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Systemic therapy of denosumab in altering surgical outcomes in patients with giant cell tumour of bone

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Table of Contents

Evidence Summary.....	2
References	12
Appendix 1: Affiliations and Conflict of Interest Declarations.....	14
Appendix 2: Literature Search Strategy.....	15
Appendix 3: PRISMA Flow Diagram	16
Appendix 4: Risk of Bias assessment	17

Systemic therapy of denosumab in altering surgical outcomes in patients with giant cell tumour of bone

Evidence Summary

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

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INTRODUCTION

Giant cell tumour of bone (GCTB) is an intermediate, osteoclastic giant cell-rich primary bone tumour that is characterized by its locally aggressive and rarely metastasizing nature. GCTB typically develops at the meta-epiphysis of the long bones but can also present in pelvic and spinal sites, which prove more difficult to treat [1]. GCTB is locally aggressive due to the presence of numerous multinucleated osteoclast-type giant cells and mononuclear stromal cells expressing receptor activator of nuclear factor-kappa B (RANK), and RANK ligand (RANKL) genes, which regulate osteoclast formation, migration and survival [2]. This results in bone resorption, causing pain, as well as limitations in range of motion, joint effusion, synovitis, and pathologic fracture in more extreme cases [3].

GCTB is an evolving category of lesions defined by a new gene marker *H3.3 p.Gly34Trp (G34W)* including diseases with associated gene mutations, which also includes two other diseases: benign fibrous histiocytoma of bone (BFHB) and secondary aneurysmal bone cyst (ABC). BFHB is a benign primary bone neoplasia characterized by fibroblasts in predominant storiform fashion, varying amounts of osteoclast-type giant cells, foamy macrophages, hemosiderin and chronic inflammatory infiltrate [4]. Secondary ABC is defined as a benign, expansile, osteolytic lesion consisting of blood-filled spaces segregated by connective tissue septa, mostly involving the long bones and is secondary to pre-existing bone lesions [5]. All three lesions are associated with pain, which is the most common indication for intervention.

Recent research studies have suggested that denosumab (DENO) is associated with favourable tumour responses and reduced need for surgery [6-9]. However, many of these studies are single-arm studies of patients on DENO (i.e., no comparison), or include patients who remain on DENO or who have completed DENO treatment but with a short follow-up [6-8]. There is some evidence that DENO treatment may cause development of new osseous tumour matrix and thickened cortical bone, possibly modifying a surgeon's ability to curettage the lesion [10].

Although the initial phase II studies of DENO were inspiring in their antitumour-effect [11], the exact role of DENO in patients with resectable disease remains unclear. What are the indications for DENO? Is there a difference in local recurrence after preoperative DENO? The purpose of this document is to provide evidence on the benefits and harms of DENO for the

treatment of patients with GCTB, BFHB, or ABC, in the perioperative setting, which will be used to inform the decisions of medical oncologists, orthopedic oncologists, pathologists and other clinicians involved in the care of patients with GCTB, BFHB, or ABC, as well patients themselves. This systematic review has been registered on the PROSPERO website (International prospective registrar of systematic reviews <https://www.crd.york.ac.uk/prospero/>) with the following registration number CRD42020196392.

RESEARCH QUESTIONS

For patients with GCTB, BFHB, and ABC, what are the benefits and harms of DENO compared with no DENO in terms of facilitation of surgery, disease recurrence, pain control, disease stability, and adverse effects (e.g., malignant transformation, osteonecrosis of jaw, atypical femur fracture)?

TARGET POPULATION

Skeletally mature adolescents (aged ≥ 12 years) and adults with GCTB, BFHB, or ABC undergoing DENO treatment. This includes patients with resectable disease, unresectable disease, recurrent disease, and primary disease.

INTENDED PURPOSE

This evidence summary is intended to provide evidence on the benefits (i.e., effectiveness) and harms of DENO compared with no DENO for GCTB, BFHB, or ABC to inform provider and patient decisions.

INTENDED USERS

Medical oncologists, orthopedic oncologists, pathologists, and other clinicians involved in the care of patients with GCTB.

METHODS

This evidence summary was developed by a Working Group consisting of two medical oncologists, one orthopedic oncologist, one pathologist, and two health research methodologists at the request of the Sarcoma Disease Site Group (DSG). The Working Group members were responsible for reviewing the identified evidence and drafting the summary. Conflict of interest declarations for all authors are summarized in Appendix 1, and were managed in accordance with the [PEBC Conflict of Interest Policy](#).

