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REVIEW ARTICLE

Denosumab versus zoledronic acid for bone metastases in *castration*-resistant prostate cancer: A systematic review and meta-analysis

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Abstract

Introduction: Bone metastases are a hallmark of castration-resistant prostate cancer (CRPC), occurring in approximately 84% of patients. These metastases result in severe skeletal-related events (SREs), such as pathological fractures, spinal cord compression, and the need for radiation therapy or surgery.

Objective: This meta-analysis evaluates the impact of bisphosphonates (zoledronic acid [ZA]) and receptor activator of nuclear factor-κB ligand-inhibitors (denosumab) as adjunctive therapies for patients with prostate cancer who have developed bone metastases.

Methods: A systematic and rigorous methodology was followed by adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines to ensure transparency and reliability. A comprehensive search was conducted across medical databases and relevant publications to identify studies comparing denosumab and ZA in managing skeletal complications in patients with CRPC. Inclusion criteria required studies to report outcomes such as SREs, symptomatic skeletal events (SSEs), bone metastasis-free survival (BMFS), progression-free survival (PFS), adverse events, and cost implications. Data extraction was performed using standardized templates to collect demographic, clinical, and economic data.

Results: The meta-analysis demonstrated that denosumab was superior to ZA in reducing SREs and SSEs in patients with CRPC. The total incidence of SREs was significantly lower with denosumab (40.7%) compared to ZA (59.3%, p=0.009). Similarly, the incidence of SSEs was reduced to 47.2% with denosumab, compared to 52.8% with ZA (p=0.029). In addition, denosumab extended BMFS by 4.2 months (33.2 vs. 29.5 months, p=0.031) and PFS by 2.4 months (21.7 vs. 19.3 months, p=0.027). However, overall survival was comparable between the two treatments. Adverse events were slightly more frequent with denosumab (93.1% vs. 91.4%), as well as higher rates of hypocalcemia (2.2% vs. 1.46%) and osteonecrosis of the jaw (ONJ) (2.8% vs. 2.41%).

Conclusion: This meta-analysis demonstrates that denosumab is superior to ZA in reducing the incidence and delaying the onset of SREs and SSEs in patients with CRPC and bone metastases. Denosumab also extends BMFS, providing an additional clinical advantage. However, these benefits come with a higher risk of adverse events such as hypocalcemia and ONJ, as well as significantly increased costs. While ZA remains an effective treatment, denosumab may be the preferred option for patients at higher risk of SREs or those who can tolerate its adverse effects and cost.

Keywords: Castration-resistant prostate cancer; Bone metastases; Skeletal-related events; Symptomatic skeletal events

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1. Introduction

Prostate cancer (PC) is the second most prevalent cancer among men worldwide, with more than 1.4 million new cases diagnosed in 2020.[1,2] The prognosis for metastatic PC is particularly poor, which was evidenced by a 5-year survival rate of only 30%.[3] The progression to castration-resistant prostate cancer (CRPC) with bone metastases further exacerbates the prognosis.[4,5] The transition from PC into CRPC represents a pivotal shift, characterized by bone metastases that significantly impair patient outcomes. Notably, over 84% of CRPC patients develop metastases, with an average survival of just 14 months post-diagnosis.[6] CRPC with bone metastases is marked by aggressive biological behavior and intricate therapeutic challenges, which distinguish it from PC with bone metastases. The development of resistance to hormonal therapy in CRPC necessitates specialized management strategies to mitigate the heightened risk of skeletal-related events (SREs) and preserve quality of life.[7] The regulatory approval of bone-targeted agents such as zoledronic acid (ZA) and denosumab is supported by their proven effectiveness in reducing the frequency of SREs.[8,9] Bisphosphonates, first discovered in the 1980s, and denosumab are the primary categories of bone-targeting drugs. Continuous refinements in bisphosphonates have led to the development of ZA, which has shown superior efficacy in preventing SREs in multiple myeloma and various solid tumors, as well as providing notable survival benefits.[10,11] ZA was the preferred medication for nearly a decade in preventing skeletal complications related to bone metastases.[12,13] However, its use has been limited by side effects such as renal impairment and acute-phase reactions.[14]

In recent years, denosumab has emerged as a promising alternative in treating bone metastases. This monoclonal antibody exerts its therapeutic effect by binding to the receptor activator of nuclear factor-κB ligand (RANKL) and obstructing its interaction with the RANK receptor, thereby inhibiting bone resorption.[15,16] Both denosumab and ZA have been recognized for their ability to delay SREs in CRPC patients.[17] The reduction of skeletal-related morbidity remains a vital objective of palliative and life-prolonging therapy in metastatic CRPC.

Skeletal involvement in metastatic CRPC (mCRPC) is a significant clinical challenge, with bone metastases occurring in approximately 90% of end-stage cases. This condition leads to a high incidence of SREs, which include pathological fractures, spinal cord compression, and severe bone pain, all of which contribute to increased morbidity and mortality.[18] The interaction between PC cells and the bone microenvironment facilitates disease progression within the bone, exacerbating the severity of SREs.[19] The problems associated with mCRPC and bone metastases are multifaceted. They not only reduce patients' quality of life due to pain and other complications but also pose challenges in treatment due to the lack of validated predictive biomarkers for therapeutic decision-making.[20] Furthermore, while the incidence of mCRPC has remained relatively stable, its prevalence has increased, indicating that patients are living longer with the disease. This trend underscores the need for effective management strategies to improve long-term outcomes. Further research is necessary to comprehensively assess the efficacy and safety of these denosumab and ZA, as well as their impact on the quality of life of surviving patients undergoing treatment.[21]

Consequently, this systematic review aimed to evaluate the impact of bisphosphonates (ZA) and RANKL-inhibitors (denosumab) as adjunctive therapies for patients with PC who have developed bone metastases.

2. Methods

The study was designed with a clear and structured research question, aligned with the Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) framework. This framework defines the scope of the study, focusing on the comparative effectiveness of denosumab and ZA in managing SREs in patients with CRPC.

By formulating a focused research question and applying the PICOS framework, the study adhered to Preferred Reporting Items for a Systematic Review and Meta-Analysis (PRISMA's) emphasis on clarity and systematic planning. The PRISMA reporting criteria were followed in this systematic review.[22]

2.1. Search strategy

A literature search was conducted using MEDLINE, the Cochrane Collaboration Library, EMBASE, and Web of Science from January 2014 to January 2024, with the following keywords: "denosumab," "zoledronic acid," "bone metastases," "castration-resistant prostate cancer," or a combination of these terms. Publications were also identified by manually searching the reference lists of selected studies. There were no restrictions on population type and size, time, period, or language. The reference lists of all relevant articles were also searched for additional information.

2.2. Criteria for study selection

Using the PICOS framework, a systematic literature search was carried out:

- Population: Patients with CRPC, including those with and without bone metastases.

- Intervention: Denosumab, a RANKL-inhibitor, administered to prevent SREs and manage bone metastases.
- Comparison: ZA, a bisphosphonate commonly used to manage bone complications in CRPC patients.
- Outcomes: The incidence of SREs, symptomatic skeletal events (SSEs), bone metastasis-free survival (BMFS), progression-free survival (PFS), adverse events, and cost implications.
- Study design: Both randomized controlled trials (RCTs) and observational studies, following PRISMA guidelines to ensure methodological rigor and transparency.

2.2.1. Inclusion criteria

The identified studies were included in the subsequent meta-analyses if they met the following criteria: (1) they were RCTs; (2) they compared denosumab and ZA for CRPC; (3) they involved human patient populations, and (4) they had no limitations on ethnicity, gender, age, or language. To ensure comprehensive data collection, multiple reports containing overlapped datasets were included. However, when multiple reports on the same study were identified, only the one with the most complete dataset was included.

2.2.2. Exclusion criteria

All studies that did not meet the inclusion criteria were excluded from the study. In addition, reviews, meta-analysis, encyclopedias, letters to the editor, animal studies, case series, and case reports were excluded from the study. All participants with primary bone tumors, a history of previous orthopedic surgical intervention, or those who had undergone non-surgical procedures were also excluded from the study.

