The epidemiology of malignant giant cell tumors of bone: an analysis of data from the Surveillance, Epidemiology and End Results Program (1975–2004)

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Abstract

Malignant giant cell tumor (GCT) of bone is a rare tumor with debilitating consequences. Patients with GCT of bone typically present with mechanical difficulty and pain as a result of bone destruction and are at an increased risk for fracture. Because of its unusual occurrence, little is known about the epidemiology of malignant GCT of bone. This report offers the first reliable population-based estimates of incidence, patient demographics, treatment course and survival for malignancy in GCT of bone in the United States. Using data from the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) program, we estimated the overall incidence and determinants of survival among patients diagnosed with malignant GCT of bone from 1975–2004. Cox proportional hazards regression was used to evaluate demographic and clinical determinants of survival among malignant GCT cases. Based on analyses of 117 malignant GCT cases, the estimated annual incidence in the United States was 1.6 per 100,000 persons per year. Incidence was highest among adults aged 20 to 44 years (2.4 per 100,000 persons per year) and most patients were diagnosed with localized (31.6%) or regional (29.9%) disease compared to distant disease (16.2%). Approximately 85% of patients survived at least 5 years, with survival poorest among older patients and those with evidence of distant metastases at time of diagnosis. The current study represents the largest systematic investigation examining the occurrence and distribution of malignancy in GCT of bone in the general U.S. population. We confirm its rare occurrence and suggest that age and stage at diagnosis are strongly associated with long-term survival.

Introduction

Giant cell tumors (GCTs) of bone occur infrequently, comprising just 5% of all bone tumors, both benign and malignant.1 However, the disease can be incapacitating, as patients with GCT of bone typically present with mechanical difficulty and pain resulting from bone destruction and are at an increased risk for fracture.12 GCTs are observed predominantly at the ends of long bones, most commonly located in and around the knee (distal femur, proximal tibia) and wrist (distal radius).1 They are categorized according to the Enneking staging system, where the pathological spectrum ranges from static and confined to the bone (Stage 1) to aggressive, extending into the surrounding soft tissue (Stage 3).4 A radiographic grading system developed by Campanacci et al. grades lesions from 1 to 3, with Grade 1 lesions having well-defined margins and an intact cortex, and Grade 3 having irregular margins and cortical destruction.2 Metastases can develop from both benign and malignant GCTs; and lung is the most frequent metastatic site.4

Histologically, GCTs are a heterogeneous mix of multinucleated giant cells resembling osteoclasts, spindle-shaped stromal cells exhibiting features of osteoblast precursors and CD-68 positive mononuclear cells.7 The neoplastic cell of origin has not been identified conclusively. Recently, expression of the ligand for receptor activator of nuclear factor κB (RANKL), a factor critical in the development and activation of osteoclasts, was detected in GCT, raising the possibility of controlling bone lysis from GCT by inhibition of the RANKL–RANK axis.5

While GCTs account for approximately 20% of all benign bone tumors,1 malignancies in GCT of bone are much rarer and are typically classified as primary or secondary according to specific criteria.1011 A primary malignant GCT of bone will most often arise concurrently and closely with a benign tumor; however, spontaneous neoplasm may occur in the absence of benign growth. Secondary malignant GCTs are more common than primary malignant GCTs and arise after treatment of a previously benign tumor and more often in patients undergoing radiation therapy with or without curettage.1 While GCT is typically associated with a favorable prognosis, the long-term prognosis for malignant transformation of a previously benign-appearing tumor is poor. Further, reports71112 indicate that those patients with a history of radiation treatment for benign GCT tend to have poorest outcomes, suggesting that rigorous follow-up of patients treated for benign tumors even decades after initial diagnosis is crucial to insuring long-term survival.

Because of the rarity of the malignant variety, there are limited sources which can be used to characterize incidence and survival following a diagnosis of malignancy in GCT of bone. Most published data on its epidemiology have been generated from hospital-based patient series, which may not accurately translate to the larger population in terms of patient and tumor characteristics and frequency of occurrence in the general population.

