A New Approach Yields High Rates of Radiographic Progression in Knee Osteoarthritis

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ABSTRACT. ***Objective.*** Progression of knee osteoarthritis (OA) has typically been assessed in the medial tibiofemoral (TF) compartment on the anteroposterior (AP) or posteroanterior (PA) view. We propose a new approach using multiple views and compartments that is likely to be more sensitive to change and reveals progression throughout the knee.

Methods. We tested our approach in the Multicenter Osteoarthritis Study, a study of persons with OA or at high risk of disease. At baseline and 30 months, subjects provided PA (fixed flexion without fluoro) and lateral weight-bearing knee radiographs. Paired radiographs were read by 2 readers who scored joint space (JS) using a 0–3 atlas-based scale. When JS narrowed but narrowing did not reach a full grade on the scale, readers used half-grades. Change was scored in medial and lateral TF compartments on both PA and lateral views and in the patellofemoral (PF) joint on lateral view. A knee showed progression when there was at least a half-grade worsening in JS width in any compartment at followup. Disagreements were adjudicated by a panel of 3 readers. To validate progression, we tested definitions for TF progression to see if malalignment on long-limb radiographs at baseline (≥ 3° malaligned in any direction with nonmalaligned knees being reference) increased risk of progression. A valid definition of progression would show that malalignment strongly predicted progression.

Results. We studied 842 knees with either Kellgren-Lawrence grade ≥ 2 or PF OA at baseline in 606 subjects (age range 50–79 yrs, mean 63.9 yrs; 66.6% women). Mean body mass index was 31.9, and 32.8% of knees had frequent knee pain at baseline. Of these, 500 knees (59.4%) showed progression. Of the 500, 75 (15%) had progression only in the PF joint, while the remainder had progression in the TF joint. Malalignment increased the risk of overall progression in TF joint and increased the risk of half-grade progression, suggesting that half-grade progression had validity.

Conclusion. PA and lateral views obtained in persons at high risk of OA progression can produce a cumulative incidence of progression above 50% at 30 months. Keys to increasing the yield include imaging PF and lateral compartments, using semiquantitative scales designed to detect change, and examining more than one radiographic view. (First Release Sept 15 2008; J Rheumatol 2008; 35:2047–54)

Key Indexing Terms:
OSTEOARTHRITIS KNEE RADIOGRAPHY

Radiographic studies of knee osteoarthritis (OA) have typically evaluated the progression of disease in the medial tibiofemoral (TF) compartments and have evaluated this compartment on anteroposterior (AP) or posteroanterior (PA) view only. Several different strategies have been used to evaluate whether knees progress in this compartment; these have included quantitative and semiquantitative assessments of joint space and positioning with the aid of fluoroscopy[1,2].

Among persons with knee OA in longitudinal natural history studies or in clinical trials, the rate of joint space loss in the medial TF compartment is low, producing few subjects who experience joint space loss. For example, in a recent large trial of knee OA[3], 8% of placebo patients had

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detectable joint space loss at 12 months defined conservatively on the AP fluoroscopic positioned view in the medial compartment. The low number of knees showing progression has made it difficult to carry out trials of knee OA, making it necessary to recruit large numbers of patients with only a few of these experiencing progression to obtain enough statistical power to address whether a treatment affects progression, and also requiring longer studies to get a larger percentage of knees showing progression.

While only a minority of knees have lateral compartment disease, a confusing situation arises in a study focused on medial progression when a knee shows lateral compartment progression. In this circumstance, the medial compartment widens (so called pseudowidening), appearing to improve. Further, by failing to count lateral narrowing among progressor knees, a study fails to include additional subjects who could be characterized as having experienced progression. Studies may attempt only to include participants with primarily medial compartment OA, but this increases recruitment costs and limits generalizability; further, some of these knees may demonstrate lateral progression.

In addition, we recently reported that progression in the TF compartments can be readily detected using a lateral weight-bearing radiograph[4], and was occasionally independent of progression seen on the AP or PA view. We have used this strategy in several studies[5-7].

