

General

diagnostic approach to bone metastasis of unknown origin: a systematic review

Yuni Artha Prabowo Putro, MD^{1,2}, Teguh Aryandono, Ph.D^{1,3}, Irianiwati Widodo, Ph.D^{1,4}, Rahadyan Magetsari, Ph.D^{1,2}, Dibyo Pramono, Ph.D^{1,5}, Muhammad Phetrus Johan, Ph.D⁶, Mos Asri Abidin, MD⁷, Ardanariswara Wikantayasa, MD², Paramita Ayu Saraswati, MD², A Faiz Huwaidi, MD⁸

¹ Doctoral Program in Medicine and Health Sciences, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Jl. Farmako, Sendowo, Sekip Utara, Sleman, 55281, D.I. Yogyakarta, Indonesia, Universitas Gadjah Mada, ² Department of Orthopedics and Traumatology, RSUP Dr. Sardjito Hospital, Jl. Kesehatan Sendowo No.1, Sleman, 55281, D.I.Yogyakarta, Indonesia., Universitas Gadjah Mada, ³ Department of Oncology Surgery, RSUP Dr. Sardjito Hospital, Jl. Kesehatan Sendowo No.1, Sleman, 55281, D.I.Yogyakarta, Indonesia., Universitas Gadjah Mada, ⁴ Department of Pathology, RSUP Dr. Sardjito Hospital, Jl. Kesehatan Sendowo No.1, Sleman, 55281, D.I.Yogyakarta, Indonesia., Universitas Gadjah Mada, ⁵ Faculty of Dentistry, Universitas Gadjah Mada, Jl. Denta No.1, Sekip Utara, Sleman, 55281, D.I.Yogyakarta, Indonesia., Universitas Gadjah Mada, ⁶ Department of Orthopaedic and Traumatology, RSUP Dr. Wahidin Sudirohusodo, Jl. Perintis Kemerdekaan Km. 11, Lt 3 RSP Unhas, Makassar, 90245, Sulawesi Selatan, Indonesia, Hasanudin University, ⁷ Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Makassar, Jl. Sultan Alauddin No. 259, Gn. Sari, Rappocini, Makassar, 90221, Sulawesi Selatan, Indonesia, Muhammadiyah University of Makassar, ⁸ Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Jl. Farmako, Sendowo, Sekip Utara, Sleman, 55281, D.I.Yogyakarta, Indonesia., Universitas Gadjah Mada

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BACKGROUND

Among all MBD cases, 3% have an unidentified origin and are commonly misdiagnosed. On average, nearly 75% of MBD cases with an unknown origin take four months to diagnose. This difficulty in identifying the primary cancer limits the treatment of skeletal metastases to palliative measures, negatively impacting a patient's prognosis. The purpose of this systematic review is to evaluate the current diagnostic work-up approaches available for MBD.

METHODS

This systematic review was carried out according to the guidelines of the (PRISMA) 2020 Statement, including studies with a population of interest of MBD with unknown primary origin. We excluded studies with non-English language and MBD cases with known origin. The intervention of the diagnostic approach was the primary outcome. The authors searched three electronic medical databases. Individual reviewers performed quality and risk of bias assessments.

RESULTS

All ten articles were cohort studies, with the median age of the subjects ranging from 55.6 to 65.2 years. The most frequently recommended supporting examination was biopsy, with a detection rate of 38.2%, followed by chest X-ray and CT scan, both with a detection rate of 26.7%. Overall, the detection rate of the primary lesion from individual examinations ranged from 2.8% to 38.2%, highlighting the difficulty of diagnosis when relying solely on a single examination.

CONCLUSIONS

Biopsy is crucial in identifying the primary lesion of metastatic bone disease with an unknown origin, with a detection rate of 38.2%, making it the most frequently recommended examination. However, this review has several limitations. A few assumptions were made in the synthesis of numerical data.

