



Autologous matrix induced chondrogenesis plus peripheral blood concentrate (AMIC+PBC) in chondral lesions at the ankle as part of a complex surgical approach - 5-year follow-up



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ABSTRACT

Background: The aim of the study was to assess 5-year-follow-up (5FU) after Autologous Matrix Induced Chondrogenesis plus Peripheral Blood Concentrate (AMIC+PBC) in chondral lesions at the ankle as part of a complex surgical approach.

Methods: In a prospective consecutive non-controlled clinical follow-up study, all patients with chondral lesion at the ankle treated with AMIC+PBC from July 17, 2016 to May 31, 2017 were included. Size and location of the chondral lesions, the Visual-Analogue-Scale Foot and Ankle (VAS FA) and the EFAS Score before treatment and at 5FU were analysed and compared with previous 2-year-follow-up (2FU). Peripheral Blood Concentrate (PBC) was used to impregnate a collagen I/III matrix (Chondro-Gide, Wolhusen, Switzerland) that was fixed into the chondral lesion with fibrin glue.

Results: One hundred and twenty-nine patients with 136 chondral lesions were included in the study. The chondral lesions were located as follows (n (%)), medial talar shoulder only, 62 (46); lateral talar shoulder only, 42 (31); medial and lateral talar shoulder, 7 (10); tibia, 18 (13). The average for lesion size was 1.8 cm², for VAS FA 45.7 and for EFAS Score 9.8. 2FU/5FU was completed in 105 (81 %)/104(81 %) patients with 112/111 previous chondral lesions. VAS FA improved to 79.8/84.2 and EFAS Score to 20.3/21.5 (2FU/5FU). No parameter significantly differed 2FU and 5FU.

Conclusions: AMIC+PBC as part of a complex surgical approach led to improved and high validated outcome scores at 2FU/5FU. 2FU and 5FU did not differ.

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1. Introduction

The optimal treatment for chondral defects at the ankle is debatable [1]. Possible options are distraction, debridement, abrasion, microfracture, antegrade or retrograde drilling, mosaicplasty or osteochondral autograft transfer system (OATS), autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), autologous matrix-induced chondrogenesis (AMIC), allogeneic stem cell transplantation, allograft bone/cartilage transplantation, or matrix-associated stem cell transplantation (MAST) [2–12]. MAST showed good results up to 5-year follow-up [1]. In 2016, the local government re-categorized MAST, i.e. the

included bone marrow aspirate concentrate (BMAC) for impregnation of the matrix, as stem cell manufacturing and heterologous transplantation [13]. Consequently, MAST and all other procedures including BMAC were not "subject to disclosure" as before but "subject to authorization" [13]. Therefore, the authors' institution was not authorized to perform MAST after July 16, 2016 [13]. Consequently, the method was changed by replacing BMAC as part of MAST to Peripheral Blood Concentrate (PBC) resulting in AMIC+PBC [13]. The effect of replacing MAST (including BMAC) by AMIC+PBC was unclear and a study was conducted to compare MAST with AMIC+PBC [13]. AMIC+PBC led to similar improved and high validated outcome scores at 2-year follow-up (2FU) in comparison with MAST [13]. No method related complications were registered [13]. Longer follow-up was considered to be important [13]. Therefore, the initial study cohort was followed until 5-year follow-up (5FU). The aim of this study was to assess the 5FU of AMIC+PBC and comparison with earlier 2FU.

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2. Material and methods

In a prospective consecutive non-controlled clinical follow-up study, all patients with chondral lesion at the ankle that were treated with AMIC+PBC from July 17, 2016 to May 31, 2017 were included.

2.1. Inclusion criteria

The only inclusion criterion was AMIC+PBC at the ankle. 141 patients were eligible for inclusion.

2.2. Exclusion criteria

Exclusion criteria were bilateral treatment ($n = 3$ patients (2 %)) and AMIC+PBC at more than one joint surface, i.e. talus and tibia ($n = 9$ patients (6 %)). Patients with revisions including joint preserving procedures were not excluded. No other exclusion criteria were defined.

