The Biological and Biomechanical Effects of Irradiation on Anterior Spinal Bone Grafts in a Canine Model*

BY SANFORD E. EMERY, M.D.†, MARK S. BRAZINSKI, M.D.†, ANURADHA KOKA, M.D.†, JAY S. BENSUSAN, M.S.†, AND SHARON STEVENSON, D.V.M., PH.D.†, CLEVELAND, OHIO

Investigation performed at the Department of Orthopaedics, Case Western Reserve University, Cleveland

ABSTRACT: We evaluated the effects of irradiation on the healing of anterior vertebral strut grafts with use of a canine model. Through a left thoracotomy, a partial corpectomy of the seventh thoracic vertebra and autogenous iliac strut-grafting from the sixth to the eighth thoracic levels were performed in twenty-two adult beagles. Four groups were established: Group I (control) received no irradiation, Group II received preoperative irradiation, Group III received postoperative irradiation that began on the third postoperative day, and Group IV received postoperative irradiation that began on the twenty-first postoperative day. The irradiation protocol was five treatments of 500 centigray three times a week for a total of 2500 centigray. Fluorochromes were administered at regular intervals postoperatively. The beagles were killed three months postoperatively, and non-destructive biomechanical testing was done to evaluate the stiffness of the construct. The quality of healing at the junctions of the graft with the sixth and eighth thoracic vertebrae, the degree of revascularization of the graft, and the amount of new-bone formation were evaluated histologically.

Statistical evaluation of the biomechanical data revealed no significant difference in the stiffness of the construct between Groups I, II, and IV. The specimens from Group III were significantly less stiff than those from Group I (the control group) in torsion ($p = 0.03$) and left lateral bending ($p = 0.04$) and than those from Group II in flexion ($p = 0.02$) and left lateral bending ($p = 0.005$). Grafts that had been irradiated immediately after implantation (Group III) had the lowest histological scores for quality of healing, degree of revascularization, and new-bone formation ($p < 0.05$).

CLINICAL RELEVANCE: Patients who have a spinal tumor that will be treated with an anterior corpectomy and arthrodesis with anterior bone strut-grafting often need perioperative irradiation. The timing of the irradiation has important effects on the quality of healing of the vertebral strut graft. Preoperative irradiation may not adversely affect healing of these anterior interbody strut grafts, but immediate postoperative irradiation has severe adverse effects. A delay in the postoperative irradiation of the spine may be indicated to promote successful fusion of the anterior interbody graft.

Metastatic or primary tumors of the spine may necessitate anterior decompression of the neural elements followed by insertion of a bone strut for arthrodesis. Many of the patients who have these tumors need perioperative irradiation to the operative site as part of the treatment for the underlying malignancy. The effects of perioperative irradiation have been studied in experimental and clinical settings[2,3,6,10,18,19]; however, this work was done in long bones rather than on the spine. Bonarigo and Rubin found that irradiation before fractures were created experimentally led to non-unions and that irradiation after the fractures had been created led to delayed unions in the long bones of rats. Hayashi and Suit demonstrated that the deleterious effects of irradiation on callus formation in mice were dose and fractionation-dependent. Green et al. reported decreased periosteal osteoblastic proliferation, formation of cartilage and osteoid, and vascularity at the sites of irradiated tibial fractures in rats. Albrektsson et al. and Jacobsson et al. used their *in vivo* titanium bone chamber to observe the response of long bones to irradiation. They noted that mature bone was relatively resistant to irradiation but that immature bone and reparative bone were quite sensitive. Unlike Green et al., they did not note any major vascular changes.

Biomechanical studies[10,13] have demonstrated decreased strength of healing of long bones in animals that received postoperative irradiation to fractures that had been created by either open or closed methods. Datta and Saha showed that preoperative irradiation was more deleterious than postoperative irradiation with regard to the strength of healing in ulnae after osteotomies in rabbits.

Studies have been done regarding the survival of cancellous mandibular bone grafts after irradiation. Marx emphasized hypoxic, hypocellular, and hypovas-

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†Department of Orthopaedics, Case Western Reserve University, 2074 Abington Road, Cleveland, Ohio 44106.

cular changes in his study. Marciani et al. placed cancellous grafts in pre-irradiated mandibular beds of dogs and monkeys; these grafts healed, although there were changes in the marrow to a mix of fibrofatty and hematopoietic tissue.

To our knowledge, no experimental studies have investigated the effects of irradiation on anterior bone grafts in the spine. Data from experiments on long bones probably cannot be extrapolated to the vertebrae since the cancellous bone of a vertebral body has a large surface area with an excellent blood supply compared with the cortical bone of the appendicular skeleton. Primary anterior strut-grafting for vertebral osteomyelitis can be performed successfully after adequate débridement[4], but this procedure is not recommended for infections in long bones. It was hypothesized that this healing capability of the vertebrae may also allow successful arthrodesis despite the use of irradiation.

