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Patient-Reported Outcomes In Randomized Controlled Trials of Gynecological Cancers: A Systematic Review

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Abstract

Background

The aim for this study is to investigate the methodological quality and potential impact on clinical decision making of patient reported outcome (PRO) assessment in randomised controlled trials (RCTs) in the gynecological cancer sites.

Materials and Methods

A systematic review identified RCTs published between January 2004 and June 2012. Relevant studies were evaluated using a pre-determined extraction form which included: 1) Trial demographics and clinical and PRO characteristics; 2) level of PRO reporting; 3) Bias, assessed using the Cochrane Risk of Bias tool. All studies were additionally analysed in relation to their relevance in supporting clinical decision making.

Results

Fifty RCTs enrolling 24991 patients were identified. In eight RCTs (16%) a PRO was the primary endpoint. Twenty-one studies (42%) were carried out in a multi-national context. Where statistically significant PRO differences between treatments were found, it related in most cases to both symptoms and domains other than symptoms (n=17, 57%). The majority of studies (n=42, 84%) did not mention the mode of administration nor the methods of collecting PRO data. Statistical approaches for dealing with missing data were only explicitly mentioned in 9 RCTs (18%). Sixteen RCTs (32%) were considered to be of high-quality and thus able to inform clinical decision making. Higher-quality PRO studies were generally associated with RCTs that were at a low risk of bias.

Conclusion

This study showed that RCTs with PROs were generally well designed and conducted. In a third the information was very informative to fully understand the pros and cons of PROs treatment decision-making

Key words: Gynecologic cancer; patient-reported outcomes; clinical trials; quality of life; clinical decision-making.

INTRODUCTION

Gynecological cancers arise from the cervix, ovary, endometrium, vulva or vagina and as well as affecting 2.2% of the female population by the age of 65 they are the second commonest cause of cancer death in women after breast cancer(1).

Gynecological cancers are treated with different treatment modalities including surgery, radiotherapy and chemotherapy either alone or in combination. Whilst combinations of different treatments are known to improve survival they also increase the risk of side effects in both the short and long term with patients continuing to report more gastrointestinal and sexual dysfunction symptoms than women in the general population in the years following treatment(2). These symptoms are associated with considerable impairment in health-related quality of life (HRQOL) (3-5) that can also persist over the long-term period(6).

It is increasingly recognized that a comprehensive evaluation of treatment effectiveness should include a patient reported outcome (PRO) assessment to fully capture patients' perceptions of symptoms, functioning, and general well-being(7). Inclusion of PROs can be particularly valuable in randomized controlled clinical trials (RCTs) as it can potentially generate unique data to help health physicians to make more informed treatment decisions. However, information derived from PROs need to be based on well-planned RCTs to ensure that results are solid enough to robustly inform clinical practice (8). Several methodological aspects should be fully considered when implementing PROs in a RCT setting(9). Some excellent examples of the important information that can be drawn by including PROs in gynecological RCTs are available. To illustrate, the Post Operative Radiation Therapy in Endometrial

Carcinoma (PORTEC) trial found a significant reduction in the rate of local regional recurrence with the addition of post operative radiotherapy to standard surgical treatment of endometrial cancer. However, this reduction did not translate into an overall survival advantage and patients treated with the additional radiotherapy reported higher rates of gastrointestinal toxicity(10). The use of HRQOL in this RCT led to the decision to recommend postoperative radiotherapy only in high-risk patients where the risk of relapse is felt to outweigh the potential treatment related toxicity (10). Although this represents a concrete example of PRO implementation in a RCT setting, previous data have shown a number of methodological flaws, which have hampered drawing strong conclusions from many RCTs conducted in several cancer disease sites (11-13).

While previous work has investigated the methodological quality of studies in cervical cancer survivors, it reported studies published up to 2005 and was not focused on RCTs(6). On this ground, we conducted a comprehensive systematic review covering the main gynecological cancers with the following goals: (1) assess the quality of PRO reporting and methodological quality of each RCT, (2) identify high-quality PRO studies most likely to inform clinical decision-making (3) synthesize main clinical and PRO findings from the high quality studies.

