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Updated Analysis: Blue-Light Transurethral Resection and Biopsy of Bladder Cancer with Hexaminolevulinate in a Single UK Centre

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Abstract

Objective: To evaluate the diagnostic yield of blue-light cystoscopy (BLC) compared with white-light cystoscopy (WLC) in detecting carcinoma in situ (CIS) and muscle-invasive bladder cancer (MIBC), and to assess recurrence-free survival (RFS) following BLC-HAL resection. Patients and Methods: We retrospectively analysed 238 patients undergoing BLC-HAL between July 2017 and July 2024. Seventy-two underwent primary BLC at initial resection, and 166 underwent BLC re-resection following WLC. Endpoints were CIS detection, tumour upstaging, and recurrence-free survival at 12 and 24 months using Kaplan–Meier analysis. Results: Overall, malignancy was confirmed in 113/238 patients (47%). Detection was higher in the secondary arm (55%) compared with the primary arm (29%). In the primary arm, CIS was detected in 19% and MIBC in 24%. In the secondary arm, CIS increased from 18% on WLC to 38% with BLC (p = 0.001), with 26% detected only under blue light; 10% were upstaged to MIBC (p = 0.022). Over one-third of patients were reclassified into a higher EAU NMIBC risk group. Kaplan–Meier analysis showed 12- and 24-month RFS of 71% (95% CI: 36–92%) and 67% (95% CI: 35–88%) in the primary arm, and 62% (95% CI: 49–74%) and 63% (95% CI: 43–79%) in the secondary arm. Median RFS was not reached within 24 months. Conclusions: BLC significantly enhances CIS detection and identifies MIBC and higher-risk disease not seen on WLC, directly influencing patient management. Despite improved detection, recurrence-free survival remains modest, consistent with high-risk NMIBC, supporting guideline recommendations for routine use of BLC at TURBT, particularly in suspected CIS and high-grade disease.

Keywords: bladder cancer; blue-light cystoscopy; carcinoma in situ; muscle-invasive bladder cancer; hexaminolevulinate

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1. Introduction

Bladder cancer is the ninth most diagnosed cancer worldwide, with an estimated 614,298 new cases and 220,596 deaths in 2022, representing a significant global health burden associated with a high risk of progression and recurrence [1]. In the UK, bladder cancer accounts for around 3% of all new cancer cases annually and is the sixth most common cancer in men [1].

Urothelial carcinoma, which arises from the lining of the urinary tract, accounts for nearly 90% of all bladder cancer cases. At diagnosis, roughly a quarter of patients present with muscle-invasive bladder cancer (MIBC), whilst the majority are diagnosed with non-muscle-invasive bladder cancer (NMIBC), involving lesions confined to the mucosa [2]. Papillary tumours confined to the mucosa and lamina propria are classified as stage Ta or T1, respectively. Flat high-grade tumours confined to the mucosa are classified as carcinoma in situ (CIS).

In the United Kingdom (UK), GIRFT's focus on early diagnosis and appropriate treatment pathways is crucial because early detection significantly improves the chances of successful treatment and survival. UK guidelines advise white-light cystoscopy (WLC)-guided transurethral resection of bladder tumour (TURBT) for the diagnosis and initial management of NMIBC, in conjunction with adjuvant tools such as photodynamic diagnosis (PDD), narrow-band imaging, cytology or a urinary biomarker test [3]. Complete tumour resection and accurate histological staging are crucial given the high risk of progression and recurrence associated with incomplete resection.

However, despite remaining the gold standard, the literature suggests notable limitations associated with WLC in detecting clinically significant, small papillary lesions and CIS, which may lead to unsatisfactory resection and under-staging. Residual tumour has been reported in up to 80% of cases following initial WLC-guided TURBT [4]. A study by Herr has shown residual tumour in 76% of cases following initial resection under WLC and between 4 and 29% of patients being upstaged to muscle-invasive disease at second TURBT, emphasising the role of enhanced tumour visualisation techniques such as PDD to guide resection to improve diagnostic accuracy and oncological outcomes [5].

