Bone-Grafting in Polyostotic Fibrous Dysplasia

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Background: Polyostotic fibrous dysplasia is a skeletal disease that results from somatic activating mutations in the gene GNAS in skeletal stem cells, leading to proliferation of immature osteogenic cells with replacement of normal marrow and bone with fibro-osseous tissue. Lesions may cause bone deformity or fracture. In the surgical care of polyostotic fibrous dysplasia, the role of grafting and the optimal grafting material are not clear. The purpose of this study was to evaluate the long-term survival of bone-grafting procedures in subjects with polyostotic fibrous dysplasia over time.

Methods: The operative reports and radiographs of a cohort of subjects with polyostotic fibrous dysplasia followed in a natural history study were reviewed. Twenty-three subjects (mean age at the time of enrollment, thirteen years [range, two to forty years]) with fifty-two bone-grafting procedures had a mean follow-up time of 19.6 years (range, twenty-nine months to forty-seven years). Kaplan-Meier life table estimates, Cox proportional hazard models, and t tests comparing means were performed to assess various aspects of graft survival.

Results: Kaplan-Meier curves showed a 50% estimate of survival of 14.5 years. Cox proportional hazards models showed no advantage comparing allograft with autograft or structural with nonstructural graft materials. The mean age of the patients was significantly greater ($p < 0.001$) in the subgroup of subjects in whom grafts were maintained over time (20.9 years) compared with the subgroup of patients whose grafts were resorbed over time (9.8 years).

Conclusions: Bone-grafting, including both allograft and autograft, is of limited value in ablating the lesions of fibrous dysplasia. The expectations of patients and surgeons should include the high probability of graft resorption over time with return of bone characteristics of fibrous dysplasia, particularly in younger patients. This suggests the maintenance of normal bone mechanics with implant support should be the priority of any surgical intervention.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

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Fibrous dysplasia is a rare disorder of bone resulting in fracture, deformity, and pain. It is caused by somatic activating mutations of the $G_s\alpha$ protein encoded by the gene GNAS[1-3]. Skeletal stem cells that harbor this mutation have an impaired ability to differentiate into mature osteoblasts and instead retain a fibroblast-like phenotype[4,5]. Mutated cells proliferate and replace normal bone and marrow with a generally undermineralized and structurally unsound fibro-osseous tissue[6,7]. Disease is a mosaic with a broad spectrum of clinical severity[8]. Fibrous dysplasia may be monostotic or polyostotic. Any area of the skeleton may be involved; however, the skull base and proximal parts of the femur are most commonly affected, with femoral lesions resulting in the most functional impairment[9,10]. Lesions may occur in isolation or may be associated with café-au-lait skin pigmentation and/or hyperfunctioning endocrinopathies, termed the McCune-Albright syndrome[11,12].

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Orthopaedic treatment of polyostotic fibrous dysplasia is challenging, particularly with multiple lesions or major deformity. Surgical management of the proximal part of the femur, given its structural importance and propensity for extensive involvement, often presents the greatest challenge[13-17]. Bone-grafting for ablation of fibrous dysplasia lesions was first popularized by Enneking and Gearen[13]. In 1986, this group of researchers reported good outcomes using allograft fibular strut grafts for stabilization of lesions of fibrous dysplasia in the proximal part of the femur[13]. However, none of the patients reported in that study had mechanical deformity, and the majority of the patients had monostotic fibrous dysplasia and were older than eighteen years of age[13]. The lack of deformity and monostotic disease suggests that these patients had what would be considered mild disease. The exuberance for bone-grafting following that landmark study[13] was tempered by subsequent reports. In 1987, Stephenson et al. reported on a relatively large series of forty-three patients with fibrous dysplasia (nineteen with polyostotic fibrous dysplasia) who had a total of twenty-four grafting procedures and were followed for a mean time of 10.4 years[18]. In that series, there was a distinct difference between what was reported as a satisfactory outcome between the groups of patients who were younger than eighteen years and those who were eighteen years of age or older. Although details on grafting materials and the length of time that graft was retained are lacking, the outcome for grafting was reported as satisfactory in only one of fourteen procedures in patients younger than eighteen years of age. A retrospective study from the DuPont Institute that included twenty-two subjects, all of whom were younger than eighteen years of age at presentation, found that curettage and bone-grafting using either morselized allograft or autograft did not improve the surgical results beyond what was achieved by mechanical fixation[15]. Additional reports of bone-grafting in fibrous dysplasia have included case reports and small series with short follow-up and sometimes included bone diseases other than fibrous dysplasia in the analysis[17-24]. Important factors in comparing the outcomes in these studies are the extent of fibrous dysplasia (monostotic fibrous dysplasia or polyostotic fibrous dysplasia), the age of the subjects, and the presence or absence of concomitant endocrine dysfunction as part of the McCune-Albright syndrome. Based on clinical observations in patients with polyostotic fibrous dysplasia, we hypothesized that bone-grafting in this population has a high rate of resorption and is ineffective for long-term management. To test this hypothesis, we performed a retrospective analysis to determine the outcomes of bone-graft survival in a relatively large, longstanding cohort of subjects with polyostotic fibrous dysplasia.

