World J Urol (2015) 33:1429–1437
DOI 10.1007/s00345-015-1485-8

ORIGINAL ARTICLE

Fluorescence-guided bladder tumour resection: impact on survival after radical cystectomy

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Received: 21 October 2014 / Accepted: 5 January 2015 / Published online: 17 January 2015

Abstract
Purpose To investigate whether photodynamic diagnosis (PDD)-guided bladder tumour resection (TUR-BT) is of prognostic value in patients undergoing subsequent radical cystectomy (RC) for bladder cancer (BC).
Methods In 224 consecutive patients who underwent RC and bilateral pelvic lymphadenectomy for BC between 2002 and 2010 (median follow-up 29 months [IQR 8–59]), we retrospectively investigated whether patients had previously undergone PDD-guided (hexaminolevulinate [HAL] vs. 5-aminolevulinate [ALA]) versus white light (WL)-TUR-BT. Kaplan–Meier analysis was used to estimate recurrence-free survival (RFS), cancer-specific survival (CSS) and overall survival (OS) using log-rank and Cox regression model for uni- and multivariable analysis.
Results Of the 224 patients, 66 (29.5 %) underwent HAL-, 23 (10.3 %) ALA- and 135 (60.2 %) WL-TUR-BT before RC. The 3-year RFS/CSS/OS was 77.8/83.9/74.0 % for HAL-, 53.6/74.5/60.9 % for ALA- and 52.4/59.7/56.5 % for WL-TUR-BT ($p = 0.002/0.023/0.037$ for HAL vs. WL/ALA). PDD-TUR-BT was associated with a higher number of TUR-BTs before RC ($p < 0.001$) and re-resections ($p = 0.015$), a longer time between the first TUR-BT and RC ($p = 0.044$) and a lower rate of post-operative systemic chemotherapy ($p = 0.001$). In multivariable analysis, performance of HAL-TUR-BT, pathologic tumour and nodal stage as well as soft tissue surgical margin status were independent predictors for RFS, CSS and OS.
Conclusions This series indicates for the first time that HAL-guided TUR-BT is an independent predictor for improved survival after RC.

Keywords Aminolevulinate · Bladder cancer · Hexaminolevulinate · Radical cystectomy · Survival · Transurethral bladder tumour resection

Introduction

5-Aminolevulinic acid is a precursor molecule in the porphyrin synthesis pathway that leads to the formation of heme. Hexaminolevulinate (HAL) is the hexylester form of 5-aminolevulinate (ALA) approved by the Federal Drug Administration and European Medicines Agency for photodynamic diagnosis of bladder cancer (BC). It acts as a porphyrin precursor molecule that is absorbed by the urothelium where it prompts intracellular accumulation of a photosensitive protoporphyrin, especially within neoplastic cells [1].

In non-muscle-invasive bladder cancer (NMIBC), randomized trials have shown that photodynamic diagnosis (PDD)-guided transurethral bladder tumour resection (TUR-BT) improves the detection of carcinoma in situ (CIS) and reduces the risk of intravesical recurrence [2, 3]. Furthermore, it has been reported that patients with NMIBC undergoing HAL-guided TUR-BT tend less likely over the long term to progress to muscle-invasive disease than are those treated white light (WL)-guided TUR-BT [4].

Electronic supplementary material The online version of this article (doi:10.1007/s00345-015-1485-8) contains supplementary material, which is available to authorized users.

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Radical cystectomy (RC) represents the mainstay of treatment for muscle-invasive bladder cancer (MIBC) [5, 6]. Recurrence-free survival (RFS) after RC depends mainly on pathologic tumour and nodal stage as well as on soft tissue surgical margins (STSMs) [7]. Whether PDD-guided transurethral management of patients with invasive bladder cancer may have an impact on the oncologic outcome after RC has not been investigated thus far. Therefore, we analysed the impact of PDD-guided TUR-BT on survival in patients who were treated with RC for BC.

Patients and methods

In this retrospective observational analysis (approved by the Local Ethics Committee, Tübingen, and conducted according to the STROBE statement—see supplementary material), the clinical and pathologic records of 243 consecutive patients were reviewed who underwent RC with bilateral pelvic lymph node dissection for BC in our department between 2002 and 2010. To obtain a uniform cohort, patients undergoing neoadjuvant chemotherapy ($N = 9$) were excluded from this analysis, while ten patients were lost to follow-up. We assessed various clinical and pathologic parameters as listed in Table 1 and whether TUR-BTs were performed in our and/or external departments. In our department, ALA-guided TUR-BT was exclusively conducted between 2002 and 2005 and HAL-guided TUR-BT between 2006 and 2010. In our department, all patients with suspicion of BC or recurrent/persistent disease >8 weeks after the last resection underwent PDD-TUR-BT. During these time intervals, TUR-BTs were performed by or under direct surveillance of an experienced urologic surgeon.

