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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 calcimimetics, 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.

Strengths and limitations of this study

- ► Our systematic review would investigate important decisional factors regarding treatment of hypercalcaemia of malignancy.
- ► It would evaluate predictors of values and preferences of patients and of physicians impacting such therapeutic decisions.
- ► It would systematically capture studies reporting on cost, acceptability, feasibility and equity of various treatments.
- ► It may be limited by the potential scarcity of identified studies and limited reporting on outcomes of interest.
- ► Some of our findings might be outdated with regard to cost, and not generalisable across different populations.

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 hypercalcemia can be associated with a wide range

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

Mechanism of hypercalcaemia of malignancy	Associated malignancies
Local osteolytic hypercalcaemia	Multiple myeloma Breast carcinoma Leukaemia Lymphoma
Humoral hypercalcaemia of malignancy: secretion of parathyroid hormone-related peptide	Squamous cell carcinoma Renal carcinoma Bladder carcinoma Breast carcinoma Ovarian carcinoma Prostate carcinoma Colorectal carcinoma Non-Hodgkin's lymphoma Leukaemia
Tumours associated with elevated calcitriol levels	Lymphoma Lymphomatoid granulomatosis/ angiocentric lymphoma Ovarian dysgerminoma
PTH secreting tumours: parathyroid carcinoma or ectopic secretion of PTH	Ovarian carcinoma Lung carcinoma Neuroectodermal tumour Neuroendocrine tumour Thyroid papillary carcinoma Rhabdomyosarcoma Pancreatic carcinoma

PTH, parathyroid hormone.

of symptoms from polyuria, polydipsia, dehydration, nephrolithiasis and muscle weakness all the way to renal failure, lethargy, coma and cardiac arrest.[4] Although not very common, HCM is associated with a longer hospital stay and greater mortality risk when compared with patients with cancer without HCM.[7] In fact, 50% of patients with HCM may die within a month.[8] Therefore, treatment is of utmost importance.

Treatment of HCM constitutes of hydration, calciuresis and inhibition of bone resorption,[4 9] 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.[10–13] This led to the replacement of calcitonin and glucocorticoids in the treatment of HCM by bisphosphonates which are now the preferred treatment options.[9] 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.[14] 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.[2 15] Approval was based on a therapy open-label one-arm phase II multicentre trial of 21 patients.[16] Both bisphosphonates and denosumab are also approved to reduce skeletal-related events in patients with solid tumours and multiple myeloma.[17] Hypercalcaemia associated with parathyroid carcinoma has been more difficult to treat. Common medical approaches such as calcitonin, glucocorticoids and bisphosphonates have failed.[18 19] Cinacalcet, a calcimimetic, was found to be effective in lowering calcium levels and maintaining them in patients with parathyroid carcinoma,[20] 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.[21] 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

Table 2 Hypercalcaemia of malignancy treatment options

Intervention	Mode of action	Examples
Conventional therapy		
Isotonic saline hydration	Restores intravascular volume Increases urinary calcium excretion	0.9% NaCl
Pharmacological therapy		
Bisphosphonates	Inhibit bone resorption	IV bisphosphonates: Pamidronate Zoledronate Oral bisphosphonates: Clodronate Ibandronate Etidronate
Denosumab	Inhibits bone resorption	–
Calcitonin	Inhibits bone resorption Promotes urinary calcium excretion	–
Glucocorticoids	Decrease intestinal calcium absorption Decrease 1,25-dihydroxyvitamin D production by activated mononuclear cells	Prednisone Methylprednisone
Calcimimetics	Calcium-sensing receptor agonist, reduces PTH synthesis and secretion	Cinacalcet

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.[22] 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.[23] 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.[24] 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, hypercalcaemia 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 (LH), 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'amilial 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.[25] 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 for 100 citations. 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

3B). All disagreements throughout the screening process will be resolved through discussion or with the help of a third reviewer as needed (TP, MHM, GE-HF). All reasons for exclusion will be recorded. We will measure the agreement between the two reviewers (AB, MR) at each screening step using the Cohen's kappa statistic.

Data collection and abstraction

Following the full-text screening, two reviewers (AB, MR) will complete data abstraction independently and in duplicate using standardised data collection tables (online supplemental material 4). We will implement a calibration exercise to familiarise the reviewers with the process. We will resolve any disagreements through discussion or with the help of a third reviewer as needed (TP, MHM, GE-HF). We will extract the first author's name, date of publication and the study design, and will collect data on the characteristics, methodology and results of each of the included studies (online supplemental material 4).

