS was present at initial resection, while it was only found in 14,6% of cases with negative repeat resections.

Tumor quantity had an impact as well: multifocality at initial resection yielded a residual tumor rate of 21,9% and only 7,8% in unifocal tumors ($p < 0{,}001$). Similarly, tumor size was also positively correlated with a higher number of residual tumors: 22,8% of patients had residual tumor when initial tumor size was >3 cm, whereas only 11,5% in those with tumors of <3 cm ($p = 0{,}014$). Tumor size of >3 cm was also more often associated with high-grade disease (39,9% HG vs. 16,1% LG; $p < 0{,}001$) and pT1 stage (48,4% T1 vs. 20,9% Ta; $p < 0{,}001$)

As expected, we found a significant positive correlation between CIS and pT1 stage: CIS was found in 37,9% of pT1 cases vs. 8,8% of pTa cases ($p < 0{,}001$).

We were particularly interested in the subgroup of Ta high-grade tumors, as current EAU guidelines do not require a repeat resection in this pathological constellation (as long as muscle was present in the specimen). In our collective, residual tumor rate following resection of Ta HG tumor was 19,1%, which is clearly lower in comparison with T1 HG (32,6%; $p = 0{,}044$) but increases considerably if the tumor was large (28%), multifocal (29,8%) or both (46,2%). A third resection (TURBT III) was performed in 5,4% of cases. It was significantly less often necessary in Ta HG in comparison with T1 HG (4,3% vs. 9,8%; $p = 0{,}004$).

Interestingly, presence of muscularis in the resection specimen did not seem to have an impact on

Table 1
general patient characteristics, results of reTURBT and residual tumor rate

Patients	n	%	
all	373		
Primary manifestation	285	76,4	
Recurrent manifestation	88	23,6	
Age	years	range	
Median	70,34	27,81–91,96	
Sex	n	%	
male	312	83,6	
female	61	16,4	
iTURBT	n	%	
Overall	373		
… of which cR0	350	93,8	
Results reTURBT	n	%	
Residual tumor	53/350	15,1	
… of which			
pTa	17/53	32,1	
pT1	16/53	30,2	
pT2	2/53	3,8	
CIS	31/53	58,5	
high grade	25/53	47,2	
low grade	28/53	52,8	
Residual tumor rate (%) in dependence of iTURBT result	n	%	***p*-value**
pTa	22/251	8,8	**<0.001****
pTa high grade	18/94	19,1	
pTa high grade, >3 cm	7/25	28	
pTa high grade, multifocal	14/47	29,8	
pTa high grade, >3 cm, multifocal	6/13	46,2	
pT1	30/95	31,6	
pT1 + CIS	12/36	33,3	
high grade (all T stages)	49/188	26,1	**<0.001****
Low grade (all T stages)	4/157	2,5	
solitary	13/167	7,8	**<0.001****
multifocal	40/183	21,9	
<3 cm	26/227	11,5	**0.014***
>3 cm	21/92	22,8	

residual tumor rate (14,3% present vs. 15,4% not present; $p = 0{,}863$).

On logistic regression, we found that the presence of residual tumor is favored by T1 disease (as opposed to Ta disease, B = 1,837; $p < 0{,}001$) and by advanced age (B = 0,032; $p = 0{,}032$). Stepwise regression additionally highlighted a lack of muscularis as a positive influence (B = –0,817; $p = 0{,}044$, which stands in contrast to the previously elaborated results of the subgroup analysis (See Table 3).

When there was residual tumor found in reTURBT, we found solitary CIS in 58,5%, Ta in 32,1%, T1 in 30,2% and ≥T2 in 3,8%. High-grade pathology was found in 47,2% of these cases and in each instance, this was also present in the initial resection.

A third resection (TURBT III) was performed in 5,4% of all cases, insignificantly more often following iTURBT with PDD compared to white light only (6,1% vs. 2,9%; $p = 0{,}181$).

Muscularis (See Table 2)

In only 24,4% of all cases in our collective, muscularis was present in histopathological reports. While this number strikes us as unexpectedly low, we have to note that we only counted muscularis as "present" when there was a definite mention thereof in the report. We have to act on the assumption that, at least in some instances, this low number was owed more to the brevity of some histopathological reports and less to a lack of resection depth.