INTRODUCTION

Metastatic bone disease (MBD) develops secondary to several cancers, including lung, thyroid, melanoma, kidney, colorectal, breast, and prostate cancer.¹ Approximately 600,000 new cases of MBD are discovered each year, making

bone the third most prevalent site of metastasis after the lung and liver.^{2,3} In Indonesia, MBD accounts for almost nine percent of all malignant cases.⁴ MBD has become a leading cause of morbidity in cancer patients and is commonly characterized by excruciating pain, decreased mobility, pathological fractures, spinal cord compression, bone

marrow aplasia, and hypercalcemia.⁵ As cancer treatment advances and patient survival improves, the number of malignancies that metastasize to bones is expected to rise.⁶

Generally, the type and location of the primary lesion remain unknown in 3–4% of patients with metastatic carcinomas, with skeletal lesions contributing to 10–15% of these cases.⁷ Among all MBD cases, up to 21.7% have an unidentified origin, and some are even misdiagnosed.⁸ Nearly three-quarters of MBD cases with unknown primary lesions take an average of four months to diagnose, hindering the administration of definitive therapy.^{9,10} The failure to identify primary lesions limits the treatment of skeletal metastases to palliative measures, despite advancements in targeted therapies, ultimately impacting a patient's prognosis.

The overall survival rate of MBD patients is approximately 5% five years after diagnosis, and this number drops to 1% after ten years, with a median survival of 5 months post-diagnosis.^{11,12} Diagnostic delay has been identified as a significant factor contributing to unfavorable patient outcomes, combined with the overall burden imposed by the unknown primary lesion of MBD. Therefore, this systematic review aims to evaluate the current diagnostic work-up approaches for MBD.

MATERIAL AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in this systematic review ([Figure 1](#)).¹³ The review protocol was registered with Prospero. The authors first searched literature databases including PubMed (MEDLINE), Scopus, and the Cochrane Library on August 2, 2024. The search strategy terms are listed in the Supplementary Material, with MeSH terminologies used where appropriate. The inclusion and exclusion criteria for this study are provided in the protocol available in the supplementary material. The included studies reported the outcome of primary lesions found after the patient was first diagnosed with metastatic bone disease of unknown origin. Articles written in languages other than English, studies involving patients with known primary lesions for metastatic bone disease, commentary reviews, and letters to the editor were excluded. Using the strategy to find relevant titles and abstracts, four authors (Y.A.P., A. W., P.A.S., and A.F.) independently screened papers that met the inclusion criteria. After study selection was completed, duplicates were eliminated, full texts of the screened studies were obtained, and senior authors (T.A., I., R.M., D.P., M.P.J., M.A.A.) were consulted.

Data were extracted using Microsoft Excel (Microsoft, Redmond, WA). Extracted data included study demographic information, participant demographics, intervention data, and outcomes of primary lesion identification, if available. The main outcome of this review is the diagnostic approach reported descriptively in the included studies. The frequency of individual examinations recommended by the studies was tallied. Examinations were grouped into four general components of diagnostic steps: history taking and physical examination, laboratory tests, imaging, and biopsy. To measure the additional outcome of interest, the

detection rate of primary lesions along with information regarding lesion sites were reported when possible. To anticipate missing data, a subgroup analysis of the presented outcomes will be synthesized, referencing which study provides the information. This will form the basis for visual heterogeneity assessment and exploration. The AMSTAR (Assessing the Methodological Quality of Systematic Reviews) Checklist, a tool for the critical evaluation of systematic reviews, will be used to self-evaluate the overall quality of this review.¹⁴ Quality and risk of bias assessments were performed individually by reviewers using the Newcastle-Ottawa Quality Assessment Scale for non-randomized studies and other critical appraisal tools by JBI of the University of Adelaide where appropriate. Differences in opinion among authors throughout the review process were resolved through group discussion. The data were integrated, extracted, and descriptively examined before being provided in tabular format.

RESULTS

The study selection process followed the PRISMA guidelines, as illustrated in [Figure 1](#). We initially obtained a total of 58 articles from searches across three databases. After removing duplicates, 51 potentially relevant articles were assessed. From these, ten studies were included in this review after reading the full texts and applying the eligibility criteria. The Newcastle-Ottawa Quality Assessment Scale identified most of the included cohort studies as having good quality. Basic information, demographics, and individual quality of the studies are presented in [Table 1](#). All ten articles were cohort studies, with the median age of the subjects ranging from 55.6 to 65.2 years. The gender ratio of the patients was generally balanced, with some studies showing a predominance of male patients. We also included three poor-quality studies, which may increase the risk of bias.

