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Hematopoietic Marrow Regeneration in Pediatric Patients Undergoing Spinal Irradiation: MR Depiction

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PURPOSE: To evaluate changes in vertebral marrow signal intensity that occur over time in children undergoing craniospinal radiation therapy, specifically evaluating for the occurrence and timing of marrow regeneration. **METHODS:** MR images of nine pediatric patients (ages 4 to 12 years) with posterior fossa medulloblastoma who received total spinal irradiation (24 to 40 Gy) and had at least three MR examinations were reviewed. Signal intensity of vertebral body marrow was graded by two pediatric neuroradiologists who were blinded to patient identity and to the timing of the studies. **RESULTS:** Eight of nine patients demonstrated increasing signal intensity of the vertebral marrow after irradiation, consistent with conversion of hematopoietic to fatty marrow. In each of these patients, this was followed by subsequent decreasing signal intensity in a mottled or peripheral band pattern indicating recovery of hematopoietic marrow. **CONCLUSION:** Changes in vertebral body signal intensity consistent with marrow reconversion commonly are seen in pediatric patients 11 to 30 months after they undergo total spinal irradiation.

Index terms: Therapeutic radiology, in infants and children; Bones, marrow; Spine, vertebrae

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Magnetic resonance (MR) imaging has proved to be an excellent modality for the evaluation of bone marrow because of its sensitivity to changes in fat and cellular content (1–4). Fatty replacement of hematopoietic marrow (marrow conversion) after irradiation has been well shown by MR imaging (5–9). MR imaging has less frequently demonstrated subsequent marrow regeneration (10–12), although this is known to occur based on histopathologic and nuclear medicine studies (13–17). Knowledge of the appearance and timing of marrow regeneration after irradiation is important to differentiate it from pathologic marrow processes such as recurrent or metastatic disease.

We studied nine pediatric patients with posterior fossa medulloblastoma who received total spinal irradiation (dose, 24 to 40 Gy), either prophylactically or for treatment of drop metastases at the time of diagnosis of their primary tumor. The advantages of evaluating radiation changes in this group are twofold: First, medulloblastoma rarely spreads to the bone or marrow; second, surveillance scanning resulted in multiple sequential MR examinations for these patients. MR examinations in these nine patients were reviewed to evaluate for evidence of fatty marrow conversion and specifically for occurrence and timing of subsequent marrow regeneration.

Subjects and Methods

Nine of 29 children recently treated at our institution for posterior fossa medulloblastoma had three or more spinal MR examinations and formed the basis of our study. MR images were obtained on a 1.5-T magnet. T1-weighted images were acquired at 550-600/11-15/2 (repetition time/echo time/excitations). Patients who had fewer than three MR studies were excluded, because we wished to evaluate for marrow changes over time. All nine patients (ages 4 to 12 years) received 24 to 40 Gy of spinal irradiation (delivered in 180 cGy per day fractions) at time of diagnosis, and all patients received chemotherapy. Patients with known drop metastases received a total irradiation dose of 40 Gy; the other patients received a total

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prophylactic dose of either 24 or 36 Gy, according to protocol. The first MR was performed within 1 month of diagnosis in eight patients, and in the third month after diagnosis in the ninth patient. The time interval between onset of treatment and final MR examination ranged from 14 to 40 months. One patient received granulocyte colony stimulating factor in addition to chemotherapy and irradiation.

The T1-weighted unenhanced sagittal MR images (a total of 34 examinations) were interpreted in random order by two experienced pediatric neuroradiologists who were blinded to patient identity and to timing of examination. A grade was assigned to each vertebral body for both the marrow signal intensity and marrow pattern. Grading of signal intensity was as follows: 1 indicated marrow signal intensity less than or equal to spinal cord; 2, marrow signal intensity greater than cord but less than fat (closer to cord); 3, marrow signal intensity greater than cord but less than fat (closer to fat); and 4, marrow signal intensity equal to fat. Pattern of signal was graded as: H indicated homogeneous; M, mottled; and P, picture-frame or peripheral band pattern (more hypointense peripherally). Vertebral bodies that had a mottled or picture-frame appearance were assigned a blended grade to reflect the percentage distribution of the different marrow signal intensities. A discrete linear area of high signal intensity along the basivertebral vein, if present, was ignored, because this has been described as a normal pattern in children (18).

