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Population-based study of giant cell tumor of bone in Sweden (1983–2011)

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ABSTRACT

Introduction: Giant-cell tumor of bone (GCTB) is a locally aggressive histologically benign neoplasm with a less common malignant counterpart. Longitudinal data sources on GCTB are sparse, limited to single institution case series or surgical outcomes studies. The Swedish Cancer Registry is one of the few national population-based databases recording GCTB, representing a unique source to study GCTB epidemiology. We estimated incidence rate (IR) and overall mortality rates based on registry data.
Materials and methods: We identified patients with a GCTB diagnosis in the Swedish Cancer Registry from 1983 to 2011: benign (ICD-7 196.0–196.9; PAD 741) and malignant (PAD 746). Results were stratified by age at diagnosis, gender, and anatomical lesion location.
Results: The cohort included 337 GCTB cases (IR of 1.3 per million persons per year). The majority (n = 310) had primary benign GCTB (IR of 1.2 per million per year). Median age at diagnosis was 34 years (range 10–88) with 54% (n = 183) females. Malignant to benign ratio for women was 0.095 (16/167) and for men 0.077 (11/143). Incidence was highest in the 20–39 years age group (IR of 2.1 per million per year). The most common lesion sites were distal femur and proximal tibia. Mortality at 20 years from diagnosis was 14% (n = 48) and was slightly higher for axial (17%; n = 6) and pelvic (17%; n = 4) lesions. Recurrence occurred in 39% of primary benign cases and 75% of primary malignant cases.
Conclusions: In our modern population-based series primary malignant cases were uncommon (8%), peak incidence 20–39 years with slight predominance in women. Recurrence rates remain significant with overall 39% occurring in benign GCTB, and 75% in malignant form. The linkage between databases allowed the first population based estimates of the proportion of patients who received surgery at initial GCTB diagnosis, and those who also received subsequent surgeries.
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1. Introduction

Giant cell tumor of bone (GCTB) is an osteoclastogenic stromal tumor, accounting for 5% of all primary bone tumors and 20% of benign skeletal tumors in the Western world [1–3]. GCTB is classified as a histologically benign lesion and composed of mononuclear stromal cells and multinucleated giant cells that exhibit ongoing osteoclastic activity [1]. GCTB affects young adults, with peak incidence in the third decade of life (median age 20–40 years); the majority of lesions occurring in the long bones around the knee, wrist and shoulder [1,4–7]. It usually appears as a lytic geographic lesion with a non-sclerotic, yet well-defined margin that often extends to the subchondral bone [1]. GCTB may be pathologically staged as a localised tumor (confined to bone), regional tumor (penetrating cortical bone, and displacing skeletal muscle), or metastatic tumor (either extra compartmental extension or metastasis) [5]. Patients with GCTB often present with pain

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and mechanical difficulty resulting from bone destruction, limitation of joint motion, and have an increased risk for pathologic fracture [5].

Uniquely, primary benign GCTB can metastasize (<5%) to the lung and metastatic GCTB lung lesions may preserve benign histologic features or assume the character of a primary sarcoma: (in order of frequency) osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, and undifferentiated pleomorphic sarcoma [8–11]. Although GCTB is classified as a benign lesion the designation does not preclude aggressive clinical behaviour with local recurrence rates ranging from in 10%–75% of patients [1,4,8,12–19]. If the tumor is located in the axial skeleton or the pelvis, surgery with curative intent may not be possible [20].

The primary malignant form of GCTB is rare, accounting for up to 5–10% of all giant cell bone tumors, and has a more aggressive phenotype and a very poor prognosis [7,21–25]. Malignant GCTB has been associated with increased risk for development of multiple pulmonary metastases or, following initial surgical resection, a predisposition to rapid local recurrence with invasion of soft tissues [23,26]. However, a recent retrospective case control study by Domovitov suggested that the behavior of primary malignant GCTB may be equivalent to that of low grade sarcoma demanding extensive surgery [24]. Due to significant bone lysis and bone structural failure, both benign and malignant forms of GCTB are associated with severe pain and substantial morbidity related to serious skeletal complications [4,12,19,25].

The diagnosis of GCTB requires a multidisciplinary and multimodal approach with clinical and histopathologic evaluation combined with imaging studies (X-ray, magnetic resonance imaging [MRI], or computed tomography [CT] scans) in order to assess the integrity of the bony cortex, heterogeneity of tumor tissue content, extent of the lesion, and any extraosseous soft tissue invasion. Local curettage is the treatment of choice for more limited lesions without soft tissue extension [1,8]. Surgery with curative intent may result in substantial morbidity as resection margins increase and in severe cases; amputation of the affected joint or limb may be required [25,27]. However, resectability with curative intent at presentation may depend on the location and extent of disease (including soft tissue) [28]. Adjuvant therapies in addition to surgery have been used with limited success. Radiotherapy with, or without surgery may result in good local control, but at an increased risk of subsequent development of a malignant GCTB. Also arterial embolization as well as intralesional chemical cell ablative adjuvant therapies, such as the application of alcohols, phenol, hydrogen peroxide, or zinc chloride have claimed reduced local recurrence rates [2,8,9,21].

