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Case study

Metastatic cancer in antiquity: Case study from 3rd-4th century Milan, Italy

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ABSTRACT

Objective: To evaluate lesions noted on a 3rd-4th century individual and to contribute to our understanding of cancer in antiquity.
Materials: Skeletal remains of a single individual recovered from the "Necropolis of the Cattolica", Milan, Italy.
Methods: Macroscopic analysis, along with computed tomography and conventional radiography were employed to investigate lesions. Differential diagnosis was undertaken to assist with the diagnosis.
Results: The individual was a male aged 40–65 years with extensive skeletal fragmentation. Osteoblastic lesions with thick new bone deposits and spiculae were present on the scapulae, vertebrae, and ossa coxae. Radiological analysis revealed increased radiodensity with a cloud-like matrix.
Conclusions: Based on lesion distribution, morphology, and the individual's biological profile, metastatic carcinoma is suggested to be the most plausible diagnosis.
Significance: This case contributes to the growing body of evidence for cancer in Roman Italy and highlights the role of paleo-oncological studies in reconstructing health patterns in past populations.
Limitations: The fragmented nature of the skeleton limited the extent of lesion analysis.
Further research: Expanding the dataset of ancient neoplastic cases will improve our understanding of cancer prevalence and evolution in past populations.

1. Introduction

Cancer encompasses a broad spectrum of diseases originating in almost any organ or tissue of the body, characterized by the uncontrolled growth of abnormal cells that invade adjacent tissues and, in advanced stages, metastasize to other organs (Lawrence et al., 2011). While cancer is often perceived as a modern disease associated with industrialization and contemporary lifestyles (World Health Organization, 2025), its existence has been documented since before the dawn of humankind (Capasso, 2005; Faguet, 2015; Kirkpatrick et al., 2018; Trivedi et al., 2023). Investigating the presence and impact of cancer in past populations is crucial not only for reconstructing their lived experiences but also for advancing our understanding of the disease's manifestations and evolution.

The prevalence of cancer in the past remains a subject of scholarly debate. Some researchers argue that cancer was far more prevalent in ancient populations than the current archaeological and historical record suggests, citing limitations related to skeletal preservation, screening method, and diagnostic sensitivity (Gaeta et al., 2017; Hunt et al., 2018; Marques et al., 2022, 2021a, 2018). Other researchers maintain that malignant neoplasms were exceedingly rare in antiquity, if they existed at all (David and Zimmerman, 2010). Although the prevalence of cancer has increased dramatically over the past century—likely due to environmental factors, rising pollution levels, and longer life expectancies—literary sources (Capasso, 2005; Topi et al., 2020), ancient medical texts (Hajdu, 2011), and physical remains (Hunt et al., 2018; Marques et al., 2021b) provide clear evidence that cancers were not rare conditions in past populations, and reveal no significant trend of increasing cancer prevalence in history (from 500 BCE) (Marques et al., 2022).

A review of the existing literature from the Cancer Research in Ancient Bodies (CRAB) database identified 105 paleopathologically

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documented cases of cancer worldwide from the Roman era or earlier, as reported up to 2017. Of these, 27 cases are confined to the modern-day defined European continent, and two were reported in Italy (Micciché et al., 2018; Tempestini et al., 1999). Since 2017, several other cases have been reported in Italy and in Central Europe (Fornaciari, 2020; Minozzi et al., 2018; Riccomi et al., 2019; Rossignani et al., 2005; Tulumello et al., 2020).

This paper presents a probable case of metastatic cancer from 3rd-4th century Milan, contributing to the paleo-oncological literature and underscoring its presence in European antiquity. This finding contributes to our understanding of cancer prevalence in ancient Italy, shedding light on the history and manifestations of the disease.

2. Materials

The skeletal remains analyzed in this study were unearthed during excavations conducted between 1998 and 1999 in Milan. The excavation site, now situated in a central area beneath the main campus of the Università Cattolica del Sacro Cuore, lies near the Basilica di Sant'Ambrogio and is archaeologically designated as the "Necropolis of the Cattolica." This necropolis is one of the largest in northern Italy, both in terms of its geographical extent and the number of graves dating back to the Roman period. In fact, the late 1990s excavations uncovered nearly 600 graves at this site (Lusuardi Siena et al., 2011).