2.3. Data extraction and management

Two independent researchers applied the search strategy to identify papers that met the inclusion criteria based on their titles and abstracts. Any disagreements were settled through consensus or by consulting a third researcher. After selecting the abstracts, four investigators carried out a comprehensive review of the papers.

Each study was assessed according to the following criteria: (i) reference information, including authorship(s), publication status (published or unpublished), year of publication, investigation time frame, and other relevant references; (ii) study characteristics, such as research design, subject matter, follow-up duration, and treatment period, (iii) population characteristics including age, Eastern Cooperative Oncology Group (ECOG) scores, Gleason scores, and prostate-specific antigen (PSA) levels; (iv) interventions, such as dosing schedules and treatment duration for denosumab and ZA; (v) principal findings, including incidence and timing of SREs and SSEs, BMFS, PFS, overall survival (OS), and adverse events; and (vi) economic data, including costs related to treatment, administration, and skeletal complications.

2.4. Quality assessment

The quality of the included studies was assessed according to the PRISMA guidelines. Specifically, the studies were evaluated for selection bias, performance bias, detection bias, attrition bias, and reporting bias. The risk of bias for all included studies was assessed using the Cochrane risk of bias assessment tool.

3. Results

This systematic review examines studies on human subjects from various literatures collected from medical databases, focusing on patients with CRPC. The review analyzes existing data to determine the superiority of denosumab over ZA in preventing SREs associated with bone metastases. Six literatures that met the inclusion criteria were included in this review, as illustrated in the PRISMA diagram (Figure 1) below.

In this study, data from six published studies included a total of 7089 CRPC patients, 16.5% of whom had bone metastases. Among them, 3533 patients (49.8%) were treated with ZA, while 3556 patients (50.2%) received denosumab for the prevention of SREs (Table 1).

The mean age was similar in both groups: 72.58±1.91 years in the ZA group and 72.38±2.05 years in the denosumab group. Both groups were age-matched, with a median age of 72 years. Most patients were over 65 years, with 80% in the ZA group and 78% in the denosumab group (Table 2).

Most patients had an ECOG score of <2% in both the ZA and denosumab groups as in Table 3. The two groups were similar in ECOG scores (p>0.05). The Gleason scores were also comparable between the ZA and denosumab groups: 39.5% and 37% had scores between 2 and 6, 29% in both groups had a score of 7, and 36.5% and 37% had scores between 8 and 10, respectively.

The average PSA levels were similar in both groups (p>0.05). In most cases (85%), PSA levels exceeded 10 µg/L in the two groups, with no statistically significant difference between them (Table 4).

SREs were observed between 41.2 and 73.2 months after CRPC diagnosis in the ZA group, with a mean of 57.2 months, and between 37.5 and 73.2 months in the denosumab group, with a mean of 55.35 months as shown

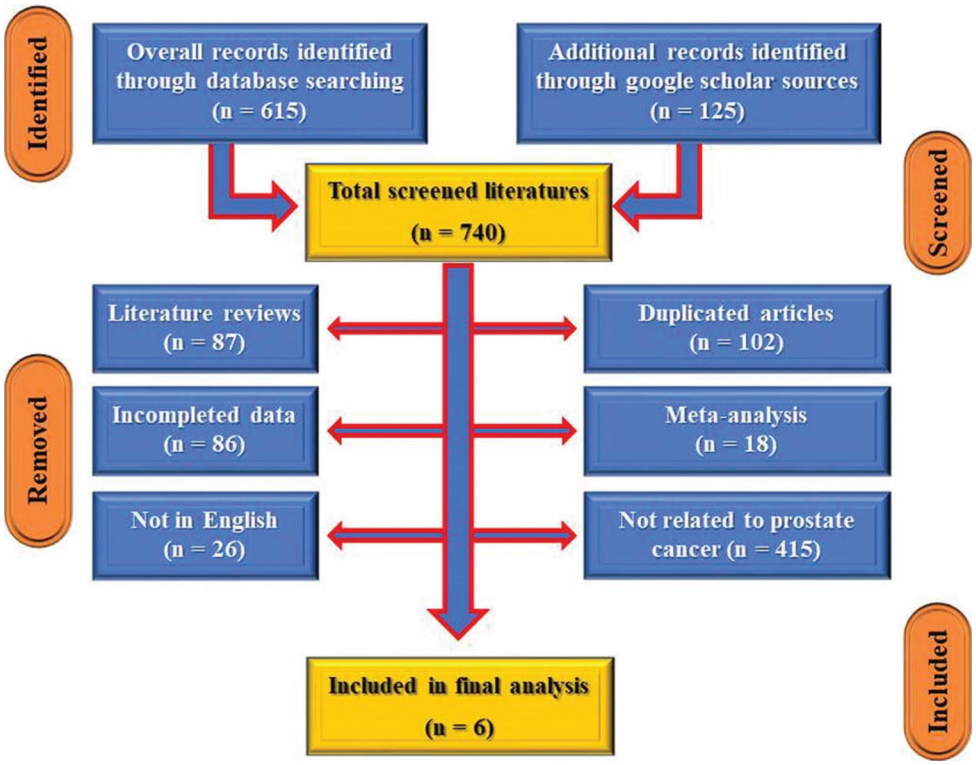


Figure 1. PRISMA flow diagram illustrating the study selection process
Abbreviation: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

in Table 5. The occurrence of SREs was similar between both groups (p>0.05).

The most common SREs reported in the reviewed literature were spinal cord compression, bone radiation, pathological fractures, bone surgery, and bone metastasis (Table 6). Overall, their incidence was significantly lower in patients treated with denosumab (40.7%) compared to those treated with ZA (59.3%), with a statistically significant difference (p=0.009).

The most common SSEs in the reviewed literatures were spinal cord compression, bone radiation, chemotherapy, pathological fractures, bone surgery, anemia, renal dysfunction, and visceral metastasis as in Table 7 below. The total incidence of SSEs was significantly lower in patients treated with denosumab (47.2%) compared to those treated with ZA (52.8%), with a statistically significant difference (p=0.029).

The first occurrence of bone metastasis was observed at 29.5 months in the ZA group, whereas it appeared later at 33.2 months in the denosumab group (p=0.031). BMFS was significantly longer in the denosumab group than in the ZA group (p=0.033). In addition, PFS was longer in the denosumab than in the ZA group (p=0.027). However, the OS was similar in both groups (p>0.05) (Table 8).

The average incidence of adverse events was slightly higher in the denosumab group (93.1%) than in the ZA group (91.4%). The serious events were more frequent in the denosumab group, with a statistically significant difference (p=0.036). However, the total number of adverse events showed no statistically significant difference between the ZA and denosumab groups (47.2% and 52.8%, respectively; p>0.05) as in Table 9.

Regression analysis of SREs after treatment with ZA and denosumab in the literatures showed a statistically significant decrease in the incidence of events in the denosumab group compared to the ZA group (p<0.001) (Table 11, Figure 2 and 3).

Regression analysis of SSEs after treatment with ZA and denosumab in the literatures showed a statistically highly significant difference between the denosumab and ZA groups (p<0.001). Denosumab resulted in fewer SSEs than ZA (Table 12, Figure 4 and 5).

Regression analysis of adverse events after treatment with ZA and denosumab in the literatures showed no statistically significant difference between denosumab and ZA groups (p=0.158). Both groups had similar adverse events (Table 13, Figure 6 and 7).