Finally, a focus on progression in the TF compartment misses the patellofemoral (PF) joint, a compartment commonly affected by knee OA and frequently the source of symptoms[8]. To date the PF joint has not generally been included in studies of progression.

If approaches were adopted that allowed lateral and PF compartment progression to be added to the current evaluation of the medial compartment, and additional views were used that could detect evidence of progression when the AP or PA view missed it, many more progressors might be identified than is done currently. This might permit studies of progression and treatments testing prevention of progression, with fewer subjects, followed over a shorter period of time. We tested this idea in the Multicenter Osteoarthritis Study (MOST), a longitudinal observational study of persons either with knee OA or at high risk of disease. Because our interest was in evaluating the risk of progression in knees that already had OA, we focused on knees where there was evidence of radiographic OA at baseline.

Our inquiry addressed 2 questions: (1) using a strategy that permitted progression to occur in multiple compartments using different views, how much additional knee OA progression could we detect compared with a traditional approach focusing on the medial TF compartment on the AP or PA view?; and (2) was the progression we detected valid — in other words, was there external evidence that the knees we defined as having experienced progression had the same major risk factors for progression as the knees that fulfilled the conventional definition? The risk factor we studied was malalignment, the factor consistently predictive of progression in recent studies.

MATERIALS AND METHODS

Study design and subjects. The MOST is a prospective epidemiological study of individuals aged 50 to 79 years; its goal is to identify risk factors for incident symptomatic knee OA and progressive OA in a sample with OA or at high risk of developing disease. Those considered at high risk included persons who were overweight or obese, those with knee pain, aching or stiffness on most of the last 30 days, a history of knee injury that made it difficult to walk for at least 1 week, or previous knee surgery. High risk for obesity was defined based on persons who weighed more than the Framingham Study median weight for their age and sex-specific group (based on Felson, *et al*[9]). For example, weight cutoffs for women: for age 50–59 years, 154 lbs; 60–69 years, 151 lbs; and for 70–79 years, 148 lbs. Weight cutoffs for men: 50–59 years, 194 lbs; 60–69 years, 187 lbs; and 70–79 years, 182 lbs. Weight was measured without shoes and heavy jewelry and in standard gown or lightweight clothing. Height was measured using a stadiometer without shoes.

All subjects were recruited from 2 US communities, Birmingham, Alabama, and Iowa City, Iowa, through mass mailing of letters and study brochures, supplemented by media and community outreach campaigns. Each center also recruited ethnic minorities according to their representation in the recruitment population.

This research was in compliance with the Helsinki Declaration, and the study protocol was approved by institutional review boards at the University of Iowa, University of Alabama, Birmingham, University of California, San Francisco, and Boston University Medical Campus. Participants all provided written informed consent.

Subjects were excluded if they screened positive for rheumatoid arthritis[10], had ankylosing spondylitis, psoriatic arthritis or Reiter's syndrome, had problems with kidneys that resulted in their need for hemo- or peritoneal dialysis, had a history of cancer (except for nonmelanoma skin cancer), bilateral knee replacement surgery or inability to walk without the help of another person or walker, or were planning to move out of the area in the next 3 years.

Radiographs. At baseline and at 30-month followup, all subjects underwent weight-bearing PA fixed-flexion knee radiographs using the protocol of Peterfy, *et al*[11]. Body weight was equally distributed between the 2 legs, and the great toes of feet and the front of thighs were placed in contact with the front plate of the plexiglass frame. External rotation of feet was fixed at 10° using a V-shaped foot angulation support on the frame. The central x-ray beam was directed to the midpoint between the back of the knees at ~10° caudal angle to allow the anterior and posterior lips of the medial tibial plateau to be optimally superimposed (film–focus distance 183 cm). (There were 3 technologists, 2 at one site and one at the other; we used a picture atlas of line drawings to provide technologists with examples of acceptable joint space visualization and carried out quality control review every 2 weeks, with immediate feedback to technologists by telephone if

Table 1. Characteristics of 608 subjects in the progression study with radiographic OA at baseline in at least one knee.

