Values and other decisional factors regarding treatment of hypercalcaemia of malignancy: a systematic review protocol

Aya Bassatne,1 Maya Rahme,1 Thomas Piggott,2 M. Hassan Murad,3 Layal Hneiny,4 Ghada El-Hajj Fuleihan 1

ABSTRACT

Introduction

Hypercalcaemia of malignancy (HCM) is the second most common cause of hypercalcaemia and is associated with significant morbidity and mortality. Several treatment options are available including pharmacological therapy with bisphosphonates, denosumab, glucocorticoids and calcimetics, as well as conventional therapy with hydration and possibly calcitonin. While guidelines have previously considered treatment effects, no guideline has yet considered a range of contextual factors impacting recommendations for the management. The aim of this study was to summarise the available evidence on important decisional factors for the development of guidelines for the treatment of HCM. These include patient’s values and preferences, cost, acceptability, feasibility and equity.

Methods and analysis

This protocol is registered in PROSPERO (registration number: CRD42021264371). This is a systematic review of observational studies, case series, trials, reviews and qualitative studies involving treatment of adult patients with HCM. We will develop and execute two independent search strategies using five databases: PubMed, Medline (OVID), Embase.com, CINAHL (EBSCO) and Cochrane, and review their combined output. Two reviewers will screen titles and abstracts and full texts and will implement data abstraction from relevant studies independently and in duplicate. The outcomes of interest are the decisional factors that influence drug selection, with possible subgroup summaries by drug class or aetiology of HCM. We will present the data collected in a narrative and thematic approach.

Ethics and dissemination

Ethical approval is not applicable for our study, since we will only collect data from available literature. This systematic review will be submitted to a peer-reviewed journal when completed.

INTRODUCTION

Hypercalcaemia affects 1%–2% of the general population. Hypercalcaemia of malignancy (HCM) is considered the second most common cause of hypercalcaemia, after hyperparathyroidism in adults.1 In fact, one-third of patients with cancer will eventually experience hypercalcaemia, with the most common causes being breast cancer, lung cancer and multiple myeloma.2 3 HCM arises due to four main mechanisms: (1) humoral secretion of parathyroid hormone-related peptide accounts for over 80% of cases and occurs most commonly in breast cancer and squamous cell carcinoma of the lung, head and neck, and the kidney; (2) local osteolytic release of calcium, known as local osteolytic hypercalcaemia, such as seen with multiple myeloma and some breast cancers; (3) high levels of calcitriol (1,25-dihydroxyvitamin D) such as noted in leukemias, HTLV1 and some lymphomas, or secretion of the native parathyroid hormone (PTH) from a carcinoma; or (4) ectopic PTH secretion by some cancers including neuroendocrine tumours (table 1).4 5 These include tumours in the head and neck, thorax, gastrointestinal system or genitourinary system.6 Hypercalcaemia can be classified into mild, moderate or severe. Although mild hypercalcaemia can be asymptomatic, moderate and severe hypercalcaemia can be associated with a wide range of effects...
of symptoms from polyuria, polydipsia, dehydration, nephrolithiasis and muscle weakness all the way to renal failure, lethargy, coma and cardiac arrest. Although not very common, HCM is associated with a longer hospital stay and greater mortality risk when compared with patients with cancer without HCM. In fact, 50% of patients with HCM may die within a month. Therefore, treatment is of utmost importance.

Treatment of HCM constitutes of hydration, calciuresis and inhibition of bone resorption, regardless of the operating mechanism (Table 2). The efficacy of different bisphosphonates was investigated in several clinical trials to determine their value in HCM treatments. This led to the replacement of calcitonin and glucocorticoids in the treatment of HCM by bisphosphonates which are now the preferred treatment options. Pamidronate was approved in 1991, and zoledronic acid was approved in 2000 for the treatment of HCM. However, results pooled from phase III trials have shown zoledronic acid to be more potent than pamidronate with faster normalisation of calcium levels, longer duration of calcium control and a higher response rate. In 2014, denosumab, a receptor activator of nuclear factor kappa-B ligand inhibitor, has been approved for the treatment of HCM refractory to bisphosphonates with significant efficacy. Approval was based on a therapy open-label one-arm phase II multicentre trial of 21 patients. Both bisphosphonates and denosumab are also approved to reduce skeletal-related events in patients with solid tumours and multiple myeloma.

Hypercalcaemia associated with parathyroid carcinoma has been more difficult to treat. Common medical approaches such as calcitonin, glucocorticoids and bisphosphonates have failed. Cinacalcet, a calcimimetic, was found to be effective in lowering calcium levels and maintaining them in patients with parathyroid carcinoma, while glucocorticoids are commonly used for the treatment of myeloma and cancers associated with elevated calcitriol levels.