In subgroup analysis, the presence of muscularis seemingly had no effect on residual tumor rate. When viewed separately, no significant difference could be

Table 2
Residual tumor rate, PDD subgroup analysis and upstaging

Muscularis	N	%	*p*-value
present	84/350	24,4	
… of which male	77/215	26,4	**0.016***
… of which female	7/51	12,1	
Residual tumor rate			***p*-value**
RTR w/ Muscularis @iTURBT	12/84	14,3	0.863
RTR w/o Muscularis @iTURBT	41/266	15,4	
RTR w/ Muscularis & pT1 @iTURBT	15/46	32,6	0.578
RTR w/o Muscularis & pT1 @iTURBT	22/58	37,9	
Results iTURBT in %	Muscularis	No Muscularis	***p*-value**
pT1	47,6	20,8	**<0.001****
high-grade	66,7	50,6	**0.012***
Tumor size >3 cm	39,8	29,2	**0.016***
third resection necessary	3,8	4,8	0.982
PDD	n	%	***p*-value**
Used in	175/373	46,9	
reported as effective	148/175	84,6	
RTR w/ PDD	19/148	12,8	0.159
RTR w/o PDD	38/208	18,3	
Results iTURBT in %	PDD used	no PDD used	***p*-value**
Number (percentage) of patients	175 (46,9%)	198 (53,1%)	
Male patients	81,8	84,6	0.413
Initial resection	79,1	73,1	0.260
Ta	66,2	74,0	0.434
T1	32,4	25,0	0.327
CIS	23,6	14,9	**0.039***
Low-grade	45,9	42,8	0.467
High-grade	53,4	55,3	0.089
cR0	95,9	99,5	**0.022***
multifocal	54,7	51,4	0.590
Size >3 cm	25,7	26,9	0.460
Muscularis present	33,8	17,8	**0.001****
Residual tumor on reTURBT	12,8	18,3	0.159
TURBT III performed	6,1	2,9	0.181
Upstaging	n	%	***p*-value**
Overall	20/349	5,7	
Upstaging w/ PDD	3/142	2,1	**0.023***
Upstaging w/o PDD	17/207	8,2	

seen in T1 cases either, where the residual tumor rate was higher when there was no muscularis in primary resection (37,9% vs. 32,6%, $p = 0{,}578$). After deducting confounding factors such as age and T-stage, logistical regression revealed that a lack of muscularis in the initial resection had a positive influence on residual tumor rate.

When there was mention of muscularis in the resection specimen, the share of high-grade tumors (66,7% vs. 50,6%; $p = 0{,}012$), T1-tumors (47,6% vs. 20,8%; $p < 0{,}001$) as well as tumors over the size of 3cm (39,8% vs. 29,2%; $p = 0{,}016$) was significantly higher in comparison to resections without histopathological report of muscularis.

Table 3
Logistic regression in dependence of residual tumor

Logistic regression dependent: residual tumor on reTURBT	coefficient B	*p*-value
Muscularis (not present vs. present)	–0.817	**0.044***
Sex (male vs. female)	–0.465	0.295
pTa vs. pT1	1.837	**<0.001****
pTa vs. pT2	2.705	0.086
PDD (no vs. yes)	–0.428	0.204
Age	0.032	**0.032***

Muscularis was reported significantly less often in females than in men (12,1% vs. 26,4%; $p = 0{,}019$) and also in recurrent disease ($p = 0{,}029$). We could not find a significant difference in presence of muscularis

and the rate of TURBT III (3,8% with muscularis vs. 4,8% without; $p = 0{,}982$).

In 44 cases with no initially reported muscularis, repeat resection was performed in constellations where there was no imperative to do so according to EAU guidelines (Ta LG; cR0). Only in two cases, residual tumor mass was found.

PDD (See Table 2)

PDD was used in 46,9% (175/373) of initial resections and was deemed efficacious by the surgeon in 84,6% (148/175). There was no significant difference in overall residual tumor rate between the PDD and non-PDD group (12,8% vs. 18,3%; $p = 0{,}159$).

On subgroup analysis, the tendency toward a higher number of T1 cases with PDD turned out to be not statistically significant (32,6% vs. 25,1%; $p = 0{,}327$), whereas CIS was found significantly more often when PDD was used (23,6% vs. 13,6%; $p = 0{,}039$).

Muscularis was found significantly more often when PDD was used (33,8% vs. 17,8%; $p = 0{,}001$).

The percentage of multifocal tumors did not increase with PDD use (54,7% PDD vs. 51,4% no PDD; $p = 0{,}59$). Concurrently, tumor size did not correlate with PDD use (percentage of tumors >3 cm with PDD: 26,6% vs. 30,8% without PDD; $p = 0{,}46$), neither did the rate of TURBT III (with PDD: 6,1%, without PDD: 2,9%; $p = 0{,}181$).

In 23,1% of cases, urothelial cancer was found (and histopathologically verified) in instances, where the surgeon only identified the lesion using PDD and not on white light. This "PDD-benefit" did however not lead to a statistically relevant increase in residual tumor rate: residual tumor rate on reTURBT was 12,8% with PDD and 18,3% without PDD, which was not significant in subgroup analysis ($p = 0{,}159$) (only counting cases of surgeon reported complete resection). Interestingly, completeness of resection was reported by the surgeon less often when PDD was used (95,9% vs. 99,5%; $p = 0{,}022$).

Upstaging (See Table 2)

Repeat resection revealed a change in tumor stage in 5,7% of all cases, of which 2,1% happened when PDD was used initially and 8,2% when not ($p = 0{,}023$). 70% of these cases were effectuated by newly diagnosed CIS, an upstaging in T-stage was seen in 1,4% of repeat resections.