PDD enhances visual demarcation between malignant and normal tissues by utilising photoactive properties of compounds like Hexaminolevulinic acid (HAL). HAL is a precursor of photoactive intermediate protoporphyrin IX (PpIx), which accumulates preferentially in malignant cells. HAL is administered via intravesical installation 1 h prior to fluorescence cystoscopy via urinary catheter. PDD fluoresces a red-pink colour when exposed to blue light (375–440 nm), producing a clear demarcation of red fluorescence from malignant tissue, in contrast to healthy urothelium, which appears blue. A 2013 meta-analysis by Burger et al. found that blue-light cystoscopy (BLC) was significantly superior to standard WLC in detecting small bladder lesions, with BLC identifying 15% and 41% more Ta and CIS lesions, respectively, with many CIS lesions only detected by blue light [6]. Similarly, another key meta-analysis from 2022 demonstrated significantly lower recurrence rates with BLC, showing a 34% reduction in the rate of recurrence compared to WLC [7].

In our centre, BLC was adopted in 2017 by the senior author. In this study we present an updated analysis of outcomes at our centre from 2017 to 2024. We evaluate the 12- and 24-month recurrence rate in patients undergoing BLC with HAL (BLC-HAL), alongside detection of CIS in patients undergoing re-TURBT with BLC following initial WLC TURBT. This single-centre retrospective analysis aims to further evaluate the impact of BLC-HAL TURBT on tumour detection and mid-term oncological outcomes.

Given the evolving role of enhanced cystoscopic techniques in NMIBC management, detailed evaluation of detection, pathological upstaging, and mid-term oncological outcomes in real-world practice remains clinically relevant.

2. Patients

Between July 2017 and 2024, 238 patients with suspected bladder cancer based on cystoscopy underwent blue-light cystoscopy ± TURBT ± biopsy. A total of 72 patients were initially referred to the primary arm and 166 patients to the secondary arm.

Inclusion criteria for referral to BLC-HAL in the primary arm are multiple red patches suggestive of CIS on cystoscopy, positive and atypical urine cytology, high-grade disease suspected on white-light cystoscopy and patients with a history of keratinising squamous metaplasia of bladder. Patients without confirmed urothelial malignancy were excluded from the denominator in detection analysis, as CIS detection is not applicable in benign conditions and would artificially underestimate detection rates.

For the secondary arm (re-resection), patients with a diagnosis of high-grade disease or who have required re-resection (where no muscle has been identified on histology confirmed at the MDT meeting) following initial white-light TURBT/biopsy, were included.

Following histological review, five patients with non-urothelial bladder cancer were excluded, resulting in final analysed cohorts of 68 patients in the primary arm and 165 patients in the secondary arm.

2.1. Study Protocol

The study was divided into two arms. The primary arm comprised patients undergoing blue-light cystoscopy (BLC) at their first-ever TURBT, with no prior diagnosis of bladder cancer. The secondary arm comprised patients undergoing BLC during repeat TURBT following an initial WLC-guided TURBT or biopsy.

In the primary arm, patients were referred based on a single dominant referral indication: red patches suspicious for CIS on WLC, atypical or positive urine cytology, high-grade disease suspected on WLC, or a history of keratinising squamous metaplasia. Multiple referral indications were not permitted.

Patients in the secondary arm had been recently diagnosed with bladder cancer from initial white-light TURBT/biopsy and were referred to re-resection BLC TURBT/biopsy based on inclusion criteria. TURBT was performed by two surgeons at the same trust (NV and CG).

In both arms, WLC inspection was performed and findings documented prior to switching to BLC. Surgeons then performed BLC, and any additional lesions detected under blue light were noted separately. Local pathologists analysed the samples and graded them using the WHO 1973 and 2004/2016 bladder tumour systems. Patients with confirmed malignancy on BLC were monitored with white-light cystoscopy at intervals based on tumour grade and stage, and were re-referred for white-light biopsy ± TURBT if recurrence was suspected.

2.2. HAL Treatment and Fluorescence Detection

Hexvix® (85 mg hexaminolevulinate [HAL] in 50 mL phosphate saline diluent) was prepared according to the manufacturer's instructions. Patients were instructed to completely empty their bladder before instillation. The Hexvix® solution was administered intravesically via a urethral catheter and retained in the bladder for 60 min. Immediately prior to cystoscopy, the bladder was drained in the operating theatre.