When patients and clinicians choose among the several treatments of HCM, consideration of benefits (effectiveness evidence) and harms about patient-important outcomes is usually the main driver of the decision. This is currently assessed by a systematic review of benefits and harms of currently used drugs to treat the various diseases associated with HCM. However, many other factors also affect the choice of treatment and are important for

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**Table 1** Mechanisms of hypercalcaemia of malignancy and examples of their associated malignancies

<table>
<thead>
<tr>
<th>Mechanism of hypercalcaemia of malignancy</th>
<th>Associated malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local osteolytic hypercalcaemia</td>
<td>Multiple myeloma, breast carcinoma, leukaemia, lymphoma</td>
</tr>
<tr>
<td>Humoral hypercalcaemia of parathyroid hormone-related peptide</td>
<td>Squamous cell carcinoma, renal carcinoma, bladder carcinoma, breast carcinoma, ovarian carcinoma, prostate carcinoma, colorectal carcinoma, non-Hodgkin’s lymphoma, leukaemia</td>
</tr>
<tr>
<td>Tumours associated with elevated calcitriol levels</td>
<td>Lymphoma, lymphomatoid granulomatosis, angiocentric lymphoma, ovarian dysgerminoma</td>
</tr>
<tr>
<td>PTH secreting tumours: parathyroid carcinoma or ectopic secretion of PTH</td>
<td>Ovarian carcinoma, lung carcinoma, neuroendocrine tumour, thyroid papillary carcinoma, rhabdomyosarcoma, pancreatic carcinoma</td>
</tr>
</tbody>
</table>

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PTH, parathyroid hormone.

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**Table 2** Hypercalcaemia of malignancy treatment options

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mode of action</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional therapy</td>
<td>0.9% NaCl</td>
<td></td>
</tr>
<tr>
<td>Isotonic saline hydration</td>
<td>Restores intravascular volume</td>
<td></td>
</tr>
<tr>
<td>Increases urinary calcium excretion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pharmacological therapy**

<table>
<thead>
<tr>
<th>Bisphosphonates</th>
<th>Inhibit bone resorption</th>
<th>IV bisphosphonates: Pamidronate, Zoledronate, Oral bisphosphonates: Clodronate, Ibandronate, Etidronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab</td>
<td>Inhibits bone resorption</td>
<td>–</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Inhibits bone resorption</td>
<td>Promotes urinary calcium excretion</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Decrease intestinal calcium absorption</td>
<td>Prednisone, Methylprednisone</td>
</tr>
<tr>
<td>Calcimimetics</td>
<td>Calcium-sensing receptor agonist, reduces PTH synthesis and secretion</td>
<td>Cinacalcet</td>
</tr>
</tbody>
</table>

IV, intravenous; NaCl, sodium chloride; PTH, parathyroid hormone.
shared decision-making. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group has developed an Evidence-to-Decision (EtD) framework for the assessment of factors that should complement evidence on the benefits and harms when guideline groups make recommendations. The EtD framework from the GRADE Working Group (EtD) describes five other such factors: patient’s values, costs and resources, feasibility, acceptability and equity. Therefore, and to better inform the recommendations to be made by the Endocrine Society in its Clinical Practice Guidelines on Treatment of Hypercalcemia of Malignancy, we decided to conduct a rigorous meta-narrative systematic review to summarise the best available evidence about the above described decisional factors.

Study objectives
The objective of this systematic review was to summarise the available evidence on important decisional factors including physicians’ and patients’ values and preferences, cost, acceptability, feasibility and equity, for the development of guidelines for the treatment of HCM.

METHODS
Due to the wide availability of different treatment options for HCM, the aim of this systematic review was to identify important contextual and decisional factors that affect choices for therapies of HCM in adult patients. This protocol is reported as per the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist. This protocol is registered in PROSPERO (registration number: CRD42021264371).

Information sources and search strategy
We initially used a search strategy through Epistemonikos database to identify any prior systematic review that addressed factors related to decisional frameworks (online supplemental material 1A) in the treatment of HCM. We were unable to find any relevant publication on the topic (online supplemental material 1B). We will therefore conduct a comprehensive search using the following online databases: Medline (OVID), PubMed, Embase.com, the Cochrane Library and CINAHL (EBSCO). The research team developed a search strategy for each database using MESH terms and keywords related to malignancy, hypercalcemia and factors guiding therapy decision such as patients’ values and preferences, acceptability, equity, cost-effectiveness and feasibility, which was applied to adults. The concept and therefore literature regarding decisional frameworks is relatively new, we therefore limited our search to the last 10 years. With no language restrictions. The strategy was reviewed and verified by the medical librarian at the American university of Beirut (LU), and two methodologists, at the Mayo Evidence Based Centre (MHM) and the McMaster University (TP) (online supplemental material 2A). We also developed another independent search using Medline, without any time limit (online supplemental material 2B). We will execute both searches up to 15 March 2021, and combine their outputs. We will test and use these two search strategies with varying sensitivity and specificity, which were developed independently by two coauthors to obtain better coverage of the literature. We will also try to identify papers by hand searching references from the included studies and studies that have cited the included studies.