The necropolis has been identified as a Late Antiquity burial ground, primarily in use from the 3rd to 5th centuries CE. However, evidence of earlier occupation from the 1st and 2nd centuries CE, as well as traces of early medieval activity, was also uncovered in certain areas of the site. The graves exhibited considerable diversity in structure and type, including simple inhumations in bare earth, burials within wooden, brick, or stone box graves, as well as single, double, and multiple burials. This evidence suggests that the necropolis served as a communal burial ground for the entire population of the city during the Imperial era and Late Antiquity, without distinction of rank or social class (Lusuardi Siena et al., 2011). To date, a total of 600 individuals from the necropolis have been examined.

The individual (US 7154) was interred in a brick box tomb (US 7153), oriented northwest-southeast, with the head positioned to the southeast. The tomb was covered with large terracotta tiles, known as *tavelloni* (US 7184). Beneath the feet of the interred individual, a marble slab decorated with a fleur-de-lys motif, was discovered. No grave goods or personal artifacts were recovered. Because of its stratigraphic position, the burial can be dated between the second half of the 3rd and 4th century.

3. Methods

State of preservation, including completeness and quality of the remains (Bello et al., 2003), was evaluated for the entire skeletal system, as per Biehler-Gomez et al. (2022). Biological sex estimation was based on morphological features of the skull and pelvic bones (Klales et al., 2012; Walker, 2008, 2005). Age-at-death was estimated by evaluating changes to the auricular surface (Buckberry and Chamberlain, 2002; Lovejoy et al., 1985), acetabulum (Rougé-Maillart et al., 2009), and pubic symphysis (Brooks and Suchey, 1990). Stature was reconstructed using regression formulae applied to measurements of the long bones (Trotter, 1970). Paleopathological analysis followed established standards in the literature (Buikstra, 2019; Ortner, 2003).

To enhance the pathological investigation, conventional radiographic imaging of the cranium, scapulae, long bones, ossa coxae, and vertebrae was obtained using a Rexstar X portable X-ray machine with Examion® software. Computed tomography (CT) imaging was also performed on the same bones using a Siemens Somatom Definition AS 64-slice CT scanner (Siemens Healthineers Erlangen, Germany). We used a standard protocol for upper extremities CT acquisition (T-D0300, SRT), with the following parameters: exposure time= 15.67 s, scanning length= 481 mm, exposed range= 456 mm, and section thickness= 1.5 mm, with CT X-Ray source parameters of 100 kVp and 20 mA. The combined use of conventional radiography and CT imaging allows for a comprehensive assessment of lesions. While radiographs provide an initial overview of lesion distribution and general characteristics, CT imaging enhances diagnostic accuracy by offering high-resolution, three-dimensional visualization of lesion density, internal structure, and cortical involvement, which may be obscured in two-dimensional radiographs.

4. Results

The individual was estimated to be a biological male approximately 40–65 years old, between 163 and 171 cm tall. Although over 75 % of the skeleton was recovered and 50–74 % of the cortical surface on the entire skeleton was sound, the skeleton was extensively fragmented, with no single bone preserved in its entirety. The most affected regions included the cranium, thorax, and spine, where the cranium, ribs, and vertebrae were fragmented into numerous small pieces (Fig. 1). Additionally, many ribs and vertebrae were missing.

The individual exhibited pathological signs of degenerative disk disease on all recovered vertebral bodies, in particular C4 to C7 and L5, caries in the right lower third molar (tooth n. 38 – ISO 3950 nomenclature), and antemortem tooth loss of the right maxillary canine (tooth n. 23) and three right molars (teeth n. 26, 27, and 28).