To better understand the epidemiology of malignancy in GCT of bone, we consulted data from the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) Program, which represents the most comprehensive and complete source of information available on the diagnosis, demographics, treatment and follow-up of cancer patients in the United States (U.S.). To our knowledge, this study represents the first systematic U.S. investigation of the descriptive epidemiology of this rare tumor using a large, population-based dataset.

Materials and Methods

Surveillance, Epidemiology and End Results registry and study population

We used data gathered as part of the National Cancer Institute’s SEER Program. SEER currently consists of 18 statewide and regional tumor registries spread throughout the U.S., covering approximately 26% of the population (http://seer.cancer.gov registries/
The individual registries are geographically located to over-sample minority populations, including African Americans, Hispanics, Asian Pacific Islanders, and Native Americans. SEER routinely collects data on patient demographics (age at diagnosis, gender, race/ethnicity and geographic residence at the time of diagnosis), tumor characteristics (size, grade, stage), first course of treatment, as well as follow-up documentation of vital status (date and cause of death). Based on the rare occurrence of malignancy in GCT of bone, coupled with our initial goal of assessing epidemiologic time trends, we limited our analyses to the longest running SEER registries (Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Utah, Seattle-Puget Sound, and Atlanta), all of which have collected information on invasive cancers diagnosed from 1975 through 2004 and represent nearly 10% of the U.S. population. Patients included in the current study were those diagnosed with malignant giant cell tumors of bone (ICD-O-3 codes, M-9250/1, M-9250/2, M-8003/3, and primary site codes C40.0-C41.9) between January 1, 1975 and December 31, 2004. Classification of tumors was based upon SEER summary staging criteria. SEER summary stage is produced using the extent of disease information from medical records and pathology reports reviewed at the time of diagnosis. A localized tumor is defined as an invasive neoplasm a.) confined to the cortex of the bone; or b.) extends beyond the cortex into the periosteum (with no break in the periosteum). Regional stage is defined as a neoplasm that has a.) extended beyond the periosteum into adjacent bone, cartilage or skeletal muscle; or b.) into regional lymph nodes by way of the lymphatic system; or c.) a combination of extension and regional lymph node involvement. A distant classification would include a neoplasm that has spread to parts of the body remote from the primary tumor either by direct extension or by metastasis to distant organs, tissues or the distant lymph nodes via the lymphatic system (http://seer.cancer.gov/tools/ssm/musculoskeletal.pdf).

### Statistical methods

Patient (age at diagnosis, gender, race/ethnicity, tumor (stage), and treatment (receipt of surgery and/or radiation)) characteristics were described for all individuals diagnosed with malignant GCT of bone across the study period (1975-2004). Annual crude and age-adjusted incidence rates per 10,000,000 persons were calculated using SEER*Stat v. 6.36 and then averaged over the entire study period and for 5-year periods using U.S. county population estimates. Estimates were age-adjusted using the 2000 U.S. population as the standard population. Chi-square tests were conducted to determine differences in incidence rates across the study period by age at diagnosis, gender, race/ethnicity (white, black, other race) and SEER summary stage (localized, regional, distant).

SEER*Stat was also used to calculate relative survival rates for the entire study cohort. SAS software version 9.1 (SAS Institute, Cary, N.C., USA) was used to build Cox proportional hazards (PH) regression models to estimate the relation of select factors and survival following a diagnosis of malignant GCT of bone. Individuals were censored at the date of death, the date last known to be alive (if lost to follow-up), or December 31, 2004, whichever came first. Variables included in the final Cox PH model were: age at diagnosis (in 5-year age groups), year of diagnosis, gender, race, stage at diagnosis, and receipt of first-line treatment (none, surgery, radiation, or a combination of surgery and radiation).

