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ORIGINAL ARTICLE

# The prognostic impact of hexaminolevulinate-based bladder tumor resection in patients with primary non-muscle invasive bladder cancer treated with radical cystectomy

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## Abstract

**Purpose** To investigate whether hexaminolevulinate-based (HAL) bladder tumor resection (TURBT) impacts on outcomes of patients with primary non-muscle-invasive bladder cancer (NMIBC) who were eventually treated with radical cystectomy (RC).

**Methods** A total of 131 consecutive patients exhibiting NMIBC at primary diagnosis were retrospectively investigated whether they had undergone any HAL-guided TURBT prior to RC. Uni- and multivariable analyses were used to evaluate the impact of HAL-TURBT on cancer-specific (CSS) and overall survival (OS). The median follow-up was 38 months (IQR 13–56).

**Results** Of the 131 patients, 69 (52.7%) were managed with HAL- and 62 (47.3%) with white light (WL)-TURBT only prior to RC. HAL-TURBT was associated with a higher number of TURBTs prior to RC ($p=0.002$) and administration of intravesical chemotherapy ($p=0.043$). A trend towards a higher rate of tumor-associated immune cell infiltrates in RC specimens ($p=0.07$) and a lower utilization rate of post-operative systemic chemotherapy ($p=0.10$) was noted for patients who were treated with HAL-TURBT. The 5-year CSS/OS was 90.9%/74.5% for the HAL-group and 73.8%/55.8% for the WL-group ($p=0.042/0.038$). In multivariable analysis, lymph node tumor involvement ($p=0.007$), positive surgical margins ($p=0.001$) and performance of WL-TURBT only ($p=0.040$) were independent predictors for cancer-specific death.

**Conclusions** The present data suggest that the resection of NMIBC under HAL exerts a beneficial impact on outcomes of patients who will need to undergo RC during their course of disease. This finding may be due to improved risk stratification as the resection under HAL may allow more patients to be treated timely and adequately.

**Keywords** Bladder cancer · Fluorescence · Hexaminolevulinate · Non-muscle invasive · Radical cystectomy · Survival

## Introduction

Bladder cancer (BC) is the 11th commonest malignancy worldwide with up to 80% of patients presenting with non-muscle invasive bladder cancer (NMIBC) at primary diagnosis (PD) [1]. Transurethral bladder tumor resection (TURBT) and intravesical instillation therapy represent the mainstay of treatment for NMIBC [2]. Despite the initially high cure rates, the long-term risk of disease recurrence and progression in NMIBC remains considerable [3]. Therefore, patients with NMIBC at high or very high risk of progression can be offered upfront radical cystectomy (RC) according to recent guidelines [1, 2].

In the past, cystoscopy and TURBT have been performed only under white-light (WL) conditions. The development

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of photodynamic diagnosis (PDD) for BC has improved the tumor detection rates during these procedures [4]. Hexaminolevulinic acid (HAL) is a hexyl ester of 5-aminolevulinic acid (ALA) and approved for PDD of the bladder [5, 6]. It improves the visibility of cancerous lesions through prompting intracellular accumulation of photoactive porphyrines, especially within neoplastic urothelial cells [7]. In a meta-analysis of randomized trials, HAL-based TURBT displayed superiority over WL-based TURBT by increasing the detection rates of Ta–T1 and carcinoma in situ (CIS) lesions by 20% and 40%, respectively [8]. Based on the new International Bladder Cancer Group (IBCG) criteria for NMIBC progression, another meta-analysis of randomized trials reported significantly lower disease progression rates for HAL compared to WL-TURBT [9]. Furthermore, the largest randomized trial on HAL to date reported that the long-term risk of undergoing RC was reduced by 44% for patients treated with HAL- versus WL-TURBT [10].

Critical determinants for survival after RC include tumor stage, lymph node status, soft-tissue surgical margins (STSMs) and the presence of lymphovascular invasion (LVI) [11]. In general, survival rates after RC for NMIBC are superior to those performed for muscle-invasive bladder cancer (MIBC) [12]. Yet, in the literature, a history of disease progression from NMIBC to MIBC was found to be associated with a lower CSS when compared to patients treated with RC for primary MIBC [13]. Therefore, we aimed to investigate the prognostic value of HAL- vs. WL-based TURBT on survival of patients who initially presented with NMIBC and required RC during their course of disease.

