Cost-effectiveness of treatments for the management of bone metastases: a systematic literature review.

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Abstract

Background

Metastatic cancers occur when cancer cells break away from the primary tumour. One of the most common sites of metastasis is the bone. Several therapeutic options are currently available for managing bone metastases. In a resource constrained environment, policy makers and practitioners need to know which options are cost-effective.

Objective

To review and appraise published economic evaluations on treatments for the management of bone metastases.

Methods

We searched eight bibliographic databases (MEDLINE, MEDLINE in Process, EMBASE, CSDR, DARE, HTA, EED and CPCI) for relevant economic evaluations published from each database's inception date until March 2017. Study selection, quality assessment and data extraction were carried out according to published guidelines.

Results

Twenty-four relevant economic analyses were identified. Seventeen of these studies focus on bone metastases resulting from a particular type of cancer (prostate (n=8), breast (n=7), lung (n=1) or renal (n=1)) while seven report results for various primary tumours. Across types of cancer, evidence suggests that bisphosphonates result in lower morbidity and improved quality of life, for an additional cost which is typically below conventional cost-effectiveness thresholds. While denosumab leads to health gains compared to zoledronic acid, it also results in substantial additional costs and it is unlikely to represent value for money. The limited literature on the radiopharmaceutical strontium-89 (Sr89) and external beam radiotherapy (EBR) suggest that these treatments are cost-effective compared to no treatment.

Conclusions

The reviewed evidence suggests that bisphosphonate treatments are cost-effective options for bone metastases, while denosumab is unlikely to represent value for money. Evidence on EBR and Sr89 is limited and less conclusive.

Key points for decision makers

- Most of the identified economic literature on treatment options for bone metastases investigate bisphosphonates and denosumab. Evidence on the cost-effectiveness of radiopharmaceuticals and radiotherapy is relatively limited.

- Studies varied in relation to perspectives adopted, inputs included and methods employed. This variability hinders comparisons and precludes drawing definite conclusions that could be applicable across health care systems.

- In general, bisphosphonates appear to be a cost-effective option compared to placebo. Evidence suggests that denosumab results in improved outcomes, but its high cost makes it unlikely to be cost-effective. Limited evidence indicated that Sr89 and radiotherapy may be cost-effective options.

1. Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide. An estimated 8.2 million people died from cancer and 14.1 million new cases of cancer occurred worldwide in 2012 [1]. Estimates suggest that 23.6 million new cases of cancer worldwide will be diagnosed each year by 2030 [1]. In the UK, cancer incidence statistics indicate that 980 cases are diagnosed every day, the equivalent to a new cancer diagnosis every two minutes [2].

Cancer cells may break away from a primary cancer, enter the bloodstream or lymphatic system and be carried to other parts of the body where they can grow into new tumours, also known as a secondary cancer(s) or metastases. In patients that develop metastases, it is not the primary tumour but its metastases that are the main cause of death [3]. Despite developments in cancer treatments, a large number of patients with cancer develop metastases. One of the most common sites where cancer spreads is the bone. Prostate, breast, lung, renal and thyroid cancer are the most common cancers to metastasise to the bone [4]. No reliable incidence or prevalence figures for people with bone metastases are available, but it is estimated that around 70% of patients with breast or prostate cancer are affected by metastatic disease to the bone [5].

Bone metastases is a debilitating condition with a detrimental impact on peoples' quality of life (QoL). Bone metastases are usually associated with skeletal related events (SREs) such as severe bone pain (often intractable pain), an increase is susceptibility for bone fragility and consequently fracture, bone deformity, hypercalcaemia (increased blood-calcium concentration) and nerve-compression syndromes such as spinal-cord compression [6].

Treatment options for bone metastases can often shrink or slow the growth of bone metastases and prevent SREs. However, treatment is predominantly palliative and is provided in order to relieve pain, prevent fractures, maintain activity and mobility, and, if possible, to prolong survival [7]. Therapeutic options for bone metastases can be divided into local and systemic. The decision on which treatment or combination of treatments to administer is dependent on the location and extent of the metastatic disease. Local treatments, which include radiotherapy, surgery and ablation techniques are directed at single areas of the body, either if the cancer has only spread to a single bone or an area requires urgent management. Systemic treatments are used in cases where the cancer has spread to several areas as these treatments can reach cancer cells that have spread throughout the body. Although contributing to the management of bone metastatic disease, systemic treatments using chemotherapy, endocrine therapy or immunotherapy are not aimed specifically at bone metastases. Radiopharmaceuticals and bisphosphonates are systemic treatments that specifically target skeletal

metastatic sites. Radiopharmaceuticals are agents that deliver a highly localised radiation dose to bone stroma [8]. These agents differ in terms of efficacy, duration of pain palliation, ability to repeat treatments, toxicity, and cost [9]. Commonly used radiopharmaceutical agents include strontium-89 (Sr89), samarium-153 and radium-223. Bisphosphonates are a class of drug that reduces osteolytic bone lesions, the tumour burden in bone, skeletal pain and skeletal complications [6, 10]. Common bisphosphonates include pamidronate, clodronate and zoledronic acid (ZA). Denosumab is a newer and expensive human monoclonal antibody that specifically binds to and blocks activity of the receptor activator of NF-κB ligand (RANKL), which mediates the formation, function, and survival of osteoclasts [11]. It has been shown to be more effective than ZA for the prevention of skeletal-related events in men with bone metastases from castration-resistant prostate cancer [12].

Within an environment of increasingly constrained resources, it is important that treatments offered to the population are not only effective, but they also represent a cost-effective use of resources. We carried out a systematic review of existing economic evaluations to appraise the available evidence on treatment options for the management of bone metastases.

2. Methods

Methods employed throughout the review were in line with guidelines for undertaking and reporting systematic literature reviews in health care [13, 14].

2.1 Study identification

Searches for relevant economic evaluations were carried out for each of the five most common types of primary cancer that metastasise to the bone (prostate, breast, lung, renal and thyroid cancer) [15] in the following electronic bibliographic databases: MEDLINE, MEDLINE in Process and EMBASE (via Ovid), CSDR, DARE, HTA and EED (Wiley Cochrane) and Conference Proceedings Citation Index (Web of Science). Searches covered the period from each database's inception date until March 2017.

The employed search strategies comprised combinations of text words (e.g. synonyms, term variants) and index terms such as Medical Subject Heading (MeSH) terms. A search filter designed by the Centre for Reviews and Dissemination in York was added to locate economic evaluations [16] and an in-built Ovid filter was used to locate systematic reviews/HTAs for background and a possible economic element. The full MEDLINE search strategy can be found in the electronic supplementary material accompanying this article (Online Resource 1). Additional searches were carried out in the reference

lists of key articles and existing systematic reviews. Literature search results were uploaded to, and managed using EndNote X7.0.1 software.

2.2 Study selection

All identified articles were considered against a list of pre-specified inclusion and exclusion criteria (Online Resource 2). Study selection was carried out in two stages. The first stage aimed to filter out clearly irrelevant publications and involved applying the inclusion and exclusion criteria on each article's title and abstract. Publications that met the inclusion criteria, as well as articles for which an exclusion or inclusion decision could not be made based on their title and abstract alone, were forwarded to the second stage, where they were judged on the basis of their full text.

For each of the five types of cancer, selection of articles was carried out independently by two of the three reviewers (LA, RD, IG). Disagreement was addressed through discussion and, if necessary, through consulting a third reviewer.

2.3 Data extraction and quality assessment

A customised form was created to extract relevant data. Such data included bibliographic information (author(s), journal and year of publication), general information (country, population, interventions and comparators), methodological characteristics (type of economic evaluation, analytic method employed, perspective, discounting, key cost categories, key outcomes) and findings (main results and authors' conclusions).

Quality assessment was carried out using the Consensus on Health Economic Criteria (CHEC-list) checklist [17], which is recommended for appraising the methodological quality of economic evaluations [14]. The list comprises 19 items, each of which represents a question which was answered by 'yes', 'no', 'unclear' or 'not applicable'. Negative answers to the CHEC-list do not necessarily indicate poor practice or result in bias. While no identified studies were discarded on the grounds of poor quality, limitations were noted and discussed in subsequent sections.

The identified studies were split into three sets, with each set being assigned to two of three reviewers (set A: IG and RD; set B: LA and IG; set C: RD and LA). Each of the assigned reviewers performed data extraction and quality assessment independently. Disagreements were resolved through discussion between reviewers and, when necessary, by seeking the opinion of a third reviewer. A further round of accuracy checks was carried out on all data extraction forms by LA. Narrative synthesis was used to interpret, summarise and present the information provided in the selected articles. Results are

reported in line with good practice recommendations for narrative summaries of health economic studies as outlined in the Cochrane Handbook for Systematic Reviews [14].

3. Results

A PRISMA diagram showing the key stages of the selection process is provided in Figure 1. A total of 3479 records were retrieved. Of these 3467 records were found through searches in bibliographic databases and 12 were identified through supplementary searches. Removal of duplicate records resulted in 2495 unique articles. Title and abstract screening of these articles led to the exclusion of 2414 citations, leaving 81 potentially relevant articles to be considered for inclusion. Full text assessment of the 81 potentially relevant studies resulted in the exclusion of a further 57 references. The remaining 24 references [18-41] formed the final set of reviewed studies.

3.1 Overview of included studies

Seventeen of the 24 identified studies [18-21, 23-25, 28-33, 35, 36, 39, 40] are concerned with bone metastases resulting from a particular type of primary cancer (Figure 2). Of these, eight studies focus on prostate cancer [18, 21, 29, 31-33, 36, 40], seven studies on breast cancer [19, 23-25, 28, 35, 39], one study on lung cancer [30] and one study on renal cancer [20]. Seven studies [22, 26, 27, 34, 37, 38, 41] report results drawn from groups involving patients with various tumours (e.g. breast, cancer, lung and other solid tumours); of these, five present results separately by type of cancer [22, 26, 34, 37, 41] and two studies report combined findings across different types of cancer [27, 38]. No economic evaluations on treatment options for bone metastases secondary to thyroid cancer were identified.

Figure 3 shows the number of identified articles by year of publication. With the exception of two studies [25, 32], all of the identified economic evaluations were published after 2000. Nearly half of those studies were published within five years, between 2010 and 2014 [20, 21, 26, 30, 35-37, 39-41].