Regression analysis of cost effectiveness after treatment with ZA and denosumab in the literatures showed a

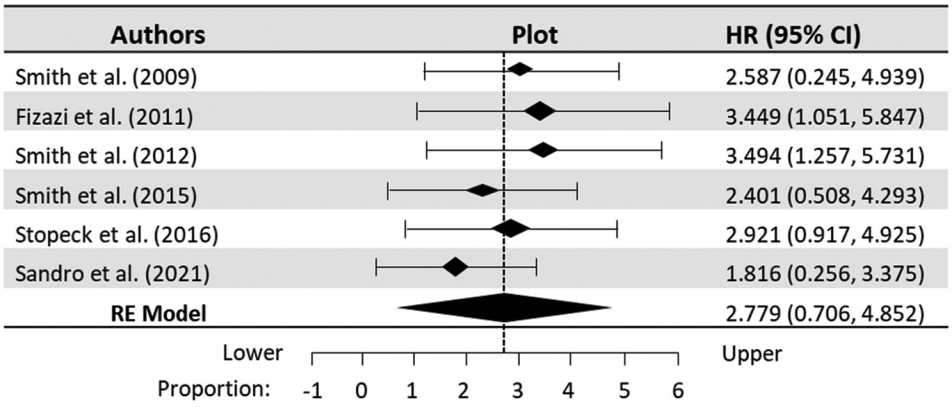


Figure 2. Forest plot for postoperative SREs among ZA- and denosumab-treated groups. Pooling of studies using a RE model with a 95% CI showed considerable heterogeneity (I^2=93.9%) and a statistically highly significant difference (p<0.001) in the longitudinal comparison between the ZA and denosumab groups. Denosumab was associated with fewer SREs than ZA.
Abbreviations: SREs: Skeletal-related events; ZA: Zoledronic acid; CI: Confidence interval; HR: Hazard ratio; RE: Random effects.

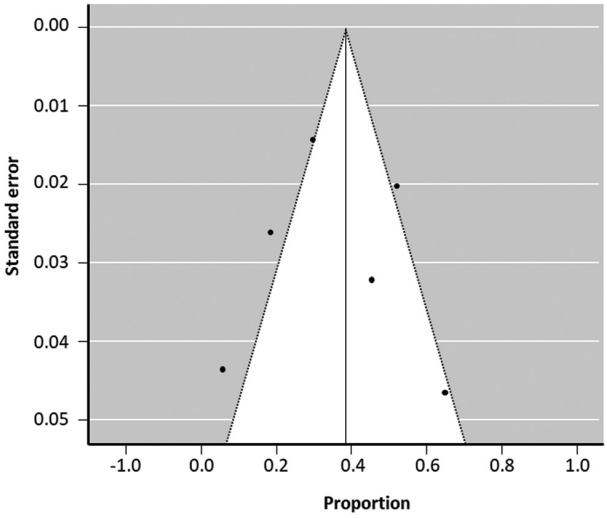


Figure 3. Funnel plot for SREs in the reviewed literatures comparing ZA and denosumab groups. There is no evidence of publication bias, as indicated by a symmetrical funnel plot. The rank correlation test and regression analysis for funnel plot asymmetry were statistically significant (r=0.9251, p<0.001) between the two groups.
Abbreviations: SREs: Skeletal-related events; ZA: Zoledronic acid.

Table 1. Summary of demographics in screened literatures

Authors	Total (no.)	ZA		Denosumab		Metastasis	
		No.	%	No.	%	No.	%
Smith *et al.* (2009)	1,468	734	50	734	50	13	0.89
Fizazi *et al.* (2011)	1,901	951	50	950	50	512	26.9
Smith *et al.* (2012)	1,432	716	50	716	50	110	7.68
Smith *et al.* (2015)	1,901	951	50	950	50	436	22.9
Stopeck *et al.* (2016)	281	128	45.6	153	54.4	78	27.8
Sandro *et al.* (2021)	106	53	50	53	50	19	17.9
Total	7,089	3,533	49.8	3,556	50.2	1168	16.5

Abbreviations: ZA: Zoledronic acid.

Table 2. Age distribution of the studied literatures

Age (years)	ZA	Denosumab	Total average
Minimum mean	71	70	70
Maximum mean	75.5	75.3	75.5
Total mean	72.58	72.38	72.48
±SD	1.91	2.05	1.98
Total median	72	72	72
>65 years (%)	80	78	79
<65 years (%)	20	22	21

Abbreviations: ZA: Zoledronic acid; SD: Standard deviation.

statistically significant increase in the cost of denosumab compared to ZA (p=0.015) (Table 14, Figure 8 and 9).

Regression analysis of patient age after treatment with ZA and Denosumab in the literatures showed no statistically significant difference in age between the denosumab and ZA groups (p=0.261) (Table 15, Figure 10).

4. Discussion

Bone metastases significantly contribute to the morbidity and mortality associated with PC, affecting nearly all individuals with advanced or fatal forms of the disease. For many patients, the bone is the primary or sole site of metastatic spread. These metastases impose a considerable health and economic burden, which lead to SREs such as pathological fractures, spinal cord compression, severe pain, and the necessity for interventions such as radiation therapy or surgical procedures. Addressing and preventing the onset of bone metastases remains a critical unmet need in the management of PC.[23]

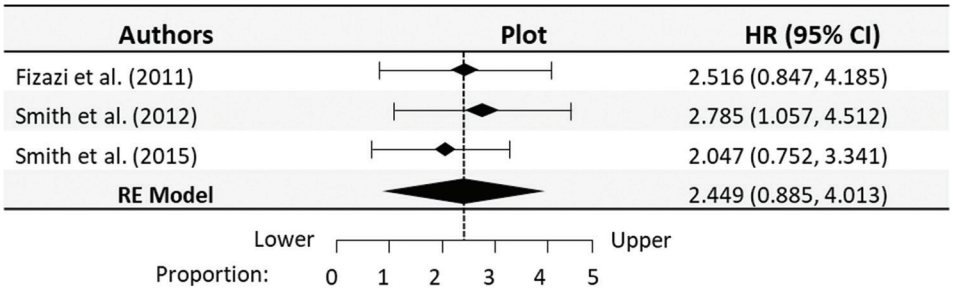


Figure 4. Forest plot for postoperative SSEs among ZA- and denosumab-treated groups. Pooling of studies using a RE model with a 95% CI showed considerable heterogeneity (I^2=84.7%) and a statistically highly significant difference (p<0.001) in the longitudinal comparison between the ZA and denosumab groups.
Abbreviations: SSEs: Symptomatic skeletal events; ZA: Zoledronic acid; CI: Confidence interval; HR: Hazard ratio; RE: Random effects.

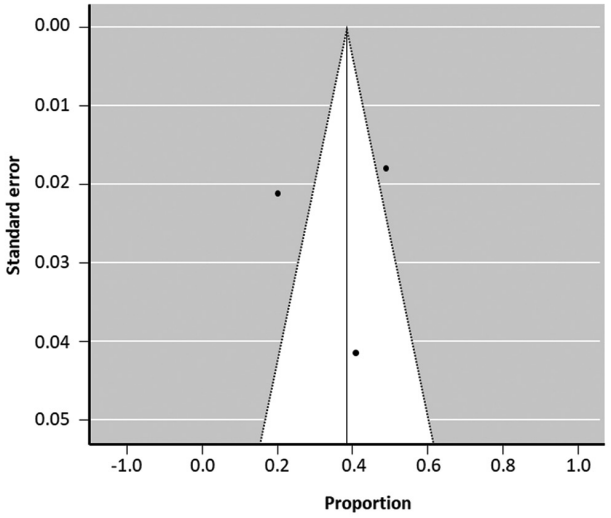


Figure 5. Funnel plot for SSEs in the reviewed literatures comparing ZA and denosumab groups. There is no evidence of publication bias, as indicated by a symmetrical funnel plot. The rank correlation test and regression analysis for funnel plot asymmetry were statistically not significant (r=0.0253, p>0.05) between the two groups.
Abbreviations: SSEs: Symptomatic skeletal events; ZA: Zoledronic acid; r: Correlation coefficient.