Results

Initially, all patients had uniform signal intensity of the cervical, thoracic, and lumbar vertebral bodies. On subsequent examinations, however, there often was some variability in signal intensity between vertebral levels. The cervical spine in particular tended to demonstrate more heterogeneity, both between cervical levels and as compared with the remainder of the spine. Therefore, to simplify analysis of the data, the signal intensity grades of the individual vertebral bodies were averaged to yield a single value for each of the 34 MR examinations. These results are displayed in Figure 1. The marrow pattern assigned was that seen in the majority of the vertebral bodies.

The first MR examination in all nine patients demonstrated homogeneous low signal intensity, which was close to or equal to the signal of spinal cord (grades 1 or 2), throughout the vertebral marrow. The second MR examination in eight of nine patients (time interval, 7 to 20 months) revealed higher signal intensity (closer to fat) in a majority of the vertebral bodies. Subsequent studies in these eight patients demonstrated progressive decreasing signal intensity of the vertebral marrow (time interval, 11 to 30 months after radiotherapy) in either a peripheral band or picture-frame pattern (6 patients) or mottled pattern (2 patients) (Figs 2 and 3). The marrow pattern never returned to the homogeneous low signal intensity seen on the initial examinations, with the exception of the single patient who had received granulocyte colony stimulating factor (Fig 4).

Fig 1. T1-weighted vertebral marrow signal intensity versus time after onset of radiation therapy for nine patients.

In one of the nine patients, brightening of the marrow signal was never observed. In this patient, the second MR examination (obtained eight months after diagnosis) demonstrated persistence of overall low signal intensity of the marrow. However, the pattern changed from homogeneous to mottled with some peripheral low-signal-intensity bands.

No difference in bone marrow response with regard to patient age (Fig 1) or total dose of spinal irradiation was evident.

Discussion

The MR signal intensity of the vertebral bodies is determined by the relative proportions of three components: hematopoietic (red) cellular marrow, fatty (yellow) marrow, and calcified matrix. During the first 2 decades, the appearance of normal vertebral body marrow by MR is of low signal intensity (usually only slightly greater than muscle) on T1-weighted images (2). There may be a band of higher (fatty) signal intensity along the basivertebral vein or peripherally, and the pattern is the same for the cervical, thoracic, and lumbar spine (18–20).

Fig 2. Six-year-old child with medulloblastoma who received 40-Gy spinal irradiation. T1-weighted unenhanced images of lumbar spine at 3 months (A), 26 months (B), 32 months (C), and 40 months (D) after onset of treatment. This case demonstrates the peripheral band pattern of regeneration.

A, At 3 months, the marrow is of homogeneous low signal intensity (slightly greater than cord) with central linear high signal intensity along the course of the basivertebral vein. This was graded as 2.0 homogeneous.

B, At 26 months, there has been considerable increase in marrow signal, graded as 4.0 homogeneous and indicative of conversion to fatty marrow.

C, At 32 months, there is decreased signal intensity in the periphery of the vertebral bodies giving a picture-frame appearance. This appearance suggests marrow regeneration. Overall grade of lumbar spine was 2.5.

D, At 40 months, there is further extent and degree of decreased signal intensity, which is now encroaching on the center of the vertebral bodies, suggesting further marrow regeneration. Overall grade of lumbar spine was 2.2.

Beginning distally in the appendicular skeleton, there is conversion of hematopoietic to fatty marrow that continues to adulthood (21). As this occurs, the MR signal intensity increases to approach that of fat (22, 23). The spine remains a site of hematopoietic marrow throughout life, although the percentage of fatty marrow gradually increases (24). At birth, the percentage of hematopoietic marrow in the spine is close to 100 percent, decreasing to approximately 75 percent by 20 years of age (24).

Studies of the MR appearance of vertebral marrow after radiation therapy have consistently demonstrated abnormally increased signal intensity of irradiated vertebral bodies related to increased fat content of the vertebral marrow (5–12). These changes have been seen as early as 6 weeks and as late as at least 15 years after radiation in doses ranging from 8 to 60 Gy (6, 8, 10, 11). Most studies using MR imaging demonstrate persistence of marrow high signal intensity without subsequent change in signal intensity to suggest marrow regeneration (5–9).