Abnormal new bone formation was found disseminated throughout the skeleton in six areas, in particular on both right and left scapulae, vertebral body of T11, neural arches of T11, T12, and an indeterminate vertebra, and most strikingly on both ossa coxae (Fig. 1). Although the extent of the lesions per bone is difficult to estimate because of taphonomic damage, they occupied less than 20 % of each recovered bone.

Spiculated and thick new bone deposits were observed on both scapulae widespread over the subscapular, supraspinous, and infraspinous fossae on the right side, and over the spine of the scapula on the left side, inferior and lateral to the acromion process (Fig. 2). The contour of the overgrowths was irregular and coarse. The thickness of the deposits varied between 0.2 and 2 mm. Similar thick and spiculated bone deposition were present on the anterior surfaces of both iliac fossae, as well as on the posterior iliac surfaces (Figs. 3 and 4). The lesions were additionally recorded in the vicinity of the anterior ischial spine on the right side. On the neural arches of the three vertebrae affected, the new bone deposits were much thinner and not spiculated, but just as irregular (Fig. 5). On T11, new bone deposits, densely arranged, were noted in the vertebral body, visible at post-depositional breaks of the bone (Fig. 5).

Radiological analysis revealed no additional lesions on the skeleton. The coarse and spiculated lesions on the scapulae and ossa coxae, as well as the areas of endosteal new bone on the vertebral body appeared as areas of increased radiodensity of cloudlike matrix with ill-defined, hazy margins (Ragsdale et al., 2018) (Figs. 2–5). No osteolytic lesions were observed macroscopically or radiologically; loss of bone substance was always post-depositional.

5. Discussion

A differential diagnosis was undertaken based on the macroscopic and radiological characteristics of the lesions. Each condition is assessed in relation to the individual's biological profile and the observed skeletal changes. In addition, the potential clinical impact of the lesions on the quality of life of the affected individual is considered, offering insights into the lived experience of advanced disease in antiquity.

5.1. Differential diagnosis

Several conditions may be responsible for the osteoblastic lesions observed disseminated throughout the skeleton of individual US 7154,