Histologic assessment

The histologic assessment was performed in a single pathology department and was based on the TNM classification approved by the AJCC [8]. The pathologic macro- and microscopic evaluation of cystectomy specimens included cross-sectioning of the entire specimen with immunohistochemical staining to identify BC [9].

Follow-up

Patients generally were seen post-operatively at least every 3 to 4 months for the first year, semiannually for the second and third years and annually thereafter with cross-sectional imaging performed at regular intervals [10]. Recurrence was defined as either local when located in the surgical bed or distant when located at distant organs. Tumour recurrence at the urethra or upper urinary tract was considered as secondary urothelial recurrence. The median follow-up was 29 months (IQR 8–59). RFS was measured from the date of RC to the date of first documented recurrence at cross-sectional imaging or the date of last follow-up when the patient had not experienced disease recurrence. Cancer-specific survival (CSS)/overall survival (OS) was measured from the date of cancer-specific death/death, respectively, as determined by patient charts and death certificates or the date of last follow-up.

Statistical analysis and model development

For univariable analysis, the Fisher exact test was used for nominal data and Student's t test for scaled data. Kaplan–Meier plots were used to estimate RFS, CSS and OS. Uni- and multivariable Cox proportional hazard analyses were carried out to evaluate risk factors for recurrence, cancer-specific death and overall death. p values are two sided with $p < 0.05$ considered significant. Statistical analysis was performed with JMP® 11.0. Values are given as mean ± SEM for normally distributed variables or as median (range) for non-normally distributed variables.

Results

Of the 224 patients, 66 (29.5 %) underwent HAL-guided TUR-BT, 23 (10.3 %) ALA-guided TUR-BT and 135 (60.2 %) WL-guided TUR-BT before RC. The median number of PDD-based TUR-BTs was 1 (mean 1.4, IQR 1–1, total range 1–6). Of the 89 PDD patients, 85 (95.5 %) underwent PDD-based TUR-BT in our department, three in external departments (3.4 %) and one in ours and an external department also (1.1 %).

Conversely, of the 135 patients treated with WL-TUR-BT only, 52 (38.5 %) underwent WL-TUR-BT in our department, 71 (52.6 %) in external departments and 12 (8.9 %) in ours and an external departments also. Within the WL group, no significant differences were found in terms of the departmental performance of TUR-BT (internal vs. external vs. external + internal), except for a higher rate of preoperative hydronephrosis in WL patients treated in our department ($p = 0.005$). The 5-year RFS was not significantly different between WL patients treated in our department (40.0 %) compared to those treated in external departments (53.0 %) or those treated in our and external departments (41.2 %; $p = 0.35$ between groups).

A total of eight patients had pTa stage disease at RC ($N = 8$; 3.6 %). Of these, two patients had extensive pTaG2 (HG) urothelial carcinoma of the bladder ($N = 2$) who opted for primary RC and six BCG-refractory BC-staged pTaG3 (HG) with/without associated pTis disease ($N = 3/N = 3$). A total of 14 patients (6.3 %) did

Table 1 Clinical and pathologic characteristics of the 224 patients undergoing hexaminolevulinate versus 5-aminolevulinate versus white light TUR-BT before RC