We extracted the diagnostic steps adapted by individual studies for diagnosing MBD of unknown origin, as shown in [Table 2](#). To provide a quantitative summary of individual examinations included within the diagnostic steps of each study, we tallied the frequency of studies recommending each examination [Table 3](#). Additionally, we calculated the mean detection rate of individual examinations reported by the included studies. Since individual examinations were not uniformly performed across the nine studies, we only calculated the detection rate from the summed population of the involved studies ([Table 4](#)). The AMSTAR tool was used to self-assess the overall quality of this review, which scored as a moderate-quality review.

Typically, the diagnostic process began with history taking and physical examination, followed by laboratory examinations. These included complete blood count, blood chemistry, serum electrophoresis, and urinalysis to assess the patient's basic health status. In addition to these general lab parameters, tumor markers were tested in seven studies. Commonly used tumor markers included CEA, CA 19-9, AFP, and PSA. Following laboratory examinations, imaging modalities ranging from simple X-ray radiography

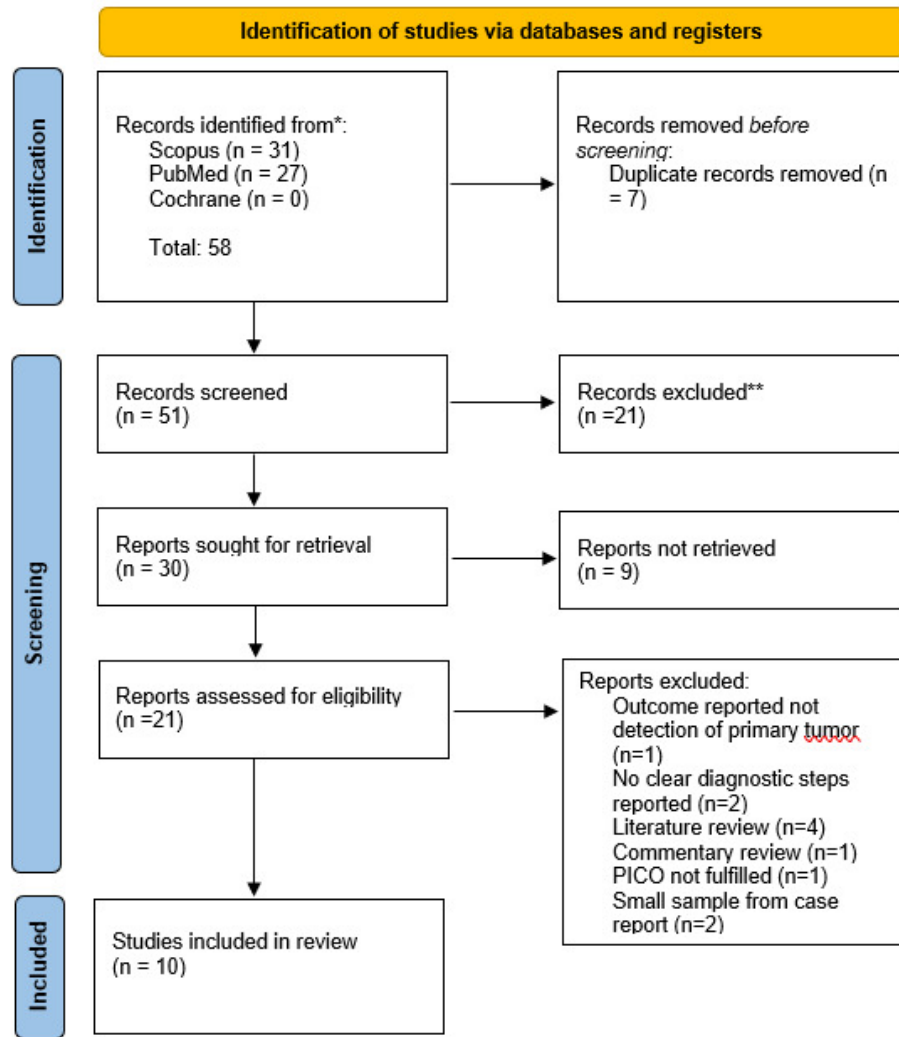


Figure 1. PRISMA Flowchart for study selection.

to advanced combinations of Positron Emission Tomography (PET) and Computed Tomography (CT) scans were recommended. Chest X-rays, bone scans, and CT scans of various organs were commonly recommended in almost all diagnostic approaches. Finally, biopsy was the most frequently recommended examination for identifying the primary origin of MBD.

