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Mid- to long-term results of open posterior bone block grafting in recurrent posterior shoulder instability: A clinical and CT-based analysis.

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The study was approved by the institutional review board (W 743) at Balgrist University Hospital, University of Zurich, prior to initiation of the study.

A waiver of the Cantonal Ethics Committee was obtained (Req-2018-01929) prior to publication.
Abstract

Background: There is little consensus on the best treatment after failed conservative management of recurrent posterior shoulder instability. The purpose of this study was to analyze our clinical and radiological mid- to long-term results of an open, posterior bone block procedure for the treatment of recurrent posterior shoulder instability.

Methods: From 1999 to 2015 fourteen patients were included in the study and available for clinical and radiographic follow-up (FU). FU included a standardized physical examination, assessment of the Constant-Murley-Score (CMS), subjective shoulder value (SSV), American shoulder and Elbow Surgeons (ASES) score, Western Ontario Shoulder Instability Index (WOSI). Conventional radiographs and a CT-scan were performed preoperatively and at latest FU. Glenohumeral arthropathy was classified according to Samilson and Prieto. The CT scans were used to evaluate the structure of the graft (resorption, union), graft positioning, glenoid version, centering of the humeral head as well as glenoid erosion and morphology.

Results: The median age at the time of surgery was 26 years (range 16-41 years) and the median follow-up period was 9 years (range 4-20 years). The rate of reported dynamic postoperative subluxation and instability was 46% (n=6), the rate of dynamic posterior instability during clinical testing at FU was 31% (n=4). The tested instability rate in the traumatic group was 14% (n=1) compared to the atraumatic group with 50% (n=3) during clinical FU. The mean CMS increased from preoperatively (77 ±11 points) to postoperatively (83 ±14 points, p=0.158). The last FU showed an ASES score of 85 ±12, the WOSI score was 715±475 points. The mean SSV increased from 58% ±19 preoperatively to 73% ±17 at final FU (p=0.005). Degenerative changes increased by at least one grade in 67% of the patients. Mean preoperative glenoid retroversion (CT) was 7.5° ±6°. The position of the graft was optimal in 86% (n=12). In 62% of the cases a major resorption of the graft (Zhu grade II) was observed.
Conclusion: The rate of tested recurrent instability at last FU was as high as 31% (n=4, atraumatic (n=3) vs. traumatic (n=1)) after a median FU of 9 years. Given the moderate improvement of clinical outcome scores, shoulder stability and the increase of degenerative joint changes by at least one grade (Samilson/Prieto) in 67% a posterior bone block procedure is not a uniformly satisfying treatment option for recurrent posterior shoulder subluxation, especially in cases of atraumatic posterior instability.

Level of Evidence: Level IV; Case Series; Treatment Study

Keywords: posterior shoulder instability; posterior bone block procedure; recurrent posterior shoulder instability; shoulder instability; posterior subluxation; posterior glenoid deficiency; bone block augmentation

Posterior shoulder instability is a rare condition accounting for only 4% of cases of recurrent shoulder instability. Causes can either be traumatic or congenital due to hyperlaxity. Clinical and anatomical findings range from bony abnormalities such as an abnormal joint surface orientation or osteochondral fracture of the glenohumeral head or cavity to posteroinferior capsuloligamentous deficiencies.\(^1\),\(^4\),\(^13\),\(^19\)

The importance of a detailed analyses of the clinical and radiological presentation to choose the correct individual treatment should not be underestimated. However, optimal treatment of recurrent posterior shoulder instability remains controversial.

A shoulder physiotherapy rehabilitation program is still the standard initial treatment. There is a paucity of information on the best treatment option after failed conservative management for recurrent posterior shoulder instability. Operative techniques involve soft-tissue repairs (capsular plication, labral repair, tendon transfers), glenoid and humeral osteotomy, filling of bony defects and posterior bone block procedures. However, there is no consensus for posterior shoulder instability management.\(^1\),\(^4\),\(^12\),\(^14\)