Characteristic	
Mean age, yrs (SD)	63.9 (7.9)
Mean body mass index (SD)	31.9 (6.1)
% Women	66.6
History of major knee injury (by knee) (%)	253/842 (30.1)
History of knee surgery (by knee) (%)	176/842 (20.9)
Tibiofemoral radiographic OA (by knee) (%)	760/842 (90.3)
Patellofemoral radiographic OA (by knee) (%)	294/842 (34.9)

Figure 1. Examples of half-grade radiographic changes seen on posteroanterior lateral view. A: the baseline radiograph; B: the followup radiograph.

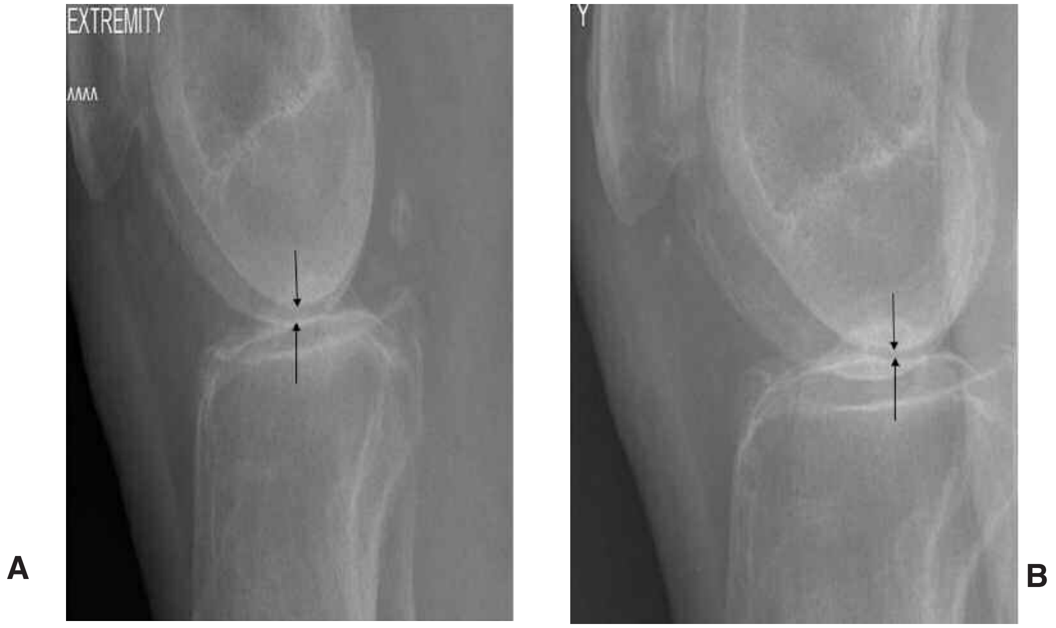

Figure 2. Examples of half-grade radiographic changes seen in the tibiofemoral compartment. A: the baseline radiograph; B: the followup radiograph.

Figure 3. Examples of half-grade radiographic changes seen on lateral view in the patellofemoral joint. A: the baseline radiograph; B: the followup radiograph.

there was drift away from acceptable visualization of the medial joint.) When 10° caudal angle did not align tibial plateaus and the medial joint space was not visualized acceptably according to our atlas, technologists obtained radiographs also at 5° and 15°, and an experienced reader (DTF) selected the beam angle that optimized imaging of the medial joint space, defined as visually minimizing the overlap of anterior and posterior tibial lips. This chosen beam angle was used for the followup radiographs.

In addition, at both timepoints, subjects provided weight-bearing, lateral radiographs with the knees flexed using the Framingham Study protocol[4]. Subjects stand perpendicular to the bucky device with the leg closest to the bucky in front and bent. The Synaflexor frame was turned so that the plexiglass plate previously against the bucky is perpendicular to the bucky and just in front of the subject. The lateral aspect of the knee of this front leg is pressed by the subject against the bucky and the patella contacts the plate of the Synaflexor frame. Consistency in flexion angle is achieved by asking the subject to put the toe of the back foot against the heel of the front foot. The central x-ray is aimed at the TF joint line, and femoral condyles are positioned so that they form a line perpendicular to the bucky. Two lateral radiographs are acquired, one of each knee (for details see LaValley, *et al*[4]).

