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REVIEW ARTICLE

Bias due to statistical handling of death and reirradiation in the assessment of duration of response after palliative radiotherapy: a scoping review and analysis of clinical data

[1]TETSUO SAITO, MD, PhD, [2]KENTA MUROTANI, PhD, [3]KEI ITO, MD, PhD, [4]NAOKI NAKAMURA, MD, PhD and [5]NATSUO OYA, MD, PhD

[1]Department of Radiation Oncology, Arao Municipal Hospital, Arao, Japan
[2]Biostatistics Center, Graduate School of Medicine, Kurume University, Fukuoka, Japan
[3]Division of Radiation Oncology, Department of Radiology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan
[4]Department of Radiation Oncology, St. Marianna University School of Medicine, Kanagawa, Japan
[5]Department of Radiation Oncology, Kumamoto University Hospital, Kumamoto, Japan

Address correspondence to: Dr Tetsuo Saito
E-mail: *tetsuosaito1977@gmail.com*

Objectives We investigated the influence of handling death and reirradiation on the estimation of duration of response (DOR).
Methods First, we performed a scoping review on methods to assess DOR in palliative radiotherapy. Second, we performed three different analyses on a subgroup of patients from a previously published prospective study. The first analysis was a competing risks analysis considering relapse of pain as the event of interest and death and reirradiation as competing events (Analysis A). The second and third analyses were standard survival analyses where the event of interest was a composite outcome of relapse of pain, death, or reirradiation (Analysis B) and relapse of pain (Analysis C), respectively.
Results Death was considered as an event of interest in less than half of the papers, while reirradiation was not considered in any of the studies. Competing risks analysis was not performed in any of the studies. In the analysis of clinical data, competing risks analysis showed that relapse of pain predominated as the cause of the end of response. Median DOR was correctly estimated to be 4.1 months in Analyses A and B, but was overestimated to be 8.1 months in Analysis C.
Conclusions Death and reirradiation should be treated as the events of interest that mark the end of response (as in Analyses A and B) to avoid overestimation of treatment efficacy and an invalid assumption of independent censoring.
Advances in knowledge The definition of end of response remains inconclusive in the assessment of DOR. We recommend competing risks analysis (Analysis A), by which we can estimate cumulative incidence of each event type and evaluate the necessity of reirradiation.

INTRODUCTION

Radiotherapy is an important treatment option for cancer-related pain.[1,2] To assess the efficacy of palliative radiotherapy, the response rate, the proportion of patients who respond to treatment, has primarily been analyzed.[3] The pain response rate after radiotherapy for painful tumors was reportedly 47–80%.[3–5] Duration of response (DOR) is another end point that is more important now than ever, as metastatic patients are having longer survival with the development of new oncologic treatments.[6,7] In palliative radiotherapy for bone metastases, stereotactic body radiotherapy is being tested for its ability to prolong DOR compared with conventional radiotherapy.[7,8]

In assessing DOR, the main interest may lie in the time when relapse of pain occurs; however, events such as death may preclude the occurrence of relapse of pain, or other events, such as reirradiation, may fundamentally alter the probability of relapse of pain.[9] This explains why DOR can be assessed using competing risks analysis. In a competing risks setting, an analysis that considers death as censoring may overestimate the cumulative incidence of the event of interest (*i.e.* the cumulative probability of having experienced relapse of symptom in the assessment of DOR)[10] and survival probability (*i.e.* the probability of still being in the initial response status).[11] Some responders may receive reirradiation for the same painful tumors because

of inadequate pain control. How should reirradiation be statistically handled in this situation? Treating reirradiation as a censoring implies an assumption of independent censoring.[10] However, patients who experience pain relapse early after palliative radiotherapy may also tend to receive reirradiation early. In the present study, we first investigated different assessments of DOR in randomized controlled trials on radiotherapy for bone metastases. In the second part of the study, we investigated how different statistical handling of death and reirradiation influence the estimate of DOR, and which analytical method is adequate in assessing DOR.

METHODS

Structure of the study

In the first part of the study, we performed a scoping review to investigate how DOR has been analyzed in trials on radiotherapy for bone metastases. In the second part, we performed three different analyses on a subgroup of patients who responded to radiotherapy from a previously published three-center observational study on miscellaneous painful tumors,[12] to investigate the influence of different statistical handling of death and reirradiation on the estimation of DOR.

