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Increasing Fusion Rate Between 1 and 2 Years After Instrumented Posterolateral Spinal Fusion and the Role of Bone Grafting

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Study Design. Two-year clinical and radiographic follow-up of a double-blind, multicenter, randomized, intra-patient controlled, non-inferiority trial comparing a bone graft substitute (AttraX® Putty) with autograft in instrumented posterolateral fusion (PLF) surgery.

Objectives. The aim of this study was to compare PLF rates between 1 and 2 years of follow-up and between graft types, and to explore the role of bone grafting based on the location of the PLF mass.

Summary of Background Data. There are indications that bony fusion proceeds over time, but it is unknown to what extent this can be related to bone grafting.

Methods. A total of 100 adult patients underwent a primary, single- or multilevel, thoracolumbar PLF. After instrumentation and preparation for grafting, the randomized allocation side of AttraX® Putty was disclosed. The contralateral posterolateral gutters were grafted with autograft. At 1-year follow-up, and in case of no fusion at 2 years, the fusion status of both sides of each segment was blindly assessed on CT scans. Intertransverse and facet fusion were scored separately. Difference in fusion rates after 1 and 2 years and between grafts were analyzed with a Generalized Estimating Equations (GEE) model ($P < 0.05$).

Results. The 2-year PLF rate (66 patients) was 70% at the AttraX® Putty and 68% at the autograft side, compared to 55% and 52% after 1 year (87 patients). GEE analysis demonstrated a significant increase for both conditions (odds ratio 2.0, 95% confidence interval 1.5–2.7, $P < 0.001$), but no difference between the grafts ($P = 0.595$). Ongoing bone formation was only observed between the facet joints.

Conclusion. This intra-patient controlled trial demonstrated a significant increase in PLF rate between 1 and 2 years after instrumented thoracolumbar fusion, but no difference between AttraX® Putty and autograft. Based on the location of the PLF mass, this increase is most likely the result of immobilization instead of grafting.

Key words: adult, autograft, bone graft substitute, calcium phosphate, fusion rate, interbody fusion, intertransverse fusion, intra-patient, posterolateral fusion, randomized controlled trial, spinal fusion.

Level of Evidence: 1

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Since the first description by Hibbs in 1911, spinal fusion surgery has evolved into an established treatment of various spinal disorders including deformity, trauma, and degenerative conditions. Over the past decades, the surgical technique has shifted from noninstrumented procedures to rigid instrumentation including pedicle screws and interbody cages.[1–4] Moreover, numerous biological and synthetic alternatives for the use of autologous bone graft have been developed.[5–7] Although the primary goal of spinal fusion is to obtain a solid arthrodesis, bony fusion

is not for granted and success rates reported in literature vary widely.[4,8,9] Outcomes are affected by surgical factors and patient factors, as well as the method and timing of radiographic fusion assessment.[4,8,10–13] Nonunion (pseudoarthrosis) is commonly defined as a failure of bony bridging ≤1 year after surgery, but there are indications that bony fusion proceeds.[14–16] This argues for prolonged follow-up to definitely evaluate fusion status. However, whether this delayed or mid-term fusion can still be ascribed to the bone graft or results from a process of facet ankylosis due to immobilization is not yet clear.[17] Fusion mass exclusively related to the graft can most likely only be assumed in the intertransverse grafting area.

This article describes the 2-year radiographic and clinical outcomes of an intra-patient controlled non-inferiority trial investigating the efficacy of a standalone ceramic bone graft substitute (AttraX® Putty, NuVasive Inc., San Diego, CA) versus autograft for instrumented posterolateral fusion (PLF) of the thoracolumbar spine. We aimed to compare PLF rates between 1 and 2 years of follow-up and between graft types, and explore the role of the grafts based on the location of the PLF mass at both timepoints. Moreover, the mid-term fusion potential of additional interbody fusion (IBF) cages and the relationship between radiographic and clinical outcomes were analyzed.