Clinical experience provides some retrospective data on the healing of anterior vertebral grafts that had been subjected to irradiation. Fielding et al. reported a survey from the Cervical Spine Research Society of twenty patients who had a spinal neoplasm that had been treated with anterior decompression and strut-grafting, but only ten had received irradiation. Eight of these ten patients had an intact graft at an average of three years postoperatively; however, roentgenographic union was not specifically addressed. Roy-Camille et al. studied the healing of eight corticocancellous grafts, of which five were vertebral strut grafts, after various doses of postoperative irradiation. All of these grafts healed and the authors concluded that there was no increased risk of pseudarthrosis from perioperative irradiation. Only four patients in the series of Siegal et al. had anterior grafting and irradiation, and no mention was made of roentgenographic healing.

These clinical reviews make it difficult to isolate the effects of irradiation on the healing of bone grafts in the spine given the different anatomical sites, types of tumors, operative procedures (including the use of internal fixation), and irradiation protocols that were used in the management of the patients. The goal of the present study was to evaluate the effects of the timing of the irradiation on the healing of canine anterior spinal bone grafts with all other variables kept constant.

Materials and Methods

The protocol was fully approved by the institutional animal care and use committee. Twenty-three adult, female beagles of similar age and weight were treated with the operative procedure while under general anesthesia and with use of a sterile technique. An infection developed one week postoperatively in one of the beagles that was assigned to the delayed-irradiation group (Group IV), and this beagle was not included in the study. One animal that received immediate postoperative irradiation (Group III) was erroneously killed one week early and was eliminated from biomechanical testing but was used for histological study. The graft in one other beagle was transected during harvest; this dog was in the control group (Group I) and the specimen was used for histological purposes only. Thus, twenty specimens were tested biomechanically and twenty-two were examined histologically.

The operative procedure involved a left thoracotomy with removal of most of the seventh rib. The segmental vessels at the level of the sixth and seventh thoracic vertebrae were coagulated, and a partial corpectomy was performed at the level of the seventh thoracic vertebra with use of a high-speed burr. A shell of bone was left dorsally to protect the neural elements; no neurological deficits occurred. Bone was also maintained on the far lateral wall and ventrally so that a trough was created in the body of the seventh thoracic vertebra but the segments were not totally destabilized. With use of the burr, the discs between the sixth and seventh and the seventh and eighth thoracic vertebrae, as well as the inferior end-plate of the sixth thoracic vertebra and the superior end-plate of the eighth thoracic vertebra, were removed to expose bleeding subchondral bone. Conical impressions were made at each end of this trough so that the graft could be countersunk and locked into place.

At the same operation, through a separate incision, a full-thickness tricortical strut graft was taken from the left iliac crest of the animal. After careful measurement, the graft was trimmed to the appropriate size of the trough and was carefully impacted into place. A stable construct was obtained in all dogs. No internal fixation was used. Antibiotics were given for approximately forty-eight hours postoperatively.

The beagles were weighed daily and the daily food intake was monitored by the veterinary staff perioperatively and during the radiation treatments. The animals were allowed free activity.

Fluorochromes were administered intravenously during the postoperative period: DCAF (twenty milligrams per kilogram of body weight) was given on the fourteenth and twenty-fourth days; xylenol orange (ninety milligrams per kilogram of body weight), on the thirty-fourth and forty-fourth days; doxycycline hyclate (five milligrams per kilogram of body weight), on the fifty-fourth and sixty-fourth days; and alizarin complexone (twenty-five milligrams per kilogram of body weight), on the seventy-fourth and eighty-fourth days.

Four experimental groups were established. Group I (six beagles) was the control group and received no irradiation; Group II (five beagles) received preoperative irradiation, with the last irradiation session performed on the day before the operation; Group III (six beagles) received immediate postoperative irradiation, with the irradiation sessions started on the third postoperative day; and Group IV (five beagles) received delayed postoperative irradiation, with the irradiation

TABLE I
HISTOLOGICAL SCORING SCALE FOR HEALING AT THE GRAFT-VERTEBRAL BODY JUNCTIONS

Score (Points)	Tissue Present
7	Bone only
6	More bone than fibrocartilage
5	More fibrocartilage than bone
4	Fibrocartilage only
3	More fibrocartilage than fibrous tissue
2	More fibrous tissue than fibrocartilage
1	Fibrous tissue only
0	Empty cleft

sessions started three weeks after the operation.

The irradiation protocol for Groups II, III, and IV was the same. Our goal was to deliver the equivalent of 3000 centigray of radiation to the spine, which is a typical dose for the treatment of metastatic disease. Rather than use ten sessions of 300 centigray each, as is often employed clinically, we used five sessions of 500 centigray each on an alternate-day basis so as to minimize the administration of anesthesia and the transportation of the dogs. The dose of 2500 centigray that was delivered with this schedule is equivalent to the dose of 3000 centigray that is administered with the use of a daily treatment schedule[12].