## Patients and methods

### Patients

In this retrospective observational analysis, approved by the Local Ethics Committee Tübingen, the clinical and histopathologic records of 131 consecutive patients who were diagnosed with NMIBC at primary diagnosis (PD) and were treated with RC with curative intent between 2004 and 2013 were reviewed. The indication for the use of HAL at TURBT was constant during study period. Generally, for patients referred primarily to our department during the investigated period, every TURBT for suspected BC was conducted under HAL. HAL-TURBT was also utilized in our department for second resection when the last TURBT was conducted more than 8 weeks ago. All 131 patients were cystectomized in our center and the indication for cystectomy was constant during study period. Indication for primary cystectomy in NMIBC was multifocal ($\geq 3$ lesions) T1 high-grade bladder cancer and extensive NMIBC of any grade and stage not amenable to endoscopic and instillation therapy. In addition, patients with persistent or progressive disease following BCG instillation therapy and progression to MIBC were recommended to undergo RC.

We assessed various clinical and histopathologic parameters: age at RC, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS) at RC, number of TURBTs prior to RC, time interval between the first and last TURBT, time between last TURBT and RC, tumor multifocality at PD, presence of CIS at PD, clinical and histopathologic tumor stage at PD and RC, tumor grade at PD and RC, lymph node tumor involvement, STSMs, LVI, tumor size at RC, hydronephrosis at RC, histological entity of BC (urothelial vs. non-urothelial), presence of tumor-associated immune cell infiltrates (TAICs) in RC specimens, administration of intravesical immuno- and/or chemotherapy and receipt of post-operative systemic chemotherapy. Clinical tumor stage at RC considers the highest tumor stage prior to RC irrespective of whether detected on histopathological analysis at any TURBT or at cross-sectional imaging prior to RC.

### Histologic assessment

The histopathologic assessment was performed in the Tubingen pathology department and was based on the TNM classification approved by the AJCC [14]. The histopathologic macro- and microscopic examination of cystectomy specimens included cross-sectioning of the entire specimen with immunohistochemical staining to identify BC [15].

### Follow-up

Generally, patients were seen post-operatively at least every 3–4 months for the first year, semiannually for the second and third years, and annually thereafter. Besides history, clinical examination and standard laboratory tests, cross-sectional imaging, endoscopy and urinary cytology were done at regular intervals to detect recurrence. Recurrence was defined as any visible tumor in the surgical bed, in distant organs or in the remnant urothelium [16]. The median follow-up after RC was 38 months (IQR 13–56). Cancer-specific survival (CSS) and overall survival (OS) were measured from the date of RC to (cancer-specific) death or last follow-up, respectively, as determined by patient charts.

### Statistical analysis and model development

For univariable analysis, the Fisher Exact/$\chi^2$ test was used for nominal data and $t$ test for scaled parameters. Values are given as mean, median and interquartile range (IQR). Kaplan–Meier plots were used to estimate CSS and OS. Uni- and multivariable Cox-proportional hazard analyses were carried out to evaluate risk factors for cancer-specific death.

$p$ values are two sided with $p < 0.05$ considered significant. Statistical analysis was performed with JMP® 12.0 (Cary, NC, USA).

## Results

Of the 131 patients, 69 (52.7%) were managed with at least one HAL- and 62 (47.3%) with WL-TURBT only prior to RC. HAL-TURBT was associated with a higher number of TURBTs before RC ($p = 0.002$) and a higher rate of administration of intravesical chemotherapy ($p = 0.043$). A trend towards a higher rate of TAICs in RC specimens ($p = 0.07$) and a lower utilization rate of palliative systemic chemotherapy after RC ($p = 0.10$) was noted for patients who were treated with HAL-TURBT (see Table 1). In the HAL-group, the median number of HAL-based TURBTs was 1.7 (median 1, IQR 1–2).