Twenty of the identified studies [18, 19, 22-29, 31, 32, 34-41] focus on a single country, while four studies report results for more than one country [20, 21, 30, 33]. Of the studies focusing on a single country, ten were conducted in Europe (seven in the UK [18, 19, 23, 24, 26, 29, 34] and one in each of Greece [41], the Netherlands [38] and Switzerland [27]), nine in North America (seven in the United States [28, 31, 35-37, 39, 40], two in Canada [25, 32]) and one in New Zealand [22]. Among studies reporting results for more than one country, three [20, 21, 30] had a focus on a small number of European countries, while one study pooled information from 17 countries, including Argentina,

Australia, Brazil, Italy and Sweden [33]. In total, the reviewed literature pertained to 20 different countries.

A summary of key characteristics of the identified studies, including the compared interventions, employed methodology and main findings are given in Tables 1 and 2. Sixteen of the identified studies were CUAs, reporting outcomes in terms of quality-adjusted life years (QALYs) [18-26, 29-31, 35, 36, 38, 41], while four [32, 34, 39, 40] were CEAs reporting outcomes such as instances of SREs prevented. Three studies [28, 33, 37] conducted both CUA and CEA analyses and one performed a CCA [27], with costs and outcomes being presented in a disaggregated form.

In relation to the analytic approach adopted, 18 of the identified evaluations [19-26, 28, 30, 31, 34-37, 39-41] involved synthesising information from various sources (e.g. evidence published in the literature, estimates drawn from patient-level data, expert opinion and other secondary sources) through some form of a decision analytic structure. The remaining six studies [18, 27, 29, 32, 33, 38] involved using statistical methods to analyse patient-level data collected from a single clinical trial (most often randomised clinical trials (RCTs)).

The perspective of the analyses, that is, the viewpoint from which costs and benefits were calculated, varied across studies. Half of the studies [18-20, 22-26, 29, 30, 34, 41] reported results from the perspective of the health care system in the countries they relate to, with eight studies [21, 27, 31, 35-37, 39, 40] adopting a third-party payer perspective, under which costs and consequences were included if they were deemed relevant to the entity covering the cost of the provided care. A societal perspective, which is meant to encompass all costs and consequences accruing across the society, was stated as the adopted viewpoint in three studies [28, 33, 38], while one study did not report the perspective of the presented analysis [32].

The time frame over which results were calculated varied across studies. A time horizon that is long enough to capture all the costs and benefits is typically recommended [42, 43] though, in the reviewed studies, this was often dictated by the follow-up period in clinical studies which provided data for the economic evaluations. One study reported results over time horizon shorter than 12 months [27], eight studies [19-21, 23, 24, 33, 39, 40] looked at costs and benefits accruing between 12 and 24 months, eight studies reported results over time horizons equal to or longer than 24 months [18, 19, 28, 29, 31, 34-36], while four studies [22, 30, 32, 37] produced results over a lifetime horizon. One study analysed costs and benefits accruing over different lengths of time [38], while in another study, by Yfantopoulos and colleagues [41], the length of time horizon varied according to the type of primary cancer investigated.

Consistently with recommendations [44, 45], discounting was carried out to account for positive time preference in 11 studies [18-20, 22, 26, 29, 34-38] which had time horizons greater than 12 months. Discounting was not performed in 9 studies reporting results over time horizons greater than 12 months [21, 23, 24, 28, 30-33, 41].

As expected, costs included in the analyses depended largely on the adopted perspective. Typically, the list of included cost categories comprised treatment-related costs (i.e. the acquisition and administration cost of the bone protecting treatments) and costs due to hospital care provided in response to skeletal problems (e.g. outpatient appointments, hospitalisation for skeletal related events). In eight studies [18, 19, 22, 28, 29, 33, 34, 38], costs extended to use of primary and community care services. Figure 4 shows the split between studies in terms of key outcomes reported. CEAs commonly adopted the outcome of avoided SREs. An SRE is typically defined as the occurrence of a pathologic fracture or spinal cord compression, or the need for radiation therapy or surgery to bone. In CUAs, outcomes were invariably reported in QALYs, a composite measure that incorporates time spent in a particular state of health and preference-based QoL associated with this state.

Indications on the methodological quality of the identified studies were obtained through assessment against the 19 items (questions) of the CHEC-list quality assessment checklist [16]. Answers to CHEC-list questions are given in Table 3. Positive answers to these questions are considered to be indicative of good practice in undertaking and reporting economic evaluations. In all of the identified studies, the number of positive ('yes') answers exceeded those of negative ('no') or other answers ('unclear' or 'not applicable'). Many of the negative responses were given to items 17, 18 and 19 of the CHEC-list, which relate to the generalisability of the study results, a discussion of the ethical and distributional issues associated with findings, and the indication of potential conflict of interest.

3.2 Findings of identified studies

Key characteristics and findings of the identified studies are presented below according to type of primary cancer.

3.2.1 Prostate cancer

Articles assessing the cost-effectiveness of treatments for bone metastases due to prostate cancer comprised the largest group of the identified studies. Treatments assessed included the radioisotope strontium-89 (Sr89), various bisphosphonates (most commonly ZA, but also pamidronate, ibadronate and clodronate), denosumab, as well as single and multiple fraction external beam radiotherapy.

In the earliest of the identified studies, McEwan *et al.* [32] assessed the cost-effectiveness of Sr89, a local treatment which settles to the site of bone metastases and delivers radiation, as a palliative option for bone-metastatic prostate cancer. The authors sought to establish the difference in costs and outcomes resulting from treatment with Sr89 (Metastron®) as compared to placebo. In doing so, McEwan *et al.* [32] analysed data retrieved from hospital records and case report forms collected as part of the Trans Canada trial of Metastron®. The authors found that the total per-patient cost of care—which included the cost of drugs, radiotherapy, investigations and stay in a tertiary unit—was lower for those who received Sr89, resulting in a total cost saving of CAN $209 per week of survival as compared to patients who received placebo. However, the authors noted that their calculations of the total cost of care did not include general practitioner visits and, crucially, the cost of Sr89 or the initial radiotherapy.

Sr89 for patients with prostatic bone metastases was also assessed in a study reported by James *et al.* [29] and Andronis *et al.* [18]. The authors analysed patient-level resource use and outcome data collected alongside the TRAPEZE factorial RCT [46], which was funded by the National Institute for Health Research Health Technology Assessment programme in the UK to compare Sr89 in addition to standard chemotherapy against no Sr89. The analysis, which was conducted from the perspective of the UK health care system, found that the addition of Sr89 to standard chemotherapy led to a small increase in costs (mainly due to radioisotope acquisition and administration costs) and a modest improvement in QoL, resulting in an additional cost of £17,000 per QALY gained as compared to no Sr89 treatment.

Data from the TRAPEZE trial were also used to evaluate the cost-effectiveness of ZA, a drug that aims to prevent loss of bone mass, as compared to no ZA. In the analysis reported by James *et al.* [29] and Andronis *et al.* [18] the authors found that the extra acquisition and administration cost for ZA was almost compensated by savings due to fewer SREs, resulting in a small additional cost (or an overall cost saving, depending on the acquisition cost of ZA) for a small improvement in QALYs. The additional cost for providing proprietary ZA alongside standard chemotherapy treatment was found to be £8000 per QALY gained; however, additional analyses carried out to reflect the availability of generic, inexpensive ZA showed this option to dominate its comparator, resulting in a lower total cost and a modestly higher number of QALYs.

ZA in addition to standard chemotherapy was also the subject of the studies by Reed *et al.* [33] and Carter *et al.* [21]. Reed *et al.* [33] analysed evidence collected alongside a multinational RCT to compare ZA against placebo in terms of the additional cost per SRE avoided, additional cost per patient free of SRE and additional cost per QALY. Findings showed ZA to be associated with an additional cost

of US $12,300 per SRE avoided, US $51,400 per patient free of SRE and US $159,200 per QALY gained. While ZA appeared to result in improved outcomes, the authors concluded that the estimated incremental cost is higher than cited values below which treatments are typically considered cost-effective.

In an analysis carried out from the perspective of payers in France, Spain, Portugal and the Netherlands, Carter *et al.* [21] synthesised costs drawn from published sources and clinical evidence obtained from an RCT to establish the cost-effectiveness of ZA in each of the four countries. Findings showed that patients who received ZA experienced fewer SREs and, as a result, a lower cost of SRE complications. However, the addition of ZA resulted in further acquisition and administration costs which led to overall higher total costs, ranging from €87 in the Netherlands to €1284 in France. Combining the total costs with a calculated increase in QALYs by 0.036 led to ICERs ranging from approximately €2,400 to €36,000 for the Netherlands and France, respectively.

The cost-effectiveness of denosumab, a newer pharmaceutical which prevents the development of osteoclasts, was assessed in five economic evaluations [26, 36, 37, 40, 41]. All of these studies employed decision analytic models to compare denosumab against ZA, the most widely-used bisphosphonate in bone-metastatic prostate cancer.

In the earliest of the identified studies on denosumab, Xie *et al.* [40] drew clinical data from a Phase III RCT and used a nine-state Markov model to calculate the incremental cost per SRE avoided over one-year and three-year time horizons. Results showed denosumab to be associated with higher total costs and fewer SREs, resulting in additional costs of US $71,027 and US $51,319 per SRE avoided over one year and three years, respectively.

Stopeck *et al.* [37] looked at the value of denosumab for the prevention of SREs in four bone-metastatic solid tumours, including prostate, breast and lung cancer, from a payer's perspective in the US. The analysis was based on a Markov model with a lifetime horizon and made use of SRE reduction rates from three RCTs. With regards to prostate cancer, the authors [37] found denosumab to be associated with additional costs of US $49,405 and US $8567 per QALY gained and SRE avoided, respectively. While Stopeck and colleagues [37] concluded that denosumab is a cost-effective treatment option, largely due to its superior efficacy in preventing SREs, they acknowledged that results are sensitive to the cost of drugs and, importantly, the employed rate of SRE occurrence.

Similarly, Yfantopoulos *et al.* [41] conducted a model-based analysis to assess the cost-effectiveness of denosumab compared to ZA in preventing SREs due to bone metastases from solid tumours, including prostate cancer. The analysis, which was carried out from a payer's perspective in Greece,

used a spreadsheet model which was populated by data drawn from the literature and health care records. The main analysis, which assumed that denosumab will be covered by a recently established overarching health insurance provider in Greece (EOPYY), indicated an additional cost of €61,296 per QALY gained and €4,889 per SRE avoided, respectively, leading the authors to conclude that denosumab is not a cost-effective alternative to ZA for prostatic bone metastases, assuming that society (or decision makers) in Greece would be willing to pay up to €30,000 for an additional QALY. The authors found that a reduction of the cost of denosumab by €15-€20 can make the treatment appear cost-effective, which is indicative of the uncertainty associated with the study findings. This uncertainty was not presented in the study, which relied on effectiveness data and model structure presented in another non-peer reviewed paper (conference abstract).