All animals were killed three months after the operation. After death, the aorta of each animal was cannulated with injection of either India ink or barium. The spine was carefully removed from the disc space of the fifth and sixth thoracic vertebrae to the level of the eighth and ninth thoracic vertebrae, so as to include the entire two-level arthrodesis. Soft tissues were removed, and the specimen was kept moist for transport to the biomechanics laboratory.

Biomechanical Analysis

All testing was done within twenty-four hours of harvest of the specimen. The ends of the specimen were potted in polymethylmethacrylate and tested on a universal testing machine (Instron, Canton, Massachusetts). This was non-destructive testing to evaluate the stiffness of the construct rather than the load to failure[16]. Although stiffness does not equal strength, we believe that an increase in stiffness reflects a more effective incorporation of the graft. This non-destructive testing method allowed for histological examination of the specimens after multiple-mode biomechanical testing. Each specimen was sequentially subjected to loading in each of six modes: flexion to 3 degrees of bending, left lateral bending to 3 degrees of angulation, extension to 3 degrees of bending, right lateral bending to 3 degrees of angulation, axial compression to 0.5 millimeter of displacement, and torsion to 3 degrees of rotation. Load-deflection records were determined for each mode with use of a rate of loading of 0.3 degree per second. Each specimen was cycled three times before the final record was obtained.

Histological Preparation and Analysis

After biomechanical testing, anteroposterior and lateral roentgenograms were made with a Faxitron x-ray cabinet (Hewlett-Packard, Atlanta, Georgia). The entire specimen was then processed through graded strengths of ethanol and xylene and was embedded in methylmethacrylate. Sections, 300 micrometers thick, were cut with an Isomet saw (Buehler, Lake Bluff, Illinois) and ground and polished to a thickness of 150 micrometers. Alternate sections were stained with toluidine blue, and the remaining sections were left unstained for fluorochrome analysis.

To allow an evaluation of healing at each end of the graft, longitudinal sections were obtained of the two graft-vertebral body junctions for all specimens. Two or three sequential sections of each junction were examined to avoid a sampling error. Transverse sections were taken through the middle portion of the body of the seventh thoracic vertebra, which included the middle portion of the iliac graft. This cross section was evaluated for revascularization and new-bone formation within the graft.

Two of us (S. E. E. and M. S. B.) reviewed all slides histologically, in a blinded fashion. Many of the specimens were in various stages of enchondral bone healing at the junctions, which made an absolute quantitative evaluation of healing unrealistic. A scale of 0 to 7 points was established for the quality of healing at the graft-vertebral body junctions on the basis of the predominant type and amount of tissue present (Table I). A score of 7 points indicated that only bone was present at the junction; 6 points, more bone than fibrocartilage; 5 points, more fibrocartilage than bone; 4 points, only fibrocartilage; 3 points, more fibrocartilage than fibrous tissue; 2 points, more fibrous tissue than fibrocartilage; 1 point, fibrous tissue only; and 0 points, an empty cleft. Scores for the proximal and distal junctions were added to obtain one score for junction-healing for each animal. The scores for both junctions, rather than only the lowest score, were included because our goal was to assess the biological activity of the entire construct for the different groups.

Revascularization and new-bone formation were evaluated for the longitudinal sections as well as for the cross sections. Both revascularization and new-bone formation were graded on a scale of 0 to 3 points, with 0 indicating no activity and 3 points, the maximum amount of revascularization or new-bone formation observed. Thus, three scores were determined for both revascularization and new-bone formation (from the two junctions and from the cross section), and these three scores were added to obtain one score for each animal. Unstained longitudinal sections and cross sections for each animal were examined with ultraviolet light microscopy for fluorochrome analysis. The amount and type of