Table 3. ECOG and Gleason scores in both groups

ECOG score	ZA		Denosumab		Significance	
	Mean	±SD	Mean	±SD	t	*p*
<2%	95.52	5.09	95.66	4.63	0.001	0.995
≥2%	4.48	0.09	4.34	0.11	0.097	0.597
Gleason score	**No.**	**%**	**No.**	**%**		
2 – 6	306	39.5	290	37	0.091	0.621
7	280	29	273	29	0.000	0.999
8 – 10	311	36.5	315	37	0.031	0.835
Missing	76	9.19	92	11	0.662	0.416

Note: p>0.05: Not significant.
Abbreviations: ZA: Zoledronic acid; t: Unpaired t-test; SD: Standard deviation; ECOG: Eastern cooperative oncology group.

Table 4. PSA levels in both groups

PSA (µg/L)	ZA		Denosumab		Significance	
	Mean	±SD	Mean	±SD	t	*p*
Average	29.2	2.67	27.9	2.65	0.101	0.513
	No.	**%**	**No.**	**%**		
<10	145	15	145	15	0.000	1.000
≥10	806	85	805	85	0.000	0.999

Note:p>0.05: Not significant.
Abbreviations: ZA: Zoledronic acid; PSA: Prostate-specific antigen; SD: Standard deviation.

As a result, this meta-analysis was conducted to compare the effectiveness of ZA and denosumab in managing bone metastases among patients with CRPC. The study aims to determine which treatment better prevents SREs and SSEs, while also considering survival rates, adverse events, and cost implications.

In terms of demographics and clinical characteristics, this meta-analysis included six pivotal studies that collectively analyzed data from 7089 patients with CRPC. Of these, 49.8% were treated with ZA, while 50.2% received denosumab. According to the studies, 16.5% of the patients exhibited bone metastases. The average age was approximately 72.5 years, with the majority (79%) being over 65 years. Both treatment groups were well-matched in baseline characteristics, such as ECOG performance scores and Gleason scores, ensuring homogeneity across the studies. For instance, Smith *et al.*[24] and Fizazi *et al.*[25] reported that over 70% of their study cohorts had an ECOG score below 2, and comparable Gleason score distributions across treatment arms.

In term of SREs, this meta-analysis showed that denosumab consistently outperformed ZA in reducing SREs across all studies. The total incidence of SREs was significantly lower in the denosumab group (40.7%)

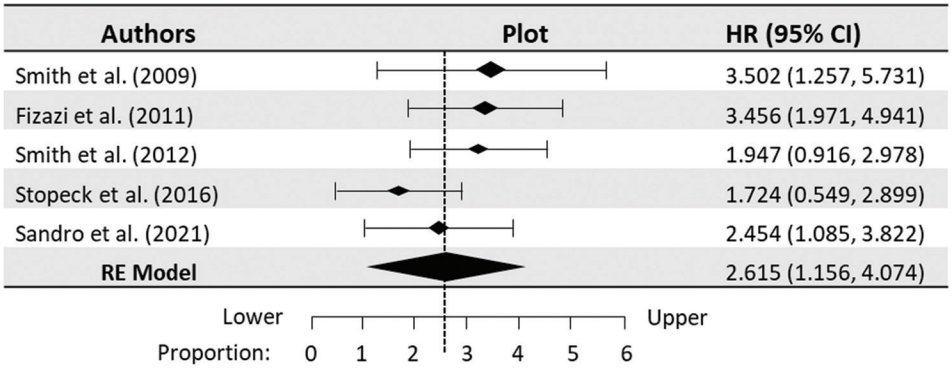


Figure 6. Forest plot for adverse events among ZA- and denosumab-treated groups. Pooling of studies using a RE model with a 95% CI showed a mild heterogeneity (I^2=43.2%) and no statistically significant difference (p>0.05) in the longitudinal comparison between ZA and denosumab groups.
Abbreviations: ZA: Zoledronic acid; CI: Confidence interval; HR: Hazard ratio; RE: Random effects.

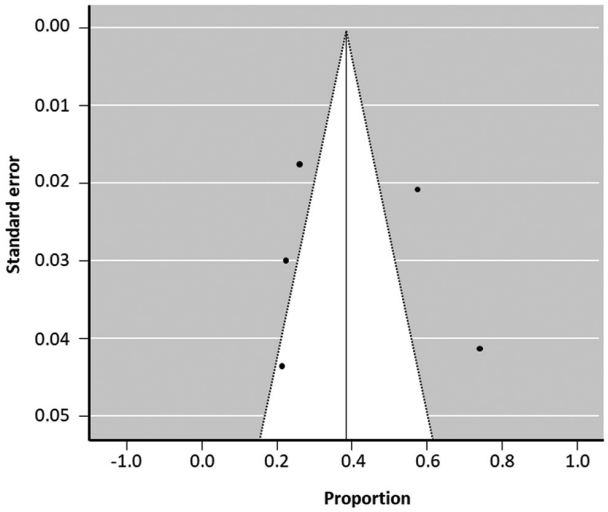


Figure 7. Funnel plot for adverse events in the reviewed literatures comparing ZA and denosumab groups. There is no evidence of publication bias, as indicated by a symmetrical funnel plot. The rank correlation test and regression analysis for funnel plot asymmetry were statistically not significant (r=0.0253, p>0.05) between the two groups.
Abbreviation: ZA: Zoledronic acid.

compared to the ZA group (59.3%) (p=0.009). Specific events, such as spinal cord compression (26.1% for denosumab vs. 21.4% for ZA) and pathological fractures (56.8% for denosumab vs. 41.9% for ZA), were notably reduced. For example, Smith *et al.*[24] revealed that the incidence of new vertebral fractures was significantly reduced in the denosumab group (1.5%) compared to the placebo group (3.9%) (relative risk: 0.38, p=0.006). Moreover, Smith *et al.*[26] reported a 22% reduction in the need for radiation to the bone in denosumab-treated patients compared to those receiving ZA. In addition, Fizazi *et al.*[25] demonstrated that denosumab significantly delayed the median time to the first

Table 5. Time for diagnosis of SREs in both groups

Time (months)	ZA	Denosumab	t	*p*
Range	41.2 – 73.2	37.5 – 73.2		
Mean	57.2	55.35	0.511	0.432
±SD	22.6	25.2		
Median	57	55		

Abbreviations: ZA: Zoledronic acid; t: Unpaired t-test; SD: Standard deviation; SREs: Skeletal-related events.
Note: p>0.05: Not significant.

Table 6. Common SREs in both groups

Common SREs	ZA		Denosumab		Significance	
	Event	%	Event	%	χ^2	*p*
Spinal cord compression	82	21.4	69	26.1	0.825	0.135
Bone surgery	4	1.04	1	0.38	8.387	0.000*
Pathological fracture	161	41.9	150	56.8	1.231	0.084
Bone radiation	246	64.1	119	45.1	1.864	0.021*
Bone metastasis	120	31.3	112	42.4	1.047	0.096
Total events (n=648)	384	59.3	264	40.7	2.131	0.009*

Note: *p<0.05: Significant.
Abbreviations: χ^2: Chi-square test; ZA: Zoledronic acid; SREs: Skeletal-related events.

SRE by 3.6 months (20.7 months for denosumab vs. 17.1 months for ZA, HR: 0.82, p=0.008). Furthermore, Smith *et al.*[17] reported that denosumab reduced the risk of first SREs by 18% (HR: 0.82, p=0.01) and delayed time to first and subsequent SREs compared to ZA, with radiation to the bone being the most frequent event. Regression analyses across the studies supported these findings, with denosumab showing a pooled HR of 0.751 (95% CI: 0.245 – 1.257), indicating a consistent reduction in SREs.