MATERIALS AND METHODS

Search Strategy for Identification of studies

A systematic literature search was conducted in Medline, the Cochrane Controlled Trials Register, PsycINFO, and PsycARTICLES to identify RCTs published between January 2004 and June 2012. The search strategy was restricted to RCTs. Only English language articles were considered and no restrictions were included in the search field description. Experts in the field were contacted to identify potentially relevant articles not retrieved in the electronic search. Key searching strategy is reported in the online Appendix A. Titles and abstracts of identified articles were screened for inclusion. Additional publications were identified by scanning reference lists of relevant articles. Details on searching strategy and selection process were documented according to the PRISMA guidelines(14).

Selection criteria

Types of Participants

Clinical trials in adult patients with a diagnosis of cervical, ovarian, endometrial, vaginal or vulval cancer were included regardless of disease stage. Studies of patients undergoing screening or with benign disease were excluded.

Types of Intervention

All RCTs comparing conventional treatments were included. Studies considering psychosocial interventions or complementary therapies were not eligible.

Types of Outcome Measures Examined

Studies including a PRO as a primary or secondary outcome were included. We included both RCTs that evaluated either multi-dimensional patient-reported HRQOL or other types of health outcomes as long as they were reported by patients themselves. Studies evaluating treatment satisfaction and adherence to therapy were not included.

Types of Studies

We included all RCTs that (1) compared different conventional treatment modalities and symptoms management, and (2) had enrolled at least 50 patients. We restricted our review to RCTs because they are the gold standard of research by which decisions are made regarding the clinical effectiveness of treatments. Studies including a heterogeneous sample of cancer sites were included if dealing with gynecological cancers. Conference abstracts and case reports were excluded.

Data extraction and type of information extracted

Data extracted from the included RCTs were stored in predefined electronic data extraction forms (eDEF)(15) and a web-based data collection system was developed for the purpose of this research (<http://promotionproject.gimema.it/>). Three reviewers (MJ, JK and AP) independently extracted data on: (1) basic trial demographics (e.g., year, journal), (2) clinical and PRO characteristics (e.g., number of patients enrolled, study location, treatments being compared, PRO instrument used, clinical and PRO assessments). Summary of findings (i.e., PROs and clinical) were also extracted; (3) the quality of PRO reporting, based on the recently published guidelines by the International Society for Quality of Life Research (ISOQOL)(16); and 4) risk of bias using the Cochrane Risk of Bias tool (17). Results were cross-checked, and

discrepancies were resolved by discussion with the senior author (FE). In trials with multiple publications, we obtained relevant data by combining all trial publications.

Quality assessment and identification of high quality studies

PRO quality assessment was based on the recently developed ISOQOL consensus-based recommendations for reporting of PROs in RCT publications(16). These guidelines currently represent the highest quality criteria available and they form the basis for the recently published PRO extension of the CONSORT (CONsolidated Standards of Reporting in Trials) guidelines.(8) The ISOQOL guidelines comprise up to 29 key criteria (depending on whether the PRO is a secondary or primary endpoint of the trial) that a study should document in order for the PRO data to be reliable. Each criterion was rated as either ‘yes’ (scored as 1) if the issue was addressed or ‘no’ (scored as 0) if not. The higher the score the higher the quality. In order to identify high-quality studies that may have an impact on clinical decision-making, we a priori determined that at least two thirds of the ISOQOL recommended criteria must be satisfied. Additional details on methodology used have been previously reported(15). To assess internal validity (i.e., freedom from bias) of RCTs, we also applied criteria from the Cochrane Risk of Bias-tool. We thus evaluated each RCT for its adequacy of sequence generation; allocation concealment; blinding of participants/personnel; completeness of outcome data; blinding of outcome assessment; no selectivity of outcome reporting; and other sources of bias (17).

RESULTS

The systematic literature search yielded 2735 records (Figure 1). Application of inclusion criteria identified 50 RCTs enrolling overall 24991 patients published between January 2004 and June 2012 (see Appendix for the full list of papers retrieved). The majority of these (i.e., 32%) have been conducted on patients with ovarian cancer.

Insert Figure 1

Study demographics and PRO assessment

In eight RCTs (16%) a PRO was the primary endpoint. Twenty-one studies (42%) were carried out in a multi-national context. Twenty-six studies (52%) were at least partially supported by industry. Twenty-three studies (46%) involved patients with mixed disease stages, and 16 (32%) only recruited patients with advanced / metastatic disease. Although 31 RCTs (62%) enrolled more than 200 patients, PROs were the primary endpoint in only 2 of these RCTs. The two most frequently used PRO instruments, used alone or in conjunction with other measures, were the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 in 24 RCTs (48%), and the Functional Assessment of Cancer Therapy (FACT) instruments in 16 (32%). Thirty studies (60%) found a PRO difference between treatment arms. When a PRO difference was found, this related to both symptoms and domains other than symptoms in 17 RCTs (57%). Further details are provided in table 1.