GCTB produce and are dependent upon RANK ligand (RANKL) for growth [8,29]. The GCTB lesion is characterized by multinucleated osteoclast-like giant cells and their precursors that express RANK and mononuclear stromal cells that produce and express RANKL, a key mediator of osteoclast formation, function, and survival. RANKL-expressing stromal cells serve as the neoplastic component of the GCTB lesion and are hypothesized to recruit the cells that fuse to form the multinucleated osteoclast-like giant cells, which are responsible for the aggressive osteolytic activity of the tumor [30,31]. Denosumab (XGEVA®), a fully human monoclonal antibody that specifically binds to and inhibits RANKL, was approved in June 2013 by the United States Food and Drug Administration, and in September 2014 by the European Medicines Agency, as the first treatment for use in adults and skeletally mature adolescents with giant cell tumors that are unresectable or where surgical resection is likely to result in severe morbidity. This study sought to examine the natural history of GCTB prior to the adoption of this agent which is likely to impact trends [32].

To date, there is very little literature concerning trends in epidemiology of GCTB; the most recent population-based study was conducted in Sweden and published in 1975 [4]. Sources of data on GCTB concerning longitudinal incidence are sparse, and most published data are from individual case reports or institutional case series or cooperative group trial experience for which the denominator is often not known [9,10,33]. Cancer registries and national cancer surveillance networks such as SEER (National Cancer Institute, Surveillance, Epidemiology and End Results Program) only report data on malignant tumors, meaning that for many populations the majority of GCTB cases are not captured and estimates of incidence may be based on a small number of surveillance sites rather than comprehensive national registry data. The Swedish Cancer Registry offers a unique source to study GCTB as it is one of the few national population-based databases that records GCTB.

The primary goal of this study was to provide a longitudinal population-based assessment of the incidence and outcomes associated with this unusual clinical entity which has its greatest impact in young adults in the third decade of life. This study provides a unique window for understanding the natural history of GCTB and clinical course of this disease using compulsory reported patient-level information from Swedish health registries. Results were stratified by key patient characteristics.

2. Materials and methods

The study was conducted with population-based, retrospective and longitudinal data from national health registries governed by the Swedish Cancer Registry. Data on all-cause mortality was obtained from the National Cause of Death Registry. Prior to 1983 considerable variations in the reporting of benign and malignant GCTB cases were observed [34]. As described elsewhere [34], this is likely due to GCTB reporting improvements such as referral to expert centers before biopsy, multidisciplinary case review for most suspected mesenchymal tumors since 1983, computerization of case reporting forms, clarifications of diagnostic modality guidelines, and the formation of the Scandinavian Sarcoma Group (SSG) in 1979 which improved case ascertainment through a smaller number of expert surgeons and pathologists reviewing lytic bone lesions [35]. We therefore identified cases using the Swedish Cancer Registry data after 1982. Cases identified in the cancer registry were linked to hospital records up to 2011.

The study cohort represents cases diagnosed with GCTB between 1983 and 2011 identified in the Swedish Cancer Registry using ICD-7 (International Classification of Diseases, 7th Revision) and PAD (Pathological Anatomical Diagnosis) codes. Benign GCTB was identified with ICD-7 196.0–196.9 and PAD 741 and malignant GCTB with ICD-7 196.0–196.9 and PAD 746. We estimated incidence rates (IR) in five year intervals (five-year cumulative incidence per observed million person years). Crude IRs were estimated by dividing the number of incidences by total observation time at risk. In order to estimate the incidence rates, the average Swedish population during the years covering the study data was taken from the national Swedish Statistics Office (www.scb.se). Mortality data was obtained from the Swedish Cause-of-death Registry and overall cumulative mortality rates were estimated. IRs and mortality rates were described by patient characteristics, including calendar year of diagnosis, age at diagnosis, gender, and histology (primary benign or primary malignant). Finally, 95% confidence intervals were calculated as a measure of precision around the incidence and mortality rates. All analyses were conducted with SAS 9.2, following review and approval of the study protocol by the governing ethical review committee registries were linked by the Swedish Board of Health and Welfare.

Using a unique patient identification number, primary diagnostic PAD data was linked to the Swedish Patient Registry to

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