Scoping review

No formalized review protocol was created for the present review; the review was not registered. A literature search was conducted in PubMed for articles on randomized controlled trials of radiotherapy for bone metastases. The last search was performed on December 10, 2021. Search terms included synonyms and lists of words related to "bone," "metastasis," "radiotherapy," "response," and "pain." The detailed search strategy is presented in Supplementary materials (Supplementary method 1). Abstracts of the identified papers published between 2000 and 2020 were screened by one reviewer (T.S.). The exclusion criteria for our abstract screening were non-English publications and stereotactic body radiotherapy. The same reviewer then assessed the screened full-text papers to select articles where DOR was analyzed (Figure 1).

We identified the event of interest, which marked the end of response in the assessment of DOR. We investigated whether DOR was analyzed by standard survival analysis where only one event was assessed or by competing risks analysis. We recorded statistical methods used in non-parametric estimation, hypothesis testing between groups, and regression analysis. Additional information obtained included year of publication and the detailed definition of DOR.

Analysis of clinical data

From a previously published prospective observational study conducted at 3 centers,[12] 66 patients with painful bone metastases who responded to palliative radiotherapy were analyzed in the present study (Figure 2). The use of the clinical data in the present study was approved by the participating centers' institutional review boards. Patient evaluation and follow-up were described previously.[12] Briefly, patients rated the worst pain they experienced during the 3 days prior to receiving radiotherapy. Patients were followed up at 1, 2, and 3 months after the start of radiotherapy. After 3 months, the follow-up interval was left to the physicians' discretion, but typically, follow-up was performed at

Figure 1. Flowchart of the study selection procedure.

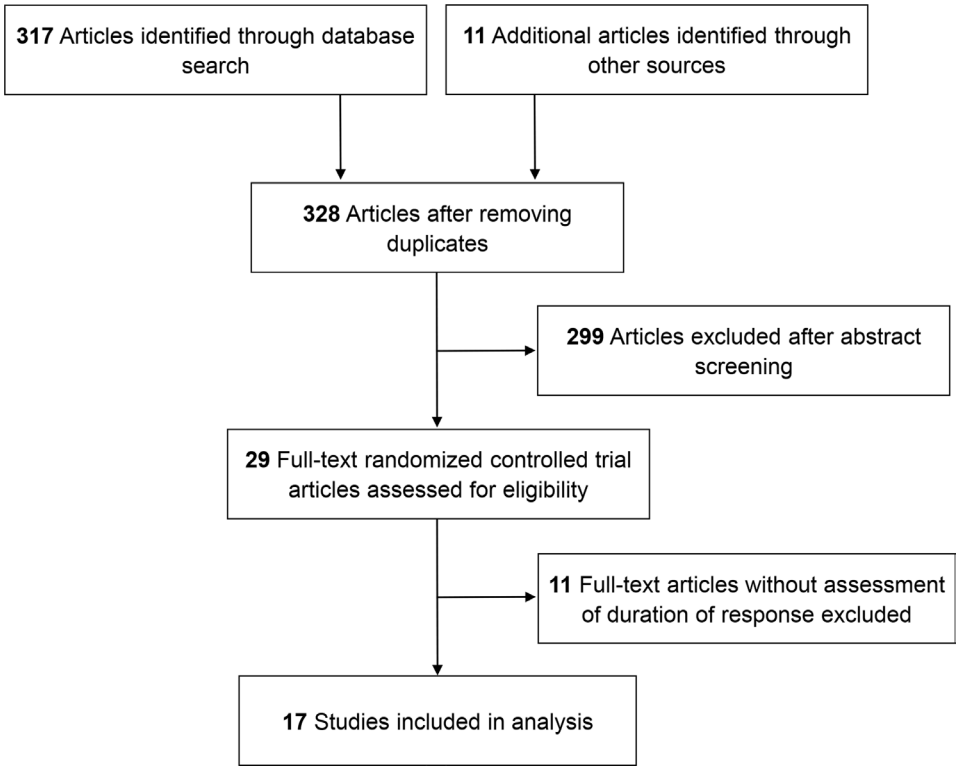
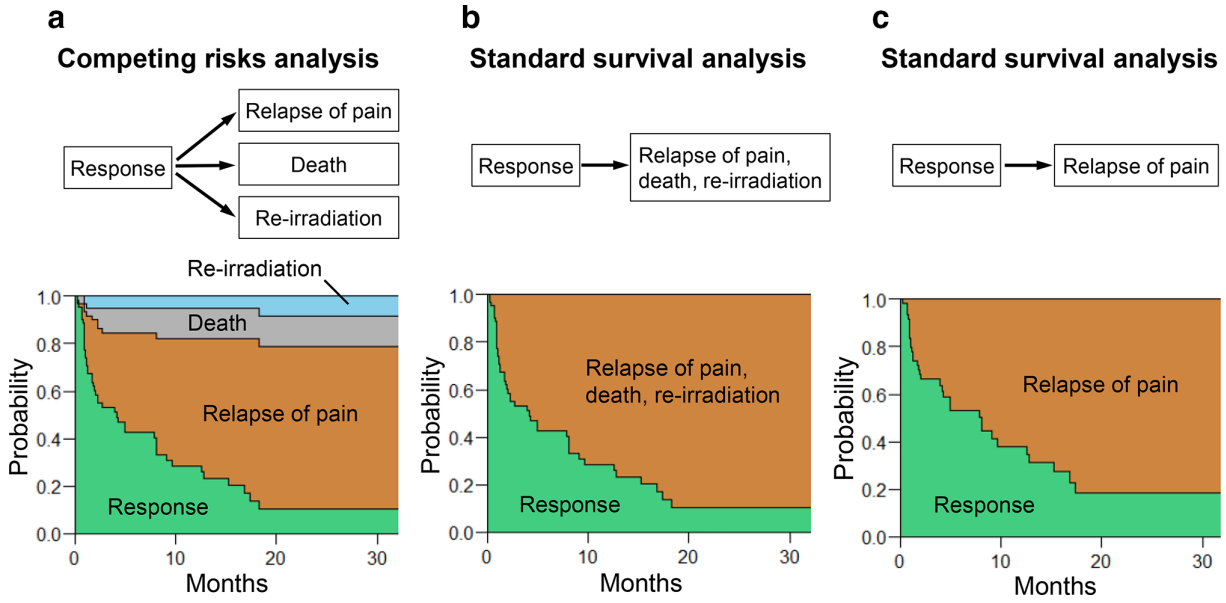