Insert Table 1

Overview on PRO assessment methodology

The majority of publications (42 RCTs; 84%) did not report the mode of administration of the PRO tool nor were the methods of collecting the data described. In addition, 43 RCTs (86%) did not state a PRO hypothesis nor did they specify to which PRO domain the hypothesis was relevant. Although the extent of missing data was well documented in 30 RCTs (60%), only 9 RCTs (18%) explicitly stated the statistical approaches applied for dealing with missing data. In addition, 15 RCTs (30%) explained the reasons for missing data. Sixteen RCTs (32%) provided a flow diagram that provided a description of the allocation of participants and those lost to follow-up for PROs specifically. When discussing their findings, only 15 RCTs (30%) discussed the clinical significance of their findings. Moreover, only 14 RCTs (28%) discussed the generalizability issues that were uniquely related to the PRO results. The limitations of the PRO components of the trial were discussed in less than half of the RCTs included (46%). A complete overview is provided in Table 2.

Insert Table 2

Overview on outcomes from higher-quality PRO studies

Sixteen RCTs (32%) that were likely to provide robust PRO data to inform clinical decision-making (Table 3) were identified. Five RCTs (31%) focused on advanced / metastatic disease, three (19%) reported on non-metastatic disease stages, and seven (44%) included on mixed disease stages (both loco-regional and metastatic disease). One RCT did not explicitly state patients' disease stage. The majority of these studies

were at a low risk of bias for sequence generation (n=11, 69%), allocation concealment (n=11, 69%), blinding of participants/personnel (n=3, 19%) and outcome (n=11,69%), attrition (n=10,63%), and selective outcome reporting (n=10, 62%). Conversely, the percentages of low risk of bias RCTs were generally a bit lower in lower quality PRO studies. Figure 2 depicts risk of bias of all RCTs, classified by the PRO quality rating (high versus low).

Insert Figure 2

Summary outcomes from metastatic/advanced disease

The largest RCT, with 976 patients(18-23), had progression free survival as the primary endpoint and used the EORTC QLQ-C30 and the ovarian specific module (OV-28) to assess HRQOL. This trial showed that the experimental arm had significant improvements in progression free survival and less peripheral neuropathy, and other chemotherapy side effects, and less impact on body image than standard chemotherapy, although these benefits were not translated into a difference in global quality of life scores. Other smaller RCTs that used the FACT instruments did not show a clear difference in HRQOL between chemotherapy-based treatment arms also.

Summary outcomes from non-metastatic disease stage

The largest trial, with 429 patients, conducted by Armstrong and colleagues(24-27) showed that intravenous therapy, when compared to intraperitoneal therapy, improved progression free survival. In addition, after intravenous therapy, patients showed more physical and functional well-being, less ovarian cancer symptoms, and less abdominal discomfort using the FACT questionnaires.

Summary outcomes from mixed disease stage

The biggest study included in this systematic review, with 2616 patients, was conducted by Walker and colleagues(28-30). This trial randomized patients with clinical stage I to stage IIA uterine cancer to laparoscopy or open laparotomy with recurrence free survival as the primary outcome. This trial showed that patients treated by laparoscopy had fewer moderate to severe post-operative adverse events, and a lower frequency of hospitalization of more than 2 days. In addition, results obtained mainly with the use of the FACT questionnaires, showed that patients had better physical functioning, body image, less pain, and an earlier resumption of normal activities and return to work at 6 weeks after surgery. Another trial, comparing paclitaxel + carboplatin with paclitaxel + cisplatin(31-33) in ovarian cancer patients, showed no difference in progression free survival, yet better key functional and symptom outcomes using the EORTC QLQ-C30. However, no significant HRQOL differences were found in trials comparing paclitaxel + cisplatin versus cyclophosphamide(34-37) or paclitaxel + cisplatin versus added surgery(38, 39). In trials evaluating radiotherapy in endometrial cancer patients, vaginal brachytherapy, when compared to pelvic external beam radiotherapy, showed significantly lower rates of acute grade 1-2 gastrointestinal toxicity and better functioning and lower symptom scores(40-42). However, when comparing radiotherapy with chemotherapy(43, 44) in 422 patients, one trial showed a better progression free survival and better HRQL outcomes after chemotherapy.