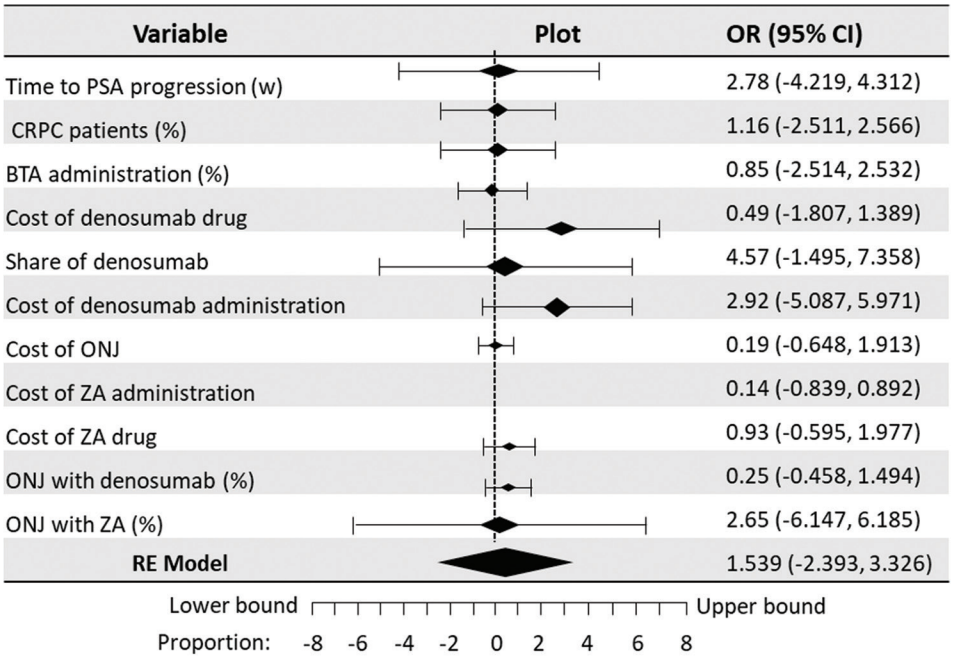


Figure 8. Forest plot for cost effectiveness among ZA- and denosumab-treated groups. Pooling of studies using a RE model with a 95% CI showed a mild heterogeneity (I^2=94.5%) and a statistically highly significant difference (p<0.01) in the longitudinal comparison between the ZA and denosumab groups. Abbreviations: ZA: Zoledronic acid; OR: Odd ratio; PSA: Prostate-specific antigen; CRPC: Castration-resistant prostate cancer: BTA: Bone-targeted agent; ONJ: Osteonecrosis of the jaw; ZA: Zoledronic acid.

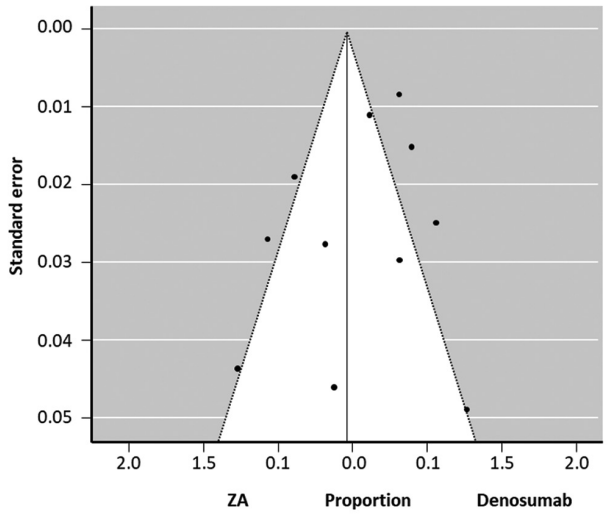


Figure 9. Funnel plot for cost effectiveness in the reviewed literatures comparing ZA and denosumab groups. There is no evidence of publication bias, as indicated by a symmetrical funnel plot. The rank correlation test and regression analysis for funnel plot asymmetry was statistically significant (r=0.4249, p=0.0153) between the two groups. Abbreviation: ZA: Zoledronic acid.

Table 7. Common SSEs in both groups

Common SSEs	ZA		Denosumab		Significance	
	Event	%	Event	%	χ^2	p
Spinal cord compression	38	3.72	26	2.85	1.621	0.042*
Bone surgery	5	0.49	3	0.33	7.385	0.000*
Pathological fracture	13	1.27	9	0.99	1.924	0.011*
Bone radiation	233	22.8	203	22.2	1.432	0.057
Chemotherapy	93	9.1	55	6.02	1.850	0.025*
Visceral metastasis	181	17.7	161	17.6	0.927	0.112
Anemia	126	12.3	125	13.7	1.413	0.062
Renal dysfunction	333	32.6	331	36.3	1.421	0.059
Total events (n=1,935)	1022	52.8	913	47.2	1.744	0.029*

Note: *p<0.05: Significant.
Abbreviations: χ^2: Chi-square test; ZA: Zoledronic acid; SSEs: Symptomatic skeletal events.

In terms of SSEs, denosumab also outperformed ZA in mitigating SSEs. The overall incidence was lower in the denosumab group (47.2%) compared to ZA (52.8%) (p=0.029). Specific event such as spinal cord compression was significantly reduced with denosumab (2.85% vs. 3.72%, p=0.042). Studies by Smith *et al.*[17] emphasized the impact of SSEs on quality of life, showing a 22% risk reduction with denosumab (HR: 0.78, p=0.005). Similarly, fewer patients in the denosumab group required radiation to the bone (22.2% vs. 22.8% for ZA). These outcomes highlight denosumab's potential in alleviating

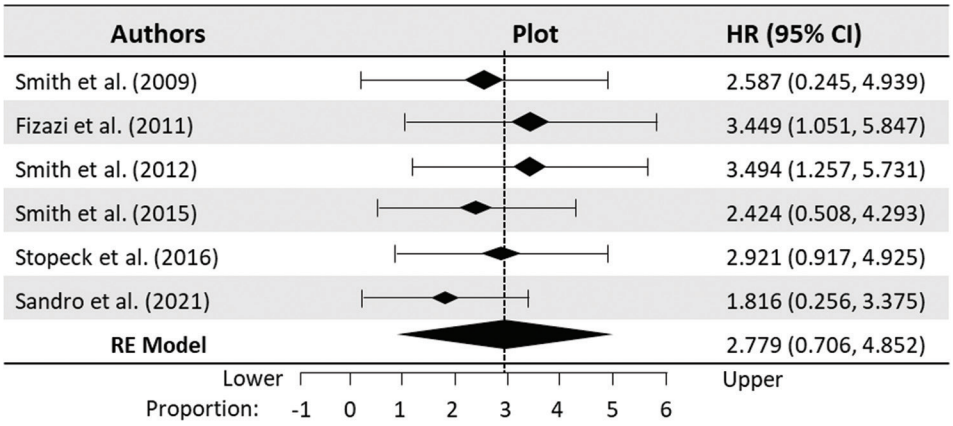


Figure 10. Forest plot for the age of patients among ZA- and denosumab-treated groups. Pooling of studies using a RE model with a 95% CI showed a mild heterogeneity (I^2=34.1%) and no statistically significant difference (p=0.348) in the longitudinal comparison between the ZA and denosumab groups. Abbreviations: ZA: Zoledronic acid; CI: Confidence interval; HR: Hazard ratio; RE: Random effects.

Table 8. BMFS and OS in both groups

BM	ZA average (months)	Denosumab average (months)	Significance	
			t	*p*
1st BM	29.5±3.21	33.2±3.56	1.227	0.031*
BMFS	25.2±2.96	29.5±3.19	1.222	0.033*
OS	44.8±5.36	43.9±5.21	0.547	0.086
PFS	19.3±2.35	21.7±2.74	1.258	0.027*

Abbreviations: BM: Bone metastasis; BMFS: Bone metastasis-free survival; OS: Overall survival; PFS: Progression-free survival; t: Paired t-test.
Note: *p<0.05: Significant.

symptomatic complications of bone metastases more effectively than ZA.

In terms of BMFS and PFS, denosumab significantly extended BMFS compared to ZA. The median BMFS was 29.5 months for denosumab versus 25.2 months for ZA (p=0.033). For instance, Smith *et al.*[26] reported that denosumab delayed the first bone metastasis to 33.2 months, compared to 29.5 months for ZA (p=0.032). In addition, PFS was longer in the denosumab group, averaging 21.7 months versus 19.3 months in the ZA group (p=0.027). Stoffel *et al.*[23] also reported that the time to PSA progression was 33.2 months. However, no significant differences were observed in OS, which was similar in both groups (43.9 months for denosumab vs. 44.8 months for ZA).