Parameter	PDD			WL					
	HAL *N* (%)	5-ALA *N* (%)	p HAL vs. ALA	*N* (%)	p PDD vs. WL	INT *N* (%)	EXT *N* (%)	EXT/INT *N* (%)	*p*
Number of patients (%)	66 (29.5)	23 (10.3)		135 (60.2)		52 (38.5)	71 (52.6)	12 (8.9)	
Follow-up (months)									
Median	35	30	0.31	28	0.39	18	29	20	0.06
IQR	9–55	10–77		7–58		4–47	9–67	3–42	
Age at RC (a)									
Mean	67	66	0.65	67	0.99	68	67	68	0.40
Median	68	67		68		69	68	70	
IQR	59–75	60–72		60–73		61–74	59–72	61–76	
Gender									
Male	48 (72.7)	19 (82.6)	0.41	104 (77.0)	0.87	41 (78.9)	54 (76.1)	9 (75.0)	0.77
Female	18 (27.3)	4 (17.4)		31 (23.0)		11 (21.1)	17 (23.9)	3 (25.0)	
cT stage at PD									
≥cT2a	28 (42.4)	13 (56.5)	0.33	80 (59.3)	0.06	30 (57.7)	43 (60.6)	7 (58.3)	0.99
≤cT1	38 (57.6)	10 (43.5)		55 (40.7)		22 (42.3)	28 (39.4)	5 (41.7)	
Number of TUR-BTs prior to RC									
Mean	2.9	2.1	0.18	1.7	**<0.001**	1.4	1.7	2.8	**0.0154**
Median	2	1		1		1	1	2	
IQR	1–4	1–3		1–2		1–1	1–2	2–3	
Total range	1–12	7		1–10		1–5	1–10	2–9	
Number of re-resections after first TUR-BT									
0	30 (45.5)	12 (52.2)	0.77	91 (67.4)	**0.0158**	42 (80.8)	46 (64.8)	3 (25.0)	–
1	10 (15.2)	4 (17.4)		21 (15.6)		5 (9.6)	11 (15.5)	5 (41.7)	
2	9 (13.6)	3 (13.0)		12 (8.9)		3 (5.8)	7 (9.9)	2 (16.7)	
≥3	17 (25.8)	4 (17.4)		11 (8.1)		2 (3.9)	7 (9.9)	2 (16.7)	
Performance of first PDD-TUR-BT at									
First resection	46 (69.7)	15 (65.3)	0.60	–	–	–	–	–	–
Second resection	5 (7.6)	3 (13.0)							
Third resection	9 (13.6)	3 (13.0)							
Fourth resection	1 (1.5)	0 (0)							
Fifth resection or later	5 (7.6)	2 (8.7)							
pT stage at RC									
pTa	3 (4.6)	1 (4.3)		4 (3.0)		2 (3.8)	2 (7.8)	0 (0)	
pT1	13 (19.7)	4 (17.4)		19 (14.1)		6 (11.5)	11 (15.5)	2 (16.7)	
pT2a	11 (16.7)	6 (26.1)		22 (16.9)		7 (13.5)	15 (21.1)	0 (0)	
pT2b	12 (18.2)	3 (13.0)		20 (14.8)		9 (17.3)	10 (14.1)	1 (8.3)	
pT3a	9 (13.6)	2 (8.7)		25 (18.5)		7 (13.5)	14 (19.7)	4 (33.3)	
pT3b	11 (16.7)	2 (8.7)		18 (18.3)		8 (15.4)	8 (11.3)	2 (16.7)	
pT4a	6 (9.1)	3 (13.0)		20 (14.8)		10 (19.2)	7 (9.9)	3 (25.0)	
pT4b	1 (1.5)	2 (8.7)		7 (5.2)		3 (5.8)	4 (5.6)	0 (0)	
≤pT2b	39 (59.1)	14 (60.9)	1.0	65 (48.1)	0.10	24 (46.2)	38 (53.5)	3 (25.0)	0.13
≥pT3a	27 (40.9)	9 (39.1)		70 (51.9)		28 (53.8)	33 (46.5)	9 (75.0)	
≤pT1	16 (24.2)	5 (21.7)	1.0	23 (17.0)	0.23	8 (15.4)	13 (18.3)	2 (16.7)	0.34
≥pT2a	50 (75.8)	18 (79.3)		112 (83.0)		44 (84.6)	58 (81.7)	10 (83.3)	
pT0 (in RC specimen)									
Present	3 (4.6)	1 (4.3)	1.0	8 (5.9)	0.76	0 (0)	7 (9.9)	1 (8.3)	0.07
Absent	63 (95.4)	22 (95.7)		127 (94.1)		52 (100)	64 (90.1)	11 (91.7)	