### Results

From 1975 through 2004, a total of 117 individuals were identified as having been diagnosed with “primary” malignant GCT of bone in the SEER 9 registry regions (Table 1). “Primary” in this context means that the tumor is the first and/or only invasive cancer diagnosed, not to be confused with the aforementioned definitions of primary versus secondary malignancy in GCT. Most patients diagnosed were between the ages of 20 and 44 years (57.3%), female (53.9%), and white (74.4%). Of these patients, nearly one-third (31.6%) were diagnosed with disease confined to the bone, 29.9% were diagnosed with cancer with evidence of extension into the surrounding soft tissue, 16% were diagnosed with distant metastasis, and 22% were of unknown stage. The primary treatment for most patients (69.3%) was surgical removal of the tumor either with (12.0%) or without (57.3%) radiation therapy. First-line treatment was associated with stage at diagnosis; as most patients with localized disease received surgery whereas patients with more advanced disease received radiation therapy (with or without surgery) as primary treatment (P<0.0001).

The incidence of malignant GCT of bone was extremely low for the thirty-year study period (1.6 per 10,000,000 persons per year) (Table 2). As one of the initial aims of the investigation was to examine trends in occurrence over time, incidence was estimated for 5-year time periods. However, because of the small number of cancers reported for each time period, no formal tests of trend over time were conducted. Annual incidence estimates varied from 1.0 per 10,000,000 in the most recent time period (2000-2004) to 2.2 per 10,000,000 persons (in 1975-1979 and 1985-1989). The average annual malignant GCT incidence across the entire study period did not differ significantly by gender or race/ethnicity. However, the annual incidence did differ depending upon age, with the highest incidence observed among those aged 20 to 44 years (2.4 per 10,000,000 persons), with estimates ranging from 1.6 in 2000-2004 to 3.2 in 1975-1979 across the study period. Metastatic GCT of bone was exceedingly rare; its incidence was lower than that of either localized or regional disease (P=0.04).

The mean survival time for patients diagnosed with malignant GCT of bone was 11 years and 11 months, with a 5-year relative survival of 84.2%. As would be expected, Cox proportional hazards modeling indicated that older age and more advanced stage at time of diagnosis were associated with an increased risk of death after controlling for other potential important determinants (Table 3). More specifically, for each 5-year increase in age at diagnosis, the risk of death increased by 41% (P<0.0001). Likewise, for patients with distant metastases detected at the time of diagnosis,

### Table 1. Characteristics of patients diagnosed with malignant giant cell tumors (GCT) of bone (SEER† 1975-2004) (N=117).

| Characteristic            | N (%) |
|---------------------------|-------|
| Age at diagnosis          |       |
| <20 years                 | 12 (10.2) |
| 20-44 years               | 67 (57.3) |
| 45+ years                 | 38 (32.5) |
| Gender                    |       |
| Female                    | 63 (53.9) |
| Male                      | 54 (46.1) |
| Race                      |       |
| White                     | 87 (74.4) |
| Black                     | 14 (12.0) |
| Other                     | 16 (13.6) |
| Stage at diagnosis        |       |
| Localized                 | 37 (31.6) |
| Regional                  | 35 (29.9) |
| Distant                   | 19 (16.2) |
| Treatment                 |       |
| Surgery only              | 67 (57.3) |
| Surgery + radiation       | 14 (12.0) |
| Radiation only            | 15 (12.8) |
| None                      | 15 (12.8) |
| Unknown                   | 6 (5.1) |
| SEER Region at diagnosis  |       |
| Detroit, MI               | 24 (20.5) |
| Connecticut               | 23 (19.7) |
| San Francisco-Oakland, CA | 21 (17.9) |
| Seattle-Puget Sound, WA   | 15 (12.8) |
| Hawaii                    | 9 (7.6) |
| New Mexico                | 7 (6.0) |
| Atlanta, GA               | 6 (5.2) |
| Iowa                      | 5 (4.3) |
| Utah                      | 7 (6.0) |
the risk of death was 5.2 times higher compared to those diagnosed with tumor confined to the bone ($P=0.007$). However, there was no significant difference in risk of death between patients with regional and localized disease ($P=0.49$). Year of diagnosis, gender and race/ethnicity were not significantly related to survival.