Materials and Methods

The database of a cohort of subjects enrolled in an ongoing, long-term study of the natural history of fibrous dysplasia or the McCune-Albright syndrome at the National Institutes of Health (NIH) was accessed. The current study was performed utilizing data collected from 1998 to 2010, including retrospective data from previous surgical procedures. All subjects had the diagnosis of fibrous dysplasia confirmed by either mutation testing or the presence of additional features of the McCune-Albright syndrome. The study was approved by the institutional review board, and informed consent or assent was obtained from all subjects and guardians.

All subjects enrolled in the study underwent evaluation for skeletal disease and endocrinopathies. Subjects with bone-grafting were identified from surgical histories and skeletal radiographs. Operative reports and serial radiographs were reviewed. Additional information was obtained by contacting patients and/or their treating surgeons.

Bone grafts were evaluated by examination of radiographs. If a subsequent grafting procedure was required at the same location, it was assumed that the previous graft had failed. Grafts were characterized as maintained if they were still visible on radiographs and appeared to have incorporated into bone (Fig. 1), partially resorbed if radiographs showed

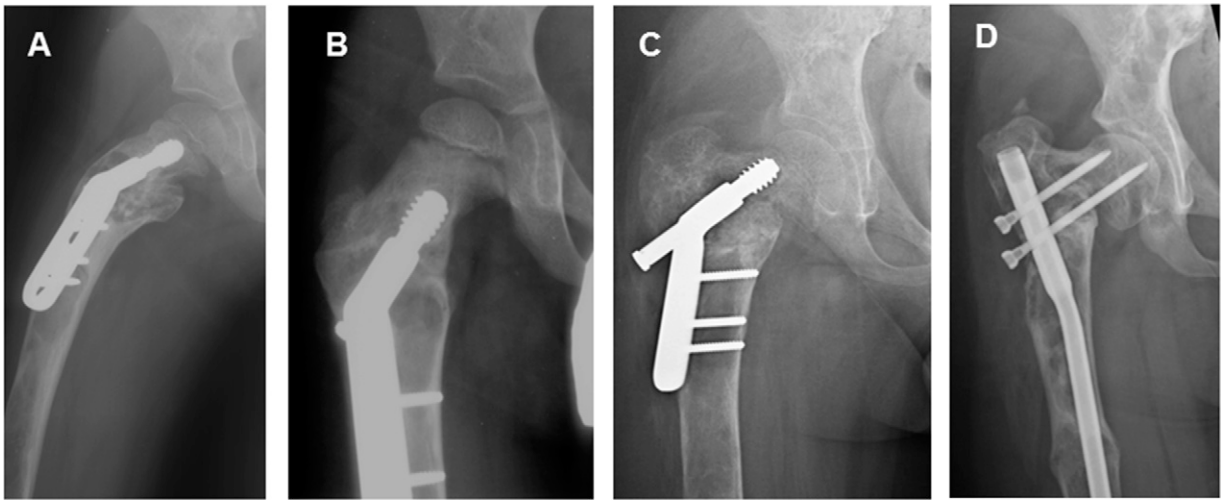

Fig. 1

Graft and implant evolution demonstrating a typical approach to restore the neck-shaft angle in proximal femoral disease using different grafting materials and devices. Grafting materials included allograft and Grafton (**Fig. 1-A**) and allograft chips (**Fig. 1-B**). Grafting material was minimally resorbed (**Fig. 1-C**), and eventually support was attempted with an intramedullary rod (**Fig. 1-D**).

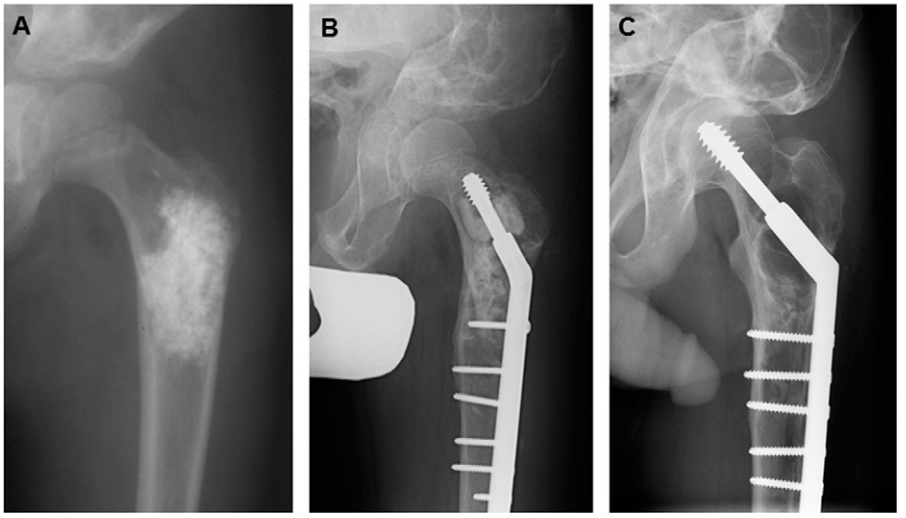

Fig. 2

Partially resorbed graft. **Fig. 2-A** The initial approach included curettage and bone-grafting with coral and iliac crest graft. **Fig. 2-B** Five years later, a hip screw and side plate as well as bone-grafting with an allograft strut and allograft chips were used. **Fig. 2-C** Eight years later, implant revision alone was performed with the lytic lesion of fibrous dysplasia visible again; the grafting material had been resorbed.