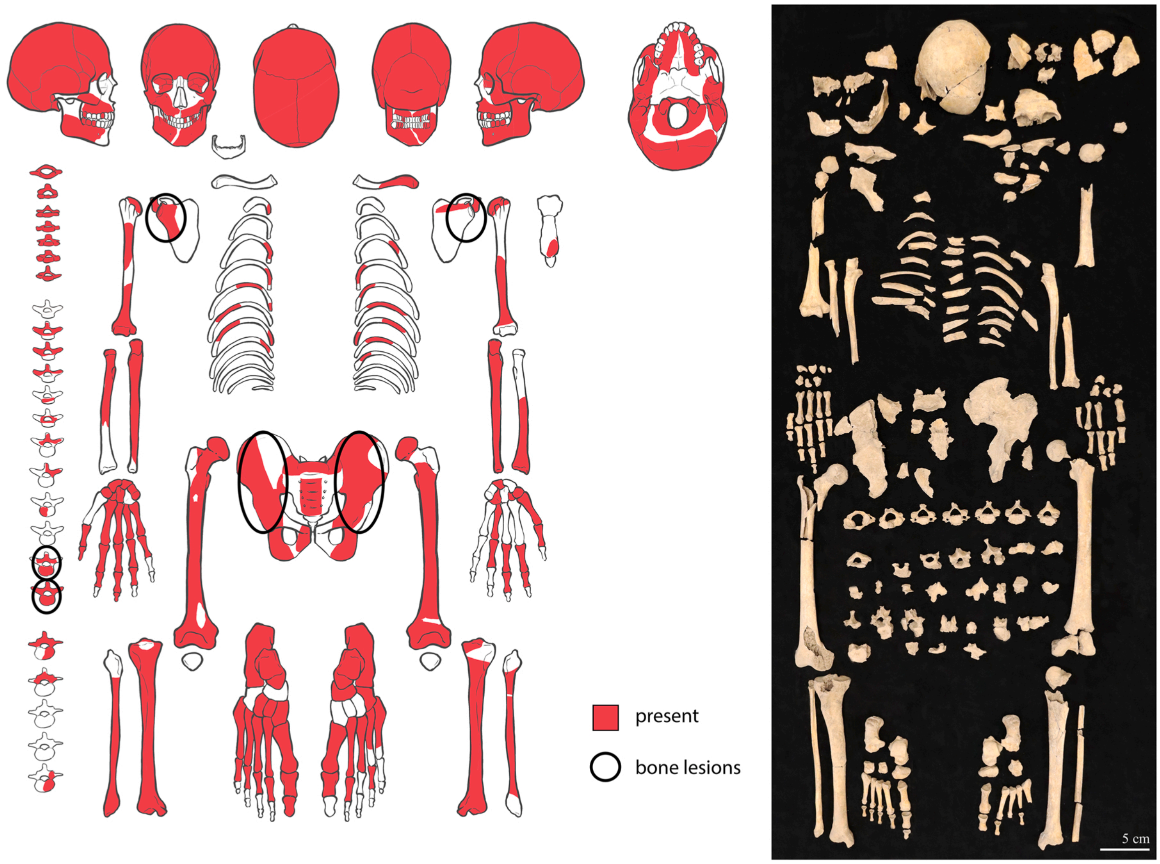

Fig. 1. Schematic (left) and photographic (right) representation of the skeletal remains of individual US 7154. The bones present during anthropological examination are colored, whereas circles indicate areas with lesions.

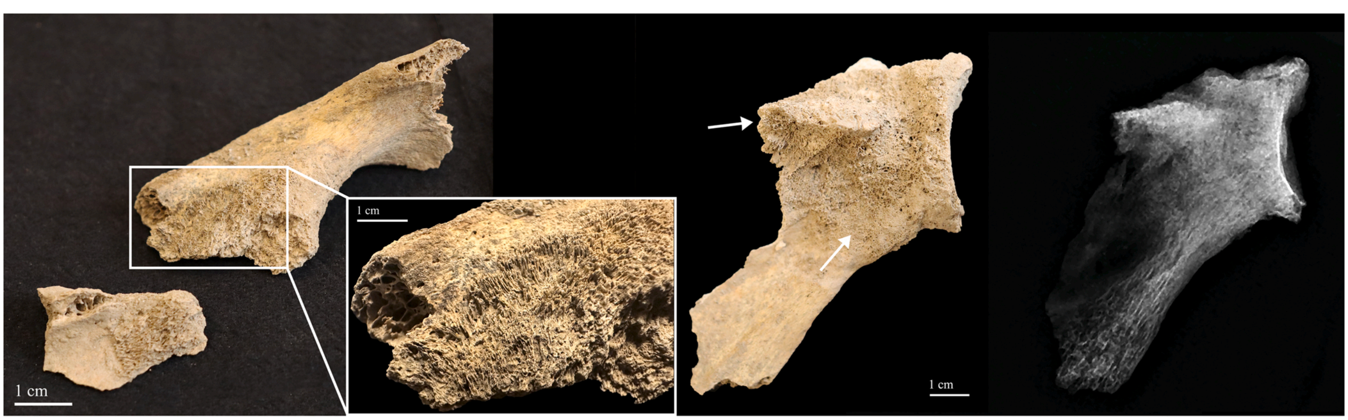

Fig. 2. Left (on the left) and right (center and x-rays on the right – posterior views) scapulae of individual US 7154 (conventional radiographs parameters: 70 kV, 2 mAs, 0.03 s). Note the thick and spiculated new bone deposits on the cortical surface (white arrows).

including osteomyelitis and other proliferative infectious diseases, Paget disease, Ewing sarcoma, osteosarcoma, fibrous dysplasia, hematopoietic malignancies, and metastatic carcinoma.