### Discussion

To our knowledge, this represents the first investigation of malignancy in GCT of bone conducted in the general U.S. population. Our results confirm that malignant GCT of bone is a rare occurrence in the United States (less than one case per million persons per year). While we observed a decrease in incidence over the decades from 2.2 cases per 10 million persons in the 1970’s to 1.0 case per 10 million persons in the 2000’s, the rarity of the tumor prevented any formal test of trend in incidence over time. Results reported in an analysis of 75 malignant GCT of bone cases from a Swedish population-based national cancer registry showed an average annual incidence of 0.63 per million from 1958 to 1968, a somewhat higher estimate than our own. However, based on the small number of cases identified in both the Swedish report and our current investigation, it is possible that the observed trends in incidence over time and/or difference in incidence rates between these reports may not be meaningful but merely a reflection of chance variability in the populations studied.

The current investigation is also the first to examine racial/ethnic differences in the incidence and survival associated with this rare disease. Our results suggest no significant racial difference in the incidence of malignant GCT of bone. Survival estimates suggest a reduction in risk of death among non-white compared with white patients, but the results were not statistically significant. And although a slightly greater proportion of cases diagnosed were females compared to males, there was no significant difference in the overall incidence of malignant GCT by gender. We found most malignant GCT cases are typically diagnosed in the third and fourth decades of life, a finding supported by most case-series.

The average 5-year relative survival rate for patients with malignant GCT of the bone in our study was 84.2%. As seen with other cancer types, older age and metastatic disease at diagnosis were associated with poorer survival. However, we did not observe any significant difference in risk of death among patients diagnosed with regionally advanced disease. No significant differences in risk of death were detected by year of diagnosis, gender, race, or treatment. Our survival rates are improved over hospital-based case-series in malignant GCT, possibly reflecting advances in treatment of these tumors over time and/or geographic differences in referral patterns to specific institutions as well as availability and access to medical care for these patients. However, these are difficult theories to prove with existing data. The SEER registry records information on first line treatment, but no subsequent treatment information is collected on patients. Anract et al. observed a 5-year relative survival rate of 50% in a case-series of 29 malignant GCT patients diagnosed between 1954 and 1993. Case ascertainment in this study began approximately twenty years prior to the establishment of the SEER registry and ended a decade prior to our patient follow-up.

Table 2. Incidence of malignant GCTs of bone (in 5-year intervals), 1975-2004, according to age at diagnosis, gender, race, and stage.

| Characteristic | Hazard ratio† | p    |
|----------------|---------------|------|
| Age at diagnosis‡ | 1.41          | <0.01|
| Year of diagnosis | 1.03          | 0.84 |
| Gender          |               |      |
| Female          | 1.00          | 0.73 |
| Male            |               | 0.46 |
| Race            |               |      |
| White           | 1.00          | 0.45 |
| Black           | 0.45          | 0.17 |
| Other           | 0.55          | 0.41 |
| Stage at diagnosis |             |      |
| Localized       | 1.00          | 1.41 |
| Regional spread | 0.49          | 0.49 |
| Distant metastases | 0.01         | 0.49 |
| Stage unknown   | 0.20          | 0.14 |
| Treatment       |               |      |
| None            | 1.00          |      |
| Surgery         | 0.99          | 0.15 |
| Radiation       | 0.76          | 0.69 |
| Surgery + radiation | 0.04        | 0.94 |