The 5-year CSS was 90.9% for patients treated with HAL-TURBT and 73.8% for patients with WL-TURBT ($p = 0.042$; see Fig. 1). The 5-year OS was 74.5% for HAL- and 55.8% for WL-TURBT ($p = 0.038$; see Fig. 2). In univariable Cox-regression analysis, advanced histopathologic tumor stage, lymph node tumor involvement, positive STSMs, lymphovascular invasion (all $p < 0.001$) and performance of WL-guided TURBT only ($p = 0.039$) prior to RC were risk factors for inferior CSS. In multivariable analysis, lymph node tumor involvement ($p = 0.005$), positive STSMs ($p = 0.001$) and absence of HAL-TURBT ($p = 0.031$) were independent prognosticators for increased cancer-specific mortality (see Table 2).

## Discussion

In this study, we found that patients with NMIBC at PD who were eventually treated with RC during their course of disease exhibited superior survival if they had undergone at least one HAL-TURBT prior to surgery compared to those who underwent only WL-based procedures. In addition, patients in the HAL-group exhibited higher rates of TURBT and intravesical chemotherapy albeit the clinical and histopathologic parameters were not significantly different at PD and RC between both groups.

HAL-based TURBT has been confirmed to increase the detection rate of malignant lesions in the bladder, especially CIS [8]. This correlates with evidence that HAL-based TURBT significantly reduces recurrence rates in patients with primary or recurrent NMIBC [5]. Moreover, a beneficial effect of HAL-TURBT on progression in both NMIBC and MIBC was reported in recent studies [5, 9, 17, 18]. Accordingly, the EAU guidelines emphasize the use of HAL especially in patients with positive urinary cytology or expected high-risk disease [2].

Advanced histopathologic tumor and nodal stage, positive STSMs and LVI have been confirmed as independent prognostic factors for inferior survival after RC [11, 19]. Likewise, in the present study, univariable and multivariable analyses confirmed advanced stage, positive lymph nodes, positive STSMs and LVI to be associated with lower CSS. This concordance underlines the reproducibility and validity of our analysis compared to larger series [11]. Taking a closer look into the literature, lymph node positivity and positive resection margins exhibit the highest prognostic potential compared to tumor stage and lymphovascular invasion. In fact, patients with locally advanced but node-negative disease with concurrent lymphovascular invasion (≥ pT3a pN0 LVI) show markedly improved survival rates compared to those with any positive lymph nodes (pTany pN + LV any; [11]. Moreover, those with positive STSMs exhibit the worst survival rates which are often associated rapid progression after RC. In other words, the adverse prognostic potential of lymph node positivity and positive soft-tissue surgical margins is higher than that of tumor stage and lymphovascular invasion. This puts into perspective the finding that pT-stage and LVI were not found to be independently associated with CSS when tested in the final model against HAL-TURBT.

Furthermore, the rate of stage cT3 disease (28.2%) for this specific cohort of patients with primary NMIBC is comparable to the results of larger series [20]. It has to be taken into consideration that radiological imaging prior to RC was usually conducted after the last TURBT which may be prone to staging inaccuracies because of TURBT-related tissue artefacts. At the time our patients were treated, the role of neoadjuvant chemotherapy for cT3 stage was controversially in our country. In addition, the EAU guidelines have upgraded the recommendation of adjuvant chemotherapy [1] based on the results of recent randomized trials [21]. Moreover, the overall rate of lymph node-positive disease at RC in this specific cohort is comparable to other series [11, 20]. In terms of the rate of positive soft-tissue surgical margins, our rates are in accordance with the results of contemporary randomized studies on the use of RC in patients with ≥ T1G3 bladder cancer (8–9%; [22]). Moreover, a total of 14 patients (10.7%) had pT4a–b disease which is associated with a considerably higher risk of positive STSMs.