Figure 2. Analyses of the duration of response and cumulative incidence of relapse of pain, death, and reirradiation, performed on a subgroup of patients who responded to radiotherapy from a previously published observational study. The distance between two adjacent curves at a given time indicates the estimate of the probability of a patient being in the state at that time. In Analysis C, death and reirradiation were treated as censoring events.



approximately 3 month intervals. The pain response was assessed using the International Consensus Pain Response Endpoints.[13] Patients who received radiotherapy for painful tumors were categorized as responders (including patients showing complete or partial response) or non-responders. A complete response was defined as a pain score of 0, with no increase in the daily oral morphine equivalent dose. A partial response was defined as $a \geq 2$ point reduction in the pain score without an increase in daily oral morphine equivalent dose or $a \geq 25\%$ reduction in the use of analgesics, without an increase in the pain score. After response, patients were confirmed to experience relapse of pain (the absence of response), when the pain score or analgesic use no longer met the criteria of response. Some responders received reirradiation for the same bone metastases despite still meeting the criteria of response, usually because the control of pain was insufficient.

Details of statistical methods used in our analyses to estimate DOR are presented in Supplementary materials (Supplementary method 2). We performed 3 different analyses on the 66 patients with bone metastases who responded to radiotherapy (Figure 2). The first analysis was a competing risks analysis considering relapse of pain as an event of interest and death and reirradiation as competing events (Analysis A). Time zero was set as the time of confirming the response. Patients lost to follow-up when they had not experienced the event of interest or the competing events were treated as censored. The second and third analyses were standard survival analyses where the event of interest was a composite outcome of relapse of pain, death, or reirradiation (Analysis B) and relapse of pain (Analysis C), respectively. In Analysis C, patients who died without relapse of pain and those who received reirradiation without relapse of pain were censored at the time of those events. Statistical analyses were performed with R v. 3.6.2. The R package "mstate"[14] was used to estimate state occupation probabilities.

RESULTS

Scoping review

Of the 328 articles identified, 29 were selected through our abstract screening (Figure 1). Six articles were excluded through abstract screening (Russian, 3; Chinese, 2, and German, 1) based on the exclusion criteria of non-English publications. Of these 29 randomized controlled trials of radiotherapy for bone metastases, 17 (59%), where DOR was analyzed, met our inclusion criteria (Table 1).[15–31] In 11 (85%) of the 13 studies that reported the patients for whom DOR was assessed, DOR was assessed only for patients who experienced response to treatment (Table 1). In the assessment of DOR, in articles where the event of interest was reported, relapse of symptom was consistently treated as the event of interest (*i.e.* an event that marks the end of response status), while death was treated as the event of interest in less than half of the papers. Reirradiation was not considered as the event of interest in any of the studies. The details of the characteristics of the included articles are presented in Supplementary materials (Supplementary result 1).