Table 1 continued

Parameter	PDD			WL					
	HAL *N* (%)	5-ALA *N* (%)	p HAL vs. ALA	*N* (%)	p PDD vs. WL	INT *N* (%)	EXT *N* (%)	EXT/INT *N* (%)	*p*
pN stage at RC									
pN0	47 (71.2)	13 (56.5)	0.27	92 (68.2)	0.75	34 (65.4)	52 (73.2)	6 (50.0)	0.36
pN1-3	16 (24.2)	8 (34.8)		34 (25.2)		15 (28.9)	15 (28.8)	4 (33.3)	
pNX	3 (4.6)	2 (8.7)		9 (6.7)		3 (5.7)	4 (7.7)	2 (16.7)	
Lymphovascular invasion									
LV0	47 (71.2)	13 (56.5)	0.30	91 (67.4)	1.0	35 (67.3)	48 (67.6)	8 (66.7)	0.97
LVI	19 (28.8)	9 (39.1)		41 (30.4)		16 (30.8)	21 (29.6)	4 (33.3)	
LVx	0 (0)	1 (4.3)		3 (2.2)		1 (1.9)	2 (2.8)	0 (0)	
STSMs									
Positive	5 (7.6)	4 (17.4)	0.22	16 (11.9)	0.82	7 (13.5)	8 (11.3)	1 (8.3)	0.87
Negative	61 (92.4)	19 (82.6)		118 (87.4)		45 (86.5)	62 (87.3)	11 (91.7)	
Not evaluable	0 (0)	0 (0)		1 (0.7)		0 (0)	1 (1.4)	0 (0)	
Tumour size (cm)									
Mean	3.2	2.8	0.26	3.4	0.17	3.9	3.1	2.5	0.38
Median	3.2	2.5		3		3.5	2.5	2.8	
IQR	2.0-4.0	1.5-3.5		2.2–4.0		2.9–4.5	2.0–3.5	2.0–3.0	
Tumour grade at RC									
G1	0	0	1.0	0 (0)	1.0	0 (0)	0 (0)	0 (0)	0.15
G2	17 (25.8)	6 (26.1)		34 (25.2)		12 (23.1)	16 (40.8)	6 (50.0)	
G3	49 (74.2)	17 (73.9)		101 (74.8)		40 (76.9)	55 (59.8)	6 (50.0)	
Prior BCG therapy									
Yes	19 (28.8)	2 (8.7)	0.08	18 (13.3)	0.07	4 (7.7)	13 (18.3)	1 (8.3)	0.17
No	47 (71.2)	21 (91.3)		117 (86.7)		48 (92.3)	58 (81.7)	11 (91.7)	
Non-pure UC pathology									
Yes	2 (3.0)	2 (8.7)	0.27	12 (8.9)	0.29	3 (5.8)	7 (9.9)	2 (16.7)	0.44
No	64 (97.0)	21 (91.3)		123 (91.1)		49 (94.2)	64 (90.1)	10 (83.3)	
Post-operative systemic chemotherapy									
Received	4 (6.5)	8 (34.8)	**0.001**	19 (14.1)	**0.007**	12 (23.1)	5 (7.0)	2 (16.7)	0.07
Not received	62 (93.5)	15 (65.4)		116 (85.9)		40 (76.9)	66 (93.0)	10 (83.3)	
Time (last TUR-BT-RC) [d]									
Median	30	34	0.11	35	0.26	22	49	25	0.09
IQR	21–49	24–46		20–70		9–41	33–86	20–74	
Time (First TUR-BT confirming BC and RC) [d]									
Median	71	55	0.33	45	**0.044**	24	71	123	0.45
IQR	19–655	32–364		21–127		13–49	34–150	22–1370	
Hydronephrosis at RC									
Present	14 (21.2)	3 (13.0)	0.54	28 (20.7)	0.86	16 (30.8)	7 (9.9)	5 (41.7)	**0.005**
Absent	52 (78.8)	20 (87.0)		107 (79.3)		36 (69.2)	64 (90.1)	7 (58.3)	
Concomitant CIS at RC									
Present	23 (34.8)	9 (39.1)	0.80	36 (26.7)	0.18	11 (21.1)	19 (26.8)	6 (50.0)	0.08
Absent	43 (65.2)	14 (60.9)		99 (73.3)		41 (78.9)	52 (73.2)	6 (50.0)	
Tumour multifocality at RC									
Present	26 (39.4)	5 (21.7)	0.20	45 (33.3)	1.0	20 (38.5)	22 (31.0)	3 (25.0)	0.65
Absent	40 (60.6)	18 (78.3)		90 (66.7)		32 (61.5)	49 (69.0)	9 (75.0)	

Bold values indicate statistically significant difference

ALA aminolevulinate, *BCG* Bacille-Calmette–Guerin, *EXT* external, *HAL* hexaminolevulinate, *PD* primary diagnosis, *INT* internal, *PDD* photodynamic diagnosis, *RC* radical cystectomy, *STSM* soft tissue surgical margin, *TUR-BT* transurethral bladder tumour resection, *WL* white light, *UC* urothelial carcinoma; univariable analysis with Fisher's exact/Student's *t* test

