

UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II



DIPARTIMENTO DI MEDICINA CLINICA E CHIRURGIA

DOTTORATO DI RICERCA IN

TERAPIE AVANZATE BIOMEDICHE E CHIRURGICHE

Ciclo XXXVIII (anni 2022-2025)

Coordinatore Prof. Carmine Settembre

Tesi di Dottorato

Primary And Metastatic Neoplasms

Arising In Pagetic Bones

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Abstract

Background. Paget's disease of bone (PDB) is a focal metabolic bone disorder. In adulthood, bones affected by PDB are predisposed to neoplastic degeneration and resistant to metastatic invasion. In this article, a clinical survey of patients enrolled in the Italian PDB registry and a systematic review with individual patient data analysis (IPD, PROSPERO database number CRD42020151209) were performed to describe the characteristic of PDB patients with primary (BC-PDB) or metastatic (BM-PDB) neoplasms arising in PDB bones.

Methods. BC-PDB were classified as osteosarcoma (Sar-PDB), giant cell tumor (GCT-PDB), and miscellaneous malignancies (MM-PDB). Patients from the Italian PDB Registry without BC-PDB and/or BM-PDB were classified as Italian PDB Controls

Results. Among 742 patients enrolled in the Italian PDB Registry, we observed 11 Sar-PDB, 6 GCT-PDB, and 1 MM-PDB, with a prevalence of 1.35%, 0.81%, and <0.01%, respectively. The IPD identified 1468 Sar-PDB, 122 GCT-PDB, 57 MM-PDB, and 70 BM-PDB. Overall, BC-PDB arises exclusively in pagetic bones and affect preferentially Caucasian men with multiple skeletal sites affected by PDB. The occurrence of cancer increases the 5-years mortality rate of affected patients. Sar-PDB and MM-PDB showed a 5-years mortality rate higher than GCT-PDB, which in turn showed a lower mean age at PDB onset compared to Sar-PDB and MM-PDB. Among 149 PDB patients enrolled in the Italian PDB Registry showing a non-bone cancer (56 with metastatic disorder), 6 showed a BM-PDB.

Conclusion. BC and BM arising in PDB patients show unique characteristics compared to non-PDB BC and BM.

Introduction

Primary bone cancer (BC) accounts for 3770 cases estimated for 2025 according to American Cancer Society, with 2190 deaths (1). Osteosarcoma is the most common and shows two peaks in incidence: adolescence and late adulthood (2). Giant cell tumor (GCT) presents a similar pattern (3). Paget's disease of bone (PDB, OMIM 602080) is the second most prevalent metabolic bone disorder worldwide (4), and is a significant risk factor for developing both osteosarcoma and GCT in late adulthood, due to neoplastic degeneration of pagetic tissue (3, 5-9). PDB is a focal disorder of bone turnover, characterized by impaired bone remodelling and abnormal skeletal architecture, affecting one (monostotic PDB) or multiple sites (polyostotic PDB), and noticeable by elevated Alkaline Phosphatase (ALP) serum levels (5, 6). Both genetic and environmental factors are implicated in the pathogenesis of PDB (5, 6). Germline mutations [i.e. *Sequestosome 1 (SQSTM1)*, *Zinc Finger Protein 687 (ZNF687)*, *Profilin-1 (PFN1)*, *Valosin Containing Protein (VCP)*, and *Tumor Necrosis Factor Receptor Superfamily Member 11a (TNFRSF11A)*] have been identified as potential cause of PDB and of related syndromes (6). These genes are involved in osteoclast differentiation and function, as well as in cell autophagy (4). Since the first description by Sir James Paget, several cases of neoplastic degeneration in affected bone have been reported (10). This complication is estimated to occur in 0.5-1.0 % of patients with PDB, increasing the risk of neoplastic transformation by 30-fold after the age of 40 (11).

Unlike BCs, bone metastases (BMs) are more common. Indeed, bone is the third site of metastasis for frequency, following lungs and liver, and its involvement worsens the prognosis of patients with any type of cancer (12). Tu and colleagues demonstrated that PDB patients who develop prostate cancer experience a delayed onset of BMs, that affect preferentially bone without PDB signs, and an improved overall survival compared to those with prostate cancer alone (13). This finding remained significant even after adjusting for bisphosphonate treatment (13). In summary, pagetic bones appear to be predisposed to neoplastic

degeneration and resistant to metastatic invasion, at least in males with prostate cancer. From a clinical perspective, the characteristic of PDB patients with BC (BC-PDB) and/or BM (BM-PDB) arising in pagetic bones have not yet been systematically analysed and clearly defined. To address this gap, a hybrid study was conducted: i) a clinical survey of PDB patients enrolled in the Italian PDB Registry to identify BC-PDB or BM-PDB, ii) a systematic review with individual patient data analysis (IPD) of all BC-PDB and BM-PDB patients described so far, iii) a comparison among clinical characteristics of BC-PDB patients, BM-PDB patients and PDB patients without BC or BM enrolled in the Italian PDB Registry. To the best of knowledge, this combined approach to this question has not been attempted yet.

Materials and methods

Clinical cross-sectional survey. The clinical data from patients included in the Italian PDB Registry were collected, according to the methodology detailed in Supplementary Table 1. The Italian PDB registry was established through the collaboration of the three main national Centers for the diagnosis and treatment of PDB, located in northern (Turin), central (Siena), and southern (Naples) Italy from several years (14).

IPD systematic review. The IPD systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15), and it was registered in the PROSPERO database (registration number: CRD42020151209). No language restriction was applied and studies in language different from English, French, and Italian were translated in English or Italian by a specialist translator. All articles were acquired as full text and the references were analyzed to tease out duplicate data. Any disagreement over the eligibility of studies was solved through collegial authors discussion (16). A standardized, pre-piloted form was used to extract relevant clinical data from selected studies. Details of the data search and extraction methods are provided in Supplementary Table 2. The quality assessment of the included studies was performed using the Joanna Briggs Institute checklist for case series (Supplementary table 3) and for case reports (Supplementary table 4) (17).

BC-PDB patients identified in the Italian PDB Registry and in the systematic review were classified into three subgroups according to Singer (18): osteosarcoma (Sar-PDB), giant cell tumor (GCT-PDB), and miscellaneous malignancies (MM-PDB). PDB patients in the Italian PDB Registry without BC and/or BM were classified as Italian PDB Controls.

Statistical analysis. All statistical analyses were performed using the IBM SPSS (Statistical Package for Social Science), version 25 (IBM, Armonk, NY, USA). Individual data from study publications were extracted and included in a single database for analysis. The Chi-squared or Fisher's exact tests were used to evaluate differences between categorical variables or

proportions. All data were expressed as absolute number (percentage) or mean $\pm$ standard deviation, as appropriate. All statistical tests were two-tailed. A p-value <0.05 was considered statistically significant.

Results

Clinical cross-sectional survey. According to the criteria outlined in Supplementary table 1, clinical data of 742 PDB patients enrolled in the Italian PDB Registry as of October 28th, 2023 were analysed. Among them, 167 (22.5%) showed solid malignancy. Of them, we identified 18 (10.8% of all malignancies and 2.4% of all PDB patients) BC-PDB patients (11 with Sar-PDB, 6 with GCT-PDB, and 1 with MM-PDB) (Table 1). Five of these cases had been previously described in the literature (19-24). The prevalence of Sar-PDB, GCT-PDB, MM-PDB was 1.35%, 0.81%, and <0.01%, respectively. No germinal mutations in *SQSTM1*, *ZNF687*, *PFN1*, *VCP*, or *TNFRSF11A* were detected in Sar-PDB and MM-PDB patients and in their relatives affected by PDB from the Italian PDB Registry. Conversely, the c.2810C>G (p.Pro937Arg) missense mutation in *ZNF687* was identified in all GCT-PDB patients. Notably, all these individuals were born in the Campania region of Southern Italy, and the same mutation was also found in their relatives affected by PDB without GCT (19).

At the same time, 149 patients have a history of primary non-bone malignancies [Male: Female 87 (20.3): 62 (19.8); mean age 69.2 ± 10.8 years; age at onset PDB 58.7 ± 9.9 years; polyostotic PDB: monostotic PDB 86 (57.7): 63 (42.3); age at onset non-bone malignancy 59.9 ± 10.2 years]. The most common non-bone malignancy reported are prostate carcinoma in males, and breast and uterine carcinomas in females, followed by colon carcinoma, melanoma, lymphoma, lung carcinoma and thyroid carcinoma in both sexes. The mean survival time was 4.7 ± 3.8 years. During cancer's clinical course, 56 (37.6%) PDB patients with primary non-bone neoplasms showed metastatic cancers. Altogether, among 149 PDB patients with non-bone malignancy 7 (4.7%) had bone metastasis. Of them, six PDB patients (2 from prostate cancer, 2 from colon-carcinoma, 1 from kidney, 1 from breast) showed bone metastasis affecting pagetic bones (BM-PDB, table 1). Another PDB patient (male, 69 years, 62 years at PDB diagnosis, polyostotic PDB involving pelvis and left femur, metastasis from lung tumor), affected by lung

adenocarcinoma stage IV (cT2N1M1) showed a bone metastasis at lumbar spine, a skeletal segment not affected by PDB.

IPD Systematic review. Following the database search, 5433 studies were identified and screened (Figure 1). Based on the inclusion and exclusion criteria outlined in Supplementary Table 1, 292 studies were selected. Additional 34 studies were identified through reference list screening, resulting in a total of 326 studies included in the systematic review (Figure 1, supplementary tables 2 and 3). The systematic search identified 1468 Sar-PDB, 122 GCT-PDB, 57 MM-PDB, and 70 BM-PDB patients. Patients with BC-PDB and BM-PDB from the Italian PDB Registry and those identified through the systematic review showed no significantly different clinical characteristics and therefore were analyzed altogether as a unique cohort: overall, 1478 Sar-PDB, 123 GCT-PDB, 58 MM-PDB, and 70 BM-PDB patients were analysed.

Sar-PDB. Sar-PDB occurs mostly in Caucasian men with polyostotic PDB (Table 2). Sarcoma involves only skeletal sites affected by PDB. The prevalence of single-site and multifocal Sar-PDB was 94.1% and 5.9%, respectively. Sar-PDB most commonly affects the femur (26.3%), pelvis (22.5%), humerus (17.1%), and skull (14.4%). Other pagetic skeletal sites are involved in fewer than 10% of cases (Supplementary Table 4). PDB was diagnosed before of sarcoma onset in 73.6% of patients, with a time-lapse of 12.4 ± 10.6 years between PDB and Sar-PDB diagnoses. At the Sar-PDB onset, serum ALP levels were elevated in 98.3% of patients, and the most common presenting symptom was bone pain in the tumour location (Table 3). Systemic metastases were documented at Sar onset in 180 patients, most commonly involving the lungs. Among the genes associated with PDB, no germinal mutation of *SQSTM-1* was reported in cases with Sar-PDB. On the other hand, the somatic mutation *C1215T* of *SQSTM-1* was detected in bone specimens from 3 Sar-PDB (25). Two somatic mutations in *ZNF687* gene, *P937R* and *R331W*, were identified in 2 Sar-PDB (26). Germinal mutations in *PFN1* were also described in an Italian family with PDB complicated by Sar (27). Green and colleagues demonstrated that the microRNA-16 is highly expressed in Sar-PDB (28).

Treatment strategies for Sar-PDB are reported in Table 4, and included primarily surgery and radiotherapy. Pharmacological treatments were mainly based on amino-bisphosphonates, such as zoledronic acid.

Giant Cell Tumours. GCTs occurred predominantly in Caucasian men with polyostotic PDB (Table 2). The involved skeletal sites were mainly the skull (42.0%), pelvis (15.9%), spine (13.0%), and femur (7.9%). Other skeletal sites affected by GCT in fewer than 6% of cases (Supplementary table 5). All GCTs arose in bones affected by PDB, to the exclusion of 7 GCTs (5.7%) located in soft tissues adjacent pagetic bones (3). In 74.8% of cases, the tumour was limited to a single bone, while multifocal GCT-PDB occurred in 25.2% of patients. At GCT-PDB onset, ALP levels were elevated in all patients. The most frequently reported symptom was bone pain (22%), and the most common clinical sign was bone deformity (46%; Table 3). In 82.6% of GCT-PDB patients, PDB was diagnosed prior to GCT, with a mean interval of 12.6 ± 8.9 years. In the remaining patients, PDB and GCT were diagnosed simultaneously. Lung metastases developed in 10.6% of cases. No germline or somatic *SQSTM1* mutations were identified in GCT-PDB patients or in their PDB-affected relatives without GCT (20). The germinal *P937R* mutation in *ZNF687* was found in 8 Caucasian GCT-PDBs patients from Italy and in their PDB-affected relatives without GCT (19). The same was also reported in one Black GCT-PDB woman from United States of America (26). Additionally, germline *PFN1* mutations were described in two Chinese Han GCT-PDB patients and their affected relatives (29). Treatment of GCT-PDB included surgery, alone or in combination with radiotherapy and/or drugs such as calcitonin, bisphosphonates, glucocorticoids or denosumab (Table 4). The 27.6% of GCT-PDB patients experienced local recurrence.

Miscellaneous bone malignancies. MM-PDB patients included 25 fibrous histiocyctomas, 17 multiple myelomas, 8 skeletal lymphomas, 2 intraosseous fibromas, 2 enchondromas, 2 neuromas, 1 adamantinoma, and 1 intraosseous lipoma. MM-PDBs predominantly affected Caucasian men with polyostotic PDB and involved skeletal sites that were macroscopically

affected by PDB (Table 2). PDB preceded the diagnosis of MMs in 50% of patients, while in the remaining 50% the diagnoses were simultaneous. The skeletal sites most affected were the pelvis (34.2%), femur (23.7%), spine (15.8%), and skull (13.2%). Other sites were involved in fewer than 6% of cases (Supplementary table 5). MM-PDB occurred in a single site in 83.8%, while 17.2% were multifocal. Signs and symptoms at onset were reported in Table 3. Lung metastases were observed at onset in 3 cases. Surgery and radiotherapy were the primary treatments (Table 3). No germline or somatic mutation in genes involved in PDB pathogenesis were found in MM-PDB patients.

Bone Metastasis on pagetic bone. BMs was reported in 4.7% of PDB patients with solid tumours. The primary cancer responsible for BMs in male PDB patients were prostate cancer (22.8%), lung cancer (15.7%), renal clear cell cancer (7.1%), colorectal cancer (4.3%), pancreatic cancer (1.4%), thyroid cancer (1.4%), and melanoma (1.4%). In females PDB patients, primary cancer responsible for BMs included breast cancer (11.6%), lung cancer (4.3%), renal clear cell cancer (2.9%), colorectal cancer (1.4%), pancreas cancer (1.4%), thyroid cancer (1.4%), and melanoma (1.4%). In 14 patients, the primary cancer site remained unidentified. BM-PDBs occurred more frequently in Caucasian males (Table 2). In 59.0% (13/22) of patients, PDB was diagnosed prior to bone metastasis, with a time-lapse of 11.8 ± 12.1 years between PDB and BM diagnoses. In the remaining cases, both diagnoses were made concurrently. At malignancy diagnosis, all BM-PDB patients showed elevated serum ALP levels. The most frequently skeletal sites involved by PDB were the pelvis (34.2%), femur (23.7%), spine (15.8%), and skull (13.2%). Other skeletal sites were affected in fewer than 6% of cases (Supplementary table 5). The most reported symptom was bone pain, but also systemic signs, such as fever, asthenia, and weight loss, were observed in BM-PDB patients (Table 3). Treatment approaches included preferentially radiotherapy and surgery (Table 4).

BC-PDB patients vs. BM-PDB patients. Altogether, the prevalence of polyostotic PDB was significantly higher among BC-PDB compared to BM-PDB patients ($p < 0.01$, Table 2). In

particular, patients with Sar-PDB and GCT-PDB had a higher prevalence of polyostotic disease than patients with BM-PDB ($p<0.01$ for both comparisons, Table 2). Furthermore, the mean age at PDB onset was significantly lower in GCT-PDB patients compared to those with Sar-PDB, MM-PDB and BM-PDB ($p<0.05$ in all cases, Table 2).

Time trends of BC-PDB and BM-PDB reported cases. Since 1970, the number of reported BC-PDB cases has progressively decreased, whereas BM-PDB cases have increases (Table 5).

During the same period, the mean age at PBC diagnosis had shown an upward trend.

Comparison BC-PDB and BM-PDB with Italian PDB Controls. The prevalence of males was significantly higher among patients with Sar-PDB, GCT-PDB, and BM-PDB compared to Italian PDB Controls ($p<0.05$ in all case, Table 2). The prevalence of polyostotic PDB was higher in Sar-PDB and GCT-PDB patients compared to Italian PDB Controls ($p<0.01$ in both cases, Table 2). Moreover, the mean age at PDB onset was significantly lower in GCT-PDB patients compared to Italian PDB Controls ($p<0.05$, table 1).

Five-years mortality rate. Five-year mortality rates were significantly higher in patients with Sar-PDB, GCT-PDB, MM-PDB, and BM-PDB compared to Italian PDB Controls ($p<0.01$ in all cases, Table 2). Furthermore, Sar-PDB and MM-PDB patients had higher five-year mortality compared to GCT-PDB patients ($p<0.01$ in both comparisons, Table 2).

Discussion

A fascinating behaviour of pagetic bone tissue is profiled in the results of our study. Pagetic bones appear to be prone to primary neoplastic degeneration of the affected tissues, up to the occurrence of some BCs with specific clinical characteristics. At the same time, however, PDB shields bone tissue from the onset of BMs, both on affected and non-affected skeletal sites. In particular, Caucasian males with polyostotic PDB appear to be at high risk of developing BCs, with a different prevalence from the general population. According to the 2006 report on tumors by the AIR-TUM (Association of Italian Tumor Registries) in Italy, primary BCs represented 0.2% of all malignancies, with an yearly average of 1.3 new bone malignant tumors diagnosed per 100,000 males and of 1.1 per 100,000 females (30). Within the Italian PDB Registry, BCs represent the 10.8% of all solid malignancies, and occurs in the 2.4% of all PDB patients, indicating a higher prevalence compared to the population not affected by PDB. The oncogenic role of PDB is furtherly supported by the evidence that almost all BCs occurs on affected skeletal tissues in the IPD systematic review and, as previously reported, mostly in polyostotic patients. Moreover, multifocal BCs was found in 5.9% of Sar-PDB patients in our results, instead of 1.5% observed by Corradi et al in Sar without PDB (31). The overproduction of insulin-like growth factor-1 by PDB osteoclasts may explain our results, because it contributes to the development of pagetic bone structure and to tumorigenesis (32) by upregulating the expression of two members of largest family of receptor tyrosine kinases, EphB2 and EphB4, in osteoclast and osteoblast (33, 34). This suggests that PDB may create a “favourable soil” for the development and progression of BCs.

On the contrary, the prevalence of BMs is lower in PDB patients compared to the general population. The largest survey about the prevalence and prognosis of bone metastases, i.e. Surveillance, Epidemiology, and End Results (SEER), indicated a prevalence of 6.0% of BMs considering all solid tumors between 2010 and 2015 (35). In our PDB population, the 4.7% of patients with solid tumor resulted with a BM, sparing pagetic and non-pagetic bones. This

result proves that PDB probably protect against cancer metastasis on bones, even if the final effect on the mortality must be proved in targeted studies. A possible reason behind this finding may be found in the protection against occurrence of bone metastasis offered by bisphosphonate treatment (36). Indeed, Pagetic bones are histologically characterized by disorganized architecture of bone matrix near Haversian canals and pathological angiogenesis (37). Zoledronic acid appear to “normalize” the architecture of pagetic bone. Histological analyses of post-treatment biopsies have shown a restoration of bone structure, indicating a near-complete reversal of the pagetic alterations (38). For this reason, treatments should be always advised to obtain remission and normalization. As recommended, our PDB population received zoledronic acid as first line treatment at least once in their lifetime, probably restoring bone tissue architecture and so preserving it from cancer (39). However, this assumption is not supported by Tu et al, whose results show a non-significant difference in the prevalence of BMs according to treatment (13). Prospective studies need to be designed to clarify the local tissue events in PDB patients with solid tumors.