Interestingly, we found that the performance of WL-TURBT only during the course of disease was an independent risk factor for inferior CSS. Therefore, the question derives how HAL-TURBT may have exerted such a strong beneficial impact of survival outcomes in this cohort. In the present study, the HAL and WL cohorts were comparable in terms of their patient characteristics and histopathologic parameters both at PD and RC. The median time interval

**Table 1** Clinical and histopathological characteristics of patients treated with radical cystectomy for bladder cancer subanalyzed according to the use of HAL or WL-TURBT

| Parameters | HAL-TURBT | WL-TURBT only | *p* |
|---|---|---|---|
| Number of patients (%) | 69 (52.7) | 62 (47.3) | |
| Gender | | | 0.82 |
| Male | 57 (82.6) | 50 (80.7) | |
| Female | 12 (17.4) | 12 (19.4) | |
| Mean age at RC [a] | 69 | 69 | 0.79 |
| Median | 71 | 70 | |
| IQR | 61–76 | 63–75 | |
| Mean time between first TURBT and RC [mo] | 7 | 4 | 0.55 |
| Median | 22 | 18 | |
| IQR | 3–30 | 1–15 | |
| Mean time between last TURBT and RC [d] | 64 | 47 | 0.25 |
| Median | 38 | 32 | |
| IQR | 23–56 | 21–49 | |
| Mean number of TURBTs before RC | 3.6 | 2.5 | **0.002** |
| Median | 3 | 2 | |
| IQR | 2–4 | 2–3 | |
| Tumor stage at PD | | | 0.30 |
| PUNLMP | 0 (0) | 1 (1.6) | |
| Ta | 24 (34.8) | 14 (22.6) | |
| Tis | 5 (7.3) | 6 (9.7) | |
| T1 | 39 (56.5) | 38 (61.3) | |
| TX | 1 (1.5) | 3 (4.8) | |
| Tumor grade at PD | | | 0.44 |
| G1 | 6 (8.7) | 4 (6.5) | |
| G2 | 34 (49.3) | 25 (40.3) | |
| G3 | 26 (37.7) | 29 (46.8) | |
| GX | 3 (4.4) | 4 (6.5) | |
| Concomitant CIS at PD | | | 0.83 |
| Present | 16 (23.2) | 13 (21.0) | |
| Absent | 53 (76.8) | 49 (79.0) | |
| Tumor multifocality at PD | | | 0.66 |
| Present | 23 (33.3) | 21 (33.9) | |
| Absent | 24 (34.8) | 17 (27.4) | |
| Not evaluable | 22 (31.9) | 24 (38.7) | |
| ECOG PS at RC | | | 0.28 |
| 0 | 61 (88.4) | 50 (80.7) | |
| 1 | 8 (11.6) | 9 (14.5) | |
| 2 | 0 (0) | 1 (1.6) | |
| 3 | 0 (0) | 2 (3.2) | |
| Clinical tumor stage | | | 0.69 |
| ≥ cT3 | 18 (26.1) | 19 (30.7) | |
| ≤ cT2 | 51 (73.9) | 43 (69.4) | |
| Stage at RC | | | 0.21 |
| NMIBC (≤ pT1N0) | 33 (47.8) | 23 (37.1) | |
| MIBC (≥ pT2N0–3) | 36 (52.2) | 39 (62.9) | |

