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The Netherlands

Optimising the treatment of patients with long bone metastases

Willeumier, J.J.

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Author: Willeumier, J.J.
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Chapter 4

Lack of clinical evidence for postoperative radiotherapy after surgical fixation of impending or actual pathologic fractures in the long bones in patients with cancer; a systematic review

J.J. Willeumier, Y.M. van der Linden, P.D.S. Dijkstra

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Abstract

Patients with disseminated cancer and bone metastases have a limited life expectancy and therefore any treatment should have a clear beneficial effect, outweighing all possible downsides. This systematic review aims to identify and evaluate available evidence regarding function, pain, quality of life, survival and complications of postoperative radiotherapy (RT) after surgical stabilization of impending or actual pathologic fractures of the long bones due to bone metastases.

A literature search resulted in two articles reporting on 64 and 110 patients of whom 55% and 28% received postoperative RT, respectively. Both studies were retrospective cohort studies and postoperative RT had been administered depending on the surgeons' choice. The first study reported better outcomes regarding function, re-interventions and survival in patients receiving postoperative RT. The second study reported no significant difference regarding complications between the two groups. The quality of the evidence was very low due to the observational character of both studies, risk of indication bias, small study sizes, use of non-standardized outcome measures, and limited statistical analyses.

The current available literature is insufficient to conclude whether postoperative RT after surgical stabilization should be standard care. It is important to realize this lack of clear evidence when calling upon RT as adjuvant palliative treatment.

Introduction

Bone metastases arise in up to 70% of all patients suffering from advanced cancer.[1,2] Half of those patients develop one or more complications, with pathologic fractures occurring in 5-10% of patients.[3,4] When a fracture affects the long bones a surgical stabilization of the bone is required to treat the pain and to retain a functional limb.[5] Surgery is also indicated as prophylaxis for patients with metastatic lesions at a considerable risk of fracturing. Surgical treatment options are vast and choices are made depending on localization, size and type of lesion, mechanical stability (i.e. fracture or impending fracture), and expected morbidity of the procedure in relation to the condition and expected survival of the patient. After surgery, patients are often referred for adjuvant radiotherapy (RT). Multiple reviews advise a short-course RT using five to ten fractions after surgical treatment as it would promote bone healing, prevent tumor progression, minimize the risk of implant failure, and decrease the rate of secondary procedures.[6-12] However, all these studies base their advice on a single, retrospective cohort study.[13] This was perceived as remarkable by the authors, especially because postoperative radiotherapy concerns a prophylactic treatment in patients with generally a limited life expectancy.

The life expectancy plays a large role in determining the most suitable treatment, including the necessity of postoperative RT. Several factors play a role to determine survival,[14,15] however primary tumor type is the most important. Postoperative events that could be prevented by radiotherapy, such as tumor progression and implant-failure, need time to develop. Therefore, the majority of the complications will likely occur only in patients who live long enough. For all other patients, the downsides of RT might outweigh the potential benefit. Downsides consist of the risk for complications, such as skin and gastro-intestinal problems, wound-healing problems in the post-operative period,[16] and non-union.[17] In addition, despite the generally short schedules that are given, multiple (up to ten) extra visits to the hospital are needed for planning and performing the treatment.

On the whole, this palliative, adjuvant and prophylactic treatment requires time and energy of a fragile patient and might negatively affect the quality of life, while the beneficial effect is unclear. The purpose of this systematic review was to identify and evaluate available evidence regarding function, pain, quality of life, survival and complications of postoperative RT after surgical stabilization compared to surgery only in patients with impending or actual pathologic fractures of the long bones due to bone metastases.

Methods

We report our results according to the MOOSE Guidelines for reporting systematic reviews.[18]

Search strategy

A literature search with the help of a medical librarian was performed on July 6th 2015 using the Pubmed, Embase, Web of Science and Cochrane databases without publication-date limits. The following keywords were searched: bone metastasis, skeletal metastasis, osseous metastasis, skeletal metastatic disease, secondary bone neoplasm, spontaneous fracture, pathologic fracture, postoperative radiation, postoperative radiotherapy, post-operative irradiation. Additionally, reference lists of retrieved papers, review articles, and clinical practice guidelines were checked for relevant publications.