In the 12 studies where time-to-event analysis was used to assess DOR, standard survival analysis where only one event was assessed was performed; none of the studies performed a competing risks analysis (Table 1). Statistical handling of death was not specified in the papers in which death was not an event that marks the end of response status (Table 2). No papers specified statistical handling of reirradiation.

Table 1. Characteristics of studies (n = 17)

Characteristic	No.	%
Patients for whom duration of response was assessed		
Responders	11	65
All registered patients	2	12
Not reported	4	24
Definition of response		
Based on pain intensity	6	35
Based on pain intensity and analgesic use	8	47
Based on pain intensity, analgesic use, and performance status	1	6
Based on walking capacity, bladder function, and back pain	2	12
Definition of relapse of symptom		
Recurrence of symptom	10	59
Progression of pain, analgesic use, or performance status	1	6
Not reported	6	35
Time zero in the assessment of duration of response		
Confirmation of response	7	41
Start of treatment	1	6
Registration	2	12
3 weeks	1	6
1 month after the end of radiation therapy	1	6
Not reported	5	29
Event(s) that mark the end of response status		
Relapse of symptom	9	53
Relapse of symptom and death	5	29
Not reported	3	18
Time-to-event analysis used to assess duration of response		
No	1	6
Yes	12	71
Indeterminate	4	24

Analysis of clinical data

Figure 2 shows the results of the three analyses. Of the 66 responders, 34 (52%) experienced relapse of pain, 11 (17%) experienced competing events (7 deaths and 4 reirradiations), and 21 (32%) experienced neither of these and were censored at the last follow-up. Table 3 shows that in the standard survival analysis where the event of interest was the composite outcome of relapse of pain, death, or reirradiation (Analysis B), the estimate of survival probability (0.10) was equivalent to that in competing risks analysis (Analysis A), and the estimate of the cumulative incidence of the event of interest (0.90) was equivalent to the summation of the estimates of the cumulative incidence of relapse of pain (0.69), death (0.13), and reirradiation (0.08) in Analysis A. In the standard survival analysis where patients who died and those who received reirradiation were censored at the time of those events (Analysis C), a larger probability of still being in response (0.18) and larger cumulative incidence of relapse of pain (0.82) were estimated than in competing risks analysis (the corresponding values were 0.10 and 0.69, respectively) (Table 3). A larger median DOR was estimated in Analysis C than in Analyses A or B.

DISCUSSION

In the first review part of the study, we found that competing risks analysis was not performed in any of the papers. In the assessment of DOR, relapse of symptom was consistently considered as an event of interest, while death was treated as a component of the composite event of interest in less than half of the papers where the event of interest was specified. Reirradiation was not considered as an event of interest in any of the studies.

In the second part of the study, when death was censored, the probability of still being in response was overestimated by counting some of the dead patients as responders as if they were still alive and in response.[9] By considering death as censoring, researchers may seek to assess how long an intervention keeps

Table 2. Statistical method for the time-to-event analysis of duration of response in the systematic review (n = 12)

Method	No.	%
Non-parametric estimation (n = 12)		
Kaplan–Meier method	10	83
Not specified	2	17
Hypothesis testing between groups (n = 11)		
Log-rank test	9	82
Generalized Wilcoxon test	1	9
Not specified	1	9
Regression analysis (n = 3)		
Cox proportional hazards model	3	100
Statistical treatment of death (n = 12)		
Component of event of interest	5	42
Not specified	7	58
Statistical treatment of reirradiation (n = 12)		
Not specified	12	100

patients in response in a hypothetical situation in which responders never die. However, we aim to assess the actual DOR *in the real world*. When DOR is evaluated, a competing risks analysis or standard survival analysis, where death is a component of the composite event of interest, should be performed; in these analyses, death is correctly assumed as the end of response.

We also showed in the second part of the study that treating reirradiation as censoring implies that patients who have received reirradiation are still in response status *due to the first radiotherapy*. Reirradiated patients indeed may maintain the response status after reirradiation, but this may be mainly caused by reirradiation. We recommend considering reirradiation as the end of response by treating it as a competing event, or as a component of the composite outcome, to avoid overrating the effect of initial radiotherapy.