2.3. AMIC+PBC indication and techniques

The indication for surgery as such with potential inclusion of AMIC+PBC was based on clinical symptoms as for example pain or instability and MRI-findings [13,14]. The definite indication for AMIC+PBC during the surgery was subjectively made by the surgeon during initial arthroscopy for unstable, fragmented or missing cartilage [4,13]. The other procedures included joint preserving measures such as synovectomy, lateral ligament reconstruction, peroneal tendon debridement/tenolysis, Gastrocnemius tendon lengthening and others [13,15,16]. The AMIC+PBC procedure was performed through a medial approach for medial chondral lesions and through a lateral approach for lateral or central lesions (Fig. 1a-c) [13]. Malleolar osteotomies were performed when judged to be necessary to adequately reach the chondral lesion [1]. Medial malleolar and anterior tibial osteotomies were performed as single oblique saw cut [1]. Lateral malleolar osteotomies were performed as anterior window cut with the anterior syndesmotom ligament attached to the cut-out fragment and the central and posterior syndesmotom ligaments attached to the remaining main fragment [1]. The osteotomized fragments were later fixed with lag screws [1]. The chondral lesion was debrided until stable surrounding cartilage was present. Subchondral cysts (MRI-stage 5, Hepple and Winson / Bristol classification) were cleared out [1,14]. Microfracturing with a 1.6 mm Kirschner wire was performed at intact subchondral bone, and at the ground and walls of subchondral bone defects [1]. Bone defects of more than 3 mm depth (cysts and others) were filled with autologous cancellous bone harvested from the distal tibia not exceeding the surrounding subchondral bone level. 15 cc peripheral venous blood was harvested with a special syringe (Arthrex-ACP, Arthrex, Naples, FL, USA). The syringe was centrifuged (10 min, 1500 rotations per minute) [13]. After centrifugation, the supernatant was aspirated including the entire fluid layer directly above the erythrocyte layer. PBC is a modification of Platelet Rich Plasma (PRP) and Autologous Conditioned Plasma (ACP) [13,17–19]. PRP is also specified by addition of an anticoagulant, such as citrate dextrose A to prevent platelet activation prior to its use [13,19]. This addition is not included in PBC by definition [13]. The difference of PBC to ACP is that for PBC the aspirated supernatant (after centrifugation) included the entire fluid layer directly above the erythrocyte layer, whereas ACP includes the only the clear fluid above [13,17]. The supernatant was used to impregnate a collagen I/III matrix (Chondro-Gide, Geistlich, Wolhusen, Switzerland) by submerging the matrix completely into the supernatant for 3 min (impregnation) [13]. The matrix was cut to the size of the cartilage lesion roughly before and more exact after the impregnation [13]. The impregnated matrix was fixed into the

chondral lesion with fibrin glue (Tissucoll or Tisseel, Baxter, Deerfield, IL, USA) (Fig. 1b) [13]. The matrix fixation was tested by moving the joint several times [13]. Adequate fixation was approved when the matrix stayed in place in the chondral lesion [13]. Closure was performed following the local standard with layer wise closure (joint capsule, subcutaneous, skin) [13]. The postoperative treatment included partial weight bearing with 15 kg with orthosis (Vacuped, Oped, Valley, Germany) for six weeks [13]. Motion of the joint was restricted for two days, and joint motion in the orthosis, i.e. approximately 10° range of motion, was started at day three after surgery [13]. Postoperative consultations were performed at 6 weeks, 3 months and then yearly [13].

2.4. Follow-up

2FU/5FU was defined as follow-up 22–26/56–64 months postoperatively.

2.5. Assessment

Before surgery and at follow-ups except at 3 months, radiographs (bilateral views (anteroposterior/Mortise and lateral with full weight bearing)) or Weightbearing Computed Tomography (WBCT) scans were obtained. Magnetic resonance imaging (MRI) was obtained before surgery and at yearly follow-ups with so-called "Cartilage-mapping" with slice thickness of 0.4 mm was obtained, and Hepple and Winson / Bristol classification used (Fig. 1d - g) [14,20]. Visual Analogue Scale Foot and Ankle (VAS FA) and EFAS Score were registered [21,22]. The EFAS Score was available at the authors' institution before official publication because the institution was included in the development and validation of the score [22]. The defect size and location were assessed intraoperatively. Complications and treatment failure were registered.

2.6. Statistical analysis

The data was analysed with SPSS software (IBM SPSS Statistics 25, IBM, Armonk, NY, USA). An unpaired t-test was used for statistical comparison of VAS FA and EFAS Score preoperatively and at follow-ups. Before using the paired t-test, the data were investigated regarding the distribution and the data were proven to be normally distributed. Chi2-test was used to compare the different MRI stages and ONEWAY-ANOVA (potential Scheffe Post Hoc test) was used to analyse differences of the follow-up scores for different lesion location, size (lesion size ≤ 2 cm or > 2 cm) and MRI-stage. The significance level was defined as $p < 0.05$. A power analysis that was carried out before each specific statistical justified sufficient power (> 0.8).

3. Results

3.1. Patients

One hundred and twenty-nine patients with 136 chondral lesions were included in the study. Table 1 shows the demographic parameter, preoperative VAS FA, EFAS Score and suspected cause and mechanism of the chondral lesions.