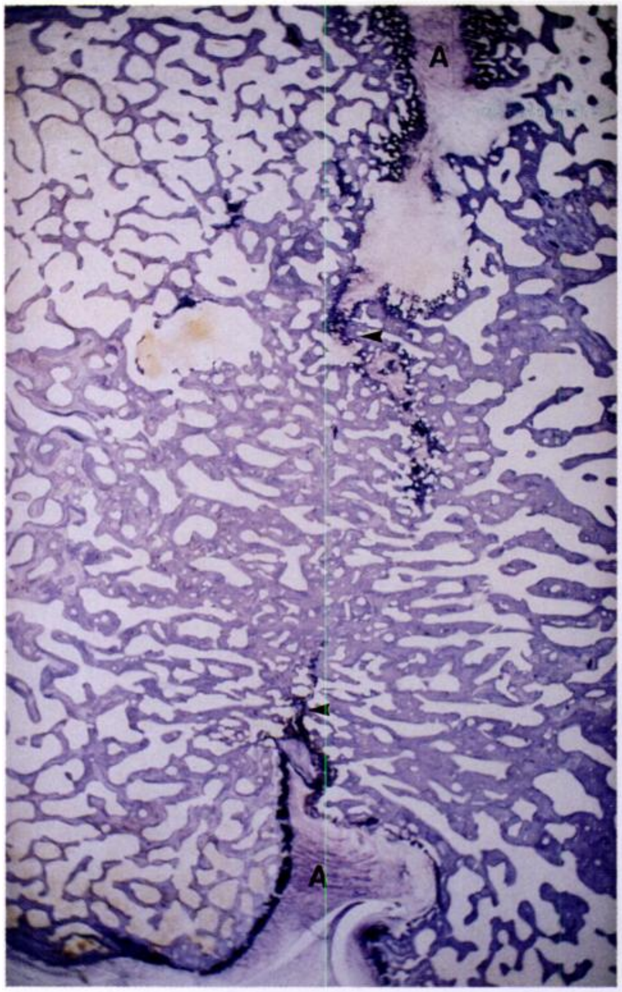

FIG. 1-A

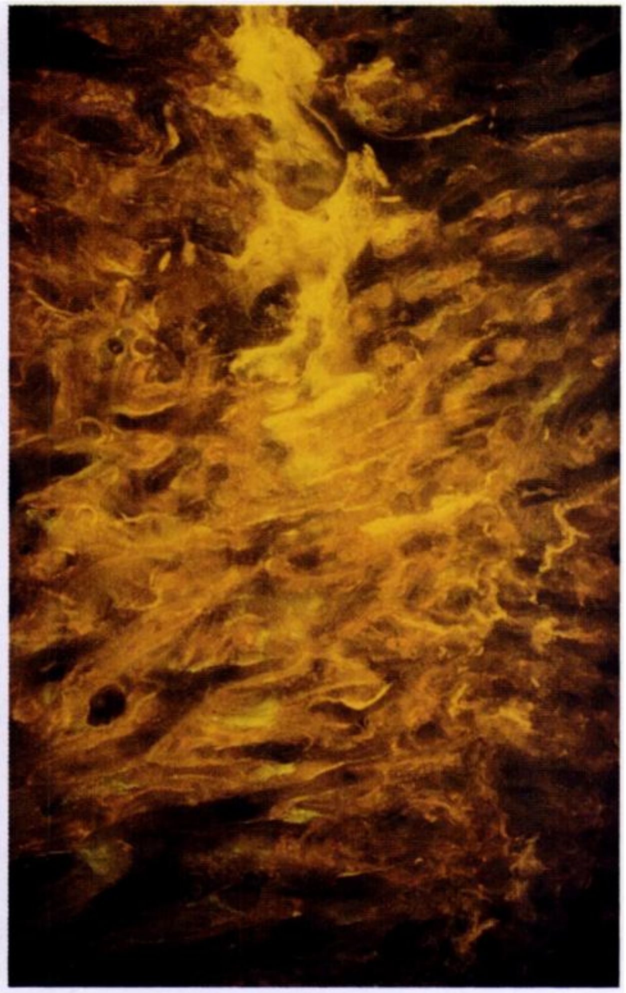

FIG. 1-B

Figs. 1-A and 1-B: Histological section of a graft-vertebral body junction from a control animal (Group I).

Fig. 1-A: Low-power longitudinal section showing excellent healing with bridging bone at the interface. There are remnants of anulus fibrosus (A). The boundaries of the graft are marked (arrowheads). Injection was done with barium, which is not seen well at this power. This junction received a histological score of 7 points (toluidine blue and barium injection, × 2).

Fig. 1-B: Fluorochrome longitudinal section. All four fluorochromes are present as shown by the green, orange, yellow, and red. This large quantity of colors indicates a substantial amount of fluorochrome uptake throughout the postoperative period and thus new-bone formation. The diffusely staining yellow structure is mineralized fibrocartilage (× 8).

fluorochromes present were analyzed qualitatively for comparison between the experimental groups.

Statistical Analysis

The biomechanical data were compared with use of analysis of variance, with a p value of less than 0.05 considered significant. The non-parametric Mann-Whitney U test was applied to the histological score for the healing at the junction, the degree of revascularization, and the degree of new-bone formation. Again, a p value of less than 0.05 was considered significant.

Results

The animals tolerated the procedure well, and the irradiation protocol had no adverse effects on appetite or body weight. There was no evidence of dislodgement of the graft at the time of harvest. A slight lateral shift in the spine was noted at the time of harvest in one animal from Group III, but the graft appeared to be grossly healed.