Another result standing out from the systematic analysis is represented by the clinical characteristics that define BCs in PDB patients compared to general population. The demographic features of Sar-PDB make it clear. Indeed, non-PDB osteosarcoma primarily affects child and adolescents, preferentially Blacks (6.8 per million persons per year) and Hispanics (6.5 per million) patients and typically involves the knee region and the metaphysis of the appendicular long bones (40). In contrast, Sar-PDB affect adult Caucasian patients and show a peculiar anatomical distribution which reflect the distribution of skeletal sites commonly involved in PDB, such as femur, pelvis, tibia, and skull (5). Sar-PDB also show a high prevalence of multifocal neoplasm, that is uncommon, as previously reported (31). Lastly, the prognosis is different, with a 5-year mortality rate approaching 30% in non-PDB osteosarcoma (40, 41) and 90% in Sar-PDB (Table 2). These unique clinical features (gender, age, localization and prognosis) picture a distinct disease in PDB patients that may require different strategies

for treatment to be studied. In this case, the lack of tailored therapies conceals a successful impact of treatment on the mortality rate.

To be noted, the prevalence resulting in the clinical cross-sectional survey overlap prior studies conducted in the field, at least for osteosarcomas (13, 42-50). In contrast, the percentage of GCT-PDB in our sample is higher compared to any other party, because of the founder effect of ZNF687 in Campania region, Southern Italy, that both increases the rate of GCT and the severity of the condition (19, 22).

A final worthing comment regarding the results is represented by the poor use of the genetic profile of PDB patients, that does not impact on the occurrence, development and prognosis of BCs or BMs. One future prospective may be represented by the demonstration of microRNA-16 hyperexpression in Sar-PDB (28). This last can be a cue for a tailored therapy, that should aim to obtain remission of PDB, even under the toughest circumstances (51).

Our study presents strengths and weaknesses. As first, the large sample size and the analogy between the patients from Italian PDB Registry and from the United Kingdom's Multi - Centre Randomised Controlled Trial of Symptomatic Versus Intensive Bisphosphonate Therapy for Paget's Disease (PRISM) study, guarantees generalizability of the results. Moreover, the IPD design allows to collect a large amount of data, that, however, results heterogeneous. Another limitation is the genetic information, which has only become available in the last 20 years, and so is lacking in many of the reported cases in the review.

In conclusion, PDB represent a risk factor for occurrence of bone neoplasms, that demonstrates unique clinical characteristics needing further investigation to tailor specific treatments. On the other hand, PDB protects bone from metastasis of solid tumors on affected and non-affected bones, probably depending on bisphosphonate treatment. For this reason, remission of PDB must be always pursued by zoledronic acid administration whenever possible.

References

1. <https://www.cancer.org/cancer/bone-cancer/about/key-statistics.html>. Accessed on 01/06/2025
2. Cole S, Gianferante DM, Zhu B, Mirabello L. Osteosarcoma: A Surveillance, Epidemiology, and End Results program-based analysis from 1975 to 2017. *Cancer*. 2022;128(11):2107-2118. doi: 10.1002/cncr.34163.
3. Rendina D, De Filippo G, Ralston SH, Merlotti D, Gianfrancesco F, Esposito T, Muscariello R, Nuti R, Strazzullo P, Gennari L. Clinical characteristics and evolution of giant cell tumor occurring in Paget's disease of bone. *J Bone Miner Res*. 2015;30(2):257-63. doi: 10.1002/jbmr.2349.
4. Seitz S, Priemel M, von Domarus C, Beil FT, Barvencik F, Amling M, Rueger JM. The Second Most Common Bone Disease: A Review on Paget's Disease of Bone. *Eur J Trauma Emerg Surg*. 2008 Dec;34(6):549-53. doi: 10.1007/s00068-008-8208-4. Epub 2008 Nov 24. PMID: 26816278.
5. Gennari L, Rendina D, Falchetti A, Merlotti D. Paget's Disease of Bone. *Calcif Tissue Int*. 2019;104(5):483-500. doi: 10.1007/s00223-019-00522-3.
6. Gennari L, Rendina D, Merlotti D, Cavati G, Mingiano C, Cosso R, Materozzi M, Pirrotta F, Abate V, Calabrese M, Falchetti A. Update on the pathogenesis and genetics of Paget's disease of bone. *Front Cell Dev Biol*. 2022;10:932065. doi: 10.3389/fcell.2022.932065.
7. Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. *Cancer*. 2009;115(7):1531-43. doi: 10.1002/cncr.24121.
8. Longhi A, Errani C, Gonzales-Arabo D, Ferrari C, Mercuri M. Osteosarcoma in patients older than 65 years. *J Clin Oncol*. 2008;26(33):5368-73. doi: 10.1200/JCO.2007.14.9104.

9. Beird HC, Bielack SS, Flanagan AM, Gill J, Heymann D, Janeway KA, Livingston JA, Roberts RD, Strauss SJ, Gorlick R. Osteosarcoma. *Nat Rev Dis Primers*. 2022 Dec 8;8(1):77. doi: 10.1038/s41572-022-00409-y. Erratum in: *Nat Rev Dis Primers*. 2022 Dec 30;8(1):82. doi: 10.1038/s41572-022-00416-z. PMID: 36481668..
10. Paget J. On a Form of Chronic Inflammation of Bones (Osteitis Deformans). *Med Chir Trans*. 1877; 60:37-64.9. doi: 10.1177/095952877706000105.
11. Price CH. The incidence of osteogenic sarcoma in South-West England and its relationship to Paget's disease of bone. *J Bone Joint Surg Br*. 1962;44-B:366-76. doi: 10.1302/0301-620X.44B2.366.
12. D'Oronzo S, Coleman R, Brown J, Silvestris F. Metastatic bone disease: Pathogenesis and therapeutic options: Up-date on bone metastasis management. *J Bone Oncol*. 2018;15:004-4. doi: 10.1016/j.jbo.2018.10.004.
13. Tu SM, Som A, Tu B, Logothetis CJ, Lee MH, Yeung SC. Effect of Paget's disease of bone (osteitis deformans) on the progression of prostate cancer bone metastasis. *Br J Cancer*. 2012;107(4):646-51. doi: 10.1038/bjc.2012.315.
14. Gennari L, Gianfrancesco F, Di Stefano M, Rendina D, Merlotti D, Esposito T, Gallone S, Fusco P, Rainero I, Fenoglio P, Mancini M, Martini G, Bergui S, De Filippo G, Isaia G, Strazzullo P, Nuti R, Mossetti G. SQSTM1 gene analysis and gene-environment interaction in Paget's disease of bone. *J Bone Miner Res*. 2010 Jun;25(6):1375-84. doi: 10.1002/jbmr.31. PMID: 20200946
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097.
16. Rendina D, Abate V, Cacace G, D'Elia L, De Filippo G, Del Vecchio S, Galletti F, Cuocolo A, Strazzullo P. Tumor-induced Osteomalacia: A Systematic Review and Individual

- Patient's Data Analysis. *J Clin Endocrinol Metab.* 2022 Jul 14;107(8):e3428-e3436. doi: 10.1210/clinem/dgac253. PMID: 35468192.
17. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Lisy K, Qureshi R, Mattis P, Mu P. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). *JBI Manual for Evidence Synthesis*. JBI, 2020. Available from <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-08>
 18. Singer FR. The evaluation and treatment of Paget's disease of bone. *Best Pract Res Clin Rheumatol.* 2020;34(3):101506. doi: 10.1016/j.berh.2020.101506.
 19. Divisato G, Formicola D, Esposito T, Merlotti D, Pazzaglia L, Del Fattore A, Siris E, Orcel P, Brown JP, Nuti R, Strazzullo P, Benassi MS, Cancela ML, Michou L, Rendina D, Gennari L, Gianfrancesco F. ZNF687 Mutations in Severe Paget Disease of Bone Associated with Giant Cell Tumor. *Am J Hum Genet.* 2016 Feb 4;98(2):275-86. doi: 10.1016/j.ajhg.2015.12.016. PMID: 26849110; PMCID: PMC4746367.
 20. Gianfrancesco F, Rendina D, Merlotti D, Esposito T, Amyere M, Formicola D, Muscariello R, De Filippo G, Strazzullo P, Nuti R, Vikkula M, Gennari L. Giant cell tumor occurring in familial Paget's disease of bone: report of clinical characteristics and linkage analysis of a large pedigree. *J Bone Miner Res.* 2013 Feb;28(2):341-50. doi: 10.1002/jbmr.1750. PMID: 22936311.
 21. Gennari L, Gianfrancesco F, Di Stefano M, Rendina D, Merlotti D, Esposito T, Gallone S, Fusco P, Rainero I, Fenoglio P, Mancini M, Martini G, Bergui S, De Filippo G, Isaia G, Strazzullo P, Nuti R, Mossetti G. SQSTM1 gene analysis and gene-environment interaction in Paget's disease of bone. *J Bone Miner Res.* 2010 Jun;25(6):1375-84. doi: 10.1002/jbmr.31. PMID: 20200946.
 22. Rendina D, Gennari L, De Filippo G, Merlotti D, de Campora E, Fazioli F, Scarano G, Nuti R, Strazzullo P, Mossetti G. Evidence for increased clinical severity of familial and

- sporadic Paget's disease of bone in Campania, southern Italy. *J Bone Miner Res.* 2006 Dec;21(12):1828-35. doi: 10.1359/jbmr.060822. PMID: 17002563.
23. Rendina D, Mossetti G, Soscia E, Sirignano C, Insabato L, Viceconti R, Ignarra R, Salvatore M, Nunziata V. Giant cell tumor and Paget's disease of bone in one family: geographic clustering. *Clin Orthop Relat Res.* 2004 Apr;(421):218-24. doi: 10.1097/00000118702.46373.e3. PMID: 15123951.
 24. Ronca M, Vuotto P, Rendina D, et al: Effects of glucocorticoid therapy in giant cell tumor associated with Paget's bone disease: A possible role of the Pai-Pa system. *Ital J Miner Elect M* 13:45–47, 1999
 25. Merchant A, Smielewska M, Patel N, Akunowicz JD, Saria EA, Delaney JD, Leach RJ, Seton M, Hansen MF. Somatic mutations in SQSTM1 detected in affected tissues from patients with sporadic Paget's disease of bone. *J Bone Miner Res.* 2009;24(3):484-94. doi: 10.1359/jbmr.081105.
 26. Scotto di Carlo F, Pazzaglia L, Mumm S, Benassi MS, De Chiara A, Franchi A, Parafioriti A, Righi A, Esposito T, Whyte MP, Gianfrancesco F. ZNF687 Mutations in an Extended Cohort of Neoplastic Transformations in Paget's Disease of Bone: Implications for Clinical Pathology. *J Bone Miner Res.* 2020;35(10):1974-1980. doi: 10.1002/jbmr.3993.
 27. Scotto di Carlo F, Pazzaglia L, Esposito T, Gianfrancesco F. The Loss of Profilin 1 Causes Early Onset Paget's Disease of Bone. *J Bone Miner Res.* 2020;35(8):1387-1398. doi: 10.1002/jbmr.3964.
 28. Green D, Mohorianu I, McNamara I, Dalmay T, Fraser WD. miR-16 is highly expressed in Paget's associated osteosarcoma. *Endocr Relat Cancer.* 2017;24(5):L27-L31. doi: 10.1530/ERC-16-0487.
 29. Wei Z, Li S, Tao X, Zhu G, Sun Z, Wei Z, Jiao Q, Zhang H, Chen L, Li B, Zhang Z, Yue H. Mutations in Profilin 1 Cause Early-Onset Paget's Disease of Bone With Giant Cell Tumors. *J Bone Miner Res.* 2021;36(6):1088-1103. doi: 10.1002/jbmr.4275.

30. Franchi A. Epidemiology and classification of bone tumors. *Clin Cases Miner Bone Metab.* 2012;9(2):92-95.
31. Agrawal M, Patil A, James T, Kumar N, Premalata CS. Multifocal Osteosarcoma: Multiple Primaries or Metastases? A Report of Rare Case and Review of Literature. *J Orthop Case Rep.* 2020;10(8):97-100. doi:10.13107/jocr.2020.v10.i08.1878
32. Wu Q, Suo Z, Risberg B, Karlsson MG, Villman K, Nesland JM. Expression of Ephb2 and Ephb4 in breast carcinoma. *Pathol Oncol Res.* 2004;10(1):26-33. doi: 10.1007/BF02893405.
33. Miyagawa K, Ohata Y, Delgado-Calle J, Teramachi J, Zhou H, Dempster DD, Subler MA, Windle JJ, Chirgwin JM, Roodman GD, Kurihara N. Osteoclast-derived IGF1 is required for pagetic lesion formation in vivo. *JCI Insight.* 2020 ;5(6):e133113. doi: 10.1172/jci.insight.133113.
34. Teramachi J, Nagata Y, Mohammad K, Inagaki Y, Ohata Y, Guise T, Michou L, Brown JP, Windle JJ, Kurihara N, Roodman GD. Measles virus nucleocapsid protein increases osteoblast differentiation in Paget's disease. *J Clin Invest.* 2016;126(3):1012-22. doi: 10.1172/JCI82012.
35. Zhang J, Cai D, Hong S. Prevalence and prognosis of bone metastases in common solid cancers at initial diagnosis: a population-based study. *BMJ Open.* 2023;13(10):e069908. Published 2023 Oct 21. doi:10.1136/bmjopen-2022-069908
36. Coleman R, Cameron D, Dodwell D, et al. Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. *Lancet Oncol.* 2014;15(9):997-1006. doi:10.1016/S1470-2045(14)70302-X
37. Ingram RT, Collazo-Clavell M, Tiegs R, Fitzpatrick LA. Paget's disease is associated with changes in the immunohistochemical distribution of noncollagenous matrix proteins in

- bone. *J Clin Endocrinol Metab.* 1996 May;81(5):1810-20. doi: 10.1210/jcem.81.5.8626840. PMID: 8626840.
38. Ralston SH, Langston AL, Reid IR. Pathogenesis and management of Paget's disease of bone. *Lancet.* 2008 Jul 12;372(9633):155-163. doi: 10.1016/S0140-6736(08)61035-1. PMID: 18620951.
 39. Rendina D, Falchetti A, Diacinti D, et al. Diagnosis and treatment of Paget's disease of bone: position paper from the Italian Society of Osteoporosis, Mineral Metabolism and Skeletal Diseases (SIOMMMS). *J Endocrinol Invest.* 2024;47(6):1335-1360. doi:10.1007/s40618-024-02318-1
 40. Ottaviani G, Jaffe N. The epidemiology of osteosarcoma. *Cancer Treat Res.* 2009;152:3-13. doi: 10.1007/978-1-4419-0284-9_1. PMID: 20213383.
 41. Misaghi A, Goldin A, Awad M, Kulidjian AA. Osteosarcoma: a comprehensive review. *SICOT J.* 2018;4:12. doi: 10.1051/sicotj/2017028. Epub 2018 Apr 9. PMID: 29629690; PMCID: PMC5890448.
 42. Porretta CA, Dahlin DC, Janes JM. Sarcoma in Paget's disease of bone. *J Bone Joint Surg Am.* 1957;39-A(6):1314-29;
 43. Barry HC. Paget's disease of bone. E. & S. Livingstone Eds (Edinburgh), 1969, pp 136-41;
 44. Fromm GA, Roca JF, Mautalén CA, Casco C. Osteitis deformante de Paget. Manifestaciones clínicas y humorales en 148 pacientes [Evaluation of clinical and humoral data in 148 patients with Piaget's bone disease]. *Medicina (B Aires).* 1980;40(6 Pt 1):635-42;
 45. Wick MR, Siegal GP, Unni KK, McLeod RA, Greditzer HG 3rd. Sarcomas of bone complicating osteitis deformans (Paget's disease): fifty years' experience. *Am J Surg Pathol.* 1981 Jan;5(1):47-59. doi: 10.1097/00000478-198101000-00008. PMID: 6941703.;

46. Greditzer HG 3rd, McLeod RA, Unni KK, Beabout JW. Bone sarcomas in Paget disease. *Radiology*. 1983 Feb;146(2):327-33. doi: 10.1148/radiology.146.2.6571760. PMID: 6571760.;
47. Mankin HJ, Hornicek FJ. Paget's sarcoma: a historical and outcome review. *Clin Orthop Relat Res*. 2005 Sep;438:97-102. doi: 10.1097/01.blo.0000180053.99840.27. PMID: 16131876.;
48. Seitz S, Priemel M, Zustin J, Beil FT, Semler J, Minne H, Schinke T, Amling M. Paget's disease of bone: histologic analysis of 754 patients. *J Bone Miner Res*. 2009 Jan;24(1):62-9. doi: 10.1359/jbmr.080907. PMID: 18767930;
49. Miladi S, Rouached L, Maatallah K, Rahmouni S, Fazaa A, Sellami M, Ferjani H, Kaffel D, Hamdi W, Abdelghani KB, Laatar A. Complications of Paget Bone Disease: A Study of 69 Patients. *Curr Rheumatol Rev*. 2021;17(4):390-396. doi: 10.2174/1573397117666210908102615. PMID: 34496735.;
50. Schajowicz F, Velan O, Santini Araujo E, Plantalech L, Fongi E, Ottolenghi E, Fromm GA. Metastases of carcinoma in the pagetic bone. A report of two cases. *Clin Orthop Relat Res*. 1988;(228):290-6; 10.1007/BF00186887
51. Merlotti D, Materozzi M, Bianciardi S, et al. Mutation of PFN1 Gene in an Early Onset, Polyostotic Paget-like Disease. *J Clin Endocrinol Metab*. 2020;105(8):dgaa252. doi:10.1210/clinem/dgaa252

Figure 1

Study flow chart.