†Estimate of relative risk adjusted for all other variables in the final multivariable model (age, year of diagnosis, gender, race, stage, treatment). ‡Hazard Ratio represents an estimate of the increase in risk of death with each increase from one 5-year age group to the next starting with and including the following age groupings (10-14 years, 15-19 years, …,>85 years).
Bertoni et al. showed that 59% of all patients diagnosed with malignancy in GCT at a single institution eventually died, most of metastatic disease. The authors also indicated a survival disparity between patients diagnosed with primary and secondary malignant GCT, though not formally tested because of the small number of patients in the series (n=17). Of notable importance, there was variability in the number of patients diagnosed with primary versus secondary malignant GCT in these studies as less than one-third of patients included in the Italian study were diagnosed with primary malignant GCT, while nearly 60% of patients in the French investigation were similarly diagnosed. A limitation of SEER with respect to this investigation is the inability to classify patients as having primary or secondary malignant GCT, as the SEER database does not record medical history of benign lesions. This information might have been useful in our evaluation of patient survival. If survival is improved among patients diagnosed with primary malignant GCT and the proportion of patients diagnosed with primary versus secondary malignant GCT is higher among patients in SEER, this might explain some of the variability in survival rates between studies. As our study demonstrates, surgery is the preferred treatment choice for most patients, particularly if the tumor appears indolent and confined to the bone. For biologically aggressive or recurrent tumors, curettage has been coupled with adjuvant chemotherapy or radiation. The typical treatment for patients with non-resectable GCT has been a course of modereate-dose radiation therapy. Reported rates of recurrence of benign, primary malignancy in GCT or secondary malignancy in GCT are variable and depend on tumor characteristics and treatment. Wide resection and the adjuvant use of polyethylene methacrylate following intralesional curettage have been associated with reduced recurrence rates. The use of intravenous and oral bisphosphonates may also reduce risk of local recurrence in patients with soft tissue extension of GCT.

The treatment of recurrent and metastatic GCT has been mostly surgical. Metastasectomy of lung nodules may result in long-term survival. Chemotherapy is generally of marginal benefit in advanced GCT, but may provide palliative treatment of primary or secondary malignancy in GCT. Results of a phase II trial of the fully human monoclonal antibody to RANKL, denosumab, in patients with recurrent or unresectable giant cell tumor of bone indicate nearly 90% of cases had a positive response to the agent (either elimination of giant cells or no radiographic progression of the target lesion) and nearly 85% of patients reported reduced pain and/or improvement in functional status, suggesting that denosumab is a viable treatment approach for patients with advanced or metastatic GCT not amenable to surgery.

Our investigation does have a few limitations which necessitate some caution in evaluating our results. As previously mentioned, our sample size prohibits the detection of statistically significant differences in incidence across the study period and determinants of long term survival among various subgroups. Therefore, analyses relating demographic differences in malignant GCT incidence as well as demographic and clinical determinants of survival must be interpreted with prudence, particularly if the observed disparities between these subsets of the population are modest. Additionally, formal review of the histopathology of patients in this investigation was not possible because of the unavailability of historical medical records on all patients through the individual SEER registries.

Nevertheless, the current investigation represents the largest population-based and most comprehensive examination of the descriptive epidemiology of malignancy in GCT of bone and the first of its kind conducted in the United States. Based on the rare nature of malignancy in GCT, only a large cancer database such as NCIs SEER has the ability to accrue an adequate number of cases to estimate rates of incidence and survival. An important strength of the SEER cancer registry is the active tracking of cases for vital status (over 97%) regardless of migration out of the registries catchment areas. Because losses to follow-up in our patient population are minimal, the calculated survival rates are an accurate representation of the survival experience of these patients. In the future, we would recommend that the SEER registries consistently and routinely collect information on cases of benign GCT of bone as well. Benign GCT of bone is unique in that it is considered to be a borderline neoplasm because of its potential to metastasize. Obtaining information on the diagnosis, treatment and follow-up of both benign and malignant GCT cases would enhance our understanding of the determinants of risk and survival among those diagnosed with this disease.

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