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REVIEW ARTICLE

Treatments and outcomes of Paget's sarcoma: Literature review and cohort study

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ABSTRACT

Background Sarcomatous transformation of Paget's disease of bone is a very rare, highly fatal complication. Isolated cohort studies have characterized these findings many times. Still, little has been established concerning the effects of patient and tumor characteristics and treatment type on the oncologic prognosis when defined as local recurrence-free, metastatic disease-free, disease-specific, and overall survival.

Questions/Purposes (1) What are the oncologic and clinical characteristics of patients who develop and are diagnosed with Paget's sarcoma? (2) What are the outcomes when examining variables such as sarcoma type, presentation at diagnosis and treatment in Paget's sarcoma patients? (3) How have treatment and oncologic prognosis changed in recent decades?

Methods A literature review of (n=1,001) Paget's sarcoma cases, retrieved from previous studies and public databases, and a retrospective analysis on a cohort of all adult patients with Paget's disease of bone (n=1,872) admitted to two large academic centers between 1979 and 2019 was performed. Medical records and the Social Security Index assessed patient survival. Surgical reports were reviewed to determine margin characteristics and intervention type. Incidences of metastasis and recurrence were based on patient notes and biopsy report review. This two-part study describes the effects of patient and tumor characteristics and treatment type on oncologic prognosis.

Results Pooled data from our literature review demonstrated a 5-year overall survival rate of 7.9%, in which patient age was significantly associated with worse survival prognosis (p=0.026). Treatment with surgery and adjuvant therapy was significantly associated with improved overall survival (p=0.006) compared to surgery alone or non-surgical treatment. Examining overall trends historically, neither presenting age nor survival appear to have a significant association with the year of diagnosis, demonstrating an R^2 of 0.003 (p=0.48) for age at diagnosis and 0.023 (p=0.39) for survival from 1960 and 2016. From our retrospective cohort study, 32 out of 1,872 Paget's patients were determined to have Paget's sarcoma, indicating a prevalence of 1.7% for our database. The 5-year local recurrence-free, metastatic disease-free, disease-specific, and overall survival rates were 12.5%, 15.6%, 12.5%, and 18.8%, respectively. Patient age was significantly associated with worse survival outcomes (p=0.005) in our institutions' patient registry.

Conclusion Including over 1,000 Paget's sarcoma patients in our study greatly strengthens the associations between treatment type and survival. While patients undergoing multimodal therapy reported the greatest longevity, concerns remain for mobility and quality of life. Our cohort study indicates that few factors can effectively predict oncologic outcomes for Paget's sarcoma patients. Age is the strongest underlying factor for poor prognosis. Patient outcomes have not changed significantly in the last 80 years; our literature and cohort study highlights the need for increased clinician awareness and improved treatment modalities for Paget's sarcoma.

Level of Evidence Level III, retrospective comparative study and review of other level III studies.

Introduction

Background

Paget's disease of bone (PDB) is a condition characterized by abnormal bone metabolism with increased osteoblastic and osteoclastic activity estimated to affect 200,000 individuals in the United States each year. The condition greatly increases in prevalence with age, approaching 10% in the 90-year-old population[24, 27, 33]. Individuals affected by PDB experience an accelerated, disorganized remodeling process, resulting in larger, deformed, and often weaker bone trabeculae[20]. Associated complications include fractures, bone pain, visible deformity, and rarely sarcomatous transformation[2, 20, 38]. Although far less common, with recent estimates demonstrating an incidence of <1% in PDB patients, sarcomas arising in the setting of Paget's disease is associated with a very poor oncologic prognosis. Little improvement has occurred in the last century, despite surgical advances and the advent of chemotherapy and radiation therapy[9,13, 15, 37]. Recent studies have demonstrated a 5-year survival rate of 18.9% in patients with Paget's sarcoma compared to 24.2% in non-Paget sarcoma patients in the same age range[17].

Rationale

This literature review aims to identify factors that may affect overall survival in patients with Paget's sarcoma. Additionally, a cohort from our institutions was compared in this review. We completed a pooled database of over 1,000 patients. Given the rarity of this condition, combining the available data addresses the statistical power limitations while elucidating trends in treatments and outcomes over time. We sought to identify patient, tumor, and treatment-specific predictors affecting the listed oncologic prognostic variables in Paget's sarcoma.