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews using varying terms of “denosumab”, “giant cell tumour of bone”, “benign fibrous histiocytoma of bone”, and “secondary aneurysmal bone cyst”. The following sources were searched for systemic reviews: ECRI Database, National Institute for Health and Care Excellence (NICE) evidence search, Canadian Partnership Against Cancer (CPAC) Database, CMA Infobase, NICE (United Kingdom), Scottish Intercollegiate Guideline Network, American Society of Clinical Oncology (ASCO), National Health and Medical Research Council, and Cancer Council Australia. MEDLINE, EMBASE, Cochrane Database of Systematic Reviews databases, Agency for Healthcare Research and Quality (AHRQ), Canadian Agency for Drugs and Technologies in Health (CADTH), and PROSPERO

databases were search from inception to June 30, 2020. The final search strategies are reported in Appendix 2. Systematic reviews were included if they addressed the research question with similar inclusion/exclusion criteria and the review had a low risk of bias for all four domains as assessed with the Risk of Bias in Systematic Reviews (ROBIS) tool [12].

Search for Primary Literature

A search for existing primary studies was completed where an existing systematic review was not found. Alternatively, if there was an existing systematic review, a primary literature search was conducted to fill any time frames that were not covered by that systematic review. Below are the methods for locating and evaluating primary studies.

Literature Search Strategy

MEDLINE, EMBASE and the Cochrane library were searched at the same time as systematic reviews from inception to June 30, 2020 to find full primary literature publications. PubMed was also searched from January 2018 to June 30, 2020. Clinicaltrials.gov was searched for trials that were ongoing, unpublished, or incomplete from January 2015 to August 19, 2020. Conference proceedings from ASCO, European Society for Medical Oncology, and the Connective Tissue Oncology Society were search from January 2017 to July 2020.

Study Selection Criteria and Process

An article or abstract was included if it was a randomized controlled trial (RCT) (≥ 20 patients). If no or only high risk of bias RCTs were available, then comparative studies (≥ 20 patients) were included if they used methods to control potential confounders such as multivariable analysis, propensity-score matching, or comparing patient characteristics to show no statistically significant differences between the comparison groups at baseline. An article was excluded if it was a single-arm study, letter, commentary, editorial, non-English full publications, tissue sample study or abstracts of a non-RCT.

A review of the titles and abstracts was conducted by LDDA. For studies that warranted full-text review, LDDA reviewed each article and discussed with the other Working Group members to confirm the final study selections.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by LDDA with all extracted data and information reviewed subsequently by an independent auditor. The risk of bias of included RCTs was assessed by the Cochrane Collaboration tools for randomized studies [13]. The risk of bias of included comparative non-randomized studies was evaluated with the Risk of Bias in non-randomized studies of interventions (ROBINS-I) [14].

Synthesizing the Evidence

Statistical analyses were executed with the statistical software package STATA version 15 [15]. When clinically and methodologically homogeneous results from two or more studies were available, a meta-analysis would be conducted. When meta-analysis was inappropriate due to clinical heterogeneity, the results of each study were presented individually in a descriptive fashion. Ratios, including hazard ratios (HR), were expressed with a ratio of <1.0 indicating a benefit for DENO treatment compared with the control. A two-sided significance level of $\alpha=0.05$ was assumed.

Assessment of the Certainty of the Evidence

The certainty of the evidence was assessed for the research question, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

RESULTS

The PRISMA flow diagram of studies considered in the systematic review is shown in Appendix 3.

Search for Systematic Reviews

Eighteen citations were identified from the systematic review search. From these, 15 were not relevant systematic reviews; one systematic review was excluded as it was a guideline's systematic review and at the time of this search only the recommendations/charts had been updated and the literature search and discussion section indicated "update in progress" [16]; two systematic reviews [17, 18] were assessed for risk of bias using the ROBIS tool (see Appendix 4) and only one met the pre-planned inclusion criteria as it had low risk of bias [18].

