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Paper Alert

Does Blue Light Cystoscopy Reduce Recurrences of Non-Muscle Invasive Bladder Cancer?

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Non-muscle invasive bladder cancers (NMIBCs) account for 75% of newly diagnosed BCs [1] and the majority are in low and intermediate EORTC risk categories [1]. Enhanced visualization during cystoscopy–particularly with fluorescence induced by an intravesically instilled photoactive porphyrin (either 5-aminolevulenic acid [ALA] or hexaminolevulinate hydrochloride [HAL]) which preferentially accumulates in hypervascular (particularly neoplastic) tissues and fluoresces (pink) when exposed to blue light (375 to 440 nm wavelength) (BL) has been purported to improve detection of subtle tumors (and tumor boarders), permitting better eradication of cancers in the bladder [2, 3]. Another form of enhanced cystoscopy, narrow band imaging (NBI) excludes the red spectrum of light, increasing the contrast between superficial vasculature (again, more in tumors) and other superficial tissue structures in the bladder and also facilitates recognition (and thus better removal) of all tumorous lesions [4]. Both techniques have been studied in single arm and randomized studies–most reporting reduced recurrence rates in those patients undergoing transurethral resections (TURBTs) guided by enhanced cystoscopy as opposed to those undergoing standard white light (WL) cystoscopy [5].

Thus, it is particularly surprising that a recently published, well conducted, randomized, "pragmatic" clinical trial found no significant differences in recurrences in a very well matched group of patients with newly diagnosed intermediate (roughly 88% in each group) and high risk (7–8%) NMIBCs [6]. At a median follow-up of 44 months 86 of 209 patients (41%) in the BL group and 84 of 217 (38.7%) in the WL group experienced recurrences (HR for recurrence = 0.94 [95% CI = 0.69 to 1.28] $p = 0.70$). At the predesignated 3-year time point, recurrence-free rates (RFS) were 57.8% (95% CI = 50.7 to 64.2) and 61.6% (95% CI = 54.7 to 67.8) in the BL and WL groups, respectively. Progression to muscle invasive disease, overall survival, bladder cancer specific deaths (very low in each group), and adverse events (AEs) were similar in terms of numbers and severity in both groups.

While the authors tried to exclude patients with higher risk cancers, over one-third in each group had grade 3 cancers and almost a third had stage T_1 disease. These histologic features however were well balanced between the groups as were the small numbers with no cancer or stage T_2 disease on index TURBT. These patients, and those with high grade stage T_1 disease who underwent early cystectomy

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were not included in the final analyses and were similar in both arms. Impressively, even the experience of the urologist performing the index TURBT was adjusted for in the analyses, and again was similar in both groups.

So, in view of the 20 year generally favorable experience with BL cystoscopy how can one explain these findings? Well there are two caveats which the authors mention but don't dwell on. First, over the first 12–15 months of follow up (Author's Figure 2 reference 6) the patients undergoing BL cystoscopy actually had a lower recurrence rate (12-month recurrence free rate roughly 75% for BL versus roughly 67% for WL). The importance of this is that many (although not all) of the prior randomized studies reported results at earlier time points (6–12 month follow up) [5].

If Blue Light really allows for a more complete TURBT to be done, that benefit, compared to ongoing factors leading to new cancers forming, may be short-lived. While additional work may be forthcoming, no molecular analyses on the recurrent or index cancers were provided to know if they were actually clonally similar (especially for later recurrences), possibly indicating an existing tumor had been overlooked at the index TURBT.

Secondly, and perhaps having a much greater impact, was that all patients (in both groups) were to receive an immediate post-operative instillation of Mitomycin C (MMC) and nearly two-thirds in each group actually did. While this again was equally balanced, the beneficial effects of this type of treatment on low and intermediate risk NMIBC patients has been well described and may overwhelm the benefits of enhanced cystoscopy [7–9]. Additionally, many patients in both groups received courses of intravesical therapy including BCG and intravesical chemotherapy after both the index TURBT and upon subsequent recurrence (following British and European guidelines). However, given that most patients had multiple tumors, one-third had high grade cancers and nearly one-third had stage T_1 index tumors (again, similarly distributed), withholding such treatments would not have been appropriate. Finally, nearly a third of patients in each group (again similarly distributed between groups) had a re-TURBT (presumably without BL) within 6 weeks after the index resection, effecting a more complete index resection in those cases.

Not surprisingly, given the equivalence of all oncologic (and non-oncologic) end points the costs attributed to BL cystoscopy (which was only done on the index TURBT), primarily the cost of special instrumentation, of HAL, and of the preoperative catherization needed to instill it, rendered BL TURBT a money loser. Not unexpectedly, there was no difference in quality of life years gained at 3 years ($p = 0{,}44$).

So, what have we learned from this well conducted trial? I believe it is likely that given the heterogenous nature of intermediate risk NMIBC, and how frequently tumors recur, designing a study in which the impact of only a single treatment is to be assessed, when many patients in each group receive effective adjuvant therapies, is very challenging for all the reasons discussed. In view of this, I'm not sure this paper will be the death notice for enhanced cystoscopy.

CONFLICTS OF INTEREST

The author has no conflicts of interest to report.

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