Ford *et al.* [26] compared denosumab against ZA by re-building and updating a model submitted to the National Institute of Health Care Excellence (NICE) Multiple Technology Appraisal programme in the UK. The analysis assessed the cost and QALYs for breast, prostate, lung and other solid tumour cancers through Markov model based on 4-week cycles over a 10-year time horizon. Results specific to prostate cancer showed that the cost-effectiveness of denosumab is contingent on the treatment's cost and, therefore, on access to a patient access scheme (PAS)—a provision that involves a pricing agreement between a drug manufacturer and the NHS. Without PAS, denosumab for prostate cancer was associated with a high cost per QALY value of £111,603 and it was not deemed cost-effective compared to ZA. With PAS, denosumab dominated ZA, being less costly and more effective (in terms of QALYs). The authors noted that, owing to small gains in QALYs estimated in the analysis, the cost-effectiveness of denosumab was highly sensitive to the price of ZA.

In the same year, Snedecor *et al.* [36] developed an eight-state Markov model and populated it with data from the literature to calculate costs and effects (SREs avoided and QALYs) over a 27-month time horizon. The analysis showed denosumab to result in fewer SREs but higher total costs. The additional costs, in the order of US $7841, and the modest gain of 0.007 QALYs due to fewer SREs resulted in a cost per QALY gained value in excess of US $1 million. The authors attribute the fact that this figure is much higher than those in the analyses by Stopeck *et al.* [37] and Ford *et al.* [26] to differences in the calculations of three key parameters: drug-associated costs, SREs avoided and QALYs gained.

Two studies [22, 31, 38] looked into the cost-effectiveness of different schedules of external beam radiotherapy (EBR) for bone-metastatic prostate cancer. EBR is a palliative therapy for relieving local metastatic bone pain which can be administered in single or multiple fractions.

Single versus multiple-fraction EBR was evaluated in an analysis carried out by Konski [31] from a payer's perspective in the US. In this study, the author developed a Markov model to evaluate various palliative treatments for bone metastases from prostate cancer, including systemic chemotherapy (mitoxantrone plus prednisone), two radiotherapy schedules and best supportive care (pain medications only). Key model inputs on transition probabilities, costs and preference-based QoL were obtained from published sources and expert opinion. The analysis showed that, compared to best supportive care, single-fraction and multi-fraction EBR resulted in an additional cost of US $6857 and US $36,000 per QALY gained, respectively, while chemotherapy was dominated by the rest of the options. While a comparison between single-fraction and multiple-fraction EBR is not reported, cost and QALY values for these two options presented in the paper result in an ICER of US $8667 per QALY gained for multiple-fraction EBR compared to single-fraction EBR.

In a more recent study carried in New Zealand, Collinson *et al.* [22] built a Markov model to evaluate the costs and QALYs associated with single and multiple-fraction EBR for metastatic bone pain in prostate, breast and lung cancer. The model synthesised data from a range of sources, including RCTs and routine data collected in New Zealand. QALYs were calculated using disability weights from the Global Burden of Disease study, rather than index values from multi-attribute utility systems (such as the EQ-5D). In relation to prostate cancer, model output showed single-fraction EBR to be associated with lower costs and a slightly greater number of QALYs compared to multiple-fraction EBR, which led the authors to conclude than single-fraction EBR is a superior option.

3.2.2 Breast cancer

Eleven articles assessing the cost-effectiveness of treatments for bone metastases due to breast cancer were identified [19, 23-26, 28, 34, 35, 37, 39, 41], of which four [26, 34, 37, 41] present results for breast cancer alongside other solid tumours. Treatments assessed included various bisphosphonates, denosumab, as well as single and multiple fraction radiotherapy.

The cost-effectiveness of bisphosphonates in bone metastases secondary to breast cancer was evaluated in six studies. Based on clinical evidence suggesting that pamidronate taken once a month reduces the incidence of SRE in breast cancer patients, Dranitsaris and Hsu [25] carried out a CUA to compare this bisphosphonate against placebo. The analysis, which was conducted through a simple decision analytic model, combined three key sources of information: rates of SRE occurrence taken from a clinical trial, drug and hospital care related costs found in routine hospital source, and QoL weights derived from a small sample of health professionals and breast cancer patients. Findings showed pamidronate to be more costly and more effective than placebo, resulting in an additional cost of CAN $18,700 per additional QALY gained.

An evaluation of the cost-effectiveness of pamidronate compared to placebo was also pursued in a model-based analysis carried out in the US by Hillner *et al.* [28]. The authors combined results on incidence of SREs from two RCTs, resource use categories and costs from routine sources and QoL weights elicited from experts to calculate incremental costs per SRE prevented and QALYs gained over a two-year period. Findings suggested that the cost of adding pamidronate to existing treatment regimens (hormonal systemic therapy or chemotherapy) exceeded the savings from reduced occurrence of SREs, resulting in additional cost per QALY values of US $108,200 and US $305,300 for chemotherapy and hormonal therapy, respectively.

A wider range of bisphosphonates—including ZA, pamidronate, chlodronate and ibadronate—were evaluated in three studies [19, 23, 24, 34]. Botteman and colleagues [19] built a decision model to compare five commonly-used bisphosphonates (oral and intravenous ibandronate, ZA, generic pamidronate and generic oral clodronate) against placebo. The analysis was carried out from the perspective of the UK health care system. Model inputs, including treatment costs, SRE costs and preference-based QoL indices were obtained from the literature. The authors reported that ZA and oral ibadronate resulted in cost savings, pamidronate and intravenous ibadronate led to additional costs, while patients on all bisphosphonate therapies experienced, on average, fewer SREs and improved quality-adjusted life expectancy. Reported findings indicate that offering bisphosphonate treatment is a cost-effective option compared to placebo. All bisphosphonates resulted in incremental cost per QALY values less than or equal to £2,400 compared with placebo, with ZA being the dominant bisphosphonate.

The cost-effectiveness of oral ibadronate was also investigated in two studies published in 2005 by De Cock and colleagues [23, 24]. The first study [23] aimed to compare oral ibadronate against intravenous pamidronate or ZA in breast cancer patients receiving hormonal therapy. For this purpose, the authors adapted a global economic model to the UK health care system. The model extrapolated costs and outcomes over a lifetime horizon by combining data on resource use and QoL with incidence of SREs. Model results suggested oral ibadronate to be more effective and less costly than ZA or intravenous ibadronate. However, the authors acknowledge that results would only hold true given certain assumptions (e.g. differences in QALYs are driven only by QoL, not survival), while the absence of efficacy data from head-to-head comparisons of the assessed bisphosphonates is a limiting factor. The second study by De Cock and colleagues [24], which shared much of the structure and inputs of the first study, compared oral ibandronate against intravenous ZA and generic intravenous pamidronate in patients undergoing chemotherapy. In this study, too, oral ibadronate was found to be less costly and more effective than its counterparts, making it the dominant option.

ZA was compared against other bisphosphonates and no ZA as options for the prevention of skeletal morbidity and hypercalcaemia in an economic evaluation conducted by Ross *et al.* [34]. The authors carried out a systematic review of existing studies and they used the retrieved information as input in a decision analytic model. The analysis focused on metastases secondary to either breast cancer or multiple myeloma, on the basis of a four-year time horizon from the perspective of the health care system in the UK. Results were presented in the form of cost per duration of normocalcaemia (i.e. normal concentration of calcium in the blood) and cost per SRE prevented. A wealth of results was presented depending on the source of the input data. The authors concluded that ZA (8mg dose) was the most cost-effective option for hypercalcaemia and bisphosphonate therapy represented value-for-money in preventing SREs, with incremental costs ranging from £250 to £1500 per event avoided.

The emergence of denosumab as an effective alternative to bisphosphonate treatment for patients suffering from bone metastases has given rise to studies evaluating the agent's cost-effectiveness, typically in comparison to ZA [35, 39]. Xie *et al.*[39] investigated the additional costs and benefits of denosumab in breast cancer patients from the perspective of a third-party payer in the US. In doing so, the authors built an 11-state Markov model and calculated outcomes over a 1-year time horizon. Clinical inputs in the model (e.g. incidence of SREs at different times) were derived from a large Phase III clinical trial comparing denosumab and ZA [47], while cost inputs (treatment-related costs and resource use due to SREs and adverse events) were obtained from various sources, including a claims dataset and available trial evidence. Denosumab was found to be more costly but more effective (in terms of number of SREs avoided in 1 year), resulting in an incremental cost of US $114,628 per SRE avoided. The same options were investigated in a study by Snedecor *et al.*[35]. Similarly to Xie et al., Snedecor and colleagues [35] built a Markov model to calculate costs and outcomes (avoided SREs and QALYs) associated with denosumab and ZA from a payer's perspective in the US. In their base-case analysis, the authors run the model over a 27-month period (60 months in sensitivity analysis), which reflected the timeframe for which patient-level data were available. Clinical, cost and QoL inputs were largely drawn from the available literature. Base-case results suggested that denosumab is associated with a significantly higher cost than ZA (largely due to drug-related costs) and a greater number of QALYs (due to a lower incidence of SREs), resulting in an overall incremental cost per QALY gained value of US $697,499 and prompting the authors to question the economic value of the drug.

Comparisons of denosumab and ZA are also reported in three of the studies looking into treatments for bone metastases secondary to various solid tumours, rather than only breast cancer [26, 37, 41]. A description of the methods used in these studies can be found under the prostate cancer heading above. In relation to breast cancer, Stopeck *et al.*[37] found denosumab to result in an additional cost

per QALY gained of US $78,915, Yfantopoulos *et al.* [41] reported a value of €56,818 per QALY gained for the same comparison, while Ford *et al.* [26] found denosumab to be associated with a high cost per QALY value of at least £190,841 depending on the assumptions employed. Calculations on the basis of access to a PAS resulted in denosumab dominating ZA, being less costly and more effective (in terms of QALYs).