DISCUSSION

VARIATION OF DIAGNOSTIC APPROACH

The diagnostic and treatment approach for MBD of unknown origin has not been uniform. Our results show that different studies have their steps to identify the primary lesion. The included studies were published between the mid-1980s and 2022, reflecting the evolution of technology and its influence on clinicians' choices.

Most studies in this review began with history taking and physical examination, which combined resulted in a detection rate of 14% (Table 3). Chief complaints that may indicate an underlying skeletal malignancy include bone pain and significant weight loss within three months. Some

studies also recommended exploring risk factors associated with specific types of primary cancer (e.g., age, smoking habits, alcoholism).¹⁵ According to Biermann et al.,¹⁶ there is a high likelihood that a single bone lesion in patients older than 40 years is metastatic carcinoma, which aligns with the median age of patients in this review, around 50-60 years (Table 1). The National Comprehensive Cancer Network guidelines also suggest that individuals aged 40 and above should undergo diagnostic work-up for potential metastasis as clinically indicated.¹⁷ Our review noted that a relatively small proportion of patients in the included studies were younger than 40 years old.

Physical examinations were then directed based on gathered information, focusing on pain referred by patients and palpable sites where malignant processes are likely to develop or metastasize. Our pooled data showed that history-taking and physical examination could primarily detect lesions originating from breast and prostate cancer (Table 4), as these are easily examined and their local symptoms often precede metastasis.^{7,18-20} Tsukamoto et al.¹⁵ supported this, recommending examinations of the thyroid gland, breast, or prostate, depending on patient gender, alongside routine head-to-toe examinations and additional assess-

Table 1. Demographic table of included studies

No	Author	Title	Type of Study	Total Patients	Sex (Male: Female)	Median Age	Primary location found (percentage)	Study Quality
1	Simon & Bartucci (1985)	The search for the primary tumor in patients with skeletal metastases of unknown origin	Cohort bidirectional	46	1:1	55,6	20 (43%)	Good quality
2	Rougraff <i>et al</i> (1991)	Skeletal metastasis of unknown origin	Cohort retrospective	40	1:1	57	36 (90%)	Fair quality
3	Jacobson <i>et al</i> (1997)	Skeletal metastases of unknown origin: A retrospective analysis of 29 cases	Cohort retrospective	29	2:1	62	22 (75%)	Poor quality
4	Katagiri <i>et al</i> (2000)	Determining the site of primary cancer in patients with skeletal metastasis of unknown origin: a retrospective study	Cohort retrospective	64	2:1	62	56 (88%)	Poor quality
5	Destombe <i>et al</i> (2007)	Investigations for bone metastasis from an unknown primary	Cohort retrospective	152	2:1	63,5	107 (70%)	Good quality
6	Ugras <i>et al</i> (2014)	Solitary bone metastasis of unknown origin	Cohort retrospective	33	3,7:1	64	33 (100%)	Poor quality
7	Kim <i>et al</i> (2014)	Non- spine Bone Metastasis as an Initial Manifestation of Cancer in Korea	Cohort prospective	84	2:1	59,1	79 (94%)	Good quality
8	Takagi <i>et al</i> (2015)	Skeletal metastasis of Unknown Primary Origin at the Initial Visit: A retrospective analysis of 286 cases	Cohort retrospective	286	1,5:1	65,2	254 (88%)	Good quality
9	Lawrenz <i>et al</i> (2020)	Does PET/CT aid in detecting primary carcinoma in patients with skeletal metastases of unknown primary?	Cohort retrospective	35	1:1	63	1 (2%)	Good quality
10	Fujibuchi <i>et al</i> (2022)	Effective examination methods for identifying the primary origins of metastatic bone tumors of unknown primary origin during the initial visit: a retrospective chart review study	Cohort retrospective	61	1,25:1	68,2	59 (96%)	Good quality

ments of lymph nodes, digital rectal examinations, and urinalysis. History taking and physical examination form the foundation of subsequent examinations, as reflected by the majority of included studies and other bone tumor guidelines.^{15,17,21}