Search for Primary Studies

The initial primary literature search, after removal of duplicates, resulted in 446 citations from which 137 were identified to be eligible for full-text review. Among these, seven met our pre-planned study criteria [19-25] and their reference lists were manually searched but no further eligible papers were found. A screen of conference abstracts yielded one abstract that met the study selection criteria [26]. Of these eight publications passing the initial screen, five underwent data extraction and were analyzed in this systematic review [19-23]. Table 1 summarizes the characteristics of these five included studies. Three publications [24-26] did not undergo data extraction as they were detailed in the included systematic review [18].

Of the five articles, one was a retrospective case-matched control study [19] and four were retrospective cohort studies [20-23]. All studies had very small number of patients who received DENO (seven to 30 patients).

Risk of bias assessments of five extracted studies are reported in Appendix 4 and the overall result for each study is moderate to serious risk of bias [19-23]. The quality of aggregate evidence for every outcome was considered low to very low when considering risk of bias, inconsistency, indirectness, imprecision, and other factors all together. Due to many of the studies being small retrospective cohort studies where DENO administration was compared to a control group, there was an increase in bias as many reported different sample sizes between groups (with no power analysis), with a shorter time frame for those in DENO group as it is a newer drug. Due to clinical heterogeneity, meta-analyses were inappropriate for any outcomes.

Outcomes

All articles that met inclusion criteria and had data extracted focused on patients with GCTB. There were no articles that met inclusion criteria for patients with BFHB or ABC.

1. Facilitation of surgery/reduced morbidity surgery

Results for facilitation of surgery/reduced morbidity surgery can be found in Table 1. Lim et al compared patients receiving no DENO, adjuvant DENO, and both adjuvant and neoadjuvant DENO, and found that mean operating time in minutes was less for patients receiving both neoadjuvant and adjuvant DENO (mean $\pm$ standard deviation [SD] = 181.2 $\pm$ 38.6 min) when compared with no DENO (199.4 $\pm$ 49.5 min) or adjuvant DENO (200.6 $\pm$ 69.8 min), but the difference did not reach statistical significance [20]. This study also found that preoperative DENO was associated with reduced blood loss during surgery ($p=0.008$) [20]. Agarwal et al noted in their study that DENO administration in patients with GCTB facilitated surgical resection by hardening the tumour and the bony shell, potentially reducing the risk of

inadvertent contamination during separation of the neurovascular bundle or tendons from the tumour margin, although it increased the rate of recurrence [19]. Similarly, Scoccianti et al found new bone formation around and partially inside the lesion in their sample of patients with GCTB receiving DENO before curettage [22]. While Medellin et al observed that the use of DENO consolidated the peripheral rim and facilitated excision in patients presenting with fractures from GCTB, they also found that DENO neoadjuvant administration was associated with significantly prolonged times before proceeding to surgery compared with no DENO (61 weeks vs. 4 weeks, $p < 0.001$) [21]. It is important to note that the number of patients in the DENO group was very small ($n=7$).

2. Disease recurrence

Tsukamoto et al (2019a) performed a systematic review of seven comparative studies to determine if preoperative DENO had an effect on local recurrence risk in patients with GCTB treated with curettage versus those treated with curettage alone and if preoperative DENO duration was associated with local recurrence after curettage [18]. Among them, three studies also reported the outcome of facilitation of surgery above [19,21,22]. Of the patients who received preoperative DENO and curettage, the local recurrence rates ranged from 20-100% (overall $n=619$ patients), while in the curettage-alone group, it ranged from 0-50% (overall $n=127$ patients). This suggests there is an increased local recurrence risk in the DENO group, but due to poor quality, non-randomized trials, a meta-analysis was not performed to determine if there was a statistically significant difference. In terms of the association between the duration of preoperative DENO and local recurrence, in three trials where preoperative DENO was given for not more than six months, the odds ratios of local recurrence between the DENO group and no DENO group were 1.07, 2.76, and 37.80, respectively. Where preoperative DENO duration was more than six months in four trials, the odds ratios for local recurrence between the DENO group and no DENO group were 0.60, 5.71, 7.75, and 28.33, respectively.

Two additional studies not covered in the included systematic review are presented in Table 1. In a retrospective cohort study, Tsukamoto et al found that local recurrences were higher in GCTB patients with surgery plus neoadjuvant DENO than those with surgery alone (50% vs. 15%, $p < 0.0001$) [23]. Lim et al compared patients in three different groups and reported local recurrence numbers of 12 in the no DENO group, two in the adjuvant DENO group, and three in the neoadjuvant and adjuvant DENO group ($p =$ not significant [NS]) [20].

