Design of interventional studies in thoracic surgery

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Abstract: Interventional studies differ from observational studies in that one or more specific interventions are evaluated. Randomized controlled trials remain the gold standard for interventional studies and can take different forms. In surgical studies, the three types of randomized controlled trials most commonly encountered are: (I) trials that compare two different medical treatments for patients undergoing surgery; (II) trials that evaluate two different surgical techniques and (III) studies that compare surgery *vs.* non-operative management. When an intervention is to be evaluated but a randomized controlled trial is not feasible, alternative interventional study designs may be considered.

Keywords: Interventional study; randomized controlled trial; thoracic surgery

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Introduction

Using definitions provided by the United States Library of Medicine and the National Institutes of Health, biomedical studies can be divided into two general categories: (I) observational studies and (II) interventional studies (also known as clinical trials) (1). In observational studies, relevant groups of patients are identified and assessed but they are not assigned to receive specific interventions. In interventional studies, patients are assigned to receive one or more specific diagnostic or therapeutic interventions in order to evaluate the effects of those interventions. Observational study design has been reviewed earlier in this series (2). In this article, we review interventional study design, with an emphasis on the types of randomized controlled trials (RCTs) commonly encountered. Surgical RCTs have been categorized into three main types (3), all of which are outlined below with examples from the thoracic surgical literature. An additional type of RCT, known as the clustered RCT, will also be reviewed. Finally, alternative interventional study designs will be summarized. These alternative study designs have been suggested for situations in which a RCT is desirable but not easily feasibly performed due to ethical concerns, difficulty with recruitment, or other issues (4).

Type 1 RCTs

Type 1 trials randomize patients undergoing surgery to different non-operative therapies, and historically these have accounted for more than 75% of surgical RCTs (3). In 2015, Pless *et al.* published such a study, comparing different induction therapies in patients with resectable stage IIIA/N2 non-small cell lung cancer (NSCLC) who ultimately underwent surgery (5). Patients were randomized to receive either induction chemotherapy followed by resection (standard therapy) or induction chemoradiation followed by resection. No significant benefit was found by the addition of radiation to the induction regimen.

Type 2 RCTs

Type 2 trials randomize patients to different surgical techniques for treatment of the same condition. An example is the 1995 study by Ginsberg *et al.* that compared lobectomy to limited resection (segmental or wedge resection) for T1N0 NSCLC (6). The authors analyzed 247 randomized patients and found that, by their statistical criteria, limited resection was associated with significantly higher local cancer recurrence and higher lung cancer-specific mortality compared to lobectomy.

Type 3 RCTs

Type 3 trials randomize patients to either surgical therapy or non-surgical therapy for treatment of the same condition. A 2009 study published by Albain *et al.* randomized patients with stage IIIA/N2 NSCLC to undergo either chemoradiation followed by surgical resection (group 1) or chemoradiation alone (group 2) (7). The authors found no significant difference in overall survival or 5-year survival between the two groups, but they did find improved progression-free survival in group 1. Notably, in an exploratory analysis, they did find improved overall survival among patients in group 1 who underwent lobectomy (but not pneumonectomy).

Cluster-randomized trials

In a cluster-randomized trial, entire groups (clusters) of participants, rather than individual participants, are randomized to interventions. An example is the study published by Bilimoria *et al.* that randomized entire surgical residency programs in the United States to either traditional work hour restrictions or more flexible work hour restrictions (8).

Alternative interventional studies

To evaluate interventions in surgical patients, traditional RCTs remain the gold standard. However, due to any number of reasons, a RCT may not be feasible. In these cases, several alternative interventional study designs have been proposed, as discussed in-depth by McCulloch and colleagues (4). Briefly, "parallel group non-randomized studies" do not randomize patients. Instead, they enroll patients interested in an intervention and match those patients against similar patients who do not want the intervention (the match is usually based on propensity scores). "Controlled interrupted time series studies" attempt to evaluate an intervention by comparing outcomes before and after implementation of that intervention on an intervention group and a parallel control group. The "step-wedge" study design involves implementing an intervention at random times often across multiple study centers. "Tracker trials" begin as RCTs but would allow clinicians to add modifications of the intervention over time, as long as these modifications were "tracked," in theory, encouraging recruitment and enrollment because of increased flexibility of the study design. "Expertise-based randomized trials" compare interventions by randomizing patients to groups of experts who specialize in different interventions. The outcomes of different expert interventions are compared.

Conclusions

Interventional studies differ from observational studies in that one or more specific interventions are evaluated. RCTs remain the gold standard for interventional studies and can take different forms. In surgical studies, the three types of RCTs mentioned above are most common. When an intervention is to be evaluated but a RCT is not feasible, alternative interventional study designs may be considered.

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Footnote

Conflicts of Interest: TA D'Amico serves as a consultant for Scanlan. The other authors have no conflicts of interest to declare.

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