**Table 1** (continued)

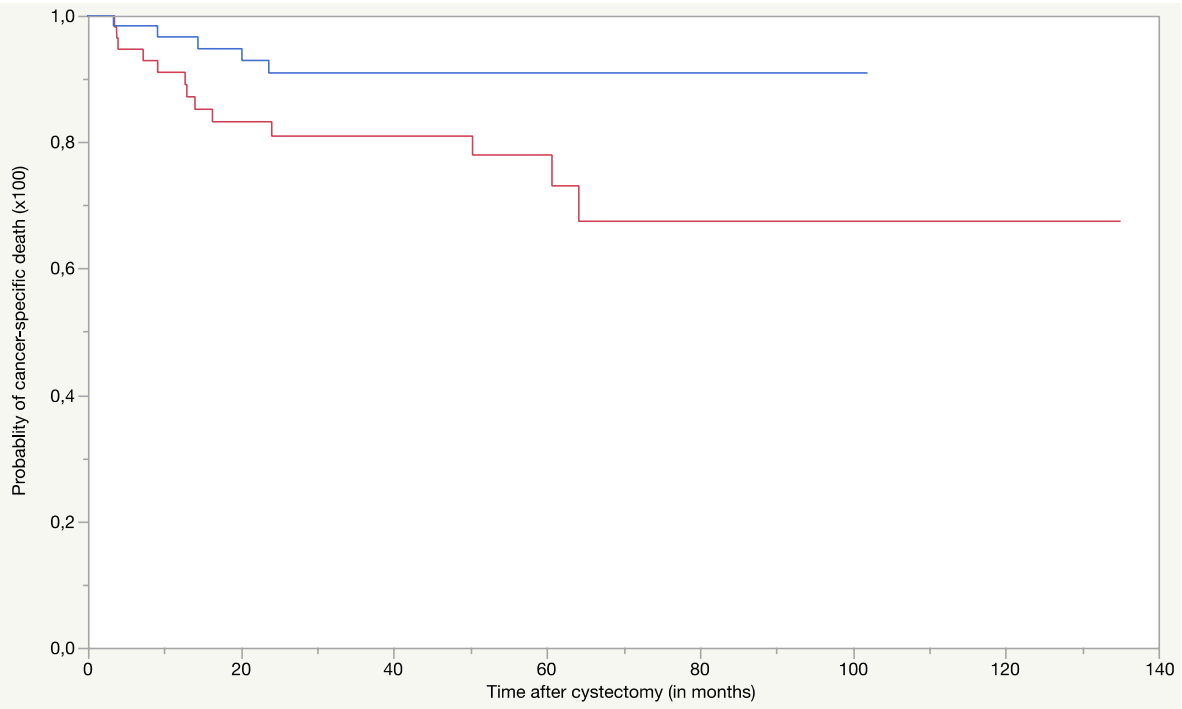
| Parameters | HAL-TURBT | WL-TURBT only | *p* |
|---|---|---|---|
| pT-stage at RC | | | 0.27 |
| ≥ pT3a | 22 (31.9) | 26 (41.9) | |
| ≤ pT2b | 47 (68.1) | 36 (58.1) | |
| pT0 | 6 (8.7) | 1 (1.6) | |
| pTa | 3 (4.4) | 6 (9.7) | |
| pTis | 9 (13.0) | 6 (9.7) | |
| pT1 | 14 (20.3) | 10 (16.1) | |
| pT2a | 5 (7.3) | 7 (11.3) | |
| pT2b | 10 (14.5) | 6 (9.7) | |
| pT3a | 10 (14.5) | 6 (9.7) | |
| pT3b | 8 (11.6) | 10 (16.1) | |
| pT4a | 4 (5.8) | 6 (9.7) | |
| pT4b | 0 (0) | 4 (6.5) | |
| Histopathological nodal stage | | | 0.25 |
| pN+ | 14 (20.3) | 11 (17.7) | |
| pN0 | 53 (76.8) | 44 (71.0) | |
| pNX | 2 (2.9) | 7 (11.3) | |
| Surgical margins | | | 0.46 |
| Positive | 6 (8.7) | 8 (12.9) | |
| Negative | 62 (89.9) | 52 (83.9) | |
| Not assessed | 1 (1.4) | 2 (3.2) | |
| Lymphovascular invasion | | | 0.69 |
| LVI | 19 (27.5) | 20 (32.3) | |
| LV0 | 44 (63.8) | 37 (59.7) | |
| LVX | 6 (8.7) | 5 (8.1) | |
| TARCs at RC | | | 0.07 |
| Present | 48 (69.6) | 33 (53.2) | |
| Absent | 21 (30.4) | 29 (46.8) | |
| Tumor multifocality | | | 0.85 |
| Present | 28 (40.6) | 24 (38.7) | |
| Absent | 41 (59.4) | 38 (61.3) | |
| Estimated tumor size at RC [cm] | | | 0.16 |
| Mean | 2.7 | 3.1 | |
| Median | 2.5 | 2.8 | |
| IQR | 1.6-3.9 | 2-4 | |
| Tumor grade at RC | | | 0.14 |
| G1 | 0 (0) | 3 (4.8) | |
| G2 | 25 (36.2) | 19 (30.7) | |
| G3 | 37 (53.6) | 39 (62.9) | |
| Data not retrievable | 7 (10.2) | 1 (1.6) | |
| Hydronephrosis at RC | | | 0.81 |
| Present | 12 (17.4) | 9 (14.5) | |
| Absent | 57 (82.6) | 52 (83.9) | |
| Data not retrievable | 0 (0) | 1 (1.6) | |
| Non-pure UC pathology at RC | | | 0.22 |
| Present | 4 (5.8) | 8 (12.9) | |
| Absent | 65 (94.2) | 54 (87.1) | |
| Intravesical BCG therapy | | | 0.21 |
| Received | 31 (44.9) | 21 (33.9) | |
| Not received | 38 (55.1) | 41 (66.1) | |