3. Pain control

There were no studies that looked at pain control in patients receiving DENO versus no DENO.

4. Disease stability/control

A total of two studies reported results of disease stability/control for patients receiving DENO versus no DENO (see Table 1). Lim et al reported disease control rates of patients receiving no DENO (66.7%) versus adjuvant DENO (77.8%) versus neoadjuvant plus adjuvant DENO (87.5%; $p=NS$) [20]. Tsukamoto et al (2019b) reported that 22 patients in the DENO and surgery group had partial response rates (73.3%) and eight patients had stable disease (26.7%); no results were reported in the no DENO group.

5. Adverse Effects

a. Malignant transformation

Tsukamoto et al (2019b) examined GCTB patients receiving DENO administration and surgery versus patients receiving surgery alone and found that patients in the two groups had similar lung metastasis rates (3.3% vs. 4.7%; $p=0.589$) [23]. Lim et al reported that two of 17

(3.2%) patients who received both neoadjuvant and adjuvant DENO had malignant transformation, but patients without DENO or only with neoadjuvant therapy of DENO did not have malignant transformation or osteonecrosis of jaw [20].

b. Osteonecrosis of jaw

There were no reported cases of osteonecrosis of the jaw in any of the identified studies.

c. Atypical femur fracture

There were no studies that reported atypical femur fractures in patients receiving DENO versus no DENO.

Ongoing, Unpublished, or Incomplete Studies

There are no ongoing, unpublished and incomplete studies found from The National Cancer Institute Clinical Trials Database (<http://www.clinicaltrials.gov/>) that met the inclusion criteria of this evidence summary. The search was conducted on August 19, 2020. However, the Working Group members indicated that there is one ongoing randomized trial being conducted by the Bone and Soft Tissue Tumor Study Group in the Japan Clinical Oncology Group, which will be the first randomized study comparing outcomes with and without DENO. The primary endpoint is relapse-free survival and secondary endpoints include disease-related survival, joint-preserved survival, adverse events, and surgical and postoperative complications. (Appendix 5).

Table 1- Studies comparing DENO administration vs no DENO administration.

Evidence Summary 11-13

Author and Study type	Patient population; Mean/ Median age; Median follow-up time	Arms or comparisons	Number of Pts analyzed	Facilitation of surgery/reduced morbidity after surgery	Disease recurrence	Pain control	Disease stability/ control	Adverse effects
Agarwal 2018, Case-matched control	54 pts with primary or recurrent GCTB located in the axial skeleton, appendicular skeleton, or distal tibia and sacrum; 32 (17-67) yr; 27-60 mths	Group 1: Neoadjuvant DENO 120mg every month for 4 mths with additional doses of 120mg on d8, d15 during 1st mth only	25	DENO aided surgical resection by hardening the tumor and the bony shell	Group 1: 11 (44%) in curettage, Group 2: 7 (21%), OR =3.03 (95% CI 0.96 to 9.54), p=0.085	NR	NR	No osteonecrosis of jaw
		Group 2: Surgery alone	34	NR				
Lim 2020, Retro cohort	64 pts with sacral GCTB; 34 (11-65) yr; 48 (12-91) mths	Group 1: Surgery alone	36	Mean operating time [mins (SD)]: 199.4 (49.5) vs 200.6 (69.8) vs 181.2 (38.6), p=NS. Blood loss during surgery [ml (SD)]: 1715 vs 1600 vs 1418, p=0.008	Local recurrence (n): 12 vs 2 vs 3. 1 yr RFS (%): 86.1 vs 100 vs 94.1, p=NS. 2 yr RFS (%) 72.2 vs 100 vs 86.3, p=NS. 3 yr RFS (%) 69.4 vs 75.0 vs 69.0, p=NS	NR	Local control rate: 66.7% vs 77.8% vs 87.5%, p=NS	NR
		Group 2: Adjuvant DENO 120 mg mthly. Continuation based on progress.	9					No osteonecrosis of jaw
		Group 3: Neoadjuvant DENO 120mg d1, d8 and d15 with additional doses on d28 and every 4 wks, if required; Adjuvant: DENO 120 mg mthly, continuously based on progression.	17					No osteonecrosis of jaw, Malignant transformation: 3.2%
Medellin 2018, Retro Cohort	120 patients with GCTB located in the femur and other bones; 33 (14-86) yr; 75 (12-301) mths	Group 1: Neoadjuvant DENO: 120mg wk 1,2,3,5 and mthly until surgery. Mean duration of denosumab treatment prior to surgery was 8.9 (3-19) mths.	7	Mean time interval until initial surgery (Group 1 vs Group 2): 61 wks (13-134) vs 4 wks (0-19), p<0.001. After initial surgery n=41 (41%) in Group 2 required further surgical intervention. No data in Group 1.	Multivariate analysis showed DENO associated with higher risk of local recurrence (HR 3.2, 95% CI 1.07-9.55, p=0.037)	NR	NR	No significant adverse effects that warranted cessation of DENO
		Group 2: Surgery alone	100					NR
Scoccianti 2018, Retro cohort	97 pts with GCTB located at the distal femur, distal tibia, distal radius and sacrum, proximal humerus, distal humerus, finger phalanx, iliac wing, proximal tibia, patella; 42 (17-66) yr; 27-39 mths	Group 1: Neoadjuvant DENO: 120mg weekly for 3 wks, then monthly for 3 mths, then surgery	12	All showed new bone formation around and partially inside the lesion.	5 (42%) pts, Median 23 (7-54) mths post-surgery	NR	NR	No malignant transformation or Osteonecrosis of jaw
		Group 2: Surgery alone	9	Curettage was considered feasible already at presentation.	1 (11%) pt, 14 mths post-surgery			NR