Figure 1 legend: The systematic search was performed according to PRISMA criteria. PRISMA= Preferred Reporting Items for Systematic Reviews and Meta-Analyses (11)

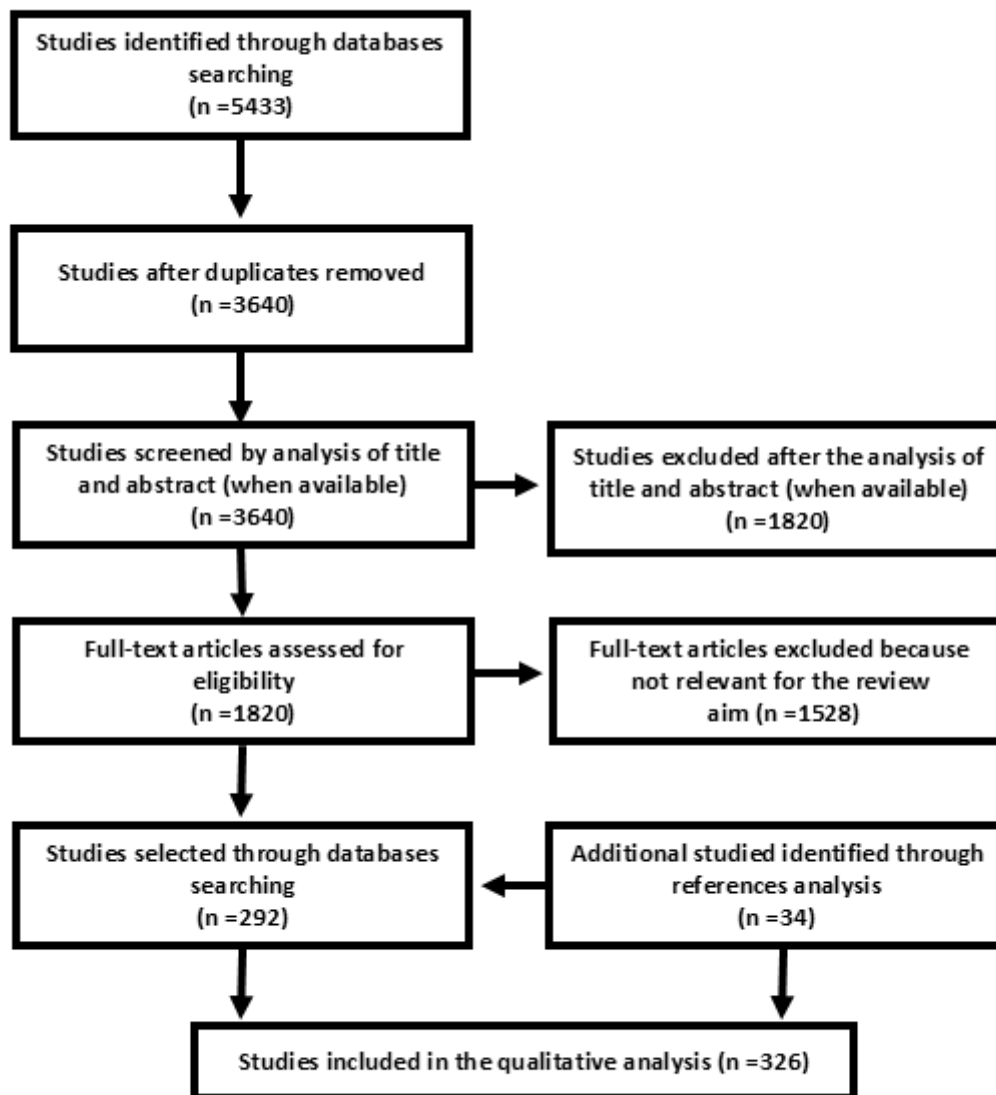


Table 1

Clinical characteristics of PDB patients with primary bone neoplasms and bone metastasis affecting pagetic bones from Italian PDB Registry

Pt	Age		PDB						Bone neoplasm						
	(yr)	Sex	Dia (yr)	ALP (%)	Symp	P/M (n)	Treatment	Rem	Neo	Dia (yr)	ALP (%)	Symp	Sites	Treatment	5y
01	59	M	42	453	BD	P (7)	Cal, Clo, Pam, Zol	no	Sar	59	463	BP, Neu	Pel	Rx	no
02	77	M	72	986	BP	P (2)	Ner	no	Sar	77	765	BP, Neu	Spi	Rx	no
03	81	M	72	586	BD, BP	P (4)	Cal, Pam	no	Sar	80	359	BP, Neu	Spi	Rx	no
04	61	M	60	1758	AS	P (7)	Cal, Pam	no	Sar	60	533	BP, Fra	Pel	Dox, Cis, Ifo	no
05	68	M	67	364	BD, BP	P (3)	Zol	no	Sar	67	364	BD, BP	Sku	None	no
06	67	M	67	115	BD, BP	P (7)	None	no	Sar	67	236	BP	Sca	None	no
07	63	M	61	577	AS	P (6)	Clo, Ris, Zol	yes	Sar	63	647	BP	Pel	None	no
08	64	M	60	168	BP, Neu	P (5)	Eti, Clo	no	Sar	63	123	BP	Pel	No	no
09	79	M	78	384	AS	P (4)	Cal	no	Sar	76	652	BP	Spi	Rx	no
10	61	F	55	273	BD	P (3)	Eti, Clo	no	Sar	60	1243	BP	Sca	Rx, Dox	no
11	68	M	52	523	AS	P (5)	Cal, Eti, Clo	no	Sar	67	891	BP, Fra	Pel	Rx, Dox	no
12	80	F	57	1536	BD	P (9)	Cal, Clo, Pam	no	GCT	67	2524	BP	Man, Sku, Max	Rx, Sur	yes
13	76	F	44	2523	BD	P (5)	Cal, Clo	no	GCT	58	1536	BP	Man	Rx, Sur	yes
14	61	M	35	1207	BD	P (12)	Cal, Clo, Pam	no	GCT	51	1136	BP	Sku	Rx	yes
15	58	M	41	1950	BD	P (6)	Clo, Pam, Ner, Zol	no	GCT	51	1185	BP	Sca, Man, Pel, Cla, Max	Sur	yes
16	67	M	45	1217	AS	P (5)	Clo, Pam, Ner, Zol	no	GCT	52	876	BP, Neu	Pel	Den	yes
17	60	M	37	345	BD, BP	P (8)	Clo	no	GCT	51	470	BD, BP, Fra, Neu	Pel	Sur, Den	yes
18	70	F	60	398	AS	P (3)	Ner	yes	MM (LN H)	61	127	BP, SS	Sku	Dox	yes

19	66	M	47	212	AS	P (3)	Pam, Zol	yes	Met	66	204	Fra	Fem	Rx, Dox	no
20	76	M	65	214	AS	P (2)	Clo, Zol	yes	Met	75	148	BP	Spi	RX	no
21	68	F	56	184	AS	P (3)	Clo, Zol	yes	Met	67	165	BP	Spi	Rx	no
22	73	M	59	204	BP	P (4)	Zol	Yes	Met	70	25	BP	Sca	Rx, Car	yes
23	62	M	58	550	BP	P (3)	Clo, Zol	yes	Met	62	550	BP	Sca	None	no
24	55	M	54	103	BP	P (2)	None	no	Met	55	116	BP	Spi	None	no

PDB= Paget's disease of bone. Pt= Patient. M: male. F= female. Age= age at the last examination. Dia= Age at diagnosis. ALP= Alkaline phosphatase serum levels expressed as percentage compared to laboratory reference range at PBD (left) and bone neoplasm (right) diagnosis. Symp = Clinical signs and symptoms at diagnosis of PDB and of bone neoplasm. BD: bone deformity. BP: Bone pain. AS: No signs or symptoms. Neu: nerve compression. Fra: pathological fracture. SS systemic symptoms. P/M polyostotic/monostotic PDB (number of skeletal sites affected by PDB). Neo: histological definition of bone neoplasm. GCT: Giant cell tumor. Sar= sarcoma. MM= miscellaneous neoplasm. LNH= skeletal non-Hodgkin lymphoma. Met= metastasis. Sytes= skeletal sites affected bone neoplasms, which occurs in skeletal sites affected by PDB in all cases. Man= Mandible. Sku= skull. Max= maxillary. Sca=Scapula. Pel= Pelvis. Cla= clavicle. Fem= femur. Spi= spine. Treatment: Treatment for PDB and bone neoplasm. Cal= calcitonin. Cln= clodronate. Pam= pamidronate. Ner= neridronate. Zol= zoledronate. Eti= etidronate. Ris= risedronate. RX= radiotherapy. Sur= surgery. Den: Denosumab. Dox: Doxorubicina. Cis: Cisplatino. Ifo: Ifofosamide. Car= carbozatinib. Rem= PDB remission, defined as ALP serum levels within the laboratory reference range after PDB treatment. 5y= 5 years' survival from bone neoplasm diagnosis

Table 2

Clinical characteristics of the patients with Paget's disease of bone and primary bone neoplasm, bone metastasis, or patients without primary bone neoplasm nor bone metastasis enrolled in the Italian Registry of Paget's disease of bone

	PBC-PDB			BM-PDB	Italian PDB Controls
	Sar-PDB	GCT-PDB	MM-PDB		
Number (n)	1478	123	58	70	718
Male gender	784/1267 (61.9) ^a	82/120 (68.3) ^a	27/37 (73.0)	39/56 (69.6) ^a	409/718 (57.0)
Caucasian	569/601 (94.7)	75/85 (88.2)	6/9 (66.7)	11/12 (91.6)	718/718 (100)
Black	13/601 (2.1)	1/85 (1.2)	2/9 (22.2)	0	0
Asian	19 /601(3.2)	9/85 (10.6)	1/9 (11.1)	1/11 (9.1)	0
Mean age, years	68.2±9.1	61.4±12.6	61.6±12.3	66.4±13.7	68.7±11.5
PDB Polyostotic	329/424 (77.6) ^{a, c}	109/118 (92.3) ^{a, c}	13/20 (65.0)	14/24 (58.3)	423/718 (58.9)
Mean age at PDB onset, years	60.3±11.6	50.8±12.1 ^{a,b,c,d}	59.1±13.7	63.4±13.3	59.3±11.9
PDB diagnosis prior to neoplasm onset	89/121 (73.6)	76/92 (82.6)	7/14 (50.0)	13/22 (59.1)	-
5-year mortality	778/834 (93.3) ^{a,d}	26/94 (27.7) ^a	11/12 (91.7) ^{a,d}	12/15 (80.0) ^a	31 (4.3) ^e

Data are expressed as absolute number/number of patients in whom the variable was available (percentage) for dichotomous variables and mean ± standard deviation for continuous variables. PDB: Paget's disease of bone. PBC-PDB: PDB patients with primary bone neoplasm. Sar: PDB patients with sarcomas. GCT: PDB patients with giant cell tumor. MM: PDB patients with miscellaneous malignancies. BM-PDB: PDB patients with bone metastasis. Italian PDB Controls: PDB patients enrolled in the Italian PDB Registry without PBC or BM. PDB polyostotic: patients with more than one skeletal sites affected by PDB. PDB monostotic: patients with one skeletal site affected by PDB. A: significantly different compared to Italian PDB Controls. B= significantly different compared to Sar-PDB. C= significantly different compared to BM-PDB. D= significantly different compared to GCT-PDB: E= 5-year mortality was

calculated in PDB patients registered in the Italian Registry of Paget's disease of bone from at least 5 years.

Table 3

Clinical signs and symptoms in patients with Paget's disease of bone and primary bone neoplasm and bone metastasis at neoplasm onset

	PBC-PDB			BM-PDB
	Sar-PDB	GCT-PDB	MM-PDB	
No sign and symptoms	0	0	0	0
Bone Pain	332 (56.6)	37 (22.2)	5 (20.0)	26 (76.5)
Bone deformity	107 (18.2)	77 (46.4)	10 (40.0)	11 (34.4)
Pathological Fractures	82 (14.0)	5 (3.0)	6 (24.0)	6 (18.8)
Contigue tissues compression	52 (89.9)	33 (19.9)	3 (12.0)	0
Systemic symptoms	10 (1.7)	2 (1.2)	1 (4.0)	12 (37.5)
Bleeding	4 (0.7)	12 (7.2)	0	0
High ALP serum	296 (98.3)	75 (96.2)	7 (87.5)	16 (100.0)

Data are expressed as absolute number (percentage). PDB: Paget's disease of bone. PBC-PDB: primary bone neoplasms. Sar: PDB patients with sarcomas. GCT: PDB patients with giant cell tumor. MM: PDB patients with miscellaneous malignancies. BM-PDB: PDB patients with bone metastasis. Systemic symptoms: fever, asthenia, significant weight loss.

Table 4
Treatment of patients with Paget's disease of bone and primary or secondary bone neoplasms

	PBC-PDB			BM-PDB
	Sar-PDB	GCT-PDB	MM-PDB	
None or palliative treatment	266 (43.8)	77 (50.3)	2 (8.0)	1 (11.1)
Surgery	212 (34.9)	38 (24.8)	9 (36.0)	5 (27.8)
Radiotherapy	108 (17.8)	4 (2.6)	8 (32.0)	11 (61.1)
Chemiotherapy	14 (2.3)	3 (1.9)	5 (20.0)	3 (16.7)
Bisphosphonate	5 (0.8)	11 (7.1)	1 (4.0)	1 (5.6)
Calcitonin	2 (0.3)	3 (1.9)	0	1 (11.1)
Glucocorticoids	1 (0.1)	13 (8.5)	0	0
Denosumab	0	4 (2.6)	0	0

Data are expressed as absolute number (percentage). PDB: Paget's disease of bone. PBC: primary bone neoplasms. Sar: PDB patients with sarcomas. GCT: PDB patients with giant cell tumor. MM: PDB patients with miscellaneous malignancies. BM-PDB: PDB patients with bone metastasis.

Supplementary table 1
Methods about data search and extraction

Systematic Review	
Database	Google Scholar; Pubmed; Cockraine; Google Book; Medline; Web Of Science; Scopus; Reference lists from other articles
Key words	Cancer; neoplasm; tumour; Paget's disease of Bone; metastasis
Search last conducted date	October 28 th , 2023
Article typology	Case report; case series; review
Article information	Title; authorship; publication year; reference
Data extracted	Age; gender; age at PDB onset; number of bones affected by PDB; age at PBC or BM onset; symptoms related to PBC or BM; histological diagnosis of PBC; histological diagnosis of primary neoplasm causing BM; family history of PDB and/or PBC; ALP serum levels at onset of PBC or BM; genetic or epigenetic data regarding PDB, PBC or BM; treatment; death; date of last follow up or death
Italian PDB Registry	
Data extracted	Age; gender; age at PDB onset; number of bones affected by PDB; age at PBC or BM onset; symptoms related to PBC or BM; histological diagnosis of PBC; histological diagnosis of primary neoplasm causing BM; family history of PDB and/or PBC; ALP serum levels at onset of PBC or BM; genetic or epigenetic data regarding PDB, PBC or BM; treatment; death; date of last follow up or death

PDB: Paget's disease of bone; ALP: Alkaline Phosphatase; PBC: primary bone cancer; BM: bone metastasis;

Supplementary table 2

Quality assessment of selected case reports with references

Ref	JBI Critical Appraisal Checklist for Case Reports							
	1	2	3	4	5	6	7	8
1	N	N	N	N	N	N	N	U
2	N	Y	N	N	Y	Y	N	U
3	N	Y	Y	N	N	N	N	N
4	Y	Y	Y	Y	N	Y	N	N
5	N	N	N	N	N	N	N	N
6	Y	Y	Y	Y	Y	Y	Y	Y
7	Y	Y	Y	Y	Y	Y	Y	Y
8	Y	Y	Y	Y	Y	Y	Y	Y
9	Y	Y	Y	Y	Y	Y	Y	Y
10	Y	N	Y	Y	Y	N	Y	N
11	Y	N	N	Y	Y	N	N	N
12	Y	Y	Y	N	Y	Y	N	N
13	Y	Y	Y	N	Y	Y	Y	Y
14	Y	Y	Y	Y	Y	Y	Y	Y
15	N	N	Y	N	N	N	N	N
16	Y	Y	Y	N	N	N	N	N
17	Y	Y	Y	N	Y	Y	Y	Y
18	Y	Y	Y	Y	Y	Y	Y	Y
19	Y	Y	Y	Y	Y	Y	Y	Y
20	Y	Y	Y	Y	Y	Y	Y	Y
21	Y	Y	Y	N	Y	N	N	N
22	Y	Y	Y	N	Y	N	N	N
23	Y	Y	Y	N	N	N	N	N
24	N	N	N	N	Y	Y	N	U
25	N	Y	Y	N	N	N	N	U
26	Y	Y	Y	N	N	N	N	N
27	Y	Y	Y	Y	Y	Y	Y	Y
28	Y	Y	Y	Y	Y	Y	Y	Y
29	Y	Y	Y	Y	Y	Y	Y	N
30	N	N	N	N	N	N	N	N
31	N	Y	N	Y	N	N	N	Y
32	Y	Y	Y	N	Y	Y	Y	Y
33	Y	Y	Y	Y	Y	Y	Y	Y
34	Y	Y	Y	Y	Y	Y	Y	Y
35	N	Y	Y	N	N	N	N	Y
36	Y	Y	Y	U	Y	N	N	Y
37	Y	Y	Y	Y	Y	Y	Y	N
38	Y	Y	Y	Y	Y	Y	Y	N.A
39	Y	Y	Y	Y	Y	Y	Y	N
40	Y	Y	Y	Y	Y	Y	Y	Y
41	Y	Y	Y	Y	N	N	N	Y
42	Y	Y	Y	Y	Y	Y	Y	Y
43	Y	Y	Y	Y	Y	Y	Y	Y
44	Y	Y	N	Y	N	N	N	N

45	Y	Y	Y	Y	N	N	N	Y
46	Y	Y	Y	Y	Y	Y	Y	Y
47	Y	Y	Y	Y	N	N	N	Y
48	Y	Y	Y	Y	Y	Y	Y	N
49	Y	Y	Y	Y	Y	Y	Y	Y
50	Y	Y	Y	Y	Y	Y	Y	Y
51	Y	Y	Y	Y	Y	Y	Y	Y
52	Y	Y	Y	Y	Y	Y	Y	Y
53	Y	Y	Y	Y	Y	Y	Y	Y
54	N	Y	N	Y	Y	N	N	Y
55	Y	Y	N	Y	Y	N	N	Y
56	Y	Y	Y	Y	Y	Y	Y	Y
57	Y	Y	Y	Y	Y	Y	Y	Y
58	N	N	N	N	N	N	N	N
59	Y	Y	Y	Y	N	N	N	N
60	N	Y	N	Y	N	N	N	N
61	Y	Y	Y	Y	N	N	N	N
62	Y	Y	Y	Y	Y	Y	Y	Y
63	Y	Y	Y	Y	N	N	N	U
64	Y	Y	Y	Y	Y	Y	Y	Y
65	Y	Y	Y	Y	Y	Y	Y	Y
66	Y	Y	Y	Y	Y	Y	Y	Y
67	N	N	N	N	N	N	N	N
68	Y	Y	Y	Y	Y	Y	Y	Y
69	Y	Y	Y	Y	Y	Y	Y	Y
70	Y	Y	Y	Y	Y	Y	Y	Y
71	N	N	N	Y	N	N	N	N
72	Y	Y	Y	Y	Y	Y	Y	Y
73	Y	Y	Y	Y	N	N	N	Y
74	Y	Y	Y	Y	Y	Y	Y	Y
75	Y	Y	Y	Y	Y	Y	Y	Y
76	Y	Y	Y	Y	Y	Y	Y	Y
77	N	N	N	N	N	N	N	N
78	Y	Y	Y	Y	Y	Y	Y	Y
79	N	N	N	N	Y	N	N	N
80	N	N	N	Y	N	N	N	N
81	Y	Y	N	Y	N	N	N	N
82	N	N	N	Y	N	N	N	N
83	Y	Y	Y	Y	Y	Y	Y	Y
84	Y	Y	Y	Y	Y	Y	Y	Y
85	Y	Y	Y	Y	Y	Y	Y	Y
86	Y	Y	Y	Y	Y	Y	Y	Y
87	Y	Y	Y	Y	Y	Y	Y	Y
88	Y	Y	Y	Y	Y	Y	Y	Y
89	Y	Y	Y	Y	Y	Y	Y	Y
90	Y	Y	Y	Y	Y	Y	Y	Y
91	Y	Y	Y	Y	Y	Y	Y	Y
92	N	N	N	N	N	N	N	N
93	Y	Y	Y	Y	Y	Y	Y	Y
94	Y	Y	Y	Y	Y	Y	Y	Y

