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Original article

Randomized controlled trials in testicular cancer: A demographic and quality assessment

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Abstract

Background: Randomized controlled trials (RCT) provide the strongest evidence to justify interventions in patients. However, trials with inadequate methods are associated with bias and exaggerated treatment effects. A search of the literature was conducted to review RCTs in testicular cancer (TC) to assess demographic and trial reporting quality patterns over time.

Methods: MEDLINE and CENTRAL were queried for TC RCTs from 1989 to 2014. Demographic information was abstracted and reporting quality score was evaluated using the Consolidated Standards of Reporting Trials criteria. Linear regression was used to assess the trend in reporting quality over time.

Results: A total of 39 RCTs were identified, of which 25 were published from 1989 to 2001 and 14 were published from 2002 to 2014. Most (59%) of the RCTs involved chemotherapy as the intervention, had a medical oncologist as the first author (87%), and took place in Europe (59%). RCTs published between 2002 and 2014 had longer enrollment periods (mean = 6.1 [2.7] vs. 3.7 [1.5] years, $P = 0.007$), whereas the number of patients randomized, median follow-up, or time from manuscript submission to acceptance were not significantly different between the periods. For each increasing year of publication, there was a significant improvement of 1.34% points (95% CI: 0.86–1.83, $P < 0.0001$) in the Consolidated Standards of Reporting Trials score.

Conclusions: Fewer RCTs in TC were published in the recent 13-year period. Although the quality of trial reporting improved compared with the preceding 13-year period, deficiencies remain. Urologists can play an important role in trial design, recruitment, and execution, and ensuring trial methodology and reporting quality is prioritized.

Keywords: Chemotherapy; Randomized controlled trials as topic; Testicular neoplasms; Reporting of methodological factors; CONSORT statement

1. Introduction

Well-designed randomized controlled trials (RCTs) are the most rigorous way of determining whether a cause-effect relationship exists between an intervention and an outcome [1]. However, trials with inadequate methods are associated with bias and exaggerated treatment effects [2,3]. Previous studies in prostate cancer, bladder cancer, and urolithiasis treatment have demonstrated that RCTs represent a small proportion of the published literature [4,5] and that there are significant inadequacies in the quality of trial reporting, making it difficult to interpret true treatment effects [5,6]. An evaluation of RCTs in testicular cancer (TC) has not been done. Given that TC is relatively rare and highly curable, it can be difficult to adequately power RCTs and attract industry support, making it that it is much more important for RCTs in TC to have valid methods and reliable results.

The objectives of this study were to assess the demographic patterns and quality of RCT reporting over time. Evaluating demographic patterns may provide insight on populations that are understudied in TC, and assessing deficiencies in RCT quality can focus future research on

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areas to improve upon in trial design and reporting of TC RCTs.

2. Methods

2.1. Identifying RCTs in the literature

A search strategy that has been previously described to identify RCTs in bladder and prostate cancer [4,5] was used by 2 independent investigators (M.N. and V.J.). The first search was performed in October 2014, with an updated search in February 2015. We chose 1989 as our index date, as there was limited access to abstracts and articles before 1989, thereby limiting feasibility for appraisal. A reproducible and detailed search strategy is available in the Appendix. Given the possibility of missing some trials with this strategy, another search was performed on CENTRAL to explore additional RCTs. Furthermore, articles and their references were also evaluated to possibly identify additional RCTs for inclusion.

Each search result was then evaluated based on the title, abstract, and if appropriate, full article to assess whether it met the following inclusion criteria: (1) patients were randomized to an intervention; (2) results of the trial were described and not merely the methodology, description, or protocol of a trial; (3) an original trial that did not describe follow-up results of a previously published trial; and (4) involved only male patients with malignant germ cell tumors. Consensus was obtained through discussion between the 2 investigators (M.N. and V.J.), with arbitration from a third investigator (R.J.H.) when needed.

2.2. RCT appraisal

The following demographic data were abstracted from trials meeting inclusion criteria: date of submission to journal, date of acceptance, year of publication, first author occupation, journal type, type of intervention, number of patients randomized, geographic region of where trial was conducted, disease stage, disease histology, enrollment status, enrollment start date, enrollment end date, and median follow-up.

Quality of trial reporting was independently evaluated (M.N. and V.J.) using the 37 criteria from 2010 Consolidated Standards of Reporting Trials (CONSORT) guidelines [7]. Each criterion was equally weighted and was assigned points according to the following criteria: 0—none of the required information was present; 0.5—some, but not all, of the required information was present; or 1—all of the required information was present. If a specific criterion was not applicable to the particular trial, then no points were assigned for that criterion. A total CONSORT score was then obtained by summing the points divided by the number of criteria applicable to each trial.

2.3. Statistical analysis

As the study period involved 26 years of published literature, trials were divided into 2 equal groups of 13 years each: trials published from 1989 to 2001 vs. trials published from 2002 to 2014. Continuous variables were compared using the *t* test or the Wilcoxon rank-sum test. Normality of continuous variables was evaluated with the Shapiro-Wilk test. Means are described with their standard deviations, whereas medians are described with their interquartile ranges (IQRs). Interobserver agreement for the CONSORT score was evaluated with the concordance correlation coefficient [8]. The mean of the CONSORT score from each observer was used in linear regression to evaluate the change in score over time. The assumptions of linear regression were evaluated and were met. All statistical analyses were performed using SAS (version 9.3; SAS Institute, Cary, NC).

3. Results

3.1. Identifying trials

A total of 2,948 results were retrieved from MEDLINE, of which 2,891 were excluded based on title or abstract. From the remaining studies, 33 (1.1%) met the inclusion criteria. Table 1 describes the breakdown of RCTs identified by year through MEDLINE. An additional 6 trials were identified through CENTRAL and article appraisal, resulting in 39 trials for evaluation (Table S1).

3.2. Demographics of all trials and by publication year

Of the trials retrieved for analysis, 25 (64%) were published between 1989 and 2001, whereas the remaining 14 (36%) were published between 2002 and 2014. Table 2 describes the demographic data for these trials. A medical oncologist was the first author on 34 (87%) trials. Of the remainder, a urologist was the first author for 2, an obstetrician-gynecologist for 1, and nonclinicians for 2 trials. Most (95%) were published in medical journals, whereas 1 was published in a surgical journal and 1 in a radiation oncology journal. Of those that were published in a medical journal, most were published in the *Journal of Clinical Oncology* (51%), followed by the *Annals of Oncology* (13%) and the *British Journal of Cancer* (10%). Only 2 (5%) trials compared different treatment modalities (chemotherapy vs. surgery and chemotherapy vs. radiation).

A total of 11 (28%) trials were closed prematurely. Of the 7 RCTs that were closed in the 1989 to 2001 group, 4 (57%) closed because of excess harm in one of the intervention arms, 2 (29%) closed because of poor enrollment, and 1 (14%) closed early as a similar trial from another group had shown there was no difference among the intervention arms. Of the 4 RCTs that were closed early