Study questions

(1) What are the oncologic and clinical characteristics of patients who developed and are diagnosed with Paget's sarcoma?

(2) What are the outcomes when examining variables such as sarcoma type, presentation at diagnosis and treatment in Paget's sarcoma patients?

(3) How have treatment and oncologic prognosis changed in recent decades?

Methods

Study design and setting

In our two-part study, we performed a literature review, pooling data from previous studies and public databases for worldwide Paget's sarcoma cases between 1927 and 2006 and a retrospective analysis on a cohort of PDB patients at our institutions between 1979 and 2019. *Search strategy and criteria: Literature review*

MEDLINE and Embase were searched for eligible studies published in English any time in the last century. The search strategy included: ["Paget's disease of bone" OR "Paget's disease" OR "Paget sarcoma" OR "osteitis deformans"] AND ["sarcoma" OR "osteosarcoma" OR "malignancy" OR "neoplasm" OR "tumor"].

Inclusion and exclusion: Literature review

Articles specifically addressing oncologic outcomes and overall survival in Paget's sarcoma patients with associated osteosarcomas, chondrosarcomas, fibrosarcomas, or previously diagnosed malignant fibrous histiocytomas were included. We excluded cohorts with less than 5 patients or patients in which the location of malignancy did not coincide with the location of underlying Paget's disease, case reports, and meeting abstracts.

Assessment of study quality: Literature review

Two independent reviewers (TK, TM) appraised all included studies. Only raw data was extracted from each study.

Data collection and abstraction: Literature review

From selected articles, the following data was extracted when available: author, year of publication, country, year of diagnosis, number of patients, age, sex, skeletal involvement, tumor type, tumor grade, disease stage, treatment type, and oncologic prognosis defined as overall survival. Treatment type was defined as surgery alone, radiation therapy alone, chemotherapy alone, surgery in combination with radiation therapy, surgery in combination with chemotherapy, or a combination of the three treatment modalities.

Table 1. Characteristics of the included studies for literature review

Author, Year	Location	Patients	Percent Male	Mean Age	Source Dates
Mangham, 2008	United Kingdom	32	71.9	73	1976-2006
Price, 1969	United Kingdom	80	67.5	68	1946-1966
Deyrup, 2007	United States	70	65.7	66	NR
Barry, 1960	Australia	29	NR	NR	1950-1959
Seret, 1987	France	12	66.6	72	1963-1983
Haibach, 1984	United States	82	67.1	60	1958-1983
Greditzer, 1983	Unites States	41	60	64	NR
Dray, 2008	New Zealand	31	54.8	72	1960-2004
Hadjipavlou, 1992	Canada	8	50	67	1970-1982
Huvos, 1983	United States	65	55	NR	1921-1981
Mankin, 2005	United States	43	43.5	68	1942-2001
Moore, 1991	New Zealand	22	54.5	71	1961-1989
Ruggieri, 2010	Italy	26	80.8	64	1961-2006
Schajowitcz, 1983	Latin America	62	NR	66	1940-1981
Seitz, 2009	Germany	6	50	73	1972-2006
Sharma, 2005	United Kingdom	13	84.6	69	1947-2004
Sharma, 2006	United Kingdom	13	76.9	67	1944-2003
Shaylor, 1999	United Kingdom	26	69.2	69	1974-1999
Smith, 1984	United States	85	60	60	1927-1982
Wick, 1981	United States	38	60.5	61	1927-1977
McKenna, 1964	United States	33	60.6	61	1925-1955
Frassica, 1991	United States	51	67	67	1927-1991
SEER Program	United States	111	61.2	71	1975-2016

Participants/study subjects: Cohort study

Inclusion required a diagnosis of Paget's disease obtained through a review of past medical history. In most cases, supporting documentation included conventional radiography or bone scans with a confirmatory histopathological diagnosis at either of our institutions. Sarcomatous transformation, histological grading, and staging through systems from the Musculoskeletal Tumor Society and the American Joint Committee on Cancer were confirmed through a review of biopsy reports performed at our institutions or elsewhere that were read at our centers[6, 26]. PDB patients diagnosed with lymphoma, myeloma, or giant cell tumor were not included in this study. PDB patients diagnosed with sarcoma in locations other than the bones affected by Paget's disease were not included as Paget's sarcoma patients.