95	N	Y	N	Y	N	N	N	N
96	N	N	N	N	N	N	N	N
97	Y	Y	Y	Y	Y	N	Y	Y
98	Y	Y	Y	Y	Y	Y	Y	Y
99	Y	Y	Y	Y	Y	Y	Y	Y
100	Y	Y	Y	Y	Y	Y	Y	Y
101	Y	Y	Y	Y	Y	Y	Y	Y
102	Y	Y	N	Y	Y	Y	Y	Y
103	Y	Y	Y	Y	Y	Y	Y	Y
104	Y	Y	N	Y	N	N	N	N
105	N	N	N	N	N	N	N	N
106	Y	Y	Y	Y	Y	Y	Y	Y
107	Y	Y	Y	Y	N	N	N	Y
108	N	N	N	N	N	N	N	N
109	Y	Y	Y	Y	N	N	N	N
110	Y	Y	N	Y	Y	N	N	U
111	N	N	N	N	N	N	N	N
112	Y	Y	Y	Y	Y	Y	Y	Y
113	Y	Y	Y	Y	Y	Y	Y	Y
114	Y	Y	Y	Y	Y	Y	Y	Y
115	Y	Y	Y	Y	Y	Y	Y	Y
116	Y	Y	Y	Y	Y	Y	Y	Y
117	N	N	N	N	N	N	N	N
118	N	N	N	N	N	N	N	N
119	N	N	N	N	N	N	N	N
120	Y	Y	Y	Y	Y	Y	Y	Y
121	N	N	N	N	N	N	N	N
122	Y	Y	Y	Y	N	N	N	Y
123	Y	Y	Y	Y	Y	Y	Y	Y
124	Y	Y	Y	Y	Y	Y	Y	Y
125	Y	Y	Y	Y	Y	Y	N	Y
126	Y	N	N	N	N	N.A	N	N.A
127	N	Y	Y	Y	N	N.A	N	Y
128	N	Y	Y	Y	Y	Y	Y	Y
129	Y	Y	Y	Y	Y	Y	Y	Y
130	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A
131	Y	N	U	N	N	N	N	N
132	N	N	U	Y	N	N.A	Y	N.A
133	Y	Y	Y	Y	Y	Y	Y	Y
134	N	N	N	N	N	N	N	N.A
135	N	N	N	N	N	N	N	N.A
136	N	Y	Y	N.A	Y	N.A	Y	Y
137	N	Y	Y	Y	Y	Y	U	Y

138	N	N	N	N	N	N	N	N.A
139	N	Y	Y	Y	Y	Y	Y	Y
140	Y	Y	Y	Y	Y	Y	Y	U
141	Y	Y	Y	Y	Y	Y	Y	Y
142	N	N	N	N	N	N	N	N.A
143	N	N	N	N	N	N	N	N.A
144	N	Y	N	N	N	N	N	Y
145	N	N	N	N	N	N	N	N.A
146	N	Y	N	N	N	N	N	N.A
147	Y	Y	Y	Y	Y	Y	Y	Y
148	N	N	N	N	N	N	N	N.A
149	Y	Y	Y	Y	Y	Y	Y	Y
150	Y	Y	Y	Y	Y	Y	Y	U
151	N	Y	Y	Y	Y	Y	Y	Y
152	N	N	N	N	N	N	N	N.A
153	N	Y	Y	Y	Y	Y	Y	Y
154	N	N.A	N.A	N.A	N.A	N.A	N.A	N.A
155	Y	Y	Y	Y	Y	Y	Y	Y
156	Y	Y	Y	Y	Y	N	N	Y
157	N	Y	Y	Y	Y	Y	Y	Y
158	Y	Y	Y	Y	Y	Y	Y	Y
159	Y	Y	Y	Y	Y	Y	N	U
160	N	Y	Y	Y	N	N	N	Y
161	N	Y	Y	Y	Y	Y	Y	Y
162	N	Y	Y	Y	Y	Y	Y	Y
163	Y	Y	Y	Y	Y	Y	Y	Y
164	N	N	N	N	N	N	N	N.A
165	N	N	Y	Y	Y	Y	Y	Y
166	Y	Y	Y	Y	Y	Y	Y	Y
167	Y	Y	Y	Y	N	N	N	Y
168	Y	Y	Y	Y	Y	Y	Y	Y
169	N	Y	Y	Y	Y	Y	U	Y
170	Y	Y	Y	Y	Y	Y	Y	Y
171	Y	Y	Y	Y	Y	Y	Y	Y
172	Y	Y	Y	Y	Y	Y	Y	Y
173	Y	Y	Y	Y	Y	Y	Y	Y
174	N	Y	Y	Y	Y	Y	U	Y
175	N	U	U	Y	Y	Y	Y	Y
176	N	Y	Y	Y	Y	Y	Y	Y
177	Y	Y	Y	Y	Y	Y	N	Y
178	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A

179	Y	Y	Y	Y	Y	Y	Y	U
180	Y	Y	Y	Y	Y	Y	Y	U
181	Y	Y	Y	Y	N	N	N	U
182	N	N	N	N	N	N	N	N.A
183	N	Y	Y	Y	Y	Y	Y	Y
184	N	N	N	N	N	N	N	N.A
185	N	Y	U	U	N	N	N	U
186	Y	Y	Y	U	N	N	N	U
187	N	N	Y	N	N	N	N	N
188	N	N	N	N	N	N	N	N.A
189	N	N	N	N	N	N	N	N.A
190	N	U	Y	N	Y	Y	Y	U
191	Y	Y	Y	Y	Y	Y	Y	Y
192	Y	Y	Y	Y	Y	Y	Y	Y
193	N	Y	Y	Y	Y	Y	Y	U
194	N	Y	Y	Y	N	N	Y	U
195	N	N	Y	Y	N	N	N	U
196	N	Y	Y	Y	N	N	N	U
197	N	N	N	N	N	N	N	N.A
198	N	Y	Y	Y	Y	Y	Y	Y
199	Y	Y	Y	N	N	N	N	U
200	N	Y	Y	Y	Y	Y	Y	Y
201	N	Y	U	Y	N	N	N	U
202	N	N	U	N	Y	N	N	N.A
203	N	Y	Y	Y	Y	Y	Y	Y
204	N	N	N	Y	N	Y	Y	N
205	N	Y	N	N	N	N	N	N
206	Y	Y	Y	Y	Y	Y	Y	Y
207	N	Y	Y	Y	Y	Y	Y	Y
208	N	Y	Y	Y	Y	Y	Y	Y
209	N	Y	N	U	N	N	N	Y
210	N	N	N	Y	N	Y	N	N
211	N	Y	Y	Y	N	Y	Y	Y
212	Y	Y	Y	Y	N	N	N	U
213	N	N	N	U	N	N	N	N
214	N	Y	Y	Y	Y	Y	Y	Y
215	Y	Y	Y	Y	Y	Y	Y	Y
216	N	Y	Y	Y	N	Y	Y	Y
217	N	Y	U	Y	Y	Y	Y	Y
218	N	N	U	Y	N	Y	Y	U
219	N	Y	Y	Y	N	N	N	Y
220	N	Y	Y	Y	Y	Y	Y	Y
221	N	Y	U	Y	Y	N	N	Y
222	N	Y	Y	Y	N	Y	Y	Y
223	N	Y	Y	Y	N	N	N	U

224	N	Y	Y	Y	Y	Y	Y	U
225	Y	Y	N	N	N	N	N	U
226	Y	Y	Y	Y	Y	N	N	Y
227	Y	Y	Y	Y	Y	Y	Y	Y
228	Y	Y	Y	Y	Y	Y	Y	Y
229	Y	Y	Y	Y	Y	N	N	Y
230	Y	Y	Y	Y	Y	Y	Y	Y
231	N	N	N	N	N	N	N	N.A
232	N	Y	Y	Y	Y	Y	Y	Y
233	N	N	N	N	N	N	N	N.A
234	N	Y	Y	Y	Y	N	N	U
235	N	Y	N	Y	Y	Y	Y	Y
236	N	Y	Y	Y	Y	N	N	U
237	N	Y	N	N	N	N	N	N.A
238	Y	Y	Y	Y	Y	Y	Y	Y
239	N	Y	Y	Y	N	N	N	Y
240	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A
241	N	Y	Y	Y	Y	Y	Y	Y
242	Y	Y	Y	Y	N	N	N	U
243	Y	Y	Y	Y	Y	Y	Y	Y
244	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A

1. Were patient's demographic characteristics clearly described?
2. Was the patient's history clearly described and presented as a timeline?
3. Was the current clinical condition of the patient on presentation clearly described?
4. Were diagnostic tests or assessment methods and the results clearly described?
5. Was the intervention(s) or treatment procedure(s) clearly described?
6. Was the post-intervention clinical condition clearly described?
7. Were adverse events (harms) or unanticipated events identified and described?
8. Does the case report provide takeaway lessons?

Ref: references. Yes: Y. No: N. U: Unclear. Not applicable: N.A.

Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Lisy K, Qureshi R, Mattis P, Mu P. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). *JBIM Manual for Evidence Synthesis*. JBI, 2020. Available from <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-08>

References

1. Agha FP, Norman A, Hirschl S, Klein R. Paget's disease. Coexistence with metastatic carcinoma. *N Y State J Med*. 1976 May;76(5):734-5. PMID: 1063322.
2. Allan. Comment following case 10. Seminar on diseases of the maxillofacial region including salivary glands. In: Foote FW, Horn RC editors. *Proceedings of the 26th Annual Seminar of the American Society of Clinical Pathologist*; Chicago; 1961. p. 31
3. Andreseen R. Pagetsche Erkrankung, Spontanfraktur und Sarkom [Paget's disease, spontaneous fracture and sarcoma]. *Bruns Beitr Klin Chir*. 1955;191(2):174-179.

4. Arkader A, Morris CD. Lymphatic spread of pagetic osteogenic sarcoma detected by bone scan. *Cancer Imaging*. 2008;8(1):131-134. Published 2008 Jun 25. doi:10.1102/1470-7330.2008.0021
5. Ashman S, Lever S, Weiss M. Osteogenic sarcoma and Paget's disease of the mandible: review of the literature and case report. *J Md State Dent Assoc*. 1986 Aug;29(2):53-5. PMID: 3463640.
6. Ansari S, Bonar F, Stalley P, Brown W. Paget's sarcoma of the patella. *Skeletal Radiol*. 2015 Jul;44(7):1057-63. doi: 10.1007/s00256-015-2144-2. Epub 2015 Apr 12. PMID: 25862337
7. Aufranc OE. Subtrochanteric fracture in a patient with Paget's disease. *JAMA*. 1961;177:908-911. doi:10.1001/jama.1961.73040390006006
8. Banfi L, Corbella G, Guzzini F, Ceppi M. Degenerazione sarcomatosa nella malattia ossea di Paget. A proposito di un caso clinico [Sarcomatous degeneration in Paget disease of bone. Apropos of a clinical case]. *Clin Ter*. 1993;142(5):433-438.
9. Barbieri E. Clinical and biochemical observations on a case of sarcome in Paget's fracture. *Arch Ortop*. 1959;72:672-676.
10. Barry HC. Sarcoma in Paget's disease of bone in Australia. *J Bone Joint Surg Am*. 1961; 43:1122-34.
11. Barry HC. Orthopedic aspects of Paget's disease of bone. *Arthritis Rheum*. 1980 Oct;23(10):1128-30. doi: 10.1002/art.1780231009. PMID: 7426076.
12. BARRY HC. Sarcoma in Paget's disease of bone. *Aust N Z J Surg*. 1960 May; 29:304-10. doi: 10.1111/j.1445-2197.1960.tb03855.x. PMID: 13797131.
13. Bartley PC, Chotai A, Ward G, Lloyd HM. Calcitonin therapy in Paget's sarcoma. *Med J Aust*. 1979;1(3):99-100. doi:10.5694/j.1326-5377.1979.tb112030.x
14. Bastoni S, Sciancalepore F, Lo Duca MG, Giardina FL, Di Bernardo A, Spinelli MS, Daolio PA. Angiosarcoma Secondary to a Paget's Disease: A Rare Clinical Case With 5 Years of Follow-Up and Review of the Literature Case Rep Series Surg 2020 Volume 1(2): 2-4 doi:10.31487/j.CRSS.2020.02.01
15. Bedard P, Uhthoff HK. Myelome et Maladie de Paget. A propos d'un cas [Myeloma and Paget's Diseases. Apropos of a case]. *Union Med Can*. 1964 Jan;93:45-9. French. PMID: 14111282.
16. Beisner DH, Sumerling MD. Orbitography. A report on twenty consecutive cases. *Am J Ophthalmol*. 1969 Aug;68(2):205-16. PMID: 4979028.
17. Benthien JP, Fuhrmann R, Venbrocks R. The operative management of a malignant proximal humerus tumor represented by secondary Paget's osteosarcoma. *J Cancer Res Clin Oncol*. 1998;124(5):270-274. doi:10.1007/s004320050165
18. Bertoni F, Unni KK, Beabout JW, Ebersold MJ. Giant cell tumor of the skull. *Cancer*. 1992;70(5):1124-1132. doi:10.1002/1097-0142(19920901)70:5<1124::aid-cnrcr2820700517>3.0.co;2-p
19. Cavaleiro BG, Sondermann A, Neto B, de Sousa J, Pinto FR, Cernea CR, Garcia Brandão L. Metástase de carcinoma folicular da tireoide em portador de doença de Paget óssea: relato de caso. *Rev. bras. cir. cabeça pescoço*. 43: 53-6. 2014
20. Bhamhani M, Lamberty BG, Clements MR, Skingle SJ, Crisp AJ. Giant cell tumours in mandible and spine: a rare complication of Paget's disease of bone. *Ann Rheum Dis*. 1992;51(12):1335-1337. doi:10.1136/ard.51.12.1335
21. Billings SD, Wurtz LD, Tejada E, Henley JD. Occult sarcoma of the femoral head in patients undergoing total hip arthroplasty. A report of two cases. *J Bone Joint Surg Am*. 2000;82(11):1536-1539. doi:10.2106/00004623-200011000-00003
22. Bloch-Michel H, Benoist M, Cophignon J, et al. Tumeurs bénignes a cellules géantes associées a une maladie de paget [Benign giant cell tumors associated with Paget's disease. Apropos of 1 case]. *Rev Rhum Mal Osteoartic*. 1975;42(11):681-686.

23. Blodi FC. Unusual orbital neoplasms. *Am J Ophthalmol.* 1969 Sep;68(3):407-12. doi: 10.1016/0002-9394(69)90703-x. PMID: 5257914.
24. Bloom ND. Primary tumors of the thoracic skeleton. *Semin Surg Oncol.* 1993;9(2):150-155. doi:10.1002/ssu.2980090214
25. Bolla M, Jacquot F, Vrousos C, Vuillemin P. Dégénérescence sarcomateuse de la maladie de Paget an niveau du sacrum. A propos d'une observation [Sarcomatous degeneration in Paget's disease of the sacrum. Apropos of a case]. *Bull Cancer.* 1971 Jul-Sep;58(3):411-36. French. PMID: 5292229.
26. Bonakdarpour A, Harwick R, Pickering J. Case report 34. *Skeletal Radiol.* 1977; 2:52-5.
27. Bosschaert P, Mailleux P. Sarcome indifferencie du coude chez un patient pagetique [Undifferentiated sarcoma of the ulna in a patient with Paget's disease]. *J Belge Radiol.* 1998;81(1):11-13.
28. Boulanger V, Chauveaux D, Kantor G, et al. Primary angiosarcoma of bone in Paget's disease. *Eur J Surg Oncol.* 1998;24(6):611-613. doi:10.1016/s0748-7983(98)94112-9
29. Brandolini F, Bacchini P, Moscato M, Bertoni F. Chondrosarcoma as a complicating factor in Paget's disease of bone. *Skeletal Radiol.* 1997;26(8):497-500. doi:10.1007/s002560050273
30. Brehant J. Sarcome ostéolytique à cellules géantes sur maladie de Paget [Osteolytic giant cell sarcoma on Paget's disease]. *Mem Acad Chir (Paris).* 1955 Feb 23-Mar 2;81(8-9):247-50. French. PMID: 14383290.
31. Bricout JH, de Kersaint-Gilly A, Menegalli-Bogelli D, Nombalais F, Lavenant F, Robert R. Ostéosarcome du crâne sur maladie de Paget [Cranial osteosarcoma in Paget's disease]. *J Radiol.* 1983 Feb;64(2):133-7. French. PMID: 6573510.
32. Brooke RI. Giant-cell tumor in patients with Paget's disease. *Oral Surg Oral Med Oral Pathol.* 1970;30(2):230-241. doi:10.1016/0030-4220(70)90368-3
33. Burgener FA, Perry PE. Solitary renal cell carcinoma metastasis in Paget's disease simulating sarcomatous degeneration. *AJR Am J Roentgenol.* 1977 May;128(5):853-5. doi: 10.2214/ajr.128.5.853. PMID: 404918.
34. Calabrò T, Mavrogenis AF, Ruggieri P. Osteoblastic osteosarcoma in monostotic Paget's disease. *Musculoskelet Surg.* 2011;95(1):37-40. doi:10.1007/s12306-011-0100-4
35. Campbell CJ, Leupold RG. Tumors and tumor-like conditions of the Os calcis. *Orthop Clin North Am.* 1973;4(1):145-156.
36. Campidelli C, Righi A, Maremonti P, et al. Giant cell tumor of the mandible in a patient with Paget's disease. *Otolaryngol Head Neck Surg.* 2007;136(4 Suppl):S62-S64. doi:10.1016/j.otohns.2006.10.023
37. Caravita T, Siniscalchi A, Montinaro E, et al. Multiple myeloma and paget disease with abnormal skull lesions and intracranial hypertension. *Mediterr J Hematol Infect Dis.* 2012;4(1):e2012068. doi:10.4084/MJHID.2012.068
38. Cattaneo E. Considerazioni istogenetiche su un caso di sarcoma mandibolare a peculiare morfologia insorto su malattia di Paget [Histogenetic considerations on a case of mandibular sarcoma with unusual morphology occurring in Paget's disease]. *Riv Ital Stomatol.* 1967 Nov;22(11):1341-52. Italian. PMID: 5239203.
39. Chakravarty K, Saeed IT, Fowler RW. A fatal case of pleural osteosarcoma mimicking mesothelioma in Paget's disease of bone. *Rheumatology (Oxford).* 2003 Dec;42(12):1578-9. doi: 10.1093/rheumatology/keg428. PMID: 14645873.
40. Chan J, Gannon FH, Thompson LD. Malignant giant cell tumor of the sphenoid. *Ann Diagn Pathol.* 2003;7(2):100-105. doi:10.1053/adpa.2003.50020
41. Chen KT. Hemangiosarcoma complicating Paget's disease of the bone. *J Surg Oncol.* 1985;28(3):187-189.

