Evaluation of the Quality of Radiotherapy Randomized Trials for Painful Bone Metastases

Implications for Future Research Design and Reporting

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BACKGROUND. The quality of randomized radiotherapy studies investigating the palliation of painful bone metastases has been questioned, with some authors recognizing the potential impact of bias on result interpretation. However, there has been no published comprehensive evaluation of quality assessment. The goals of the current study were to evaluate the quality of randomized studies using a validated checklist and to discuss implications and future directions.

METHODS. The authors performed a search for studies that could be reliably assessed using the validated quality assessment instrument. Independent assessors scored study quality using the instrument.

RESULTS. The median quality score of the 17 identified randomized studies was 1 of 5 (range, 0–3). The majority (71%) of points were awarded for the authors describing the study as "randomized." The method of randomization and description of withdrawals and dropouts were scored poorly for most studies. None of the studies were awarded points for allocation concealment (blinding). The overall quality was deemed poor (a score of 0–2) for 16 of 17 (94%) studies.

CONCLUSIONS. The quality of published randomized evidence comparing efficacy of fractionation schedules for the palliation of bone metastases was suboptimal. As a result of the potential biases present, subjective end points (e.g., retreatment rates) cannot be reliably evaluated. Greater efforts are required by radiation oncology trial groups to improve quality, with a particular focus on developing methods of allocation concealment and comprehensively reporting results. ***Cancer* 2005;103:1976–81.** © *2005 American Cancer Society.*

KEYWORDS: radiotherapy, randomized controlled trials, bone metastases, dose fractionation, pain, double-blind method, random allocation, metaanalysis, research design, palliative care.

Several recent metaanalyses of randomized radiotherapy studies have investigated the role of differing fractionation schedules for palliation of painful bone metastases.[1,2] The quality of previous evidence in this area has been questioned,[3] and it is known that poor-quality randomized studies may potentially invalidate the results and conclusions of individual studies and subsequent metaanalyses.[4] In particular, subjective end points such as retreatment rates (an important end point for many patients[5]) may not be reliably ascertained due to potential biases that are a direct result of study design, a finding acknowledged by several authors.[6,7] For this reason, any debate on the subject should consider evidence quality. However, there has been no quantitative report of the quality of randomized studies included in the recent overviews. Our aims were to assess the quality of the published randomized evidence using a validated assessment

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TABLE 1
Quality of Radiotherapy Studies Comparing Radiotherapy Fractionation for Palliation of Bone Metastases

Action	Was the study described as randomized?[a] Yes: Score 1 No: Score 0	Was the method to generate the sequence of randomization described AND appropriate?[b] Yes: Score 1 No: Score 0	Was the method to generate the sequence of randomization described AND it was inappropriate?[b] Yes: Score −1 No: Score 0	Was the study described as double blind?[c] Yes: Score 1 No: Score 0	Was the method of double-blinding described AND appropriate?[d] Yes: Score 1 No: Score 0	Was the study described as double blind but the method of blinding was inappropriate?[d] Yes: Score −1 No: Score 0	Was there a description of withdrawals and dropouts?[e] Yes: Score 1 No: Score 0	Total score[f] (0–5)
Gaze et al.[9]	1	0	0	0	0	0	0	1
Ozsaran et al.[10]	1	0	−1	0	0	0	0	0
Bone Pain Working Party[11]	1	0	0	0	0	0	1	2
Nielsen et al.[12]	1	1	0	0	0	0	0	2
Price et al.[13]	1	0	0	0	0	0	0	1
Steenland et al.[6]	1	0	0	0	0	0	0	1
Sarkar et al.[17]	1	0	0	0	0	0	0	1
Cole[15]	1	0	0	0	0	0	0	1
Niewald et al.[16]	1	1	0	0	0	0	0	2
Salazar et al.[17]	1	0	0	0	0	0	0	1
Hoskin et al.[18]	1	0	0	0	0	0	0	1
Madsen[19]	1	0	0	0	0	0	1	2
Jeremic et al.[20]	1	0	0	0	0	0	1	2
Okawa et al.[21]	1	1	0	0	0	0	0	2
Rasmusson et al.[22]	1	0	0	0	0	0	0	1
Tong et al.[23]	1	0	0	0	0	0	0	1
Poulter et al.[24]	1	1	0	0	0	0	1	3

[a] This includes the use of words such as "randomly," "random," and "randomization."

[b] A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Appropriate methods include table of random numbers, computer generated. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

[c] A study must be regarded as double blind if the word "double blind" is used.

[d] The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned. Inappropriate methods include comparison of tablet versus injection with no double dummy.

[e] Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number AND the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

[f] Poor quality = 0–2 points; good to excellent quality = 3–5 points.

instrument[8] and to discuss the implications for result interpretation and future research design.