Variables, outcome measures, data sources, and bias: Cohort study

Patient age, sex, location of sarcoma, tumor type, grade, and stage, location of metastasis, and treatment type were collected and analyzed. Sarcomatous transformation and histological grading were confirmed by the Musculoskeletal Tumor Society and American Joint Committee on Cancer systems[6, 26]. Oncologic prognosis was measured as local recurrence-free, metastatic disease-free, disease-specific-free, and overall survival. Medical reports (e.g., patient notes and reports) and the Social Security Index were reviewed to assess these prognostic measures. Surgical reports were reviewed to determine margin characteristics and surgical intervention types. Chemotherapeutic and radiation therapy regimens were recorded for each patient from their medical record.

Table 2. Patient demographics for cohort study

Variable	Number (%)
Paget's Disease of Bone	
Male	992 (53.0)
Female	880 (47.0)
Paget's Sarcoma	
Male	14 (43.8)
Female	18 (56.3)
Age at Sarcoma Diagnosis	
<60	1 (3.1)
60-69	7 (21.9)
70-79	16 (50.0)
80-89	8 (25.0)
Treated with Radiation Therapy Prior to Sarcoma Diagnosis	2 (6.3)
Treated for Paget's Prior to Sarcoma Diagnosis	6 (18.8)
Sarcoma Histology	
Osteosarcoma	19 (59.4)
Osteoblastic	12 (37.5)
Chondroblastic	2 (6.3)
Fibroblastic	2 (6.3)
Osteoblastic/Chondroblastic	1 (3.1)
Osteoblastic/Fibroblastic	1 (3.1)
Telangiectatic	1 (3.1)
Malignant Fibrous Histiocytoma	10 (31.3)
Chondrosarcoma	2 (6.3)
Fibrosarcoma	1 (3.1)

Demographics and description of study population: Cohort study

1,872 patients with PDB, aged 18 years or older, were identified in the screening process of this study. 814 and 922 patients presented with monostotic and polyostotic disease, respectively. 136 patient records did not indicate precise disease location in bone. The majority of patients in our series were male (52.5%), and the average age was 67.4. The most common bones affected included the pelvis (909), thoracic and lumbar vertebrae (322), skull (238), and sacrum (78). Of these patients, 32 were diagnosed with Paget's sarcoma. 17 of which were female, and the remaining 15 were male. The mean age of sarcoma diagnosis was 75 years old.

Statistical analysis

Statistical analyses using both univariate and multivariate models were performed with StataSE 15.1 (StataCorp LP, College Station, TX, USA) using a log-rank test and the Cox-proportional hazards model for both the pooled data and cohort study. Pearson's correlation coefficient and t-tests were used to determine the association of variables with time. Kaplan-Meier analyses were performed to construct survival curves. Survival censorship was performed in cases where survival data was missing.

Results

1. What are the oncologic and clinical characteristics of patients diagnosed with Paget's sarcoma?

Literature review

For the pooled data, the mean age at sarcoma diagnosis was 66.5 years old (n=917), with 62.1% of patients being male. Of the 205 cases with available treatment details, 131 patients received surgical intervention, 66 received chemotherapy or radiation therapy alone, and 8 received no treatment for their disease. Of the 273 patients with available tumor type information, 203 presented with osteosarcomas, 39 with fibrosarcomas, 26 with malignant fibrous histiocytomas, and 5 with chondrosarcomas.

Table 3. Functional outcomes from included studies for literature review

Author, Year	Number of Patients	Mean Age	% Osteosarcoma	% Received Surgery	5 Year Survival %
Mangham, 2008	32	73	100	NR	NR
Price, 1969	80	68	68	49	12.5
Deyrup, 2007	70	66	88	59	10
Barry, 1960	29	NR	90	24	3.4
Seret, 1987	12	72	58	42	0
Haibach, 1984	82	60	94	46	3
Greditzer, 1983	41	64	85	47	8
Dray, 2008	31	72	100	32	10
Hadjipavlou, 1992	8	67	63	63	13
Huvos, 1983	65	NR	22	NR	5
Mankin, 2005	43	68	NR	55	NR
Moore, 1991	22	71	73	NR	5
Ruggieri, 2010	26	64	69	85	23
Schajowitcz, 1983	62	66	63	NR	1.6
Seitz, 2009	6	73	NR	NR	NR
Sharma, 2005	13	69	23	92	15
Sharma, 2006	13	67	77	46	0
Shaylor, 1999	26	69	85	42	3.5
Smith, 1984	85	60	88	47	4
Wick, 1981	38	61	84	45	7.9
McKenna, 1964	33	61	64	58	0
Frassica, 1991	51	67	85	NR	11
SEER Program	111	71	NR	59	13