42. Cheng YS, Wright JM, Walstad WR, Finn MD. Osteosarcoma arising in Paget's disease of the mandible. *Oral Oncol.* 2002;38(8):785-792. doi:10.1016/s1368-8375(02)00065-9
43. Christie DR, Cahill SP, Barton MB. Primary bone lymphoma (osteolymphoma). *Australas Radiol.* 1996;40(3):319-323. doi:10.1111/j.1440-1673.1996.tb00410.x
44. Chua GT, Kelvin F, Ericson DP. CT findings in coexistent Paget's disease and multiple myeloma. *Indiana Med.* 1988 Jul;81(7):616-7. PMID: 3209855.
45. Colarinha P, Fonseca AT, Salgado L, Vieira MR. Diagnosis of malignant change in Paget's disease by Tl-201. *Clin Nucl Med.* 1996 Apr;21(4):299-301. doi: 10.1097/00003072-199604000-00008. PMID: 8925612.
46. Cones DM. An unusual bone tumour complicating Paget's disease. *J Bone Joint Surg Br.* 1953; 35-B(1):101-5.
47. Conrad GR, Johnson AW. Solitary adenocarcinoma metastasis mimicking sarcomatous degeneration in Paget's disease. *Clin Nucl Med.* 1997;22(5):300-302. doi:10.1097/00003072-199705000-00003
48. Copelan HI. Coexistence Of Multiple Myeloma And Paget's Disease Of Bone. *Calif Med.* 1964;101(2):118-120.
49. Cornejo A. Degeneración sarcomatosa de la enfermedad de Paget. *Rev. Asoc. Arg. Ortop. y Traumatol.* 1994 Vol. 60, NQ 2, págs. 184-187.
50. Cornil L, Paoli J, Gastaut H, Spitalier H. Osseous tumors of Paget. *Sem Hop.* 1950; 26:2357-61.
51. Cowie Rs, Barr Js, Dudley Hr Jr. Bone sarcoma in Paget's disease; report of a case with long survival. *J Bone Joint Surg Br.* 1958;40-B(4):730-734. doi:10.1302/0301-620X.40B4.730.
52. Crouzet J, Beraneck L, Boutry S, Camus JP. Tumeurs bénignes à cellules géantes et maladie osseuse de Paget. *Rhumatologie.* 1978; 30:123.
53. Crozier F, Margain D, Lebrigand B, et al. Ostéosarcome révélant une maladie de Paget [Osteosarcoma manifesting as Paget's bone disease]. *J Radiol.* 2000;81(3):243-245.
54. Dahlin DC. Caldwell Lecture. Giant cell tumor of bone: highlights of 407 cases. *Am J Roentgenol.* 1985;144:955-60.
55. Dacquino G, Jona G. [Anatomo-clinical study of a case of Paget's disease with sarcomatous degeneration]. *Minerva Neurochir.* 1960 Jul-Dec;4:131-2. Italian. PMID: 13719270.
56. Davie MW, Worsfold M, Sharp CA. Differential response of serum alkaline phosphatase and serum osteocalcin in Paget's osteosarcoma. *Ann Clin Biochem.* 1991;28 (Pt 2):194-195. doi:10.1177/000456329102800216.
57. De Chiara A, Apice G, Fazioli F, Silvestro P, Carone G, Manco A. Multicentric giant cell tumor with viral-like inclusions associated with Paget's disease of bone: a case treated by steroid therapy. *Oncol Rep.* 1998;5(2):317-320.
58. De Vulpian P, Kirsch J. Sur la transformation de la maladie osseuse de Paget en tumeur maligne [Transformation of Paget's disease of bone into malignant tumor]. *Paris Med.* 1950 Nov 25;40(44):622-5. Undetermined Language. PMID: 14797311.
59. de Waele S, Lonneux M, Vande Berg B, Nzeusseu A, Brasseur JP, Lecouvet FE. Paget disease and osteosarcoma of the calcaneus. *Clin Nucl Med.* 2001;26(3):244-246. doi:10.1097/00003072-200103000-00018
60. deSantos LA, Edeiken B. Purely lytic osteosarcoma. *Skeletal Radiol.* 1982;9(1):1-7. doi:10.1007/BF00367373
61. Di Scioscio M, Manfrini M, Avella M, Mignani G. Osteosarcoma associated with Paget's disease: a description of a rare case. *Chir Organi Mov.* 1990 Jul-Sep;75(3):279-85. English, Italian. PMID: 2095333.

62. Dickson DD, Camp JD, Ghormley RK. Osteitis deformans: Paget's disease of the bone. *Radiology*. 1945; 44:449–70.
63. Diehl M, Morandi A, González Salvia M, Specterman S, Gruenberg M, Plantalech L. Paget's disease and giant cell tumor. *Bone*. 2006; 38:S8.
64. Dixon GR, Ritchie DA, Myskow MW. Case report: benign giant cell tumour associated with Paget's disease of bone. *Clin Radiol*. 1995; 50:269–71.
65. Donati U, Martucci E. Giant cell tumour in a vertebra affected by Paget's disease of bone. *Ital J Orthop Traumatol*. 1979; 5:253–7.
66. Donato G, Lavano A, Volpentesta G, Chirchiglia D, Veraldi A, De Rose F, Iannello AN, Strosio C, Signorelli CD. Telangiectatic osteosarcoma of the skull. A post-Paget case. *Clin Neuropathol*. 1997 Jul-Aug;16(4):201-3. PMID: 9266145.
67. Douniau R, Fievez C, Petit P. Sarcome ostéogénique de la mandibule [Osteogenic sarcoma of the mandible]. *Acta Stomatol Belg*. 1973 Apr;70(3):325-33. French. PMID: 4520248.
68. Dowling K, Hutto RL, Dowling EA. Sternal mass in a patient with Paget's disease. *Invest Radiol*. 1991 Jun;26(6):615-9. doi: 10.1097/00004424-199106000-00023. PMID: 1860772.
69. Drago M, Casadei R, Donati DM. Sarcomatous Transformation in the Paget's Disease: A Case Report with a Review of Literature. *Bone Rep Recommendations*. 2016, 2:2
70. El Mansouri L, Meadeb JM, Albert JD, et al. Bifocal sarcomatous transformation of Paget's disease: a case report. *Joint Bone Spine*. 2009;76(5):574-575. doi:10.1016/j.jbspin.2009.01.013
71. el-Labban NG. Ultrastructural study of intranuclear tubulo-filaments in a giant cell tumour of bone in a patient with Paget's disease. *J Oral Pathol*. 1984;13(6):650-660. doi:10.1111/j.1600-0714.1984.tb01467.x
72. Epley KD, Lasky JB, Karesh JW. Osteosarcoma of the orbit associated with Paget disease. *Ophthalmic Plast Reconstr Surg*. 1998 Jan;14(1):62-6. doi: 10.1097/00002341-199801000-00013. PMID: 9513246.
73. Erlich RB, Romano S, Meohas W, Smith J. Synchronous Paget's sarcoma of tibiae in which Paget's disease was limited to these bones. *Skeletal Radiol*. 1999;28(10):599-603. doi:10.1007/s002560050627
74. Feinerman LK, Shapiro L. Osteogenic sarcoma: report of a case arising in Paget's disease of the bone with extension to the scalp. *Int J Dermatol*. 1970 Apr-Jun;9(2):96-101. doi: 10.1111/j.1365-4362.1970.tb04586.x. PMID: 5269263.
75. Ferreira RM, Vieira L, Pimenta S, Pinto J, Costa L. Chondrosarcoma as inaugural manifestation of monostotic Paget's disease of Bone. *Acta Reumatol Port*. 2019 Apr-Jun;44(2):163-164. English. PMID: 31455754.
76. Fölsch E. Ostitis deformans Paget und sarkomatöse Entartung [Osteitis deformans (Paget's) and sarcomatous degeneration]. *Langenbecks Arch Chir*. 1968;321(4):359-369. doi:10.1007/BF01442317
77. Fontaine R, Muller Jn, Strazielle J. [Osseous sarcoma on Paget's disease]. *Strasb Med*. 1959 Dec;10:698-707. French. PMID: 13823821.
78. Formica C. Association of myeloplaxic tumor and Paget's disease. *Chir Organi Mov*. 1979;65:601–6.
79. Fourrier P, Godeneche JL, Debrigode. Un cas de dégénérescence maligne de la maladie de PAGET [A case of malignant degeneration in Paget's disease]. *Lyon Chir*. 1969 Jul-Aug;65(4):594-6. French. PMID: 5402297.

80. Francis R, Lewis E. CT demonstration of giant cell tumor complicating Paget disease. *J Comput Assist Tomogr.* 1983; 7:917–8.
81. Friedman AC, Orcutt J, Madewell JE. Paget disease of the hand: radiographic spectrum. *AJR Am J Roentgenol.* 1982 Apr;138(4):691-3. doi: 10.2214/ajr.138.4.691. PMID: 6978033.
82. Galed-Placed I, García-Ureta E, Sánchez-Blas M, Lago-Novoa M. Giant-cell tumor in soft parts in a patient with osseous Paget's disease: diagnosis by fine-needle aspiration. *Diagn Cytopathol.* 1998;19(5):352-354. doi:10.1002/(sici)1097-0339(199811)19:5<352::aid-dc8>3.0.co;2-8
83. Gandolfi A. Sarcoma arising in Paget's disease of the skull: case report. *Acta Neurol (Napoli).* 1979;1(6):498-504.
84. Gandolfi A, Brizzi R, Tedeschi F, Cusmano F, Gabrielli M. Fibrosarcoma arising in Paget's disease of the vertebra: review of the literature. *Surg Neurol.* 1983 Jan;19(1):72-6. doi: 10.1016/0090-3019(83)90213-6. PMID: 6828998.
85. Ghosh ML, Sayeed A. Unusual cases of myelomatosis. *Scand J Haematol.* 1974;12(2):147-54. doi: 10.1111/j.1600-0609.1974.tb00193.x. PMID: 4524662.
86. Goldberg S, Slamovits TL, Dorfman HD, Rosenbaum PS. Sarcomatous transformation of the orbit in a patient with Paget's disease. *Ophthalmology.* 2000 Aug;107(8):1464-7. doi: 10.1016/s0161-6420(00)00180-9. PMID: 10919890.
87. Goldenberg RR. Neoplasia in Paget's disease of bone. *Bull Hosp Joint Dis.* 1961;22:1–38.
88. Goldstein BH, Laskin DM. Giant cell tumor of the maxilla complicating Paget's disease of bone. *J OralSurg.* 1974;32:209–13.
89. Govender D, Lazarus NG. Test and teach. An unusual cause of multiple bilateral pulmonary metastases. Osteosarcoma arising in monostotic Paget's disease of the femur. *Pathology.* 2003 Oct;35(5):444-7. doi: 10.1080/00313020310001602666. PMID: 14555390.
90. Griffey LE, Tedeschi LG. Giant cell tumor of ethmoid. Complication of Paget's disease of bone. *Arch Otolaryngol.* 1968;87:615–7.
91. Griffin JF, Colclough A, Twentyman O, Jenkins JP. Chordoid sarcoma complicating Paget's disease of bone: a case report and review of the literature. *Br J Radiol.* 1984 Sep;57(682):836-40. doi: 10.1259/0007-1285-57-681-836. PMID: 6478143.
92. Hadders HN. [Paget's disease of bone with sarcomatous degeneration]. *Ned Tijdschr Geneesk.* 1960 Apr 2;104:661-5. Dutch. PMID: 13830748.
93. Hakky M, Kolbusz R, Reyes CV, Chinoy MJ. Fine needle aspiration cytology in a case of osteogenic sarcoma in Paget's disease. *Cytopathology.* 1990;1(3):183-6. doi: 10.1111/j.1365-2303.1990.tb00344.x. PMID: 2102357.
94. Heike C, Coons DA, Youngberg R, Benson MJ, Pitcher JD. Recurrent arm pain in a 77-year-old man. *Clin Orthop Relat Res.* 2000 Oct;(379):283-6, 289-91. doi: 10.1097/00003086-200010000-00033. PMID: 11039817.
95. Henin D, Weiss AM, Dairou A, Masson M. Sarcome ostéogène crânien sur maladie de Paget [Osteogenic cranial sarcoma in Paget's disease (author's transl)]. *Ann Med Interne (Paris).* 1979;130(3):169-72. French. PMID: 285636.
96. Hermann G, Szporn A, Schwartz I, Hauser AD. Metastatic carcinoma involving Paget disease of the bone: an unusual association. *Mt Sinai J Med.* 1983 Nov-Dec;50(6):537-9. PMID: 6607412.
97. Hillmann JS, Mesgarzadeh M, Tang CK, Bonakdarpour A, Reyes TG. Case report 481: Benign intraosseous fibroma (desmoplastic fibroma) associated with Paget disease of

- the iliac bone. *Skeletal Radiol.* 1988;17(5):356-9. doi: 10.1007/BF00367183. PMID: 3175695.
98. Hilton G. Osteoclastoma associated with generalized bone disease. *Br J Radiol.* 1950;23:437–9.
 99. Hirsch EF. Osteitis deformans (Paget's disease) with osteogenic sarcoma of the spine. *Ill Med J.* 1950 Dec;98(6):364-7. PMID: 14794125.
 100. Hoch B, Hermann G, Klein MJ, Abdelwahab IF, Springfield D. Giant cell tumor complicating Paget disease of long bone. *Skeletal Radiol.* 2007;36:973–8.
 101. Hoffman CD, Huntley TA, Wiesenfeld D, Kleid S, Kung IT. Maxillary giant cell tumour associated with Paget's disease of bone. *Int J Oral Maxillofac Surg.* 1994; 23:161–4.
 102. Huvos AG. Bone tumors. Diagnosis, treatment and prognosis. WB Saunders Company, Philadelphia, PA, 1979
 103. Ibáñez R, Gutierrez R, Fito C, del Val N, Loza E. Chondrosarcoma in Paget's disease of bone. *Clin Exp Rheumatol.* 2005 Mar-Apr;23(2):275. PMID: 15895907.
 104. Irani L, Hilliquin P, Dreyfus F, Renoux M, Louvel G, Menkès CJ. Maladie de Paget compliquée d'un lymphome Ki-1 avec sécrétion de facteur de croissance G-CSF [Paget disease, complicated by Ki-1 lymphoma with G-CSF growth factor secretion]. *Rev Rhum Ed Fr.* 1994 Oct;61(9):641-4. French. PMID: 7532068.
 105. Ishikawa Y, Tsukuma H, Miller RW. Low rates of Paget's disease of bone and osteosarcoma in elderly Japanese. *Lancet.* 1996 Jun 1;347(9014):1559. doi: 10.1016/s0140-6736(96)90714-x. PMID: 8684133.
 106. Jacobson HG, Siegelman SS. Some miscellaneous solitary bone lesions. *Seminars in Roentgenology*, Volume 1, Issue 3, Part 1, 1966, Pages 314-335
 107. Jelin G, Grados F, Fardellone P, Goëb V. Une complication rare de la maladie de Paget [A rare complication of Paget's disease]. *Rev Med Interne.* 2018 Oct;39(10):832-833. French. doi: 10.1016/j.revmed.2016.12.012. Epub 2017 Jan 26. PMID: 28131441.
 108. Juhasz J. Monostoticus Paget-kór kapcsán keletkezett malignus osteoclastoma [Malignant osteoclastoma in monostotic Paget's disease]. *Orv Hetil.* 1956 Feb 12;97(7):189-92. Hungarian. PMID: 13335148.
 109. Kalinowski DT, Goodwin CA. Case report 179: Metastatic disease developing in Paget disease of bone in the distal end of femur. *Skeletal Radiol.* 1981;7(3):229-31. doi: 10.1007/BF00361873. PMID: 7330684.
 110. Kannan V, von Ruden D. Malignant fibrous histiocytoma of bone: initial diagnosis by aspiration biopsy cytology. *Diagn Cytopathol.* 1988;4(3):262-4. doi: 10.1002/dc.2840040317. PMID: 2855512.
 111. Karakasis DT. Karkinos tou edaphous tou stomatos epi asthenous ek nosou tou Paget ton oston [Carcinoma of the floor of the mouth in a patient with Paget's disease of bone (a diagnostic problem)]. *Odontostomatol Proodos.* 1970 Sep-Oct;24(5):291-6. Greek, Modern. PMID: 4993903.
 112. Karakida K, Ota Y, Aoki T, Akamatsu T, Kajiwarra H, Hirabayashi K. Multiple giant cell tumors in maxilla and skull complicating Paget's disease of bone. *Tokai J Exp Clin Med.* 2010; 35:112–7.
 113. Katzer A, Beecken WD, Meenen NM, Jungbluth KH, Delling G. Pathologische Oberarmfraktur beim sekundären Osteosarkom des Humerus: eine seltene Komplikation der Osteodystrophia deformans Paget [Pathologic humeral fracture in secondary osteosarcoma of the humerus: a rare complication of osteodystrophia deformans Paget]. *Unfallchirurgie.* 1997 Feb;23(1):18-22. German. PMID: 9173645.

114. Kelemen G. Temporal bone showing otosclerosis, paget's disease and adenocarcinoma. *Ann Otol Rhinol Laryngol*. 1977 May-Jun;86(3 Pt 1):381-5. doi: 10.1177/000348947708600316. PMID: 869441.
115. Khor TH, Pang MW. Paget's sarcoma of the skull--a long term survivor with radiotherapy. *Australas Radiol*. 1986 May;30(2):121-3. doi: 10.1111/j.1440-1673.1986.tb02401.x. PMID: 3778380
116. Kim GS, Kim SH, Cho JK, et al. Paget bone disease involving young adults in 3 generations of a Korean family. *Medicine (Baltimore)*. 1997;76:157-69.
117. Klimova MK. [Malignant degeneration of osteodystrophia deformans--Paget's disease]. *Vestn Rentgenol Radiol*. 1962 May-Jun;37:45-50. Russian. PMID: 14456977.
118. Koenigsberg M, Freeman LM. Radionuclide bone imaging. *Curr Probl Diagn Radiol*. 1976 Sep-Oct;6(5):1-54. doi: 10.1016/s0363-0188(76)80004-7. PMID: 797529.
119. Lasserre C, Lachapele AP. La dégénérescence sarcomateuse (D.S.) l'ostéopathie déformante progressive de Pagen (O.D.P.) [Sarcomatous degeneration (D.S.) progressive deforming osteopathy of Pagen (O.D.P.)]. *J Med Bord*. 1954 Oct;131(10):1060-72. French. PMID: 13233700.
120. Leonard J, Gökden M, Kyriakos M, Derdeyn CP, Rich KM. Malignant giant-cell tumor of the parietal bone: case report and review of the literature. *Neurosurgery*. 2001; 48:424-9.
121. Lesure J. Sarcome osteolytique sur maladie de Paget [Osteolytic sarcoma with superimposed Paget's disease]. *Rev Med Nancy*. 1958 Apr;83:278-80. French. PMID: 13555316.
122. Levack B, Dowd GS. Pulsatile cutaneous haemorrhage in Paget's disease of the bone. *Br J Clin Pract*. 1983 Sep;37(9):311-2. PMID: 6578836.
123. Lewis MM, Rudin BJ, Steiner GC. Multifocal Paget's sarcoma. *Bull Hosp Jt Dis Orthop Inst*. 1985 Fall;45(2):162-8. PMID: 3000497.
124. LiVolsi VA. Osteogenic sarcoma of the maxilla. *Arch Otolaryngol*. 1977 Aug;103(8):485-8. doi: 10.1001/archotol.1977.00780250079009. PMID: 267450
125. Ziambaras K, Totty WA, Teitelbaum SL, Dierkes M, Whyte MP. Extraskelatal osteoclastomas responsive to dexamethasone treatment in Paget bone disease. *J Clin Endocrinol Metab*. 1997; 82:3826-34.
126. Zhong X, Ye Y, Ou X. Impressive Paget Disease of the Lumbar Spine Masks the Coexisting Multiple Myeloma. *Clin Nucl Med*. 2017 Sep;42(9):e417-e421. doi: 10.1097/RLU.0000000000001733. PMID: 28639953.
127. Zehr RJ, Bauer TW, Recht MP. Enchondroma associated with Paget's disease. *Orthopedics*. 2000 Dec;23(12):1287-90. doi: 10.3928/0147-7447-20001201-16. PMID: 11144499.
128. Young HA, Hardy DG, Ashleigh R. Osteogenic sarcoma of the skull complicating Paget's disease: case report. *Neurosurgery*. 1983 Apr;12(4):454-7. doi: 10.1227/00006123-198304000-00015. PMID: 6574342.
129. Windle-Taylor PC. Osteosarcoma of the upper jaw. *J Maxillofac Surg*. 1977 Feb;5(1):62-8. doi: 10.1016/s0301-0503(77)80078-7. PMID: 66302.
130. Whitten CR, Saifuddin A. MRI of Paget's disease of bone. *Clin Radiol*. 2003 Oct;58(10):763-9. doi: 10.1016/s0009-9260(03)00264-2. PMID: 14521884.
131. Wellinger C, George P, Martin JL. Paraplégie secondaire à la dégénérescence sarcomateuse de vertèbres lombaires pagétiques [Secondary paraplegia with sarcomatous degeneration of the pagetic lumbar vertebrae]. *Rhumatologie*. 1967 Aug-Sep;19(7):235-47. French. PMID: 5259267.

