The End of Photodynamic Surgery for Bladder Cancer Has Arrived

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The PHOTO study was a real-world—or "pragmatic" in the proper diction of the UK investigators—prospective randomized controlled trial (RCT) to evaluate bladder cancer recurrence rates with over 3 years of follow-up. This is the longest RCT performed on this technology published. It was extraordinarily vigorous—even for the high standards of any RCT. There was central randomization with concealed allocation, blinding of personnel and outcome assessors, low rates of attrition, and a pre-published analytics plan. Critically, the funding was governmental not pharmaceutical. The control arm and study arm were equally balanced. This study did allow for the appropriate use of postoperative intravesical therapy and adjuvant treatment, all of which were equally balanced in both arms. A real-world trial has shown—without any doubt at all—that the use of photodynamic diagnosis (PDD) for the express purpose of preventing recurrence after the initial diagnosis of bladder cancer is unhelpful.

This negative result should not be a surprise. Urologists only have to recall the original randomized trial that formed the basis for the approval of PDD at the FDA to remind themselves this technology was always borderline[1]. In the final phase 3 trial, PDD met only one of its prespecified endpoints and failed to achieve superiority in comparison for follow-up recurrence rates. The proportion of the PDD group patients detected (16%) did exceed the prespecified 10% threshold, however. Supporting documentation at the time (Study 304), which did randomize to white light versus PDD, did not show a reduction in recurrence. The FDA advisory committee voted 9 to 8 in favor of sufficient risk to benefit for using PDD. A "slow-clap" approval if there ever was one.

After the PHOTO study has been disseminated, studied, and dissected—we should see an international steep decline in the pro forma use of PDD for the purposes of preventing bladder cancer recurrence. Why? It doesn't work. In countries such as the United States where pharmaceutical representatives foot the bill for the lion's share of postgraduate education, PDD use will likely plod along buttressed by conflicted experts. In the United Kingdom, home of the PHOTO study and where general adherence to evidence-based medicine can happen, PDD use will peter out and be used in select cases only.

Physicians do not consider one study to inform their practice. Instead, physicians should consider all the high-value studies packaged into a meta-analysis. Urologists should therefore appreciate the work of Maisch et al.[2], who in 2021 (prior to PHOTO) performed a rigorous systematic review of all studies on PDD and recurrence rates. Those authors downgraded the certainty of evidence by two levels according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. They found there was significant unexplained heterogeneity in the data on PDD and recurrence. If the PHOTO trial was added, according to Heer et al. [3], and the analysis was restricted to only robust trials with a priori protocols—the entirety of all PDD RCT studies would result in a nonsignificant result. PDD just cannot get a break.

There are many reports in the literature that PDD provides superior diagnostic capabilities in the setting of carcinoma in situ (CIS), a point the PDD lobbyists will surely cling to. Those reports—while numerous and retrospective—have heterogeneous patient characteristics and study design[4]. Now, we have the clear cover of a modern real-world

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RCT, which was enriched with 12.9% of the PDD group versus 11.1% of the WL group, with CIS, showing no clear difference in recurrence rates.

Modern high-definition cystoscopy, unavailable in the original RCT but available to all currently, is one obvious reason PDD crumbled in this non-pharmaceutically sponsored PHOTO trial. The real-world addition of intravesical therapy and re-resection of tumors also undoubtedly contributed. All told, payors and national health services should restrict this expensive technology immediately. Thomas Jefferson was fond of saying, "He who knows nothing is closer to the truth than he whose mind is filled with falsehoods and errors." Time to shed the errors and realize the truth: PDD is past its prime and high-definition optics has come to the fore.

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