Evidence Summary 11-13

Tsukamoto 2019b Retro Cohort	411 pts with GCTB located in the distal radius and other sites such as the fibula, distal ulna, proximal radius, scapula, and patella; 29 (23-41) yr; 85 (IQR 54-124)	Group 1: Neoadjuvant DENO 120mg once weekly for first mth and then once a mth for 6-9 mths, then surgery	30	NR	15 (50%) pts vs 58 (15.2%) pts, p <0.0001	NR	Partial response: 22 (73.3%) pts, stable disease: 8 (26.7%) pts	1 (3.3%) pt experienced lung metastases vs 18 (4.7%) pts, p=0.589
		Group 2: Surgery alone	381				Not applicable	

CI = confidence interval; d = day; DENO = denosumab; GCTB = giant cell tumour of bone; HR = hazard ratio; IQR = interquartile range; mins = minutes; ml = milliliter; mthly = monthly; mths = months; NR = not reported; NS = not significant; OR = odds ratio; pts = patients; Retro = retrospective; RFS = recurrence-free survival; SD = standard deviation; vs = versus; wks = weeks; yr = years.

DISCUSSION

This systematic review included five eligible original papers and one existing systematic review that described differences in peri-operative outcome for patients with GCTB who did or did not receive DENO. It was found that either adjuvant or both adjuvant and neoadjuvant DENO administration was associated with a shorter mean operating time than patients receiving no DENO, but the difference was not statistically significant [20]. Further, it was observed that neoadjuvant DENO resulted in less blood loss during surgery [20], more tumour and bony shell hardening [19], more new bone formation around and partially inside the lesion [22], and consolidated the peripheral rim and facilitated excision [21]. One systematic review found that patients receiving preoperative DENO prior to curettage had an increased risk of local recurrence compared with patients who received curettage alone [18]. A separate study not included in the published systematic review supported this conclusion [23]. This could suggest an increase in local recurrence risk with DENO, but due to poor quality, non-randomized studies fraught with selection bias, it is difficult to determine if a significant difference does exist.

None of the included studies reported any osteonecrosis of the jaw for either group. In regards to the development of metastasis, one study found that patients receiving DENO and surgery had similar incidence of lung metastases to patients receiving surgery alone [23].

This systematic review only included RCTs or comparative studies that included a control group where patients did not receive DENO. Thus, the large phase II trials of DENO were not included in the analysis. This systematic review has some limitations. First, among the eligible articles, there were no articles for patients with BFHB or ABC. DENO as a systematic treatment option for BFHB and ABC may not have been well studied to date. Second, the quality of aggregate evidence for every outcome was low to very low. Third, there were no studies that looked at pain control in patients receiving DENO versus no DENO. Fourth, the median range of follow-up time is from 27 to 85 months, which may be not long enough to explore malignant transformation or osteonecrosis of jaw.

