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Critical Review

Systematic Review of Radiation Therapy Toxicity Reporting in Randomized Controlled Trials of Rectal Cancer: A Comparison of Patient-Reported Outcomes and Clinician Toxicity Reporting

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The use of multimodal treatments for rectal cancer has improved cancer-related outcomes but makes monitoring toxicity challenging. Optimizing future radiation therapy regimens requires collection and publication of detailed toxicity data. This review evaluated the quality of toxicity information provided in randomized controlled trials (RCTs) of radiation therapy in rectal cancer and focused on the difference between clinician-reported and patient-reported toxicity. Medline, EMBASE, and the Cochrane Library were searched (January 1995-July 2013) for RCTs reporting late toxicity in patients treated with regimens including preoperative (chemo)radiation therapy. Data on toxicity measures and information on toxicity reported were extracted using Quantitative Analyses of Normal Tissue Effects in the Clinic recommendations. International Society for Quality of Life Research standards on patient-reported outcomes (PROs) were used to evaluate the quality of patient-reported toxicity. Twenty-one RCT publications met inclusion criteria out of 4144 articles screened. All PRO studies reported higher rates of toxicity symptoms than clinician-reported studies and reported on a wider range and milder symptoms. No clinician-reported study published data on sexual dysfunction. Of the clinician-reported studies, 55% grouped toxicity data related to an organ system together (eg "Bowel"), and 45% presented data only on more-severe (grade $\geq$3) toxicity. In comparison, all toxicity grades were reported in 79% of PRO publications, and all studies (100%) presented individual symptom toxicity data (eg bowel urgency). However, PRO reporting quality was variable. Only 43% of PRO studies presented baseline data, 28% did not use any psychometrically validated instruments, and only 29% of studies described statistical methods for managing missing data. Analysis of these trials highlights the lack of reporting standards for adverse events and

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reveals the differences between clinician and patient reporting of toxicity. Recommendations for improving the quality of adverse event data collection are provided, with the aim of improving critical appraisal of outcomes for future studies.

Introduction

Rectal cancer is diagnosed in approximately 40,000 people annually in the United States (1). The approach to rectal cancer treatment is multimodal, with the majority of patients receiving either preoperative radiation or chemoradiation. The use of multimodal treatments has improved cancer-related outcomes; however, it has also led to an increase in substantial immediate and late adverse events and toxicity (2, 3).

Reliable collection and analysis of adverse event data in oncology is challenging because complex multimodal regimens, such as in locally advanced rectal cancer, involve not only different treatments but also variations in dose intensity and duration (4). Methods for toxicity data capture and reporting in oncology were developed from other disciplines that use treatments with a different, and often less toxic profile, such as antibiotics (4). Adverse events in oncology may be inadequately captured by these methods and are often underreported (5). A number of international reports, including QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic), have highlighted that, to optimize future radiation treatment regimens, a systematic approach to the collection and publication of detailed toxicity data is required (5). Newer radiation therapy techniques, such as intensity modulated radiation therapy, aim to reduce toxicity by reducing the amount of normal tissue exposed to high doses of radiation. One important consequence is that more organs are exposed to a low dose of radiation than in conventional treatment. This has an unknown impact on late toxicity, and rigorous toxicity reporting methods are required to capture these data (6).

The clinician-reported Common Terminology Criteria for Adverse Events (CTCAE) version 4 has recently been accepted as the preferred instrument for collection of adverse event data in cancer trials (7). However, patient-reported outcomes (PROs) included in trials are increasingly used as a surrogate measure of late toxicity, usually as a secondary outcome. Using PROs has been found to increase the number and variety of adverse events recorded and highlight discrepancies between clinician and patient reporting (8, 9). The inclusion of PROs in clinical trials may therefore provide additional information to better inform clinical decision making. However, a number of reviews of PROs in clinical trials have revealed concerns regarding the methodologic quality and reporting of the results (10-12). Two recently published, internationally developed guidelines highlight this area of concern (13, 14).

Previous reviews of radiation therapy treatment in rectal cancer have focused on survival outcomes and descriptions of late adverse events or functional outcomes in a variety of different trial settings, including retrospective studies (15-19). This review focuses on randomized controlled trials (RCTs) in rectal cancer, as the research gold standard, with the following objectives: (*1*) to establish the clinician- and patient-reported toxicity instruments used; (*2*) to assess the methodologic quality of the studies and quality of PRO reporting; and (*3*) to report a summary of the percentage of toxicity reported by treatment received and compare differences in clinician and patient reporting. The review concludes with recommendations for improving adverse event data collection from clinicians and PROs and describes the impact of reporting quality of adverse events on the ability to establish safe dose constraints for normal tissues in future optimization studies for radiation treatments.

Methods

Search strategy

Medline, EMBASE, and the Cochrane Library were searched from January 1995 to July 2013 for RCTs reporting late toxicity in patients treated with regimens including preoperative (chemo)radiation therapy. The search followed Centre for Reviews and Dissemination recommendations for undertaking systematic reviews (20) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (21) (Appendix 1.1; available online at www.redjournal.org). Only English language publications were included. Relevant studies listed as references were hand searched.

Selection criteria

All phase 2 and 3 RCTs in adult patients with a localized resectable rectal cancer were eligible if patients were randomized to at least 1 arm of preoperative radiation or chemoradiation. Studies of patients treated only with postoperative radiation were excluded unless in a comparison study with a preoperative radiation therapy arm. Studies of surgery alone, intraoperative radiation, or brachytherapy were not eligible. Conference abstracts were excluded.

Outcome measures examined

Studies including clinician-reported toxicity and/or patient reporting on symptoms or some other aspect of health-related quality of life (HRQOL) as a primary or secondary outcome were considered. The PROs were defined as any