5.1.1. *Osteomyelitis*

Osteomyelitis, a bone infection predominantly affecting the medullary cavity of long bones, is marked by the formation of a sequestrum (necrotic bone) enveloped by an involucrum (reactive new bone) and frequently includes a draining cloaca. The condition may induce inflammation in the periosteum (periostitis) or in the endosteum (osteitis) (Ortner, 2003, pp. 181–205; Roberts, 2019, pp. 279–301). A diagnosis of chronic pyogenic infection is therefore inconsistent with the evidence reported in the present case due to the absence of diagnostic sequestra, involucra, and cloacae. Other proliferative infectious diseases, such as syphilis (Grauer and Roberts, 2019; Roberts, 2019; Roberts and Buikstra, 2019), can be ruled out based on discrepancies in the location and morphological aspect of the lesions.

5.1.2. *Paget disease*

Paget disease is a chronic metabolic disorder marked by abnormal bone remodeling and skeletal deformity. Its etiology is complex, and factors include genetic mutation and viral infections. The condition progresses through three stages: (1) an initial osteolytic phase, (2) a mixed osteolytic-sclerotic phase with dominant osteoblastic formation

Fig. 3. Left os coxae of individual US 7154 (posterior view) and x-ray (conventional radiographs parameters: 70 kV, 2 mAs, 0.03 s). Note the thick new bone deposits on the cortical surface (white arrows).

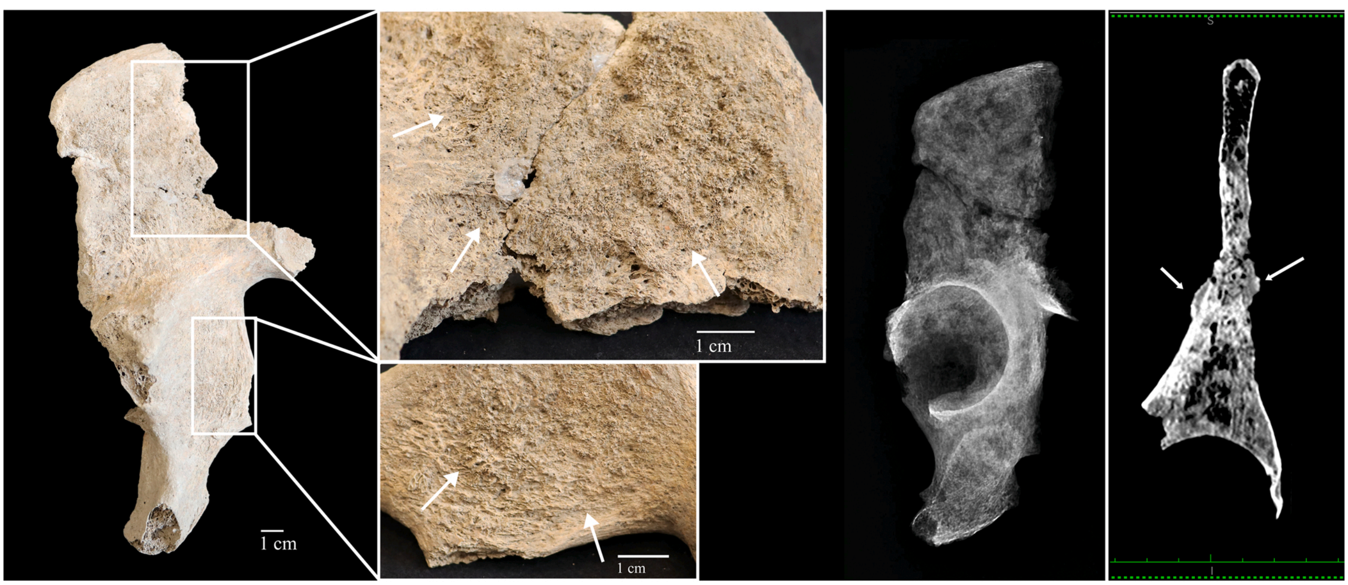

Fig. 4. Right os coxae of individual US 7154, x-ray (medio-lateral orientation – middle) and coronal CT slice (lesions indicated with arrows – right) (conventional radiographs parameters: 70 kV, 2 mAs, 0.03 s, computed tomography parameters: exposure time= 15.67 s, scanning length= 481 mm, exposed range= 456 mm, and section thickness= 1.5 mm, with CT X-Ray source parameters of 100 kVp and 20 mA). Note the thick and spiculated new bone deposits on the cortical surface (white arrows).