METHODS

Study Design

This double-blind, multicenter, randomized, intra-patient controlled, non-inferiority trial including 2-year follow-up was designed to investigate the 1-year efficacy of AttraX® Putty as a standalone bone graft substitute for instrumented fusion of the thoracolumbar spine. This product is made of a microporous biphasic calcium phosphate.[18] The study was approved by the Medical Ethics Review Committee of the UMC Utrecht and local board of each participating hospital and registered in ClinicalTrials.gov (NCT01982045). At 1-year follow-up, non-inferiority of AttraX® Putty versus autograft in terms of PLF performance based on a margin of 15% was demonstrated.[18] The present study focuses on predefined secondary analyses of the fusion status and clinical outcomes at 2-year follow-up with specific attention to the role of the bone grafts.

Study Population

The study population consisted of 100 adult patients treated with a primary single or multilevel instrumented PLF between T10 and S1/ilium after at least 6 months of unsuccessful non-operative treatment. Indications for surgery were deformity, structural instability and/or expected instability (for example as a result of decompression for spinal stenosis). In- and exclusion criteria are listed in the 1-year article.[18]

Intervention

The surgical technique comprised a standard open PLF via a midline approach. When indicated, additional IBF with a titanium or PEEK cage (based on surgeon preference) filled with local bone was performed. After instrumentation and thorough preparation of the PLF bed, including the posterior surfaces of the transverse processes and laminae, the randomized allocation side (left/right) of the two different grafts was disclosed. The decorticated gutters at one side of each fusion trajectory were grafted with 10cc AttraX® Putty per level, whereas a mixture of iliac crest bone and available local bone was applied to the other side. A volume of 8–10cc autograft (≥50% iliac crest bone) per fusion level was intended.

Fusion Assessment

The PLF rate was assessed after 1 year using thin slice (≤1 mm) computed tomography (CT) scans and multiplanar reconstructions. Each side of each instrumented segment, as well as each interbody cage, was scored in 3 planes by 2 blinded spine surgeons using a detailed 3-point classification system (Appendix 1, http://links.lww.com/BRS/B577).[18–20] To gain further insight into the contribution of the grafts, intertransverse fusion (lateral to the rod) and facet/lamina fusion (at/medial to the rod) were scored separately. Any disagreements between the reviewers were resolved by re-assessment and consensus. Patients without fusion at all instrumented segments at 1 year were pursued for an additional CT-assessment at 2-year follow-up.

Clinical Assessment

To evaluate the clinical effect of the fusion surgery, patient-reported outcome measures (PROMs) including the Oswestry Disability Index (ODI), 0–100 Visual Analogue Scale (VAS) for back pain and EQ-5D-5L were collected preoperatively and at 6 weeks, 3 months, 6 months, 1 year, and 2 years postoperatively.

To evaluate safety, unexpected (serious) adverse events, whether or not considered related to the use of AttraX® Putty, were documented until last follow-up.

Statistical Analyses

Study data were collected using paper case report forms, processed in Research Online for Researchers (Julius Center, UMC Utrecht) and analyzed with SPSS Statistics Version 25 (IBM). Baseline characteristics, surgical details, fusion rates, and locations as well as PROMs are described by descriptive statistics.

Fusion scores were dichotomized into "fused" (fusion) and "not fused" (doubtful fusion or nonunion). Interobserver reliability of the fusion assessments was evaluated by percentage agreement and Cohen's kappa. Differences in PLF rates on segment level between 1 and 2 years and between treatment conditions were analyzed using a logistic regression Generalized Estimating Equations (GEE) model with an independent correlation structure to account for