132. Viola MV, Ellon G, Lazarus M. Virus-like inclusions in osteosarcoma cells arising in Paget's disease. *Lancet*. 1982 Apr 10;1(8276):848. doi: 10.1016/s0140-6736(82)91891-8. PMID: 6122071.
133. Vincent SD, Lilly GE, Ruskin JD. Recurrent enlargement of the left maxillary alveolus. *J Oral Maxillofac Surg*. 1993 Jun;51(6):671-5. doi: 10.1016/s0278-2391(10)80268-x. PMID: 8492206.
134. Villiaume J, Di Menza C, Rotterdam M, Voisin MC, Cherot A. Nouvelle observation de dégénérescence sarcomateuse du rachis Pagétique [A new case of sarcomatous degeneration of the spine in Paget's disease of bone]. *Rev Rhum Mal Osteoartic*. 1975 Nov;42(11):687-91. French. PMID: 1063431.
135. Villar Arias MA, Elena Ibáñez A, López Martín JA, Benito Urbina S. Enfermedad de Paget y degeneración sarcomatosa [Paget's disease and sarcomatous degeneration]. *An Med Interna*. 1998 Mar;15(3):171-2. Spa
136. Vergnon JM, Cheix F, Vauzelle JL, Charhon S, Meunier PJ. Localisations sarcomateuses multifocales dans un cas de maladie osseuse de Paget. Effets du dichlorométhylène diphosphonate [Multifocal sarcoma associated with Paget's disease of bone. Effects of dichloromethylene diphosphate (author's transl)]. *Nouv Presse Med*. 1981 Jun 27;10(28):2353-4, 2359-60. French. PMID: 6455648.
137. Verdier JM, Commandre F, Rivollier P, Ziegler G. Triple association pelvispondylite, Paget et myélome [A triple association: pelvispondylitis, Paget's disease and myeloma]. *Rev Rhum Mal Osteoartic*. 1974 May;41(5):353-6. French. PMID: 4845404.
138. Venturoli L, Brusori G. L'evoluzione sarcomatosa, insolita e grave complicanza della malattia di Paget [Sarcomatous development as an unusual and severe complication of Paget's disease]. *Minerva Med*. 1976 Mar 3;67(11):694-6. Italian. PMID: 1256688.
139. Van Zyl FH, Conradie M, Barnard K, Hough S, Ascott-Evans B. (). Telangiectatic osteosarcoma, a rare complication of Paget's disease of bone. *JEMDSA* 2014;19(1):36-38. 10.1080/16089677.2014.11073597.
140. Valletta G, di Lauro F, Bucci E, Tanzi VG. Paget's disease and maxillary myeloplastic tumor. Clinical contribution. *Arch Stomatol (Napoli)*. 1977; 18:95-113.
141. Upchurch KS, Simon LS, Schiller AL, Rosenthal DI, Campion EW, Krane SM. Giant cell reparative granuloma of Paget's disease of bone: a unique clinical entity. *Ann Intern Med*. 1983; 98:35-40.
142. Ueda T, Healey JH, Huvos AG, Panicek DM. Scapular pain and swelling in a 60-year-old man with Paget's disease. *Clin Orthop Relat Res*. 1996; 326:284-6, 310-2.
143. Tubbax J, Egyedi P, Van den Broek A. Bespreking van een geval van chondrosarkoma als verwikkeling bij de ziekte van Paget [Report on a case of chondrosarcoma as a complication of Paget's disease]. *Acta Stomatol Belg*. 1975;72(2):341-51. Dutch. PMID: 173167.
144. Treves R, Sauvage P, Hugon J, Gualde N, Desproges-Gotteron R. Association myélome non excretant et maladie osseuse de paget [Association of non-excreting myeloma and Paget's disease of bone]. *Rev Rhum Mal Osteoartic*. 1981 Jul-Sep;48(7-9):605. French. PMID: 7291939.
145. Tillman HH. Paget's disease of bone. A clinical, radiographic, and histopathologic study of twenty-four cases involving the jaws. *Oral Surg Oral Med Oral Pathol*. 1962;15:1225-34.
146. THURNER J, NIGRISOLI P. Multiple böartige Gewächse; Sarkom bei Ostitis deformans Paget, Ösophagus- und Prostatakarzinom [Multiple malignant growth; sarcoma in Paget's ostitis deformans, esophagus and prostate cancer]. *Zentralbl Allg Pathol*. 1957 Mar 4;96(3-4):161-7. German. PMID: 13443454

147. Thomson AD, Turner-Warwick RT. Skeletal sarcomata and giant-cell tumour. *J Bone Joint Surg Br.* 1955; 37-B(2):266–303.
148. Taylor R, Shklar G. Carcinoma Of The Maxillary Antrum In A Patient With Osteitis Deformans (Paget's Disease Of Bone): Report Of Case. *J Oral Surg Anesth Hosp Dent Serv.* 1964 Sep;22:428-33. Pmid: 14178804
149. Taurel JP, Fages A, Amouroux J, de Sèze S, Kahn MF. Degenerescence sarcomateuse d'une atteinte pagetigue du rachis cervical, revelation par un syndrome de Pancoast et Tobias [Sarcomatous degeneration in Paget's disease of the cervical spine, revealed by a Pancoast-Tobias syndrome]. *Rev Rhum Mal Osteoartic.* 1973 Feb;40(2):145-8. French. PMID: 4705338.
150. Tanaka T, Slavin J, McLachlan SA, Choong P. Anti-osteoclastic agent, denosumab, for a giant cell tumor of the bone with concurrent Paget's disease: A case report. *Oncol Lett.* 2017 Apr;13(4):2105-2108. doi: 10.3892/ol.2017.5693. Epub 2017 Feb 8. PMID: 28454368; PMCID: PMC5403716.
151. Takahashi S, Eriguchi A, Tanabe H, Kawamoto K, Koike H. A case of giant cell tumor of the maxilla associated with Paget's disease. *Nihon Koku Geka Gakkai Zasshi.* 1976;22:91–5.
152. Stolovitzky JP, Waldron CA, McConnel FM. Giant cell lesions of the maxilla and paranasal sinuses. *Head Neck.* 1994 Mar-Apr;16(2):143-8. doi: 10.1002/hed.2880160207. PMID: 8021133.
153. Stewart JP. Osteoclastoma in association with Paget's disease of the left ethmoid bone. *J Laryngol Otol.* 1946; 61:653.
154. Stephens GC, Lenington WJ, Schwartz HS. Primary lymphoma and Paget's disease of the femur. *Am J Clin Pathol.* 1994 Jun;101(6):783-6. doi: 10.1093/ajcp/101.6.783. PMID: 8209869.
155. State University of New York Upstate Medical Center, Syracuse, New York. Correlation conferences in radiology and pathology. Calcified thigh mass. *N Y State J Med.* 1979 Mar;79(3):354-6. PMID: 284209.
156. Standish SM, Gorlin RJ. Bone disorders affecting the jaws. In Thoma's Oral Pathology. Ed 6 St- Louis CV Mosby, 1970, p.549.
157. Soprana M, Verdi M. Su di un caso di doppia degenerazione sarcomatosa in morbo di Paget [On a case of double sarcomatous degeneration in Paget's disease]. *Fracastoro.* 1969 May-Jun;62(3):267-74. Italian. PMID: 5355942.
158. Song IS, Chan KF, Tey PH, Choi HH. Case report 159. *Skeletal Radiol.* 1981; 6:299–301.
159. Som PM, Hermann G, Sacher M, Stollman AL, Moscatello AL, Biller HF. Paget disease of the calvaria and facial bones with an osteosarcoma of the maxilla: CT and MR findings. *J Comput Assist Tomogr.* 1987 Sep-Oct;11(5):887-90. doi: 10.1097/00004728-198709000-00029. PMID: 3477577.
160. Smith J, Yuppa F, Watson RC. Primary tumors and tumor-like lesions of the clavicle. *Skeletal Radiol.* 1988; 17:235–46.
161. SINGER M. Sarcoma superimposed on Paget's disease of the femur. A case report. *S Afr Med J.* 1962 Nov 3;36:918-20. PMID: 13977611.
162. Singer FR, Mills BG. Giant cell tumor arising in Paget's disease of bone. Recurrences after 36 years. *Clin Orthop Relat Res.* 1993; 293:293–301.
163. SIMONETTA B. Condrosarcoma del mascellare associato a Paget? Considerazioni cliniche e terapeutiche [Maxillary chondrosarcoma associated with Paget's disease? Clinical and therapeutic aspects]. *Boll Mal Orecch Gola Naso.* 1956 Mar-Apr;74(2):109-17. Italian. PMID: 13328997.
164. Shlapoberskiĭ V Ia, Vinogradova TP. Materialy ob ozlokachestvlenii dobrokachestvennykh patologicheskikh protsessov v kostiakh [Data on malignant

- degeneration of benign pathological processes in bones]. *Ortop Travmatol Protez*. 1969 Jun;30(6):48-54. Russian. PMID: 5368655.
165. Shinonaga M, Gondo G, Fujitsu K, Kuwabara T. Intracranial osteogenic sarcoma complicating Paget's disease of bone--case report. *Neurol Med Chir (Tokyo)*. 1985 Jan;25(1):45-9. doi: 10.2176/nmc.25.45. PMID: 2581160.
 166. Shimoda M, Matsuoka T, Shibuya N, Sato O. Giant cell tumor of the skull associated with Paget's disease of bone. Case report. *Neurol Med Chir (Tokyo)*. 1988; 28:1119-22.
 167. Shetty S, Shetty S, Prabhu AJ, Kapoor N, Hepzibah J, Paul TV. An unusual presentation of metastatic bone disease in a subject with Paget's disease of bone. *J Family Med Prim Care*. 2016 Apr-Jun;5(2):488-490. doi: 10.4103/2249-4863.192326. PMID: 27843872; PMCID: PMC5084592.
 168. Panzoni E, Marchesi A, Maffei P. Giant cell tumor of the upper jaw in Paget's disease: presentation of a case. *Riv Ital Stomatol*. 1984; 53:753-9.
 169. Papadogeorgakis NG, Lygidakis NN, Semergidis T. Osteosarcoma of the maxilla in a case of Paget's disease of bone. *Br J Oral Maxillofac Surg*. 1997 Feb;35(1):71-2. doi: 10.1016/s0266-4356(97)90030-9. PMID: 9043011.
 170. Pathak HJ, Nardi PM, Thornhill B. Multiple giant cell tumors complicating Paget's disease. *AJR Am J Roentgenol*. 1999; 172:1696-7.
 171. Pazzaglia UE, Barbieri D, Ceciliani L. An epiphyseal giant cell tumor associated with early Paget's disease. A case report. *Clin Orthop Relat Res*. 1988;234:217-20.
 172. Pearlman AW, Friedman M. Radiation therapy of benign giant cell tumor arising in Paget's disease of bone. Iso-effect recovery study. *Am J Roentgenol Radium Ther. Nucl Med* 1968; 102:645-51.
 173. Pecorella I, Ciardi A, Amadeo G, Baiocchi A, Marasco A, Di Tondo U. Orbital osteoclastoma of apparent extraskeletal origin in a pagetic patient: a case report. *Hum Pathol*. 2000; 31:1527-31.
 174. Penfold CN, McCullagh P, Eveson JW, Ramsay A. Giant cell lesions complicating fibro-osseous conditions of the jaws. *Br J Oral Maxillofac Surg*. 1993;22:158-62.
 175. Pfliegerer AG, Molyneux AJ, Tee MK. Metastatic spread of osteosarcoma to the temporal bone in a patient with Paget's disease: a case report. *J Otolaryngol*. 1992 Apr;21(2):112-4. PMID: 1583704.
 176. Phelip X, Gras JP, Mouries D, Pasquier B, Pasquier D, Cabanel G. Radiculomedullary compressions by osteosarcoma and by giant cell tumor of the spine occurring in Paget's disease. *Rev Rhum Mal Osteoartic*. 1975; 42:573-81.
 177. Picchetta F, Muratore G. DEGENERAZIONE FIBRO-SARCOMATOSA DI MORBO DI PAGET A LOCALIZZAZIONE MONOSTOTICA. *Acta Orthopeda Italica*, 1964, 10, 15
 178. PIQUE JA, TAMINI RA, SEREBRINSKY F. Transformación sarcomatosa en una osteítis deformante de Paget [Sarcomatous transformation into a deforming Paget's osteitis]. *Bol Tr Soc Argent Cir*. 1946;7(4):138-49. Spanish. PMID: 20987972.
 179. PIRODDA E. [Contribution to the knowledge of Paget's disease with sarcoma: a case of fronto-ethmoidal localization]. *Rass Med Sarda*. 1959 Sep-Oct;61:487-500. Italian. PMID: 14433217.
 180. Potter HG, Schneider R, Ghelman B, Healey JH, Lane JM. Multiple giant cell tumors and Paget disease of bone: radiographic and clinical correlations. *Radiology*. 1991; 180:261-4.
 181. Pourabdollah M, Chang H. Coexistence of multiple myeloma and Paget disease of bone. *Blood*. 2017 Aug 31;130(9):1173. doi: 10.1182/blood-2017-05-784199. PMID: 28860326.
 182. Pujol A, Cardellach F, Ferrer O, del Olmo A, Ingelmo M, Balcells Gorina A. Enfermedad de Paget ósea degenerada en un histiocitoma fibroso maligno [Paget's disease of bone degenerating into a malignant fibrou

183. Qureshi A, Zahid KF, Ibrahim SI, Burney I. Osteosarcoma arising on a background of Paget's disease report of an unusual case. *BMJ Case Rep.* 2013 Jan 29;2013:bcr2012007770. doi: 10.1136/bcr-2012-007770. PMID: 23365160; PMCID: PMC3603794.
184. RABINOVICH Iula. Osteogennye sarkomy, razvivshiesia na pochove bolezni Pedzheta [Development of osteogenic sarcoma as a result of Paget's disease]. *Khirurgiia (Mosk).* 1957 Jul;33(7):91-7. Russian. PMID: 134923
185. Image interpretation session: 1997. Giant cell tumor associated with Paget disease. *Radiographics.* 1998;18(1):205-207. doi:10.1148/radiographics.18.1.9460120
186. Ramirez A, Liu B, Rop B, Edison M, Valente M, Burt J. Renal Cell Carcinoma Metastasized to Pagetic Bone. *Cureus.* 2016 Aug 15;8(8):e737. doi: 10.7759/cureus.737. PMID: 27660736; PMCID: PMC5025293.
187. Ravault MP, Sourdille P, Franck JP. Exophthalmie unilatérale par dégénérescence sarcomateuse d'une maladie osseuse de Paget [Unilateral exophthalmia caused by the sarcomatous degeneration of Paget's bone disease]. *Bull Soc Ophthalmol Fr.* 1970 Apr;70(4):509-11. French. PMID: 5474585.
188. Rázmán H, Tóth K. Paget-kór sarcómás átalakulása [Sarcomatous degeneration of Paget's disease]. *Orv Hetil.* 1981 Apr 12;122(15):895-7. Hungarian. PMID: 6942380.
189. Reich NE, Seidelmann FE. Radiology clinic. *J Am Osteopath Assoc.* 1975 Oct;75(2):216-8. PMID: 1058922.
190. Reinstein L, Govindan S, Reahl GE Jr, Fazekas VA. Electromyographic abnormalities in osteosarcoma arising in Paget disease of the vertebral column. *Arch Phys Med Rehabil.* 1979 Sep;60(9):411-5. PMID: 291386.
191. Rendina D, Mossetti G, Soscia E, et al. Giant cell tumor and Paget's disease of bone in one family: geographic clustering. *Clin Orthop.* 2004; 421:218–24.
192. Rendina D, Gennari L, De Filippo G, et al. Evidence for increased clinical severity of familial and sporadic Paget's disease of bone in Campania, southern Italy. *J Bone Miner Res.* 2006; 21:1828–35.
193. Robbie MJ, Pratsis KK, Lockie DJ. Intraosseous lipomata in Paget's disease: an unusual CT appearance. *Australas Radiol.* 1991 Aug;35(3):268-70. doi: 10.1111/j.1440-1673.1991.tb03023.x. PMID: 1763992.
194. Roberts JA. Paget's disease and metastatic carcinoma. A case report. *J Bone Joint Surg Br.* 1986 Jan;68(1):22-3. doi: 10.1302/0301-620X.68B1.3941136. PMID: 3941136.
195. Roblot P, Alcalay M, Payen J, Clarac JP, Fontanel JP, Bontoux D. Metastases of a lingual epidermoid carcinoma in a femur affected by Paget disease. Report of a case. *J Bone Joint Surg Am.* 1987 Dec;69(9):1440-1. PMID: 3440803.
196. Roussel J, Schoumacher P, Pernoot M, Haefeli J. Ostéo-sarcome sur maladie de Paget [Osteo-sarcoma on Paget's disease]. *J Radiol Electrol Arch Electr Medecale.* 1959 Mar-Apr;40(3-4):193-5. French. PMID: 13642391.
197. Roy-Camille R M, Laugier A, Guillaumon JL, Lelièvre JF. Histoire d'une paraplégie néoplasique [History of a patient with paraplegia due to neoplasms]. *Rev Chir Orthop Reparatrice Appar Mot.* 1974 Jul-Aug;60(5):415-24. French. PMID: 4282158.
198. RUBENS-DUVAL A, VILLIAUMEY J, MILHAUD A. [Sarcomatous degeneration of the vertebra in Paget's disease]. *Bull Mem Soc Med Hop Paris.* 1959 Jun 19-26;75:686-93. French. PMID: 14439850.
199. Ruggieri P, Biagini R. Caso quiz. Istiocitoma fibroso maligno in m. di Paget [Quiz case. Malignant fibrous histiocytoma in Paget's disease]. *Chir Organi Mov.* 1984 Jan-Mar;69(1):97-100. Italian. PMID: 6092008.
200. Russell DS. Malignant osteoclastoma and the association of malignant osteoclastoma with Paget's osteitis deformans. *J Bone Joint Surg Br.* 1949; 31B(2):281–90.