Cohort study

In our cohort study, 32 of the 1,872 PDB patients were determined to have Paget's sarcoma, a prevalence of 1.7%. Of the 32 patients with Paget's sarcoma, 19 had osteosarcomas. Of the remaining patients, 10 were diagnosed with malignant fibrous histiocytomas, 2 with chondrosarcomas, and 1 with fibrosarcomas. All but 4 patients received treatment at our institutions. 21 patients had surgery (resection or amputation); in addition to their surgery, 4 also received both chemotherapy with radiation therapy, 7 received radiation therapy alone, 2 chemotherapy alone, and 8 received surgery only. Surgical intervention involved resection with negative margins and reconstruction with endoprosthesis in 2, with allograft reconstruction in 1, and resection alone in 13. 1 had a resection followed by amputation, and 4 had amputations only. Metastasis occurred in 15 patients, 11 of which were discovered at the time of sarcoma diagnosis. In 13 of these cases, the lungs were the site of metastasis. The lungs and lymph nodes, lungs and bones, and liver only were affected in 1 patient, respectively.

Table 4. Patient and treatment characteristics for cohort study of Paget's sarcoma cases

Variable	Number (%)
Bony involvement of Paget's disease	
Monostotic	19 (59.4)
Polyostotic	13 (40.6)
Sarcoma Grade*	
1-2/3	2 (6.5)
2/3	6 (19.4)
2-3/3	7 (22.6)
3/3	16 (51.6)
MSTS Stage*	
I	1 (3.2)
II	19 (61.3)
III	11 (35.5)
Patients Receiving Surgical Treatment†	
Surgery Only	8 (27.6)
Surgery + Chemo	2 (6.7)
Surgery + XR	7 (24.1)
Surgery + Chemo + XR	4 (13.8)
Patients Receiving Non-Surgical Treatment†	
Radiotherapy	4 (13.8)
Chemotherapy	1 (3.5)
Both	2 (6.7)

* Pathology data available for 31 patients, percentage based on those 31
† Treatment data available for 29 patients, percentage based on those 29

2. What are the outcomes when examining variables such as sarcoma type, presentation at diagnosis, and treatment in Paget's sarcoma patients?

Literature review

Survival data analyzed for 930 patients demonstrated an overall 5-year survival rate of 7.9% and a median survival of 7 months (range, <1 to 439). Treatments were separated into three categorical types: no surgery (chemotherapy and/or radiation therapy or no treatment), surgery alone, and surgery with adjuvant therapy (chemotherapy and/or radiation therapy). Patient age at the time of diagnosis demonstrated a strong univariate association with survival (p=0.026). Univariate and multivariate survival analyses demonstrated a significant association between survival and treatment type (p=0.012) and age and treatment type (p=0.006), respectively. Surgical intervention with adjuvant therapy demonstrates a mean survival of 34.7 months, while surgery alone corresponds to a mean survival of 23.3 months. Patients who did not receive any surgical intervention had a mean survival of 16.0 months. In comparing the association between tumor types, there was no significant difference in outcomes in either univariate or multivariate analysis, even when including age at diagnosis for any of the histological subtypes.

Table 5. Treatment type and outcome for literature review

Treatment Type	Number	Mean Age	Mean Survival (months)
No Treatment	8	66.4	2.9
Non-Surgical	66	66.0	16.0
Radiation Only	58	66.2	16.6
Chemo Only	1	72.0	5
Chemo + Radiation	7	63.4	12.7
Surgical	131	67.1	27.8
Surgery Only	80	67.5	23.3
Surgery + Chemo and/or Radiation	51	66.4	34.7

Table 6. Tumor type and outcome for literature review

Tumor Type	Number	Mean Age	Mean Survival (months)
Osteosarcoma	203	67.2	19.6
Fibrosarcoma	39	65.7	17.1
Malignant Fibrous Histiocytoma	26	70.8	30.0
Chondrosarcoma	5	63.2	39.3

Figure 1. Kaplan-Meier survival curves from literature review for all Paget's sarcoma patients (n=334)