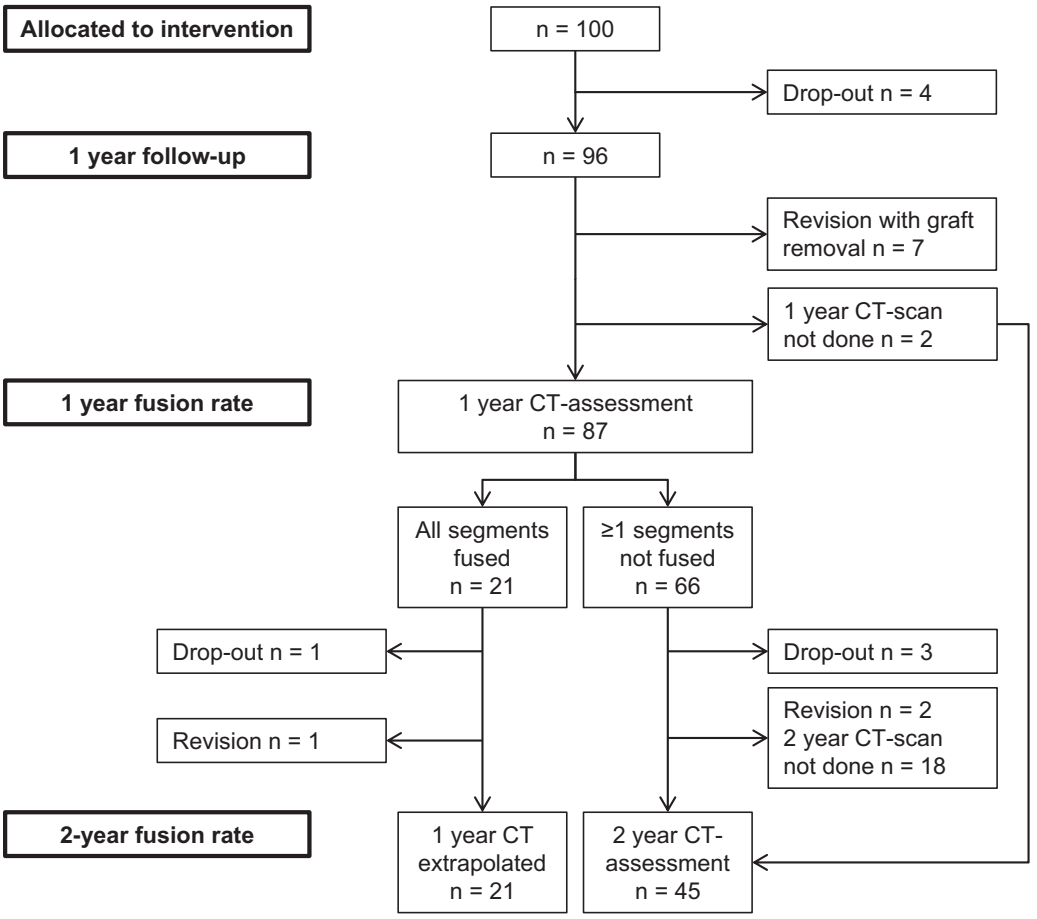

Figure 1. CONSORT flow diagram showing the flow of patients through each stage of the study.

clustering of fusion scores within segments and within subjects ($P < 0.05$). Similar GEE models were used to compare the IBF rates between 1 and 2 years and between titanium and PEEK cages, as well as the relation between successful IBF and PLF on either or both sides. Odds ratios (ORs) along with their 95% confidence interval (CI) are reported.

PROMs at each timepoint were described as median and interquartile range (IQR) based on an intention to treat principle. Changes from baseline to 2-year follow-up were analyzed using the paired samples *t* test ($P < 0.05$) and the minimal clinically important difference (MCID) was set to 15 points for both the ODI and VAS back pain.[21,22] Cases with missing values were omitted by pairwise deletion.

A mixed model for repeated measures with a random intercept was used to analyze the relationship between radiographic fusion and ODI ($P < 0.05$). Fixed effects were timepoint (1 and 2 years), pre-operative ODI, and fusion status. Successful fusion was defined as posterolateral and/or interbody fusion at all instrumented segments.

RESULTS

Patient Characteristics

As illustrated by Figure 1, 96 of the 100 operated patients reached the 1-year follow-up and 87 were included in the primary efficacy analysis. During the second year, three patients underwent revision surgery and seven patients (including three revisions) dropped out, resulting in a final follow-up rate of 89%.

Baseline characteristics and surgical details of both the entire study population and patients included in the fusion analysis at 2 years are presented in Table 1. The main indication for surgery was structural and/or expected instability and two-thirds of the patients underwent a single level fusion. The additional titanium and PEEK cages had a ratio of 1:2.

