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Reporting adverse events in cancer surgery randomized trials: A systematic review of published trials in oesophago-gastric and gynecological cancer patients☆

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ABSTRACT

Background: Few reports describe how adverse events (AEs) are reported in cancer surgery trials.
Materials and methods: We systematically reviewed 179 consecutive study reports issued between January 1, 1990 and November 15, 2014, which investigated surgery in oesophago-gastric (OG) or gynecologic (GY) cancer patients. Based on the reviewed reports, we assessed how AEs were reported according to CONSORT statement.
Results: Morbidity assessment was the primary objective of 56 studies (31.3%). Postoperative AEs were described in 161 studies (90%). Definition of AEs and grading scale (NCI-CTC AE, Dindo-Clavien scale, etc ...) were given in 27.3% and 16.8% of studies, respectively. AEs were

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reported by event and grade in 8.3% of studies. Definition of expectedness, seriousness, causality and safety population were present in 0.5%, 1.1%, 7.8%, and 7.2% of the studies, respectively. Reporting of AEs did not improve over time nor better in high-impact factor journals.
Conclusion: The reporting of AEs in cancer trials investigating surgery needs to be improved.

1. Introduction

Surgery remains the cornerstone of curative-intent treatment of the majority of solid tumors, even if surgery is associated with neo-adjuvant or adjuvant treatment such as, chemotherapy, hormonal therapy, external radiation therapy, brachytherapy, etc... Current randomized clinical trials (RCTs) in cancer surgery are mainly assessing the role of mini-invasive surgery and the impact of combination treatments (Diaz-Nieto et al., 2013; Galaal et al., 2012).

RCTs provide the highest level of evidence and may lead to changes in practice. The primary objective of most RCTs is the assessment of the effectiveness of the "investigational" treatment compared to recognized standard of care. However, the accurate measurement of both benefits and harms of the "investigational" treatment, whether pharmacological or not, are of major importance to properly weight the benefit-risk balance (Moher et al., 2001; Ioannidis et al., 2004). Thus, the reporting of adverse events (AEs) should be standardized, objective and reproducible in order to compare the different therapeutic approaches. The CONSORT (The Consolidated Standards of Reporting Trials) issued recommendations concerning the report of AEs in pharmacological clinical trials (Ioannidis et al., 2004). However, the description of surgical AEs significantly differs from the description of AEs in pharmacological clinical trials. To date there are no recommendations for the report of surgical AEs. To the best of our knowledge, few reports assessed the quality of AEs reporting in cancer surgery randomized trials (Blencowe et al., 2012).

Based on these facts, we have conducted a systematic literature review to measure how AEs are reported in two different clinical settings: oesophago-gastric cancer surgery and gynecological cancer surgery, both of which represent our fields of expertise. The main objective of our work was to analyze the quality of the reporting of surgical AEs in cancer surgery clinical trials. Our secondary objective was to identify factors influencing the description of AEs.

2. Materiel and methods

2.1. Selection of relevant publications and data extraction

We conducted a systematic review of the literature using the PubMed database. Selection criteria of relevant publications were as follow: randomized clinical trials (RCTs) assessing surgery in two clinical settings (of special interest for the study coordinators of our institutions) gynecological cancers patients (endometrium, cervix, ovary and vulva) and in oesophago-gastric cancers patients, with surgical procedure(s) in at least one of the treatment arms, including more than 50 patients, fully published in English and issued between 01st January 1990 and 15th November 2014. We have used several research equations taken into account the different primary locations (see supplemental Figs. 1–6 in the On-line appendix). Limits used were: randomized clinical trials, English, published between January 1, 1990 and November 15, 2014. Two expert surgeons (Pr C. Mariette and Dr F. Narducci) have reviewed, and validated the list of relevant publications to ensure its completeness. All consecutive fully published reports had been selected.

For each publication the following variables were collected: the year of publication, the journal and its impact factor (IF), the number of patients included, the study sponsor (academic or industrial), the continent of the study coordinator, type of cancer (gynecologic or oesophago-gastric), the study design (surgery A against surgery B or multimodal treatment) and the main objective of the trial (efficiency or morbidity).

2.2. Systematic analysis of the reporting of AEs

We have developed a grid composed of 18 items derived from the CONSORT recommendations for the report of AEs in clinical trials (Ioannidis et al., 2004). Each item was as objective as possible and coded in a binary fashion (present or absent; see Table 1).

We have analyzed each and every publication. For each publication, we have assessed the quality of the AEs reporting according the 18-items grid. Validation of the coding was done by a double blind reading of a random sample of articles by Dr. N. Penel and L. Meghelli (total of 28 articles, 5 articles by primary locations, except for vulvar cancer, all published articles (3 articles) have been reviewed by Dr N. Penel and L. Meghelli). A reconciliation was performed for any discrepancy in coding. Consensual rules were established after the double blind reading, then subsequently applied to all the publications, read and scored by L. Meghelli. The established consensual rules are as follow:

Surgical AEs were considered as described if at least an overall number of post-operative morbidity events was given in the results section of the publication.

Surgical AEs were considered as defined if there was a clear definition given by the authors (for example, definition of cellulitis or delayed gastric emptying), or if a standardized or a recognized classification (for example, NCI-CT) was given in "Materials and Methods" section or "Results" section.

"Unexpectedness" was considered as defined if there was a list of expected or usual AEs for the surgical intervention.

"Seriousness" was considered as defined if a precise definition of serious AEs was present.

Causality was considered as defined if there was at least one sentence giving a time limit to consider AEs as related to surgery (for example: AEs were considered related to the surgery if they occurred within 30 days post-operative).

Per-operative AEs were considered as described separately if they were clearly stated in the results or if the author clearly stated that there were no per-operative AEs.

The early and late AEs should be described separately in the text (with a timeframe given in the text).

Regarding the modality of AEs collection, the authors should specify who collected the information about peri operative period (clinical research nurse, blinded investigator, the surgeon ...), when the information was collected (prospective or retrospective), and the postoperative monitoring modalities.

The severity of surgical AEs was considered as "graded" if a grading scale described by the authors in the "Materials and Methods" section or a recognized grading scale was used (ex: NCI-CT, Dindo-