loss of the graft over time but some graft remaining (Figs. 2-A and 2-B), and completely resorbed if there was no radiographic sign of the graft (Fig. 2-C).

Survival analyses were performed using Kaplan-Meier life table estimates and Cox proportional hazard models. Student t tests were used to compare means. Significance was set at $p < 0.05$. All analyses were performed using SAS (version 9.2; SAS Institute).

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Results

Twenty-five subjects with polyostotic fibrous dysplasia were studied. The subjects underwent fifty-four bone-grafting procedures. In two patients with one graft each, documentation and imaging were insufficient to determine both graft type and graft fate, and these grafts were eliminated from the analyses. Thus, there were a total of twenty-three patients with fifty-two total grafts included in the analyses. Of these fifty-two grafts, autograft was used in sixteen procedures, allograft was used in twenty-five procedures, and both were used in five procedures; in six cases, the specific details of the materials were not in the operative report. Allograft materials included Grafton (BioHorizons), AlloMatrix (Wright), boplant, and coral, as well as human demineralized bone cubes, chips, and struts. Structural grafts were defined as those that offer support to the implanted devices and ultimately become mechanically efficient structures once incorporated into surrounding bone. The list of specific grafts is included in Table I. The bone grafts had structural properties in eighteen cases and were morselized to fill space in thirty-four cases. The mean subject age at the time of the surgical procedure was thirteen years (range, two to forty years). Forty (74%) of the grafting procedures were performed in subjects younger than eighteen years of age, and fourteen (26%) were performed in subjects eighteen years of age and older. Fifteen patients were male and ten patients were female. Endocrinopathies were present in twenty-three subjects, including eighteen with FGF23 (fibroblast growth factor 23)-mediated phosphate