**Table 1** (continued)

| Parameters | HAL-TURBT | WL-TURBT only | *p* |
|---|---|---|---|
| Intravesical chemotherapy | | | **0.034** |
| Performed | 25 (36.2) | 12 (19.4) | |
| Not performed | 44 (63.8) | 50 (80.7) | |
| Post-operative systemic chemotherapy | | | 0.10 |
| Received | 8 (11.6) | 14 (22.6) | |
| Not received | 61 (88.4) | 48 (77.4) | |

Bold values indicate statistically significant difference

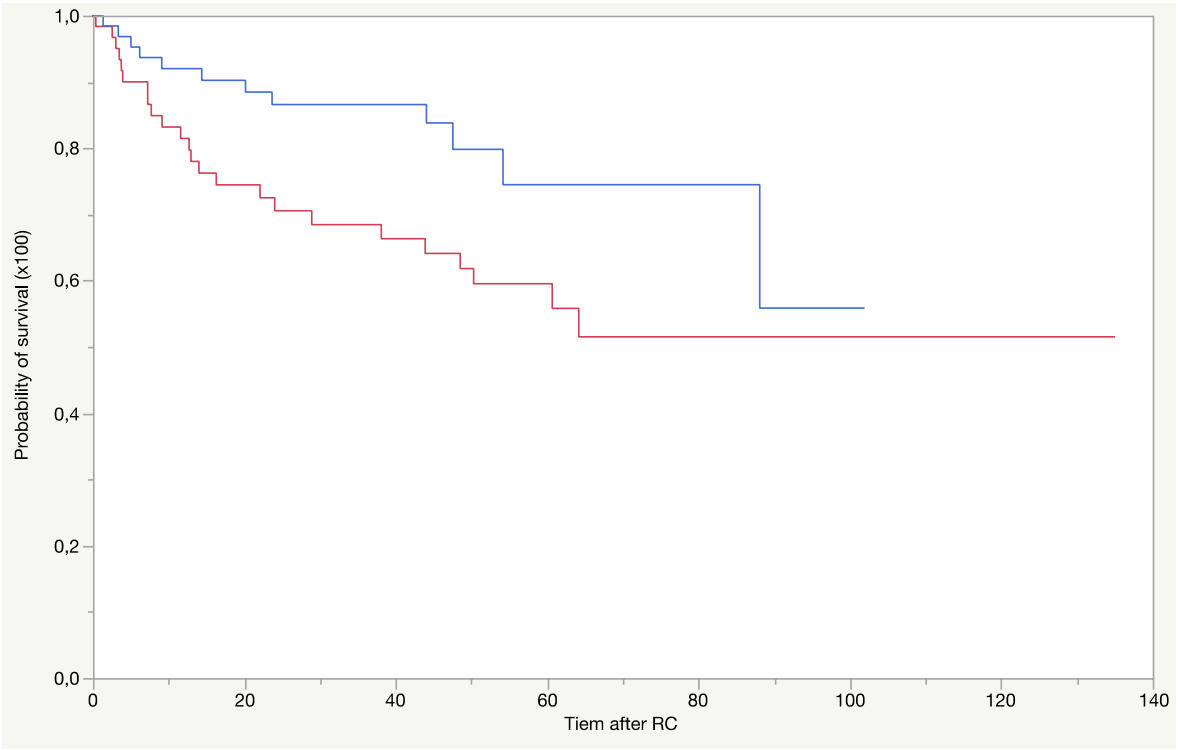
*a* year, *BCG* Bacille-Calmette-Guérin, *d* days, *ECOG PS* Eastern Cooperative Oncology Group performance status, *HAL* hexaminolevulinate, *IQR* interquartile range, *MIBC* muscle-invasive bladder cancer, *MMC* mitomycin-C, *mo* months, *p p* value, *PD* primary diagnosis, *RC* radical cystectomy, *TURBT* transurethral bladder tumor resection, *UC* urothelial carcinoma, *WL* white light