Presence of muscularis in initial resection did not seem to have an effect on restaging.

Muscle invasive urothelial cancer was observed in two cases of reTURBT. In both instances, initial stage was T1 HG plus CIS and in neither one, muscularis was reported.

DISCUSSION

When PDD was used, there was significantly more often mention of muscularis in the histopathological in comparison to white-light resections. It remains to be debated if PDD use itself leads to a more careful operative approach by the surgeon. The observation that incomplete resections were reported more often when PDD was used, possibly seconds this. Maybe a more thorough or deeper resection was prompted by PDD-positive residuals in the tumor foundation, but this could not be systematically proven.

Special attention should also be granted to the observation that in up to a quarter of PDD resections, additional and histopathologically proven tumors have been resected which were not visible in white light and would therefore be missed. This "PDD-Benefit" did not lead to a significant impact on residual tumor rate in our study. Even more interesting would be the question of tumor recurrence, which was not the scope of our work. It has partially been answered by Grossman et al. in a prospective trial, where the difference on tumor recurrence rate following PDD- and non-PDD resections was shown to differ up to nine months after a follow-up of more than four years [16].

Residual tumor rate on repeat resection was 8,8% (Ta) and 31,6% (T1) in our collective. This projects our data on the lower margin of distributions which have been reported in comparable literature: a meta-review showed 19–56% (Ta) and 15–55% (T1) [17]. This is possibly a consequence of PDD use and its associated effect in our collective, but as we could only observe a non-significant trend toward less residual tumors under PDD, other effects will play a role here as well.

Upstaging was a rare occurrence in our collective. Apparently, it did not make a difference if muscularis was reported in the primary resection or not, albeit reporting of muscularis was relatively scarce in our collective, potentially owing to an undue brevity of pathological reposts. Our results have to be interpreted in light of this potential limitation. Comparable literature mentions upstaging rates of 9,5%

and 23,3% in T1 tumors [18] but it has to be said that this was evaluated using routine biopsy of the tumor foundation, which has not been performed routinely in our study. As the quality of the histopathological diagnosis suffers from cauterization artifacts [19], there will necessarily be a difference in reports of muscularis.

The rate of upstaging was comparably low overall in our collective, but there was a further significant reduction when PDD was used, which we interpret to be an effect of improved initial staging quality.

There was more mention of muscularis in the resection of large (>3 cm) tumors and in tumors, which later turned out to be T1 on histopathological report. There is a possibility that the macroscopic aspect of such tumors triggered a more thorough and radical approach by the surgeon. In addition, such cases are more often performed by senior surgeons. An interesting question in this regard would be if a more radical resection correlates with better outcome parameters when also applied to tumors which appear less malign on first sight.

A possible limitation of our study was the comparably low rate of muscularis in specimens. Least mention of muscularis was seen in women and patients with recurring disease. A previous study could show that muscularis is lacking in up to 51% of all resections [19]. This was more often associated with low-grade tumors and was subject to significant inter-observer variability. This dependence on the pathologist's report is also an important aspect under which our data has to be interpreted.

The subgroup of Ta HG tumors deserves to be highlighted in context of our findings. Current guidelines are unequivocal on this topic. According to current EAU guidelines, tumor size and multifocality are no determinators which routinely trigger a change in therapeutic approach [4] CUA guidelines categorize large multifocal Ta tumors as 'high-risk', where a routine reTURBT is recommended [20]. It is partially reflected in the current NCCN guidelines, where size is a triggering factor in papillary tumors [21]. Residual tumor rate of Ta HG cases (19,1%) itself was lower than that of T1 HG, but in the case of large (>3 cm) and multifocal Ta high-grade tumors, it is significantly higher, and we are not the only ones reporting this. In our opinion, tumor size and multifocality are parameters which deserve justification as determinators triggering an obligatory repeat resection in Ta HG disease.

In Ta LG tumors, our observation of low residual tumor rate supports current guideline recommendations, where a systematical second resection can be omitted.

CONCLUSION

When PDD was used in the initial resection, residual tumor rate was lower and tumor staging was shown to be more precise. Furthermore, muscularis was significantly more often present in resections when PDD was used and more instances of pT1 and CIS tumor was detected.

In about a quarter of resections using PDD, histopathologically proven tumor tissue was resected which was not apparent to the surgeon when not using PDD. More in-depth research into the implications of these apparently more complete resections on long-term recurrence rate and survival, as shown by Grosman et al., should be worthwhile.

In contrast to current guideline recommendations, tumor size and multifocality seems to have an effect on residual tumor rate in repeat resections in our collective. In light of our observations, we argue that Ta high-grade tumors which are over 3 cm of size or multifocal should routinely be subject to a repeat transurethral resection. Further long-term research into overall mortality and tumor progression is warranted.

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AUTHOR CONTRIBUTIONS

Sailer E., Krause FS., Tauber V. and Graf S. contributed equally in conception of the study, interpretation of data and creation of the manuscript. Schimetta W. contributed in statistical planning and execution.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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