3.2.3 Lung cancer

Five studies reported economic evaluations of treatments for patients with bone metastases due to lung cancer. Of these, the study by Joshi *et al.* [30] focused on lung cancer only, while the remaining studies investigated lung cancer alongside other conditions [22, 26, 37, 41].

Joshi and colleagues [30] carried out an economic evaluation to assess the cost-effectiveness of ZA compared to placebo in patients with non-small cell lung cancer (NSCLC) in five European countries (France, Germany, UK, Portugal and the Netherlands). The analysis, which has the form of a model-based CUA, made use of data from various sources. Estimates of survival and SRE incidence were calculated on the basis of data from a large RCT [48, 49], resource use and costs were taken from the literature and routinely collected hospital data, while QoL was estimated according to values published in the literature. In their base-case analysis, the authors found ZA to be associated with fewer SREs, more QALYs and cost savings or a modest increase in costs, depending on the country. Overall, ZA appeared to be less costly and more effective than placebo in Germany, UK and Portugal, and resulted in incremental cost per QALY gained values of €786 and €8278 in France and the Netherlands, respectively.

The rest of the studies [22, 26, 37, 41] presenting results for lung cancer did so alongside findings for other types of primary cancers. A fuller description of this work has been given above, under other headings. Three of these studies compared denosumab with ZA [26, 37, 41]. Stopeck *et al.* [37] found that denosumab is more costly and more effective than ZA in lung cancer patients with bone metastases, resulting in an incremental cost per QALY gained value of US $67,931. Yfantopoulos *et al.* [41] found that denosumab would cost the country's social insurance funds an additional €80,830 per QALY gained as compared to ZA for patients with solid tumour metastases secondary to cancers other than breast or prostate. In an analysis carried out from the viewpoint of the health care system in the UK, Ford *et al.* [26] calculated an incremental cost per QALY of £12,743 provided that denosumab is reimbursed through a PAS and £110,671 in the absence of the scheme. Lastly, Collinson *et al.* [22], evaluated delivery schedules for EBR and found that, from the viewpoint of the health care system in New Zealand, single-fraction EBR is less costly and more effective (in QALYs) than multiple-fraction EBR.

3.2.4 Renal cancer

Only one economic evaluation with a focus on bone metastases secondary to renal cancer was identified. In this study, Botteman *et al.* [20] set out to assess the cost-effectiveness of ZA against placebo in patients with renal cancer in three countries: France, Germany and the UK. The purposes of the study were pursued through a simple decision analytic model which combined patient-level data from an RCT funded by the manufacturer of ZA, assumptions and information from the literature. The authors found ZA to be the dominant option, being associated with lower costs and a gain in QALYs in all three countries.

3.2.5 Studies reporting combined results for various types of primary cancers

Two studies [27, 38] presented results which were combined across different types of cancer. Van den Hout *et al.* [38] carried out a CUA to compare a single-fraction against a multiple-fraction (six fractions) schedule in patients with various solid tumours (breast, lung, prostate and other types of cancer). The analysis, which included costs accruing to the Dutch health care system and the patient, drew on data collected alongside a Dutch RCT. Results were presented as cost per quality-adjusted life expectancy and cost per QALY for all patients, rather than by type of primary cancer. The study showed single fraction radiotherapy to be less costly and more effective (in terms of quality-adjusted life expectancy), however none of the reported differences were statistically significant. It is worth noting that the latter results relate to a comparison of total societal cost over 12 weeks and QALYs over 2 years. The authors justify this difference in measurement periods on the ground that no statistically significant differences in costs were observed after the period of 12 weeks.

Similarly, Gessner *et al.* [27] evaluated two dosage regimens of pamidronate, a second-generation bisphosphonate, in an analysis carried out on the basis of data from 70 trial participants suffering from different types of advanced cancer (breast cancer, multiple myeloma and other tumours). The total cost (ECU 12,060) comprised treatment-related, inpatient and outpatient costs and was presented for all patients (i.e. irrespective of type of primary cancer) and for both treatments combined. In relation to outcomes, the authors found the 60mg dose of pamidronate to lead to a 36% reduction in pain intensity compared to baseline, while the 90mg dose led to a smaller reduction, by 15%. The authors concluded that treatment with pamidronate resulted in a significant reduction in pain, but did not add noticeably to the costs.

4. Discussion

Bone metastasis is a frequent and highly debilitating complication of cancer with important economic consequences. We reviewed existing economic evaluations to summarise the available evidence on the economic value of treatment options for the management of bone metastases. The review identified 24 economic evaluations assessing treatments in patients with different primary cancers. Such treatments include i) the radioisotope Sr89 (compared against no treatment), ii) single and multiple fraction EBR (compared with each other and against no EBR) iii) bisphosphonates (most often ZA, compared against placebo or other bisphosphonates) and iv) denosumab (invariably compared against ZA).

4.1 Key findings

While the diversity in the inputs and evaluation methods used across the identified studies calls for caution in drawing definitive conclusions, the review offers useful insights into the cost-effectiveness of treatment options for bone metastases.

Much of the reviewed economic evaluation literature on bone metastases due to prostate cancer focuses on bone-targeted therapies such as denosumab and bisphosphonates, most commonly ZA. In general, evidence suggests that ZA leads to fewer SREs and a greater number of QALYs, but it also results in higher costs, the magnitude of which appears to be contingent on the acquisition cost of ZA. Denosumab, a newer alternative to bisphosphonates, was invariably found to be marginally more effective than ZA in preventing SREs and improving patients' QoL. Nonetheless, findings suggest that superior effectiveness comes at a considerable additional cost; while this cost varies across studies and countries, there is an agreement between authors that, in the absence of special arrangements such as PAS, denosumab is unlikely to represent 'value for money'. A small number of the reviewed studies assessed the value of radiation therapies and radiopharmaceuticals in prostatic bone metastases. In general, findings suggest that Sr89 is likely to result in improved outcomes for a relatively modest increase in costs (or even cost savings) compared to no Sr89 treatment. However, results on the cost-effectiveness of different delivery schedules of EBR are less conclusive, with the limited identified literature suggesting that either single-fraction EBR or multiple-fraction EBR may be superior.

In breast cancer, evidence suggests that bisphosphonate treatments are more effective in improving QoL and reducing the occurrence of SREs when compared to placebo. While such treatments are also more costly, the estimated additional cost per QALY gained values are typically lower than commonly

cited cost-effectiveness thresholds. Similarly to findings in patients with prostate cancer, denosumab is shown to be more effective but considerably more costly than ZA, with the lowest incremental costs per QALY value reported being in excess of €57,000 [41]. Denosumab dominated ZA—being less costly and more effective—only when access to PAS was considered [26].

With regards to lung cancer, findings suggest that, in comparison to placebo, ZA leads to QALY gains at an additional cost that is relatively low. In line with findings for breast and prostate cancer, denosumab is seen to be more effective but substantially more costly than ZA, resulting in incremental cost per QALY values greater than $68,000 [37], unless a PAS arrangement is in place. Single-fraction EBR is shown to result in cost savings and gains in QALYs compared to multiple-fraction EBR, thought these findings come from a single study. Last, in the only economic study on bone metastases for renal cancer, evidence suggests that ZA would result in gains in QALYs for a modest additional cost (or cost savings in some countries).

In summary, across types of cancer, the reviewed evidence suggests that offering bisphosphonates such as pamidronate, ibadronate and ZA to patients with bone metastases results in lower SRE incidence and additional QALYs achieved at costs below conventional thresholds. While denosumab, an alternative to bisphosphonate treatment, leads to small health gains compared to ZA, it also results in substantial additional costs and it is unlikely to represent 'value for money'. The limited evidence on radiopharmaceuticals suggest that Sr89 is a cost-effective option. While external beam radiotherapy is shown to be cost-effective for patients with localised bone metastases, the evidence on the economic superiority of multi-fraction over single fraction EBR is inconclusive.

4.2 Methodological issues and comparability

As noted above, combining the findings of the 24 identified studies into conclusive statements is hindered by a number of factors. First, notable diversity stems from the fact that identified studies relate to a variety of countries. While, from a clinical perspective, the effectiveness of compared treatments can be assumed to be generalisable across countries, comparisons of cost-effectiveness results need to be exercised with caution, given the considerable variability in the structure of health care systems, differences in the delivery and cost of health care services, and diversity in patient access schemes and reimbursement mechanisms available in different countries [26, 41].

Secondly, considerable variability arises from the fact that studies report analyses from different perspectives, including those of a third-party payer (e.g. Medicaid in the US), health care systems (e.g. the NHS in the UK) or the society. Inevitably, costs and benefits that are included in studies conducted from a particular perspective (e.g. societal) may have been left out from analyses adopting other

perspectives. Similarly, differences in the unit cost of care and price of pharmaceuticals across jurisdictions makes drawing conclusions on the basis of reported cost and benefit figures haphazard.

Thirdly, there is variation in the interpretation of results, which is particularly prominent in the common situation when a treatment is overall more effective but also more costly. This variation is directly linked to uncertainty around what constitutes the maximum amount that decision makers in different jurisdictions should be willing to pay for a unit of outcome. Various WTP values are used as thresholds for judging cost-effectiveness across the 24 studies. For example, Yfantopoulos *et al.* [41] assumes a threshold of €30,000 per QALY in Greece, which they justify on grounds of the country's recent economic downturn, while Collinson *et al.* [22] use a value of NZ $45,000 based on WHO's suggestions that links WTP for a QALY with a country's gross domestic product. However, WTP values for a unit of benefit vary across jurisdictions, depending on various socioeconomic factors and characteristics of health care systems [50]. Thus, ambiguity around an acceptable WTP is exacerbated by the paucity of specific guidance about acceptable WTP values in particular countries, including the US [51]. While in this review we have endeavoured to present authors' conclusions as closely as possible, to facilitate judgements on what may be perceived to be cost-effective when a WTP value was not mentioned we based such judgements on indicative values of WTP for an additional QALY suggested by NICE in the UK [43].