of disorganized woven bone, and (3) a sclerotic phase characterized by reduced osteoblastic activity (Ortner, 2003, pp. 435–440; Waldron, 2008, pp. 122–126). Bone involvement is usually asymmetric and most commonly affects the skull, lumbar spine, pelvis, and proximal femur in individuals over 40. In its advanced stages, the disease leads to bone enlargement with cortical thickening due to periosteal bone deposition. The hallmark of Paget's disease is its histological mosaic pattern (De Boer et al., 2013; Grauer and Roberts, 2019, pp. 455–459; Ortner, 2003, pp. 435–440; Waldron, 2008, pp. 122–126). Although the biological profile of the individual (male over 40 years), the distribution of the lesions (axial skeleton), and their osteoblastic nature are elements consistent with the condition, the lack of extensive and deforming changes with both osteolytic and osteoblastic components do not support this diagnosis. The absence of osteolytic lesions/radiolucency, bone enlargement, and cortical thickening and lamination, both macroscopically and in radiological imaging, is not consistent with this diagnosis, further reducing its likelihood.

5.1.3. *Ewing sarcoma and osteosarcoma*

The osteoblastic lesions observed, in particular in their spiculated form, are consistent with bone changes observed in primary bone malignancies, particularly Ewing sarcoma and osteosarcoma. However, metastatic Ewing sarcoma and osteosarcoma are exceedingly rare and axial involvement is uncommon (Biermann and Baker, 2000; Brothwell, 2008; Marques, 2019, pp. 680–684; Miller, 2008). Additionally, the age of the individual and the location and radiographic characteristics of the lesions are inconsistent with these diagnoses.

5.1.4. *Fibrous dysplasia*

Fibrous dysplasia is a rare benign fibro-osseous condition, even more

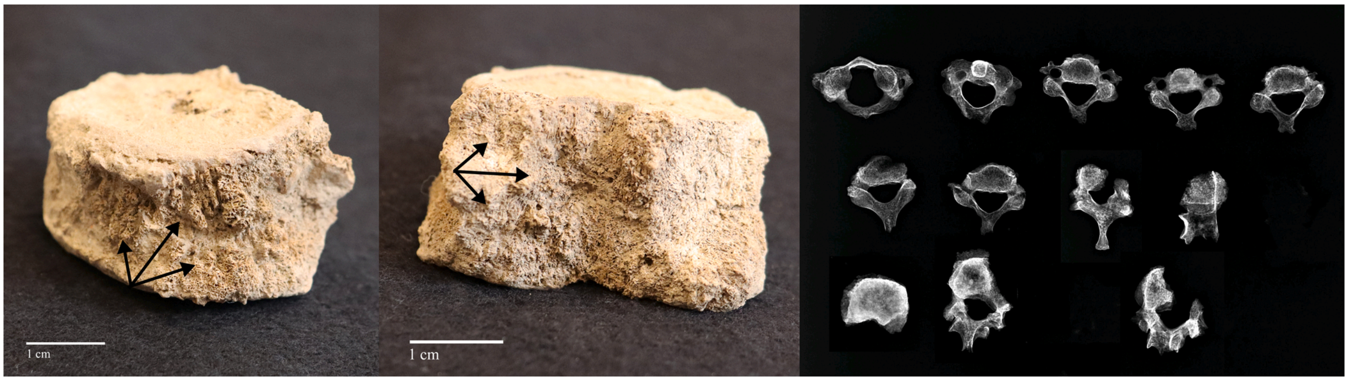

Fig. 5. Anterior (left) and posterior (fragmented bone, showing the internal structure of the vertebral body – center) views of the vertebral body of T11, and x-rays (right) of the vertebrae recovered (conventional radiographs parameters: 70 kV, 2 mAs, 0.03 s). Note the new bone deposits on the anterior vertebral body, and the endosteal new bone deposits in the vertebral body (black arrows), visible through post-depositional breaks.

uncommon when polyostotic (affecting multiple bones) (Meier et al., 2024). The condition typically affects juveniles and young individuals, manifesting as osteolytic lesions/radiolucent areas with well-defined sclerotic geographic margins, diffuse with a ground-glass appearance, or dense radiopaque lesions, leading to bone enlargement and deformities, as well as pathological fractures (Marques, 2019, pp. 658–660). None of these signs were observed in the present case, making with this diagnosis highly unlikely.