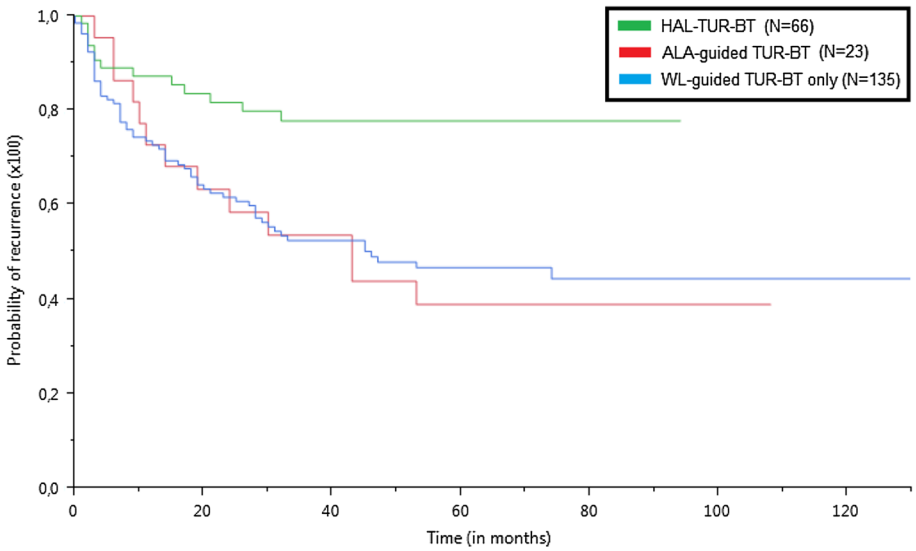

Fig. 1 Recurrence-free survival for patients who underwent HAL versus ALA versus WL-guided TUR-BT prior to RC ($p = 0.002$ for HAL vs. ALA/WL)

not undergo lymph node dissection at RC as they were clinically suspected to have abdominal and/or pelvic wall infiltration. Post-operatively, ten of these 14 patients were staged pT4b at RC, while the other four patients displayed pT3b ($N = 2$) and pT4a ($N = 2$) stage at final pathologic analysis.

In univariable analysis, PDD-guided TUR-BT before RC was associated with a higher median number of TUR-BTs before RC ($p < 0.001$) and re-resections ($p = 0.015$), a longer median time interval between the first TUR-BT (confirming BC) and RC ($p = 0.044$) and a lower rate of post-operative systemic chemotherapy ($p = 0.001$). In the PDD group, a significantly lower rate of administration of post-operative chemotherapy was found for patients treated with HAL versus ALA-TUR-BT ($p = 0.007$). No significant differences were found among the three groups (HAL vs. ALA vs. WL) with regard to other clinical and pathologic parameters listed in Table 1.

RFS at 3 and 5 years in the total cohort was 59.8 and 53.8 %, respectively. Recurrence was observed in 13 patients (19.6 %) treated with HAL-TUR-BT, 13 (19.6 %) with ALA-TUR-BT and 64 (47.4 %) with WL-TUR-BT after RC. The median 3-year RFS was 77.8 % for patients with HAL-based TUR-BT, 53.6 % for ALA-based TUR-BT and 52.5 % for WL-guided TUR-BT before RC ($p = 0.002$ for HAL vs. ALA or WL, see Fig. 1).

Cancer-specific death occurred in ten patients (15.2 %) treated with HAL-TUR-BT, 5 (21.7 %) with ALA-TUR-BT and 45 (33.3 %) with WL-TUR-BT. The overall 3- and 5-year CSS was 67.5 % and 65.9 %, respectively. The median 3-year CSS was 83.9 % in patients with HAL-TUR-BT, 74.5 % with ALA-TUR-BT and 59.7 % with WL-guided TUR-BT ($p = 0.023$ for HAL vs. WL, $p = 0.21$ for ALA vs. WL).

A total of 23 patients (34.9 %) treated with HAL-TUR-BT, 14 (60.9 %) with ALA-TUR-BT and 70 (52.2 %) with WL-TUR-BT died after RC. The 3- and 5-year OS in the total cohort was 63.2 and 52.8 %, respectively. The 3-year OS was 74.0 % in patients with HAL-TUR-BT, 60.9 % with ALA-TUR-BT and 56.5 % with WL-guided TUR-BT ($p = 0.037$ for HAL vs. ALA/WL).

