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Systematic review

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

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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.

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 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

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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, postoperative irradiation. The complete literature search is presented in Appendix 1. 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 (Fig. 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].

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 (Fig. 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.

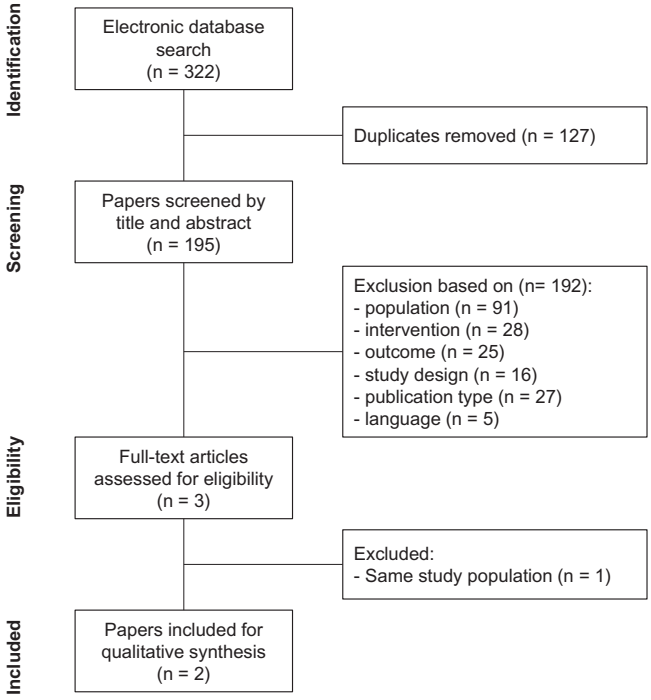

Fig. 1. Flowchart of the study selection process. *N* = number of studies.

Study description

Both included studies were retrospective reviews of patient cohorts. Table 1 presents the characteristics of the included studies. The outcome measures differed between the studies and therefore a quantitative analysis was not possible.

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 thought this necessary. This occurred in 55% of the cases (Table 2).

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 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 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 3). At univariate level, postoperative RT ($p = 0.025$) and type of fracture ($p = 0.05$) were