5.1.5. *Hematopoietic malignancies*

Hematopoietic malignancies, in particular leukemia and multiple myeloma, constitute the main differential diagnosis for metastatic bone disease. Leukemias are malignancies of the myeloid and lymphoid hematopoietic cells within the bone marrow. While adult and chronic forms of leukemia can impact the skeleton, their skeletal manifestations are nonspecific and often challenging to diagnose. Although periosteal reactions may occur, the predominant skeletal changes are osteolytic, characterized by generalized bone loss and diffuse, small osteolytic lesions, leading to joint compression, vertebral collapse, and pathological fractures (Klaus, 2016; Marques, 2019, p. 520; Rothschild et al., 1997). Similarly, multiple myeloma—a malignant disorder of plasma cells—-frequently affects multiple skeletal sites, particularly the axial skeleton. However, this malignancy inhibits local osteoblastic activity, resulting in exclusively osteolytic lesions and reduced bone mineral density (Biehler-Gomez et al., 2019a; Edwards et al., 2008; Kumar et al., 2017; Marques, 2019, pp. 520–524; Rothschild et al., 1998; Strouhal, 1991). The absence of osteolytic lesions, both macroscopically and radiologically, and the presence of only osteoblastic lesions in the skeleton of individual US 7154, are not consistent with these diagnoses.

5.1.6. *Bone metastases*

Bone metastases are significantly more common than primary bone tumors, and the skeleton ranks as a major metastatic target following the liver and lungs (Coleman, 2001; Gruber, 2012). The prevalence of metastatic bone disease correlates with age, predominantly affecting individuals over 40–50 years. Skeletal metastases, though variable in metastatic patterns across neoplasm types, predominantly affect bone sites with high marrow content, such as the spine, sacrum, *ossa coxae*, sternum, ribs, skull, and proximal femur and humerus. Metastatic spread beyond the knees and elbows is unusual (Lipton and Vigorita, 2016; Mundy, 1997; O'Sullivan et al., 2015; Randall, 2015). Multiplicity of lesions is a defining feature of metastatic bone disease, especially when involving hematopoietic regions of the skeleton (Marques, 2019, pp. 696–702). This pattern and epidemiological profile are consistent with the case described here.

Metastatic lesions are typically classified as osteolytic, osteoblastic, or mixed, reflecting a spectrum of activity from predominantly resorptive to predominantly bone-forming (Brothwell, 2012, 2008; Coleman, 2006, 2001; Mundy, 2002; Randall, 2015). In particular, osteoblastic metastases, characterized by the deposition of new bone deposits on trabeculae coating existing trabeculae, appear as blotchy or diffuse densities on radiographs. In advanced stages, these lesions may coalesce and exhibit a solid sclerotic pattern, occasionally showing a spiculated "sunburst" appearance in cases like prostate carcinoma (Marques, 2019, pp. 696–702). The macroscopic and radiological lesions observed in the present case are highly consistent with paleopathological (Brothwell, 2008; de la Rúa et al., 1995; Ghabili et al., 2016; Klaus, 2018; Marques, 2019, pp. 696–702; Mays et al., 1996; Merczi et al., 2014; Prates et al., 2011; Rando and Waldron, 2018; Schultz et al., 2007) and clinical descriptions of bone metastases (Coleman, 2001; Lipton and Vigorita, 2016; Randall, 2015), as well as literature from known cases (Biehler-Gomez et al., 2019b, 2019c; Castoldi et al., 2017; Marques et al., 2018; Rothschild et al., 1998, 1997; Rothschild and Rothschild, 1995). The evidence observed in individual US 7154 is therefore highly consistent with a diagnosis of metastatic cancer.

