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CLINICAL INVESTIGATION **Benign Disease**

RADIATION THERAPY FOR GORHAM-STOUT SYNDROME: RESULTS OF A NATIONAL PATTERNS-OF-CARE STUDY AND LITERATURE REVIEW

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Purpose: The German Cooperative Group on Radiotherapy for Benign Diseases conducted a national patterns-of-care study to investigate the value of radiation therapy (RT) in the management of Gorham-Stout syndrome.
Methods and Materials: In 2009 a structured questionnaire was circulated to 230 German RT institutions to assess information about the number of patients, the RT indication and technique, and the target volume definition, as well as accompanying treatments, outcome data, and early or late radiation toxicity.
Results: In November 2009 responses were available from 197 departments (85.6%): 29 university hospitals (14.7%), 89 community hospitals (45.2%), and 79 private RT offices (40.1%). Of these institutions, 8 (4.0%) had experience using RT, for a total of 10 cases in various anatomic sites. Four patients underwent irradiation post-operatively, and six patients received primary RT. The total doses applied after computed tomography–based treatment planning ranged from 30 to 45 Gy. After a median follow-up period of 42 months, local disease progression was avoided in 8 cases (80.0%). In 2 of these cases a progression occurred beyond the target volume. Acute and late toxicity was mild; in 4 patients RT was associated with Grade I side effects according to Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer criteria. The literature analysis of 38 previously published articles providing results after the use of RT in 44 patients showed stable or regressive disease in 77.3%.
Conclusions: RT may prevent disease progression effectively in Gorham-Stout syndrome in 77% to 80% of cases. Total doses ranging from 30 to 45 Gy applied after computed tomography–based treatment planning are recommended. © 2011 Elsevier Inc.

Radiotherapy, Gorham-Stout syndrome, Bone tumors, Patterns-of-care study, Benign disease.

INTRODUCTION

Gorham-Stout syndrome (GSS), synonymously named "massive osteolysis," "phantom bone," "disappearing bone disease," or "vanishing bone disease," is a rare, benign disorder of unknown etiology affecting the musculoskeletal system. Since the first description by Jackson in 1838 (1), up to 200 cases have been reported in the literature (2). In 1955 the clinical and histopathologic features were summarized by Gorham and Stout (3) in a review of 24 cases with analysis of the pathologic specimens of 8 cases.

Histologic GSS is characterized by a local intraosseous proliferation of small blood or lymphatic vessels causing a resorption of bone, which is replaced by nonmalignant fibrovascular tissue (3). The precise pathophysiologic mechanism of bone resorption remains unclear (4): a disturbance of the physiologic osteoblast–osteoclast balance due to hyperemia (5), increased hydrolytic enzyme activity caused by localized hypoxic acidosis (6), enhanced osteoclast activity associated with increased interleukin-6 levels (7), and increased osteoclast precursor activity induced by humoral factors (8) have been discussed as potential mechanisms.

GSS mostly becomes symptomatic within the first three decades of life, showing no racial, gender, or familial preference (4, 9). It may develop in any anatomic region, but it

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shows a predilection for the following sites: the skull; particularly the mandible; the rib; the shoulder; and the pelvis (3, 9, 10). Initially, subcortical or intramedullary foci are detectable, which extend over a period of months to years to contiguous bones (12) and may involve the adjacent tissue in up to 60% to 76% of cases (3, 11). The clinical course is unpredictable (9, 12), and spontaneous arrest or regression as well as rapidly progressive disease has been reported (11, 13–17). The symptoms are nonspecific, including muscular weakness or limb tenderness, and a pathologic fracture occurring after inadequate trauma is not uncommonly the initial symptom (2, 9, 10, 12). In general, the prognosis is good, with an estimated overall mortality rate of 13.3%, increasing up to 33.3% in lesions affecting the spine with associated neurologic deficits (18). The highest mortality rate, approximately 52%, is noted in cases with involvement of the thoracic skeleton due to a chylothorax caused by occlusion of the thoracic duct and respiratory compromise (18).