Eligibility criteria
We will include observational studies (cohort, cross-sectional and case–control studies), trials, reviews and qualitative studies conducted in adult patients (≥18 years of age) with HCM. We will include studies reporting on pharmacological therapy such as bisphosphonates, denosumab, diuretics, calcitonin and calcimimetics, as well as conservative management including hydration, avoiding calcium-rich diet and vitamin D supplementation. We will exclude case reports, studies conducted in the paediatric population or in patients with hypercalcaemia from a condition unrelated to malignancy, for example, parathyroid disease, familial hypocalciuric hypercalcaemia, vitamin D intoxication and side effects of medications.

Outcomes
Our outcomes of interest are EtD factors:

- Patients’ or physicians’ values (how patients’ familial hypocalciuric hypercalcaemia or physicians’ value each outcome in terms of its importance to their context and daily life).
- Cost and resources (cost effectiveness, actual charges, out-of-pocket costs).
- Acceptability (of treatment options and their method of administration).
- Feasibility (of the intervention as it relates to the healthcare environment).
- Equity (whether the intervention would exacerbate health disparities or create inequities).

We will exclude studies with inadequate outcome measurement or reporting.

Study selection
We will download the literature search results into Covidence software. We developed a screening sheet for title and abstract and another for the full texts (3) based on our exclusion and inclusion criteria of individual studies. We will perform a calibration exercise to familiarise the reviewers with the screening process.

All reviewers (AB, MR, TP, MHM, GE-HF) will contribute to pilot testing the screening at the title and abstract level. Two reviewers (AB, MR) will then screen the remaining titles and abstracts using the screening sheet developed independently and in duplicate (online supplemental material 3A). We will retrieve the full texts of all included citations. Two reviewers (AB, MR) will screen these records independently and in duplicate using the full-text screening guide (online supplemental material...
Quality assessment of included studies
The methodological quality of the included studies will be evaluated using tools appropriate for each study design, including randomised trials, cohort and case–control studies, case series and qualitative research.26–31 Quality assessment will be done independently and in duplicate. To assess the quality of any identified RCTs (Randomized Controlled Trials), we will use the Cochrane Risk of Bias tool which assesses the following domains: bias due to sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data and selective outcome reporting.27 To assess the quality of observational studies, we will use the New Castle-Ottawa quality assessment scale assessing the following categories: selection, comparability and outcome.28 For case series, we will assess four domains: selection, ascertainment, causality and reporting.29 Finally, for qualitative articles, we will use the CASP (Critical Appraisal Skills Programme) appraisal checklist.30

Data synthesis
Data will be analysed thematically and presented narratively. Two independent reviewers will identify themes from each article that can map to a concept in the EtD framework. For example, a theme about whether patients prefer a certain treatment characteristic can map to the acceptability domain in the framework. Consensus among the two reviewers about themes is reached via discussion. We will seek a state of saturation in which the two reviewers agree that further data collection would yield similar results. The next step after saturation is to confirm emerging themes and conclusions. A third reviewer will adjudicate when consensus is not reached.

The certainty of evidence derived from the studies will be evaluated using the GRADE-CERQual approach which appraises qualitative research domains analogous to GRADE. This approach focuses on four domains: methodological limitations, coherence, adequacy and relevance.33 The overall assessment of confidence in the review findings will be based on the assessment of these individual domains.

The methodological limitations domain is assessed in individual studies based on the appropriate design, conduct, and data collection and analysis methods.32 The coherence domain assesses how clear and consistent the individual studies data are with the overall results of the review.33 The adequacy domain assesses the extent of details and available information provided in the review.34 Finally, the relevance domain assesses the extent to which the gathered individual data answers the review’s objectives and questions.35

Discussion
Treatment of HCM is sometimes challenging due to the extensive variety of options available and wide range of benefits and harms. This systematic review will provide data on important decisional factors, which will help shape future guidelines on the management of HCM. This study will also allow physicians and patients to decide on a therapy option based on the current evidence.

To our knowledge, this is the first systematic review conducted in HCM to detect important decisional factors such as patient’s values, costs and resources, feasibility, acceptability and equity. The strength of this systematic review stands in its novelty, and extensive and systematic search of the literature. However, some limitations might be encountered due to the scarcity of available data and lack of reporting of our outcomes of interest.

Ethics and dissemination
Ethical approval is not applicable for our study, since we will only collect data from available literature. This systematic review will be submitted to a peer-reviewed journal when completed.

