Continued Use and Expansion of Photodynamic TURBT

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Doubt is not a pleasant condition, but certainty is an absurd one. – Voltaire

Urology has been fraught with informing practice based on weak evidence, and when a randomized controlled trial comes along in our field, it should be applauded. But to applaud the completion of a trial does not mean to kneel at its altar. We should ask ourselves 2 questions of every clinical trial: (1) does the trial address an important question, and (2) was the trial designed and conducted in such a way to successfully answer the intended question. The PHOTO trial, which was recently published in the *New England Journal of Medicine Evidence* is a trial that successfully answers a question that is largely unimportant.

Among patients with intermediate-risk non-muscle invasive bladder cancer (NMIBC) with low rates of both carcinoma in situ (CIS) and adjuvant Bacillus Calmette-Guérin (BCG) therapy, initial photodynamic transurethral resection of bladder tumor (TURBT) did not perform any better than traditional white-light TURBT in terms of 3-year disease recurrence in a large, multicenter, randomized trial[1]. As such, many urologists now wonder if photodynamic TURBT should be abandoned, especially given the costs associated with this technology. The answer is no. In fact, we favor the continued use and expansion of photodynamic TURBT in appropriate patients.

The risk for disease recurrence in intermediate-risk NMIBC ranges from 40% to 56% based on European Organisation for Research and Treatment of Cancer (EORTC) estimates, while up to 75% to 80% of patients with high-risk disease will experience a recurrence[2]. As such, the PHOTO trial enrolled patients with suspected intermediate or high-risk NIMBC who were expected to have recurrences. However, study enrollment was based on tumor cystoscopic appearance (eg, flat velvety erythematous mucosal changes) or imaging characteristics (eg, tumor ≥ 3 cm), not pathology specimens. This resulted in 89 patients (16.5%) being automatically excluded from the trial due to having muscle-invasive bladder cancer (MIBC) or no tumor at the time of TURBT. In addition, 374 (88%) patients enrolled in the trial had EORTC intermediate-risk disease (46% intermediate-risk by National Institute for Health and Care Excellence criteria[3]), while 32 (7.5%) had high-risk disease and 18 (4.2%) could not be classified. This enrollment design reduced the number of potential tumor recurrences (the main study outcome) that could have been observed in the trial by 1) enrolling patients who would never have a recurrence, and 2) primarily enrolling patients at only intermediate risk for recurrence. The authors explain that the primary implication of this limitation is a reduction in predefined study power from 90% to around 80%. However, we believe this enrollment methodology likely also shifted the population of interest away from patients who would benefit from photodynamic TURBT the most.

Patients with high-risk NMIBC experience the greatest benefit from photodynamic TURBT, particularly those with CIS[4,5]. Photodynamic TURBT has been shown to detect 32% more high-risk tumors compared to white-light TURBT and 36% more CIS lesions, specifically[6]. In fact, multiple studies have demonstrated the additive benefit of photodynamic TURBT in detecting CIS compared with white-light TURBT[7,8]. Unfortunately, only 32 (7.5%) and 51 (9.5%) patients enrolled in the PHOTO trial had EORTC high-risk NMIBC and CIS, respectively. Thus, the results of the PHOTO trial likely do not adequately represent the true potential benefit of photodynamic TURBT in high-risk patients, for which the technology is most appropriate for.

Key Words

Bladder cancer, NMIBC, blue light cystoscopy

Competing Interests

None declared.

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Abbreviations

BCG Bacillus Calmette-Guérin
CIS carcinoma in situ
EORTC Organisation for Research and Treatment of Cancer
NMIBC non-muscle invasive bladder cancer
TURBT transurethral resection of bladder tumor

Another important limitation of the PHOTO trial was the underutilization of adjuvant BCG, an intravesical therapy known to reduce tumor recurrences and progression in NMIBC[9]. Only 68 (16.0%) patients in the final analysis cohort received induction plus maintenance BCG and 35 (8.2%) received induction BCG alone. BCG use was particularly dismal among patients with high-risk disease, with only 14 patients receiving induction and 7 receiving maintenance. These utilization rates are concerning given the known oncological benefits of BCG in high-risk NMIBC[2]. Most importantly, these rates suggest that many patients did not receive standard of care for adjuvant intravesical therapy. It is therefore not surprising that although at 1 year there is separation of the recurrence-free survival curves favoring photodynamic TURBT, by 3 years there was no difference. The fact that most patients in the trial were EORTC intermediate-risk NMIBC without CIS means that the trial is studying a population with fewer recurrences, lower stakes for patients and providers, and less proven outcomes with use of photodynamic technology. In the small group of patients with EORTC high-risk NMIBC, the fact that a small fraction was treated with standard-of-care intravesical therapy means that the trial merely demonstrates that untreated high-risk NMIBC leads to recurrences.

A recent meta-analysis of 12 randomized trials found that photodynamic TURBT improved recurrence-free survival compared to white-light TURBT at 2 years of follow-up[4]. The PHOTO trial does not erase this prior evidence supporting the utility of photodynamic TURBT. Instead, it adds to a growing literature base available to urologists to continue to improve the quality of care delivered to patients with bladder cancer. Overall, NMIBC care is highly nuanced with varying disease trajectories, surveillance strategies, and treatment options. The PHOTO trial suggests that photodynamic TURBT may have limited utility when used at the initial diagnosis of patients with intermediate-risk disease, but there are many patients and clinical scenarios that other studies have shown derive benefit from photodynamic TURBT. Our approach to the patient demands that we be nuanced in interpreting the trial's findings. An example of this is the use of immediate postoperative intravesical chemotherapy in intermediate-risk NMIBC. Intermediate-risk patients with an EORTC recurrence score ≥ 6 (e.g., multiple tumors, at least one ≥ 3 cm) do not benefit from postoperative intravesical chemotherapy. However, those with a score < 6 can experience up to a 35% reduction in recurrence risk[10]. Despite not having any oncologic benefit in some intermediate-risk patients, postoperative intravesical chemotherapy is commonly pursued in all intermediate-risk patients because the potential benefit for some patients outweighs the risk in most patients. If 1 in 10 or 1 in 20 patients derives benefit from the introduction of a technology, then all it takes is a few interventions like that to impact a sizable portion of patients with bladder cancer. Because the PHOTO trial did not enroll many patients with CIS or high-risk NMIBC, it was not powered to identify these differences.

Based on the limitations of the PHOTO trial, available prior research, and the nuances of bladder cancer care, we support the continued use and expansion of photodynamic TURBT in NMIBC. This technology should be used in patients with high-risk NMIBC, especially those with CIS. Use in intermediate-risk disease is also likely justified for many patients, despite the trial results. Based on our experience, we also believe there is significant utility for this technology in restaging TURBTs to identify CIS, during mucosal mapping for partial cystectomy and trimodality therapy planning, and for assessing response to intravesical therapy.

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