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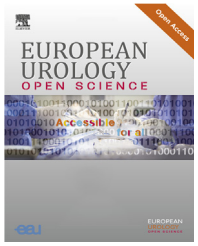

European Association of Urology

Letter to the Editor

Re: Rakesh Heer, Rebecca Lewis, Thenmalar Vadiveloo, et al. A Randomized Trial of PHOTOdynamic Surgery in Non-muscle-invasive Bladder Cancer. NEJM Evid. In press. https://doi.org/10.1056/EVIDoa2200092

Heer and colleagues [1] investigated the effect of photodynamic diagnosis (PDD)-assisted surgery compared to white light–guided transurethral resection of the bladder (TURB) on recurrence-free survival (RFS) in a randomized trial with a superiority design. Indicating a lack of improvement in RFS with PDD-assisted TURB (hazard ratio 0.94, 95% confidence interval 0.7–1.3), the data reported are in contrast to results from several previous trials of similar design, although all were performed a decade ago. This suggests that the effect size of the intervention in a more modern setting might not be the same as previously found. The findings also included no difference in health-related quality of life and a lack of cost-effectiveness, and the proportion of patients diagnosed with carcinoma in situ was only marginally improved by PDD (from 11% to 13%). In addition, the PHOTO trial highlights that misinterpretation of the endoscopic features of bladder tumors by urologists is not infrequent, since 14% of the patients with presumed intermediate- or high-risk non–muscle-invasive bladder cancer (NMIBC) included in the trial had muscle-invasive tumors and 7% were benign.

The quality of the TURB performed by the individual surgeon affects RFS. The proportion of cases with recurrence at first cystoscopy after TURB among patients with multiple tumors varied from 7% to 46% among institutions in an analysis of seven EORTC trials performed between 1979 and 1989 [2]. Awareness of such differences in outcomes has contributed to the implementation of multiple measures to improve RFS for patients with NMIBC, including the use of PDD [3]. In addition, the effect of surgical experience on outcomes after TURB [4] might have been improved by education initiatives, and it is likely that technical advances for image quality and instruments for TURB have also contributed to improvements in long-term outcomes over time in population-based settings [5].

In the PHOTO trial, ten consultants carried out the surgery for 430/538 (80%) of the randomized patients, so high-volume surgeons were performing the majority of the TURB procedures. Furthermore, two out of three patients received a single postoperative instillation with mitomycin, and 178 patients were treated with further adjuvant serial instillations. Thus, any improvement in outcome due to PDD in the intervention arm might have been mitigated by the very experienced surgeons and the frequent addition of adjuvant measures in the trial. However, in another setting, such as a Swedish population with large interhospital variation in 5-yr RFS (10–60% for primary low- and intermediate-risk NMIBC treated between 2012 and 2016; $n = 5828$; https://statistik.incanet.se/Urinblasecancer/), the effect of PDD addition might be more pronounced. This is also the conclusion in a recent Cochrane review of 16 randomized trials: the clinical effect of PDD addition greatly depends on the baseline risk of recurrence [6].

The results from the PHOTO study highlight the need for all units treating NMIBC to keep track of their outcomes before systematically applying PDD-assisted TURB, with assessment of either long-term RFS or other adequate proxy measures, such as the proportion of patients with detrusor muscle in the resected specimen or the proportion of patients with NMIBC without recurrence at first cystoscopy.

Conflicts of interest: The authors have nothing to disclose.

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