The review gave rise to a number of observations related to the methods used in the identified literature. Across studies, the reviewed evidence suggested that a large part of the total incremental costs is due to the acquisition cost of treatments. As the identified studies span a 23-year period (with 11 of them being published before 2007) one should bear in mind that drug acquisition prices, as well as other health care related costs, are subject to change. This can be seen in studies assessing ZA in the UK: while early studies [33, 34] used a British National Formulary (BNF) unit cost of £195 per dose of ZA (2004 prices), later studies, making use of more recent versions of BNF employed lower prices per dose in their calculations (£174 in Ford et al. [26] and £155 in Andronis et al. [18]). More importantly, the degree to which robust inference can be made on the basis of early studies is influenced by changes in the price of treatments due to patent expiration and emergence of generic alternatives. Such is the case with ZA (Zometa®), which lost patent protection in 2013. While much of the identified literature suggests that offering ZA results in greater overall costs than not offering the treatment, more recent analyses carried out on the basis of inexpensive non-proprietary ZA report a high likelihood that this treatment may actually result in cost savings [18, 29]. Additionally, although it is sensible to expect that a share of the burden of caring for a patient who developed an SRE,

especially a pathological fracture, may fall to the patient's informal carers, costs reflecting this burden have not been included in most of the identified analyses.

The review also raised a number of points in relation to outcomes. The most commonly used measure in identified CEAs was instances of SREs avoided. Indeed, this is a sensible choice of a 'natural' outcome which captures a key intended goal of bone metastatic treatment. However, measuring outcomes in such natural units is less useful for informing decisions aiming to allocate resources across different disease groups or health care programmes [52]. Such decisions are facilitated by using outcomes such as QALYs, which were the measure of health benefit in all of the reviewed CUAs. QALYs take into account both the length of time spent in a particular state and the preference-based QoL associated with this state. Despite these advantages, the use of QALYs in the identified studies poses some limitations. Firstly, there are variations across studies in the methods used to derive preferences for health care states. Secondly, there are concerns that QALYs generated from generic measures may not be appropriately sensitive to reflect changes in cancer [53, 54]. Thirdly, while end-of-life may be an important consideration, there were no indications that this was taken into account across the reviewed studies [37, 38]. Last, in cases where preference-based QoL scores have not been obtained at points in time when individuals suffered from SREs, impairments in QoL are unlikely to have been captured in patient-level data [18]. Thus, to incorporate these decrement in their analyses, researchers have unavoidably resorted to making assumption about the magnitude and duration of the effect, with the later varying from one month [20, 28, 30] to one year [25].

An additional point relates to authors' normative assumptions of what cost or outcome-related parameters to include in analyses. For example, Snedecor and colleagues [36] did not consider disease progression and adverse events in their analysis on the basis that these were not significantly different between treatment comparators. It is important that key assumptions are comprehensively tested in sensitivity analyses and that the uncertainty associated with key study findings is reported clearly. This will help explore the robustness of the study findings to variations in key assumptions and analytical methods used and will allow more definitive conclusions to be drawn, particularly in a context where most of the identified studies did not indicate that there is no potential conflict of interest of study researchers and funders.

We carried out simple comparisons to assess whether certain study characteristics (above and beyond treatment of interest, country and type of cancer) appear to have a bearing on reported cost-effectiveness values and authors' conclusions. To disentangle the influence of a particular aspect, one would ideally compare studies with similar aims and characteristics which would however differ with respect to the aspect of interest. However, the relatively small number of the selected studies and the

diversity in type of primary cancer, treatments and methods used limit the comparability between studies and the scope for dependable conclusions. With this in mind, we found no discernible influences of either the time horizon of the analysis or the analytic approach employed (e.g. trial or model-based evaluation) on reported cost per outcome values. For example, in the five studies comparing denosumab against ZA in the US [35-37, 39, 40], a longer time horizon corresponded with both more and less favourable cost per outcome ratio for the treatment. A similarly picture emerged when comparing outcomes from trial-based economic evaluations versus model-based evaluations; both favourable and unfavourable cost per outcome values were reported irrespective of the type of analysis. Similarly, two [28, 33] of the three studies that adopted a societal perspective as compared to narrower (health care system and third-party payer) perspectives reported results which were on par with conclusions drawn in the rest of the literature for the particular treatments (i.e. bisphosphonates more cost-effective than placebo). The third study that adopted a societal perspective compared multiple fraction EBR with single fraction EBR in the Netherlands [38], with the authors reporting results comparable to a study investigating the same treatment regimens in the US, which, however, adopted a third-party perspective [22]. All in all, our investigation failed to find evidence that particular factors or design characteristics appear to have a systematic influence on reported cost per outcome values.

In addition to informing treatment recommendations, an explicit representation of uncertainty is useful in determining whether funding and conducting further research would be economically worthwhile [55]. Analytic methods such as 'value of information' (VoI) and 'prospective payback of research' are available to provide estimates of the potential value of research and indicate whether further evidence should be pursued [56, 57]. The value of, and methodology for, conducting such analyses—particularly VoI—is well established [58], with VoI calculations being increasingly undertaken in different disease areas, including cancer [59-61]. Despite this, and the fact that such calculations require little additional time or inputs [62-64], none of the reviewed studies undertook such work to explore the need for further research, especially around key uncertain parameters such as SRE incidence.

4.3 Strengths and limitations

The review has a number of strengths. In line with recommendations, we searched key electronic bibliographic databases by using combinations of free text and indexing terms. Additional searches were carried out on reference lists of known and identified references, including systematic reviews. Identified studies were independently assessed by two reviewers for inclusion against a set of predetermined criteria. No restrictions were applied on types of economic evaluation or analytic

approach used: all types of full economic evaluations, as per the definition by Drummond *et al.* [45] were considered relevant, including both trial and model-based economic evaluation.

Nonetheless, our review presents certain limitations. First, for pragmatic reasons, only articles published in English were included in our review. While excluding articles published in other languages poses the risk of missing out important information, research suggests that exclusion of articles in languages other than English is unlikely to result in systematic bias [65, 66]. Secondly, our review's focus on full economic evaluations means that studies reporting only costs (such as cost-analyses) were not included. While such partial evaluations studies can offer detailed information into the costs associated with a treatment, they do not provide information that would allow answering resource allocation decisions and, they are, as a result, less valuable for decision making [45]. Lastly, our review excluded non-peer-reviewed studies (e.g. internal reports), work not reporting original research (e.g. opinion papers) or work published in a restricted format (conference abstracts). While all this literature is likely to provide insights into the review question, such studies are of no direct interest as far as they do not report complete results of an economic evaluation carried out to assess the value of treatments for bone metastases.

5. Conclusions

In summary, the reviewed evidence suggests that bisphosphonate treatment is a cost-effective option for bone metastases. While denosumab is shown to result is small reductions in SREs and modest gains in QoL, there is broad agreement that, due to treatment's substantial additional costs, the treatment is unlikely to represent value for money. Evidence on the economic value of EBR and the radiopharmaceutical Sr89 is relatively limited and less conclusive. Sr89 is likely to be a cost-effective option, but findings around the most beneficial delivery schedule are equivocal.

6. Data availability statement

All data generated or analysed during this study are included in this published article.

Compliance with Ethical Standards

Disclosure of potential conflicts of interests

Authors' conflict(s) of interest:

- LA: no conflict of interest declared
- IG: no conflict of interest declared
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Authors' contribution

- LA: Contributed to study conception and design, article selection, data extraction, data interpretation and manuscript preparation.
- IG: Contributed to study conception and design, article selection, data extraction, data interpretation and manuscript preparation.
- SB: Contributed to study conception, designed and conducted search strategies, retrieved identified articles and contributed to manuscript preparation.
- RD: Contributed to study conception and design, article selection, data extraction, data interpretation and manuscript preparation.

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Tables

Figures

Electronic Supplementary Material

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Table 1. Summary of methods employed in the reviewed studies.

Study (year)	Country (perspective)	Type of economic evaluation (analytic method employed)	Time horizon (discounting and rate)	Main cost categories and year of valuation	Measure of benefit (instrument)
Andronis *et al.* [18], James *et al.* [29] (2016)	UK (health care system)	CUA (trial-based economic evaluation)	24 months (discounting performed at 3.5% per year)	-Treatment-related costs -Hospital care cost -Primary/community care costs Valuation year: 2011/12	QALY (EQ-5D-3L)
Botteman *et al.* [19] (2006)	UK (health care system)	CUA (model-based economic evaluation)	10 years (discounting performed at 3.5% per year)	-Treatment-related costs -Hospital care costs -Primary/community care costs Valuation year: 2005	QALY (QoL weights taken from the literature)
Botteman *et al.* [20] (2011)	France, Germany, UK (health care system)	CUA (model-based economic evaluation)	21 months (discounting performed at 5% per year for France and Germany, 3.5% per year for the UK)	- Treatment-related costs - Hospital care costs Valuation year: 2008	QALY (QoL weights taken from the literature)
Carter *et al.* [21] (2011)	France, Germany, Portugal, the Netherlands (third-party payer)	CUA (model-based economic evaluation)	15 months (discounting not performed)	-Treatment-related costs -Hospital care cost Valuation year: 2011	- SRE avoided -QALY (QoL weights taken from the literature)
Collinson *et al.* [22] (2016)	New Zealand (health care system)	CUA (model-based economic evaluation)	Lifetime (discounting performed at 3% per year)	-Treatment-related costs -Hospital care cost -Primary/community care costs -Patient out-of-pocket expenditures (travel costs) Valuation year: 2011	QALY (calculated using disability weights from the Global Burden of Disease study [67])
De Cock *et al.* [23] (2005)	UK (health care system)	CUA (model-based economic evaluation)	14.3 months (discounting not performed)	-Treatment-related costs -Hospital care costs Valuation year: 2003	QALY (QoL weights taken from the literature)

De Cock *et al.* [24] (2005)	UK (health care system)	CUA (model-based economic evaluation)	14.3 months (discounting not performed)	- Treatment-related costs - Hospital care costs Valuation year not reported	QALY (QoL weights taken from the literature)
Dranitsaris and Hsu [25] (1999)	Canada (health care system)	CUA (model-based economic evaluation)	12 months (discounting not applicable)	- Treatment-related costs - Hospital and specialist care costs Valuation year: 1999	QALY (derived through a TTO exercise)
Ford *et al.* [26] (2013)	UK (health care system)	CUA (model-based economic evaluation)	10 years (discounting performed at 3.5% per year)	- Treatment-related costs - Hospital care costs Valuation year: 2010	- QALY (QoL weights taken from drug manufacturer's evidence submission to NICE) - SRE avoided
Gessner *et al.* [27] (2000)	Switzerland (third-party payer)	CCA (trial-based economic evaluation)	10.5 months (discounting not applicable)	- Treatment-related costs - Hospital and specialist care costs Valuation year: 1995	Linear analogue scale measuring pain levels
Hillner *et al.* [28] (2000)	US (societal)	CEA, CUA (model-based economic evaluation)	24 months (discounting not performed)	- Treatment-related costs - Hospital care costs - Primary/community care costs - Productivity cost of patients' companion Valuation year not reported	- SRE avoided - QALY (instrument not reported)
Joshi *et al.* [30] (2011)	France, Germany, Netherlands, Portugal, UK (health care system)	CUA (model-based economic evaluation)	Unclear (discounting not performed)	- Treatment-related costs - Hospital care costs Valuation year: 2007/08	QALY (QoL weights taken from the literature)
Konski [31] (2004)	US (third-party payer)	CUA (model-based economic evaluation)	24 months (discounting not performed)	-Treatment-related costs -Hospital care costs Valuation year not reported	QALY (QoL weights taken from the literature)
McEwan *et al.* [32] (1994)	Canada (not reported)	CEA (trial-based economic evaluation)	Lifetime (discounting not performed)	-Treatment-related costs -Hospital care costs	Length of survival