In univariable Cox regression analysis, inferior RFS, CSS and OS were associated with the absence of HAL-guided TUR-BT before RC, advanced pathologic tumour and nodal stage, positive STSMs, lymphovascular invasion, delivery of post-operative systemic chemotherapy, hydronephrosis at RC and the absence of prior BCG therapy. Inferior CSS was associated with non-pure UC pathology ($p = 0.031$). Advanced age was associated with both inferior CSS and OS (continuously coded; $p = 0.038/0.029$). No further significant differences were found for all other parameters listed in Table 2.

In multivariable analysis, adjusted for all significant parameters of univariable analysis, for the number of TUR-BTs and the time interval between the last TUR-BT and RC, performance of HAL-guided TUR-BT, advanced pathologic tumour and nodal stage as well as positive STSMs were independent predictors for recurrence, cancer-specific death and overall death after RC (see Table 2).

Discussion

In the PDD group, the number of TUR-BTs was significantly higher than in the WL group; hence, the interval between the first TUR-BT and RC was also significantly longer. The reason for this finding may be that PDD patients tended to undergo BCG treatment more frequently before RC than did WL patients ($p = 0.07$). Of note, no

Table 2 Uni- and multivariable analysis of risk factors for recurrence-free, cancer-specific and overall survival

Variable	Univariable RFS		Univariable CSS		Univariable OS		Multivariable RFS		Multivariable CSS		Multivariable OS	
	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*
HAL versus ALA/WL-TUR-BT	0.37 (0.20–0.64)	**<0.001**	0.44 (0.21–0.83)	**0.01**	0.53 (0.31–0.85)	**0.007**	0.30 (0.14–0.58)	**<0.001**	0.48 (0.21–0.98)	**0.044**	0.56 (0.32–0.93)	**0.025**
≥pT3a versus ≤pT2b	4.43 (2.82–7.19)	**<0.001**	4.93 (2.78–9.33)	**<0.001**	3.11 (2.08–4.74)	**<0.001**	2.22 (1.24–4.03)	**0.006**	2.59 (1.25–5.56)	**0.010**	1.76 (1.05–2.96)	**0.030**
pN+ versus pN0	6.39 (4.07–10.1)	**<0.001**	5.11 (2.97–8.89)	**<0.001**	4.63 (3.01–7.14)	**<0.001**	3.71 (2.02–6.90)	**<0.001**	2.71 (1.33–5.57)	**0.006**	3.26 (1.86–5.71)	**<0.001**
pR+ versus pR0	5.07 (2.95–8.35)	**<0.001**	7.79 (4.24–13.69)	**<0.001**	6.11 (3.63–9.91)	**<0.001**	2.86 (1.31–6.04)	**0.009**	2.84 (1.19.6.59)	**0.019**	3.14 (1.54–6.20)	**0.002**
LVI versus LV0	3.45 (2.26–5.28)	**<0.001**	2.99 (1.79–5.05)	**<0.001**	3.11 (2.09–4.64)	**<0.001**	1.05 (0.60–1.82)	0.86	0.96 (0.49–1.88)	0.91	1.11 (0.66–1.87)	0.70
Post-operative chemotherapy received versus not received	3.30 (2.06–5.15)	**<0.001**	2.81 (1.57–4.83)	**<0.001**	2.50 (1.55–3.90)	**<0.001**	1.26 (0.70–2.22)	0.43	0.81 (0.38–1.66)	0.58	0.83 (0.46–1.46)	0.53
Preoperative hydronephrosis Present versus absent	1.76 (1.08–2.78)	**0.023**	1.82 (0.99–3.18)	0.050	1.60 (0.99–2.49)	0.055	1.17 (0.65–2.01)	0.58	1.07 (0.52–2.04)	0.85	1.26 (0.73–2.08)	0.60
Prior versus no prior BCG therapy	0.54 (0.27–0.98)	**0.042**	0.28 (0.08–0.67)	**0.002**	0.51 (0.26–0.89)	**0.015**	0.92 (0.39–2.01)	0.84	0.54 (0.12–1.80)	0.33	0.86 (0.40–1.71)	0.66
Non–UC pathology present versus absent	1.48 (0.66–2.87)	0.31	2.50 (1.09–4.97)	**0.031**	1.78 (0.83–3.35)	0.12	1.09 (0.37–2.60)	0.86	1.19 (0.40-2.81)	0.72	1.16 (0.59–2.48)	0.74
Median number of TUR-BTs prior to RC (continuously, over the total risk range)	0.78 (0.20–2.46)	0.69	0.70 (0.18–2.18)	0.56	0.50 (0.13–1.60)	0.26	2.83 (0.51–12.48)	0.21	0.42 (0.02–4.18)	0.49	1.55 (0.32–6.10)	0.56
1 versus >1 resections	1.25 (0.82–1.96)	0.29	1.52 (0.90–2.68)	0.12	1.08 (0.73–1.64)	0.69						
Median time interval between TUR-BT and RC (continously, over the total risk range)	2.45 (0.38–8.56)	0.29	2.89 (0.27–12.61)	0.31	1.80 (0.29–6.23)	0.47	0.34 (0.03–2.08	0.27	0.78 (0.04–6.80)	0.84	0.40 (0.04–2.33)	0.34
Age at RC (in years) continuously coded	1.66 (0.62–4.59)	0.32	3.74 (1.07–13.73)	**0.038**	2.59 (1.02–6.80)	**0.046**	1.05 (0.64–1.74)	0.37	1.71 (0.92–3.31)	0.09	2.07 (0.79–5.63)	0.13
Tumour grade G3 versus G2	1.37 (0.91–2.10)	0.12	1.64 (0.99–2.79)	0.056	1.14 (0.77–1.68)	0.51						
Gender (female versus male)	1.23 (0.75–1.95)	0.39	1.10 (0.58–1.95)	0.74	1.46 (0.93–2.23)	0.09						
Concomitant CIS at RC present versus absent	0.83 (0.52–1.29)	0.41	0.73 (0.40–1.26)	0.72	0.72 (0.46–1.10)	0.13						
Median time interval between first TUR-BT and last TUR-BT (continuously, over the total risk range)	1.42 (0.27–5.12)	0.61	0.34 (0.01–2.72)	0.35	0.36 (1.91–2.80)	0.25						