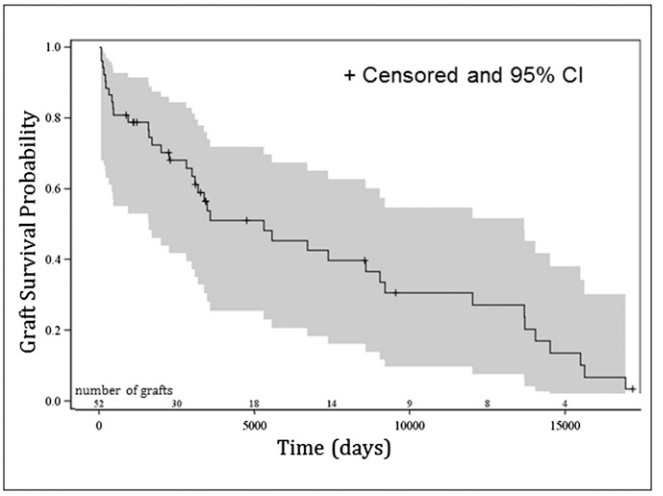

Fig. 3

Graft survival for all materials. The Kaplan-Meier survival curve for the entire population and for all materials is shown. The number of surviving grafts at specific intervals is indicated above the x axis. The time points at which data censoring took place are indicated by the plus signs. 95% CI = 95% confidence interval.

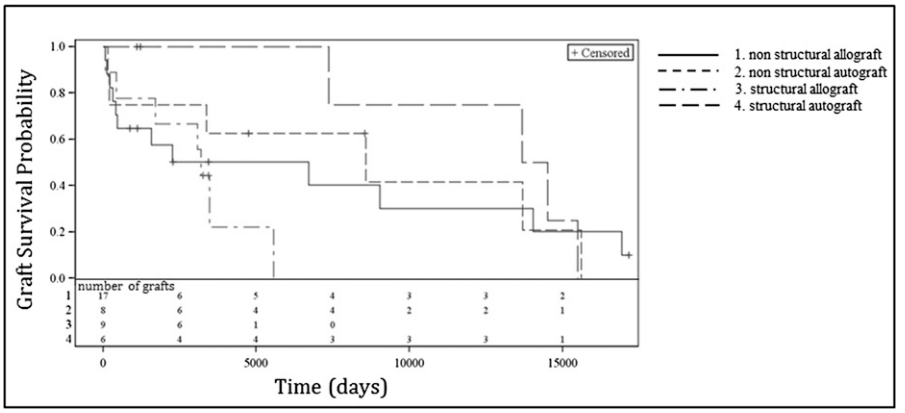

Fig. 4

Graft survival by material. The Kaplan-Meier survival curves were stratified into four groups consisting of nonstructural allograft (solid line), nonstructural autograft (small dashed line), structural allograft (dashed and dotted line), and structural autograft (large dashed line), as indicated. There was no significant difference between any of the curves, indicating no selective advantage of one type of graft over another. The number of each type of graft surviving at fixed intervals is indicated in the lower section of the panel above the x axis. The time points at which data censoring took place are indicated by the plus signs.

wasting, ten with precocious puberty, eleven with hyperthyroidism, and four with growth hormone excess. The majority of lesions were located in the proximal part of the femur (twenty-one), the tibia (three), and the proximal part of the humerus (one). Four (16%) of twenty-five subjects had had treatment with bisphosphonates prior to the surgical procedure with the intent to treat bone pain and/or to decrease the size of the fibrous dysplasia lesion. The mean alkaline phosphatase (and standard deviation) was 503 ± 413 IU/L (normal, 44 to 147 IU/L), indicating substantial disease activity. Grafts were assessed by evaluating radiographs. All but one graft was located intraosseously. Graft fate was determined in fifty-two grafts. Of these, thirty-nine (75%) were resorbed over time (included in this group were two grafts that were noted to have partial resorption), and thirteen (25%) survived and seemed to be incorporated. The mean length of follow-up was 19.6 years, with a median of 14.5 years (range, 2.4 to 47.0 years).