Fluorescence detection was performed using a D-Light system (Karl Storz, Tuttlingen, Germany) in combination with a photodynamic diagnosis (PDD)-compatible telescope. The charge-coupled device (CCD) camera head included a push-button control, allowing intraoperative switching between white-light and blue-light modes as required.

2.3. Analysis

Pathological data were collected for all patients with BLC confirmed by a local pathologist. In the secondary arm, patients with malignancy confirmed on BLC-HAL biopsy/TURBT also had retrospective data gathered from their initial white-light pathology.

Using these pathological findings, patients were stratified into prognostic risk groups according to the 2021 EAU scoring model. For multifocal tumours with or without CIS, the highest grade and stage were recorded, and the presence of CIS was specifically noted.

The primary detection endpoint was the proportion of patients with histologically confirmed CIS or tumour upstaging identified under BLC, among those with malignancy confirmed on WLC. Upstaging to MIBC was defined as progression from ≤T1 disease on initial WLC pathology to ≥T2 disease on BLC-guided biopsy or TURBT, based on the identification of muscularis propria invasion.

Patients with non-urothelial or metastatic bladder cancer were excluded. Both study arms were followed for recurrence over 12 and 24 months from the first BLC TURBT/biopsy confirming malignancy.

The primary recurrence endpoint was the proportion of patients with histologically confirmed bladder cancer (CIS, Ta, T1) at BLC TURBT/biopsy who developed recurrent, histologically proven bladder cancer (CIS, Ta, T1–T4) within 24 months.

The recurrence endpoint was recurrence-free survival (RFS), analysed using the Kaplan–Meier method with censoring at death, cystectomy, or last follow-up. Recurrence events were recorded at the time of histological confirmation. RFS estimates are reported with 95% confidence intervals, and median RFS was calculated when estimable. The primary detection endpoint was CIS detection or pathological upstaging identified on BLC. McNemar's test was applied only to paired within-patient comparisons. Statistical significance was set at $p < 0.05$.

Follow-up and recurrence analyses were performed using time-dependent inclusion criteria. Patients were included in point estimates for recurrence at 12 and 24 months only if they had sufficient follow-up to the relevant timepoint. Patients who underwent cystectomy or cystoprostatectomy, died, or received radical radiotherapy prior to 12 or 24 months were excluded from point estimates at those timepoints but were censored appropriately in Kaplan–Meier recurrence-free survival analyses. This approach accounts for variation in follow-up duration and definitive treatment pathways following initial BLC TURBT/biopsy.

3. Results

3.1. Cohort Characteristics

A total of 238 patients underwent BLC between July 2017 and July 2024. Seventy-two patients were initially referred to the primary arm and 166 to the secondary arm. Following exclusion of five patients with non-urothelial malignancies, the final analysed cohorts consisted of 68 and 165 patients, respectively, consistent with Figure 1.

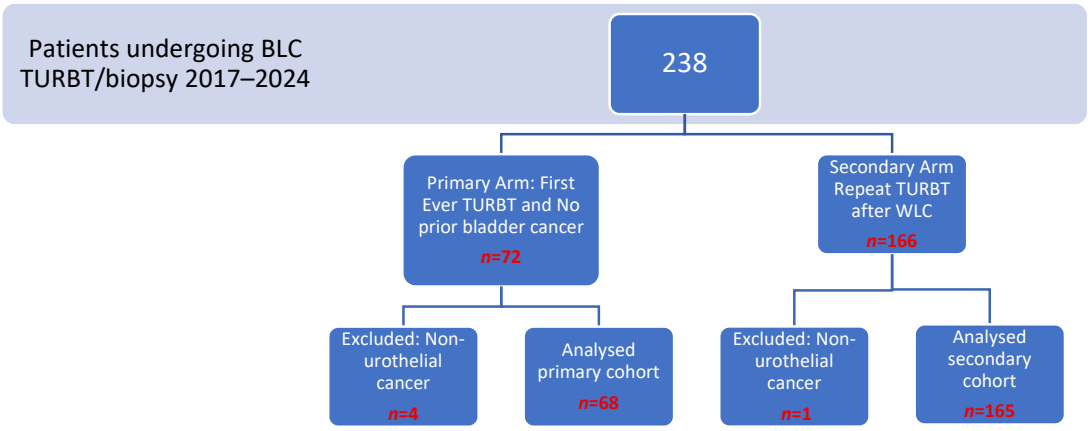

Figure 1. Cohort allocation of primary and secondary arms.