Study selection

Two authors (JW, PDS) independently selected studies for inclusion. Titles and abstracts were screened using predefined eligibility criteria. Studies reporting on outcomes regarding function, pain, quality of life, survival and complications of patients undergoing surgery and adjuvant radiotherapy compared to patients undergoing surgery only for metastases of the long bones in English, Dutch or German were included. Meeting abstracts, case reports, guidelines, reviews and editorials were excluded (figure 4.1).

Data extraction

One author (JW) abstracted the following data items: patient demographics, treatment details, follow-up reports, functional outcomes, complications, failures, and quality of evidence.

Quality assessment

Assessment of the methodological quality of the included articles was performed according to the grading of recommendation, assessment, development and evaluation (GRADE) approach.[19] The evidence for each outcome is rated as high, moderate, low or very low. Randomized controlled trials (RCTs) provide high-quality evidence unless they are downgraded depending on risk of bias, inconsistency, indirectness, imprecision and publication bias. Evidence from non-randomized studies is regarded low-quality evidence unless they are up- or downgraded.[19]

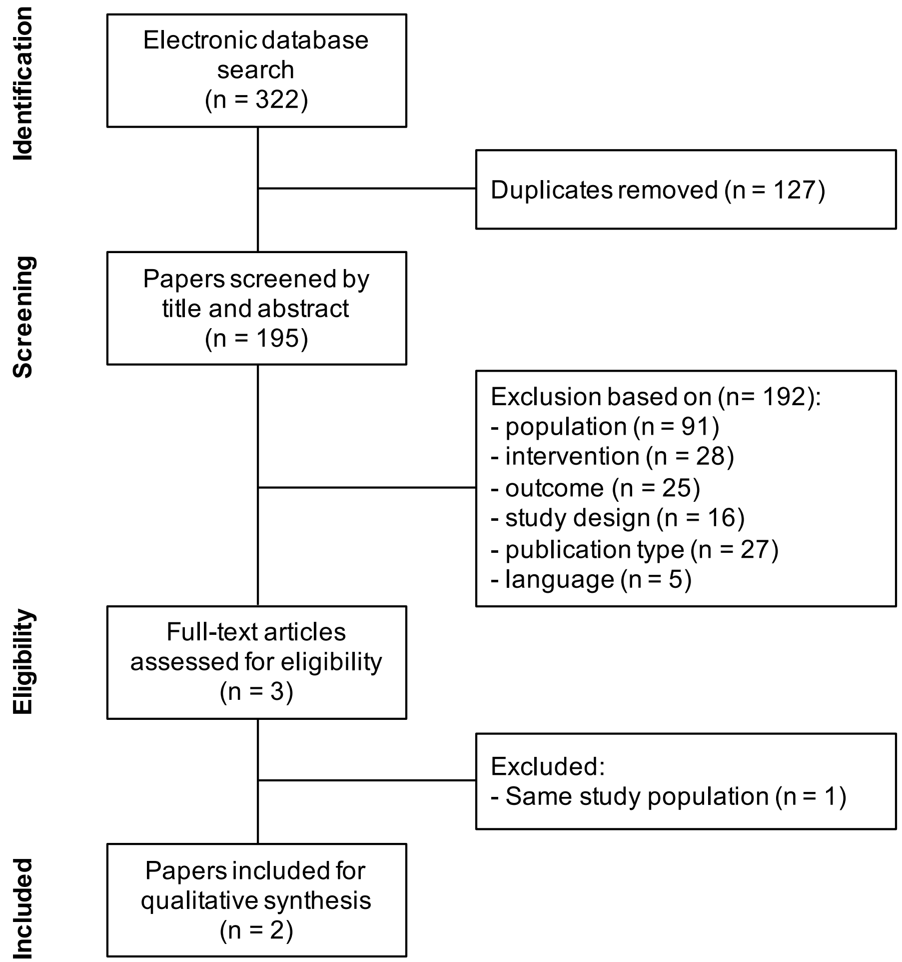

Figure 4.1 Flowchart of the study selection process. *N* = number of studies.