Regeneration of hematopoietic marrow after irradiation has been documented histopathologically in animal models (13). In a study of irradiated bone marrow in rats (20-Gy single dose), there was maximum loss of hematopoietic elements and increased fat at 3 months, and at 6 months there was scattered hematopoietic regeneration (13). Scintigraphic and ferrokinetic studies in humans also have demonstrated marrow regeneration at doses of 20 to 40 Gy (14–16). Most marrow recovery occurred by 12 months, with some additional recovery in the 12- to 24-month period (15, 16).

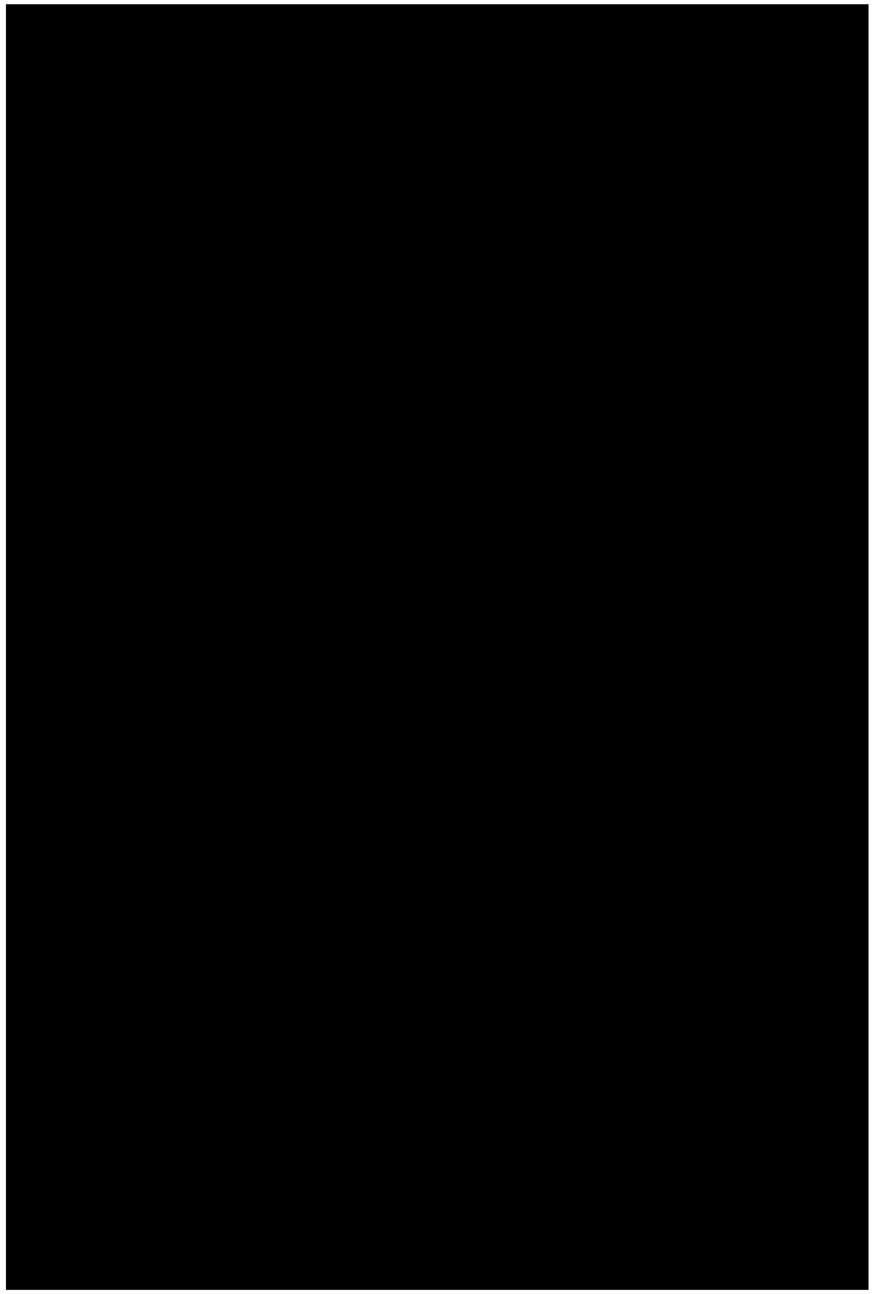

Fig 3. Seven-year-old child with medulloblastoma who received 36-Gy spinal irradiation. T1-weighted unenhanced images of the cervicothoracic and lumbar spine at 2 weeks (A and B), 7 months (C and D), and 15 months (E and F) after diagnosis. This case demonstrates the mottled pattern of regeneration.

