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Time-to-event endpoints reporting in operable non-small-cell lung cancer randomized clinical trials: A systematic review

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ABSTRACT

Purpose: The aim of the study was to evaluate the reporting of time-to event endpoints (TTEE) in operable non-small-cell lung cancer randomized clinical trials.
Methods: Eligible trials were randomized trials with pre-operative or perioperative or adjuvant chemotherapy for operable NSCLC. Articles were extracted from two Cochrane meta-analyses.
Results: Thirty-four studies were included in the review. Among the 34 articles, a total of 62 TTEE were recorded. Overall survival (OS) was the most frequent TTEE used (32 terms, 51.6%). Other TTEE used were 16 disease-free survival (25%), 5 progression-free survival (8%), 3 time to recurrence (4.8%), 1 time to disease progression (1.6%), 1 recurrence free survival (1.6%), 1 event free survival (1.6%), 1 disease specific survival (1.6%), 1 disease free interval (1.6%), 1 cancer free survival (1.6%). In the Methods section, using the four key points to define TTEE we observed that the "starting point", "events", "information on censoring", "assessment of events" were clearly defined for 43 (69.4%), 34 (54.8%), 6 (9.7%), 33 (53.2%) endpoints respectively. In the results section, using the five key points, we observed that the "Kaplan-Meier estimation", "estimation of effect size", "precision (confidence interval)", "number of events", "number of patients at risk", "multivariate analysis" were clearly identified for 46 (74.2%), 31 (50%), 30 (48.4%), 37 (59.7%), 28 (45.2%), and 17 (27.4%) endpoints, respectively.
Conclusion: A majority of articles failed to provide a complete reporting of TTEE. Guidelines for TTEE reporting in operable NSCLC randomized clinical trials is warranted.

Contents

Introduction

Endpoints refer to clinical and biological measurements that assess the efficacy of therapeutic Strategies [1]. As the American Society of Clinical Oncology stated, active treatment in cancer is

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generally undertaken with the goal of providing improved quantity and/or quality of patient survival [2]. Cancer randomized clinical trials are conducted to obtain clinical evidence on the safety and efficiency of new interventions. The selection of an appropriately valid primary endpoint is an important aspect of clinical trial design to achieve this objective. The publications of the CONSORT (Consolidated Standards of Reporting Trials) statement encouraged the reporting of clearly defined primary and secondary outcome measures especially time-to event endpoints (TTEE) [3]. This implies specifying the date of origin (time zero), the list of events to be considered as failures and the censoring process. Composite endpoints combine multiple events (called components) such as local and distant progression, local and distant recurrence, development of metachronous cancer, death or severe toxicity into a single endpoint. An event is said to occur if any one of the prospectively defined components of the composite occurs. In the absence of at least one component considered in the composite endpoint, the patient is censored at the time of the last follow-up.

The US FDA considers OS benefit as the foundation for the approval of new anticancer drugs in the USA nevertheless composite endpoints are frequently used as primary outcome in oncologic clinical trials for several reasons. First, they can increase statistical power. A higher event rate than with OS is observed, so clinical trials need fewer numbers of patients to achieve required power. Then they are assessed earlier than OS. The fewer number of subjects and the smaller duration of trials contribute to an economic benefit of less costly trials [4–6].

Nevertheless, composite endpoints suffer from important limitations especially heterogeneity of the definitions of composite endpoints like progression-free survival (PFS), disease-free survival (DFS), time-to-treatment failure and so on. Consequently the definition of the same 'endpoint' is variable in different studies of the same disease [4]. Birgisson et al. demonstrated that the inclusion of a second primary cancer other than the incident colorectal cancer as an event in the definition of DFS significantly impacted the results. The estimated DFS rate for patients with stage I–III disease was 62% after 5 years if this event was not taken into account as an event, compared with 58% if it was. The difference was larger for stage II (68 versus 60%) than for stage III (49 vs 47%) [5]. Another example is the PETACC 03 randomized study [6] where results were either significant or non significant depending on whether or not second primary tumors were accounted for in the DFS definition.