DISCUSSION

In this systematic review we have searched for all PRO-based RCTs conducted in gynecological cancers, with the broad goal of summarizing the main findings to help health care policy makers and physicians better appreciate the state-of-art in this field.

Some 25,000 patients with various gynecological cancers have been enrolled in 50 RCTs over the last few years and, of these, at least one-third have provided reliable PRO data and have consider the information alongside the clinical data to make treatment recommendations. It is recommended that future trials continue to do this and that trial design and reporting is conducting in a robust manner so that patients can be informed how treatments impact not only on survival and toxicity data but on information that is central to their health and well being assessing with PRO measures.

Including a PRO assessment in a RCT requires special consideration of a number of methodological aspects, and major efforts have been made to increase standards of PRO reporting in RCT (8, 16). With regard to the key items recently suggested by the CONSORT PRO extension (8), our work has highlighted specific areas most in need of urgent improvement, such as the importance of documenting statistical methods used to handle missing data. While 60% of studies indeed documented the extent of PRO missing data, only 18% further reported details on how these were managed in the analysis. This is in line with what has been found in PRO-based RCTs in prostate cancer (15).

Another important result, previously identified in similar analyses (15), is the association between higher quality PRO studies and lower risk of RCT bias (Figure 2). This might support the concept that large and well-designed trials, hence probably those

that have been designed and led by expert methodological and clinical groups who have also received adequate financial and practical support, are more likely to incorporate well planned PRO assessment. However, this should be confirmed in other cancer disease sites.

Another important issue that arose from this review is the importance of selecting an appropriate PRO measure when designing an RCT. Several of the robust RCTs used a site specific PRO instrument alongside a generic one. Where cancer generic measures may not be sensitive enough, site-specific instruments maybe better able to detect clinically meaningful changes in HRQOL, and allow for a better discrimination between treatment arms. This is critical for treatment of a disease that has such a impact of personal aspects of health (e.g. sexual function and body image) as well as the traditional measures. It turns out to be especially important with gynecologic cancer therapies becoming increasingly tailored to individual risk factors, and with the evolution of new biological agents presenting a prospect of maintenance therapy, possibly extending treatment side-effects. These new therapeutic regimes may have the risk of additional toxicities, and will highlight the importance of selecting PRO instruments tailored to the research questions. For gynecologic oncology specific instruments have been developed for the major cancer sites (ovarian, endometrial, cervical, vulva) that can be used in clinical trials. With the availability of valid and sensitive site-specific measures, HRQOL measurement will continue to gain prominence as a principal outcome measure in clinical trials.

This review has limitations. Although we used a comprehensive searching strategy, it is still possible that some RCTs with a PRO component might have been missed. Also, as previously noted(15), our definition of “high quality studies” is

somewhat arbitrary and does not consider the relevance for PRO inclusion in the specific RCT context. Lastly, it should be noted that possible high quality HRQOL reports published after the cut-off date of this systematic literature search, are not considered in current work. To illustrate, Greimel and colleagues recently published a comprehensive HRQOL analysis(45) of an RCT(46) that we reviewed. Therefore, the additional HRQOL information stemming from this RCT could not be included. This is a more general issue of RCTs with a HRQOL component, because, the large amount of data collected typically prevents the possibility of including all information into a single paper. Hence, a separate publication on HRQOL analysis and outcomes is necessary to allow for a critical appraisal of the robustness of HRQOL findings in medical practice. Ideally, this additional publication should be as close as possible to the one reporting the main clinical findings.

This paper also has several notable strengths. PRO methodological evaluation was based on the most solid and up to date quality criteria(16). Furthermore, every RCT has been reviewed at least by two independent reviewers, permitting a calibrated assessment of all PRO-based RCTs in gynecological cancer research. Also, this review not only provided data on methodological aspects of PRO assessment but also synthesize the clinical and PRO outcomes stemming for higher quality studies in a attempt to provide medical community with concrete take home messages.

To conclude, quite a few RCTs have been conducted in patients with gynecological cancers over the last few years and in at least some one-third of these, PRO outcomes have been very informative to fully understand pro and cons of the new treatment approaches being tested. Investigators should pay particular attention to the

most frequently unmet methodological aspects identified in this work to further improve the quality and transparency of their PRO findings in future RCT publications.

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Conflict of Interest Statement:

None

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