In the secondary arm (n = 166), 51 patients (30.7%) were referred for BLC re-resection due to incomplete WLC resection, and 115 patients (69.3%) were referred due to high-grade disease on WLC. One patient with non-urothelial bladder cancer was excluded from the analysis.

Overall, 113 patients were found to have malignancy on their first BLC biopsy/TURBT: primary arm (21/72, 29.2%) and secondary arm (92/166, 55.4%). In the primary and secondary arms, respectively, risk groups for patients with malignancy confirmed with histology on BLC TURBT were low risk 1/21 (4.76%) vs. 5/92 (5.43%), intermediate risk 4/21 (19.04%) vs. 21/92 (22.8%), high risk 5/21 (23.8%) vs. 48/92 (52.17%) and very high risk 11/21 (52.38%) vs. 18/92 (19.6%). Furthermore, the numbers of patients with CIS on initial BLC resection in the primary arm and secondary arm, respectively, were 4/21 (23.8%) and 25/92 (38%).

3.2. Detection

In the primary arm, 4/21 patients (19.0%) had CIS detected at initial BLC resection. Five of 21 (23.8%) were upstaged to MIBC. WLC-visible lesions were not systematically biopsied prior to BLC, reflecting institutional practice and introducing potential detection bias. Cumulative CIS findings refer to all CIS lesions identified during a single operative session (WLC, BLC, targeted and random biopsies).

In the secondary arm, 17/92 patients (18.5%) had CIS on their initial WLC resection. At re-resection, CIS was detected in 35/92 patients (38.0%), of which 24/92 (26.1%) represented new CIS lesions identified on BLC but not visible on WLC at the same timepoint.

Thus, BLC re-resection detected significantly more CIS than WLC (24/92 vs. 17/92; p = 0.001). Additionally, 9/92 patients (9.7%) were upstaged to MIBC, which was statistically significant (p = 0.0215). Following BLC-HAL re-resection, 33/92 patients (35.9%) were upstaged to a higher 2021 EAU NMIBC risk group. Overall, 49/92 (53.3%) had re-resection within 3 months, with median time re-resection being 3.06 months.

3.3. Recurrence

Recurrence analyses were based on evaluable follow-up at each timepoint rather than the total number of patients with malignancy confirmed at initial BLC. Not all patients were eligible for 12- or 24-month recurrence assessment due to death, cystectomy or cystoprostatectomy, radical radiotherapy, or insufficient duration of follow-up. Consequently, the number of evaluable patients differs between 12- and 24-month analyses and between study arms. These exclusions and follow-up pathways are summarised in Figure 2.

Follow-up was available for patients at 12 or 24 months, with censoring applied at death, cystectomy, or last known follow-up.

In the primary arm, 21 patients had malignancy confirmed on initial BLC TURBT/biopsy and formed the baseline cohort for recurrence analysis. Of these, 11 were followed to 12 months and four were excluded (one death, two cystectomy/cystoprostatectomy, one radical radiotherapy), leaving seven evaluable patients. Two of these developed recurrence: one with intermediate-grade disease after MMC, and one with MIBC not fit for surgery or BCG. For the 24-month group, six were excluded (five cystectomy, one death), leaving nine evaluable patients. Three recurred (two high-risk, one very high-risk); two had received BCG after initial BLC resection.

In the secondary arm, 63 patients were evaluable at 12 months. Eight were excluded (two deaths, six cystectomy/cystoprostatectomy), leaving 55 patients, of whom 21 (38.2%) recurred. Distribution of these recurrences was low:intermediate:high:very high:MIBC = 5:4:8:1:3. Patients with high-grade recurrence received BCG; those with MIBC were either treated with cystectomy, BCG (if unfit/unwilling for surgery), or pal-

liative radiotherapy. At 24 months, 24 patients were evaluable, of whom nine recurred (high:intermediate:low = 6:2:1). Six received BCG, and 50% of those treated with BCG had high-risk disease. This is demonstrated in Figure 2.

