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Short communication

Uniform and blinded cause of death verification of the NELSON lung cancer screening participants☆

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ABSTRACT

Primary outcome of the Dutch-Belgian lung cancer screening trial (NELSON) is lung cancer-specific mortality. Accurate assessment of the cause of death (CoD) is crucial. As death certificates regarding the CoD can be inaccurate, a clinical expert committee (CEC) was formed to assign the CoD. In this study, the medical files of deceased lung cancer patients were reviewed and the outcomes were compared with official death certificates. The first 266 completed medical files of Dutch deceased participants who were diagnosed with lung cancer during the study or of those with lung cancer on the death certificate were selected and blinded towards arms and patients identity. The end product of the review process consisted of six possible categories which defined the graduation of certainty that lung cancer was the primary CoD. The percentage agreement and the Cohen's kappa statistics between the two CEC-memberswere calculated. The sensitivity and specificity of the official death certificates were determined. The results indicated that, the overall concordance and the Cohen's kappa between the CEC-memberswere 86.1% and 0.57(0.45–0.69, $p < 0.001$), respectively. This level increased with the numbers of cases evaluated. The sensitivity and the specificity of the official death certificate were 92.6% and 98.8%; 6.5% cases were reclassified to lung cancer specific death, which is lower than in the National Lung Screening trial(22.0%). Concluding, each death should be reviewed by at least two members. So far, in the NELSON trial, possible biases related to lung cancer death seem relatively small.

1. Introduction

In cancer screening trials, the cause of death (CoD) is often determined by a review committee of medical scientists who (independently) review the blinded medical files of the deceased participants and achieve consensus regarding the underlying cause of death [1–4]. This is done to overcome different biases, as sticky-diagnosis (if more cancers are being diagnosed in the screening group, it's likely that more death are attributed to that cancers compared to the control group with no screening), and slippery-linkage bias (where deaths are due to the screening process, but are not traced back to screening and are certified as due to other causes). This also should overcome the variable sensitivity and specificity of the official death certificates which depends on the accuracy of the certifying clinicians [5–7].

A clinical expert committee (CEC) was formed to independently, and in a uniform and blinded matter to review the first 266 completed medical files of deceased lung cancer participants of the NELSON trial – the Dutch Belgian lung cancer screening trial [8,9]. Furthermore, these files and official death certificates were compared.

2. Methods

2.1. Pilot study

Previously, a pilot study (n = 50) by a uniform classification (review committee vs. death certificates) demonstrated an agreement of 90% (Cohen's kappa 0.65) [9]. The sensitivity and specificity of the official death certificates for lung cancer specific mortality were 95.2% and 62.5%, respectively, what implied that the final NELSON outcomes should be established with predetermined criteria and an independent review of blinded cases.

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2.2. Selection of subjects

For this study, all Dutch deceased participants who were diagnosed with lung cancer (during the study or at autopsy), deceased participants who were in the diagnostic work-up for lung cancer, and participants with a notation of lung cancer on the death certificate (International Classification of Diseases and related health problems (ICD) version 10:34) were selected. Lung cancer cases and the death certificates were obtained through linkages with the National Cancer Registry of the Netherlands (100% coverage), and Statistics Netherlands (100% coverage; 2003–2014), respectively. Thereafter, it was verified if the participant had indeed been diagnosed with lung cancer, during a separate procedure. All relevant medical data pertaining to the CoD (all outpatient and discharge letters, radiology and pathology reports, and place of death) was collected.

2.3. The NELSON clinical expert committee

The CEC consisted of an independent pulmonologist-oncologist and a pathologist specialized in lung oncology. In cases with no consensus, a third reviewer (a clinical epidemiologist specialized in screening) was consulted [9].

2.4. The CoD review process

After blinding the medical files for patients identity and study arm, they were uploaded onto a secure online database. The end product of the evaluation consisted of six possible categories which defined the graduation of certainty that lung cancer was the primary cause of death, which is based upon the CoD review process followed in the European Randomized Screening for Prostate Cancer trial [10]. After reaching consensus between the two CEC-members, and the third reviewer, the end product was considered as the golden standard (Fig. 1). At all time, the reviewers had no access to the official death certificates.