Biomechanical Data

There was no significant difference in the mean stiffness values between Groups I, II, and IV for any of the six modes of testing. However, the specimens from the animals that had received immediate postoperative irradiation (Group III) were significantly less stiff in torsion ($p = 0.03$) and left lateral bending ($p = 0.04$) than the specimens from the control group (Group I) (28 ± 17 and 83 ± 44 newton-millimeters per degree, respectively, for torsion, and 30 ± 13 and 98 ± 60 newton-millimeters per degree, respectively, for left lateral bending). Group III was also significantly less stiff in flexion ($p = 0.02$) and left lateral bending ($p = 0.005$) than Group II (32 ± 18 and 199 ± 133 newton-millimeters per degree, respectively, for flexion, and 30 ± 13 and 131 ± 66 newton-

TABLE II
BIOMECHANICAL DATA

Group	No. Tested	Flexion* (Nmm/Degree)	Left Lateral Bending* (Nmm/Degree)	Right Lateral Bending* (Nmm/Degree)	Extension* (Nmm/Degree)	Compression* (Nmm)	Torsion* (Nmm/Degree)
I	5	164 ± 53	98 ± 60	111 ± 72	170 ± 87	753 ± 576	83 ± 44
II	5	199 ± 133	131 ± 66	161 ± 153	194 ± 99	434 ± 162	72 ± 41
III	5	32 ± 18†	30 ± 13†‡	42 ± 10	86 ± 32	268 ± 54	28 ± 17‡
IV	5	103 ± 29	68 ± 33	79 ± 54	175 ± 69	623 ± 227	42 ± 17

*Values are given as the mean and the standard deviation.
†Significant difference between Groups II and III ($p < 0.05$).
‡Significant difference between Groups I and III ($p < 0.05$).

millimeters per degree, respectively, for left lateral bending) (Table II).

Plain Roentgenographic Data

The roentgenographic findings generally correlated with the histological findings but were thought to be a less accurate reflection of the process of enchondral ossification at the graft-vertebral body junctions. Plain roentgenograms did show slight collapse of the graft in two of the animals in Group III. One of these specimens appeared roentgenographically to have a non-union at both junctions and the other had some healing at the