A musculoskeletal radiologist (PA) and a rheumatologist (BS) experienced in reading study radiographs, both blinded to clinical data, graded all posteroanterior radiographs according to the Kellgren and Lawrence (K-L) and individual radiographic features including joint space score, the latter being scored 0–3 using the OARSI atlas[12]. Lateral radiographs were read using the protocol as described[4]. In that protocol, joint space is also scored 0–3 in medial and lateral TF compartments and in the PF compartment. Atlases and protocols for AP and lateral view readings are intended for cross-sectional evaluations of joint space width. In preliminary readings, we found that knees often showed joint space narrowing longitudinally but did not show enough narrowing to move from one grade to the next (e.g., grade 1 to 2). When joint space narrowed in either the TF or PF compartments, but when narrowing did not achieve a full grade on the 0–3 scale, readers were instructed to use half-grades.

Radiographs were read paired and unblinded to sequence. Each subject's knee radiographs were read by both readers working independently. If readers disagreed on the presence of progression using any of the definitions below, the readings were adjudicated by a panel of 3 readers (PA, BS, and DTF) to decide whether progression had occurred. Radiographic OA was considered present if K-L grade was ≥ 2. While we adjudicated any reader disagreements regarding progression or no progression, we did not adjudicate disagreements as to whether half-grade or full-grade progression occurred, and frequencies of half-grade progression presented in this report are based on those of our senior reader (PA), an academically based musculoskeletal radiologist.

Table 2. Location and description of radiographic progression in 500 knees, with progression by subsets of compartment and radiographic approach.

Definition/Location of Progression	No. (%) of 500 Progressed Knees in This Category
PF compartment only	75 (15)
TF compartment (± PF compartment)	425 (85)
Traditional approach: medial compartment on PA view	247 (49.4)
All TF compartment progression (PA or lateral view, medial or lateral compartment)	425
On PA view only	90 (18.0)
On lateral view only	94 (18.8)
On both PA and lateral views	241 (48.2)
All TF compartments showing JSN on either PA or lateral view, either half or full-grade	425
1 grade JSN change	235 (47.0)
Half-grade JSN change	188 (37.6)
JSN without change in K-L grade	252 (50.4)
All TF compartment progression (PA or lateral view, medial or lateral compartment)	425
Medial compartment only	327 (65.4)
Lateral compartment only	88 (17.6)
Both compartments	8 (1.6)
K-L change without JSN change	2 (0.4)

PF: patellofemoral; TF: tibiofemoral; PA: posteroanterior; JSN: joint space narrowing; K-L: Kellgren-Lawrence radiographic grade.

Interreader agreement on half-grade progression was $\kappa = 0.58$ ($p < 0.001$) and if we characterized agreement on progression as agreement for either half or full-grade progression, interreader agreement was $\kappa = 0.66$ ($p < 0.001$). Note that any disagreements on progression were adjudicated.

Full-limb radiographs of both legs were obtained at baseline using the method of Sharma, *et al*[13]. The mechanical axis was defined as the angle formed by the intersection of a line from the center of the head of femur to the center of the tibial spines, and a second line from the center of talus to the center of the tibial spines. Interobserver intraclass correlation coefficient for mechanical axis was 0.99 ($p < 0.0001$).

We present mostly descriptive statistics. For the analysis of malalignment as a predictor of progression, we used logistic regression, adjusting for the correlation between knees using generalized estimating equations. Progression was the dependent variable, with malalignment, age, sex, and body mass index at baseline as independent variables.

RESULTS

We focused our efforts on subjects in the MOST study who had evidence of radiographic OA in at least one knee at the baseline examination. This constituted 608 subjects, in whom there were 842 knees with radiographic OA. Most subjects with disease were women (Table 1) and met criteria for obesity. In almost half of the knees there was frequent knee pain, defined as pain, aching, or stiffness on most days of a recent month. The K-L score on the PA view showed grade 2 or 3 disease in roughly 90% of knees in the TF joint (Table 1). The remainder had PF OA. Knee surgery without replacement and major knee injury were both common features of these knees.