3.2. Chondral lesions

The chondral lesions were located as follows (n (%)), medial talar shoulder only, 62 (46); lateral talar shoulder only, 42 (31); medial and lateral talar shoulder, 7 (10) (7 lesions medial plus 7 lesions lateral = 14 lesions, i.e. 10 % of all lesions); tibia, 18 (13). The lesion size was 1.8 cm² on average (range, 0.6–4 cm²). Table 2 shows the

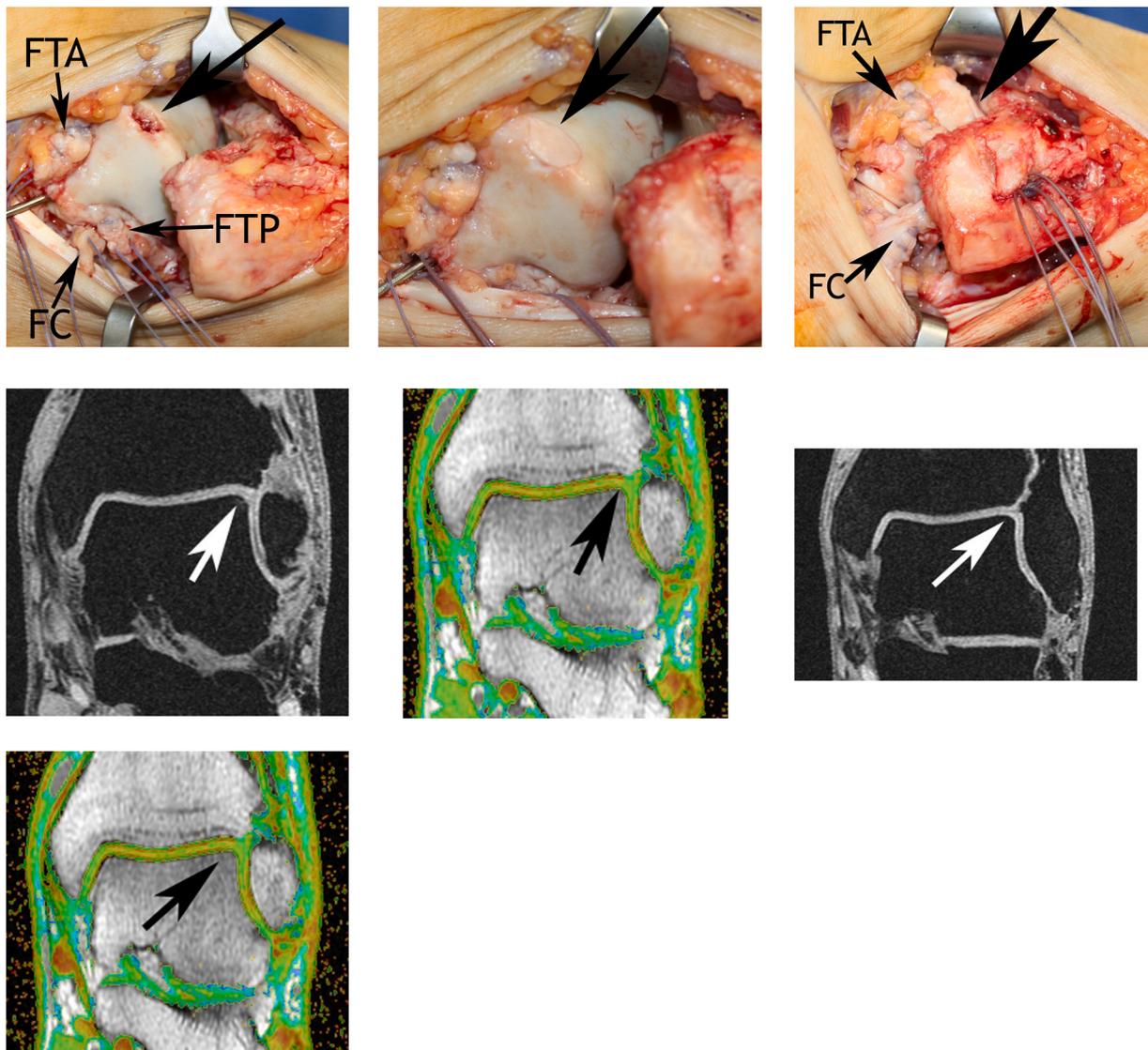


Fig. 1. a-g. AMIC+PBC at left lateral talar shoulder in a 43-year-old male patient. The VAS FA/EFAS Score preoperatively was 52.6/12.6. Fig. 1a shows the chondral lesion (large black arrow). The size of the lesion was 1.4×1.8 cm (2.5 cm^2), and the maximal depth 0.8 cm. All three lateral ligaments (Fibulocalcaneal (FC), anterior and posterior tibiotalar (FTA and FTP) were elongated and partly dystopic. The ligaments were detached from the fibula, the dystopic parts were debrided and remaining ligaments were sheathed with a suture (Orthocord, DepuySynthes, Raynham, MA, USA). A 2.0 mm Kirschner wire was inserted in the talus as joystick. Figure 2b shows the chondral lesion after AMIC+PBC (large black arrow) including autologous cancellous bone transplantation into the subchondral bone lesion, harvested from the distal tibia. Fig. 1c shows the situs after reinsertion of the lateral ligaments. 4.5 mm drill holes were drilled from the origins of the three ligaments (FTA, FC, FTP) towards proximal and lateral. The sheathed ligaments were pulled into these holes, and the sutures were knot at the proximal end of the holes. The patient completed follow-up at 24.2/60.3 months. The VAS FA/EFAS Score was 89.6/22.1 at 2FU and 90.1/22.5 at 5FU. Fig. 1d shows a coronal MRI reformation of "Cartilage-mapping" T2 specification with 0.4 mm slice thickness at 2FU. At the lateral talar shoulder (arrow, location of earlier chondral lesion), the cartilage is clearly visible as well as the minimal joint gap between the tibial and talar cartilage despite minimal irregular surface of the subchondral bone. No subchondral bone oedema is visible (MRI-stage for chondral or osteochondral lesion negative)[14]. Fig. 1e shows a colour coded visualization of the cartilage at 2FU. At the lateral talar shoulder (arrow, location of earlier chondral lesion), the fluid percentage/content is not increased (green colour). An increased fluid percentage/content would be a sign for chondral damage which often precedes morphologically visible damage[1,13]. Fig. 1f and g show MRI images at 5FU with similar interpretation and scoring as 2FU.

