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Letter to the Editor

Reply to Fredrik Liedberg and Johannes Bobjer's 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>

We thank Drs. Liedberg and Bobjer for their comments relating to the recent PHOTO trial [1,2]. They point out that photodynamic diagnosis (PDD) is among the measures used to address the wide range of variability in recurrence rates among institutions in European Organisation for Research and Treatment of Cancer (EORTC) trials, a variability that is also noted among hospitals in Sweden [3,4]. The variability in recurrence rates in the EORTC review by Brausi et al [3] was most pronounced for those with multifocal tumours receiving adjuvant therapy (7–46%). As well as variation in the quality of transurethral resection of bladder tumour (TURBT), this may also be partly explained by the heterogeneity of adjuvant therapies used in this cohort. These adjuvant therapies, which are known to affect recurrence rates, included immediate post-resection single-dose intravesical chemotherapy, variable maintenance schedules for a range of intravesical chemotherapy agents, or an induction course of bacillus Calmette-Guérin [3]. Drs. Liedberg and Bobjer also refer to a Swedish trial by Sörenby et al. [5] that included all non-muscle-invasive bladder cancer (NMIBC) risk categories, differing from the inclusion criteria in PHOTO, which was restricted to presumed intermediate and high-risk NMIBC. The Swedish trial reported an improvement in recurrence rates following the development and implementation of a standardised protocol, elements of which included PDD for first resection, a systematic approach to TURBT as per European Association of Urology guidance, and risk-stratified use of adjuvant therapy [5]. The protocol reduced the recurrence rate from 22% to 9.6% at a minimum follow-up of 38 mo. Of note, PDD use markedly increased, but so too did the number of patients receiving appropriate adjuvant treatment for high-risk disease, increasing from 51% to 88% in the group of patients with T1 disease.

Sörenby et al. [5] hypothesise that very experienced surgeons and adjuvant therapy could have mitigated some of the improvement in the PDD arm. While it is true that ten consultants carried out most of the surgery within the PHOTO trial, it is worth pointing out that of the patients

included in the intention-to-treat analysis, 27% (111/426) were operated on by registrars [1]. Furthermore, in a multivariate analysis of factors prognostic for recurrence, there was no clear evidence that surgeon grade was prognostic (consultant grade: hazard ratio 0.94, 95% confidence interval 0.67–1.33 vs registrar/nonconsultant career grade; $p = 0.736$), although the confidence interval is wide enough to include important differences in recurrence rates both for and against consultants. With regard to “frequent addition” of adjuvant therapy, PHOTO did not define these treatment schedules; instead, institutions within the trial administered adjuvant therapy on the basis of current guidelines, which therefore represents routine clinical practice.

It is important to note that one of the limitations of the current systematic reviews on the subject, such as the Cochrane review [6] to which the authors refer, is that the adjuvant therapy used within the different trials is varied or in some cases not reported. This is in addition to the low certainty of evidence due to bias, inconsistency, and imprecision among the trials included. This low certainty means that the available research provides some indication of the likely effect, but there is a high likelihood that the correct result could be substantially different. The limited quality of evidence available to date was, in part, the motivation for the PHOTO trial, which was designed in a pragmatic way and performed in accordance with its prepublished protocol [7].

The authors propose that units treating bladder cancer audit their own outcomes to assess the need for PDD. We would suggest, however, that measures with a stronger evidence base such as adherence to guidelines for adjuvant treatment, along with good surgical technique, should be implemented first.

Conflicts of interest: The authors have nothing to disclose.

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