Acknowledgements
Dr AB would like to acknowledge the training received under the Scholars in HeAlth Research Program (SHARP) that set the required foundations for a career in clinical and translational research.

Contributors
AB, TP, MHM and GE-HF designed and reviewed the search strategy. AB drafted the protocol. TP, MHM and GE-HF designed and reviewed the search strategy. AB drafted the protocol. TP, MHM and GE-HF provided major input on the protocol.

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Patient consent for publication
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Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
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REFERENCES

Supplemental material 1A: Epistemonikos search for relevant systematic reviews (April 2nd, 2020)

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(title:((hypercalcemi* OR Calcinosis) AND (cancer* OR carcinoma* OR adenocarcinoma* OR hepatocarcinoma* OR carcinosarcoma* OR sarcoma* OR histiocytoma* OR fibrosarcoma* OR osteosarcoma* OR chondrosarcoma* OR lymphosarcoma* OR rhabdomyosarcoma* OR leukemi* OR leukaemi* OR erythroleukem* OR erythroleukaem* OR lymphoma* OR melanoma* OR Hodgkin* OR "multiple myeloma" OR mesothelioma* OR neoplas* OR malignan* OR metastas* OR carcinoid* OR neuroblastoma* OR Sezary-Syndrome OR Retinoblastoma* OR pheochromocytoma* OR nephroblastoma* OR choriocarcinoma* OR Pleuropulmonary-Blastoma* OR glioblastoma* OR glioma* OR astrocytoma* OR ependymoma* OR medulloblastoma* OR meningioma* OR craniopharyngioma* OR myelodysplastic OR myeloproliferative OR macroglobulinemi* OR macroglobulinaemi* OR pineoblastoma* OR onc* OR cyst OR tumor* OR tumour*) AND (preference* OR attitude* OR accept* OR perspective* OR valu* OR view* OR feasib* OR sustain* OR barrier* OR access* OR cost* OR resource* OR implement* OR inequit* OR disparit* OR inequalit* OR income OR socioeconomic OR gamble OR utilit* OR health stat* OR adhere* OR quality of life OR willing* OR burden* OR satisf*)) OR abstract:((hypercalcemi* OR Calcinosis) AND (cancer* OR carcinoma* OR adenocarcinoma* OR hepatocarcinoma* OR carcinosarcoma* OR sarcoma* OR histiocytoma* OR fibrosarcoma* OR osteosarcoma* OR chondrosarcoma* OR lymphosarcoma* OR rhabdomyosarcoma* OR leukemi* OR leukaemi* OR erythroleukem* OR erythroleukaem* OR lymphoma* OR melanoma* OR Hodgkin* OR "multiple myeloma" OR mesothelioma* OR neoplas* OR malignan* OR metastas* OR carcinoid* OR neuroblastoma* OR Sezary-Syndrome OR Retinoblastoma* OR pheochromocytoma* OR nephroblastoma* OR choriocarcinoma* OR Pleuropulmonary-Blastoma* OR glioblastoma* OR glioma* OR astrocytoma* OR ependymoma* OR medulloblastoma* OR meningioma* OR craniopharyngioma* OR myelodysplastic OR myeloproliferative OR macroglobulinemi* OR macroglobulinaemi* OR pineoblastoma* OR onc* OR cyst OR tumor* OR tumour*) AND (preference* OR attitude* OR accept* OR perspective* OR valu* OR view* OR feasib* OR sustain* OR barrier* OR access* OR cost* OR resource* OR implement* OR inequit* OR disparit* OR inequalit* OR income OR socioeconomic OR gamble OR utilit* OR health stat* OR adhere* OR quality of life OR willing* OR burden* OR satisf*)))))
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Supplemental material 1B: Screening results retrieved from Epistemonikos (April 2nd, 2020)

36 records retrieved and screened at the titles and abstracts levels

6 records screened at the full text level

All records were excluded: no systematic review done on decisional factors for treatment of Hypercalcemia of Malignancy
Supplemental material 2A: Original search strategies

1- Pubmed

#12 Search #10 AND #11
#11 Search 2010/04:2020/04[crdt]
#10 Search #8 AND #9
#8 Search #6 OR #7
#7 Search HHM*[tw] or LOH*[tw]
#6 Search #1 AND #5
#5 Search #2 OR #3 OR #4
#4 Search (c calcinos*[tw] OR hypercalcemi*[tw])
#3 Search Hypercalcemia [MESH: NOEXP]
#2 Search Calcinosis[MESH: NOEXP]
2- Medline (OVID)