Radiographic Fusion

In 21 patients, all 26 segments assessed for PLF and all 14 interbody cages were scored as fused at 1 year. Of the remaining patients that were not considered completely fused, 43 underwent an additional CT-scan at 2-year follow-up. Furthermore, two patients were only assessed at 2 years (Figure 1). Interobserver agreement of the 2-year CT scans was 83% (kappa = 0.65) for PLF and 88% (kappa = 0.75) for IBF, which appeared slightly better than the 1-year assessments (72% [kappa = 0.45] and 78% [kappa = 0.56], respectively). Extrapolating the successful fusions at 1 year, the 2-year PLF rate was based on 113 segments and the IBF rate on 55 segments. Fusion rates at 1 and 2 years of follow-up are presented in Figure 2.

TABLE 1. Baseline Characteristics and Surgical Details of Entire Study Population at Baseline (n = 100) and Patients Included in the Fusion Analysis at 2-Years' Follow-up (n = 66)

	Baseline, n = 100	2-Year Follow-up, n = 66
Age, mean ± SD (range), year	55.4 ± 12.0 (27–79)	54.9 ± 11.5 (27–79)
Sex, n (%)		
Male	49 (49%)	33 (50%)
Female	51 (51%)	33 (50%)
Smokers, n (%)	34 (34%)	19 (29%)
Indication(s) for surgery, n (%)		
Deformity	12 (12%)	8 (12%)
Structural instability	45 (45%)	26 (39%)
Expected instability	60 (60%)	41 (62%)
Missing	7 (7%)	6 (9%)
Number of segments fused, median (range)	1 (1–8)	1 (1–8)
1	66 (66%)	45 (68%)
2	20 (20%)	11 (17%)
>2	14 (14%)	10 (15%)
Interbody device(s), n (%)	62 (62%)	48 (73%)
Type of interbody device, count (%)		
Titanium	26 (37%)	18 (33%)
PEEK	45 (63%)	37 (67%)

N indicates number of patients; SD, standard deviation; y indicates Years.

The overall PLF rate, that is, left and/or right side of a segment scored as fused, increased from 71% to 80%. At 2-year follow-up, the fusion rate at the AttraX® Putty side was 70% and 68% at the autograft side, compared to 55% and 52% at 1 year. GEE-analysis demonstrated a significant increase in unilateral PLF rate between 1 and 2 years (OR = 2.0, 95% CI = 1.5–2.7, $P < 0.001$), but no difference between the treatment conditions (OR = 0.9, 95% CI = 0.6–1.3, $P = 0.595$).

After exclusion of the two patients with only a 2-year CT scan, further analyses of the PLF location (intertransverse vs. facet fusion) in time were based on 64 patients and 111 segments. Table 2 demonstrates that for both grafts the number of intertransverse fusions at 1 and 2 years of follow-up was very similar, whereas the PLF rate (either intertransverse or interfacet) increased from 58% to 70% indicating an increase of facet fusions. Of the additional fusions at 2-year follow-up, 59% were scored as nonunion at 1 year and 41% as doubtful fusion.

The IBF rate (Figure 2) increased as well, from 62% to 78% (OR = 2.2, 95% CI = 1.3–3.7, $P = 0.002$). Breakdown by cage type showed that 91% of the titanium cages were fused at 1 year and 100% at 2 years, whereas the fusion rate for PEEK increased from 48% to 68%. This difference was highly significant (OR = 17.8, 95% CI = 3.8–82.8, $P < 0.001$). In line with the 1-year results, a positive relation between successful IBF and PLF was found (OR = 8.5, 95% CI = 1.8–39.9, $P = 0.006$).