A and *B*, At 2 weeks, there is homogeneous low signal intensity of the vertebrae graded 1.5 homogeneous.

C and *D*, At 7 months, there has been considerable increase in marrow signal intensity (fatty marrow conversion) of thoracolumbar vertebrae with slight mottled pattern also seen. Overall grade was 3.0.

E and *F*, At 15 months, further low-signal-intensity mottling is now evident, suggesting marrow regeneration. Overall grade was 2.1.

With MR imaging, the changes of subsequent hematopoietic regeneration after irradiation have been only rarely described (10–12). Two retrospective studies found normal or near-normal vertebral marrow signal (and therefore presumed hematopoietic recovery) in slightly more than half of patients irradiated with 16 to 36 Gy (on basis of single MR study obtained 2 to 23 years after treatment) (10, 12). No recovery was noted in any patient treated with 50 Gy or more. The conclusion of these studies was that at doses higher than 36 Gy there was little chance of recovery, and at lower than 30 Gy there was a good chance of recovery. In a prospective study of 14 patients (13 to 73 years of age), half of the patients demonstrated a "band" pattern of peripheral low signal intensity at 6 weeks to 1 year after irradiation, at doses of 15 to 44 Gy (11). An identical band pattern also has been seen in the vertebral bodies of bone marrow transplant patients, and in 1 case histopathologic correlation confirmed that the peripheral low-signal-intensity bands were composed of repopulating hematopoietic cells (25).