The supporting examinations recommended by the ten studies varied greatly. Routine laboratory examinations included complete blood count (CBC), blood chemistry and electrolytes, serum electrophoresis, urinalysis, alkaline phosphatase (ALP), and tumor markers. Our study found that laboratory parameters had a 17.3% detection rate, primarily detecting hematologic and prostate cancer ([Table 4](#)). This was largely due to the use of electrophoresis in detecting multiple myeloma and PSA in identifying primary prostatic malignancy.^{8,16,22-24} When combined with clin-

ical findings and elevated bone-resorptive markers, the specificity of PSA in confirming primary prostate malignancy is enhanced.²⁵ Tumor markers, released by corresponding malignant organs, were expected to provide information regarding the origin of metastatic bone disease. Other recommended tumor markers included CEA, AFP, beta hCG, acid phosphatase, PSA, CA19-9, and PIVKA-II, depending on indications from other examination results.^{7, 8,18,22,24} Several studies agreed that laboratory tests were valuable for evaluating the patient's general condition and revealing treatable abnormalities, such as anemia or hypercalcemia, but not for identifying primary lesions.^{7,18}

Further examinations included imaging of skeletal lesion sites to investigate and confirm metastatic characteristics. Plain radiography of the chest, with a pooled detection rate

Table 2. Diagnostic step recommendations by individual study

No	Author (year)	Title	Recommendations
1	Simon & Bartucci (1985)	The search for the primary tumor in patients with skeletal metastases of unknown origin	Medical history, physical exam (breast, prostate, thyroid focused), CBC, blood chemistry (Calcium level), urinalysis, acid phosphate level (male), chest radiograph, bone scan, CT of abdomen and pelvic followed by biopsy
2	Rougraff <i>et al</i> (1991)	Skeletal metastasis of unknown origin	Medical history, physical exam (breast, prostate, thyroid focused), CBC, electrolyte level, ALP, serum electrophoresis, chest x-ray bone involved, bone scan, CT of chest, abdomen, pelvic, biopsy at most- accessible lesion
3	Jacobson <i>et al</i> (1997)	Skeletal metastases of unknown origin: A retrospective analysis of 29 cases	Medical history (smoking habits), physical exam (prostate, breast, thyroid, skin focused), CBC, ESR, PSA, urinalysis, chest radiographs/- CT, bone scan, CT of the abdomen, a biopsy from the most accessible lesion at the end of the evaluation
4	Katagiri <i>et al</i> (2000)	Determining the site of primary cancer in patients with skeletal metastasis of unknown origin: a retrospective study	Medical history, physical exam (breast, prostate, thyroid focused), CBC, blood chemistry (electrolyte, liver enzyme, urinalysis), serum of selected tumor marker, chest radiograph, bone scan, CT of chest and abdomen, most accessible biopsy (primary lesion or skeletal)
5	Destombe <i>et al</i> (2007)	Investigations for bone metastasis from an unknown primary	Medical history, physical exam, CBC + serum electrophoresis, selected tumor marker, chest radiograph, bone scan, USG of the abdomen, most accessible + bone lesion biopsy. PSA was the only useful tumor marker
6	Ugras <i>et al</i> (2014)	Solitary bone metastasis of unknown origin	In solitary bone lesion, the diagnostic strategy (proposed by Katagiri) is important. Selected IHC based on biopsy result the sample was taken from bone
7	Kim <i>et al</i> (2014)	Non- spine Bone Metastasis as an Initial Manifestation of Cancer in Korea	Medical history, physical exam, CBC + serum chemistry, chest radiograph, CT of thorax, biopsy most accessible site. PET scan alone not helpful
8	Takagi <i>et al</i> (2015)	Skeletal metastasis of Unknown Primary Origin at the Initial Visit: A retrospective analysis of 286 cases	Medical history, physical exam, chest radiograph, blood test (tumor marker : CEA, Ca 19-9, AFP, PSA, PIVKA II, IL-2, IEP), whole body CT scan, bone biopsy, origin biopsy+specific exam, BMP, PET scan. Medical history - whole CT : common exam, biopsy- PET scan : advanced exam.
9	Lawrenz <i>et al</i> (2020)	Does PET/CT aid in detecting primary carcinoma in patients with skeletal metastases of unknown primary?	PET scan only do not give additional benefit
10	Fujibuchi <i>et al</i> (2022)	Effective examination methods for identifying the primary origins of metastatic bone tumors of unknown primary origin during the initial visit: a retrospective chart review study	The authors proposed a sequential examination process. The first step involves a physical examination, blood tests (including tumor markers and serum protein electrophoresis), chest radiography, and a thoracoabdominal CT scan. The second step is a PET CT scan, followed by a biopsy of any metastatic lesions. The final steps include other examinations such as GI endoscopy or a biopsy of the suspected primary lesion.