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 are reasonably assured 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.[31] 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]

Patient and public involvement

No patient involved.

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.

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Contributors AB, TP, MHM and GE-HF designed the study. AB, LH, MR, 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. All authors read and approved the final manuscript.

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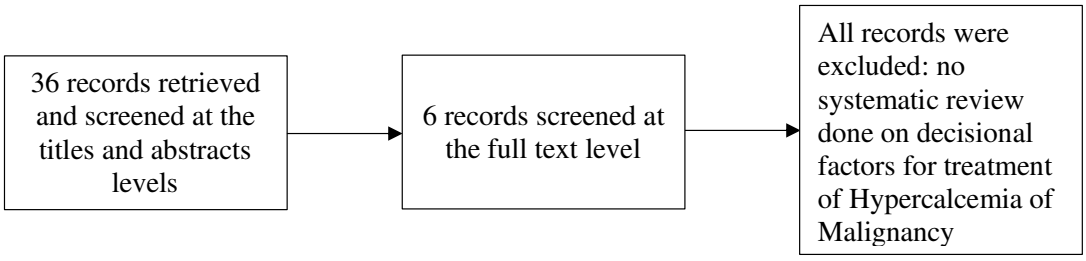
Supplemental material 1A: Epistemonikos search for relevant systematic reviews (April 2nd, 2020)

(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 oncol* 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 oncol* 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*)))

Supplemental material 1B: Screening results retrieved from Epistemonikos (April 2nd, 2020)



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
#9	Search "Attitude to Health"[MESH] OR Patient Participation[MESH:NOEXP] OR Patient Preference[MESH:NOEXP] OR Cost-Benefit Analysis[MESH:NOEXP] OR preference*[tw] OR choice*[tw] OR valu*[tw] OR expectation*[tw] OR attitude*[tw] OR acceptab*[tw] OR knowledg*[tw] OR sustain*[tw] OR barrier*[tw]] OR access*[tw] OR implement*[tw] OR inequit*[tw] OR disparit*[tw] OR inequalit*[tw] OR income[tw] OR socioeconomic*[tw] OR gamble[tw] OR utility*[tw]OR health sat*[tw] OR adhere*[tw] OR quality life[tw] OR Qol[tw] OR willing*[tw]OR burden*[tw] OR satisf*[tw] OR opinion*[tw] OR Patient participation*[tw] OR patients participation*[tw] OR user participation*[tw] OR users participation*[tw] OR health participation*[tw] OR healthcare participation*[tw] OR health-care participation*[tw] OR Patient perception*[tw] OR patients perception*[tw] OR user perception*[tw] OR users perception*[tw] OR health perception*[tw] OR healthcare perception*[tw] OR health-care perception*[tw] OR (decision*[tw] AND (board*[tw] OR tool*[tw] OR analy*[tw] OR support[tw]) OR equit*[tw] OR equality[tw] OR feasib*[tw] OR perspective*[tw] OR cost*[tw] OR resource*[tw]) OR balance sect*[tw] OR discrete choice*[tw] OR (("decision making"[mesh] OR decision mak*[tw]) AND (patient*[tw] OR user*[tw] OR Famil*[tw] OR customer*[tw] OR consumer*[tw] OR client*[tw] OR men[tw] OR man[tw] OR women[tw] OR woman[w] OR individual[tw] OR individuals[tw]))
#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 (calcinos*[tw] OR hypercalcemi*[tw])
#3	Search Hypercalcemia [MESH:NOEXP]
#2	Search Calcinosis[MESH:NOEXP]
#1	Search (cancer*[tw] OR carcinoma*[tw] OR adenocarcinoma*[tw] OR hepatocarcinoma*[tw] OR carcinosarcoma*[tw] OR sarcoma*[tw] OR histiocytoma*[tw] OR fibrosarcoma*[tw] OR osteosarcoma*[tw] OR chondrosarcoma*[tw] OR lymphosarcoma*[tw] OR rhabdomyosarcoma*[tw] OR leukemi*[tw] OR leukaemi*[tw] OR erythroleukem*[tw] OR erythroleukaem*[tw] OR lymphoma*[tw] OR melanoma*[tw] OR hodgkin*[tw] OR multiple myeloma*[tw] OR mesothelioma*[tw] OR neoplas*[tw] OR malignan*[tw] OR metastas*[tw] OR carcinoid*[tw] OR neuroblastoma*[tw] OR Mycosis Fungoid*[tw] OR Sezary Syndrome*[tw] OR Retinoblastoma*[tw] OR pheochromocytoma*[tw] OR nephroblastoma*[tw] OR chORiocarcinoma*[tw] OR Pleuropulmonary Blastoma*[tw] OR glioblastoma*[tw] OR glioma*[tw] OR astrocytoma*[tw] OR ependymoma*[tw] OR medulloblastoma*[tw] OR meningioma*[tw] OR craniopharyngioma*[tw] OR myelodysplastic[tw] OR myeloproliferative[tw] OR macroglobulinemi*[tw] OR macroglobulinaemi*[tw] OR pineoblastoma*[tw] OR oncol*[tw] OR cyst[tw] OR tumor*[tw] OR tumour*[tw] OR Neoplasm [MESH]