So far, a large variety of treatment approaches have been published, which are used alone or in various combinations. Drug therapy includes the use of bisphosphonates (2, 19–22), alpha-interferon 2b (22, 23), androgens, calcium fluoride, suprarenal or placental extracts, vitamins, and somatotropic hormone (24), as well as calcitonin, or cytotoxic drugs like actinomycin D or cisplatin (25). Surgical treatment include resection of the lesions, reconstruction with bone grafts or alloplastic prostheses in case of instability, and amputation of extremities (9, 12, 17, 18, 26–30). A sufficient analgesic effect of embolization has been reported (31). The value of radiation therapy (RT) in the management of GSS has been investigated in numerous articles, mostly single case observations (2, 6, 11, 32–69).

We summarize the results of a national patterns-of-care study being conducted by the German Cooperative Group on Radiotherapy for Benign Diseases to collect clinical information from German RT institutions and to analyze the treatment patterns. On the basis of the outcome data of the study and the results of a comprehensive literature review, we attempted to define the current role of RT in the management of GSS.

METHODS AND MATERIAL

In April 2009 a structured questionnaire developed by the German Cooperative Group on Radiotherapy for Benign Diseases was circulated to 230 German RT departments to assess data concerning the number of patients, RT indication and technique, target volume definition, dose concepts, outcome, and possible early or late toxicity of RT. In August 2009 a second questionnaire was mailed to the institutions that had not responded.

In November 2009 responses were available from 197 of 230 departments (85.6%): 29 university hospitals (14.7%), 89 community hospitals (45.2%), and 79 private RT practices (40.1%). Lacking details regarding the clinical information, treatment parameters, or incomplete follow-up data were assessed by phone calls or e-mail contact. The results of all participating institutions were analyzed from previously published and unpublished data, and they were assured of the confidentiality of the provided data.

Table 1. Institutions providing evaluable cases

Institution	No. of cases
Franziskus Hospital Bielefeld	2
Ansbach Hospital	2
University of Freiburg	1
University of Jena	1
University of Tübingen	1
Alfried Krupp Hospital Essen	1
Aschaffenburg Hospital	1
Offenbach Hospital	1

For comparison, a systematic literature research was conducted using the four international electronic databases (Medline, Embase, Current Contents, and Science Citation Index), and a conventional library search was done to identify older publications.

RESULTS

Structural data

Among the responding institutions, experiences with RT in GSS were reported from 4 community hospitals, 1 private practice, and 3 university hospitals (Table 1). Complete clinical information was available for a total of 10 patients, 5 women (50.0%) and 5 men (50.0%), with a mean age of 33.3 years (range, 22–61 years; median, 41 years). The predominant areas of involvement were the skull and the cervical spine, followed by the pelvic girdle (Figs. 1 and 2). The patients' characteristics are summarized in (Table 2).

The referral to RT was performed by various surgical and nonsurgical disciplines including surgeons, orthopedists,

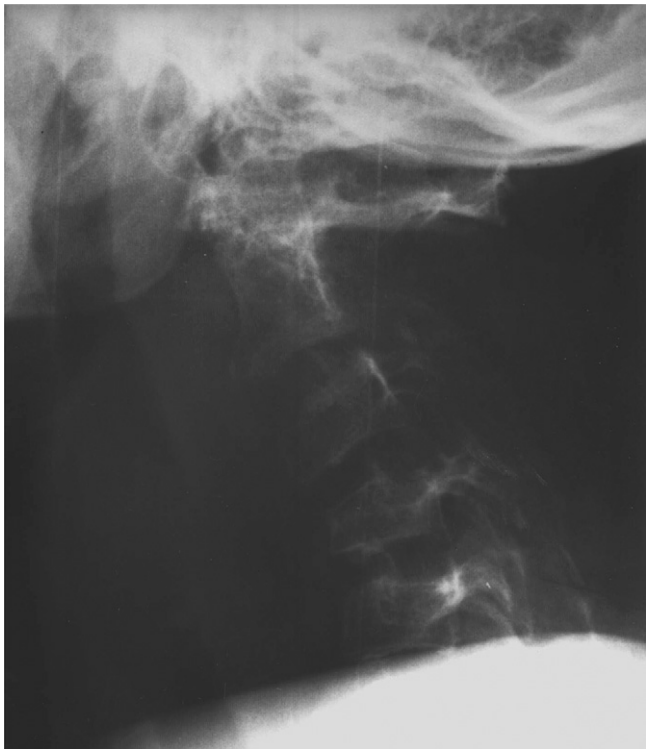

Fig. 1. Plain radiograph from lateral view of 10-year-old boy showing osseous destruction of upper cervical spine.