**Number of patients at risk of cancer-specific death at given time intervals**

| Variable/Time | 0 | 12 | 24 | 36 | 48 | 60 |
|---|---|---|---|---|---|---|
| HAL-TURBT | 69 | 53 | 46 | 35 | 19 | 12 |
| WL-TURBT only | 62 | 47 | 37 | 33 | 28 | 16 |

**Fig. 1** Cancer-specific survival of patients with primary NMIBC who were treated with at least one HAL- (blue line) vs. WL-guided only TUR-B (red line) and underwent radical cystectomy during the course of disease (Leg.: *HAL* hexaminolevulinate, *NMIBC* non-muscle invasive bladder cancer, *TURBT* transurethral bladder tumor resection, *WL* white light)




| Number of patients at risk of death at given time intervals | | | | | | |
|---|---|---|---|---|---|---|
| **Variable/Time** | **0** | **12** | **24** | **36** | **48** | **60** |
| **HAL-TURBT** | 69 | 54 | 47 | 35 | 22 | 12 |
| **WL-TURBT only** | 62 | 48 | 37 | 33 | 28 | 17 |

**Fig. 2** Overall survival of patients with primary NMIBC who were treated with at least one HAL- (blue line) vs. WL-guided only TURBT (red line) and underwent radical cystectomy during the course of disease (Leg.: *HAL* hexaminolevulinate, *NMIBC* non-muscle invasive bladder cancer, *TURBT* transurethral bladder tumor resection, *WL* white light)

**Table 2** Uni- and multivariable Cox-regression analyses for survival of risk factors in patients with primary non-muscle bladder cancer treated with radical cystectomy during the course of disease

| Parameters | Univariable | | Multivariable | |
|---|---|---|---|---|
| | CSS | | CSS | |
| | HR (95% CI) | *p* | HR (95% CI) | *p* |
| WL vs. HAL-TURBT | 2.80 (1.05–8.73) | **0.039** | 4.12 (1.21–17.10) | **0.031** |
| ≥ pT3a vs. ≤ pT2b | 6.08 (2.32–17.6) | **< 0.001** | 2.43 (0.43–15.76) | 0.33 |
| pN+ vs. pN0 | 14.21 (4.85–47.52) | **< 0.001** | 13.69 (2.46–103.50) | **0.005** |
| Positive vs. negative surgical margins | 12.94 (4.80–34.27) | **< 0.001** | 10.12 (2.40–45.41) | **0.001** |
| LVI vs. LV0 | 11.58 (4.11–41.16) | **< 0.001** | 3.36 (0.73–16.86) | 0.12 |
| CIS (at PD and/or RC) present vs. absent | 1.90 (0.72–5.92) | 0.2 | 1.62 (0.40–8.27) | 0.51 |

Bold values indicate statistically significant difference

*CI* confidence interval, *CIS* carcinoma in situ at RC, *CSS* cancer-specific survival, *HAL* hexaminolevulinate, *HR* hazard ratio, *LV0* lymphovascular invasion absent, *LVI* lymphovascular invasion present, *WL* white light

between the first TURBT and RC was not significantly different between both groups. By contrast, the median number of performed TURBTs per patient was higher in the HAL-group. This might also explain the fact that the number of patients receiving intravesical chemotherapy was about two-fold higher in the HAL compared to the WL cohort. Theoretically, a possible explanation for these findings may be that the use of HAL-TURBT resulted in improved tumor detection and completeness of resection that also translated into improved risk stratification and optimized management with chemoinstillation.