Results

Study selection

The search strategy resulted in 195 unique titles. Reviewing the reference lists did not lead to additional papers. After screening, three studies[13,20,21] met the inclusion criteria (figure 4.1). However, two publications by Townsend et al. were nearly identical; they describe the same cohort with the same research questions and multiple identical paragraphs. The most complete paper was included in the current study.

Study description

Both included studies were retrospective reviews of patient cohorts. Table 4.1 presents the characteristics of the included studies. The outcome measures differed between the studies and therefore a quantitative analysis was not possible.

Table 4.1 Descriptive data of included studies

Author (year)	*Study design (study period)*	*Nr of patients (lesions)*	*Actual fractures / impending fractures*	*Surgical treatment*	*Mean follow-up in months (range)*	*Outcome parameters*
Townsend (1994)[20]	Retrospective cohort study (1979 – 1992)	60 (64)	39 (55%) / 25 (45%)	Arthroplasty 16 (25%) Fracture fixation 48 (75%) + Methyl-methacrylate 23 (36%)	10.7 (3 days – 32.4)	1. Function 2. Re-interventions 3. Survival
van Geffen (1997)[21]	Retrospective cohort study (1983 – 1993)	116 (152)	85 (56%) / 67 (44%)	Surgery (72%) - plate-osteosynthesis 51% - intramedullary nail 23% - prosthesis 14% - (partial) resection 6% Irradiation only (18%) Conservative (10%) + Methyl-methacrylate 60 (55%)	**	1. Complications

**Data not reported.

Townsend et al.[20] aimed to compare the outcome of orthopedic stabilizations for impending or pathologic fractures with or without postoperative RT in 60 patients with 64 procedures. Patients who had received previous RT to the fracture site were excluded. After surgery patients were referred for RT if the treating orthopedic surgeon ought this necessary. This occurred in 55% of the cases (table 4.2).

Table 4.2 Distribution of treatments by fracture type

		Surgery only	*Surgery + RT*
Townsend (1994)[20]	All fractures	29 (45%)	35 (55%)
	Actual fracture	21 (72%)	18 (51%)
	Impending fracture	8 (28%)	17 (49%)
van Geffen (1997)[21]	All fractures	79 (72%)	31 (28%)
	Actual fracture	**	**
	Impending fracture	**	**

**Data not reported. RT: radiotherapy.

Table 4.3 Outcomes and results per treatment group

	Outcome	*Total*	*Surgery only*	*Surgery + RT*	*p*
Townsend (1994)[20]	1. Function status 1 or 2		11.5%	53%	<0.01
	2. Re-intervention	5 (7.8%)	4 (14%)	1 (3%)	0.035
	3. Survival (months; median)	7.3 (3 days – 40.6)	3.3 (3 days – 43.5)	12.4 (8 days – 48.6)	0.025
van Geffen (1997)[21]	1. Complications	21 (20%)	17 (21%)	4 (13%)	0.301*

RT: radiotherapy. *As calculated by the authors of this review (Chi-square test). Van Geffen et al. reported the outcome merely as 'not significant'.

A self-developed scoring system was used to analyze functional outcomes. The endpoint for analysis of function (functional status 1 or 2) was defined as 'normal, pain-free use of the extremity (status 1)' or 'normal use with pain (status 2)'. The other functional outcomes (status 3 or 4) were defined as 'significantly limited use requiring some type of prosthesis (e.g. walker, cane, crutches)' or 'non-functional (e.g. wheelchair-bound or bedridden)'. In the group of patients who had received RT the observed proportion of patients with a functional limb at any time was 53% versus 11.5% for surgery only (table 4.3). On multivariate analysis, including postoperative RT (univariate p = 0.026), pre-fracture functional status (univariate p = 0.045), type of surgical procedure (univariate: not reported), and use of methylmetacrylate (univariate: not reported), only postoperative RT was significant to achieve a functional status 1 or 2 (*p*=0.026). It is not reported why fracture type was not included in the multivariate model. Moreover, according to the methods section of the article, the Cox model analysis was run twice with different sets of variables because of the limited sample size, however this is not described as such in the results section. The study reports less second orthopedic procedures to the same site for patients receiving surgery and RT (1 of 35 sites vs. 4 of 29 sites; table 4.3). Finally, the study reports a better survival in patients receiving surgery with RT: median 12.4 months compared to 3.3 months (*p*=0.025; table 4.3). At univariate level, postoperative RT (*p*=0.025) and type of fracture (*p*=0.05) were significant predictors for survival. On multivariate analysis, postoperative RT (*p*=0.025; table 4.3) and type of surgery (*p*=0.05) remained significant. No results of other variables in uni- or multivariate analysis are reported.