In terms of adverse events, the profiles were slightly more concerning for denosumab compared to ZA. The incidence of total adverse events was 93.1% with denosumab and 91.4% with ZA. Serious adverse events were significantly higher in the denosumab group (49.2% vs. 42.2%, p=0.036), including increased rates of hypocalcemia (2.2% vs. 1.46%) and osteonecrosis of the jaw (ONJ) (2.8% vs. 2.41%). For instance, Fizazi *et al.*[25] reported that serious adverse events occurred in 63% of patients treated with denosumab versus 60% with ZA. Hypocalcemia was more common in patients treated with denosumab (13% vs. 6%, p<0.001). Moreover, ONJ occurred infrequently (2% with denosumab vs. 1% with ZA, p=0.09). Similarly, Smith *et al.*[17] found that ONJ was higher in the denosumab group (approximately 2%), and hypocalcemia was more frequent (5% with denosumab vs. 1% with ZA).

Despite these differences, adverse events were generally manageable, and the higher efficacy of denosumab justified its use in many clinical scenarios. Long-term safety studies, such as study by Stopeck *et al.*[27] who reported that the cumulative incidence of ONJ increased with longer denosumab exposure, reaching 6.9% in patients continuing denosumab and 5.5% in those switching from ZA to denosumab. Most cases were mild or moderate, treated conservatively, and linked to dental risk factors such as poor oral hygiene and tooth extractions. Similarly, hypocalcemia occurred in 4.3% of patients continuing denosumab and 3.1% of those switching from ZA to denosumab. Severe cases requiring intravenous calcium were rare (1 – 2%), which emphasizes the importance of dental monitoring and calcium/Vitamin D supplementation to mitigate these risks.

In terms of cost implications, the economic burden of denosumab was substantially higher than that of ZA. The annual cost for denosumab was reported at $8,628,524, compared to $589,485 for ZA ($p$=0.015). Stoffel *et al.*[23] noted that denosumab's higher price accounted for 93% of total treatment costs, driven by drug and administration expenses. However, denosumab's ability to reduce the frequency and severity of SREs and SSEs may offset some

Table 9. Adverse events in both groups

Adverse events	ZA		Denosumab		Significance	
	Event	%	Event	%	χ^2	*p*
Average events	576	91.4	592	93.1	0.036	0.582
Serious events	236	42.2	314	49.2	1.656	0.036*
Pneumonia	11	0.58	11	0.51	0.911	0.121
Syncope	5	0.26	8	0.37	1.553	0.045*
Dyspnea	3	0.16	8	0.37	1.682	0.033*
Decreased appetite	274	14.3	267	12.5	0.074	0.357
Nausea	130	6.8	146	6.82	0.001	0.987
Constipation	148	7.74	145	6.78	0.007	0.769
Diarrhea	70	3.66	75	3.5	0.001	0.983
Anemia	126	6.59	131	6.12	0.001	0.964
Fatigue	94	4.92	108	5.05	0.078	0.321
Back pain	134	7.01	146	6.82	0.051	0.484
Bone pain	93	4.86	138	6.45	0.072	0.362
Extremity pain	124	6.49	126	5.89	0.055	0.468
Asthenia	125	6.54	134	6.26	0.002	0.897
Arthralgia	103	5.39	108	5.05	0.002	0.874
Infection	137	7.17	154	7.2	0.001	0.989
Flushing	32	1.67	38	1.78	0.113	0.287
Urinary tract infection	32	1.67	37	1.73	0.149	0.277
Hematuria	24	1.26	35	1.64	0.247	0.254
Urine retention	31	1.62	54	2.52	1.475	0.054
Peripheral edema	111	5.81	123	5.75	0.005	0.813
Hypocalcemia	28	1.46	47	2.2	0.015	0.642
Jaw osteonecrosis	46	2.41	60	2.8	0.008	0.735
Dizziness	31	1.62	41	1.92	0.006	0.798
Total (*n*=4,052)	1,912	47.2	2,140	52.8	0.013	0.671

Note: *$p<0.05$: Significant.
Abbreviations: χ^2: Chi-square test; ZA: Zoledronic acid.

of these costs by decreasing hospitalizations and the need for interventions such as radiation or surgery. Strategies to mitigate denosumab's financial burden, such as extending dosing intervals or negotiating pricing, could improve its cost-effectiveness.

The meta-analysis underscores significant pharmaco-economic implications when comparing denosumab and ZA for managing bone metastases in patients with CRPC. While denosumab demonstrates superior clinical efficacy in reducing SREs and SSEs, as well as prolonging BMFS, these benefits come with a considerably higher cost compared to ZA. The mean annual cost of denosumab was reported at $8,628,524, which is substantially higher than the $589,485 associated with ZA (p=0.015). These cost disparities are largely attributable to denosumab's higher drug price and more frequent administration.

Table 10. Estimated cost of BTA for continuous use of denosumab and ZA in mCRPC patients

Mode of administration	Administration number (mean)	Denosumab (US$)	ZA (US$)
Every 4 weeks	36.1		
• Drug cost		4,085,811	181,819
• Add-on cost		1,130,574	196,143
• Sum		5,216,385	377,962
Every 4 w/2 y, then 1/12 w	29.4		
• Drug cost		2,078,521	0
• Add-on cost		575,142	0
• Sum		2,653,663	0
Every 4 w/1 y, then 1/12 w	20.7		
• Drug cost		292,973	0
• Add-on cost		81,068	0
• Sum		374,041	0
Every 12 weeks	12		
• Drug cost		0	60,606
• Add-on cost		0	65,381
• Sum		0	125,987
Every 24 weeks	6		
• Drug cost		170,242	30,303
• Add-on cost		47,107	32,690
• Sum		217,349	62,994
Total SREs costs		8,461,439	566,943
Cost of ONJ		167,084	22,542
Total costs		8,628,524	589,485

Abbreviations: BTA: Bone-targeted agent; mCRPC: Metastatic castration-resistant prostate cancer; ONJ: Osteonecrosis of the jaw; ZA: Zoledronic acid; SREs: Skeletal-related events; w: Week; y: Year.

Table 11. Meta-analysis of SREs in patients treated with ZA and denosumab

SREs	ZA		Denosumab	
Events: No. (%)	384 (59.3%)		264 (40.7%)	
HR	4.611		0.751	
95% CI	**LB**	**UB**	**LB**	**UB**
Intercept	3.375	5.847	0.245	1.257
Significance	r=0.9251		$p<0.001$	

Note: $p<0.001$: Highly significant.
Abbreviations: SREs: Skeletal-related events; ZA: Zoledronic acid; HR: Hazard ratio; CI: Confidence interval; SD: Standard deviation; LB: Lower bound, UB: Upper bound, r: Correlation coefficient.

Table 12. Meta-analysis of SSEs in patients treated with ZA and denosumab

SSEs	ZA		Denosumab	
Events: No. (%)	1022 (52.8%)		913 (47.2%)	
HR	3.9265		0.9045	
95% CI	**LB**	**UB**	**LB**	**UB**
Intercept	3.341	4.512	0.752	1.057
Significance	r=0.7694		$p<0.001$	

Note: $p<0.01$: Significant.
Abbreviations: ZA: Zoledronic acid; HR: Hazard ratio; CI: Confidence interval; SSE: Symptomatic skeletal events; LB: Lower bound, UB: Upper bound, r: Correlation coefficient.

Table 13. Meta-analysis of adverse events in patients treated with ZA and denosumab

Adverse events	ZA		Denosumab	
Events: No. (%)	1912 (47.2%)		2140 (52.8)	
HR	2.435		3.140	
95% CI	**LB**	**UB**	**LB**	**UB**
Intercept	1.971	2.899	0.549	5.731
Significance	r=0.0253		$p=0.158$	

Note: $p>0.05$: Not-significant.
Abbreviations: ZA: Zoledronic acid; HR: Hazard ratio; CI: Confidence interval; LB: Lower bound, UB: Upper bound, r: Correlation coefficient.