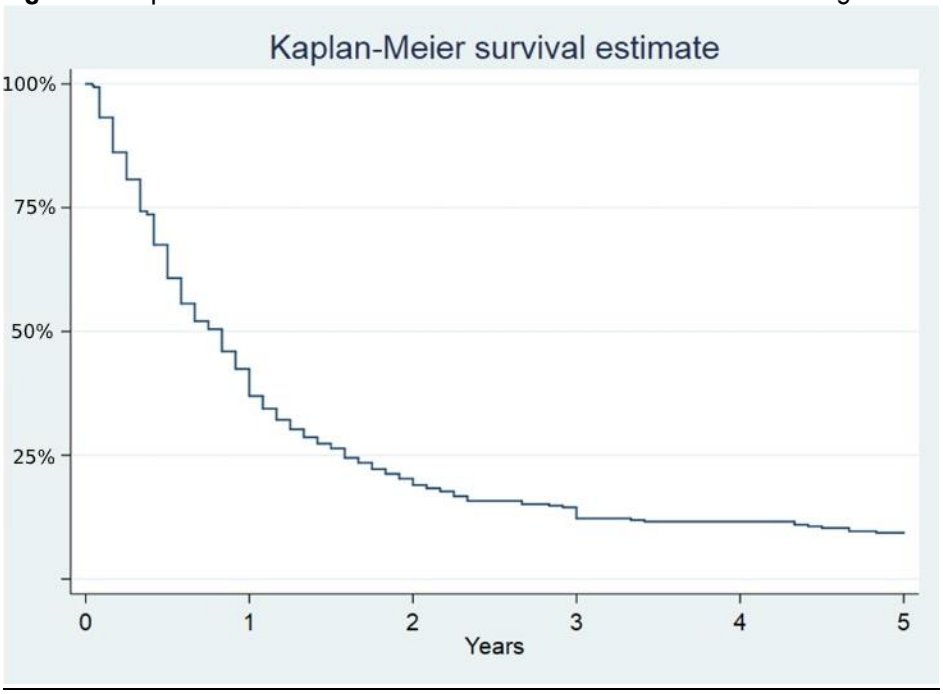
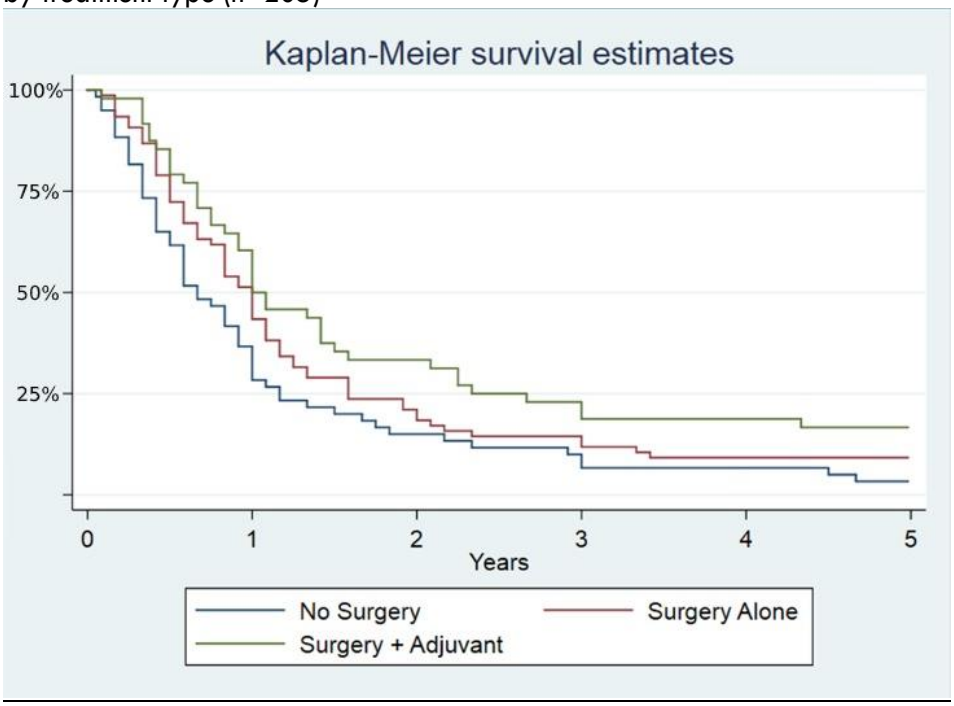