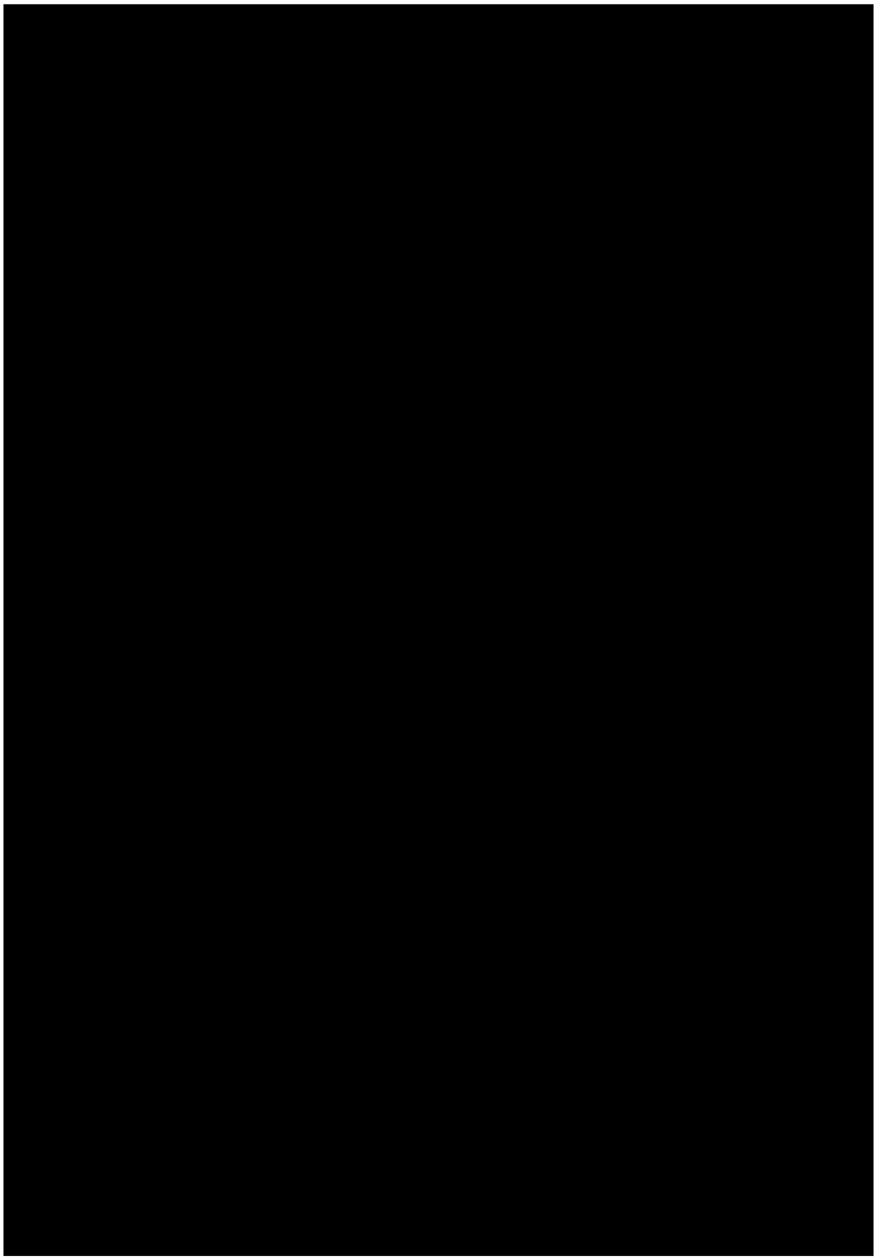

Fig 4. Seven-year-old child with medulloblastoma who received 36-Gy spinal irradiation followed by granulocyte colony stimulating factor. T1-weighted unenhanced images of the cervicothoracic and lumbar spine at time of diagnosis (A and B), 9 months (C and D), and 16 months (E and F).

A and *B*, At time of diagnosis there is homogeneous low signal intensity of the vertebrae graded as 1.6 homogeneous.

C and *D*, At 9 months, there is a picture-frame appearance to most of the vertebrae with hyperintensity centrally (fat) and bands of lower signal intensity peripherally (areas of marrow regeneration). Overall grade was 2.2.

E and *F*, At 16 months, the vertebral bodies are now homogeneously hypointense compared with spinal cord (overall grade, 1.0). These findings are compatible with further marrow regeneration. Extent of regeneration appeared greater on this than any of the other patients in this study, perhaps because of the superimposed effect of granulocyte colony stimulating factor.

Chemotherapy does not appear to affect the MR findings of marrow conversion or regeneration (11). Well-defined abnormal signal within radiation ports (with normal marrow signal outside) are seen in both patients who received chemotherapy (9) and those who did not (8).

In eight of nine patients in our study increasing signal intensity of the vertebral marrow consistent with fatty conversion developed 7 to 20 months after onset of treatment, at doses of 24 to 40 Gy. In these patients, subsequent decreasing signal intensity in a mottled (2 of 8) or band (6 of 8) pattern occurred between 11 and 30 months after radiation therapy. In the ninth patient, the marrow pattern changed from initial homogeneous signal intensity to a mottled pattern at 8 months without any increase in overall signal intensity. (It is possible that changes of fatty conversion occurred in this patient between 0 and 8 months and were not documented.) These findings suggest that there was some level of hematopoietic recovery in all nine patients. In only the single patient who received granulocyte colony stimulating factor did the marrow pattern eventually return to homogeneous low signal intensity. Granulocyte colony stimulating factor has been previously shown to enhance marrow reconversion (26).

We did not find any difference in bone marrow response with regard to patient age or total amount of spinal irradiation. However, small sample size precludes us from drawing any conclusions as to whether there is a difference in marrow response.

In our population of nine pediatric patients, hematopoietic recovery appears to be occurring more commonly than has been seen in previous MR studies. We see two possible contributing factors. First, the young age of these patients may make recovery at a given dose more likely. Sacks et al, using Indium 111 as a marrow scanning agent, studied 48 patients treated with local radiation therapy for malignant neoplasm (mostly lymphoma). Those few patients who underwent radiation therapy at younger than 20 years of age demonstrated a marked superiority in capacity for hematopoietic marrow regeneration (16). A small number of pediatric patients in the predominantly adult studies in which MR was used to assess recovery also had full to partial regeneration (10, 11). Second, all our patients had total spinal irradiation, as opposed to the vast majority of patients in the other MR studies who had partial spinal irradiation. Sacks et al found marrow regeneration more likely to occur with increasing volume of irradiated tissue (16). Partial spinal irradiation may not provide enough stimulus for regeneration, because remaining uninvolved marrow is sufficient to meet hematopoietic needs.