Certain cancers exhibit a pronounced affinity for bone metastasis (osteotropism), with prostate and breast cancers presenting skeletal involvement in up to 60–80 % of cases. Lung, kidney, and thyroid neoplasms also frequently spread to bone (30–65 %), while cancers such as those of the gastrointestinal tract and melanoma are less commonly associated with bone metastasis (Coleman, 2001; Lipton and Vigorita, 2016). Carcinomas display variable patterns, with prostate cancer tending toward osteoblastic metastases and cancers of the breast, lung, thyroid, and kidney producing predominantly osteolytic lesions. Mixed metastatic lesions, which reflect both osteolytic and osteoblastic activities, are often associated with cancers originating from the breast, ovary, or colon (Coleman, 2006; Marques, 2019, pp. 696–711; Waldron, 2008, pp. 184–190). However, metastatic lesions often exhibit both osteolytic and osteoblastic components, forming a continuum rather than discrete categories (Mundy, 2002; Randall, 2015). Consequently, while osteotropic patterns may provide insight into possible origins, they do not allow for definitive identification of the primary site (Marques, 2019, pp. 696–711). Given the morphological diversity of metastatic bone disease, accurate identification of a primary site based solely on skeletal changes can range from extremely challenging to impossible. While paleopathological studies have referenced clinical literature and documented skeletal collections to infer potential sources of metastasis (Marques, 2019, pp. 696–711), such identifications remain tentative at best. In this case, the male sex of the individual and the exclusively osteoblastic nature of the lesions are consistent with cancers known to produce predominantly osteoblastic metastases, such as prostate, bladder, or neuroendocrine malignancies. However, given recent oncological research evidencing that metastatic potential may be more influenced by genomic rather than strictly organ-specific factors (Nguyen et al., 2022), no conclusive primary site can be determined.

5.2. Clinical implications and paleopathological significance

Bone metastases significantly impact patient morbidity and quality of life, with skeletal-related events (SREs) being common and contributing to pain, disability, and reduced mobility. SREs include severe bone pain, pathologic fractures, neurological complications, hypercalcemia, and spinal cord compression, which together affect nearly half of patients with bone metastases (Coleman, 2006). During the 2000s, metastatic cancer patients were reported to experience an SRE approximately every six months (Coleman, 2006). Clinical data show that about 70 % of patients with bone metastases experience bone pain and impaired mobility (Vassiliou et al., 2013). In the present case, vertebral collapse and bone fractures were not observed, but the advanced stage of progression of the malignancy suggest that the condition was long-standing and that the individual may have experienced severe bone pain. This highlights the burden metastatic bone disease placed on the quality of life and physical health of the individual presented in this paper.

The present case contributes to the paleo-oncological literature by documenting a case of metastatic carcinoma from Roman times, by integrating macroscopic analyses with radiological imaging (conventional radiographs and computed tomography). This finding enriches our understanding of the prevalence and nature of cancer in Late Antiquity Northern Italy, offering insights into the health of the ancient Milanese. Additionally, the discovery of another neoplastic condition, multiple myeloma, within the same necropolis—confirmed through proteomic analysis (Cattaneo et al., 2001)—further highlights the relevance of this study in reconstructing the health profiles of past communities.

6. Conclusion

This finding contributes to the paleo-oncological literature and represents a rare and significant example of cancer evidence from such an ancient period in human history. It challenges the perception of cancer as a predominantly modern disease, demonstrating its presence and diffusion in ancient times. Moreover, documenting such cases is essential for providing a more accurate and nuanced reconstruction of the past, enabling a deeper understanding of the interplay between health, disease, and historical context.

CRediT authorship contribution statement

Lucie Biehler-Gomez: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Carlotta Sala:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Mirko Mattia:** Data curation. **Marco Sannazaro:** Supervision, Project administration. **Cristina Cattaneo:** Supervision, Project administration.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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