Table 2 continued

Variable	Univariable RFS		Univariable CSS		Univariable OS		Multivariable RFS		Multivariable CSS		Multivariable OS	
	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*	HR (95 % CI)	*p*
Median time interval between first TUR-BT (confirming BC) and RC (days), (continuously, over the total risk range)	1.21 (0.27–4.03)	0.77	0.29 (0.01–2.04)	0.24	0.39 (0.06–1.69)	0.22						
Tumour multifocality present versus absent	1.05 (0.67–1.62)	0.82	1.10 (0.63–1.87)	0.73	0.94 (0.61–1.42)	0.77						

Bold values indicate statistically significant difference

ALA aminolevulinate, *BCG* Bacille-Calmette–Guerin, *HAL* hexaminolevulinate, *PD* primary diagnosis, *PDD* photodynamic diagnosis, *RC* radical cystectomy, *STSM* soft tissue surgical margin, *TUR-BT* transurethral bladder tumour resection, *WL* white light, *UC* urothelial carcinoma

other significant differences were found in terms of the rates of locally advanced disease at RC. Only 4.5 % of the PDD patients underwent TUR-BT in external departments compared to 61.5 % of the WL patients. For WL patients, patient and tumour characteristics were not different between those who underwent external versus internal TUR-BTs, except for the rate of preoperative hydronephrosis. Altogether, these data suggest a balanced nature of the groups with regard to tumour and patient characteristics.

In univariable analysis, inferior RFS, CSS and OS was associated with advanced pathologic tumour and nodal stage, positive STSMs, lymphovascular invasion, hydronephrosis at RC, absence of prior BCG therapy and delivery of post-operative chemotherapy. CSS was also associated with the presence of non-pure urothelial carcinoma histology, whereas age at RC was associated with both CSS and OS. These data are in accordance with those of larger series [5, 7, 11, 12] and support the assumption that the present cohort is comparable to other larger series in terms of the impact of tumour characteristics on outcomes after RC.

RFS, CSS and OS were significantly higher in patients who underwent at least one HAL-guided TUR-BT before RC than in those who underwent only ALA- or WL-guided TUR-BT. These findings are interesting in the light of previous randomized studies in NMIBC of the effects of HAL versus ALA on intravesical recurrence: improved bladder tumour detection in ALA patients did not translate into improved intravesical RFS [13], although this has been reported for patients with NMIBC treated with HAL-TUR-BT [14]. As yet, however, possible molecular reasons for these findings have not been investigated. The results of this study suggest that the prognostic benefit of PDD owes to the performance of HAL-TUR-BT. Therefore, for uni- and multivariable Cox regression analyses, patients treated with HAL-TUR-BT were compared to the group of patients treated with either ALA- or WL-TUR-BT. Absence of HAL-TUR-BT, advanced pathologic tumour and nodal stage as well as positive STSMs were independent risk factors for recurrence, cancer-specific death and overall death. These findings suggest that HAL-TUR-BT affects outcomes in patients with advanced BC, which is surprising and raises the possibility of an inherent beneficial prognostic effect that cannot be conclusively explained by differences in clinical and pathologic outcome measures. Nonetheless, in this respect, a lower risk of progression to MIBC has been reported for patients with primary NMIBC randomized to HAL-based TUR-BT when compared with WL-guided TUR-BT ($p = 0.06$) [4].