The retrospective MR imaging studies of Casamassima et al and Orlandini et al did not demonstrate hematopoietic recovery earlier than 2 years after treatment but MR studies before 2 years after treatment were rarely obtained (10, 12). Seven of 14 patients in the prospective study by Stevens et al had MR imaging evidence of regeneration between 6 weeks and 14 months after irradiation (11). Ferrokinetic and scintigraphic studies found most marrow regeneration occurring during the first 12 months after irradiation, with some further recovery over the next 2 to 3 years (14–16). The time course of regeneration in our patients of 11 to 30 months is in agreement with these earlier studies.

Knowledge of the patterns of marrow reconversion after radiation therapy is important in order to help distinguish between this process and pathologic marrow replacement. In eight of nine patients in our study, the appearance of the vertebral marrow after irradiation progressed from homogeneous low MR signal intensity to higher (fatty) signal intensity, then darkened to a mottled or picture-frame pattern. In the remaining one patient, the findings were the same, with the exception that the change of fatty conversion was not observed, likely a result of the timing of the imaging studies. Our findings suggest that at least some recovery of hematopoietic marrow after total spinal irradiation in the dose range of 24 to 40 Gy is a common event in pediatric patients, and that the evidence of recovery is usually seen 1 to 2 years after therapy.

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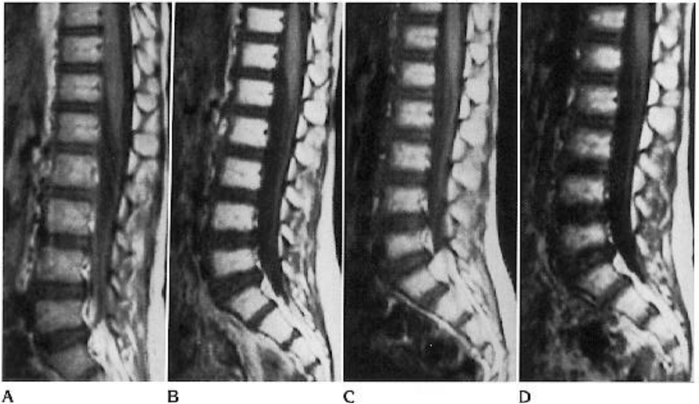
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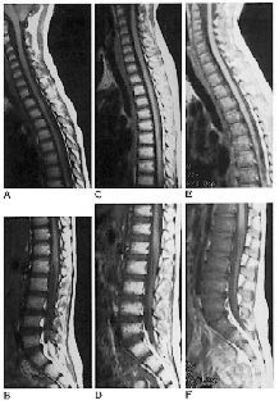
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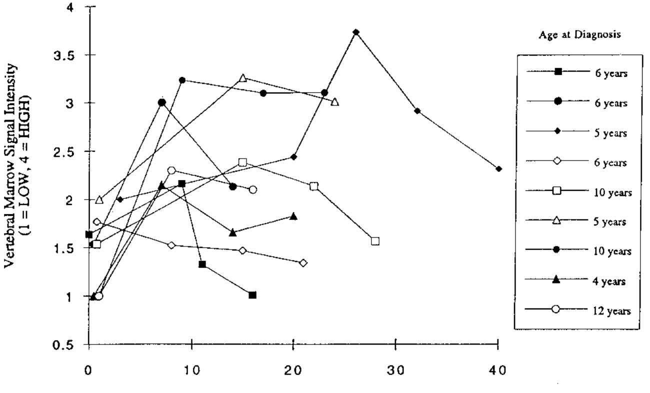
Vertebral Marrow Signal Intensity
(1 = LOW, 4 = HIGH)
Months after Radiation Therapy
Age at Diagnosis
6 years
6 years
5 years
6 years
10 years
5 years
10 years
4 years
12 years
0.5
1
1.5
2
2.5
3
3.5
4
0
10
20
30
40