MATERIALS AND METHODS

We performed an electronic search of Medline, Embase, and the Cochrane Library in May 2003 to obtain randomized, controlled trials of external-beam radiotherapy for the palliation of painful bone metastases. Eligible trials were those for which the assessment instrument had been validated.[8] Trials had to be in English and published in full form (i.e., not as an abstract). Two assessors scored articles independently (blinded to each other). The criteria for scoring are shown in Table 1. In their instrument validation, Jadad et al.[8] found that 99% of poor-quality studies scored 0–2 (of a maximum score of 5), whereas 71% of studies considered to be excellent scored 3–5. This cutoff has thus been used for subsequent research,[4] and was used in our assessment.

RESULTS

We identified 17 eligible randomized trials.[6,9–24] All eligible trials identified by the two most recent overviews[1,2] were included. The scoring of the quality of each study is shown in Table 1. The median score was 1 of 5 (range, 0–3), with 1 study (6%) scoring 0, 9 (53%) scoring 1, 6 (35%) scoring 2, and 1 (6%) scoring 3. There was almost complete agreement in scoring by the two assessors. Only 2 of 119 (1.7%) quality assessment criteria were scored differently by the two asses-

sors, both discrepancies due to oversight. After discussion, the differences were fully resolved. The majority of points were awarded (17 of 24 [71%]) because the authors stated that their studies were randomized. No points were awarded for allocation concealment (i.e., blinding). Only 4 studies (24%) adequately described an appropriate method of randomization, and 4 (24%) described the withdrawals and dropouts for each group. Only 1 study (6%) adequately described both. Using the cutoff suggested by Jadad et al.,[8] 94% (16 of 17) studies were considered to be of poor quality.

DISCUSSION

The importance of radiotherapy research quality has been repeatedly emphasized.[3,25,26] Poor-quality studies are prone to unquantifiable biases that can exaggerate the relative effectiveness of treatments,[4] and there has been some concern about potential bias in randomized radiotherapy studies.[7,27] Thus, the evaluation of study quality is vital when undertaking an overview of randomized studies,[25,26,28] and failure to report the quality of included studies limits the validity of any conclusions reached.[4]

How does one evaluate randomized study quality? Most authors reviewing the quality of studies investigating analgesic interventions (including studies evaluating radiotherapy) have used Jadad's instrument, which is the only validated tool currently available.[1,2,4,28,29] This instrument was specifically designed for use in assessing randomized studies in pain research, but is not without drawbacks. One limitation is that it has only been validated for English-language studies published in full form. For this reason, we did not evaluate other published evidence. Another limitation of Jadad's instrument, as with most quality assessment tools, is the reliance on reporting of relevant information. Therefore, it is possible that investigators conducted trials adequately but failed to report relevant information. However, there is evidence that unreported information has little impact on overall study quality.[30] This also appears to be true for randomized studies of palliative radiotherapy for bone pain, for which little additional information was obtained after contacting study authors.[3]

Jadad's checklist is not the only tool that demands a high level of trial design and reporting. The International Committee of Medical Journal Editors (ICMJE)[31] and CONSORT statements[32] also request details of randomization, blinding, and dropouts (losses to observation), i.e., the criteria forming the instrument we used. The CONSORT statement specifically mentions that details should be provided of the methods used to generate random allocation sequence and how blinding was implemented and assessed. A further requirement is for a description for each group of numbers of participants completing the study protocol and analyzed for the primary outcome, including a description of the reasons for protocol violations. Many of the other items included in the CONSORT and ICMJE recommendations were evaluated in Jadad's initial validation research, but were subsequently excluded from the final instrument due to the lack of face validity, reliability, or discriminative power.[8]

Despite the acknowledged importance of evaluating and reporting study quality, recent metaanalyses[1,2] failed to comprehensively report the quality of those included. Others have noted this problem,[25] and we provide the only complete quality assessment. When comparing radiotherapy fractionation for the palliation of bone pain, Wu et al.[1] assessed the effect of study quality on outcomes but did not publish their findings. Wu only reported, "no apparent effect of study quality on response rates" (pg. 599). However, as the eligible studies all rated poorly in our evaluation (using the same checklist that Wu et al. used), it is not surprising that study quality had no effect because there were no high-quality studies with which to compare. Sze et al.,[2] in a similar metaanalysis, mentioned that all included studies were evaluated using the assessment scale proposed by Jadad. Disappointingly, scores are neither reported nor used as a weighting factor for subsequent analyses.