Patient-reported Outcome Measures

Clinical outcomes up to 2 years are illustrated by Figure 3. Both the ODI (Figure 3A) and VAS back pain (Figure 3B)

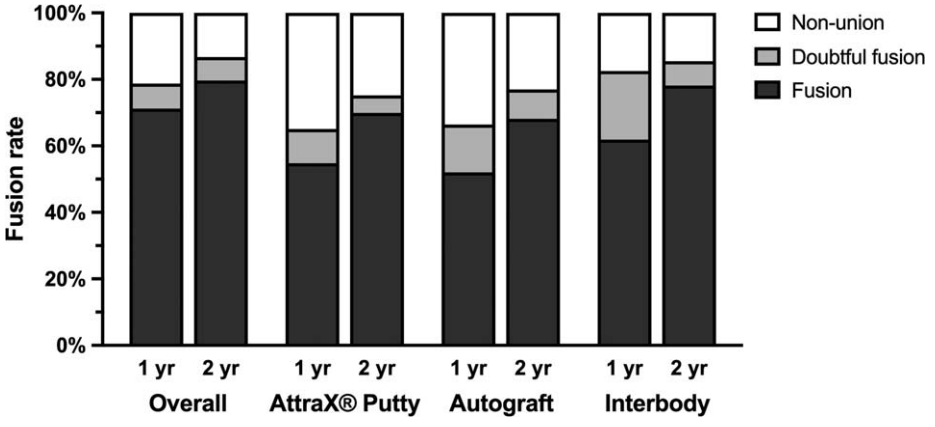

Figure 2. Fusion rates on segment level at 1 and 2 years of follow-up. From left to right: overall posterolateral fusion rate (*i.e.*, either or both sides fused), unilateral posterolateral fusion rate at the AttraX® Putty or autograft side and interbody fusion rate.

TABLE 2. Number of Segment Sides Scored as Posterolateral Fusion and Specifically as Intertransverse Fusion (n = 64 Patients, With 111 Spinal Segments and 222 Segment Sides)

	Posterolateral Fusions			Intertransverse Fusions	
Timepoint	Fusion Rate	AttraX® Putty Side	Autograft Side	AttraX® Putty Side	Autograft Side
1 years	129/222 (58%)	67/111 (60%)	62/111 (56%)	28/67	33/62
2 years	156/222 (70%)	79/111 (71%)	77/111 (69%)	28/79	31/77

improved above the MCID with a mean difference of -20 ± 19 and -31 ± 27, respectively ($P < 0.001$). At 2-year follow-up, 58% of the patients achieved the MCID of the ODI. The MCID for the VAS back pain was reached by 66%. The EQ-5D Dutch utility index (Figure 3C) increased from median 0.529 (IQR 0.394–0.683) to 0.805 (IQR 0.651–0.874). The mixed model analysis, adjusted for baseline scores, revealed that patients with a bony bridge at all instrumented segments had a lower ODI (estimated difference 8.9 points, 95% CI 2.4–15.4, $P = 0.008$), indicating a relationship between successful fusion and improved clinical outcome.