Van Geffen et al.[21] reported on the effect of RT on complication rate as a secondary outcome in their retrospective cohort study. The study focused primarily on the mobility levels before and after surgery, independent of adjuvant therapy. Postoperative RT was administered to 28% of all surgical patients (table 4.2). Details concerning indications for certain strategies are not provided. The results concerning postoperative RT report 21% complications in the non-irradiated group versus 14% of the patients receiving postoperative RT (table 4.3). All complications were bone-related, i.e. failure of the osteosynthetic device or implant, and progression or recurrence of disease. The authors describe this as a remarkable, but not statistically significant difference. Unfortunately, no further details are presented. The authors report no difference in pain relief, or use of analgesic drugs between the two groups however this is not supported by reported numbers.

Quality assessment

Due to the retrospective cohort design and the risk of bias of both included studies, the evidence for all study outcomes is regarded as 'very low' quality according to the GRADE approach.

Discussion

This study aimed to evaluate available evidence regarding the effect of postoperative RT after surgical stabilization of (impending) pathologic fractures. A search of the literature resulted in only two publications that met the inclusion criteria. The outcomes of the included studies should be interpreted with caution due to the very low quality of the evidence.

Firstly, the study designs lead to a large risk of indication bias. In both studies the allocation of adjuvant RT was performed by judgment of the surgeon. Neither article elaborates on the reasons for referring some patients for postoperative RT and not referring others. However, it is very plausible that patients who are in relatively good health and with a longer expected survival are considered for postoperative RT, while those in poor health and with a short expected survival are not referred. As Townsend et al. acknowledge, this is likely to explain the large difference in survival they register between the groups with or without postoperative RT. The distribution of the number of patients with an actual fracture between the treatment groups also supports this bias; a larger proportion of surgery-only patients had an actual fracture (72%) than the surgery plus radiotherapy patients (51%) (table 4.2). Patients with actual fractures are generally in a more advanced disease stadium. Moreover, in the study by Townsend et al. these patients were older and had worse pre-fracture functional status. It is quite likely that these patients had further progressive disease.

Secondly, the small number of patients (64 and 110 patients) limits the generalizability of the studies. Although Townsend et al. had enough patients to detect a significant difference, the results of these small retrospective, non-randomized cohorts cannot be projected as advice for treatment in future patients.

Thirdly, Townsend et al. applied a self-designed, non-validated functional scoring system as outcome. The authors do not describe the definition of normal use; is normal use implied if walking-aids were not needed, or if a patient was not wheelchair-bound or bedridden? Furthermore, a more detailed functional outcome by the range of motion or impairment of flexion or extension for example, is not described. The difference between status 1 and 2 is defined by the presence of pain, however the use of pain medication is not taken into account. Neither does the article report whether the function is reported by the patient, or whether it is interpreted by the clinician.

Fourthly, due to the lack of complete reporting of uni- and multivariate analyses it is unclear how the authors adjusted for confounding variables and the effect this had on the outcomes. Hazard ratios are not presented, so the actual effect of the prognostic factor is not known. In the article by van Geffen et al. statistical results were not described at all. For the functional status in the article by Townsend et al. the p-value for post-operative radiotherapy was the same on uni- and multivariate analysis without further clarification; this appears as a strange coincidence. Neither article describes how they accounted for the effect of primary tumor type, while this is of great effect on the both functional outcome[17,22] and survival.[15,23] Also, the analysis on the effect of RT on functional outcome should not only have considered the type of fracture and surgery, but also the extent of tumor excision. Extensive surgery including curettage and possibly augmentation will leave less residual tumor, while minimally invasive procedures leave all tumor mass in situ. The expected benefit of radiotherapy is thus less likely after a more extensive excision, than after a minimally invasive procedure. The manner in which the surgery types have been classified in the study by Townsend et al. does not sufficiently take the extent of tumor excision into consideration.