201. Saifuddin A, Hassan A. Paget's disease of the spine: unusual features and complications. *Clin Radiol*. 2003 Feb;58(2):102-11. doi: 10.1053/crad.2002.1152. PMID: 12623038.
202. SALMON, TRIFAUD, LEGRE. Sarcome fibro-blastique de l'humérus sur os pagétoïde; désarticulation inter-scapulo-thoracique [Fibroblastic sarcoma of the humerus developing on bone affected with Paget-like disease; interscapulo-thoracic disarticulation]. *Mars Chir*. 1957 May-Jun;9(3):443-4. French. PMID: 13515679. 81 Jun 27;10(28):2353-4, 2359-60. French. PMID: 6455648.
203. Salvati M, Ciappetta P, Capoccia G, Capone R, Raco A. Osteosarcoma of the skull. Report of a post-Paget and post-radiation case in an elderly woman. *Neurosurg Rev*. 1994;17(1):73-6. doi: 10.1007/BF00309991. PMID: 8078612.
204. Sanerkin NG. Malignancy, aggressiveness, and recurrence in giant cell tumor of bone. *Cancer*. 1980; 46:1641-9.
205. Schajowicz F, Santini Araujo E, Berenstein M. Sarcoma complicating Paget's disease of bone. A clinicopathological study of 62 cases. *J Bone Joint Surg Br*. 1983 May;65(3):299-307. doi: 10.1302/0301-620X.65B3.6573330. PMID: 6573330.
206. Schajowicz F, Slullitel I. Giant-cell tumor associated with Paget's disease of bone. A case report. *J Bone Joint Surg Am*. 1966; 48:1340-9.
207. Schwinn CP. Differential diagnosis of giant cell lesions of bone. In Ackerman LV, Spjut HJ, Abell MR Eds *Bone and Joints AP monograph n°17*. Baltimore. Williams and Wilkins; 1976.p.236-99
208. LiVolsi VA. Osteogenic sarcoma of the maxilla. *Arch Otolaryngol*. 1977 Aug;103(8):485-8. doi: 10.1001/archotol.1977.00780250079009. PMID: 267450.
209. López C, Thomas DV, Davies AM. Neoplastic transformation and tumour-like lesions in Paget's disease of bone: a pictorial review. *Eur Radiol*. 2003 Dec;13 Suppl 4:L151-63. doi: 10.1007/s00330-003-1927-3. PMID: 15018182.
210. LOUYOT P, GAUCHER A. [Post-traumatic Paget's disease followed for 33 years. Generalizations. Sarcomatous degeneration]. *Rev Med Nancy*. 1961 Jun;86:582-9. French. PMID: 13763743.
211. MACGREGOR AJ. Multilocular cyst of the mandible in a patient with Paget's disease. *Proc R Soc Med*. 1961 Jun;54(6):510-1. PMID: 13764791; PMCID: PMC1870434.
212. Magitsky S, Lipton JF, Reidy J, Vigorita VJ, Bryk E. Ultrastructural features of giant cell tumors in Paget's disease. *Clin Orthop Relat Res*. 2002; 402:213-9.
213. Maldonado A, Abdenour G, Hodes PP. The masquerading effect of Paget's disease. *Rev Interam Radiol*. 1976 Oct;1(2):31-4. PMID: 1027068.
214. Mancebo-Aragoneses L, Lacambra-Calvet C, Jorge-Blanco A, Coarasa-Cerdan A, Guadaño-Salvadores V. Paget's disease of the skull with osteosarcoma and neurological symptoms associated. *Eur Radiol*. 1998;8(7):1145-7. doi: 10.1007/s003300050524. PMID: 9724428.
215. Mañós-Pujol M, Cánovas Robles E, Lorenzo JC, Mañós M. Sinus injuries caused by giant cells: giant cell granuloma and giant cell tumor coexisting with Paget's disease of the cranium. *An Otorrinolaringol Ibero Am*. 1984; 11:111-26.
216. Marsal S, Arnal C, Garcia F, Azorin L, Lience E. Pigmented villonodular synovitis of the knee in a patient with Paget's disease of the adjacent femoral bone. *Br J Rheumatol*. 1993; 32:166-8.
217. Marshall LE. Comment following case 10. Seminar on diseases of the maxillofacial region including salivary glands. In: Foote FW, Horn RC editors. *Proceedings of the 26th Annual Seminar of the American Society of Clinical Pathologist*; Chicago; 1961. p. 31
218. Martínez-Tello FJ, Navas-Palacios JJ. The ultrastructure of conventional, parosteal, and periosteal osteosarcomas. *Cancer*. 1982 Sep 1;50(5):949-61. doi:

- 10.1002/1097-0142(19820901)50:5<949::aid-cnrcr2820500525>3.0.co;2-h. PMID: 6953992.
219. Matiotti SB, Tramunt CS, Duarte RD, Duarte RD, Duarte WL, Soder JB. Sarcomatous degeneration of Paget's disease in the calcaneus: a case report. *Radiol Bras.* 2009;42(1):63–65.
 220. Matsukuma S, Kawabata M, Takemoto T, Wada R, Kuwabara N. Paget sarcoma of the cervical vertebrae: an autopsy case report and review of the literature. *Pathol Int.* 1995 Nov;45(11):885-9. doi: 10.1111/j.1440-1827.1995.tb03411.x. PMID: 8581154.
 221. McKenna RJ, Schwinn CP, Soong KY, Higinbotham NL. Osteogenic sarcoma arising in Paget's disease. *Cancer.* 1964, 17:42–66.
 222. Megas PD, Panagopoulos AM, Tsamandas AC, Lambiris EE. Femoral chondrosarcoma complicating Paget's disease of bone. *Orthopedics.* 2004 Jan;27(1):63-4. doi: 10.3928/0147-7447-20040101-21. PMID: 14763533.
 223. Mehta RC, Wilson MA, Perlman SB. Osteosarcoma arising in Paget's disease of the calvarium. *J Nucl Med.* 1988 Mar;29(3):414-6. PMID: 3162256.
 224. Merino S, Arrazola J, Saiz A, Blanco JA, Ortega L. Post-Paget telangiectatic osteosarcoma of the skull. *Skeletal Radiol.* 1999 Aug;28(8):470-2. doi: 10.1007/s002560050549. PMID: 10486018.
 225. Michou L, Morissette J, Gagnon ER, et al. Novel SQSTM1 mutations in patients with Paget's disease of bone in an unrelated multiethnic American population. *Bone.* 2011; 48:456–60.
 226. Miller AS, Cuttino CL, Elzay RP, Levy WM, Harwick RD. Giant cell tumor of the jaws associated with Paget disease of bone. Report of two cases and review of the literature. *Arch Otolaryngol.* 1974;100:233–6.
 227. Mirra JM, Finerman G, Lindholm S. Diffuse pigmented villonodular synovitis in association with Paget's disease of bone: report of a case. *Clin Orthop Relat Res.* 1980; 149:305–9.
 228. Mirra JM, Bauer FC, Grant TT. Giant cell tumor with viral-like intranuclear inclusions associated with Paget's disease. *Clin Orthop Relat Res.* 1981; 158:243–51.
 229. Mischis-Troussard C, Maillefert JF, Baulot E, Ramon JF, Tavernier C. Osteosarcoma of the sacrum complicating Paget's disease of bone. *Rev Rhum Engl Ed.* 1998 May;65(5):361-2. PMID: 9636960.
 230. Mohamed M. Two diagnoses from bone marrow biopsy: multiple myeloma and Paget's disease of bone. *BMJ Case Rep.* 2016 Feb 24;2016:bcr2015213809. doi: 10.1136/bcr-2015-213809. PMID: 26912764; PMCID: PMC4769461.
 231. Molle D, Bard H, Kuntz D, Voisin C, Farcet JP, Delepine D, Ryckewaert A. Ostéolyse révélatrice d'un lymphome développé sur un os pagétique [Osteolysis disclosing a lymphoma developed on a pagetic bone]. *Rev Rhum Mal Osteoartic.* 1983 Mar;50(3):217-21. French. PMID: 6867594.
 232. Mooney WW, Bridger GP, Baldwin M, Donellan M. Recurrent giant cell tumour of the maxilla associated with both Paget's disease and primary hyperparathyroidism. *ANZ J Surg.* 2003; 73:863–4.
 233. Moore TE, King AR, Kathol MH, el-Khoury GY, Palmer R, Downey PR. Sarcoma in Paget disease of bone: clinical, radiologic, and pathologic features in 22 cases. *AJR Am J Roentgenol.* 1991 Jun;156(6):1199-203. doi: 10.2214/ajr.156.6.2028867. PMID: 2028867.
 234. Mooy CM, Naus NC, de Klein A, van den Bosch WA, Paridaens DA. Orbital chondrosarcoma developing in a patient with Paget disease. *Am J Ophthalmol.* 1999 May;127(5):619-21. doi: 10.1016/s0002-9394(98)00405-x. PMID: 10334366.
 235. Morlock G, Cadène C, Feru M, Durand J. Ostéosarcome du fémur révélateur d'une maladie de Paget unifocale débutante. Evolution favorable avec un recul de 7 ans [Femoral osteosarcoma revealing onset of unifocal Paget's disease. Favourable

- course with 7-year follow-up]. *Rev Rhum Mal Osteoartic*. 1991 Nov 30;58(11):813-7. French. PMID: 1780659.
236. Morris CS. Paget's disease with headache and disorientation. *Invest Radiol*. 1990;25:1279–84.
 237. Nager GT. Paget's disease of the temporal bone. *Ann Otol Rhinol Laryngol*. 1975 Jul-Aug;84(4 Pt 3 Suppl 22):1-32. doi: 10.1177/0003489475084S2201. PMID: 1080381.
 238. Neuner O. Ein Sarkom de Oberkiefers auf dem Boden einer Ostitis deformans (Paget). *Oest Z Stomatol*. 1956; 53:655–65.
 239. Nguyen TP, Burk DL Jr. Musculoskeletal case of the day. Sarcomatous degeneration of Paget disease. *AJR Am J Roentgenol*. 1995 Jul;165(1):202-3. doi: 10.2214/ajr.165.1.7785597. PMID: 7785597.
 240. Nicholas JJ, Srodes CH, Herbert D, Hoy RJ, Peel RL, Goodman MA. Metastatic cancer in Paget's disease of bone. A case report. *Orthopedics*. 1987 May;10(5):725-9. doi: 10.3928/0147-7447-19870501-13. PMID: 3588418.
 241. Novo Veleiro I, Perianes Díaz ME, Alvela Suárez ML, Alonso Claudio G, Moralejo Alonso L, Jiménez López A. Dolor en la región isquiopubiana en un paciente con enfermedad de Paget [Ischiopubic pain in a patient with Paget's disease]. *Reumatol Clin*. 2011 Nov-Dec;7(6):419-20. Spanish. doi: 10.1016/j.reuma.2011.01.003. Epub 2011 Apr 19. PMID: 22078705.
 242. Nusbacher N, Sclafani SJ, Birla SR. Case report 155. Polyostotic Paget disease complicated by benign giant cell tumor of left clavicle. *Skeletal Radiol*. 1981; 6:233–5.
 243. Nuzzo V, Ferrara T, Zuccoli A, et al. Infiltrating giant cell tumor in a case of Paget's disease of bone. *Arch Osteoporos*. 2009;4:91–4.
 244. Padilla F, Ellis LD, Westerman MP, Jensen WN. Needle biopsy of bone and marrow in metabolic and infiltrative disease of bone. *Clin Orthop Relat Res*. 1967 May-Jun;52:53-61. doi: 10.1097/00003086-196700520-00006. PMID: 6048919.

Supplementary table 3

Quality assessment of the selected case series with references

	JBI Critical Appraisal Checklist for Case Series									
Ref.	1	2	3	4	5	6	7	8	9	10
1	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
2	Y	Y	Y	Y	Y	N	N	N	N	Y
3	Y	Y	Y	Y	Y	N	N	N	Y	Y
4	Y	Y	Y	Y	Y	Y	N	N	Y	Y
5	Y	Y	Y	Y	Y	N	N	N	N	Y
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Y	Y	Y	Y	Y	N	N	N	N	Y
8	Y	Y	Y	Y	Y	N	N	N	N	Y
9	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
11	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12	Y	Y	Y	Y	Y	N	N	N	Y	Y
13	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
14	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
15	N	Y	Y	N	N	N	N	N	N	Y
16	N	N	Y	N	N	N	N	N	N	Y
17	Y	Y	Y	N	Y	N	N	N	N	Y
18	N	Y	Y	N	N	N	N	N	N	N.A.
19	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
20	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
21	N	Y	Y	N	N	Y	Y	Y	Y	Y
22	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
23	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
24	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
25	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
26	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
27	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
28	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
29	N.A.	Y	Y	N.A.	Y	Y	Y	Y	Y	Y
30	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
31	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
32	N.A.	Y	Y	U	U	Y	Y	Y	Y	Y
33	N.A.	Y	Y	N.A.	Y	N	Y	Y	N	Y
34	N.A.	Y	Y	N.A.	N.A.	Y	Y	Y	Y	N.A.
35	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
36	N	Y	Y	Y	Y	Y	N	Y	N	Y
37	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

38	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
39	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
40	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
41	Y	N	U	Y	Y	N	N	Y	N	Y
42	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
43	N.A.	Y	Y	N.A	N.A	Y	Y	Y	Y	N.A.
44	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
45	N.A.	Y	Y	N.A.	N.A.	N	N	Y	N	N.A.
46	N.A.	Y	Y	N.A.	N.A.	N	N	Y	N	N.A.
47	N	Y	Y	Y	Y	N	N	N	N	Y
48	N.A.	N.A.	N.A.	N.A.	N.A.	N	Y	Y	Y	N.A.
49	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
50	Y	Y	Y	Y	Y	N	N	Y	N	Y
51	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
52	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
53	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
54	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
55	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
56	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
57	N.A.	N.A.	N.A.	N.A.	N.A.	N	N	Y	N	N.A.
58	Y	Y	Y	N.A.	N.A.	N	Y	Y	Y	N.A.
59	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
60	N.A.	N.A.	N.A.	N.A.	N.A.	N	N	N	N	N.A.
61	N	N	N	N	N	N	Y	Y	Y	N.A.
62	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
63	N.A.	N.A.	N.A.	N.A.	N.A.	N	Y	N	Y	N.A.
64	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
65	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
66	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
67	Y	Y	Y	Y	Y	N	N	Y	N	Y
68	N.A.	N.A.	N.A.	N.A.	N.A.	N	Y	Y	Y	N.A.
69	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
70	N	N	N	N	N	N	Y	N	Y	N.A.
71	N.A.	N.A.	N.A.	N.A.	N.A.	N	Y	N	Y	N.A.
72	N.A.	N.A.	N.A.	N.A.	N.A.	N	Y	N	Y	N.A.
73	Y	Y	Y	Y	Y	N	N	Y	N	N.A.
74	N	Y	Y	N	N	N	N	Y	N	N.A.
75	Y	Y	Y	Y	Y	N	Y	N	Y	Y
76	Y	Y	Y	Y	Y	N	Y	N	Y	Y
77	Y	Y	Y	N	Y	N	Y	Y	Y	N.A.
78	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
79	Y	Y	Y	N	Y	Y	Y	Y	Y	N.A.
80	Y	N	Y	N	N	N	Y	Y	Y	N.A.
81	N.A.	N.A.	N.A.	N.A.	N.A.	N	Y	Y	Y	N.A.
82	N.A.	Y	Y	N	Y	N	Y	Y	Y	N.A.

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow-up results of cases clearly reported?
9. Was there clear reporting of the presenting sites'/clinics' demographic information?
10. Was statistical analysis appropriate?

Yes: Y. No: N. Unclear: U. Not Applicable: N.A.

Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Lisy K, Qureshi R, Mattis P, Mu P. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). *JBIM Manual for Evidence Synthesis*. JBI, 2020. Available from <https://synthesismanual.jbi.global>. <https://doi.org/10.46658/JBIMES-20-08>

References

- 1) Barwick KW, Huvos AG, Smith J. Primary osteogenic sarcoma of the vertebral column: a clinicopathologic correlation of ten patients. *Cancer*. 1980 Aug 1;46(3):595-604. doi: 10.1002/1097-0142(19800801)46:3<595::aid-cnrcr2820460328>3.0.co;2-8. PMID: 6930985.
- 2) Boutin RD, Spitz DJ, Newman JS, Lenchik L, Steinbach LS. Complications in Paget disease at MR imaging. *Radiology*. 1998 Dec;209(3):641-51. doi: 10.1148/radiology.209.3.9844654. PMID: 9844654.
- 3) Brackenridge CJ. A statistical study of sarcoma complicating Paget's disease of bone in three countries. *Br J Cancer*. 1979 Aug;40(2):194-200. doi: 10.1038/bjc.1979.166. PMID: 383126; PMCID: PMC2010013.
- 4) Brooks S, Starkie CM, Clarke NM. Osteosarcoma after the fourth decade. A clinico-pathological review. *Arch Orthop Trauma Surg* (1978). 1985;104(2):100-105. doi:10.1007/BF00454247
- 5) Buirski G, Ratliff AH, Watt I. Cartilage-cell-containing tumours of the pelvis: a radiological review of 40 patients. *Br J Radiol*. 1986;59(699):197-204. doi:10.1259/0007-1285-59-699-197
- 6) Buraczewski J, Dabska M, Guzecki A. Przemiana złośliwa w chorobie Paget'a kości (omówienie 5 przypadków, w tym jeden u 20-letniego mężczyzny [Malignant transformation in Paget's disease of bone (report of 5 cases including that of a 20-year-old man)]. *Nowotwory*. 1973 Jul-Sep;23(3):297-308. Polish. PMID: 4518942.
- 7) Carcassonne Y, Bouvenot G, Gastaut JA, Sebahoun G. Myélome associé à une maladie de Paget. A propos de trois observations [The association of a myeloma and Paget's disease (author's transl)]. *Ann Med Interne (Paris)*. 1979;130(3):177-184.
- 8) Carles D, Rivel J, Devars F, et al. Giant cell tumors developing in Paget's disease. Presentation of 2 cases with an ultrastructural study. *Ann Pathol*. 1989; 9:47-53.
- 9) Cerdà D, Guañabens N, Peris P, Combalia A, Álvarez L, Pomés J, Tomás X, Monegal A, Ros I, Muñoz-Gómez J. Osteosarcoma in Paget's disease. Report of six cases. *Rev Esp Reumatol* 2002;29(7):356-8

- 10) Choquette D, Haraoui B, Altman RD, Pelletier JP. Simultaneous multifocal sarcomatous degeneration in Paget's disease of bone. A hypothesis. *Clin Orthop Relat Res*. 1983;(179):308-311. doi:10.1097/00003086-198310000-00046
- 11) Cossetto D, Nade S, Blackwell J. Malignant fibrous histiocytoma in Paget's disease of bone. A report of seven cases. *Aust N Z J Surg*. 1992 Jan;62(1):52-5. doi: 10.1111/j.1445-2197.1992.tb05354.x. PMID: 1310002.
- 12) Crouzet J, Beraneck L, Bellony R, Bouteiller G, Bontoux D, Camus JP, Liote' F, Prost A, Taillandier J, Wendling L. Maladie de Paget et métastase d'épithéliomas sur le même os. Onze nouvelles observations et revue de la littérature [Paget's disease and metastatic epithelioma on the same bone. 11 new cases and review of the literature]. *Rev Rhum Mal Osteoartic*. 1990 Jul-Sep;57(7-8):517-20. French. Erratum in: *Rev Rhum Mal Osteoartic* 1990 Dec;57(12):903. PMID: 2082998.
- 13) Dahlin DC, Coventry MB. Osteogenic sarcoma. A study of six hundred cases. *J Bone Joint Surg Am*. 1967 Jan;49(1):101-10. PMID: 5225072.
- 14) Deyrup AT, Montag AG, Inwards CY, Xu Z, Swee RG, Krishnan Unni K. Sarcomas arising in Paget disease of bone: a clinicopathologic analysis of 70 cases. *Arch Pathol Lab Med*. 2007 Jun;131(6):942-6. doi: 10.5858/2007-131-942-SAIPDO. PMID: 17550323.
- 15) Douis H, Saifuddin A. The imaging of cartilaginous bone tumours. II. Chondrosarcoma. *Skeletal Radiol*. 2013 May;42(5):611-26. doi: 10.1007/s00256-012-1521-3. Epub 2012 Oct 4. PMID: 23053201.
- 16) Dray MS, Miller MV. Paget's osteosarcoma and post-radiation osteosarcoma: secondary osteosarcoma at Middlemore Hospital, New Zealand. *Pathology*. 2008 Oct;40(6):604-10. doi: 10.1080/00313020802320663. PMID: 18752128
- 17) Dubost JJ, Galtier B, Ristori JM, Sauvezie B, Bussiere JL, Rampon S. Maladie de Paget et cancer prostatique. Un difficile problème diagnostique illustré par 3 observations [Paget's disease and prostatic cancer. A difficult diagnostic problem illustrated by 3 cases]. *Rev Rhum Mal Osteoartic*. 1987 Nov;54(11):771-4. French. PMID: 3423722.
- 18) Esselinckx W, Huaux JP, Devogelaer JP, Noël H, Malghem J, Maldague B, Godiscals H, Nagant de Deuxchaisnes C. Transformation sarcomateuse dans la maladie osseuse de Paget. A propos de trois observations [Sarcomatous transformation in Paget's disease of bone. Apropos of 3 case reports]. *Acta Orthop Belg*. 1985 Jan-Feb;51(1):5-17. French. PMID: 3857833.
- 19) Eyre-Brook AL, Price CH. Fibrosarcoma of bone. Review of fifty consecutive cases from the Bristol Bone Tumour Registry. *J Bone Joint Surg Br*. 1969 Feb 1;51(1):20-37. PMID: 5766357.
- 20) Fenton P, Resnick D. Metastases to bone affected by Paget's disease. A report of three cases. *Int Orthop*. 1991;15(4):397-9. doi: 10.1007/BF00186887. PMID: 1809725.
- 21) Fransen P, Mestdagh C, Dardenne G. Pagetic sarcoma of the calvarium: report of two cases. *Acta Neurol Belg*. 1998 Dec;98(4):352-5. PMID: 9922824.
- 22) Frassica FJ, Sim FH, Frassica DA, Wold LE. Survival and management considerations in postirradiation osteosarcoma and Paget's osteosarcoma. *Clin Orthop Relat Res*. 1991 Sep;(270):120-7. PMID: 1884530.
- 23) Fromm GA, Roca JF, Mautalén CA, Casco C. Osteitis deformante de Paget. Manifestaciones clínicas y humorales en 148 pacientes [Evaluation of clinical and humoral data in 148 patients with Piaget's bone disease]. *Medicina (B Aires)*. 1980 Nov-Dec;40(6 Pt 1):635-42. Spanish. PMID: 22167694.
- 24) Giunti A, Laus M. Sarcoma in Paget's disease (11 cases). *Ital J Orthop Traumatol*. 1979;5(3):311-320