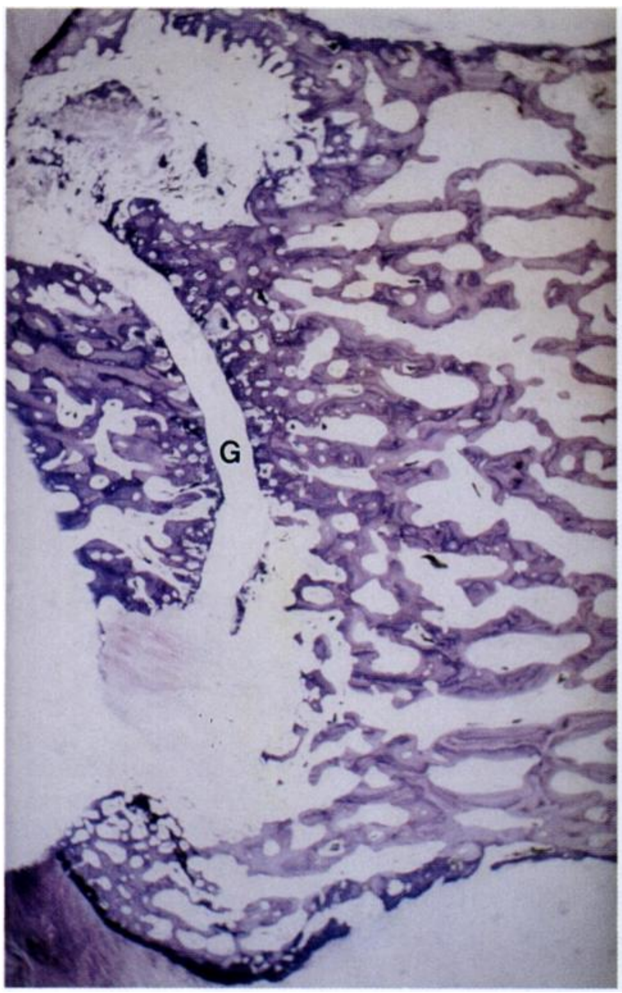

FIG. 2-A

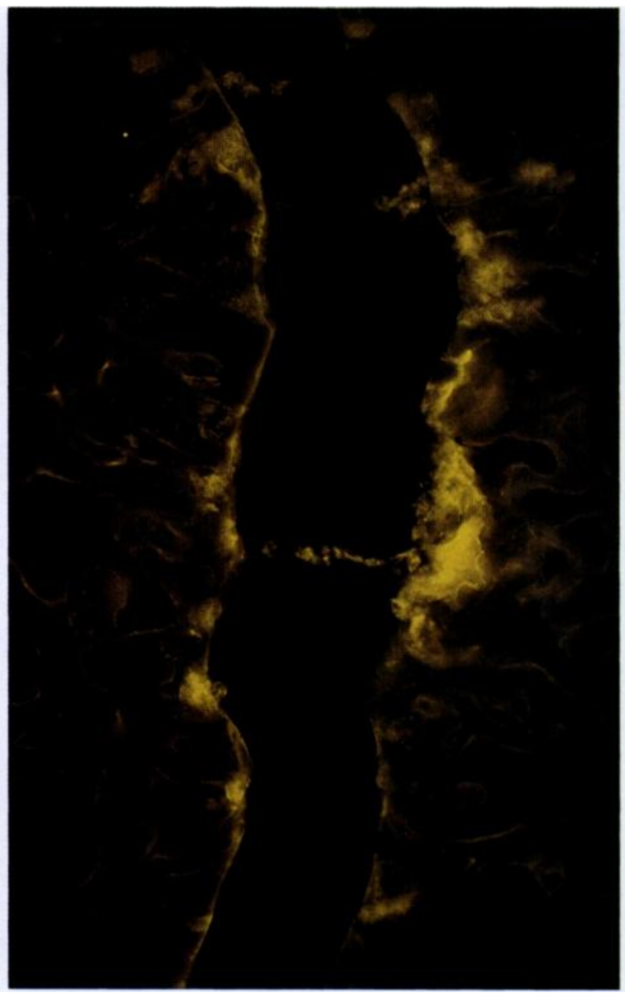

FIG. 2-B

Figs. 2-A and 2-B: Histological sections of a graft-vertebral body junction from an animal that received immediate postoperative irradiation (Group III).

Fig. 2-A: Longitudinal section showing a gap remaining between the host bone and the bone graft (G). There is a paucity of India ink-filled vessels throughout the section. The histological score was 0 (toluidine blue and India ink, × 2.5).

Fig. 2-B: Fluorochrome longitudinal section showing a small amount of yellow color. This represents an uptake of tetracycline, which was given on the fifty-fourth and sixty-fourth postoperative days. The dark green is background color and does not represent fluorochrome uptake. The minimum amount of fluorochrome uptake shows that there has been almost no new-bone formation (× 8).

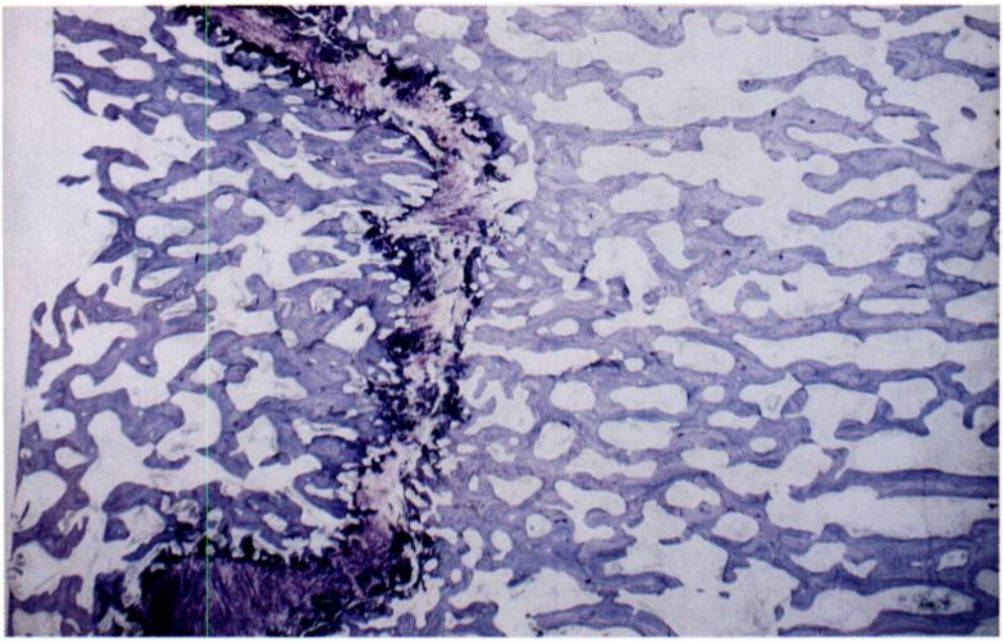

FIG. 3

Longitudinal section of the graft-vertebral body junction from an animal that received delayed postoperative irradiation (Group IV). Although somewhat disorganized, there is fibrocartilaginous healing of the entire junction. The histological score was 4 points (toluidine blue and barium injection, × 2.5).

proximal junction only. The biomechanical data for these two specimens were similar to the data for the three other specimens in Group III.

Histological Data

Histological study of the graft-vertebral body junctions showed changes that ranged from no cellular activity to those that progressed across the spectrum of enchondral ossification (Figs. 1-A through 4). Several junctions had some combination of fibrous tissue, fibrocartilage, and bone. Equal scores were given for the proximal and distal junctions in eight specimens, and the junctions varied by only 1 point in another eight; the junctions in the remaining six specimens varied by 2 or