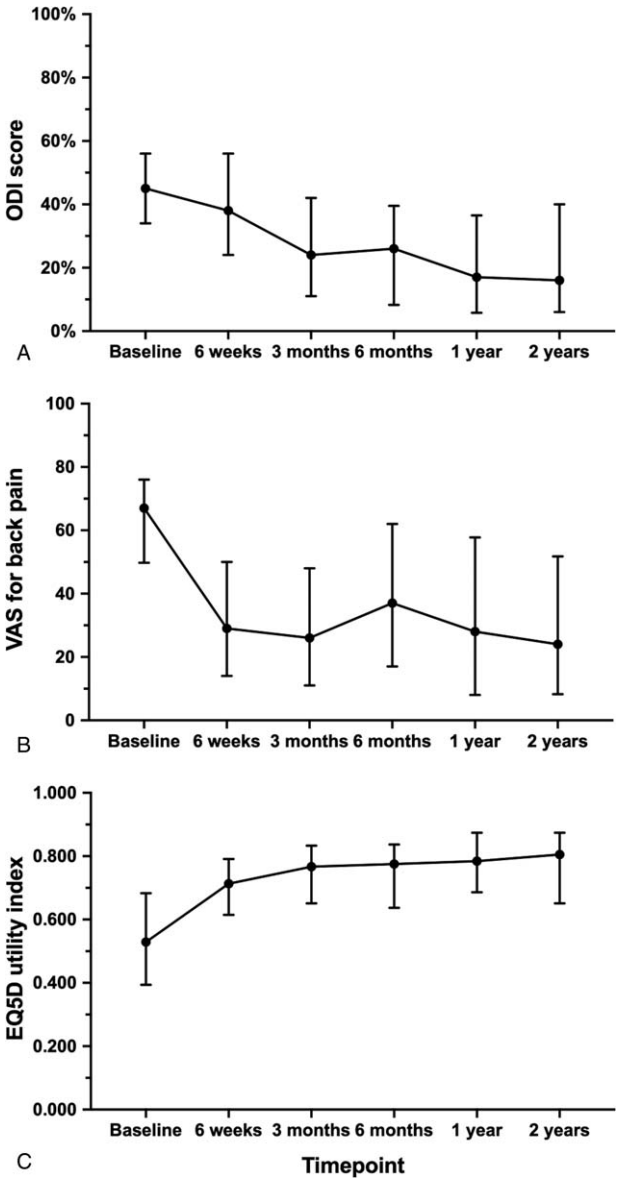

Figure 3. (**A**) Oswestry Disability Index (ODI) (0–100%), (**B**) Visual Analogue Scale (VAS) for back pain (0–100), and (**C**) EQ-5D utility index (−0.329 to 1.000) at baseline and each follow-up. Median values along with their interquartile range are displayed as the data are not normally distributed.

Adverse Events

In addition to the events described in the 1-year article,[18] eight serious adverse events were registered between 1 and 2 years of follow-up. Two patients were diagnosed with failed back surgery syndrome, one patient underwent revision surgery for pseudoarthrosis and screw loosening, and another patient had a deep wound infection after revision surgery. The remaining serious events were unrelated to the fusion surgery, but required hospitalization: cardiovascular disease (n = 2), humerus fracture (n = 1), and gastric bypass (n = 1). Of the 15 adverse events, six described back and/or leg pain. The total reoperation rate was 13%, including three revisions for pseudoarthrosis.

DISCUSSION

This study examined the progression of posterolateral and interbody fusions between 1 and 2 years as part of a randomized, intra-patient controlled trial investigating AttraX® Putty *versus* autograft. Currently, there is no consensus on the method and timing of radiographic fusion assessment. This impedes the comparison of many treatment outcomes. Moreover, little is known on the progression of bone formation over time and especially to what extent this can be related to bone grafting.

The CT-based PLF rate of both AttraX® Putty and autograft, as well as the additional IBF rate, increased between 1 and 2 years of follow-up. Interestingly, ongoing bone formation was not observed in the intertransverse fusion area, but only between the immobilized facet joints and in/around the interbody cages. Based on the location of the grafts and the fact that both grafts were completely resorbed on the 1-year CT-scans, the increase in PLF rates is unlikely the result of grafting. This is in agreement with other studies that have shown that bone graft-induced fusion by creeping substitution mainly occurs during the first 6 months.[23,24] The observations that resorbable bone graft is particularly effective within 1 year, and that facet

fusions most likely occur as a result of immobilization, has important consequences for research in this field. We believe that true assessment of bone graft (substitutes) should be no later than 1 year after surgery and preferably limited to the area where this graft is most likely crucial, that is, the intertransverse process area.