of 16.9% predominantly for lung cancer (**Table 4**), was frequently recommended. Piccioli *et al.* suggested that chest X-rays should be routinely performed in MBD cases due to their simplicity, low cost, and substantial proportion of metastases originating from malignant lung masses, which can be identified by this modality.¹² With the development of better technologies, modalities such as CT scans are preferred for inspecting lesions throughout the body. Previous studies have agreed that chest CT scans are among the most valuable for identifying primary lesions in unknown metastasis.⁸ Our review found that CT scans had the second-highest detection rate of 26.7%, particularly useful in identifying lung abnormalities (**Table 4**). All studies included in this review emphasized the importance of

chest imaging due to the high contribution of occult lung malignancy in MBD of unknown origin. Examining deep-seated organs, such as the gastrointestinal and female reproductive organs, was often misleading and costly without clear indications.^{7,18,26} Abdominal and pelvic organs were most commonly identified as primary malignant origins only post-autopsy.²⁷ Therefore, CT scans of the GI tract and gynecological organs should be supported by other examinations and performed selectively.

Since 1985, Simon and Bartucci¹⁸ have utilized bone scans to screen potential MBD patients by identifying bone masses distributed throughout the body, a method adopted by several subsequent studies.^{7,19,20,22} Our systematic review reported bone scan sensitivity as high as 83.3%,¹⁸ al-

Table 3. Frequency of recommendation from extracted data

Type of Examination	Number of studies recommending examination	Studies recommending examination
History taking	7	Simon & Bartucci 1985; Rougraff <i>et al</i> 1991; Jacobson <i>et al</i> 1997; Katagiri <i>et al</i> 2000; Destombe <i>et al</i> 2007; Kim <i>et al</i> 2014; Takagi <i>et al</i> 2015
Physical examination	8	Simon & Bartucci 1985; Rougraff <i>et al</i> 1991; Jacobson <i>et al</i> 1997; Katagiri <i>et al</i> 2000; Destombe <i>et al</i> 2007; Kim <i>et al</i> 2014; Takagi <i>et al</i> 2015; Fujibuchi <i>et al</i> 2022
Laboratory test - Complete blood count - Blood chemistry - Serum electrophoresis - Urinalysis - Tumor marker	7 4 3 3 7	Simon & Bartucci 1985; Rougraff <i>et al</i> 1991; Jacobson <i>et al</i> 1997; Katagiri <i>et al</i> 2000; Destombe <i>et al</i> 2007; Kim <i>et al</i> 2014; Fujibuchi <i>et al</i> 2022. Simon & Bartucci 1985; Rougraff <i>et al</i> 1991; Katagiri <i>et al</i> 2000; Kim <i>et al</i> 2014. Rougraff <i>et al</i> 1991; Destombe <i>et al</i> 2007; Fujibuchi <i>et al</i> 2022 Simon & Bartucci 1985; Jacobson <i>et al</i> 1997; Kim <i>et al</i> 2014. Simon & Bartucci 1985; Rougraff <i>et al</i> 1991; Jacobson <i>et al</i> 1997; Katagiri <i>et al</i> 2000; Destombe <i>et al</i> 2007; Takagi <i>et al</i> 2015; Fujibuchi <i>et al</i> 2022
Imaging - Chest X-ray - CT scan - Thorax - Abdomen - Pelvis - PET scan - USG abdomen - Bone scan	8 8 6 5 3 2 1 5	Simon & Bartucci 1985; Rougraff <i>et al</i> 1991; Jacobson <i>et al</i> 1997; Katagiri <i>et al</i> 2000; Destombe <i>et al</i> 2007; Kim <i>et al</i> 2014; Takagi <i>et al</i> 2015; Fujibuchi <i>et al</i> 2022. Simon & Bartucci 1985; Rougraff <i>et al</i> 1991; Jacobson <i>et al</i> 1997; Katagiri <i>et al</i> 2000; Kim <i>et al</i> 2014; Takagi <i>et al</i> 2015; Lawrenz <i>et al</i> 2020; Fujibuchi <i>et al</i> 2022. Rougraff <i>et al</i> 1991; Jacobson <i>et al</i> 1997; Katagiri <i>et al</i> 2000; Kim <i>et al</i> 2014; Takagi <i>et al</i> 2015; Fujibuchi <i>et al</i> 2022. Simon & Bartucci 1985; Rougraff <i>et al</i> 1991; Katagiri <i>et al</i> 2000; Takagi <i>et al</i> 2015; Fujibuchi <i>et al</i> 2022. Simon & Bartucci 1985; Rougraff <i>et al</i> 1991; Takagi <i>et al</i> 2015. Takagi <i>et al</i> 2015; Fujibuchi <i>et al</i> 2022. Takagi <i>et al</i> 2015; Fujibuchi <i>et al</i> 2022. Destombe <i>et al</i> 2007 Simon & Bartucci 1985; Rougraff <i>et al</i> 1991; Jacobson <i>et al</i> 1997; Katagiri <i>et al</i> 2000; Destombe <i>et al</i> 2007.
Biopsy	9	Simon & Bartucci 1985; Rougraff <i>et al</i> 1991; Jacobson <i>et al</i> 1997; Katagiri <i>et al</i> 2000; Destombe <i>et al</i> 2007; Ugras <i>et al</i> 2014; Kim <i>et al</i> 2014; Fujibuchi <i>et al</i> 2022.