To our knowledge there is just one long-term study analyzing the clinical and radiographic outcome of posterior shoulder instability treated by an open posterior bone block procedure,
showing significant deterioration of the outcome parameters after a follow-up (FU) period of 18 years. Only one recent study analyzed an arthroscopically assisted technique of posterior glenoid bone augmentation clinically and radiologically based on CT scans. The authors reported on 18 patients (follow-up rate 61%) with a minimum follow-up of 5 years and a mean follow-up of 7.3 years. The indication for surgery was a recurrent posterior shoulder instability due to glenoid dysplasia, posterior glenoid bone loss or irreparable soft-tissue defect, and in case of revision for persistent instability following a soft-tissue stabilization. Despite a high number of reoperations for symptomatic screw irritation, acceptable clinical outcomes with a significant improvement of the Constant-Murley (p=0.05) and ASES scores (p=0.03) were described. Clinical tests for instability showed a posterior apprehension rate of 22% (n=4).³ The purpose of this study was to analyze clinical and radiological (radiographs and CT) mid- to long-term outcome of an open bone block procedure in recurrent posterior shoulder instability. Our hypothesis was that patients that underwent a posterior bone block procedure after recurrent posterior shoulder instability had a greatly improved stability but might develop osteoarthritis at mid- to long-term follow-up.

**Patients and Methods**

This is a retrospective case-control study of patients with recurrent posterior shoulder instability who underwent a posterior bone block augmentation. Ethical approval was obtained from the cantonal ethics committee a declaration of consent was signed by all participating patients. From 1999 to 2015 twenty-one consecutive patients (21 shoulders) were treated with posterior bone block augmentation due to recurrent posterior shoulder instability. Inclusion criteria were met when the patient had a complete medical record regarding routine diagnostics (preoperative standard radiographs, MRI or CT of the shoulder) and clinical examination.
In order to reduce performance bias, we excluded the following patients from our analysis:

Two patients who had a later shoulder arthroplasty, two patients with multidirectional shoulder instability, and one patient with poor medically controlled convulsive disorder leaving 16 eligible patients.

At the time of final follow-up one of these patients had died unrelated to the surgery and another one was lost to follow-up.

The resulting study group consisted of fourteen patients (14/16, 87%; 10 male, 4 female), who agreed to partake in a questionnaire survey (ASES and WOSI scores). Thirteen patients could also be clinically and radiologically re-examined.

The median age at the time of surgery was 26 (range 16-41) years. Prior surgery was performed in 6 of the patients.

Based on an initial trauma triggering the instability either documented in the medical records or the survey we divided the patients into a traumatic and atraumatic group. In 8 (57%) patients the first episode of instability was the result of a clear traumatic event. Out of this group 4 patients received the bone block procedure as the primary stabilization procedure, the other 4 as a revision after failed soft tissue stabilization procedures.

A bone block procedure as a revision after failed soft tissue stabilization procedures was done in 50% (n=7) of all cases (traumatic and atraumatic).

In our cohort mild to moderate dysplasia of the glenoid with rounding of the postero-inferior glenoid rim and convexity of the inferior bony glenoid was seen in the majority of cases (n=10, Table I, indication =1). In 4 of the patients of the traumatic group a bone deficiency was radiologically interpreted as posttraumatic bone deficiency (Table I, indication =2). Further details regarding the study cohort are provided under Table 1.
All patients with an atraumatic posterior shoulder instability (n=6) reported multiple subluxation events preoperatively. None of the patients in the reported study group required closed reduction.

The physical examination included the measurement of active and passive ranges of motion, stability testing (posterior apprehension sign, jerk test), and assessment of the Constant-Murley-Score (CMS), American Shoulder and Elbow Surgeons (ASES) score and Western Ontario Shoulder Instability Index (WOSI). Clinical outcome parameters included etiology of dislocation, complications, revision surgery, sports participation and work capacity. Recurrent instability and subjective shoulder value (SSV) were additionally evaluated. A positive jerk test and/or posterior apprehension test were defined as objective dynamic posterior shoulder instability. Tests for dynamic posterior instability were considered positive either with subluxation with pain or an uncomfortable sensation reproducing the symptoms of the patient.

Subluxation was defined as the subjective sensation of posterior translation of the humeral head over the glenoid rim followed by spontaneous reduction. An event requiring reduction by either the patient or a third person was defined as dislocation.

Radiographically, conventional radiography and CT scans were performed preoperatively and at the time of the last FU. The radiographic measurements and classifications were performed by a fellowship trained musculoskeletal radiologist (C.S.) who was blinded from the clinical results. Glenohumeral arthropathy was classified according to the modified classification of Samilson and Prieto. Due to lacking data on interobserver agreement for this classification the radiographs were graded by two observers (C.V., C.S.)