| 1 | (cancer* or carcinoma* or adenocarcinoma* or hepatocarcinoma* or carcinosarcoma* or sarcoma* or histiocytoma* or fibrosarcoma* or osteosarcoma* or chondrosarcoma* or lymphosarcoma* or rhabdomyosarcoma* or leuk?emi* or erythroleukem* or erythroleukaem* or lymphoma* or melanoma* or Hodgkin* or "multiple myeloma" or mesothelioma* or neoplas* or malignan* or metastas* or carcinoid* or neuroblastoma* or (Mycosis adj Fungoid?s) or (Sezary adj Syndrome) or Retinoblastoma* or pheochromocytoma* or nephroblastoma* or choriocarcinoma* or (Pleuropulmonary adj Blastoma?) or glioblastoma* or glioma* or astrocytoma* or ependymoma* or medulloblastoma* or meningioma* or craniopharyngioma* or myelodysplastic or myeloproliferative or macroglobulinemi* or macroglobulinaemi* or pineoblastoma* or oncol* or cyst or tumo?r*).mp. or exp Neoplasm/ |
| 2 | Calcinosis/ or hypercalcemia/ or (calcinos?s or hypercalcemi*).mp. |
| 3 | (HHM or LOH).mp. |
| 4 | 1 and 2 |
| 5 | 3 or 4 |
| 6 | exp Attitude to Health/ or Patient Participation/ or Patient Preference/ or Cost-Benefit Analysis/ or (preference* or choice* or valu* or expectation? or attitude* or acceptab* or knowledg* or sustain* or barrier* or access* or implement* or inequit* or disparit* or inequalit* or income or socioeconomic* or gamble or utilit* or (health adj stat*) or adhere* or (quality adj2 life) or Qol or willing* or burden* or satisf* or opinion* or ((patient* or user* or health*) adj3 (participat* or perce*)) or (Decision adj3 (board* or tool* or analy* or support)) or equit* or equality or feasib* or perspective* or cost* or resource* or (balance adj1 sect*) or (discrete* adj1 choice*),mp. or ((exp Decision Making/ or (decision* adj1 mak*).mp.) and (patient* or user* or Famil* or customer* or consumer* or client* or women or men or individual?).mp.) |
| 7 | 5 and 6 |
| 8 | limit 7 to ez="20100407-20200407" |
3- Embase.com

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#13. [1-4-2010]/sd
#12. #10 AND #11
#11. 'attitude to health'/exp OR 'patient participation'/de OR 'patient preference'/de OR 'cost benefit analysis'/de OR preference*:ti,ab,kw OR choice*:ti,ab,kw OR valu*:ti,ab,kw OR expectation$:ti,ab,kw OR attitude*:ti,ab,kw OR acceptab*:ti,ab,kw OR knowledge*:ti,ab,kw OR sustain*:ti,ab,kw OR barrier*:ti,ab,kw OR access*:ti,ab,kw OR implement*:ti,ab,kw OR inequit*:ti,ab,kw OR disparit*:ti,ab,kw OR inequalit*:ti,ab,kw OR income:ti,ab,kw OR socioeconomic*:ti,ab,kw OR gamble:ti,ab,kw OR utilit*:ti,ab,kw OR (health NEXT/0 stat*)ti,ab,kw OR adherence*:ti,ab,kw OR (quality NEAR/2 life:ti,ab,kw) OR qol:ti,ab,kw OR willing*:ti,ab,kw OR burden*:ti,ab,kw OR satisf*:ti,ab,kw OR opinion*:ti,ab,kw OR ((patient* OR user* OR health*) NEAR/3 (participat* OR perce*)):ti,ab,kw) OR ((decision NEAR/3 (board* OR tool* OR analy* OR support)):ti,ab,kw) OR equit*:ti,ab,kw OR equality:ti,ab,kw OR feasib*:ti,ab,kw OR perspective*:ti,ab,kw OR cost:ti,ab,kw OR resource*:ti,ab,kw OR ((balance NEAR/1 sect*):ti,ab,kw) OR ((discrete* NEAR/1 choice*):ti,ab,kw) OR (decision making/exp AND (patient*:ti,ab,kw OR user*:ti,ab,kw OR famil*:ti,ab,kw OR customer*:ti,ab,kw OR consumer*:ti,ab,kw OR client*:ti,ab,kw OR women:ti,ab,kw OR men:ti,ab,kw OR individual*:ti,ab,kw))
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#9. #3 AND #7
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4- CINAHL (EBSCO)