- 25) Gleich LL, Eberle RC, Shaha AR, Solomon M. Paget's sarcoma of the mandible. *Head Neck*. 1995 Sep-Oct;17(5):425-30. doi: 10.1002/hed.2880170513. PMID: 8522445.
- 26) Greditzer HG 3rd, McLeod RA, Unni KK, Beabout JW. Bone sarcomas in Paget disease. *Radiology*. 1983 Feb;146(2):327-33. doi: 10.1148/radiology.146.2.6571760. PMID: 6571760.
- 27) Grimer RJ, Cannon SR, Taminiau AM, Bielack S, Kempf-Bielack B, Windhager R, Dominkus M, Saeter G, Bauer H, Meller I, Szendroi M, Folleras G, San-Julian M, van der Eijken J. Osteosarcoma over the age of forty. *Eur J Cancer*. 2003 Jan;39(2):157-63. doi: 10.1016/s0959-8049(02)00478-1. PMID: 12509946.
- 28) Grimer RJ, Carter SR, Tillman RM, Spooner D, Mangham DC, Kavukcuoglu Y. Osteosarcoma of the pelvis. *J Bone Joint Surg Br*. 1999 Sep;81(5):796-802. doi: 10.1302/0301-620x.81b5.9241. PMID: 10530839.
- 29) Gruszkiewicz J, Doron Y, Borovich B, Zaaroor M. Spinal cord compression in Paget's disease of bone with reference to sarcomatous degeneration and calcitonin treatment. *Surg Neurol*. 1987 Feb;27(2):117-25. doi: 10.1016/0090-3019(87)90282-5. PMID: 3810440.
- 30) Hadjipavlou A, Lander P, Srolovitz H, Enker IP. Malignant transformation in Paget disease of bone. *Cancer*. 1992 Dec 15;70(12):2802-8. doi: 10.1002/1097-0142(19921215)70:12<2802::aid-cnrc2820701213>3.0.co;2-n. PMID: 1451058.
- 31) Haibach H, Farrell C, Dittrich FJ. Neoplasms arising in Paget's disease of bone: a study of 82 cases. *Am J Clin Pathol*. 1985;83:594-600.
- 32) Hauw JJ, Henin D, Chomette G, Escourolle R. Bone sarcoma developed upon spinal localization of Paget's disease. Apropos of 4 cases. *Arch Anat Pathol (Paris)*. 1973; 21:241-9.
- 33) Healey JH, Buss D. Radiation and pagetic osteogenic sarcomas. *Clin Orthop Relat Res*. 1991 Sep;(270):128-34. PMID: 1884531.
- 34) Huaux JP, Esselinckx W, Noel H, Grodos J, Nagant de Deuxchaisnes C. Paget's sarcoma--with two illustrative cases. *Clin Rheumatol*. 1984 Dec;3(4):459-66. doi: 10.1007/BF02031268. PMID: 6597050.
- 35) Huebert HT. Osteosarcoma in Manitoba: review of 95 patients. *Can J Surg*. 1979 Nov;22(6):564-8, 572. PMID: 291464.
- 36) Hunter D, Turnbull HM. Hyperparathyroidism: Generalized osteitis fibrosa. With observations upon the bones, the parathyroid tumours, and normal parathyroid glands. *Brit J Surg*. 1931; 19:203-84.
- 37) Hutter RV, Foote FW Jr, Frazell EL, Francis KC. Giant-cell tumors complicating Paget's disease of bone. *Cancer*. 1963; 16:1044-56.
- 38) Huvo AG, Butler A, Bretsky SS. Osteogenic sarcoma associated with Paget's disease of bone. A clinicopathologic study of 65 patients. *Cancer*. 1983 Oct 15;52(8):1489-95. doi: 10.1002/1097-0142(19831015)52:8<1489::aid-cnrc2820520826>3.0.co;2-x. PMID: 6577936.
- 39) Huvo AG, Heilweil M, Bretsky SS. The pathology of malignant fibrous histiocytoma of bone. A study of 130 patients. *Am J Surg Pathol*. 1985 Dec;9(12):853-71. doi: 10.1097/00000478-198512000-00002. PMID: 3000204.
- 40) Jacobs TP, Michelsen J, Polay JS, D'Adamo AC, Canfield RE. Giant cell tumor in Paget's disease of bone: familial and geographic clustering. *Cancer*. 1979; 44:742-7.
- 41) Johnson RJ, Bonfiglio M, Cooper RR. Osteosarcoma. *Clin Orthop Relat Res*. 1971;78:314-22. doi: 10.1097/00003086-197107000-00027. PMID: 4106763.

- 42) Jones P. Hindquarter amputations: review of a personal series. *Aust N Z J Surg.* 1974 Feb;44(1):1-11. doi: 10.1111/j.1445-2197.1974.tb06509.x. PMID: 4604532.
- 43) Keene GS, Stavrou P, Clarnette R, Graves SE. Metastatic deposits in Paget's disease of bone. *Aust N Z J Surg.* 1999 Feb;69(2):158-60. doi: 10.1046/j.1440-1622.1999.01474.x. PMID: 10030823.
- 44) Kumar R, Kumar M, Malhotra K, Patel S. Primary Osteosarcoma in the Elderly Revisited: Current Concepts in Diagnosis and Treatment. *Curr Oncol Rep.* 2018 Feb 28;20(2):13. doi: 10.1007/s11912-018-0658-1. PMID: 29492676.
- 45) Le Breton C, Méziou M, Laredo JD, Amouroux J, Mazabraud A, Bigot JM, Tubiana JM. Sarcomes pagétiques rachidiens. A propos de huit observations [Sarcoma of the spine in Paget's disease of bone. Apropos of 8 cases]. *Rev Rhum Ed Fr.* 1993 Jan;60(1):16-22. French. PMID: 8242021.
- 46) Ledoux-Lebard G, Lote J, Guerin Ra, Guerin Mt. Les aspects radiologiques de la dégénérescence sarcomateuse de la maladie osseuse de Paget; a propos de 10 observations [Radiologic aspects of the sarcomatous degeneration of Paget's disease; 10 observations]. *J Radiol Electrol Arch Electr Medicale.* 1957 Jan-Feb;38(1-2):115-8. French. PMID: 13429552.
- 47) López C, Thomas DV, Davies AM. Neoplastic transformation and tumour-like lesions in Paget's disease of bone: a pictorial review. *Eur Radiol.* 2003 Dec;13 Suppl 4:L151-63. doi: 10.1007/s00330-003-1927-3. PMID: 15018182.
- 48) Macintosh DJ, Price CH, Jeffree GM. Malignant lymphoma (reticulosarcoma) in bone. *Clin Oncol.* 1977 Sep;3(3):287-300. PMID: 334431.
- 49) Marsden FW, Sharland M. Osteosarcoma: then and now. A fifty year review at Royal Prince Alfred Hospital. *Aust N Z J Surg.* 1992 Jan;62(1):45-51. doi: 10.1111/j.1445-2197.1992.tb05353.x. PMID: 1731737.
- 50) Martin E, Senders JT, Ter Wengel PV, Smith TR, Broekman MLD. Treatment and survival of osteosarcoma and Ewing sarcoma of the skull: a SEER database analysis. *Acta Neurochir (Wien).* 2019 Feb;161(2):317-325. doi: 10.1007/s00701-018-3754-y. Epub 2018 Dec 21. PMID: 30578430; PMCID: PMC6373276.
- 51) Mayilvahanan N, Bose JC, Paraskumar M, Rajkumar G, Sivaseelam A, Jaheer H, Natarajan S. Paget's sarcoma: limb salvage by custom mega prosthesis: four case reports. *J Orthop Surg (Hong Kong).* 2004 Dec;12(2):243-7. doi: 10.1177/230949900401200221. PMID: 15621916.
- 52) McNairn JD, Damron TA, Landas SK, Ambrose JL, Shrimpton AE. Inheritance of osteosarcoma and Paget's disease of bone: a familial loss of heterozygosity study. *J Mol Diagn.* 2001 Nov;3(4):171-7. doi: 10.1016/S1525-1578(10)60669-1. PMID: 11687601; PMCID: PMC1906967.
- 53) Miller C, Rao VM. Sarcomatous degeneration of Paget disease in the skull. *Skeletal Radiol.* 1983;10(2):102-6. doi: 10.1007/BF00360793. PMID: 6577612.
- 54) Moore TE, King AR, Kathol MH, el-Khoury GY, Palmer R, Downey PR. Sarcoma in Paget disease of bone: clinical, radiologic, and pathologic features in 22 cases. *AJR Am J Roentgenol.* 1991 Jun;156(6):1199-203. doi: 10.2214/ajr.156.6.2028867. PMID: 2028867.
- 55) Nora FE, Unni KK, Pritchard DJ, Dahlin DC. Osteosarcoma of extragnathic craniofacial bones. *Mayo Clin Proc.* 1983 Apr;58(4):268-72. PMID: 6572774.
- 56) Parry MC, Laitinen M, Albergo J, Jeys L, Carter S, Gaston CL, Sumathi V, Grimer RJ. Osteosarcoma of the pelvis. *Bone Joint J.* 2016 Apr;98-B(4):555-63. doi: 10.1302/0301-620X.98B4.36583. PMID: 27037440.

- 57) PHELAN JT, CABRERA A. OSTEOSARCOMA OF BONE. *Surg Gynecol Obstet*. 1964 Feb;118:330-6. PMID: 14119114.
- 58) Powell N. Metastatic carcinoma in association with Paget's disease of bone. *Br J Radiol*. 1983 Aug;56(668):582-5. doi: 10.1259/0007-1285-56-668-582. PMID: 6871610.
- 59) Pradhan A, Reddy KI, Grimer RJ, Abudu A, Tillman RM, Carter SR, Jeys L. Osteosarcomas in the upper distal extremities: are their oncological outcomes similar to other sites? *Eur J Surg Oncol*. 2015 Mar;41(3):407-12. doi: 10.1016/j.ejso.2014.11.038. Epub 2014 Nov 20. PMID: 25442503.
- 60) ROMIEU C, BETOULIERES P, POURQUIER H, JAFFIOL C, LAMARQUE JL. [The sarcomatous degeneration of Paget's disease. Apropos of 6 cases]. *Presse Med* (1893). 1961 Oct 25;69:1955-8. French. PMID: 14493618.
- 61) Ross, F. G. M., MIDDLEMISS, J. H. & FITTON, J. M. (1973) Bone-Certain Aspects of Neoplasia. Eds. C. H. G. Price & F. G. M. Ross. London: Butterworth. p. 41.
- 62) Ruggieri P, Calabrò T, Montalti M, Mercuri M. The role of surgery and adjuvants to survival in Pagetic osteosarcoma. *Clin Orthop Relat Res*. 2010 Nov;468(11):2962-8. doi: 10.1007/s11999-010-1473-7. PMID: 20652460; PMCID: PMC2947701.
- 63) SALAUN O, PROT, GIRARD. Trois cas de dégénérescence sarcomateuse de la maladie de Paget [Three cases of sarcomatous degeneration of Paget's disease]. *J Radiol Electrol Arch Electr Medicale*. 1956 Nov-Dec;37(11-12):993-4. French. PMID: 13406802.
- 64) Salvati M, Cervoni L, Raguso M, Raco A. Post-Paget osteosarcomas of the skull. Remarks on five cases. *Tumori*. 1993 Oct 31;79(5):363-6. doi: 10.1177/030089169307900517. PMID: 8116084.
- 65) Schajowicz F, Velan O, Santini Araujo E, Plantalech L, Fongi E, Ottolenghi E, Fromm GA. Metastases of carcinoma in the pagetic bone. A report of two cases. *Clin Orthop Relat Res*. 1988 Mar;(228):290-6. PMID: 3342581.
- 66) Seitz S, Priemel M, Zustin J, Beil FT, Semler J, Minne H, Schinke T, Amling M. Paget's disease of bone: histologic analysis of 754 patients. *J Bone Miner Res*. 2009 Jan;24(1):62-9. doi: 10.1359/jbmr.080907. PMID: 18767930.
- 67) Seret P, Basle MF, Rebel A, Renier JC, Saint-Andre JP, Bertrans G, Audran M. Sarcomatous degeneration in Paget's bone disease. *J Cancer Res Clin Oncol*. 1987;113(4):392-9. doi: 10.1007/BF00397726. PMID: 3474235.
- 68) SHERMAN RS, SOONG KY. A roentgen study of osteogenic sarcoma developing in Paget's disease. *Radiology*. 1954 Jul;63(1):48-58. doi: 10.1148/63.1.48. PMID: 13186112.
- 69) Smith J, Botet JF, Yeh SD. Bone sarcomas in Paget disease: a study of 85 patients. *Radiology*. 1984 Sep;152(3):583-90. doi: 10.1148/radiology.152.3.6235535. PMID: 6235535.
- 70) Suchett-Kaye AI. Paget's disease of bone. *Gerontol Clin (Basel)*. 1970;12(4):241-55. doi: 10.1159/000245285. PMID: 4915366.
- 71) Sun SG, Lau YS, Itonaga I, Sabokbar A, Athanasou NA. Bone stromal cells in pagetic bone and Paget's sarcoma express RANKL and support human osteoclast formation. *J Pathol*. 2006 May;209(1):114-20. doi: 10.1002/path.1953. PMID: 16482498.
- 72) Sundaram M, Khanna G, El-Khoury GY. T1-weighted MR imaging for distinguishing large osteolysis of Paget's disease from sarcomatous degeneration. *Skeletal Radiol*. 2001 Jul;30(7):378-83. doi: 10.1007/s002560100360. PMID: 11499777.

- 73) Sundaresan N, Huvos AG, Rosen G, Galicich JH. Combined-modality treatment of osteogenic sarcoma of the skull. *J Neurosurg.* 1985 Oct;63(4):562-7. doi: 10.3171/jns.1985.63.4.0562. PMID: 3861791.
- 74) Thomson AD, Turner-Warwick RT. Skeletal sarcomata and giant-cell tumour. *J Bone Joint Surg Br.* 1955; 37-B(2):266–303.
- 75) Ueda T, Healey JH, Huvos AG, Ladanyi M. Amplification of the MYC Gene in Osteosarcoma Secondary to Paget's Disease of Bone. *Sarcoma.* 1997;1(3-4):131-4. doi: 10.1080/13577149778209. PMID: 18521214; PMCID: PMC2395365.
- 76) Uribarri Echevarría, A, Buenechea Imaz, R, Argüero González, M, Gay Escoda, C. Enfermedad de Paget u osteítis deformante. A propósito de tres casos con afectación craneofacial *Archivos de Odontoestomatología*, 1997, vol. 13, num. 2, p. 84-94
- 77) Vuillemin-Bodaghi V, Parlier-Cuau C, Cywiner-Golenzner C, Quillard A, Kaplan G, Laredo JD. Multifocal osteogenic sarcoma in Paget's disease. *Skeletal Radiol.* 2000 Jun;29(6):349-53. doi: 10.1007/s002560000214. PMID: 10929418.
- 78) Wick MR, Siegal GP, Unni KK, McLeod RA, Greditzer HG 3rd. Sarcomas of bone complicating osteitis deformans (Paget's disease): fifty years' experience. *Am J Surg Pathol.* 1981 Jan;5(1):47-59. doi: 10.1097/00000478-198101000-00008. PMID: 6941703.
- 79) Wu RK, Trumble TE, Ruwe PA. Familial incidence of Paget's disease and secondary osteogenic sarcoma. A report of three cases from a single family. *Clin Orthop Relat Res.* 1991 Apr;(265):306-9. PMID: 2009672.
- 80) Yeh SD, Rosen G, Benua RS. Gallium scans in Paget's sarcoma. *Clin Nucl Med.* 1982 Dec;7(12):546-52. doi: 10.1097/00003072-198212000-00004. PMID: 6959752.
- 81) Yochum TR. Paget's sarcoma of bone. *Radiologe.* 1984 Sep;24(9):428-33. PMID: 6593768.
- 82) Zichner L. Sarkomatöse Entartung bei Ostitis deformans Paget [Sarcomatous transformation in Paget's disease (author's transl)]. *Langenbecks Arch Chir.* 1974;336(1):57-65. German. doi: 10.1007/BF01291873. PMID

Supplementary table 4

Skeletal and extra skeletal sites involved by primary and secondary bone neoplasm in PDB patients

	PBC-PDB			BM-PDB
	Sar-PDB	GCT-PDB	MM-PDB	
Femur (n; %)	352/1336 (26.3)	11/138 (7.9)	9/38 (23.7)	15/67 (22.4)
Pelvis (n; %)	301/1336 (22.5)	22/138 (15.9)	13/38 (34.2)	16/67 (23.9)
Humerus (n; %)	229/1336 (17.1)	2/138 (1.4)	0	7/67 (10.4)
Skull (n; %)	193/1336 (14.4)	58/138 (42.0)	5/38 (13.2)	9/67 (13.6)
Tibia (n; %)	114/1336 (8.5)	4/138 (2.9)	2/38 (5.3)	5/67 (7.5)
Spine (n; %)	84/1336 (6.2)	18/138 (13.0)	6/38 (15.8)	8/67 (11.9)
Scapula (n; %)	30/1336 (2.4)	7/138 (5.1)	1/38 (2.6)	2/67 (3.0)
Tarsus (n; %)	13/1336 (0.9)	0	0	0
Radius (n; %)	6/1336 (0.4)	0	0	0
Ulna (n; %)	5/1336 (0.3)	1/138 (0.1)	0	0
Hand (n; %)	3/1336 (0.2)	0	0	0
Clavicle (n; %)	2/1336 (0.1)	8/138 (5.8)	0	1/67 (1.5)
Fibula (n; %)	1/1336 (0.1)	0	0	1/67 (1.5)
Sternum (n; %)	1/1336 (0.1)	0	1/38 (2.6)	0
Rib (n; %)	1/1336 (0.1)	0	1/38 (2.6)	2/67 (3.0)
Patella (n; %)	1/1336 (0.1)	0	0	0
Extraskeletal neoplasm (n; %)	0	7/138 (5.0)	0	-

Data are expressed as absolute number (percentage). PDB: Paget's disease of bone. PBC-PDB: PDB patients with primary bone cancers. Sar: PDB patients with sarcomas. GCT: PDB patients with giant cell tumor. MM: PDB patients with miscellaneous malignancies. BM-PDB: PDB patients with bone metastasis