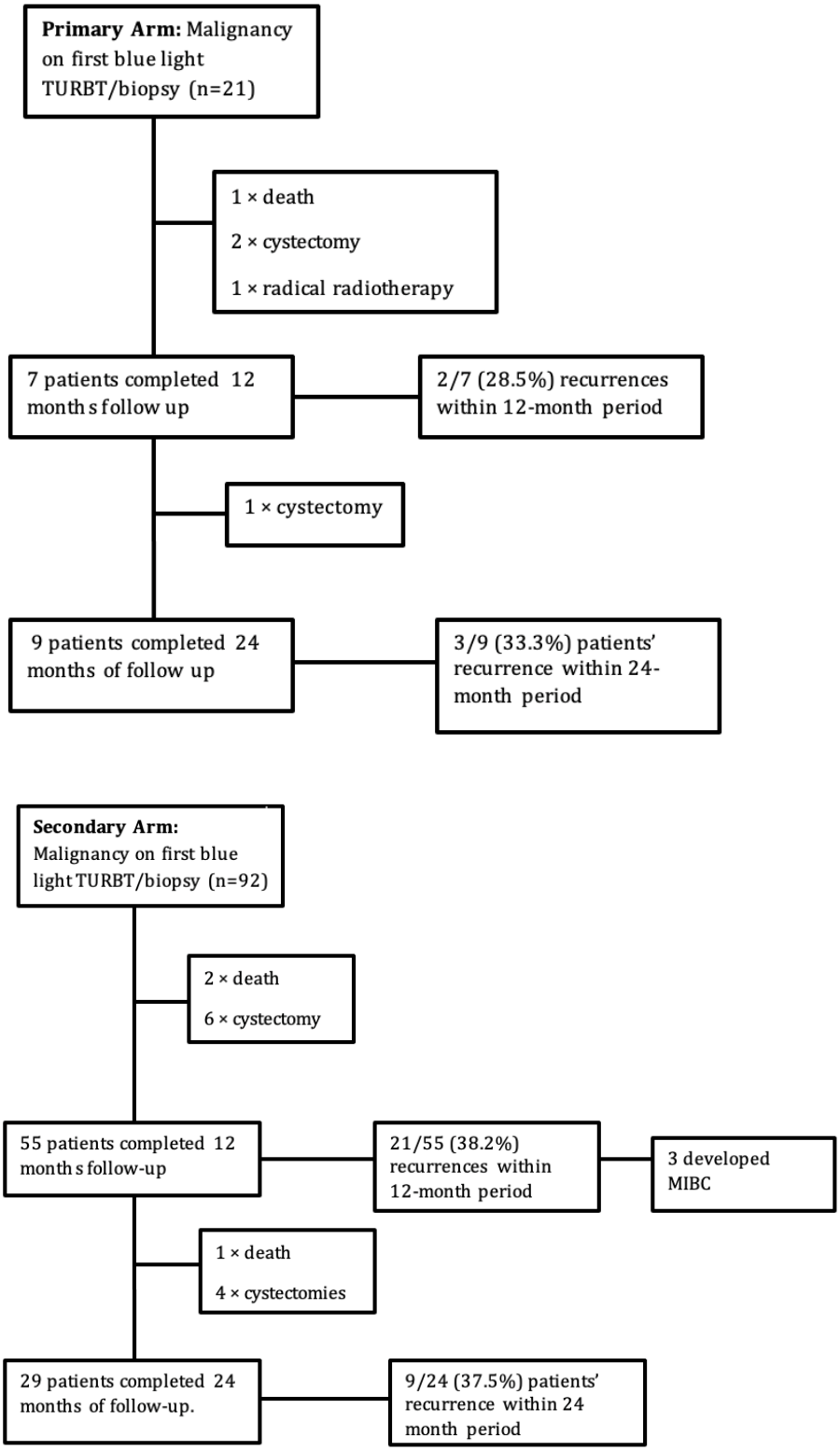

Figure 2. Flowchart of patients in primary and secondary arms being followed up for 24 months. Patients were excluded from point estimates due to death, cystectomy or cystoprostatectomy, radical radiotherapy, or insufficient follow-up, and were censored appropriately in Kaplan–Meier analyses.