Examples of half-grade progression on these radiographs are shown in Figures 1 to 3 (these examples come from different subjects).

Of 842 knees examined at baseline, 500 (59.4%) showed radiographic progression at the 30-month followup. Of these 500, 75 (15%) had progression only in the PF joint, while the remainder had progression in the TF joint (Table 2, Figure 4). If we had obtained only a PA view and counted progression only when there was joint space loss in the medial compartment, as in traditional studies of radiographic progression, we would have identified 247 progressor knees. These 247 represent slightly less than 50% of all the cases of progression among those studied (Table 2, Figure 4). A substantial number of knees showed TF progression only on the lateral view (94 knees, 18.4% of all knees that progressed in either TF or PF compartment), which would not have been identified if only the PA view was used. Eighty-eight knees (17.6% of all progressed knees) had progression only in the lateral TF compartment, progression that also would not have been identified using a traditional approach focusing on the medial compartment.

A large percentage of the knees showed only one half-grade joint space narrowing change in the TF compartment (Figure 4). We should note that if change of K-L grade had been used to define progression, as has been done in some epidemiologic studies, more than half of the TF progression would not have been identified.

We examined which view yielded the highest sensitivity for medial TF progression, and found that 190 knees with medial progression showed evidence of this on both PA and lateral views. However, when only one view showed progression, it was slightly more likely to be the lateral ($n = 82$) than the PA view ($n = 63$). For progression in the lateral TF compartment, the PA view was slightly better. Among knees with lateral progression, 58 knees showed evidence of this progression on both views, but 25 showed evidence only on the PA view compared to 13 on the lateral view.

We examined the validity of one half-grade progression by testing whether malalignment predicted and increased the risk of half-grade progression. If malalignment were not associated with half-grade progression, then its validity as a measure of progression would be in question. We found that varus and valgus malalignment strongly predicted the risk of half-grade progression (Table 3).

DISCUSSION

We tested a comprehensive approach to evaluating radiographic progression anywhere in the knee. Using this approach, we found that progression rates were higher than any previous reports, with 59% of knees with radiographic OA showing evidence of radiographic progression at 30 months. We suggest that if this new approach is used, studies examining radiographic progression as an outcome may feasibly be done over shorter periods of time and with smaller numbers of subjects than currently required. Further, we suggest that slightly over half of progression in the knee is missed when only the medial TF joint is targeted on the PA