Table 14. Meta-analysis of the annual pharmacological cost of denosumab and ZA, including and drug costs and administration expenses

Events	ZA		Denosumab	
Mean annual cost	589,485		8,628,524	
OR	3.303		4.125	
95% CI	**LB**	**UB**	**LB**	**UB**
Intercept	−6.147	−0.458	0.892	7.358
Significance	r=0.4249		$p=0.015^*$	

Note: $p<0.01$: Significant.
Abbreviations: ZA: Zoledronic acid; OR: Odd ratio; CI: Confidence interval; LB: Lower bound; UB: Upper bound; r: Correlation coefficient.

The economic burden of denosumab is compounded by the costs of managing adverse events, such as hypocalcemia and ONJ, which occur more frequently than with ZA. For instance, ONJ incidence was 2.8% with denosumab versus 2.41% with ZA, often requiring costly interventions such as dental consultations and surgical treatments in severe cases. In addition, healthcare systems in resource-constrained settings may face challenges in justifying the routine use of denosumab despite its clinical advantages, particularly for patients with lower risks of SREs or SSEs.

Table 15. Meta-analysis of the age of patients treated with denosumab and ZA, including drug administration

Events	ZA		Denosumab	
Mean age (years)	71.9±6.35		72.58±1.91	
OR	1.810		3.494	
95% CI	**LB**	**UB**	**LB**	**UB**
Intercept	0.245	3.375	1.257	5.731
Significance	r=0.0144		$p=0.261$	

Note: $p>0.05$: Not significant.
Abbreviations: ZA: Zoledronic acid; OR: Odd ratio; CI: Confidence interval; LB: Lower bound; UB: Upper bound; r: Correlation coefficient.

However, denosumab's ability to significantly reduce the frequency and severity of skeletal complications may offer long-term economic benefits by lowering indirect costs associated with hospitalizations, pain management, and loss of productivity. Stoffel *et al.*[23] highlighted that most total treatment costs are from drug prices and administration expenses, which account for over 90% of expenditures for denosumab. This suggests that strategies such as extending dosing intervals or negotiating drug prices could help mitigate its financial impact without compromising clinical outcomes.

This study provides a meta-analysis of the age distribution and its correlation with treatment outcomes in patients with CRPC undergoing therapy with ZA and denosumab. The mean age across both treatment groups was comparable, with ZA patients averaging 71.9±6.35 years and denosumab patients averaging 72.58±1.91 years. This uniformity ensures that observed differences in outcomes are less likely to be influenced by age disparities between groups.

Both ZA and denosumab showed similar efficacy across age groups. However, denosumab demonstrated a slight trend toward better outcomes in older patients due to its greater effectiveness in reducing SREs, regardless of age. For instance, in patients over 65 years (constituting approximately 79% of the population), denosumab delayed the time to first bone metastasis (mean=33.2 months) compared to ZA (mean=29.5 months). This suggests that denosumab may offer an advantage in prolonging BMFS in older adults, who are more likely to experience rapid disease progression.

From an economic standpoint, denosumab has significantly higher direct costs compared to ZA. However, its ability to reduce the frequency and severity of SREs may offer long-term economic benefits by lowering indirect costs such as hospitalizations, pain management, and loss of productivity associated with severe skeletal complications. In high-risk patients prone to frequent SREs, the clinical

benefits of denosumab may justify its higher upfront costs by reducing healthcare utilization and improving quality of life. On the other hand, ZA remains a more cost-effective alternative for patients with a lower metastasis burden or limited financial resources. Therefore, individualized treatment strategies that consider factors, such as age, disease severity, performance status, comorbidities, and indirect cost implications are essential for optimizing therapeutic outcomes and cost-effectiveness.

Patient adherence is a key factor in treatment success. Denosumab, administered subcutaneously every 4 weeks, offers greater convenience compared to ZA, which requires intravenous infusion and renal monitoring. However, the higher incidence of adverse events with denosumab, such as hypocalcemia, necessitates vigilant follow-up, which may impact adherence. Thus, educating patients on the importance of supplementation and regular follow-ups can help mitigate this issue.

Supportive care strategies, including tailored nutritional counseling and routine monitoring for adverse effects, can enhance treatment tolerability. In addition, regional variations in healthcare infrastructure, drug availability, and economic disparities play a role in treatment selection. For instance, denosumab may be preferred in high-resource settings due to its superior efficacy, while ZA may be a more practical option in regions with limited financial or medical resources.

This meta-analysis examined the efficacy and safety of denosumab compared to ZA in patients with CRPC and bone metastases. However, substantial heterogeneity across studies was observed, arising from differences in study designs, patient populations, treatment protocols, and measured outcomes. These differences have significant implications for the overall reliability and interpretation of the findings.

Differences in treatment protocols introduced another layer of heterogeneity. While denosumab was consistently administered subcutaneously at 120 mg every 4 weeks, ZA dosing often varied between studies due to required adjustments based on renal function. Furthermore, treatment duration differed, with cumulative exposures ranging from 12 months to over 33 months. These disparities could significantly influence the timing and frequency of SREs, adverse events, and BMFS across studies.

This meta-analysis incorporated diverse endpoints, including SREs, SSEs, BMFS, OS, PFS, and adverse events. Variability in how these outcomes were defined and measured further contributed to heterogeneity. For instance, some studies focused on time-to-first SRE, while others considered cumulative events. Similarly, definitions of adverse events such as hypocalcemia and ONJ varied, leading to differences in reported incidence rates. These inconsistencies in endpoints made direct comparison of outcomes across studies more challenging.

4.1. Strengths of the meta-analysis

This meta-analysis offers several strengths that enhance its credibility and relevance. First, it includes a large and diverse patient population of over 7000 participants with CRPC from multiple high-quality studies, ensuring strong statistical power and broad generalizability. The consistent use of RCTs as primary sources further strengthens the reliability of the findings. In addition, the meta-analysis offers a comprehensive evaluation of critical outcomes, such as SREs, SSEs, BMFS, adverse events, and cost implications, providing a holistic view of the comparative benefits of denosumab and ZA. Advanced statistical approaches, including random-effects (RE) models, can address substantial heterogeneity across studies and ensure the accuracy of pooled estimates. Furthermore, the meta-analysis highlights key clinical endpoints relevant to PC management, making it valuable resources for clinicians in guiding treatment decisions.

Preventing hypocalcemia is critical when administering denosumab or ZA. Patients should receive routine calcium (1,000 – 1,500 mg/day) and Vitamin D (400 – 800 IU/day) supplementation throughout the treatment period. Before initiating therapy, baseline serum calcium levels should be assessed, and periodic monitoring is recommended, especially for patients with higher risk, such as those with renal dysfunction or malabsorption disorders.[15]

To minimize the risk of ONJ, a dental assessment should be conducted before initiating treatment, and any necessary invasive dental procedures should be completed beforehand. During the treatment, patients should maintain optimal oral hygiene and avoid dental extractions or other invasive procedures unless necessary.[17]

4.2. Limitations of the study

Despite its strengths, this meta-analysis has several notable limitations. A major limitation is the significant heterogeneity across studies, with I^2 values reaching 93.9% for SRE outcomes, which indicates substantial variability in study designs, patient populations, and treatment protocols. Differences in the definitions of endpoints, such as SREs, SSEs, and adverse events, introduce further inconsistencies. For example, some studies included radiation therapy in SREs, while others focused on fractures or surgical interventions. Variability in treatment durations and dosing protocols, particularly for ZA, further complicates direct comparisons. In addition, the analysis does not fully account for real-world factors

such as adherence to therapy, variations in supportive care (e.g., calcium and Vitamin D supplementation), and comorbidities, all of which may influence outcomes. The absence of granular subgroup analyses for factors such as age, baseline bone metastasis burden, or prior SREs limits insights into which patients benefit most from denosumab versus ZA. Finally, cost analyses are based on limited data and may not fully capture variations in healthcare systems or economic conditions across regions.