though past studies have shown sensitivity up to 50%.²⁸⁻³⁰ Bone scans are popular for detecting metastatic bone lesions, despite their cost and limited availability in some regions. A cheaper alternative, bone surveys, require no radiotracer injection and, when combined with clinical manifestations, offer better detection rates than bone scans.¹⁴

Moving on to more invasive approaches, this systematic review has highlighted the importance of biopsy, with the highest detection rate of 38.2% (**Tables 3 and 4**). Various guidelines and studies by the National Comprehensive Cancer Network, European Society for Medical Oncology, and the American Academy of Orthopaedic Surgeons have emphasized making diagnostic decisions based on the histopathology of lesion samples.^{16,17,24,31,32} Katagiri *et al.*⁷ reported that complete diagnoses in their study were confirmed by biopsy of palpable masses. Biopsy samples taken from metastatic lesions could identify the primary origin in up to 25% of MBD cases without additional information from other examinations.^{20,22} This proportion could be improved by enhancing histopathology assessment using immunohistochemistry.³³ An epidemiological

study in India showed that minimally invasive biopsy sampling with Fine Needle Aspiration Cytology (FNAC) and Core Needle Biopsy (CNB) confirmed primary lesions in more than 80% of MBD cases, whereas open biopsy detected only 15%.²³

BIOPSY AS DIAGNOSTIC STANDARD IN DETERMINING PRIMARY LESION OF MBD

Even though patients with MBD of unknown origin and a single lesion have a better prognosis than those with multiple lesions, the latter is more common and contributes to a lower survival rate.^{8,34,35} Additionally, patients with MBD of unknown origin often present with metastatic lesions in other organs. These extra-skeletal metastases, most commonly found in the liver, lungs, pleura, and brain, further decrease the survival rate, especially in cases of liver metastases, which have an overall survival of 13.5 months.³⁶ Given this demographic, performing a biopsy to diagnose the primary lesion of MBD from bone or extra-skeletal lesions may be recommended. According to Destombe *et al.*, a biopsy of extra-skeletal masses may be performed if the bone mass is in a difficult location, such

Table 4. Subgroup synthesis of mean detection rate

Type of Examination	Location of Primary	Detection rate (primary lesion found divided by all MBD of unknown origin in presenting cases)
History taking & physical examination	- Breast: 14 - Prostate: 12 - Kidney: 1 - Thyroid 1 - Bladder 1	14%
Blood tests including tumor Marker Test	- Prostate: 35 - Liver: 6 - Malignant lymphoma: 6	17,3%
Chest X-ray	- Hematology: 30 - Lung: 98	16,9%
CT Scan Thorax	- Hematology: 1 - Breast: 16 - Lung: 111 - Gastrointestinal: 3 - Thyroid: 6 - Malignant lymphoma: 1	26,7%
CT Scan Abdomen and Pelvis	- Hematology: 2 - Pancreas: 8 - Prostate: 16 - Kidney 38 - Uterus: 1 - Ovary: 1	17,3%
Bone Scan	- Lung: 7 - Kidney: 4	23,9%
PET/CT scan	- Thyroid: 3 - Lung: 6 - Prostate: 1 - Breast: 3 - Kidney: 2 - Uterus: 2	2,8%
USG	- Thyroid: 1 - Kidney: 2 - Ovary: 1 - Liver 5 - Thyroid: 1 - Gastrointestinal: 1 - Pancreas: 1 - Soft tissue sarcoma: 1	6,7%
Endoscopy	- Gastrointestinal: 5 - Lung: 1	4%
Biopsy	- Breast: 23 - Prostate: 31 - Lung: 59 - Kidney: 10 - Ovary: 1 - Liver: 3 - Hematology: 2 - Thyroid: 8 - Bladder: 14	38,2%