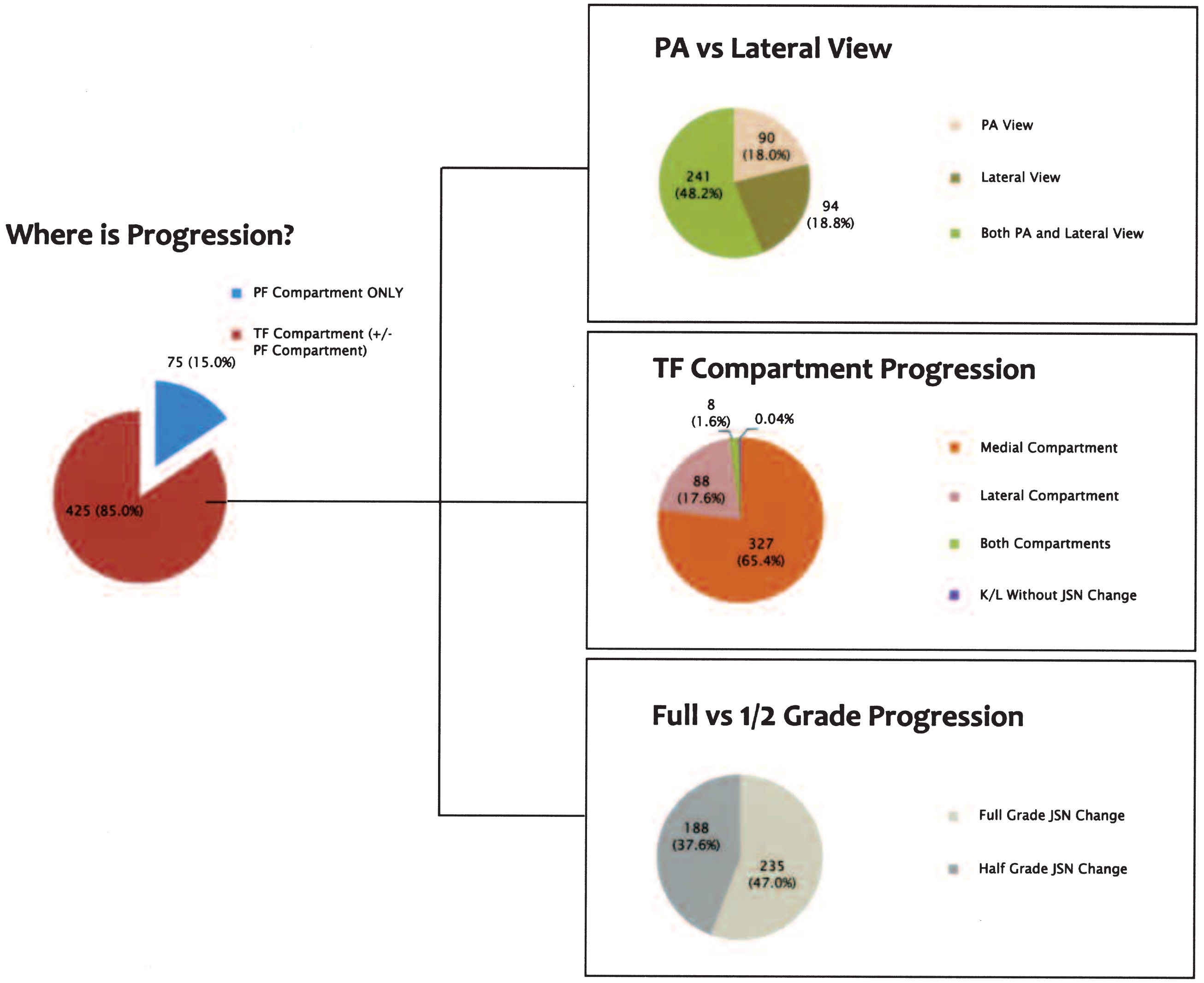

Figure 4. Where is progression? Left: a depiction of tibiofemoral (TF) compared to patellofemoral (PF) compartment as a source of progression. Top panel: TF progression in posteroanterior (PA) view versus lateral view versus both. Middle panel shows which TF compartment showed progression. Bottom panel shows the percentage of half-grade versus full-grade TF progression.

or AP view. The elements to this approach include incorporating information on the PF joint and imaging the knee from more than one plane, especially the sagittal plane (lateral view), where TF joint space narrowing is sometimes better detected than on the PA view. Further, lateral TF compartment progression should be counted. Previous reports[5,7] from our group have used some, but not all, of the approaches advocated here.

The rate of progression we observed may be high, in part, because we selected subjects especially likely to experience progression — our subjects were selected to be older, to be obese, and/or to have sustained prior knee injuries. Some, but not all, evidence suggests that these are indeed risk factors for radiographic progression in the knee[14-16]. Even if these factors increased the risk of radiographic progression, we doubled the rate of radiographic progression by expanding the assessment of progression from its current focus on the AP or PA view and medial compartment to other compartments and other views.

It may not be feasible to obtain both PA and lateral views (obtaining lateral views of each knee adds 2 additional radiographs at each timepoint), as this adds expense and time of acquisition, additional radiation exposure, and expense and time of reading. How much progression is detected on lateral views that would be missed if only PA or AP views were obtained? Of the 500 progressed knees we identified, 75 with PF progression and 94 with TF progression would have been missed (Table 2), a total of 169 knees with progression — around one-third of all progressed knees. Once radiographs are acquired, reading radiographs for lateral compartment progression adds little expense. Lateral compartment progression accounted for 22% (94/425) of the TF joint progression.

Table 3. Does malalignment predict the risk of half-grade TF radiographic progression?