Posterior acromial height (PAH) as well as the anterior (AAC) and posterior acromial coverage (PAC) and acromial tilt were measured on the lateral radiographs according to Meyer et al. to assess acromial morphology and position to check a possible relationship of acromial anatomy to glenohumeral stability.
The CT scans were used to evaluate graft resorption, union and graft positioning. The resorption of the graft was graded according to Zhu et al, grade I if only the screw head, grade II if part of the screw shaft was exposed, and grade III if there was total bone block resorption with a fully exposed screw.

The glenoid version according to Friedman et al, and the centering of the humeral head according to Walch et al, as well as preoperative glenoid shape and bone loss at the posterior edge of the glenoid were additionally assessed. Glenoid erosion and morphology were determined based on the modified Walch criteria.

**Surgical Technique and postoperative regimen**

The patient was placed in a standard lateral decubitus position under general anesthesia. As a preoperative antibiotic prophylaxis a single shot of 1.5 g Cefuroxim was administered. A posterior transdeltoid approach to the shoulder joint was done through the interval between the infraspinatus and teres minor muscle. The infraspinatus tendon was not detached from the greater tuberosity. Through a vertical incision of the posterior capsule the posterior labrum was detached with preparation of the posterior glenoid rim. A tricortical bone graft was either harvested from the posterior acromion (1 case), scapular spine (4 cases) or the iliac crest (9 cases).

The harvested bone block was shaped and fixed with two 3.5mm screws in flush position to the posterior glenoid. The graft was positioned flush with the glenoid trying to avoid an overhang of the graft with respect to the glenoid surface. The graft was intraarticular and not recovered with capsule, thus corresponding to a graft as using in the Latarjet procedure for anterior instability.

The postoperative regimen consisted of immobilization of the shoulder joint in a neutral-wedge shoulder brace for 6 weeks. Active-assisted elevation and abduction was allowed to a maximum of 60° in neutral rotation, without internal rotation or transverse adduction in front.
of the scapula plane. After 6 weeks active-assisted elevation and abduction was allowed until full range of motion was achieved. With reaching full active range of motion gradual build-up of strength was started under physical therapy guidance.

**Statistical Analysis**

Normal distribution of data was assessed with the Shapiro-Wilk test. Descriptive data were calculated using mean and standard deviation. Preoperative and postoperative functional scores were compared with the paired t test (normal distribution) and the Wilcoxon signed-rank test (non-normal data). Subgroup analysis was conducted using the Mann-Whitney U test. For categorical variables, the Chi-squared and the Fisher exact test (if n<5) were used. Survival without signs of posterior instability in the entire series (including the 2 patients who died or were lost to follow-up) was assessed using Kaplan-Meier curve analysis. Significance was set as p<0.05 and all p values were two-tailed.

Inter-observer reliability was measured for dislocation arthropathy by means of the Intraclass Correlation Coefficient (ICC) for absolute agreement, with 1 indicating perfect reliability.

**Results**

The median age at the time of surgery was 26 years (range 16-41 years) and the median follow-up period was 9 years (range 4-20 years). Subluxation events before the index surgery were documented in 85% of cases, the median age at the event of first subluxation was 18 years (range 13-39 years). Two patients only reported subluxation after a trauma, the other patient had repetitive subluxation events without a preceding trauma or dislocation.

**Clinical Outcome**

At final follow-up, six patients had recurrence of posterior instability (46%). Four patients had physical findings of dynamic posterior instability (positive posterior apprehension/Jerk test) (31%). The mean SSV significantly improved over the preoperative state (58 ±19 vs. 73 ±17; p=0.005). The improvement of absolute and relative CMS, pain score, active anterior
elevation, abduction and abduction strength was not statistically significant (p>0.05). Active internal rotation was reduced by a mean of 2 CMS points at final follow-up (p=0.011). At final follow-up, the ASES score averaged 85 ±12 points, the WOSI score 715 ±475 points. Further details about clinical outcome are provided under Table II. At the time of final follow-up 10 patients (77%) reported no change in working capacity, two had undergone retraining and one patient remained on sick leave 9 years after the index procedure. Patients with an initial traumatic posterior shoulder dislocation (n=7) showed a significantly higher abduction strength and SSV compared with patients with initial atraumatic posterior shoulder instability symptoms (n=6; 12 vs. 23 CMS points, p=0.013; 84% vs. 62%, p=0.014). Surgery before posterior glenoid bone grafting had no significant influence on any clinical outcome measure (p>0.05). Recurrent dynamic postoperative instability (n=6) was significantly associated with inferior ASES (79 vs. 93 points; p=0.035) and WOSI scores (377 vs. 975 points; p=0.008) compared with patients with an ultimately stable shoulder (n=7). Patients with postoperative subluxations had a significantly lower relative CMS preoperatively than those with a stable postoperative shoulder (70% vs 85%; p=0.042).