Kaplan-Meier survival curves for the grafts were constructed, showing an overall median survival estimate of 5302 days (approximately 14.5 years) (Fig. 3). Separate curves for different graft materials showed no significant advantage ($p > 0.05$) of any particular grafting material (Fig. 4). Furthermore, Cox proportional hazard models, used to analyze survival and the effect of covariates, assessed various clinical characteristics and graft materials and did not show any patient demographic characteristic (including the presence of any endocrinopathy and/or bisphosphonate treatment) that significantly affected graft survival ($p > 0.05$), nor was any grafting material significantly more advantageous ($p > 0.05$). However, when subjects were analyzed as the group in which the graft survived compared with the group with graft resorption, there was a significant difference ($p < 0.001$) between the groups in the age at which the grafting procedure was performed (Fig. 5). According to the t test, subjects in whom the graft was resorbed were significantly younger ($p < 0.001$) than those in whom the graft survived; the mean age was 9.8 ± 6.3 years for the patients in whom the graft was resorbed and 20.9 ± 9.6 years for the patients in whom the graft survived. Analyses of structural compared with nonstructural allografts in patients younger than eighteen years of age and in patients eighteen years of age or older showed no significant differences ($p > 0.05$) (data not shown).

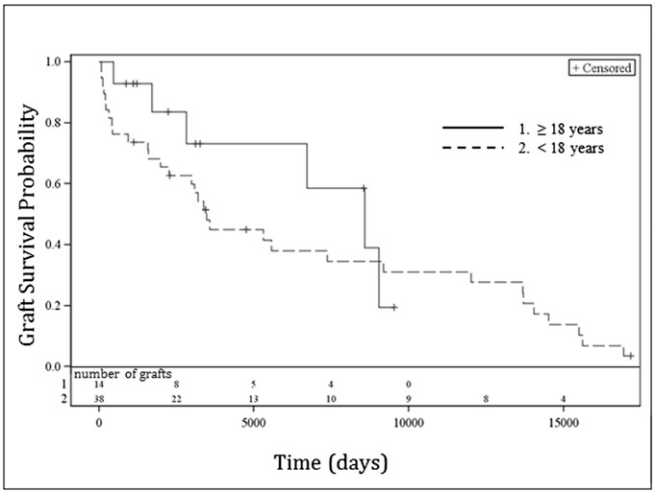

Fig. 5

Graft survival by age. Kaplan-Meier survival curves for all grafts grouped according to age at which a graft was used. The length of survival of the grafting material in subjects who received grafting at eighteen years of age or older are shown by the solid line, and survival of the grafting material for those who were younger than eighteen years of age at the time of grafting is shown by the dashed line. Time points at which data censoring took place are indicated by the plus signs.