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

#14. #12 AND #13
#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$:ti,ab,kw OR attitude*:ti,ab,kw OR acceptab*:ti,ab,kw OR knowledg*:ti,ab,kw OR sustain*:ti,ab,kw OR barrier*:ti,ab,kw OR access*:ti,ab,kw OR implement*:ti,ab,kw OR inequit*:ti,ab,kw OR disparit*:ti,ab,kw OR inequalit*:ti,ab,kw OR income:ti,ab,kw OR socioeconomic*:ti,ab,kw OR gamble:ti,ab,kw OR utilit*:ti,ab,kw OR ((health NEXT/0 stat*):ti,ab,kw) OR adhere*:ti,ab,kw OR ((quality NEAR/2 life):ti,ab,kw) OR qol:ti,ab,kw OR willing*:ti,ab,kw OR burden*:ti,ab,kw OR satisf*:ti,ab,kw OR opinion*:ti,ab,kw OR (((patient* OR user* OR health*) NEAR/3 (participat* OR perce*)):ti,ab,kw) OR ((decision NEAR/3 (board* OR tool* OR analy* OR support)):ti,ab,kw) OR equit*:ti,ab,kw OR equality:ti,ab,kw OR feasib*:ti,ab,kw OR perspective*:ti,ab,kw OR cost:ti,ab,kw OR resource*:ti,ab,kw OR ((balance NEAR/1 sect*):ti,ab,kw) OR ((discrete* NEAR/1 choice*):ti,ab,kw) OR ('decision making'/exp AND (patient*:ti,ab,kw OR user*:ti,ab,kw OR famil*:ti,ab,kw OR customer*:ti,ab,kw OR consumer*:ti,ab,kw OR client*:ti,ab,kw OR women:ti,ab,kw OR men OR individual*:ti,ab,kw)) OR (((decision* NEAR/1 mak*):ti,ab,kw) AND (patient*:ti,ab,kw OR user*:ti,ab,kw OR famil*:ti,ab,kw OR customer*:ti,ab,kw OR consumer*:ti,ab,kw OR client*:ti,ab,kw OR women:ti,ab,kw OR men:ti,ab,kw OR individual*:ti,ab,kw))
#10. #8 OR #9
#9. #3 AND #7
#8. hhm:ti,ab,kw OR loh:ti,ab,kw
#7. #4 OR #5 OR #6
#6. calcinos$s:ti,ab,kw OR hypercalcemi:ti,ab,kw
#5. 'hypercalcemia'/de
#4. 'calcinosis'/de
#3. #1 OR #2
#2. 'neoplasm'/exp
#1. 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 erythroleukem*:ti,ab,kw OR erythroleukaem*: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/0 fungoid$s):ti,ab,kw) OR ((sezary NEXT/0 syndrome):ti,ab,kw) OR retinoblastoma*:ti,ab,kw OR pheochromocytoma*:ti,ab,kw OR nephroblastoma*:ti,ab,kw OR choriocarcinoma*:ti,ab,kw OR ((pleuropulmonary NEXT/0 blastoma$):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 craniopharyngioma*: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

4- CINAHL (EBSCO)

S29	MW S14 AND S28
S28	S15 OR S16 OR S17 OR S18 OR S24 OR S25 OR S26 OR S27
S27	MW (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 W0 stat*)) OR adhere* OR ((quality N2 life)) OR qol OR willing* OR burden* OR satisf* OR opinion* OR (((patient* OR user* OR health*) N3 (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