**Radiographic Outcome**

Preoperative dislocation arthropathy on standardized conventional radiographs was mild (Class 1 Samilson and Prieto) in 3 cases. There was a significant increase in degenerative changes by at least one grade from preoperative to postoperative in 9 patients (p=0.005). (Figure 1, Table III) The acromial tilt, AAC, PAC, and PAH measured on the preoperative conventional radiographs averaged 58° ± 23°, 6° ±10°, 54° ±11°, and 24mm ± 7mm, respectively. Interobserver reliability was reported to be either excellent or good for acromial tilt, PAH, AAC and PAC. PAH was significantly higher in the traumatic, compared to the atraumatic group (27mm ± 6mm vs 20mm ± 5mm, p=0.038). Otherwise, no significant differences in those with initial
traumatic posterior shoulder dislocation (n=7) compared with patients with initial atraumatic 
posterior shoulder instability symptoms (n=6; p>0.05) could be shown. None of the factors were significantly associated with self-reported postoperative subluxation 
events (p>0.05).

Glenoid version measured on the CT scans was preoperatively -7.5° ±6° and postoperatively -
3.9° ±4° (p=0.005) at the final follow-up.

In 4 cases, a bone defect at the posterior glenoid margin was found. The mean preoperative 
posterior glenoid defect was 5% ±9% (range 6-27%), measured as described by Sugaya H. 18. 
The rest showed no preoperative posterior bone defect.

In 75% (n=9/12) the preoperative CT scan showed a centered humeral head without signs of 
degeneration or static posterior subluxation and a mean subluxation index of 56%.

Preoperatively only one patient showed a static preoperative posterior subluxation without 
degeneration (Walch B0, subluxation index >65%), one patient showed a preoperative 
narrowing of the posterior joint space with posterior subluxation of the humeral head (Walch 
B1, subluxation index >65%) and another patient showed a borderline centering of the 
humeral head with narrowing of the posterior joint space.

At FU the glenoid was classified as B0 in 4 cases, none of them showed a posterior 
subluxation preoperatively. The two patients with a static posterior subluxation 
preoperatively, both showed a centered humeral head with a normal subluxation index at FU.

We evaluated the position of the graft as optimal in 86% (n=12) of the cases, in the remaining 
2 patients the graft was positioned with a lateral step of 2mm. The humeral head was centered 
in 71% (n=10/14) of cases, the remaining 4 patients showed a posterior subluxation. At 
follow-up major graft resorption (grade II) was detected in 8 (62%) cases (Figure 2). Osseous 
consolidation was seen in all cases.

The SSV remained postoperatively significantly lower in those with major graft resorption 
(68% vs. 86%; p=0.048). Major graft resorption was not significantly associated with
postoperative instability symptoms or humeral head subluxation. Humeral head subluxation was not significantly associated with any clinical outcome parameter (p>0.05). The inter-observer reliability for dislocation arthropathy was excellent (r=0.94; 95% CI 0.83 - 0.98).

Complications and Reoperations

Of note, that two operated patients had been excluded because they had undergone TSA in the postoperative period. In our cohort total of 3 (21%) patients underwent a reoperation following the index surgery. In one patient the reoperation was done due to persistent pain and soft tissue snapping in the region of the screw with screw removal due to disturbing screws 2.8 years after the bone block procedure.