Kaplan–Meier analysis estimated recurrence-free survival (RFS) with censoring at death, cystectomy, or last follow-up. In the primary arm, the estimated RFS was 71.4% (95% CI: 35.9–91.8%) at 12 months and 66.7% (95% CI: 35.4–87.9%) at 24 months. Median RFS was not reached within 24 months. In the secondary arm, the estimated RFS was 61.8% (95% CI: 48.6–73.5%) at 12 months and 62.5% (95% CI: 42.7–78.8%) at 24 months. Median RFS was also not reached within 24 months. Kaplan–Meier survival curves for both arms are shown in Figure 3.

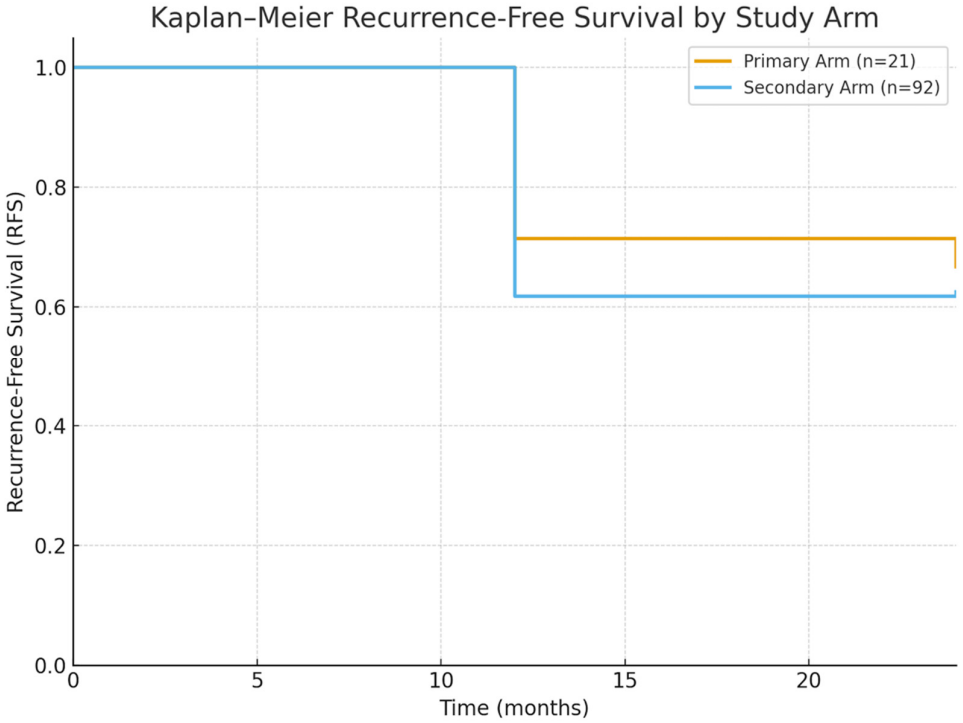

Figure 3. Kaplan–Meier RFS for primary and secondary arms followed up for 24 months.

4. Discussion

In this series, BLC identified significantly more CIS than prior WLC, especially in the re-resection cohort. In the secondary arm, CIS was detected in 38% of BLC cases compared with 18.4% on initial WLC, with 26% identified exclusively under blue light.

One in three patients were upstaged to a higher EAU NMIBC risk category and 9.7% were upstaged to MIBC. These findings are in line with AUA and EAU guidance, both of which recommend offering BLC during TURBT when available for suspected CIS or high-grade disease [8,9]. Our detection and staging results align with published RCTs and meta-analyses showing superior sensitivity of BLC for CIS and small papillary lesions. In the re-resection cohort, the 26.1% absolute uplift in CIS detection is at the upper end of reported figures—most trials and pooled analyses show a 10–20% improvement over WLC. Similarly, our rates of risk upstaging (35.9% to a higher EAU NMIBC category) and MIBC identification (9.7%) are comparable to other series, underlining that BLC can materially alter management by prompting earlier re-resection, adjuvant BCG, or cystectomy.