TABLE I Summary of Patient and Graft Characteristics

Patient	Sex	Age (yr)	Site	Graft Type	Structural or Nonstructural	Concurrent Instrumentation*	Graft Fate	Length of Follow-up (yr)
1	F	7	Right femur	Morselized portion of femur	Nonstructural	Howmedica screw and sideplate with Ender nail	Resorbed	9.3
2	M	8	Left femur	Femoral allograft	Nonstructural	4.5 cortical compression screws	Maintained	9.4
		8	Right femur	Unknown	Structural	NA	Maintained	9.4
3	M	3	Left femur	Bone bank chips from femoral head	Nonstructural	NA	Resorbed	46.3
		4	Right femur	Bone chips	Nonstructural	NA	Resorbed	45.9
		6	Left femur	Cortical strips of tibia bone	Structural	NA	Resorbed	43.8
		7	Right femur	Cortical bone	Structural	NA	Resorbed	42.4
4	F	14	Left tibia	Fibular wedge	Structural	NA	Resorbed	20.2
5	M	2	Right femur	Fibular strut	Structural	Small threaded Steinmann pin	Resorbed	4.7
		2	Left femur	Fibular strut	Structural	Small threaded Steinmann pin	Resorbed	4.7
6	M	3	Right femur	Bone bank ribs	Nonstructural	NA	Resorbed	44.8
		4	Right femur	Iliac bone	Nonstructural	NA	Resorbed	43.7
		5	Right femur	Iliac bone	Nonstructural	NA	Resorbed	43.3
		5	Right femur	Cancellous bone	Nonstructural	Blount plate	Resorbed	42.8
		23	Right humerus	Freeze-dried rib, cancellous bone chips	Nonstructural	Cerclage wire	Resorbed	24.8
7	F	7	Left femur	Struts	Structural	NA	Resorbed	8.8
8	M	7	Right femur	Fibular strut, bone chips	Both	Anterior 6-0 dynamic compression plate	Resorbed	14.5
9	F	13	Right femur	Freeze-dried cortical strut	Structural	65-mm 5-hole 130° blade plate	Resorbed	9.7
		13	Right femur	Freeze-dried cortical bone	Unknown	70-mm 5-hole 95° condylar plate	Resorbed	9.5
10	M	12	Left femur	Bone bank rib	Nonstructural	NA	Maintained	47.0
11	F	18	Left femur	Crushed cancellous bone chips	Nonstructural	Zickel nail, tri-fin nail	Resorbed	19.7
		19	Left femur	Morselized freeze-dried bone bank bone	Nonstructural	Lukey wire	Resorbed	18.3
12	M	13	Right femur	Iliac crest bone	Nonstructural	NA	Maintained	21.7
		26	Right femur	Fibular strut	Structural	NA	Maintained	8.7
		29	Right femur	Fibular strut	Structural	NA	Maintained	5.7
		32	Right femur	Cancellous cubes	Nonstructural	Locking screws	Maintained	2.4
13	F	19	Left femur	Tibial strut	Structural	Blade plate	Resorbed	4.7
14	F	28	Right femur	Morselized cancellous iliac bone, reconstituted coral, bone matrix gel	Nonstructural	38-cm Richards intramedullary hip screw, 115-mm femoral head and neck screw	Resorbed	7.8

continued

TABLE I (*continued*)

Patient	Sex	Age *(yr)*	Site	Graft Type	Structural or Nonstructural	Concurrent Instrumentation*	Graft Fate	Length of Follow-up *(yr)*
15	M	4	Right femur	Unknown	Unknown	NA	Resorbed	9.8
16	M	7	Right femur	Unknown	Unknown	NA	Resorbed	8.2
		7	Right femur	Bone chips, Grafton	Nonstructural	3-hole 130° plate with 45-mm screw	Resorbed	7.7
		7	Left femur	Cancellous bone chips	Nonstructural	Lateral nail	Resorbed	7.6
		7	Right femur	Cancellous bone chips	Nonstructural	4-hole plate	Resorbed	7.3
		8	Left femur	Allomatrix	Nonstructural	Nancy nail	Resorbed	7.0
		9	Left femur	Allomatrix	Nonstructural	NA	Resorbed	6.2
17	F	15	Left femur	Bone bank bone	Nonstructural	NA	Maintained	3.0
		15	Left humerus	Unknown	NA	NA	Partially resorbed	3.0
18	M	21	Left femur	Unknown	Unknown	Kuntscher nail	Maintained	26.1
19	M	5	Right femur	Fibular strut	Structural	NA	Resorbed	8.6
		6	Right femur	Intercalary cortical bone, Grafton crunch, cancellous cubes	Nonstructural	NA	Resorbed	6.9
		9	Right femur	Freeze-dried corticocancellous fibular strut, cancellous cubes	Both	NA	Resorbed	4.3
20	M	10	Left femur	Fragmented bone bank rib	Nonstructural	NA	Resorbed	38.4
		10	Right femur	Ground cancellous boplant (soaked in thrombin)	Nonstructural	NA	Resorbed	38.3
		15	Right femur	Unknown	Unknown	NA	Resorbed	34.1
		16	Right tibia	Cortical tibia bone, fragmented bone bank rib	Both	Compression plate	Resorbed	32.8
		40	Right femur	Cortical strut	Structural	NA	Maintained	8.9
21	F	23	Left femur	Corticocancellous iliac crest bone	Nonstructural	Zickel nail	Resorbed	23.5
		23	Right femur	Corticocancellous iliac crest bone	Nonstructural	Zickel nail	Resorbed	23.4
22	M	24	Right femur	Unknown	Unknown	NA	Resorbed	14.6
		32	Right femur	Unknown	Unknown	NA	Maintained	6.1
23	M	11	Left femur	Cortical cancellous bone	Structural	Richards intermediate hip screw	Resorbed	13.8
		15	Left femur	Iliac crest, Interpore-500 coral	Nonstructural	NA	Resorbed	8.4