Figure 2. Kaplan-Meier Survival Curve from systematic review for all Paget's sarcoma patients compared by treatment type (n=205)



Cohort study

Complete survival follow-up was obtained for 30 patients. The 5-year local recurrence-free survival rate was 13.3% (n=4), metastatic disease-free survival rate was 16.7% (n=5), disease-free survival rate was 13.3% (n=4), and overall survival rate of 20.0% (n=6). The average overall survival time was 3.1 ± 6.7 years (range, <1-20 years). The 4 patients with recurrent disease had a median local recurrence-free and disease-free survival of 2.3 and 0.79 years, respectively. Univariate analysis using a log-rank test demonstrated that age at sarcoma diagnosis was significantly associated with survival (p=0.005). This finding was not reflected in the multivariate analysis. No significant differences were identified when investigating treatment type-dependent survival. Bony involvement, tumor grading and staging appear to have no significant relationship with survival in either univariate or multivariate analyses. Adjuvant treatment with chemotherapy and radiation therapy showed no advantage over surgery alone. Surgical intervention did not appear to significantly increase survival when compared to patients treated non-surgically.

3. *How have treatment and outcomes changed in recent decades?*

Our analysis of trends over time shows that neither presenting age nor survival appear to have a significant association with the year of diagnosis, as demonstrated by an R^2 of 0.003 (p=0.48) for age at diagnosis and 0.023 (p=0.39) for survival, respectively, between 1960 and 2016.