S29 MW S14 AND S28
S28 S15 OR S16 OR S17 OR S18 OR S24 OR S25 OR S26 OR S27

MW (preference* OR choice* OR valu* OR expectation# OR attitude* OR acceptab* OR knowledge*) OR sustain* OR barrier* OR access* OR implement* OR inequit* OR disparit* OR inequalit* OR income OR socioeconomic* OR gamble OR utilit* OR ((health W0 stat*)) OR adherence* OR ((quality N2 life)) OR qol OR willing* OR burden* OR satisf* OR opinion* OR ((patient* OR user* OR health*) (participat* OR perce*)) OR ((decision N3 (board* OR tool* OR analy* OR support)) OR equit* OR equality OR feasib* OR perspective* OR cost OR resource* OR ((balance N1 sect*)) OR ((discrete* N1 choice*)) OR ((decision N1 mak*)) AND
S11  S5 OR S6 OR S7 OR S8 OR S9
S10  S1 OR S2 OR S3 OR S4
S9   MW calcinos* OR hypercalcemi*
S8   AB calcinos* OR hypercalcemi*
S7   TI calcinos* OR hypercalcemi*
S6   (MH "Hypercalcemia")
S5   (MH "Calcinosis")

MW TI (cancer* OR carcinoma* OR hepatocarcinoma* OR carcinosarcoma* OR sarcoma* OR histiocytoma* OR fibrosarcoma* OR osteosarcoma* OR chondrosarcoma* OR lymphosarcoma* OR rhabdomyosarcoma* OR leukeni* OR leukaemi* OR erythroleukem* OR erythroleukaem* OR lymphoma* OR melanoma* OR hodgkin* OR multiple myeloma* OR mesothelioma* OR neoplas* OR malignan* OR metastas* OR carcinoma* OR neuroblastoma* OR (mycosis W0 fungoid#s)) OR (sezyary W0 syndrome) OR retinoblastoma* OR pheochromocytoma* OR nephroblastoma* OR choriocarcinoma* OR ((pleuropulmonary W0 blastoma#)) OR glioblastoma* OR glioma* OR astroctoma* OR ependymoma* OR medulloblastoma* OR meningioma* OR craniofaryngioma* OR myelodysplastic OR myeloproliferative OR macroglobulinemi* OR macroglobulinaemi* OR pineoblastoma* OR oncol* OR cyst OR tumo#r*)

S4   AB TI (cancer* OR carcinoma* OR hepatocarcinoma* OR carcinosarcoma* OR sarcoma* OR histiocytoma* OR fibrosarcoma* OR osteosarcoma* OR chondrosarcoma* OR lymphosarcoma* OR rhabdomyosarcoma* OR leukeni* OR leukaemi* OR erythroleukem* OR erythroleukaem* OR lymphoma* OR melanoma* OR hodgkin* OR multiple myeloma* OR mesothelioma* OR neoplas* OR malignan* OR metastas* OR carcinoma* OR neuroblastoma* OR (mycosis W0 fungoid#s)) OR (sezyary W0 syndrome) OR retinoblastoma* OR pheochromocytoma* OR nephroblastoma* OR choriocarcinoma* OR ((pleuropulmonary W0 blastoma#)) OR glioblastoma* OR glioma* OR astroctoma* OR ependymoma* OR medulloblastoma* OR meningioma* OR craniofaryngioma* OR myelodysplastic OR myeloproliferative OR macroglobulinemi* OR macroglobulinaemi* OR pineoblastoma* OR oncol* OR cyst OR tumo#r*)

S3   TI TI (cancer* OR carcinoma* OR hepatocarcinoma* OR carcinosarcoma* OR sarcoma* OR histiocytoma* OR fibrosarcoma* OR osteosarcoma* OR chondrosarcoma* OR lymphosarcoma* OR rhabdomyosarcoma* OR leukeni* OR leukaemi* OR erythroleukem* OR erythroleukaem* OR lymphoma* OR melanoma* OR hodgkin* OR multiple myeloma* OR mesothelioma* OR neoplas* OR malignan* OR metastas* OR carcinoma* OR neuroblastoma* OR (mycosis W0 fungoid#s)) OR (sezyary W0 syndrome) OR retinoblastoma* OR pheochromocytoma* OR nephroblastoma* OR choriocarcinoma* OR ((pleuropulmonary W0 blastoma#)) OR glioblastoma* OR glioma* OR astroctoma* OR ependymoma* OR medulloblastoma* OR meningioma* OR craniofaryngioma* OR myelodysplastic OR myeloproliferative OR macroglobulinemi* OR macroglobulinaemi* OR pineoblastoma* OR oncol* OR cyst OR tumo#r*)

S2   (MH "Neoplasms+")