				Valuation year: 1989	
Reed *et al.* [33] (2004)	US (societal)	CEA, CUA (trial-based economic evaluation)	15 months (discounting not performed)	-Treatment-related costs -Hospital care cost -Primary/community care costs Valuation year: 2000	- SAE avoided - QALY (EQ-5D-3L)
Ross *et al.* [34] (2004)	UK (health care perspective)	CEA (model-based economic evaluation)	4 years (discounting performed for the assessment of treatments for skeletal morbidity: 6% per year for costs, 1% per year for outcomes (SREs).	- Treatment-related costs - Hospital care costs - Primary and community care costs (only for the assessment of skeletal morbidity) Valuation year: 2000/2001	- LYG - SRE avoided
Snedecor *et al.* [35] (2012)	US (third-party payer)	CUA (model-based economic evaluation)	27 months (discounting performed at 3% per year)	- Treatment-related costs - Hospital care costs Valuation year: 2010	QALY (QoL weights taken from the literature)
Snedecor *et al.* [36] (2013)	US (third-party payer)	CUA (model-based economic evaluation)	27 months (discounting performed at 3% per year)	- Treatment-related costs - Hospital care costs Valuation year: 2010	QALY (QoL weights taken from the literature)
Stopeck *et al.* [37] (2012)	US (third-party payer)	CEA, CUA (model-based economic evaluation)	Lifetime (discounting performed at 3% per year)	-Treatment-related costs -Hospital care costs Valuation year: 2011	-SRE avoided -QALY (various including EQ-5D-3L and TTO exercises)
Van den Hout *et al.* [38] (2003)	UK (societal)	CUA (trial-based economic evaluation)	12 months for outcomes (discounting performed at 3% per year)	- Treatment-related costs - Hospital and specialist care costs - Primary/community care costs - Patient payments Valuation year: 2002	QALY (EQ-5D-3L)
Xie *et al.* [39] (2012)	US (third-party payer)	CEA (model-based economic evaluation)	12 months (discounting not applicable)	- Treatment-related costs - Hospital care costs Valuation year: 2011	- SRE avoided - Pathologic fracture avoided

Xie *et al*. [40] (2011)	US (third-party payer)	CEA (model-based economic evaluation)	12 months (discounting performed at 3% per year)	- Treatment-related costs - Hospital care costs - Terminal care costs Valuation year: 2012	SRE avoided
Yfantopoulos *et al.* [41] (2013)	Greece (health care system)	CUA (model-based economic evaluation)	14.5 months for breast cancer; 22.5 months for prostate cancer (discounting not performed); 9 months for other solid tumours (discounting not applicable)	- Treatment-related costs - Hospital care costs Valuation year: 2013	-QALY (QoL weights taken from the literature)
CBA: cost-benefit analysis; CCA: cost consequences analysis; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; EQ-5D: EuroQol 5D; LYG: life-year gained; NICE: National Institute for Health and Care Excellence; SRE: skeletal-related event; QALY: quality-adjusted life year; QoL: quality of life; TTO: time trade-off elicitation method.					

Table 2. Summary of findings reported in the reviewed studies.

Study (year)	Type(s) of primary cancer investigated	Intervention(s) and comparator(s)	Main findings
Andronis *et al.* [18], James *et al.* [29] (2016)	Prostate	Interventions: ZA; Sr89 Comparators: No ZA; No Sr89	-ICER (ZA vs. no ZA): £8,005 per QALY -ZA is less costly and more effective than no ZA if the price of generic ZA is less than £31. -ICER (Sr89 vs. no Sr89): £16,884 per QALY gained.
Botteman *et al.* [19] (2006)	Breast	Interventions: ibandronate (oral or intravenous); ZA; pamidronate; clodronate (oral). Comparator(s): placebo	-ZA vs no therapy: cost savings of £2,267 and 0.205 additional QALYs. -Oral ibandronate vs. placebo: cost savings of £2,114 and 0.185 additional QALYs. - ICER (pamidronate vs. placebo): £584 per QALY gained. - ICER (intravenous ibandronate vs. placebo): £2,370 per QALY gained.
Botteman *et al.* [20] (2011)	Renal cancer	Intervention: ZA Comparator: placebo	- ZA vs placebo: cost savings and additional SREs avoided in all countries considered. - ZA vs placebo: cost savings and additional QALYs in all countries considered.
Carter *et al.* [21] (2011)	Prostate	Intervention: ZA Comparator(s): placebo	- ICER (France, ZA vs placebo): €36,007 per QALY gained. -ICER (Germany, ZA vs placebo): €23,582 per QALY gained. -ICER (Portugal, ZA vs placebo): €8,655 per QALY gained. -ICER (Netherlands, ZA vs placebo): €2,430 per QALY gained.
Collinson *et al.* [22] (2016)	Breast, prostate, lung	Intervention: single-fraction EBR Comparators: multi-fraction EBR; analgesia (in a secondary analysis)	Single-fraction EBR was less costly and more effective than multi-fraction EBR.
De Cock *et al.* [23] (2005)	Breast (patients receiving oral hormonal therapy)	Intervention(s): pamidronate (oral) Comparator(s): ZA (intravenous); pamidronate (generic, intravenous).	-Oral ibadronate vs. intravenous ZA: cost savings of £307and 0.018 additional QALYs. -Oral ibadronate vs. intravenous generic pamidronate: cost savings of £158 and 0.019 additional QALYs.
De Cock *et al.* [24] (2005)	Breast (patients receiving chemotherapy)	Intervention: pamidronate (oral) Comparators: ZA (intravenous); pamidronate (generic, intravenous)	-Oral ibadronate vs. intravenous ZA: cost savings of £386 and 0.019 additional QALYs. -Oral ibadronate vs. intravenous generic pamidronate: cost savings of £224 and 0.02 additional QALYs.
Dranitsaris and Hsu [25] (1999)	Breast	Intervention: pamidronate Comparator: placebo	ICER (pamidronate vs. placebo): CAN $18,700 per QALY gained.

Ford *et al.* [26] (2013)	Breast, prostate, lung, other solid tumours	Intervention: denosumab Comparator: ZA	*Breast cancer:* - ICER (denosumab vs ZA, without PAS): £245,264 per QALY gained. - Denosumab vs ZA (with PAS): cost savings and additional QALYs. *Prostate cancer:* - ICER (denosumab vs ZA, without PAS): £111,603 per QALY gained. - Denosumab vs ZA (with PAS): cost savings and additional QALYs. *Lung cancer:* - ICER (denosumab vs ZA, without PAS): £110,671 per QALY gained. - ICER (denosumab vs ZA, with PAS): £12,743 per QALY gained. *Other solid tumours:* - ICER (denosumab vs ZA, without PAS): £139,739 per QALY gained. - ICER (denosumab vs ZA, with PAS): £9,004 per QALY gained.
Gessner *et al.* [27] (2000)	Breast, multiple myeloma, other cancer types	Intervention(s): pamidronate 60mg Comparator(s): pamidronate 90mg	- Average total cost (for both treatments): ECU 12,060 +/- 4,380 - Change in pain intensity compared to baseline value (pamidronate 60mg): -36%. - Reduction in pain intensity compared to baseline value (pamidronate 90mg): -15%.
Hillner *et al.* [28] (2000)	Breast	Intervention: pamidronate (given with either hormonal systemic therapy or chemotherapy) Comparator: placebo	-ICER (pamidronate plus chemotherapy vs. placebo): US $3,940 per SRE avoided. - ICER (pamidronate plus chemotherapy vs. placebo): US $108,200 per QALY gained. -ICER (pamidronate plus hormonal systemic therapy vs. placebo): US $7,685 per SRE avoided. - ICER (pamidronate plus hormonal systemic therapy vs. placebo): US $305,300 per QALY gained.
Joshi *et al.* [30] (2011)	Lung	Intervention: ZA Comparator: placebo	- ZA vs placebo (Germany, UK and Portugal): costs savings and additional QALYs. - ICER (ZA vs placebo; France): €786 per QALY gained. -ICER (ZA vs placebo; Netherlands): €8278 per QALY gained.
Konski [31] (2004)	Prostate	Interventions: chemotherapy only (mitoxantrone plus prednisolone); single-fraction EBR; multi-fraction EBR. Comparator: BSC (pain medications only)	-ICER (single-fraction EBR vs. BSC): US $6857 per QALY gained. -ICER (multiple-fraction EBR vs. BSC): US $36,000 per QALY gained. -ICER (single-fraction EBR vs. multiple fraction EBR) (calculated)[a]: US $8,667 per QALY gained. -Chemotherapy is more costly and less effective than all other options.