Figure 3. Historical trends from literature review: Age at sarcoma diagnosis

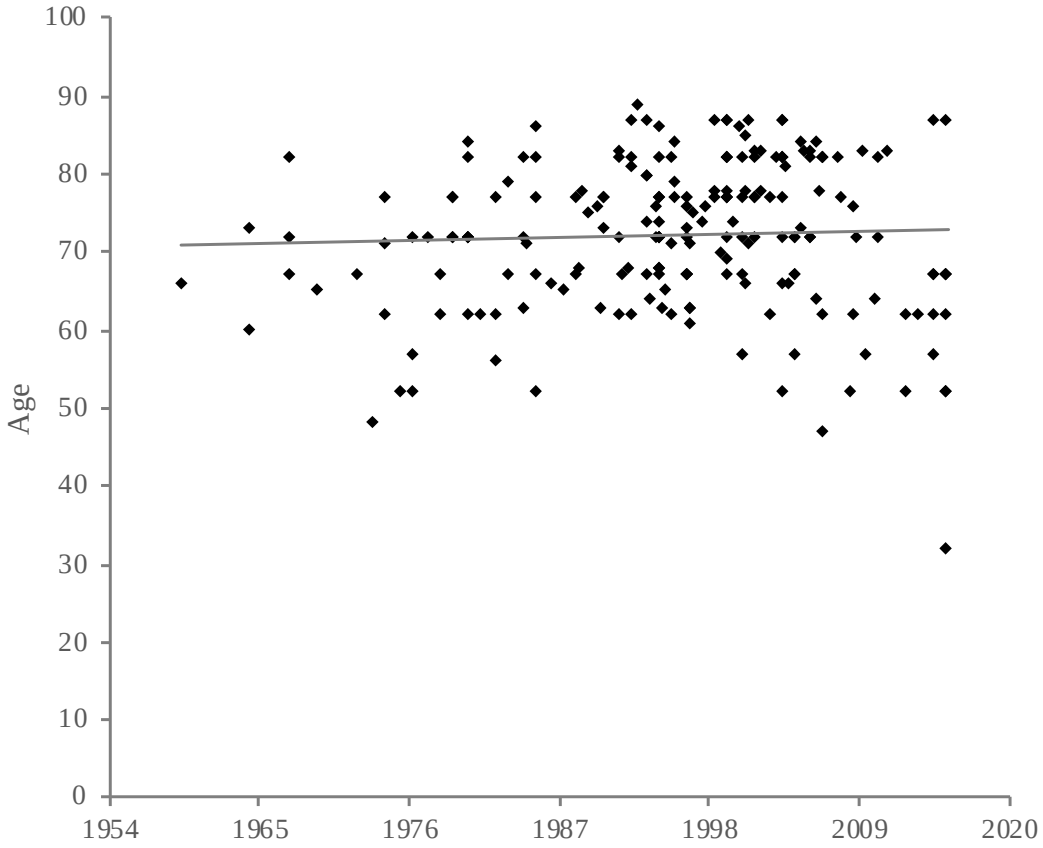
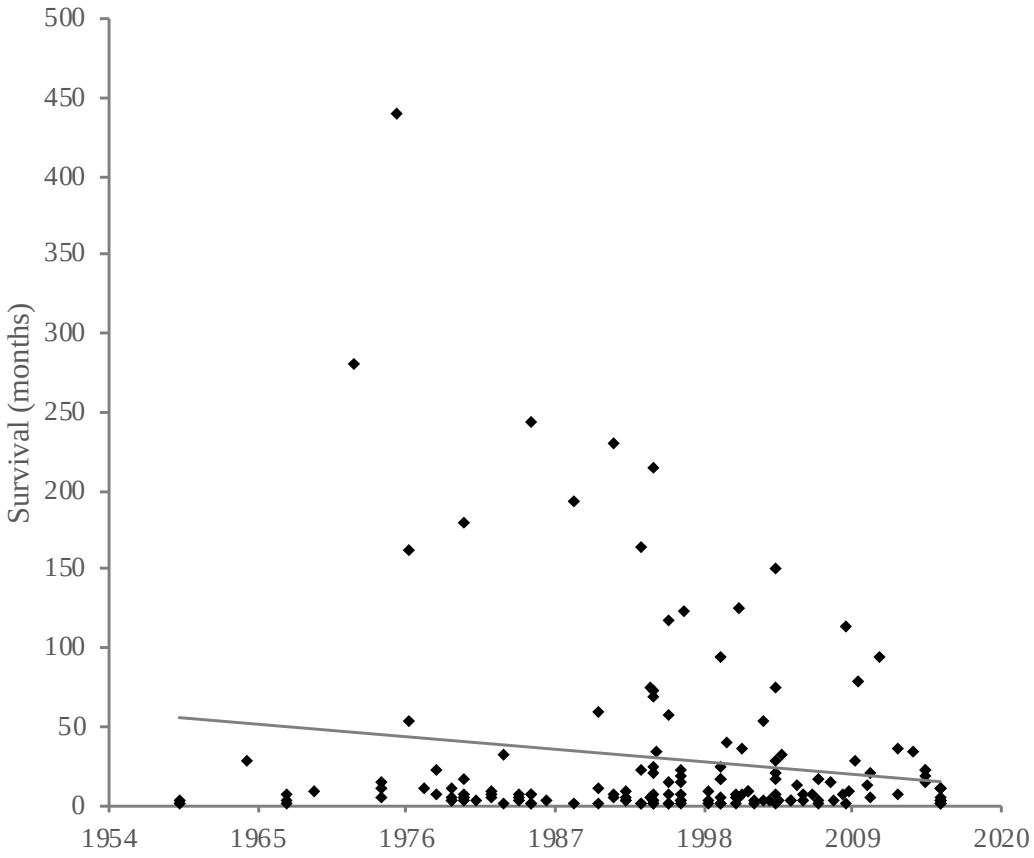


Figure 4. Historical trends from literature review: Survival



Discussion

Background and rationale

Sarcoma in the setting of PDB is not a recent finding, being noted as early as Sir James Paget's initial observations in the late 19th century, in which he reported osteogenic sarcomas developing in 5 of the 23 PDB patients he observed[19]. While frequency estimates are much lower today, osteosarcomas appear to develop in the presence of PDB at far higher rates than that of non-PDB patients. In 1986, it was found that 56% of primary sarcomas in patients over the age of 60 developed in association with Paget's disease[11]. In 2009, the SEER program published results finding that in the general population, the incidence of osteosarcoma after age 60 is estimated to be around 4.2 per million. Of these cases, Paget's sarcoma made up 9.5%. This was observed to be a nearly 10-fold increase compared to the 1% of Paget's sarcoma in patients aged 25 to 59[17]. With an increasingly aging population and longer life expectancy, it is of great interest for clinicians to better understand factors that may be related to the development and treatment of sarcoma developing in PDB patients. The biggest obstacle in coming to these conclusions is the limited data available. With only a handful of cases occurring every decade at even the largest medical institutions and referal centers, additional analyses are imperative for more informed conclusions. Our larger-scale data compilation helps clarify this deadly complication's characteristics.