CONCLUSIONS

To date, there is insufficient evidence to understand the value of DENO in the peri-operative setting in patients with GCTB. Well-designed prospective comparative studies or RCTs are expected to better answer this research question.

INTERNAL REVIEW

The evidence summary was reviewed by Jonathan Sussman and Emily Vella. The Working Group members were responsible for ensuring any necessary changes were made.

Acceptance by the Sarcoma Disease Site Group

After internal review, the report was presented to the Sarcoma Disease Site Group on January 15 2021. The Sarcoma Disease Site Group reviewed the document, and formally accepted the document.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Name	Affiliation	Declarations of interest
Michelle Ghert Primary Clinical/Content Lead Orthopedic Oncologist	Department of Surgery McMaster University Hamilton, Ontario	Dr. Ghert reports personal fees from Wright Medical, grants from Canadian Institutes of Health Research, grants from Canadian Cancer Society, grants from Hamilton Academic Health Sciences, outside the submitted work.
Abha Gupta Primary Clinical/Content Lead Medical Oncologist/Haematologist	Division of Haematology/Oncology The Hospital for Sick Children Toronto, Ontario	None declared
Richard Tozer Clinical/Expert Member Medical Oncologist	Division of Medical Oncology and Department of Supportive Care Hamilton Health Sciences Hamilton, Ontario	None declared
Snezana Popovic Clinical/Expert Member Pathologist	Department of Pathology and Molecular Medicine McMaster University Hamilton, Ontario	None declared
Lisa Durocher-Allen Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario	None declared
Xiaomei Yao Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario	None declared

Appendix 2: Literature Search Strategy

Giant Cell Tumour of Bone

Embase:

1. exp osteoclastoma/
2. osteoclastoma.mp.
3. (giant cell tumo\$r adj4 bone).mp.
4. exp denosumab/
5. (denosumab or amgiva or prolia or xgeva or amg_162 or amg162).mp.
6. (1 or 2 or 3) and (4 or 5)

Medline:

1. exp "giant cell tumor of bone"/
2. (giant cell tumo\$r adj4 bone).mp.
3. exp denosumab/
4. (denosumab or amgiva or prolia or xgeva or amg_162 or amg162).mp.
5. (1 or 2) and (3 or 4)
6. remove duplicates from 5