This study has limitations inherent to any retrospective analysis, which have to be considered in the interpretation of the results. The rates of pT0 at RC between the three groups were not significantly different. Therefore, the observed differences in survival are not attributable to

a more complete resection of the tumour under HAL guidance. Our median follow-up was 29 months which is comparable to larger contemporary studies [15] and did not differ significantly between PDD and WL patients.

We acknowledge that the retrospective character of our study challenges the interpretation of the data, especially with regard to the indication to perform either PDD- or WL-TUR-BT. However, for the PDD group, as only 4.5 % of the PDD patients were treated in external departments and two-thirds of the PDD-based resections were performed at the first TUR-BT, this finding may be regarded as supportive of our statement in terms of our policy for selection of patients for PDD-TUR-BT during study period. In this respect, in our department, all patients with suspicion of primary BC, recurrent or persistent disease more than 8 weeks after the last resection undergo regularly HAL-TUR-BT. During the study period, the substance used for PDD was based on its availability in Germany at that time. Generally, as a tertiary referral centre, a selection bias in terms of those who were referred to RC but were externally diagnosed and treated for BC cannot be excluded. We cannot adjust for the indication to perform either PDD or WL-TUR-BT for those patients who underwent TUR-BT in external departments. However, in the setting of RC, one may think that the referral cases may have had more advanced disease and therefore inferior outcomes which may explain the superior outcomes for HAL-TUR-BT who were mainly treated in our department. For this reason, we analysed our database whether tumour and patients characteristics between WL patients treated in our department were different from those of external departments. We did not observe any significant differences in terms of clinical and tumour characteristics, except for the rate of preoperative hydronephrosis. Yet, survival rates were not significantly different between groups. Therefore, these data underline that the referral cases did not display more advanced stages and did not have inferior outcomes. In turn, these data suggest for the internal cases that the surgeons' decision to use either PDD or WL was less likely dependent on patients and tumour characteristics.

Another explanation for the favourable outcomes of HAL-TUR-BT might be improved patient management. In the present series, patients with HAL-TUR-BT had significantly more resections prior to RC compared to WL patients, while the rate of NMIBC at PD of BC tended to be higher in the PDD group. Despite this, the rates of locally advanced tumour stage at RC were not significantly different between the HAL, the ALA and the WL group. Therefore, the question arises of how the performance of HAL-TUR-BT translates into improved survival in patients who will undergo RC during the course of disease. One possible explanation might be that HAL-TUR-BT increased the awareness of the treating urologist to perform a more vigilant follow-up which resulted in a more timely indication to perform RC. The multivariable analysis confirms the prognostic benefit of HAL-TUR-BT since it was found to be an independent predictor for RFS, CSS and OS. Upfront optimized patient management might be therefore as critical for outcomes as the prognostic effect of standard pathologic risk factors, especially for those with NMIBC at PD who will progress to advanced disease. In this regard, HAL-TUR-BT may be regarded as a surrogate marker for improved BC management. Therefore, to our opinion, the most conclusive rationale for the data presented herein is improved patient management with HAL-TUR-BT which can make a difference in outcomes even for those patients who display advanced disease at RC. Nevertheless, owing to these limitations, the results of this study await further external validation.

Conclusions

This is, to our knowledge, the first contemporary RC series to evaluate the prognostic effect of HAL-based TUR-BT in a homogenous, consecutive series of patients undergoing RC for BC. The findings of this study suggest that performance of HAL-guided TUR-BT is of prognostic importance for those who will have to undergo RC during the course of their disease. Further prospective studies should yield a better understanding of how transurethral resection of invasive bladder tumours under HAL exerts a positive therapeutic impact on survival after RC.

Conflict of interest G. Gakis and A. Stenzl have received speaker honoraria from IPSEN Pharma GmbH, Ettlingen, Germany. All other authors have nothing to disclose. No funding was obtained for this study.

Ethical standard This study was approved by the Local Ethics Committee, Tübingen, and conducted according to the Declaration of Helsinki and according to the STROBE statement (see supplementary material).

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