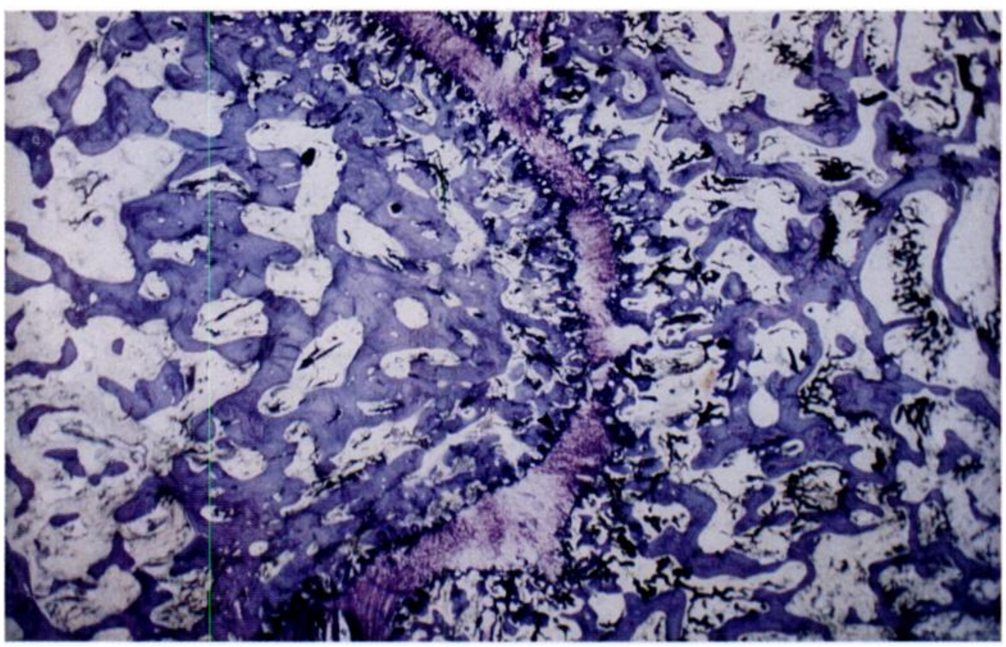

FIG. 4

Longitudinal section of a graft-vertebral body junction from an animal that received preoperative irradiation (Group II). There is well organized fibrocartilage bridging the entire graft-host interface, with tidemarks of mineralizing cartilage evident (arrowhead). India ink is present throughout the graft and the adjacent vertebral body. The histological score was 4 points (toluidine blue and India ink, × 2.5).

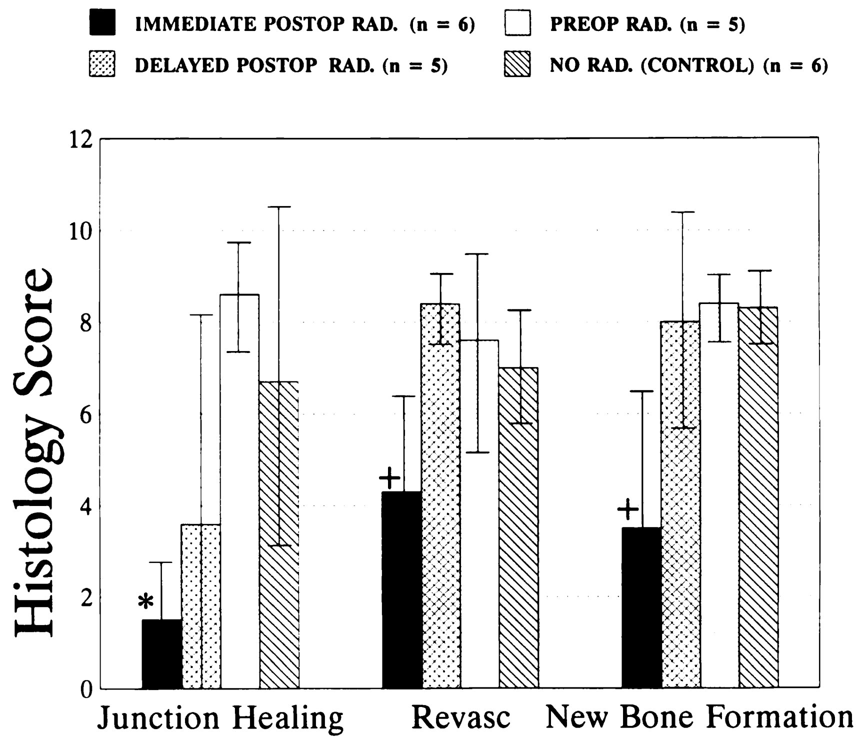

FIG. 5

Bar graph of the histological scores. The data are given as the mean and the I bars indicate the standard deviations. An asterisk = a significant difference between Groups I and III ($p = 0.02$) and between Groups II and III ($p = 0.006$), and a plus sign = a significant difference between Group III and the remaining three experimental groups ($p < 0.05$).

more points. The most consistent group with respect to the scores at the proximal and distal junctions was Group III, in which the junctions in one specimen varied by 1 point and those in the remaining five specimens had equal scores.

Histological evaluation of the cross sections showed that all grafts in Groups I, II, and IV had healed circumferentially to the sides of the partially corpectomized seventh thoracic vertebra. In contrast, three of the six grafts in Group III had a predominant mix of fibrous and fibrocartilaginous tissue around the graft; the remaining three grafts in Group III had osseous healing with small areas of fibrocartilage evident.