Benign Fibrous Histiocytoma of Bone and Secondary Aneurysmal Bone Cyst

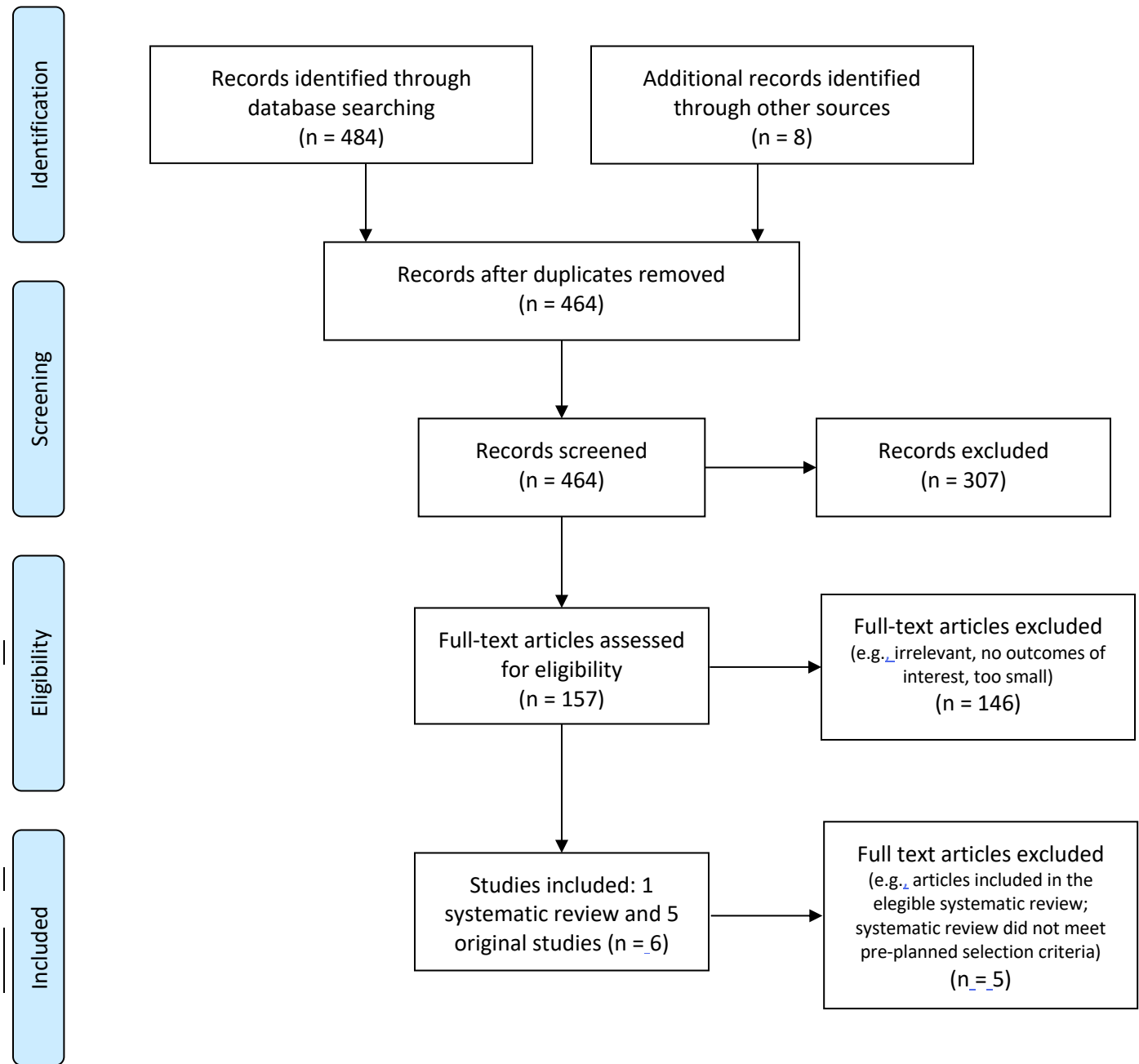
Embase:

1. exp osteoclastoma/
2. osteoclastoma.mp.
3. (giant cell tumo\$r adj4 bone).mp.
4. (benign fibrous histiocytoma).mp.
5. exp bone cysts, aneurysmal/
6. (aneurysmal bone cyst\$).mp.
7. exp denosumab/
8. (denosumab or amgiva or prolia or xgeva or amg_162 or amg162).mp.
9. (4 or 5 or 6) not (1 or 2 or 3)
10. 9 and (7 or 8)
11. Remove duplicates from 10

Medline:

1. exp "giant cell tumor of bone"/
2. (giant cell tumo\$r adj4 bone).mp.
3. exp Histiocytoma, Benign Fibrous/
4. Exp Bone Cysts, Aneurysmal/
5. (aneurysmal bone cyst\$).mp.
6. exp denosumab/
7. (denosumab or amgiva or prolia or xgeva or amg_162 or amg162).mp.
8. (3 or 4 or 5) not (1 or 2)
9. 8 and (6 or 7)
10. Remove duplicates from 9

Appendix 3: PRISMA Flow Diagram



Appendix 4: Risk of Bias assessment of Included systematic reviews and non-randomized studies

ROBIS evaluation of included systematic reviews

Study	Domain 1: Study Eligibility Criteria	Domain 2: Identification and Selection of studies	Domain 3: Data Collection and Study Appraisal	Domain 4: Synthesis and Findings	Overall Risk of Bias
Charest-Morin, 2016[17]	Unclear	Low	Unclear	Unclear	Unclear
Tsukamoto, 2019[18]	Low	Low	Low	Low	Low

ROBIN-I evaluation of included non-randomized studies

Study	Bias due to confounding	Bias due to selection of participants	Bias in measurement of interventions	Bias due to deviations of interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results	Overall Risk of Bias judgement
Agarwal 2018[19]	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious
Lim 2020 [20]	Serious	Moderate	Moderate	Serious	Moderate	Moderate	Moderate	Serious
Medellin 2018[21]	Moderate	Serious	Moderate	Serious	Moderate	Serious	Moderate	Serious
Scoccianti 2018[22]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Tsukamoto, 2019b [23]	Moderate	Serious	Moderate	Serious	Moderate	Serious	Moderate	Serious