Type of Examination	Location of Primary	Detection rate (primary lesion found divided by all MBD of unknown origin in presenting cases)
	- Gastrointestinal: 7 - Skin: 1	

as the spine, as there is no difference in diagnostic accuracy for the primary lesion.²²

Numerous studies and organizations debate when a biopsy should be performed relative to other non-invasive tests. A bone biopsy diagnosis should always follow the completion of all imaging evaluations and involve collaboration with a multidisciplinary team, including histopathologists, radiologists, and surgeons.³⁷ One common reason to delay a biopsy is the risk of contaminating surrounding tissues if the lesion is primary, which could compromise the possibility of performing limb-sparing procedures as a primary skeletal tumor treatment.^{7,8,19,38} Surgeons should consider the lesion site when planning a biopsy to ensure the subsequent operative treatment follows the biopsy pathway.³⁹ Hage et al. agree with this approach but suggest early biopsy when skeletal metastasis occurs in multiple locations, indicating a higher likelihood of it being metastatic.⁴⁰

On the other hand, there are arguments for performing an early biopsy. The worsening survival rate of MBD patients correlates with prolonged diagnostic delays and increased treatment costs.⁴¹ The Indonesian Ministry of Health concluded that the high cost of cancer treatment is due to late detection, leading to a greater service workload and more extensive treatment modalities.⁴² Since histological diagnosis is crucial for effectively selecting treatment options, a delayed biopsy negatively impacts treatment timing and reduces the patient's quality of life.^{7,16} Ideally, a well-planned biopsy with a shorter initial work-up may be optimal. However, whether a biopsy should be performed earlier than extensive imaging modalities remains highly debatable, considering the risk of contaminating surrounding tissue if the lesion is not metastatic.

THE LATEST ADVANCEMENT IN IDENTIFYING PRIMARY LESIONS OF MBD OF UNKNOWN ORIGIN

Our review demonstrated the progression of significant advancements in diagnostic modalities for MBD cases ([Table 2](#)). One notable advancement is PET/CT imaging, which is widely used to observe changes in metabolic and pathological processes before anatomical structural changes occur, allowing for more rapid detection than conventional radiological examinations. Although our study reported a low

detection rate of 2.8%, PET/CT successfully confirmed the primary lesion site in all patients who had their primary lesion detected before the PET/CT examination. It is worth noting that this detection rate was only extracted from one study. PET/CT scans are generally recommended for MBD patients to identify other existing metastases rather than the primary origin.⁴³ Therefore, CT scans are preferable due to their lower costs and shorter waiting times.

An interesting recent diagnostic suggestion by Grávalos et al. involves the use of micro-RNAs (miRNA), small non-coding RNA molecules that have been linked to cancer development in recent years.²¹ Analysis of each miRNA molecule can reveal various impacts, with some exhibiting pro- or anti-tumorigenic characteristics. Several miRNAs, including miR-10b, miR-16, and miR-378, have been suggested for identifying bone metastases in breast cancer patients with acceptable sensitivity (64%) and specificity (69%). MiR-326, a specific type of miRNA, has been recommended as a biomarker for monitoring metastatic progression in bones.^{44,45}

This systematic review has its limitations. First, due to the specificity of our population of interest (MBD with unknown origin), our search strategy may have been overly narrow, resulting in fewer than 100 articles. We identified some articles that met our inclusion criteria but were not found using our search strategy [19,20,21,22,24]. Instead, we used these articles as comparisons and references in our discussion. Meta-analysis was deemed inappropriate because the data were too dissimilar. Some assumptions were also made to generate quantitative data.

CONCLUSION

We recommend a shorter initial work-up before performing a biopsy, as this would result in faster diagnosis and treatment administration. A well-planned biopsy is necessary to ensure the quality of the samples taken and to avoid contamination of surrounding tissues if the suspected lesion is indeed a primary malignancy. detection of primary tumors potentially increases patients' life expectancy; it is crucial for assessing the extent of skeletal metastasis.

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