*NA = not applicable.

Discussion

These data demonstrate that in relatively young subjects with polyostotic fibrous dysplasia, the majority of bone grafts failed to incorporate, and the lesions eventually returned to a dysplastic state. Within a time frame of just more than fourteen years, half of the patients had complete loss of the graft. This suggests that bone-grafting is of limited value in younger patients with polyostotic fibrous dysplasia and not likely to induce a reliable or durable biological response. Surgical planning should look more toward restoration of the mechanical axes and support of the bone with appropriate implant fixation.

The work of Enneking and Gearen, which is widely cited and popularized the use of fibular allograft struts in patients with fibrous dysplasia, examined a population of mostly skeletally mature patients, the majority of whom had monostotic fibrous dysplasia (ten with monostotic fibrous dysplasia and five with polyostotic fibrous dysplasia)[13]. Yet even in that study, fibular grafts failed in two of five subjects with polyostotic fibrous dysplasia. Our study included a larger proportion of younger subjects, all of whom had polyostotic fibrous dysplasia, and found that allograft and autograft bone disappeared, with no selective advantage to either material. Thus, given these data, the application of the principles that appeared to be effective in older subjects with monostotic fibrous dysplasia to younger patients with polyostotic fibrous dysplasia or the McCune-Albright syndrome is not warranted.

Although the length of graft survival was significantly less in subjects younger than eighteen years of age, the presence of an endocrinopathy did not independently contribute to graft loss. A greater degree of graft loss in younger subjects may be because fibrous dysplasia lesions are typically more active in younger patients. Fibrous dysplasia lesions have long been reported to burn out with age. This concept is supported by recent evidence demonstrating that, in fibrous dysplasia, there are proportionally more active mutation-bearing bone cells in younger patients and that the drop-out of mutation-bearing cells can be accompanied by the emergence of microscopic areas of normal-appearing bone[25]. This effect presumably results from apoptosis of mutant skeletal progenitor cells, while adjacent normal progenitor cells self-renew and enable formation of a normal skeletal structure. The radiographic correlate of this finding is the observation that fibrous dysplasia lesions tend to become more sclerotic with age. Thus, in younger patients, the effect that fibrous dysplasia has on adjacent normal bone, in terms of erosion and destruction of adjacent normal structures, seems to be mimicked by the effect of fibrous dysplasia cells on bone graft material. Although the goal of curettage, which precedes bone-grafting, is to clear the lesion of these diseased, mutation-bearing cells, the fact that grafting material is eroded suggests that, in practice, removing all of the mutant cells is not possible and is not advisable to attempt. An approach to increase the likelihood of clearing the lesions of mutation-bearing cells so as to enhance graft incorporation is the addition of cryoablative techniques. Although two series studying this technique have included subjects with fibrous dysplasia[21,26], neither suggested that this technique improved the outcome in younger patients with polyostotic fibrous dysplasia, the group most in need of ablation of residual mutation-bearing cells. Therefore, in deciding which surgical approach to take, surgeons must determine which set of data is more applicable to the patient under consideration: for an older patient with monostotic fibrous dysplasia, or for a younger patient with polyostotic fibrous dysplasia. The recent assertion offered in surgical series and expert opinion reports that bone-grafting should be abandoned in younger patients with polyostotic fibrous dysplasia[17,27-29] is supported by the current study.