Another older metaanalysis by McQuay et al.[29] included only three randomized studies common to our evaluation,[13,15,33] but did report study quality using a version of Jadad's checklist.[8] However, the quality of the scoring process is questionable. One of the three studies is in Japanese,[33] a language for which the checklist has not been validated. Although we agreed with McQuay's scoring of the study by Cole,[15] we question the score applied to Price et al.[13] For the latter study, McQuay gave a score of 1 to the criterion of adequately describing dropouts and withdrawals for each group (and a total score of 2). However, on close examination of Price et al.'s published article, it is apparent that there were significant problems with dropouts and withdrawals, yet numbers and reasons were not given for each arm (a specific requirement of Jadad's checklist). Thus, the criterion should score 0, with the Price et al. study scoring a total of 1. This error may be related to the actual checklist used by McQuay, which appears to have been modified from that reported by Jadad—a modification that has not been validated.

From our own evaluation, it is apparent that the quality of published randomized evidence comparing various fractionation regimens for palliation of bone metastases is poor when using Jadad's instrument.[8]

The radiotherapy studies that we reviewed had common deficiencies. All but five failed to describe the method of generating the sequence of randomization. In 1 (20%) of the studies that did,[10] the method was actually inappropriate (the authors used alternation, and the study is thus considered nonrandomized). This trial subsequently scored 0. Indeed, this is an excellent example that emphasizes the need for adequate reporting of relevant information, and why we cannot assume that unreported information will support high-quality research design.

In addition, double-blinding was universally absent in the studies we reviewed. The importance of allocation concealment to avoid bias, particularly where end points are subjective, cannot be overemphasized. There is ample evidence that nonblinded studies may lead to biased results, often favoring new treatments.[4] Indeed Marcus et al.[27] found in a double-blind, placebo-controlled study of radiotherapy for macular degeneration that there was no benefit despite previously positive studies. The authors postulate that the results of previous studies may well be biased due to knowledge of treatment allocation and subjective end points.

It should be noted that poor-quality randomized evidence is not limited to radiotherapy research. Similar findings have been found for obstetrics and gynecology, where the majority of published studies fail to detail randomization and allocation concealment.[34]

What are the implications of our findings? The potential biases that may exist affect the subjective end points that predominate in palliative radiotherapy studies, and make definitive conclusions difficult. Although most radiation oncologists would agree that there appears to be no difference in efficacy between single and multiple fractionation regimens for bone pain, even this end point is potentially open to bias. Perhaps the most compelling evidence to support equivalence between fractionation schedules is that the multiple published studies show the same results. However, for end points for which conflicting results exist, or for which only a few randomized studies are available, poor study design makes interpretation of results, with any measure of certainty, impossible.[4]

One good example is the issue of retreatment rates, where there are less, and conflicting, data. This is particularly relevant given that there is evidence to suggest many patients prefer longer fractionation schedules to decrease the chance of retreatment, despite the additional cost and inconvenience.[5] Further, eminent authors believe that fractionation decisions should rest with the individual wishes of the patient.[35] It is particularly ironic that study authors[6,7] readily recognize that secondary end points such as retreatment rates may differ due to bias resulting from the study design (e.g., lack of allocation concealment), yet fail to acknowledge that other subjective primary end points (such as pain response) might also be affected by bias. These issues apply to any randomized studies of radiotherapy for which subjective end points exist. Such end points include many evaluations of symptom response, toxicity, and quality of life, and are thus not confined to palliative care research.

Given the concern about avoiding bias in the published radiation oncology literature,[26] clinical trial groups should actively pursue various means to improve the conduct and reporting of high-quality research, and in particular revisit the oft-ignored concept of allocation concealment. Although some have stated that placebo control and double-blinding are not possible in radiotherapy studies,[29] there is good evidence that this can be achieved using "sham" irradiation.[27,36–38] The success of blinding in sham radiotherapy studies has been demonstrated by the finding that end point evaluators have been unable to distinguish between patients who had received real or sham radiotherapy.[36] Developing this aspect of radiotherapy clinical studies appears to be of high priority. In addition, adequately reporting future studies is essential. Full reporting validates trial design, and allows the research to be reproduced by other groups. Inadequate reporting makes attempts to interpret randomized studies difficult, if not impossible,[32] and undoubtedly hampers the practice of evidence-based medicine. Furthermore, "inadequate reporting borders on unethical practice when biased results receive false credibility" (pg. 1191).[32]

In summary, the quality of published radiotherapy randomized trials for bone pain is suboptimal. Regardless of whether this is due to poor design or poor reporting, the ability to interpret study results is hindered. In radiation oncology, as in other areas of clinical medicine, "the quality of evidence has a strong effect on shaping clinical practice and needs to be continually assessed" (pg. 645).[39] We have assessed the quality of the current evidence, and it has been found wanting. It is now time to improve it.

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