S1   (MH "Calcinosis")
5- Cochrane

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<th>#1</th>
<th>MeSH descriptor: [Neoplasms] explode all trees</th>
</tr>
</thead>
<tbody>
<tr>
<td>#2</td>
<td>cancer*:ti,ab,kw OR carcinoma*:ti,ab,kw OR adenocarcinoma*:ti,ab,kw OR hepatocarcinoma*:ti,ab,kw OR carcinosarcoma*:ti,ab,kw OR sarcoma*:ti,ab,kw OR histiocytoma*:ti,ab,kw OR fibrosarcoma*:ti,ab,kw OR osteosarcoma*:ti,ab,kw OR chondrosarcoma*:ti,ab,kw OR lymphosarcoma*:ti,ab,kw OR rhabdomyosarcoma*:ti,ab,kw OR leukemi*:ti,ab,kw OR leukaemi*:ti,ab,kw OR erythroleuken*:ti,ab,kw OR erythroleukaem*:ti,ab,kw OR lymphoma*:ti,ab,kw OR lymphoma*:ti,ab,kw OR melanoma*:ti,ab,kw OR hodgkin*:ti,ab,kw OR 'multiple myeloma':ti,ab,kw OR mesothelioma*:ti,ab,kw OR neoplas*:ti,ab,kw OR malignan*:ti,ab,kw OR metastas*:ti,ab,kw OR carcinoid*:ti,ab,kw OR neuroblastoma*:ti,ab,kw OR ((mycosis NEXT fungoid$):ti,ab,kw) OR ((sezary NEXT syndrome):ti,ab,kw) OR ((sezyary NEXT syndrome):ti,ab,kw) OR retinoblastoma*:ti,ab,kw OR pheochromocytoma*:ti,ab,kw OR nephroblastoma*:ti,ab,kw OR choriocarcinoma*:ti,ab,kw OR ((pleuropulmonary NEXT blastoma$):ti,ab,kw) OR glioblastoma*:ti,ab,kw OR glioma*:ti,ab,kw OR astrocytoma*:ti,ab,kw OR ependymoma*:ti,ab,kw OR medulloblastoma*:ti,ab,kw OR meningioma*:ti,ab,kw OR craniohypophyrgioma*:ti,ab,kw OR myelodysplastic:ti,ab,kw OR myeloproliferative:ti,ab,kw OR macroglobulinemi*:ti,ab,kw OR macroglobulinaemi*:ti,ab,kw OR pineoblastoma*:ti,ab,kw OR oncol*:ti,ab,kw OR cyst:ti,ab,kw OR tumo$r*:ti,ab,kw</td>
</tr>
<tr>
<td>#3</td>
<td>#1 or #2</td>
</tr>
<tr>
<td>#4</td>
<td>MeSH descriptor: [Calcinosis] this term only</td>
</tr>
<tr>
<td>#5</td>
<td>MeSH descriptor: [Hypercalcemia] this term only</td>
</tr>
<tr>
<td>#6</td>
<td>calcinos*:ti,ab OR hypercalcemi*:ti,ab</td>
</tr>
<tr>
<td>#7</td>
<td>#4 or #5 or #6</td>
</tr>
<tr>
<td>#8</td>
<td>#3 and #7</td>
</tr>
<tr>
<td>#9</td>
<td>hhm:ti,ab OR loh:ti,ab</td>
</tr>
<tr>
<td>#10</td>
<td>#8 or #9</td>
</tr>
<tr>
<td>#11</td>
<td>MeSH descriptor: [Attitude to Health] explode all trees</td>
</tr>
<tr>
<td>#12</td>
<td>MeSH descriptor: [Patient Participation] this term only</td>
</tr>
<tr>
<td>#13</td>
<td>MeSH descriptor: [Patient Preference] this term only</td>
</tr>
<tr>
<td>#14</td>
<td>MeSH descriptor: [Cost-Benefit Analysis] this term only</td>
</tr>
<tr>
<td>#15</td>
<td>MeSH descriptor: [Decision Making] explode all trees</td>
</tr>
<tr>
<td>#16</td>
<td>(patient*:ti,ab,kw OR user*:ti,ab,kw OR famil*:ti,ab,kw OR consumer*:ti,ab,kw OR client*:ti,ab,kw OR woman:ti,ab,kw OR man:ti,ab,kw OR individual?:ti,ab,kw)</td>
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<tr>
<td>#17</td>
<td>#15 AND #16</td>
</tr>
<tr>
<td>#18</td>
<td>(decision NEAR/3 (board* OR tool* OR analy* OR support)):ti,ab,kw) OR equit*:ti,ab,kw OR equality:ti,ab,kw OR feasib*:ti,ab,kw OR perspective*:ti,ab,kw OR resource*:ti,ab,kw OR ((balance NEAR/1 sect*:ti,ab,kw) OR ((discrete* NEAR/1 choice*):ti,ab,kw) OR (((decision* NEAR/1 mak*:ti,ab,kw) AND (patient*:ti,ab,kw OR user*:ti,ab,kw OR famil*:ti,ab,kw OR consumer*:ti,ab,kw OR man:ti,ab,kw OR individual?:ti,ab,kw)</td>
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</tbody>
</table>
(consumer*:ti,ab,kw OR client*:ti,ab,kw OR women:ti,ab,kw OR woman:ti,ab,kw OR men:ti,ab,kw OR man:ti,ab,kw OR individual*:ti,ab,kw))