Our observed recurrence rates in both primary (28.6–33.3%) and secondary (37.5–38.2%) arms align with recurrence rates reported in intermediate to high-risk NMIBC populations in the literature. The Cochrane review by Maisch et al. demonstrated a 30–35% relative reduction in recurrence and progression with blue-light cystoscopy (BLC) compared to white-light [7]. Consistent with this, our data show that BLC detected an additional 26% of carcinoma in situ and upstaged 8.7% of patients to muscle-invasive disease, highlighting its value in improved tumour detection and risk stratification. These findings

support that BLC enhances identification of aggressive disease, which may translate into better patient management and outcomes.

Recurrence rates at 12 and 24 months remained high—28.6% in the primary arm and 38.2% in the secondary arm at 12 months—despite most patients receiving intravesical therapy. This mirrors the pattern seen in the PHOTO trial: BLC reduces early recurrence (pooled RRs around 0.7 at 12 months in meta-analyses) but has an inconsistent impact on long-term recurrence and progression, particularly in high- and very high-risk NMIBC [10]. Differences between our absolute recurrence rates and those reported in trial settings likely reflect our high-risk, re-resection-enriched case mix, the median 3-month interval to re-resection, variation in adjuvant therapy delivery, and the observational design. These findings should be interpreted as demonstrating diagnostic and staging benefit rather than definitive modification of long-term oncological outcomes.

Blue-light cystoscopy (HAL) is only validated for detection of urothelial NMIBC. Evidence that PDD reliably detects pure non-urothelial bladder cancers (e.g., squamous cell, adenocarcinoma or urachal) is lacking; reported fluorescence in such tumours is limited to mixed-histology tumours in in vitro studies or observational reports [11,12]. However, our data shows eight patients that were detected with non-urothelial malignancy in a total cohort of 238 patients. BLC may incidentally visualise non-urothelial malignancies; however, no conclusions regarding diagnostic utility can be drawn from this small, non-significant subset.

The strengths of this study include the relatively large consecutive cohort over seven years and the separation of primary vs. re-resection indications, reflecting actual referral practice.

This retrospective, single-centre study is subject to selection bias, particularly in the enriched primary arm. Follow-up was incomplete in some subgroups, and recurrence analyses—especially in the primary arm—were based on small numbers. The median interval to re-resection was approximately three months, limiting distinction between residual and newly developed CIS. Heterogeneity in adjuvant intravesical therapy (BCG/MMC) and absence of progression-free or overall survival endpoints limit causal inference. Non-urothelial malignancies were rare, precluding definitive conclusions regarding BLC utility in these tumours. The data reflects similar data capture from our unit of previous publications [13,14].

Overall, these data support guideline recommendations to offer BLC at TURBT, especially for high-risk and suspected CIS cases. The high rates of CIS detection and clinically relevant upstaging reinforce its diagnostic value, but better integration with perioperative and intravesical strategies will be required to translate early detection into sustained long-term benefit.

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Institutional Review Board Statement: Ethical review and approval were waived for this study because it involved a retrospective analysis of existing data that were collected as part of routine clinical practice. The study did not involve any prospective intervention, interaction with human participants, or collection of identifiable private information. All data were fully anonymized prior to analysis, ensuring that individual participants could not be identified directly or indirectly. As such,

the study posed no additional risk to participants and met the criteria for exemption from ethical review in accordance with applicable institutional and national research ethics guidelines.

Informed Consent Statement: Patient informed consent was waived because the study was retrospective in nature and involved the analysis of anonymized data only. Obtaining informed consent was impracticable due to the large sample size and the historical nature of the data. The waiver did not adversely affect the rights or welfare of the participants, as no identifiable information was used and no additional procedures were performed beyond standard care. This approach is consistent with ethical standards and relevant regulations governing the use of anonymized retrospective data for research purposes.

Data Availability Statement: The data presented in this study are not publicly available due to ethical and privacy restrictions. The data were generated from routine clinical records and contain sensitive patient information. Anonymised data may be made available from the corresponding authors upon reasonable request, subject to institutional approvals and data governance regulations.

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Conflicts of Interest: The authors declare no conflicts of interest.

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