1. What are the oncologic characteristics of patients diagnosed with Paget's sarcoma?

Nevertheless, this literature review and cohort study confirm that patients with Paget's sarcoma are often older and male. The risk of developing Paget's sarcoma increases with age when compared to the general population having primary bone sarcomas in the absence of PDB. At least in our series, pelvic location seems to be a predictor factor of malignant transformation. The 1.7% incidence of malignant transformation is low, comparable to other case series and the reported data in the literature. Combined with our review, we determined the average incidence of Paget's sarcoma is 1.4% (n=18,191). As in our series, patients are mostly males and older than 60 in the published literature. Osteosarcoma is the most common histology.

2. *What are the outcomes when examining variables such as sarcoma type, presentation at diagnosis and treatment in Paget's sarcoma patients?*

The prognosis for Paget's sarcoma is poor. In our institutional cohort, 15 of the 32 Paget's sarcoma patients developed metastatic disease, with 11 presenting metastases at their initial Paget's sarcoma diagnosis. The average local recurrence-free survival was 2.3 years, with a subsequent median disease-specific survival of just over a half year. Our cohort demonstrated better overall 5-year survival than reported in the literature (34.4% vs. 7.9%) and longer overall survival time (3.1 years vs. 7 months).

3. *How have treatment and outcomes changed in recent decades?*

The clinical characteristics of patients did not appear to change over time. Male patients older than 60 most consistently developed Paget's sarcoma, with the pelvis being the most common location. Modalities of treatment have not changed substantially; multimodal therapy (combination of surgery with chemotherapy plus/minus radiation therapy) remains the most effective in increasing survival time. However, this is at a significant expense of function and quality of life. Surgical intervention reported longer mean survival times than those of non-surgical nature (27.8 months vs. 16 months). Some patients in our cohort and the literature report no active treatment but just palliation.

While the prognosis for Paget's sarcoma reamins poor, diagnostic tools and a better understanding of genetic underpinnings allow for earlier detection. Potential prophylactic drugs and advanced surgical techniques may also improve patient quality of life. The development of PDB has both environmental and genetic underlying factors, with SQSTM1 mutations reported in approximately 20% to 40% and 5% of familial and sporadic cases, respectively, in 2004.[40-41] Researchers also previously thought an infection with paramyxoviruses may have contributed to the etiology of PDB, as they detected viral mRNA and proteins in pagetic bone. Similar studies have failed to substantiate this claim, as they could not detect viral RNA or proteins in pagetic bone.[42-45] Clinicians can now detect asymptomatic PDB through measurements of total serum alkaline phosphatase (ALP) markers and use CT scans and MRI to guide biopsy planning.[46] While the long-term efficacy of prophylactic treatment of asymptomatic PDB patients remains unclear, antiresorpitives, such as bisphosphonates, may reduce disease progression and bone deformity.[47-48] Advances in surgical techniques, such as 90/90 plating and locked plating techniques, allow for early return to function and mobilization, thereby addressing disease management and quality of life concerns associated with Paget's sarcoma treatment.[49]

Conclusion

Paget's sarcoma is a rare condition with a prevalence rate of 1.4% in those with PDB. Male patients over 60 presenting with PDB of the pelvis represent the most at-risk population. Such characteristics merit closer attention and stricter clinician surveillance to ensure early detection. While multimodal treatment may improve oncologic prognosis, it is at the expense of function and quality of life. Treatments and outcomes of Paget's sarcoma have not changed through time. The aging population and prospective increase in the prevalence of PDB warrants an increase in research efforts to improve the sensitivity of methods used to detect malignant transformation and develop less morbid and more successful treatment interventions.

Limitations

The literature review portion of this study is limited by its heterogeneous patient population, treatment style, and descriptions of certain oncologic characteristics. The broad range of locations and dates from which we have pooled data may be the culprit. Surgical techniques, chemotherapeutic options, and radiation therapy have changed over the last century at different rates worldwide. While our analysis does not show a clear trend in outcomes with time, it is impossible to isolate the many differences between cohorts. Additionally, not all variables of interest were recorded for every study, decreasing the statistical power of certain analyses. The cohort study is limited by a small sample of cases, which is not unexpected given the rarity of this condition. It is difficult to analyze relationships between variables of interest and outcomes. Establishing a uniform multi-center data repository of Paget's sarcoma patients may address shortcomings in analyses related to treatments, outcomes, and their corresponding trends.

Conflicts of Interest Statement

The authors have no conflicts of interest to share.

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