The second patient underwent a diagnostic arthroscopy and screw removal with an additional posterior soft tissue stabilization due to persistent pain 2.3 years after the index procedure. One patient had 4 documented reoperations after the posterior bone block procedure. He underwent a soft tissue stabilization 7 months before the index surgery. Due to persistent pain of unclear origin a diagnostic arthroscopy was done 1.1 years after the bone block procedure with an additional posterior soft tissue stabilization. Furthermore, an anteroinferior soft tissue stabilization was done due to multidirectional instability over time. 2 years after the index surgery another diagnostic arthroscopy including a microbiological sampling was done which showed a low grade Cutibacterium acnes infection so that an antibiotic treatment was initiated over a time period of three months. Persistent pain 5 months after the last arthroscopic surgery led to another shoulder arthroscopy with once more microbiological sampling, at this time with negative results. In the follow-up 19,4 years after the index procedure this patient presented with persistent shoulder pain (SSV 70%, compared to 60% preoperative) with moderate to severe osteoarthritis.

Survival Analysis


The overall rate of survival without a positive posterior apprehension or Jerk test at final follow-up was 83% at 5 years and 46% at 10 and 20 years (Fig. 3-A). The survival rate with postoperative subluxation or re-dislocation as the end point was 83% at 5 years and 32% at 10 and 20 years (Fig. 3-B).

Discussion

The most important findings of this study were, that almost half of the patients reported a recurrent or persistent dynamic posterior instability after a mean follow-up period of 9 years. Nevertheless, the SSV had improved in most patients representing 75% of a normal shoulder. Although there are favorable short- to mid-term clinical and radiographic results in the literature there is controversy regarding long-term results of posterior bone block procedures. Servien et al\textsuperscript{16} showed good clinical and radiological results after a mid-term follow-up of 6 years. One out of 21 patients complained of persistent apprehension, another had recurrent dislocations of the shoulder.\textsuperscript{16} Meuffels et al\textsuperscript{10} published the only long-term study with a median follow-up of 18 years following a mid-term report with a 6-year follow-up. The clinical results deteriorated significantly over time. Poor long-term results were also shown with a high rate of recurrent posterior instability and glenohumeral arthritis. After a mean follow-up of 18 years only 3 out of eleven patients had a stable shoulder, all showed signs of osteoarthritis. Interestingly and in agreement with our data, the clinical outcome was significantly better in patients with a traumatic onset of posterior shoulder instability. In our cohort, patients with a traumatic onset (n=7) showed postoperatively a significantly higher SSV (84\% vs. 62\%, p=0.014) but also abduction strength (23 vs. 12 Constant points, p=0.013) compared with patients with initial atraumatic posterior shoulder instability symptoms (n=6). The tested instability rate in the traumatic group was 14\% (n=1) compared to the atraumatic group with 50\% (n=3) during clinical FU.
In contrast to our results and those of Meuffels et al, Godeneche et al reported no difference in functional outcome scores for traumatic and atraumatic posterior shoulder instability. However, in this study surgical treatment included Bankart repair, capsular retention as well as bone-block-procedures without doing a subgroup-analysis regarding the operative treatment method. Camenzind et al could also not find a significant difference between traumatic posterior bone loss and dysplastic glenoids regarding final clinical outcomes.

Resorption rate in our study was determined based on the CT images with 62% of the patients showing major resorption of the graft (grade II). Compared to our findings Meuffels et al described a resorption rate of 18% in conventional radiographs but without grading of the resorption. Clavert et al described a major resorption rate in nearly one-third of the study population and another one third which showed partial lysis of the bone blocks. Camenzind et al described partial lysis of all grafts at a mean follow-up of 7.3 years after arthroscopic bone grafting. Interestingly, our patients with major resorption of the bone block were pre- and postoperatively significantly worse in SSV and Constant scores. Conversely, resorption of the bone block was not related to persistent or recurrent instability symptoms or static posterior subluxation.

The incidence of glenohumeral osteoarthritis in our study group increased by one grade according to Samilson and Prieto from pre-to postoperatively in 67% of the patients. Meuffels et al also demonstrated a significant increase of radiological osteoarthritis over a long-term follow-up with glenohumeral osteoarthritis in all 11 cases. Regarding acromial morphology Meyer et al described a significantly greater mean posterior acromial height (PAH) and posterior acromial tilt in patients with posterior instability compared to a control group. A higher and more horizontally oriented acromion was shown to be strongly associated with recurrent posterior shoulder instability. This may be explained by a possible mechanical predisposition in posterior instability with a lack of
osseous restraints created by the posterior aspect of the acromion predisposing to posterior  
instability. In our study population the mean PAH was 24mm ± 6mm. Meyer et al compared  
the PAH of patients with posterior instability (mean = 31mm) with a control group (mean =  
20mm). As stated by the authors, a cutoff value of 23mm for PAH was highly significant  
associated with developing a posterior instability (OR 32).