2.5. Analysis

The primary CoD was defined as 'the disease that initiated the chain of morbid events directly leading to death'. Lung cancer mortality, was defined as 'definitely' or 'probable lung cancer death'. All other four possible categories ('possible', 'unlikely', 'definitely no lung cancer death', and 'intercurrent death with lung cancer as contributing factor') were considered as 'another CoD'. CEC-members Cohen's Kappa represented the percentage agreement between the CEC-members. Sensitivity (true positives (lung cancer death assigned by both sources) divided by the sum of true positives and false negative diagnoses according to the official death certificates) and specificity (true negatives (other cause of death assigned by both sources) divided by the total death due to other cause according to the official death certificates) were calculated. All continuous variables were presented as medians and interquartile ranges (IQR), as appropriate. Differences between variables were calculated by using the Median Test or ANOVA (continuous variables), chi-square test (nominal), and Kruskall-Wallis test (categorical). For all analysis SPSS version 21 was used.

3. Results

In total, 266 medical files of Dutch deceased participants, who deceased between 28th August 2004 and 26th April 2014, were selected for the review (Table 1).

Agreement between the CEC-members based on six possible categories was reached in 71.1% (189/266) of the online reviewed cases. Divided in a lung cancer death (definitely or probably lung cancer death), agreement between the two members was reached in 86.1% of the cases (Cohen's kappa of 0.57 (95% CI, 0.45–0.69, $p < 0.001$)). Nonconsensual cases were discussed in a meeting. Reasons of disagreement were: recently received lung cancer treatment (n = 1), autopsy revealed lung cancer death (n = 2), other possible CoD (n = 2), too little information (n = 2), intercurrent death with another CoD (n = 2), another CoD was more obvious (n = 2), and reports were available about progressive tumor (n = 26). No third reviewer was required to reach consensus.

Compared to the pilot study (in which 49 comparable cases were evaluated by two different reviewers), in seven out of 49 cases there was a disagreement (Fig. 1). These cases were re-evaluated and discussed in a meeting by the CEC and the third reviewer. In four cases the outcome of the CoD review process was changed to 'definitely lung cancer death'. Reasons for these changes were: autopsy showed lung cancer death (n = 2), euthanasia because of cerebral metastasis of lung cancer (n = 1) and all the clinicians who treated the patient addressed the death of the patient to lung cancer (n = 1).

From 266 participants, three participants did not provide informed consent to obtain their official death certificate. Therefore, the consensus reached in the CoD review process will be used as the primary CoD for these cases.

When the official death certificates noted 'lung cancer death', but the CoD review process noted it as another CoD', a third independent review took place (n = 21). In three cases the outcome of the COD review committee was changed to 'lung cancer death'. In all the three cases the patient suffered from metastasized lung cancer with no treatment options. The overall sensitivity and specificity of the death certificates were 92.6% and 98.8%, respectively. Death review resulted in a reclassification of 12.2% (32/263) of the cases (Table 1).

4. Discussion

In this study, medical files of deceased NELSON lung cancer participants were reviewed concerning the underlying CoD and were compared with the official death certificates. Weak to moderate agreement of 86.1% (Cohen's kappa of 0.57) between the two committee members was reached, what underlies the need for a CoD committee. As expected, the level of agreement increased with the numbers of cases evaluated (data not shown) [9].

The National Lung Screening Trial (NLST) [3,4], which also used a death review committee to verify the CoD, showed a comparable sensitivity and specificity of the official death certificates (NLST: 91% and 97%, and NELSON 92.7% and 98.8%, respectively). However, the NLST review was not restricted to the files of lung cancer patients only [4]. Secondly, only one member reviewed the medical files of the NLST first. In case of concordance with the death certificate this was considered as certified. In the NELSON trial, two members reviewed each file, independently. Furthermore, less official death certificates were re-classified in the NELSON trial compared to the NLST (12.2% vs. 26.0%). The NLST showed a higher reclassification of deaths to lung cancer specific deaths than the NELSON trial (22.0% vs. 6.5%). Dutch clinicians and Statistics Netherlands may have a more uniform method in reporting the cause of death. Furthermore, the NLST showed that the mortality benefit of screening did not significantly change with reviewing the CoD [4]. For the NELSON trial, we are waiting the final results and the CoD review process will be continued until then.

No comparison of the death review was made with other trials, since data about the death review process (e.g. reclassifications after the death review) was not available.

Strengths of this study are the blinded (for study arm and official death certificate) and uniform review process by the independent reviewers that had access to participant's complete medical file. A potential limitation is the selection of the first 266 deceased participants from whom all medical data was collected, what possibly over represents participants with an aggressive lung cancer leading to more assignable death due to lung cancer and few cases to be reclassified. Secondly, a subset of deaths was selected for the CoD review (e.g. participants with a diagnosis of lung cancer or with a notation of lung