Finally, the statistical analyses do not take the competing risk of death into account when analyzing the risk factors for local progression and implant failure. This would have given a more realistic, and possibly reduced, risk of complications.[24]

It is remarkable that although the supporting evidence of postoperative RT is limited to only two studies with low quality of evidence this adjuvant treatment has found such a widespread implementation throughout the Western countries. In addition, although a few other studies on the same topic report on outcomes after surgery with or without RT, they lack a comparison of the outcomes between both treatment strategies.[22,25,26] Comparing the outcomes of all these studies was not possible due to the heterogeneity of the treatments and study populations. Also, the descriptions of the results concerning postoperative RT are not detailed enough to enable analysis. This leaves the significant clinical question of the efficacy of postoperative RT unanswered. Reasons for the apparent lack of research are unclear, but might be due to the palliative setting of the surgical treatment, the way surgeons are trained and the multidisciplinary aspect of the treatment. Together this might lead to less awareness of the need for evidence of this adjuvant treatment.

The article by Townsend et al. has been cited multiple times, however referring papers seldom question the quality of the study.[7,8,12,27] Several authors have reported a possible irrelevance or disadvantage of adjuvant RT, however not based on concise research.[28-31] Dijkstra et al. report the risk of impaired healing due to the suppression of the chondrogenetic phase of secondary ossification caused by radiotherapy.[29] Hoskin mentions that postoperative RT might be irrelevant in many patients due to the short survival.[31] He makes an important comment on the lack of knowledge concerning the true incidence of tumor progression as well as the clinical significance of progression. However, Hoskin also warns for potential problems when a patient survives a sufficient time for tumor progression to occur. Epstein et al. also recognize the limited available evidence for postoperative RT.[32]

The effect of postoperative RT should be analyzed with consideration of the expected survival of patients with disseminated cancer and in the context of quality of life, instead of in quantitative outcomes such as number of complications or revision surgeries. Despite improvements in survival over the last decades, median survival for patients ranges from 2 months for lung cancer to 7 months for prostate and 19 months for breast cancer.[14] It is plausible that the benefits of RT will outweigh the downsides in patients with a long-term survival. However, for patients with a medium-term or short-term survival, the negative effects of RT on the quality of life might be larger than the risk of local progression or implant-failure. While a beneficial effect of radiotherapy on the quality of life has been shown in the setting when radiotherapy is the only treatment, this has not been investigated when radiotherapy is administered post-operatively. It is possible that all improvements in quality of life for patients after surgery and adjuvant radiotherapy are due to the surgical stabilization. In that case, adjuvant radiotherapy costs time and brings a risk of side effects, which can negatively influence the quality of life.

Additionally, it is essential to recognize the increase of pharmacological bone-directed therapies and their role in bone strengthening and prevention of complications. Although the specific impact of such treatments on postoperative quality of life is unknown, it is not unimaginable that they reduce the risk of local tumor expansion and corresponding complications. This would even further dilute any effect of postoperative radiotherapy. Furthermore, the role of these therapies should be taken into account when interpreting the results of the study by Townsend et al., for this study was performed in an era before systemic therapies were widely administered.

Based on the results of this review, a firm conclusion on the standard use of postoperative radiotherapy cannot be drawn. However, it can be concluded that substantial evidence for postoperative radiotherapy is lacking. In an era where evidence-based medicine is the backbone of all decision-making, this can be considered as peculiar at the least, especially when it concerns a palliative treatment in patients with a limited life expectancy. The number of patients with bone metastases in need of surgical fixation will increase in the future. To provide the most optimal palliative care to maintain quality of life, conclusive research should determine whether postoperative RT has a beneficial effect. Establishing a large, multi-center randomized study will provide further insights and lead to a firmer substantiated treatment plan for patients with bone metastases of the long bones. Foremost, all clinicians should realize that any firm evidence for or against postoperative RT is lacking and that it is unknown whether the treatment is a superfluous or vital element of optimal care.

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