We did not observe a significant association between postoperative subluxation and acromial  
anatomy. The acromial tilt, AAC, PAC, and PAH were not significantly associated with  
postoperative instability symptoms (p>0.05).

There are limitations to this study with its retrospective study design. A control group is  
missing and with 14 cases the sample size is rather small. In addition the drop out of 2  
patients is an additional limitation but in view of the length of follow-up this is to be  
expected. Furthermore for clinical analysis one additional patient was missing and could not  
be included in the clinical results.

Heterogeneity concerning the study cohort itself, the surgical indications and the surgeries  
performed by 4 different surgeons as shown in Table 1 are additional limitations. All  
indications, however, were approved by the senior author (A) and the surgeries were  
performed under his supervision so that the variability is limited. As the necessity for such  
treatment is rare, marked differences in follow-up may represent another limitation.

Posterior instability is a rare and complex problem with no gold standard treatment. This case-
control study can give an insight into a mid- to long-term follow-up of one treatment option  
including clinical- and detailed radiological outcome measures.

**Conclusion**

The rate of tested recurrent instability at last FU was as high as 31% (n=4, atraumatic (n=3)  
vs. traumatic (n=1)) after a median FU of 9 years. Major graft resorption (Zhu grade II) was  
observed in 62% of cases.
Given the moderate improvement of clinical outcome scores, shoulder stability and the increase of degenerative joint changes (at least one grade (Samilson/Prieto) in 67%) a posterior bone block procedure is not a uniformly satisfying treatment option for recurrent posterior shoulder subluxation, especially for younger patients and cases of atraumatic posterior instability.

The hypothesis that shoulder stability is reliably restored must be rejected, whereas the hypothesis that osteoarthritis progresses can be confirmed.

**Literature**


**Figure Captions:**

Fig 1: Pre- (a) and postoperative (b) anteroposterior (ap)-shoulder radiographs of a 41-year old male patient, left non-dominant shoulder, that underwent posterior bone block augmentation of the glenoid due to recurrent posterior shoulder instability.
Nine years postoperatively a progression of the glenohumeral osteoarthritis can be observed (Samilson-Prieto from grade 1 to 2).

Fig 2: Postoperative CT scan of a left dominant shoulder 7 months (top) and 9 years (bottom) after posterior bone block augmentation of the glenoid (bottom) due to recurrent posterior shoulder instability. A progression of the graft resorption can be seen. A major bone block resorption (Zhu Grade II) can be observed at the final follow-up.

Fig 3: Kaplan-Meier survivorship analysis. Fig. 3-A The rate of survival without a positive posterior apprehension or Jerk test at final follow-up was 83% at 5 years and 46% at 10 and 20 years. Fig. 3-B The rate of survival without postoperative subluxation or re-dislocation was 83% at 5 years and 32% at 10 and 20 years.
### Table I: Etiology of instability, indication for surgery, surgeon, graft type

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<th>Patient</th>
<th>Atraumatic (=0), Traumatic (=1) shoulder instability</th>
<th>Hyperlaxity (0=no, 1=yes)</th>
<th>Indication 1-dysplasia 2-bone loss R-revision after previous soft-tissue stabilization</th>
<th>Surgeon</th>
<th>Graft type 1= posterior acromion 2= scapular spine 3= iliac crest</th>
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Table II: Clinical findings preoperatively and at final FU.

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<td>AAE, °</td>
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<td>+ 14</td>
<td>0.317</td>
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<td>Abduction, °</td>
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<td>172 ±14</td>
<td>+ 14</td>
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<td>External rotation, °</td>
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<td>- 7</td>
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<td>Satisfaction, n (%)</td>
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CS = Constant score; SSV = Subjective Shoulder Value; ROM = range of active motion; AAE = active, anterior elevation

* Data are presented as mean ± standard deviation
Table III: Radiographic results preoperatively and at final FU.

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<th>Glenohumeral arthropathy classification of Samilson and Prieto&lt;sup&gt;16&lt;/sup&gt;</th>
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Fig. 1
Fig 3A
Fig. 3B