Group II had the highest histological scores for quality of healing at the junctions, followed by Groups I, IV, and III sequentially (Fig. 5). Non-parametric statistical analysis showed that the scores for Group III were significantly lower than the scores for Groups I and II ($p = 0.02$ and 0.006, respectively). There was no significant difference between healing at the junctions when Groups III and IV were compared. There was a statistical trend for the histological scores at the junctions in Group IV to be lower than those in Group II ($p = 0.09$).

The scores for revascularization and new-bone formation were significantly lower for Group III when compared with the three remaining experimental groups ($p < 0.05$) (Fig. 5). No other comparisons were significant.

Fluorochrome analysis was notable for the relative homogeneity of new-bone formation in Groups I, II, and IV (Fig. 1-B). Two of the five specimens in Group IV showed a relative predominance of the first fluorochrome given at two weeks and at three and one-half weeks postoperatively, but otherwise no major differences in these three groups were detected. For five of the six specimens in Group III, however, there was a marked decrease in fluorochrome deposition both at the junctions and at the cross-sectional locations (Fig. 2-B).

Discussion

The present model was designed to simulate an anterior decompression with strut-grafting, such as would be used to treat a spinal neoplasm with compression of the spinal cord in the clinical setting. The partial corpectomy in our series was probably less destabilizing than are many tumors, as we left a posterior shell of bone to protect the dogs from neurological injury and to minimize the resulting instability. We removed a portion of the seventh rib laterally as well as the head of the seventh rib for exposure, which was probably destabilizing to some degree. This is comparable with our clinical practice, however, as we commonly remove much of the rib in thoracotomy procedures and always remove the head of the rib when an anterior decompression of the spinal canal is performed, in order to visualize the appropriate pedicle.

Our biomechanical and histological data show that the timing of irradiation is critical with respect to the effects on healing of the bone graft. Early postoperative irradiation resulted in a substantial reduction in stiffness of the spinal construct. This correlated well with an absent or inferior healing response at the graft-vertebral body junctions and with less revascularization and new-bone formation in the graft. The group in which irradiation had been delayed for three weeks (Group IV) had a slightly inferior histological picture, with less well organized fibrocartilage or fibrous tissue present, although biomechanical testing showed no significant difference in the stiffness of these specimens. The results suggest that delayed irradiation had some negative effect but that the grafts had enough time to begin to heal, in contrast to the grafts in the animals that had received immediate postoperative irradiation (Group III). It should be noted that our results were recorded at one time-point only (three months), and it is possible that more time could have allowed eventual healing of the grafts in Group III.

It is of interest that preoperative irradiation in this model and at this dosage did not have any deleterious effects. This contradicts what has been documented in experiments with perioperative irradiation of long bones[3]. The vascularity of vertebral cancellous bone may not be affected by this dosage of radiation, or perhaps the changes are more time-dependent and would have become manifest weeks or months later than the time at which the results were recorded in our protocol. It is possible that the hypovascular effects on bone may be overemphasized, as suggested by the experimental data of Jacobsson et al. with use of the titanium bone chamber. Another factor that is relevant to the group that received preoperative irradiation could be the survival of osteoblasts and, potentially, local growth factors within the iliac strut, since the graft itself would not have received irradiation.

The healing of corticocancellous grafts may involve the process of enchondral ossification, particularly at the host-graft interfaces of non-rigid constructs. Local marrow and blood-borne cells initiate an inflammatory response that lasts for a few days. With time, microvascular growth into the graft begins. A fibrocartilage scaffold is laid down at the graft-host junction by osteogenic precursor cells, followed by mineralization of the fibrocartilage. This mineralized tissue serves as a substrate for the formation of bone and may be removed and replaced with bone by the coupled action of pre-existing osteoclasts and osteoblasts as well as those derived from local osteoprogenitor cells. The body of the graft is replaced by creeping substitution after it is revascularized. All of these processes are dependent to a large degree on division and replication of the cells.

The most important adverse effects of irradiation on soft tissue as well as on bone-healing involve the cellular processes[15]. Dividing cells, such as mesenchymal cells or immature osteoblasts, are the most sensitive to irradiation[8], a characteristic that is consistent with our data that showed the detrimental effects of irradiation in the immediate postoperative period. At this time, the operation has just been performed and the healing response of the wound that initiates endochondral ossification is just getting under way. In contrast, there is no stimulus for cell division in the preoperative setting; thus, irradiation given at that time would not necessarily have a great influence on the ability of the bone to heal after the operative procedure.

We believe that our findings have clinical relevance in the management of patients who have a spinal neoplasm. If anterior decompression and arthrodesis with a bone strut is indicated, we recommend a delay of postoperative irradiation in order to maximize the chances of a successful arthrodesis, provided that this does not compromise the over-all treatment plan for the patient. A three-week delay allowed healing of the graft in dogs, but a longer period of time may be more appropriate in humans. This, however, should be a joint decision of the spine surgeon, the oncologist, and the radiation therapist for any given patient. Preoperative irradiation of the spine with the use of middle-range dosages may not be an important risk factor for non-union.

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