5. Conclusion

Denosumab demonstrates superior efficacy over ZA in reducing SREs and SSEs among patients with CRPC and bone metastases. However, its benefits vary across specific patient populations. Older patients more than 65 years appear to experience prolonged BMFS and PFS with denosumab compared to younger cohorts, possibly due to their higher baseline risk of rapid disease progression. In addition, patients with a high burden of bone metastases or a history of SREs see greater benefits from denosumab's ability in preventing SRE. In contrast, those with lower metastasis burden may respond just as well to ZA while keeping costs lower. Importantly, patients with lower ECOG performance scores (<2) show greater PFS and BMFS with denosumab, indicating its potential advantage in fitter individuals. However, the increased risk of hypocalcemia and ONJ associated with denosumab requires careful consideration, especially in older adults or those with compromised renal function. These findings underscore the need for individualized treatment strategies that consider age, disease severity, performance status, and comorbidities to optimize both therapeutic outcomes and cost-effectiveness.

Based on the findings, denosumab is recommended for high-risk CRPC patients with extensive bone metastases due to its superior efficacy in reducing SREs and prolonging BMFS and PFS. However, careful monitoring for hypocalcemia and ONJ is essential. ZA remains a cost-effective alternative for patients with a lower metastasis burden or financial constraints. Treatment decisions should be personalized based on factors, such as age, disease severity, and comorbidities. Future research should include subgroup analyses and longer follow-up periods to refine recommendations and assess long-term safety and cost-effectiveness.

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Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

Conceptualization: All authors
Writing – original draft: All authors
Writing – review & editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

The data used in the study can be obtained and available.

References

1. Kruger TE, Miller AH, Godwin AK, Wang J. Bone sialoprotein and osteopontin in bone metastasis of osteotropic cancers. *Crit Rev Oncol Hematol*. 2014;89(3):330-341.

   doi: 10.1016/j.critrevonc.2013.08.013

2. Gandaglia G, Leni R, Bray F, *et al*. Epidemiology and prevention of prostate cancer. *Eur Urol Oncol*. 2021;4(6):877-892.

   doi: 10.1016/j.euo.2021.09.006

3. Terrisse S, Karamouza E, Parker CC, *et al*. Overall survival in men with bone metastases from castration-resistant prostate cancer treated with bone-targeting radioisotopes: A meta-analysis of individual patient data from randomized clinical trials. *JAMA Oncol*. 2020;6(2):206-216.

   doi:10.1001/jamaoncol.2019.4097

4. Chodak GW, Thisted RA, Gerber GS, *et al*. Results of conservative management of clinically localized prostate cancer. *N Engl J Med*. 1994;330(4):242-248.

   doi: 10.1056/NEJM199401273300403

5. Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, Schmid HP, Zattoni F. EAU guidelines on prostate cancer. *Eur Urol*. 2008;53(1):68-80.

   doi: 10.1016/j.eururo.2007.09.002

6. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: A systematic review. *Int J Clin Pract*. 2011;65(11):1180-1192.

   doi: 10.1111/j.1742-1241.2011.02799.x

7. Labrecque MP, Coleman IM, Brown LG, *et al*. Molecular profiling stratifies diverse phenotypes of treatment-refractory metastatic castration-resistant prostate cancer. *J Clin Invest*. 2019;129(10):4492-4505.

   doi: 10.1172/JCI128212

8. European Medicines Agency (EMA). *Zometa*® (*Zoledronic Acid*): *Summary of Product Characteristics*. Basel, Switzerland: Novartis Europharm Limited; 2014.

9. European Medicines Agency (EMA). *XGEVA*® (*Denosumab*): *Summary of Product Characteristics*. Netherlands: Amgen Europe B.V.; 2014.

10. Coleman R, Body JJ, Aapro M, *et al*. Bone health in cancer patients: ESMO clinical practice guidelines. *Ann Oncol*. 2014;25(Suppl 3):124-137.

doi: 10.1093/annonc/mdu103

11. Rosen LS, Gordon D, Tchekmedyian NS, *et al*. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: A randomized, Phase III, double-blind, placebo-controlled trial. *Cancer*. 2004;100(12):2613-2621.

doi: 10.1002/cncr.20308

12. Grávalos C, Rodríguez C, Sabino A, *et al*. SEOM clinical guideline for bone metastases from solid tumours. *Clin Transl Oncol*. 2016;18(12):1243-1253.

doi: 10.1007/s12094-016-1590-1

13. Terpos E, Kleber M, Engelhardt M, *et al*. European myeloma network guidelines for the management of multiple myeloma-related complications. *Haematologica*. 2015;100(10):1254-1266.

doi: 10.3324/haematol.2014.117176

14. Smith MR. Zoledronic acid to prevent skeletal complications in cancer: Corroborating the evidence. *Cancer Treat Rev*. 2005;31(Suppl 3):19-25.

doi: 10.1016/j.ctrv.2005.09.004

15. McClung MR, Lewiecki EM, Cohen SB, *et al*. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2006;354(8):821-831.

doi: 10.1056/NEJMoa044459

16. Yee AJ, Raje NS. Denosumab for the treatment of bone disease in solid tumors and multiple myeloma. *Future Oncol*. 2018;14(3):195-203.

doi: 10.2217/fon-2017-0403

17. Smith MR, Coleman RE, Klotz L, *et al*. Denosumab for the prevention of skeletal complications in metastatic castration-resistant prostate cancer: Comparison of skeletal-related events and symptomatic skeletal events. *Ann Oncol*. 2015;26(2):368-374.

doi: 10.1093/annonc/mdu519

18. Raje N, Terpos E, Willenbacher W, *et al*. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: An international, double-blind, double-dummy, randomised, controlled, phase 3 study. *Lancet Oncol*. 2018;19(3):370-381.

doi: 10.1016/S1470-2045(18)30072-X

19. Henry DH, Costa L, Goldwasser F, *et al*. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol*. 2011;29(9):1125-1132.

doi: 10.1200/JCO.2010.31.3304

20. Cleeland CS, Body JJ, Stopeck A, *et al*. Pain outcomes in patients with advanced breast cancer and bone metastases: Results from a randomized, double-blind study of denosumab and zoledronic acid. *Cancer*. 2013;119(4):832-838.

doi: 10.1002/cncr.27789

21. Zheng GZ, Chang B, Lin FX, *et al*. Meta-analysis comparing denosumab and zoledronic acid for treatment of bone metastases in patients with advanced solid tumours. *Eur J Cancer Care* (*Engl*). 2017;26(4):e12541.

doi: 10.1111/ecc.12541

22. McInnes MDF, Moher D, Thombs BD, *et al*. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: The PRISMA-DTA statement. *JAMA*. 2018;319(4):388-396.

doi: 10.1001/jama.2017.19163

23. Stoffel ST, von Moos R, Thürlimann B, *et al*. Patterns of care and economic consequences of using bone-targeted agents for castration-sensitive prostate cancer patients with bone metastases to prevent skeletal-related events in Switzerland - the SAKK 95/16 prostate study. *Swiss Med Wkly*. 2021;151:w20464.

doi: 10.4414/smw.2021.20464

24. Smith MR, Egerdie B, Hernández Toriz N, *et al*. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med*. 2009;361(8):745-755.

doi: 10.1056/NEJMoa0809003

25. Fizazi K, Carducci M, Smith M, *et al*. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomised, double-blind study. *Lancet*. 2011;377(9768):813-822.

doi: 10.1016/S0140-6736(10)62344-6

26. Smith MR, Saad F, Coleman R, *et al*. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: Results of a phase 3, randomised, placebo-controlled trial. *Lancet*. 2012;379(9810):39-46.

doi: 10.1016/S0140-6736(11)61226-9

27. Stopeck AT, Fizazi K, Body JJ, *et al*. Safety of long-term denosumab therapy: Results from the open label extension phase of two phase 3 studies in patients with metastatic breast and prostate cancer. *Support Care Cancer*. 2016;24(1):447-455.

doi: 10.1007/s00520-015-2904-5