	(patient* OR user* OR famil* OR customer* OR consumer* OR client* OR women OR woman OR men OR man OR individual*))
S26	AB (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 W0 stat*)) OR adhere* OR ((quality N2 life)) OR qol OR willing* OR burden* OR satisf* OR opinion* OR (((patient* OR user* OR health*) N3 (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 (patient* OR user* OR famil* OR customer* OR consumer* OR client* OR women OR woman OR men OR man OR individual*))
S25	TI (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 W0 stat*)) OR adhere* OR ((quality N2 life)) OR qol OR willing* OR burden* OR satisf* OR opinion* OR (((patient* OR user* OR health*) N3 (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 (patient* OR user* OR famil* OR customer* OR consumer* OR client* OR women OR woman OR men OR man OR individual*))
S24	S19 AND S23
S23	S20 OR S21 OR S22
S22	MW patient* OR user* OR famil* OR customer* OR consumer* OR client* OR women OR woman OR men OR man OR individual*
S21	AB patient* OR user* OR famil* OR customer* OR consumer* OR client* OR women OR woman OR men OR man OR individual*
S20	TI patient* OR user* OR famil* OR customer* OR consumer* OR client* OR women OR woman OR men OR man OR individual*
S19	(MH "Decision Making+")
S18	(MH "Cost Benefit Analysis")
S17	(MH "Patient Preference")
S16	(MH "Consumer Participation")
S15	(MH "Attitude to Health+")
S14	S12 OR S13
S13	TI HHM OR LOH
S12	S10 AND S11

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")
S4	MW TI (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 ((mycosis W0 fungoid#s)) OR ((sezary W0 syndrome)) OR retinoblastoma* OR pheochromocytoma* OR nephroblastoma* OR choriocarcinoma* OR ((pleuropulmonary W0 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*)
S3	AB TI (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 ((mycosis W0 fungoid#s)) OR ((sezary W0 syndrome)) OR retinoblastoma* OR pheochromocytoma* OR nephroblastoma* OR choriocarcinoma* OR ((pleuropulmonary W0 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*)
S2	TI TI (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 ((mycosis W0 fungoid#s)) OR ((sezary W0 syndrome)) OR retinoblastoma* OR pheochromocytoma* OR nephroblastoma* OR choriocarcinoma* OR ((pleuropulmonary W0 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*)
S1	(MH "Neoplasms+")

5- Cochrane

#1 MeSH descriptor: [Neoplasms] explode all trees

#2 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 erythroleukem*:ti,ab,kw OR erythroleukaem*: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$s):ti,ab,kw) OR ((sezary NEXT syndrome):ti,ab,kw) OR retinoblastoma*:ti,ab,kw OR pheochromocytoma*:ti,ab,kw OR nephroblastoma*:ti,ab,kw OR choriocarcinoma*:ti,ab,kw OR ((pleuropulmonary NEXT blastoma$):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 craniopharyngioma*: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

#3 #1 or #2

#4 MeSH descriptor: [Calcinosis] this term only

#5 MeSH descriptor: [Hypercalcemia] this term only

#6 calcinos*:ti,ab OR hypercalcemi*:ti,ab

#7 #4 or #5 or #6

#8 #3 and #7

#9 hhm:ti,ab OR loh:ti,ab

#10 #8 or #9

#11 MeSH descriptor: [Attitude to Health] explode all trees

#12 MeSH descriptor: [Patient Participation] this term only

#13 MeSH descriptor: [Patient Preference] this term only

#14 MeSH descriptor: [Cost-Benefit Analysis] this term only

#15 MeSH descriptor: [Decision Making] explode all trees

#16 (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 woman:ti,ab,kw OR men:ti,ab,kw OR man:ti,ab,kw OR individual?:ti,ab,kw)

#17 #15 AND #16

#18 ((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* NEAR/1 mak*):ti,ab,kw) 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 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 #13 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 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	accessability.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

<u>Supplemental material 3A:</u> 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

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

Methodological characteristics of included studies

Author, year (Country)	Sampling method	Sample size calculation	Response Rate	Administration method	Tool Validation and Pilot testing	Limitations

Summary of results of included studies

Author, year (Country)	Outcomes					
	Patients/Physicians values	Patients/Physicians preferences	Acceptability	Equity	Cost & Resources	Feasibility