	Neutral	Varus Moderate Malalignment (3°-6°)	Severe Malalignment (≥ 7°)
Proportion with medial TF progression using half and full-grade definitions of progression on either PA or lateral view (% of knees)	85/280 (30.4)	166/281 (59.1)	56/80 (70.0)
Adjusted OR for progression (95% CI)*	1 (reference)	3.2 (2.2, 4.6)	5.0 (2.8, 9.0)
Proportion with medial TF progression using only half-grade definition of progression on either PA or lateral view (% of knees)	27/222 (12.2)	84/199 (42.2)	31/55 (56.4)
Adjusted OR for progression (95% CI)	1 (reference)	5.6 (3.4, 9.4)	9.6 (4.6, 19.7)
		Valgus	
Proportion with lateral TF progression using half and full-grade definitions of progression on either PA or lateral view (% of knees)	41/280 (14.6)	35/72 (48.6)	9/14 (64.3)
Adjusted OR for progression	1 (reference)	5.6 (3.2, 9.9)	8.5 (2.7, 27.0)
Proportion with lateral TF progression using only half-grade definition of progression on either PA or lateral view (% of knees)	14/253 (5.5)	16/53 (30.2)	5/10 (50)
Adjusted OR for progression (95% CI)	1 (reference)	6.8 (3.2, 14.9)	16.5 (4.0, 68.7)

* Adjusted for age, sex, body mass index at baseline. Definitions as in Table 2.

Skyline views are likely to yield even higher rates of PF progression than lateral views[17], but if these were obtained with PA views only, an examiner would miss the TF progression seen on the lateral view. We could not readily determine PF compartment progression, and this also would be readily determined with a skyline view that could permit detection of relations of alignment to PF progression.

One other limitation is our neglect of osteophyte progression in this investigation. We focused more on joint space, as it is the central focus of progression studies. Osteophyte imaging is complicated by its sensitivity to changes in rotation during imaging. Also, while we used malalignment as a known risk factor for progression, we recognize that malalignment is part of the disease process itself.

We did not assess the reproducibility of half-grade change, which would have been difficult to accomplish as readers sometimes did not agree that change was half-grade or full-grade compared to half-grade versus no change (these disagreements were adjudicated). While we focused on joint space narrowing, the most widely accepted measure of progression[7,13], there is no reason why the same approach could not be applied to assess enlargement of osteophytes.

Sample-size requirements for performing a trial testing a new agent depend critically on the expected rate of disease progression in the nontreated and treated groups. We performed additional analyses using a dichotomous (progression/no progression) outcome and chi-square analysis, testing how much power we would have if treatment prevented expected progression with an odds ratio of 1.9 in favor of active treatment. We found that power was maximized when progression rates ranged from 30% to 50% (power was highest around 40%) and that power diminished steeply when expected progression rates in the nontreated group fell below 20%. This same pattern was observed for different rates of control response and for treatment effects, defined as percentage improvements over control. Our progression rates of 59% are slightly too high to optimize power (power 82% at 40% progression rate vs 76% at 60% progression rate), but they reveal accurately what is happening in the knees. Further, one might shorten time to followup to lower progression rates, and this would facilitate study design.

While it might be argued that an approach using a quantitative continuous measure would reveal even more progression, that was not the point of this study. Rather, it was to argue that allowing multiple sites where progression could occur, imaged in multiple different ways, would increase detection rates and identify more accurately change in an OA knee. We also increased the sensitivity of the semiquantitative approach by using half-grade increments in an integer scale, which makes them far more sensitive to change. One could readily take advantage of our proposed multiple view/multiple compartment method using a quantitative approach to our findings, measuring joint space on both PA and lateral views and not limiting quantitative assessments on the PA view only to the medial compartment.

Our approach would be especially useful for detecting effects of treatment or other factors that may have measurable effects anywhere in the knee. It could also help in assessing compartment-specific treatments. It is not a substitute for global measures of the amount of disease.

We suggest that a comprehensive approach to detecting progression in knee OA, including all compartments and multiple views of the knee, is likely to identify far more progression than traditional approaches.

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