Treating a competing event as a censoring implies an assumption of independent censoring.[32] The relapse of pain and death are interrelated; patients who experience relapse of pain early after palliative radiotherapy may tend to die early under the circumstance that insufficient control of tumors may be associated with both death and relapse of tumor-related pain. In many competing risks situations, the assumption of independent censoring is violated.[33,34] When death is considered as independent censoring, patients censored due to death are assumed to be represented by those that remain in follow-up (*i.e.* were they still alive, these patients would relapse at the same rate as those who are actually alive), which may lead to biased results; by contrast, in competing risks analysis, an assumption of independence between the event of interest and competing events is not required.[35]

In DOR assessment, standard survival analysis using a composite outcome, as in our Analysis B, is valid. By using competing risks analysis, cumulative incidence of each event type can additionally be assessed. For example, where death predominates as the cause of the end of response, the durability of the effect of palliative radiotherapy may be sufficient for these patients. This is because palliative radiotherapy for bone metastases is performed to palliate pain and may not prolong survival; the aim is to keep patients symptom-free as long as they are alive. By contrast, where relapse of pain predominates as in our clinical example, the initial radiotherapy was not durable enough, and reirradiation for patients with relapse of pain should be offered as a salvage therapy. More information can be derived by a competing risks analysis than standard survival analysis using a composite outcome that consists of all events that mark the end of the effect of treatment.

A sufficient sample size is required to derive an accurate estimation of regression coefficients and associated quantities in competing risks analysis.[36] Competing risks analysis might lead to an increase in the sample size required for analysis because of fewer events of interest than standard survival analysis, where the event of interest is a composite outcome of relapse of pain, death, or reirradiation. We, however, do not recommend this latter analysis with a composite outcome because each event has a different clinical meaning; relapse of pain and reirradiation mean that a response is not sufficiently durable, whereas death without relapse of pain means that radiotherapy exerted sufficiently durable symptom palliation throughout the lives of these patients.

Table 3. Estimates of probabilities and duration of response according to the three analytic methods in the analysis of clinical data

Analysis	Probability of still being in response at 20 months	Probability of having experienced relapse of pain at 20 months	Probability of having died at 20 months	Probability of having received reirradiation at 20 months	Estimate of median duration of response, months
Competing risks analysis (Analysis A)	0.10	0.69	0.13	0.08	4.1
Standard survival analysis (Analysis B)	0.10	0.90[a]			4.1
Standard survival analysis (Analysis C)	0.18	0.82	-	-	8.1

[a]Probability of having experienced either of relapse of pain, death, or reirradiation.

Overrating of the DOR may be caused by reasons other than statistical reasons rooted in the handling of death or reirradiation as censoring. First, systemic therapy (*e.g.* chemotherapy, hormone therapy, and immunotherapy) may prolong the duration of pain response and inflate the effect of radiotherapy. Second, the patient population for whom DOR is assessed may be a factor. As we found, DOR is usually assessed only in responders, and non-responders, for whom radiotherapy did not provide sufficient palliation that meets the criteria for response, are excluded from the analysis. Third, attrition of patients may make DOR seem longer than it actually is. As patients become less well and death approaches, they tend not to attend hospital and receive an assessment of their symptoms. For such patients, relapse of pain tends not to be detected and the duration of response may be overrated. In the prospective observational study from which we analyzed data in the present study, the assessment of the relapse of pain was permitted either in the hospital, by mail, by fax, or by telephone.[12] Although care was taken to also assess less well patients who cannot attend hospital, the attrition rate was relatively high,[12] which is expected in studies on palliative radiotherapy.[37] Finally, in patients who receive reirradiation, ideally, the response should be deemed as ended when the decision to reirradiate is made, rather than on the day that reirradiation commences. However, considering the date of the commencement of reirradiation as the end of response may be a pragmatic way to define DOR.

A limitation of this study is that we did not include non-English papers in the review. None of the six non-English papers excluded through abstract screening contained the word "duration" in their English abstracts. We are not certain how many of these six articles had the duration of response assessed and thus could be included in our review.

CONCLUSIONS

When death or reirradiation is treated as censoring, the probability of still being in response is overestimated by counting patients who are dead or have received reirradiation as still being in response status due to the first radiotherapy. Moreover, treating death or reirradiation as an independent censoring may be problematic because these events may be interrelated with relapse of pain. We recommend that death and reirradiation should be treated as events that mark the end of response status. By standard survival analysis where the event of interest is a composite outcome of relapse of pain, death, or reirradiation, DOR is correctly estimated. By competing risks analysis, cumulative incidence of each event type can additionally be estimated. When relapse of pain predominates as the cause of the end of response, the initial radiotherapy was not durable enough, and reirradiation for patients with relapse of pain should be offered as a salvage therapy. We recommend the use of competing risks analysis, which enables the assessment of how the response status ends, and how large the necessity of reirradiation is. The finding that competing risks analysis seems to be highly underutilized in palliative radiotherapy is surprising, considering the usefulness and widespread use of competing risks analysis in medical research.

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