Progression of NMIBC to MIBC was shown to be associated with inferior cancer-related outcomes after RC compared with primary MIBC [13]. We did not find a significant difference in the various histopathologic determinants for survival at PD and after RC between both groups which does not allow to draw the conclusion that HAL-TURBT may have delayed histopathologic progression of NMIBC to MIBC. Although the use of intravesical chemoinstillation was more frequent in the HAL cohort, a large randomized trial has shown intravesical chemoinstilation to be associated with improved intravesical recurrence-free but not progression-free survival in intermediate- to high-risk NMIBC patients [23]. Therefore, it is unlikely that chemoinstillation can reduce risk of progression translating into lower T- and N-stage and thus improved CSS after RC. However, while the number of TURBT was significantly higher in the HAL-cohort the time interval between primary diagnosis and last TURBT as well as the time interval between last TURBT and RC were similar. This underscores that the "density of treatment" was much higher in the HAL cohort which may also have exerted a beneficial therapeutic impact on outcomes. Nonetheless, since progression to MIBC at RC was noted to a similar extent in both groups, the role of HAL-TURBT deserves further attention with regard to its possible molecular effects on tumor and immune cells.

The presence of TAICs in specimens has been reported as a beneficial prognostic factor in various solid tumors, including BC [24–27]. The higher rate of TAICs in RC specimens in the HAL-group raises the question about the cytotoxic or immunogenic activities of HAL. In fact, the cytotoxicity of photosensitizers has been investigated in various studies in the last years [28]. Zenzen et al. investigated the cytotoxic and mutagenic effect of the 5-aminolevulinic acid hexylester (h-ALA) on tumor and fibroblast cell lines, and found h-ALA to display a favorable selective cytotoxic effect on tumor cells [29]. Ekroll et al. investigated the destructive effect of the photodynamic therapy using HAL-mediated photodynamic therapy (PDT) on bladder urothelial carcinoma cell lines in the rat. They detected a noticeable increase of cellular apoptosis and proposed modifications of the PDT protocol for adjustment of the light wavelengths to increase the rate of apoptosis [30].

There are limitations of our study that have to be taken into account in the interpretation of results. First, the results have to be interpreted cautiously with consideration of its retrospective nature and the number of the included patients. We admit that our cohort is rather a heterogenous group of high-risk patients. Second, although the indication for the use of HAL for patients treated with TURBT in our hospital was constant during this period, a confounding bias may exist with regard to those patients who were treated once, several times or exclusively in external hospitals with TURBT at any time point during the course of their disease. In this regard, we cannot adjust for the in-hospital policy of external hospitals in terms of the use of HAL during the investigated time period. Thus, we cannot extrapolate the magnitude of bias for this specific aspect. In terms of recurrence and progression rates, we acknowledge that our database does not capture data on the effects of instillation therapy since intravesical instillation therapy is usually conducted in Germany by office urologists. Since intravesical recurrence-free survival is improved with HAL [5, 6, 8], it can be assumed that resection under HAL improves the quality and completeness of the procedure which may translate into improved outcomes reflected by standard clinical and histopathological parameters. In addition, possible molecular mechanisms of how HAL may have influenced bladder cancer cell proliferation remain hypothesis generating. In addition, external validation and data from larger series are also necessary to verify these findings.

In summary, this analysis suggests that patients who have undergone bladder tumor resection with HAL exhibit improved outcomes even when they progress to disease stages which require RC for definitive treatment compared to patients who undergo WL-based procedures only prior to RC. This may be due to improved risk stratification as the detection and resection of BC under HAL may allow more patients to be treated timely and adequately. Albeit these data warrants further validation, they are supportive of results of recent studies on the beneficial long-term impact of HAL-based TURBT in patients with BC.

**Author contributions** MR and OF manuscript writing. TS, FH and AS project development. MAS data collection. GG project development, data analysis, manuscript writing and editing.

## Compliance with ethical standards

**Conflict of interest** G. Gakis: receipt of speaker honoraria and travel grants from IPSEN, Ettlingen, Germany. All other authors have nothing to disclose in relation with the content of the manuscript.

**Ethical approval** The study was approved by the local ethics committee of the university of Tübingen (Approval number: 417/2010A).

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