McEwan *et al.* [32] (1994)	Prostate	Intervention: Sr89 (Metastron®) Comparator: placebo	-Cost per week survival (Metastron® vs. placebo): cost savings of CAN $209.
Reed *et al.* [33] (2004)	Prostate	Intervention: ZA Comparator: placebo	-ICER (ZA vs placebo): US $12,300 per SRE avoided. -ICER (ZA vs placebo): US $51,400 per additional patient free of SRE. -ICER (ZA vs placebo): US $159,200 per QALY gained.
Ross *et al.* [34] (2004)	Breast, multiple myeloma	Intervention(s): pamidronate (30mg, 60mg and 90mg); clodronate (1500mg); ZA (4mg and 8mg); ibandronate (2mg, 4mg, 6mg) Comparator(s): no bisphosphonate treatment	*Breast cancer:* - ICER (treatment of hypecalcaemia, ZA 8mg vs no bisphosphonate treatment): £17,100 per LYG - ICER (prevention of skeletal morbidity, ZA vs no bisphosphonate therapy): £250 per SRE avoided. *Multiple myeloma:* - ICER (prevention of skeletal morbidity, ZA vs no bisphosphonate therapy): £1,497 per SRE avoided.
Snedecor *et al.* [35] (2012)	Breast	Intervention: denosumab Comparator: ZA	-ICER (denosumab vs. ZA): US $697,499 per QALY gained.
Snedecor *et al.* [36] (2013)	Prostate	Intervention: denosumab Comparator(s): ZA	-ICER (denosumab vs. ZA): US $1,058,741 per QALY gained.
Stopeck *et al.* [37] (2012)	Prostate, breast, lung	Intervention: denosumab Comparator: ZA	*Prostate cancer* -ICER (denosumab vs ZA): US $49,405 per QALY gained. -ICER US $8,567 per SRE avoided. *Breast cancer* -ICER (denosumab vs ZA): US $78,915 per QALY gained. -ICER (denosumab vs ZA): US $13,557 per SRE avoided. *Lung cancer* - ICER (denosumab vs ZA): US $67,931 per QALY gained. - ICER (denosumab vs ZA): US $13,557 per SRE avoided.
Van den Hout *et al.* [38] (2003)	Breast, lung, prostate, other	Intervention: single-fraction EBR Comparator(s): multiple-fraction EBR (six fractions)	Single-fraction EBR was less costly and more effective than multi-fraction EBR.
Xie *et al.* [39] (2012)	Breast	Intervention: denosumab Comparator: ZA	-ICER (denosumab vs. ZA): US $114,628 per SRE avoided. -ICER (denosumab vs. ZA): US $290,136 per pathological fracture avoided.
Xie *et al*. [40] (2011)	Prostate	Intervention: denosumab Comparator: ZA	-ICER (denosumab vs. ZA, 12 months): US $71,027 per SRE avoided. -ICER (denosumab vs. ZA, 36 months): US $51,319 per SRE avoided.

Yfantopoulos *et al.* [41] (2013)	-Breast, prostate, other solid tumours (not specified)	Intervention: denosumab Comparator: ZA	*Breast cancer* -ICER (denosumab vs ZA): €56,818 per QALY gained. *Prostate cancer:* -ICER (denosumab vs ZA): €61,296 per QALY gained. Other solid tumours - ICER (denosumab vs ZA): €80,830 per QALY gained.

[a] Calculated on the basis of information given in the article.

BSC: best supportive care; EBR: external beam radiotherapy; ECU: European Currency Unit; ICER: incremental cost effectiveness ratio; LYG: life-year gained; NICE: National Institute for Health and Care Excellence; OST: other solid tumours; PAS: patient-access scheme; QALY: quality-adjusted life year; Sr89: strontium-89; TTO: time trade-Off elicitation method; ZA: zoledronic acid.

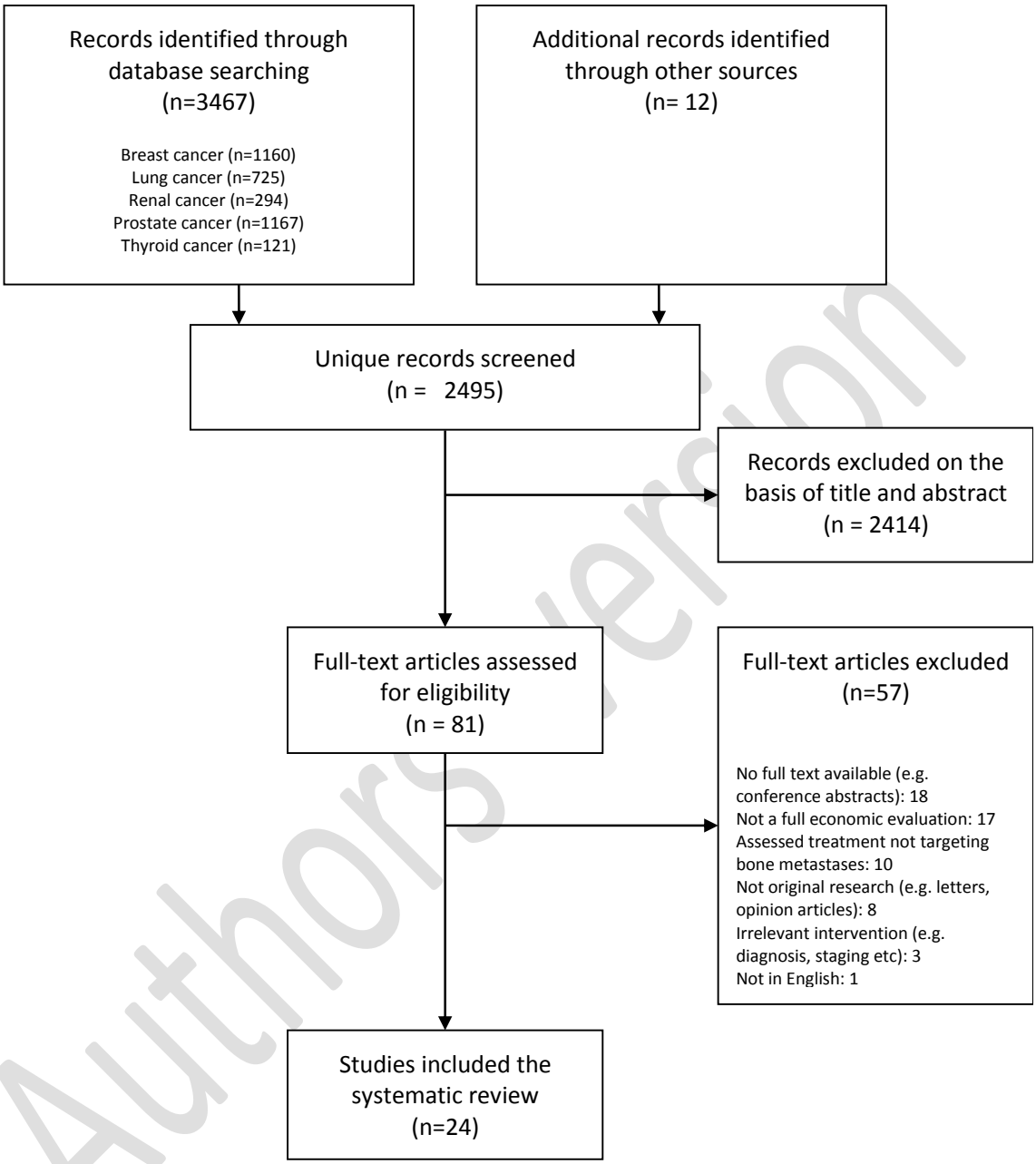
Table 3. Answers to the Consensus on Health Economic Criteria (CHEC) checklist [17]

Study	Item																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Andronis *et al.* [18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Botteman *et al.* [19]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N	N*	N
Botteman *et al.* [20]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N*	N
Carter *et al.* [21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	N*	N
Collinson *et al.* [22]	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
De Cock *et al.* [23]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	N*	N
De Cock *et al.* [24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
Dranitsaris & Hsu [25]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y	N	N*	N
Ford *et al.* [26]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
Gessner *et al.* [27]	Y	Y	Y	U	N	Y	U	Y	Y	Y	Y	Y	N	N/A	U	Y	N	N*	N
Hillner *et al.* [28]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	U	Y	N	Y	Y	N	Y	N
James *et al.* [29]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
Joshi *et al.* [30]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N*	N
Konski [31]	Y	Y	Y	Y	Y	Y	U	Y	U	U	U	Y	Y	N	Y	Y	N	N	Y
McEwan *et al.* [32]	Y	Y	Y	Y	Y	U	N	Y	Y	N	Y	Y	Y	N	N	Y	N	Y	N
Reed *et al.* [33]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	U	U	Y	Y	N*	N
Ross *et al.* [34]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Snedecor *et al.* [35]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
Snedecor *et al.* [36]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
Stopeck *et al.* [37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
van den Hout *et al.* [38]	Y	Y	Y	U	U	Y	U	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	N
Xie *et al.* [40]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N*	N
Xie *et al.* [39]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N*	N
Yfantopoulos *et al.* [41]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	N*	N

Y: Yes; N: No; U: Unclear; N/A: Not applicable.
* Funding sources and potential conflicts of interests are acknowledged.

Item 1: Is the study population clearly described? Item 2: Are competing alternatives clearly described? Item 3: Is a well-defined research question posed in answerable form? Item 4: Is the economic study design appropriate to the stated objective? Item 5: Is the chosen time horizon appropriate to include relevant costs and consequences? Item 6: Is the actual perspective chosen appropriate? Item 7: Are all important and relevant costs for each alternative identified? Item 8: Are all costs measured appropriately in physical units? Item 9: Are costs valued appropriately? Item 10: Are all important and relevant outcomes for each alternative identified? Item 11: Are all outcomes measured appropriately? Item 12: Are outcomes valued appropriately? Item 13: Is an incremental analysis of costs and outcomes of alternatives performed? Item 14: Are all future costs and outcomes discounted appropriately? Item 15: Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis? Item 16: Do the conclusions follow from the data reported? Item 17: Does the study discuss the generalizability of the results to other settings and patient/ client groups? Item 18: Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)? Item 19: Are ethical and distributional issues discussed appropriately?