Fusion rates depend on many factors including the modality and method of fusion assessment itself.[11–13] The detailed classification system used in this study resulted in an interobserver agreement for both PLF and IBF that was substantial based on Cohen's kappa.[19] Between 1 and 2 years, the overall PLF rate (*i.e.*, uni-/bilateral fusion) had increased from 71% to 80% and the unilateral fusion rate from 52%–55% to 68%–70%. These fusion rates seem to be higher than the results of a similar intra-patient controlled trial by Cammisa *et al*, but they only assessed intertransverse fusion.[25] In contrast, Dimar *et al* reported 1 and 2 years after single-level instrumented fusion with autograft a bilateral intertransverse fusion rate of 72% and 84%, respectively.[15] In a randomized trial comparing 2 bone graft substitutes in combined posterolateral and interbody fusion, the uni- and/or bilateral fusion rate increased from 53% to 56% at 1 year to 80% at 2-year follow-up.[26] Recently, Kim *et al* demonstrated the significance of facet joint fusion and increase of these fusions between 6 and 12 months after PLF. An additional interbody fusion procedure negatively influenced PLF, probably due to the associated facetectomies.[27] This effect was not observed in the present study, possibly because we mostly performed posterior instead of transforaminal interbody fusion. Contrary, a positive relation between successful IBF and PLF at both 1 and 2-year follow-up was found. This may be related to patient factors or increased stability. Despite the challenges to compare the radiographic outcomes of different studies, the present study adds to the evidence that spinal fusion is an ongoing process and radiological nonunion after 1 year should not be regarded as definitive failure.

In line with comparable study populations, improvements in clinical outcomes continued up to 2 years and were clinically relevant for both the ODI and VAS back pain.[15,28–31] Despite the low median ODI of 16% (IQR 6–40) at final follow-up indicating minimal disability, 42% of the patients did not reach the MCID of 15 points. Further exploration revealed that one-third of these patients had an ODI $\leq$20 at baseline and/or 2-year follow-up.

The relationship between radiographic and clinical outcomes is still controversial.[32] Several studies have shown increased fusion rates by the addition of instrumentation, but no difference in clinical outcomes, whereas others have demonstrated the long-term clinical benefits of arthrodesis over pseudoarthrosis.[33–36] The present study indicated a positive relationship between radiographic fusion and ODI. However, the estimated difference in ODI (8.9 points, 95% CI 2.4–15.4) was below the assumed MCID.

Strength of this study is the excellent follow-up rate of 89% at 2-year follow-up. Nonetheless, we do recognize some limitations. To limit the exposure to ionizing radiation, only patients without fusion at all of the instrumented segments were scheduled for an additional CT-scan at 2 years. For logistical reasons, this decision was made by the treating physician. Unfortunately, 14 patients were not re-assessed as the treating physician, unlike the blinded observers, qualified these as complete fusion. Another limitation is the assumption that successful fusions can be extrapolated. However, of the 43 patients that were re-assessed, only 6.5% of the segment sides that were scored as fused at 1 year were scored differently at 2 years. This is most likely the result of variance in (re-)assessment, as also reflected in the 72% interobserver agreement at 1 year. Furthermore, the contribution of the bone grafts to the fusion process during the first and second year after surgery was only explored visually based on the location of the PLF mass. Imaging-based quantification of bone (graft) resorption and remodeling over time is still in its infancy.[23,24,37] Last, the intra-patient design limits the separate attribution of adverse events to the treatment conditions. Nevertheless, the observed adverse events were not likely related to AttraX® Putty and the reoperation rate is in accordance with literature.[38–41]

In conclusion, this intra-patient controlled trial comparing two bone grafts demonstrated an increase in fusion rates between 1 and 2 years after instrumented PLF in the thoracolumbar spine. Moreover, there was no difference between AttraX® Putty and autograft. During the second year after surgery, bony fusion around the facet joints and additional interbody cages continued, whereas the number of intertransverse fusions that can be fully ascribed to the grafts remained unchanged. This indicates that bone graft-induced fusion occurs within the first year and mid-term progression of bony fusion is most likely the result of immobilization. Further research is needed to elucidate the mechanisms behind spinal fusion over time, to guide optimal material (resorption) characteristics and fusion assessment.

➢ Key Points

- ❑ This multicenter, randomized, intra-patient controlled trial, comparing the efficacy of a standalone ceramic bone graft substitute (AttraX® Putty) with autograft, investigated the increase in posterolateral spinal fusion between 1 and 2 years follow-up and explored the role of bone grafting based on the location of the fusion mass.
- ❑ The PLF rate at the AttraX® Putty side increased from 55% to 70% *versus* 52% to 68% at the autograft side.
- ❑ Ongoing bone formation was only observed between the facet joints, not in the intertransverse area, and is therefore most likely the result of immobilization instead of grafting.

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