#19 (preference*:ti,ab,kw OR choice*:ti,ab,kw OR valu*:ti,ab,kw OR expectation$:ti,ab,kw OR attitude*:ti,ab,kw OR acceptab*:ti,ab,kw OR knowledg*:ti,ab,kw) OR sustain*:ti,ab,kw OR barrier*:ti,ab,kw OR access*:ti,ab,kw OR implement*:ti,ab,kw OR inequit*:ti,ab,kw OR disparit*:ti,ab,kw OR inequalit*:ti,ab,kw OR income:ti,ab,kw OR socioeconomic*:ti,ab,kw OR gamble:ti,ab,kw OR utilit*:ti,ab,kw OR ((health NEXT stat*):ti,ab,kw) OR adhere*:ti,ab,kw OR ((quality NEAR/2 life):ti,ab,kw) OR qol:ti,ab,kw OR willing*:ti,ab,kw OR burden*:ti,ab,kw OR satisf*:ti,ab,kw OR opinion*:ti,ab,kw OR (((patient* OR user* OR health*) NEAR/3 (participat* OR perce*)):ti,ab,kw)

#20 #11 OR #12 OR #14 OR #17 OR #18 OR #19

#21 #10 AND #20

#22 #10 AND #20 with Cochrane Library publication date Between Apr 2010 and Apr 2020
Supplemental material
Supplemental material 2B: Second independent search strategy

Medline (OVID)

1. hypercalcemia.mp. or exp Hypercalcemia/
2. cancer.mp. or exp Neoplasms/
3. 1 and 2
4. patient preference.mp. or exp Patient Preference/
5. decision making.mp. or exp Decision Making/
6. values.mp. or exp Social Values/
7. cost.mp. or exp "Costs and Cost Analysis"/
8. "Delivery of Health Care"/ or Health Equity/ or equity.mp. or Health Services Accessibility/ or Health Status Disparities/
9. trade off.mp.
10. standard gamble.mp. or Attitude to Health/
11. patient satisfaction.mp. or exp Patient Satisfaction/
12. feasibility.mp.
13. accessibility.mp.
14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 3 and 14
16. remove duplicates from 15
**Supplemental material 3A: Titles and abstracts screening guide**

**We will include all study designs except case reports**

- Case report → Exclude
- Any other study design → go to the next question

**Is the study population adult patients with hypercalcemia of malignancy?**

- No → Exclude
- Yes/not clear → go to the next question

**Does the study report on any of the following decisional factors: patients’ values, cost and resources, acceptability, equity or feasibility?**

- No → Exclude
- Yes/not clear → Include
Supplemental material 3B: Full texts screening guide

Is the study population adult patients with hypercalcemia of malignancy?

☐ No  → Exclude
☐ Yes  → go to the next question

Does the study report on any of the following decisional factors: patients’ values, cost and resources, acceptability, equity or feasibility?

☐ No  → Exclude
☐ Yes  → Include

Reasons for exclusion:
Code 1: Study population does not include patients with hypercalcemia of malignancy
Code 2: None of the outcomes of interest are described
### Supplemental material 4: Data Abstraction tables

#### Characteristics of included studies

<table>
<thead>
<tr>
<th>Author, year (Country)</th>
<th>Study design</th>
<th>Sample size (N)</th>
<th>Study Setting</th>
<th>Level of care</th>
<th>Health care delivery model</th>
<th>Age (mean ± SD)</th>
<th>Gender (% women)</th>
<th>Cause of hypercalcemia</th>
<th>Type of treatment</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td>Inpatient</td>
<td>Primary</td>
<td>Secondary</td>
<td>Tertiary</td>
<td>HMO</td>
<td>Private</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Outpatient</td>
<td>Secondary</td>
<td>Tertiary</td>
<td>HMO</td>
<td>Private</td>
<td>Government</td>
<td>Other</td>
</tr>
</tbody>
</table>

#### Methodological characteristics of included studies

<table>
<thead>
<tr>
<th>Author, year (Country)</th>
<th>Sampling method</th>
<th>Sample size calculation</th>
<th>Response Rate</th>
<th>Administration method</th>
<th>Tool Validation and Pilot testing</th>
<th>Limitations</th>
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</thead>
</table>

#### Summary of results of included studies

<table>
<thead>
<tr>
<th>Author, year (Country)</th>
<th>Outcomes</th>
<th>Patients/Physicians values</th>
<th>Patients/Physicians preferences</th>
<th>Acceptability</th>
<th>Equity</th>
<th>Cost &amp; Resources</th>
<th>Feasibility</th>
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<tr>
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