Figure 1. PRISMA flowchart



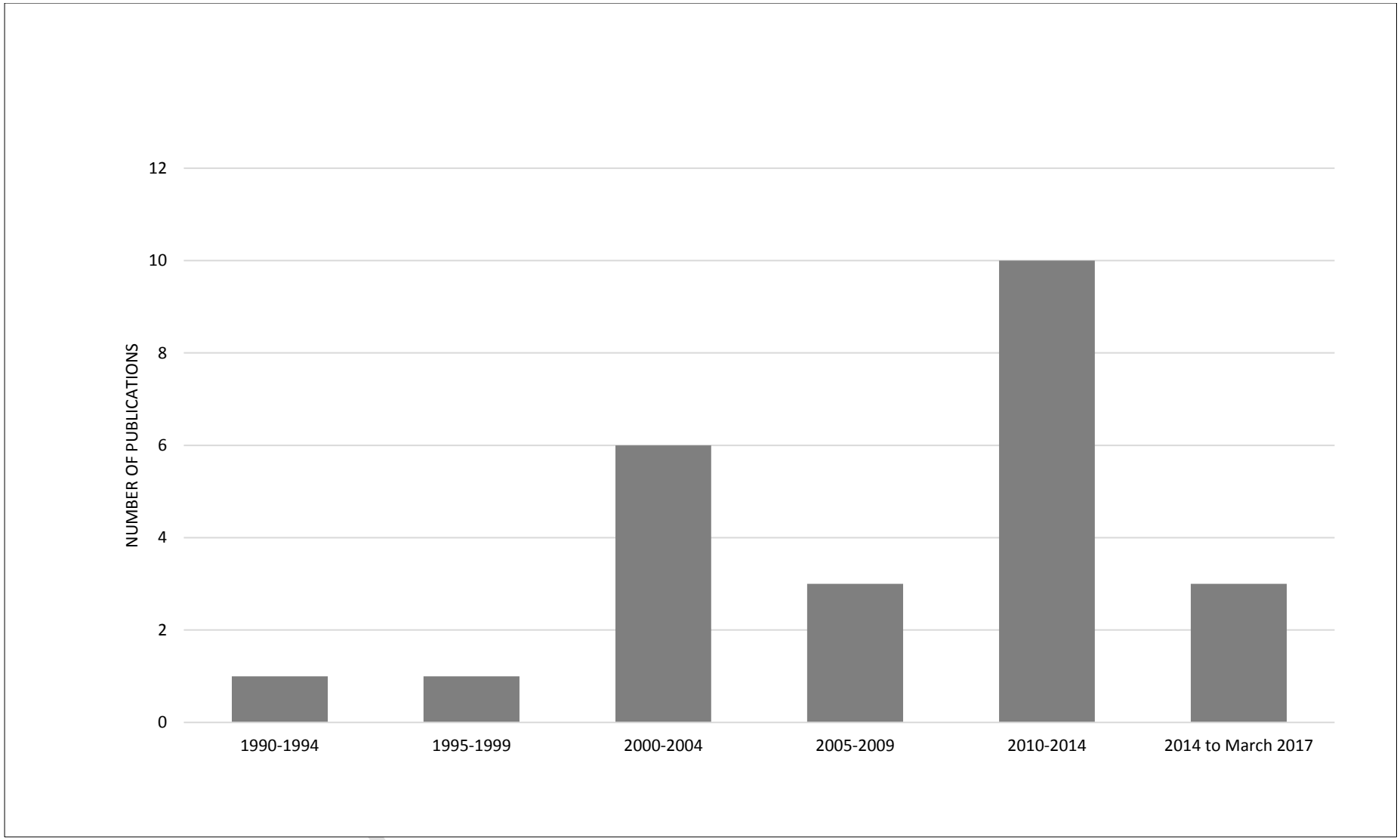


Figure 2. Identified studies by type of primary cancer investigated.

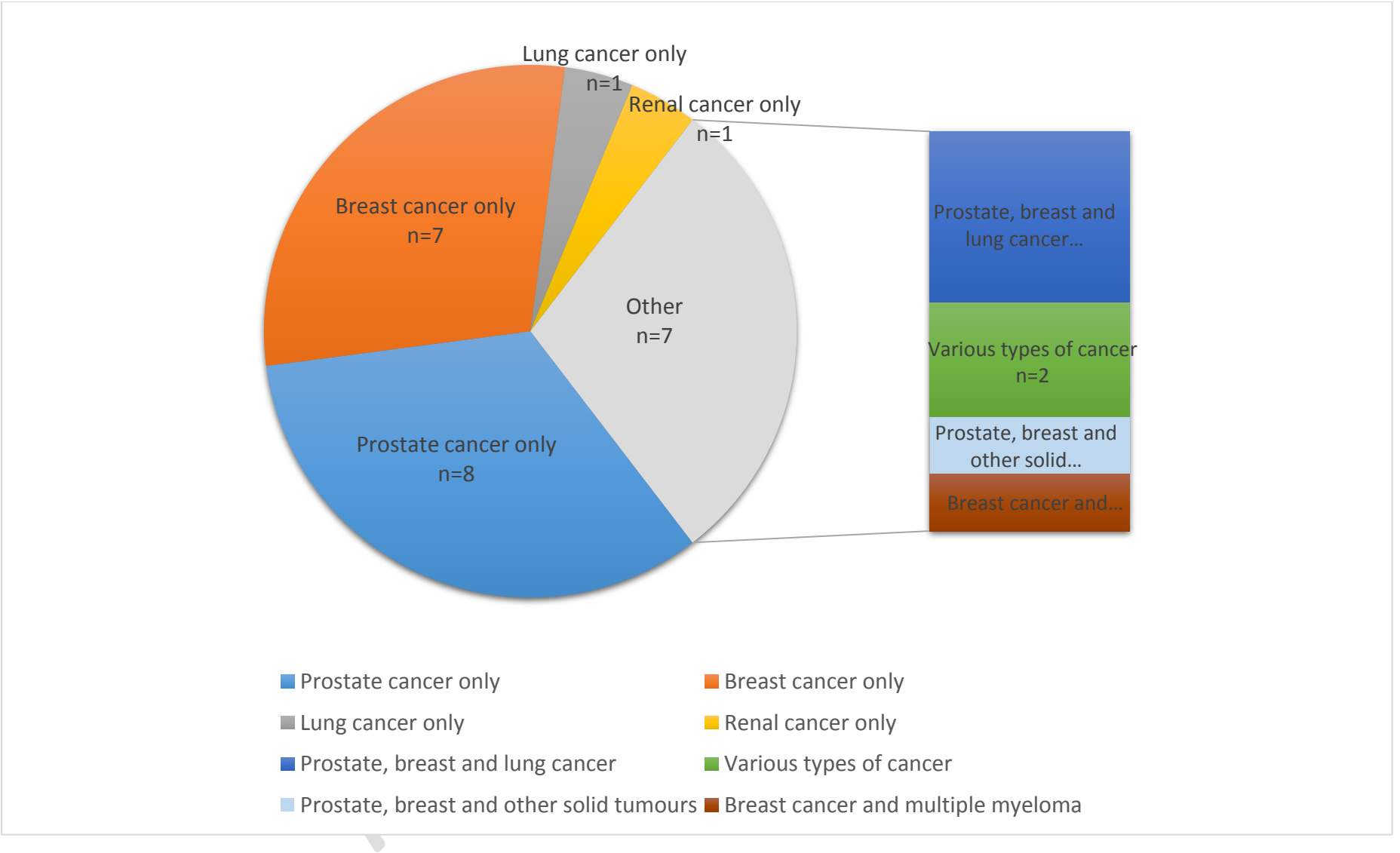


Figure 3. Identified studies by publication year.

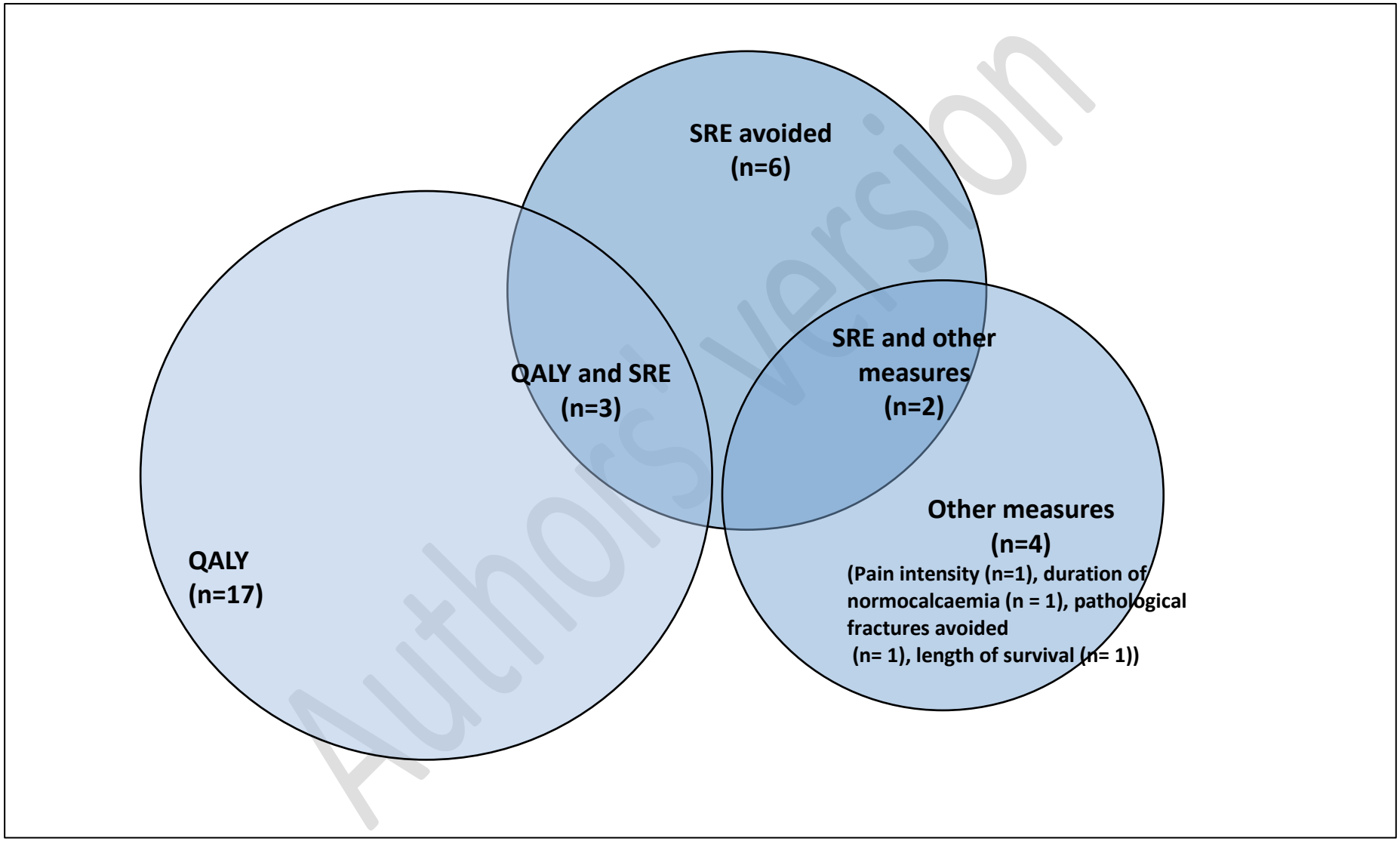


Figure 4. Identified studies by measures of outcomes.