Optimal surgical management of femoral fibrous dysplasia has not been determined. The age of the patient and the location, size, and biological behavior of the lesions all influence the selection of the type of intervention. The poor physical qualities of the dysplastic bone make conventional internal fixation devices such as plates and screws less effective. Stable fixation is a technique with the potential to allow early weight-bearing, to decrease chronic bone pain at rest and with weight-bearing, and to improve function. Our current recommended practice (albeit without peer-reviewed evidence of its effectiveness) is to utilize intramedullary nailing in the surgical procedure for severe fibrous dysplasia involvement of weight-bearing long bones. Intramedullary nailing provides long-term stabilization of widely affected femora, preventing fractures and major progressive deformities. It may be used acutely for fracture treatment or in elective surgical procedures. Interlocking intramedullary nailing with neck cross-pinning to control rotation may improve functional results and prevent deformity by stabilizing mechanical alignment and sharing load to allow early rehabilitation. The newly available small-diameter pediatric interlocking intramedullary nails provide new treatment options for young patients.

The strengths of this study included a relatively large cohort and a robust follow-up period. Subjects were well characterized with regard to endocrine dysfunction and were heterogeneous in both age and grafting material. The subject numbers were necessarily limited given the disease rarity; however, the population provided sufficient power for analyses of the primary outcomes of interest, including the effect of age on graft survival. The subject numbers and the variability in the length of follow-up limited the ability to perform additional subanalyses examining the effects of other subject characteristics on graft outcomes. It is therefore possible (but unlikely) that if the subgroups of subjects with various types of grafting material, surgical techniques, or specific aspects of endocrine dysfunction were larger, differences between the survivals of various materials may have been demonstrated. The use of bisphosphonates by four subjects is a potential confounding variable. Although the effects of bisphosphonates on fibrous dysplasia have not been definitively determined, available data suggest that these medications do not improve fibrous dysplasia appearance or bone quality and would thus not be expected to have an impact on graft survival[30].

The limitations of this study included the inability to accurately determine the specific indications for the initial or

repeat operation(s) or to directly assess pathological fractures in relationship to bone-grafting. This is because the orthopaedic care was not performed at the NIH, and those data were collected retrospectively as part of a natural history study. The data collection tool did not capture data of sufficient detail to answer these questions. The evaluation of graft fate was also limited to the assessment of radiographs. Important potential confounders include the inherent bias of retrospective design and referral bias at the NIH, which may reflect a more severely affected population. Studies in diseases with broad clinical phenotypes such as fibrous dysplasia or the McCune-Albright syndrome are frequently confounded by heterogeneity in patient cohorts, which may limit generalizability of results. As is typical in fibrous dysplasia or the McCune-Albright syndrome, there was clinical heterogeneity among the subjects in this analysis with regard to disease severity and presence of endocrinopathies. The impact of specific endocrinopathies on graft fate and other clinical outcomes in fibrous dysplasia is unknown and requires additional, larger studies to determine.

In summary, bone-grafting in young patients with polyostotic fibrous dysplasia is of very limited value. Further research is needed to determine the role of additional techniques such as metallic implant support in surgical management of fibrous dysplasia lesions, particularly in younger patients with higher disease burden. ■

NOTE: This article is dedicated to the memory of the first author, the late Dr. Arabella Leet (1965-2013), who died suddenly and tragically during the preparation of the manuscript.

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