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Generalizability from well-designed RCTs underpin their scientific strength



TO THE EDITORS: A recent commentary by Nezhat et al¹ attempts to draw conclusions regarding the results of a prospective randomized study (Laparoscopic Approach to Cervical Cancer trial) that demonstrated lower disease-free survival in patients who undergo minimally invasive radical hysterectomy compared with the open approach.² In response, we aim to highlight how the fundamental principles of study design and analysis have been overlooked by Nezhat et al. The design strength of randomization in a well-conducted clinical study ensures that all factors, both measured and unmeasured, are balanced among the groups being compared and guarantees that comparisons give unbiased and consistent estimates of the true underlying differences.³ Heterogeneity in surgical experience is inevitable; while being controlled for by randomization, it also preserves the generalizability of the result. Surgical volume, although potentially impacting on outcome, would, by randomization, be balanced between the groups and add strength to the external validity of the results, particularly because, contrary to the implication in the commentary, the volume was not uniformly distributed across the participating surgeons. Additionally, the Laparoscopic Approach to Cervical Cancer trial was indeed stratified by site (a surrogate for surgeon) and stage of disease.

The suggested multilevel adjustment by Nezhat et al¹ would be an exercise in statistical acrobatics that would provide a limited and confusing interpretation of the resulting analyses. Limitations include (1) the results being anchored to the choice of model(s) selected, the appropriateness of which are never evaluated, (2) the distribution of factors being adjusted in the trial having little resemblance to the distribution in the wider surgical population, (3) the assumption (incorrect) that all heterogeneity can be explained by statistical adjustment, (4) potential numeric non-convergence/instability in the fitting process, and (5) introduction of missing values in the analyses when some of the factors being adjusted for are missing.

A further advantage of randomization, aside from the scientific rigor in study design, is the ability to perform unadjusted analyses that rely only on minimal assumptions. Although this may provide conservative estimates, it is underpinned by a robust design and strong scientific principles

and provides a clear interpretation of the study results. The suggested post-hoc adjusted analysis is 1 of many possible approaches and, as with multiple comparisons, the risk of the selection of that method of adjustment that would support preconceived views is always present. The basic principle of clinical research dictates that new standards of care and changes in patterns of practice should be supported by well-conducted and adequately powered randomized trials. ■

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REPLY



There is nothing scientific about surgical randomized controlled trials (RCTs) when investigators do not take into consideration differences in surgical skills in the performance of a new complex procedure and adjust for it or if they cannot ensure that the new procedure was performed appropriately.