The purpose of this study was to evaluate the reporting of TTEE in randomized clinical trials of operable NSCLC. This is the first step of the development of standardized definitions of TTEE in lung cancer trials.

Methods

Search strategy and selection for studies

Eligible trials were randomized trials with pre-operative or perioperative or adjuvant chemotherapy for operable NSCLC. Articles were extracted from two Cochrane meta-analyses published by Burdett et al. in 2014 and 2015: "Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data" and "Adjuvant chemotherapy for resected early-stage non-small cell lung cancer" [7,8]. Four studies of preoperative chemotherapy and four studies of adjuvant chemotherapy were not included because they were unpublished; no data about their endpoints were available. Radiotherapy trials were not included.

Data extraction

Two authors (F. F., M.J.P) independently extracted information using predefined data abstraction forms. To assess interobserver reliability, one reviewer independently resolved disagreements (F. B). The following details were extracted: general items (number of patients, year of publication, study period, number of centers, nationality of the first author, academic or industrial trial); items related to each TTE endpoint and their section location in the articles (primary endpoint and its definition: date of origin, events, censoring process; secondary endpoints and their definitions; these items were based on CONSORT reporting items [3]); other items related to methods of randomized clinical trials conduct (intent-to-treat-analysis [ITT], interim analysis, follow-up definition).

We assessed each TTEE according to eight key parameters: definition of TTEE clearly reported in the methods section (four key points: time of origin, events of interest, censoring events, assessment of events) and availability of TTEE results (six key points: Kaplan-Meier estimation, estimation of effect size, precision (confidence interval), number of events, number of patients at risk, multivariate analysis). Each key point was coded as "yes," "unclear," or "no".

Data analyses

We conducted a descriptive analysis of selected publications and of the TTEE with each key point.

Quantitative variables were descripted with median and range. Qualitative variables were descripted with absolute frequencies (number) and relative frequencies (proportion).

Analyses were conducted with the use of SAS software, version 9.3 (SAS Institute).

Results

Thirty-four studies were included in the review. Twenty-two studies were adjuvant chemotherapy trials and 12 studies were preoperative chemotherapy trials. Fifteen trials were Europeans (46.7%), 12 Asians (29%) and 7 Americans (22.6%). All the studies (100%) were academic. The median number of including centers was 40 (range, 1 to 101 centers). The median number of patients was 287 (range, 26 to 1867).

Among the 34 articles, a total of 62 TTEE were recorded. Overall survival (OS) was the most frequent TTEE used (32 terms, 51.6%). Other TTEE used were 16 disease-free survival (DFS) (25%), 5 progression-free survival (PFS) (8%), 3 time to recurrence (TTR) (4.8%), 1 time to disease progression (TTP) (1.6%), 1 recurrence free survival (RFS) (1.6%), 1 event free survival (EFS) (1.6%), 1 disease specific survival (DSS) (1.6%), 1 disease free interval (DFI) (1.6%), 1 cancer free survival (CFS) (1.6%). The primary endpoint was specified in 22 studies (64.7%): 20 OS (90.9%), 1 PFS (4.5%), 1 DFS (4.5%) and was defined in 15 studies (68.2%) (Table 1).

For OS, starting point was defined in 21 cases (65.7%) (15: date of randomization, 6: date of surgery) and events of interest defined in 16 cases (50%) (15: death from any cause, 1: death from lung cancer) (Table 2).

For DFS, starting point was defined in 12 cases (75%) (9: date of randomization, 3: date of surgery) and events of interest defined in 12 cases (8: local recurrence, 8: distant recurrence, 1: disease progression, 1: first progression for patients not undergoing surgery, 1: second lung cancer, 8: death from any cause) (Table 2). Assessment of "Disease progression" was not defined and assessment of "first progression for patients not undergoing surgery" was done with WHO criteria. DFS was used in 6 pre-operative or