MRI-stage of the lesions. Most common stages were 1 (cartilage lesion only) in 54 lesions (42 %).

3.3. Additional surgical procedures

Table 3 shows the additional surgical procedures. Synovectomy was performed in all cases, lateral ligament reconstruction in 99 % and Gastrocnemius tendon lengthening in 93 %.

3.4. Complications / revisions

No complications (Neuropraxia, stiffness, wound healing delay, thrombosis, infection) were registered until latest follow-up. Three patients (2 %) underwent another joint preserving ankle surgery

after 8, 13 and 16 months including another AMIC+PBC procedure. Each patient reported subsequent ankle sprains during sports activity before the second surgery. These 3 patients completed follow-up.

3.5. Follow-up

2FU/5FU was completed in 105 (81 %)/104(81 %) patients with 112/111 previous chondral lesions after 23.8/60.2 months on average (range 22–25/55–63 months).

VAS FA improved to 79.8/84.2 and EFAS Score to 20.3/21.5 (2FU/5FU). Both scores differed between 2FU/5FU and preoperative (t-test, each $p < 0.05$). Both scores did not differ between 2FU and 5FU (t-test, each $p > 0.6$).

Table 1

Demographic parameter, preoperative VAS FA, EFAS Score, cause and suspected mechanism of chondral lesions (patient-based analysis, i.e. 129 patients in total for each group).

Age (average, range)	35.6 (13–68)
Gender (male; n (%))	77 (60)
VAS FA (mean, range)	45.7 (17.5–78.9)
EFAS Score (mean, range)	9.8 (0–20)
Cause (n (%))	
Traffic accident	5 (4)
Sports-related trauma	62 (48)
Non-vehicular / sports-related trauma	43 (33)
Deformity without trauma	7 (5)
Hindfoot/ankle varus	4 (3)
Hindfoot/ankle valgus	3 (2)
Other	5 (4)
Unknown	5 (4)
Mechanism (n (%))	
Fracture	7 (5)
Single sprain	21 (16)
Multiple sprains	70 (54)
Other	3 (2)
Unknown	28 (22)

Cause and mechanism are independently listed.

The MRI stage improved between preoperative and 2FU/5FU (Table 2; Chi2, each $p < 0.01$), and did not differ between 2FU and 5FU (Table 2, Chi2, $p = 0.82$).

In 42/41 of the previous lesion locations (38%/37%)(2FU/5FU), no lesion was visible in the MRI at follow-up (MRI-stage for chondral or osteochondral lesion negative) [14]. Different lesion location (medial/lateral talar shoulder, tibia), lesion size (≤ 2 cm or > 2 cm) or MRI-stage did not lead to different VAS FA or EFAS Score at follow-ups (ONEWAY-ANOVA, all $p > 0.05$, Post Hoc-test not applicable). Highest scores were registered in lesions located at the tibia, size ≤ 2 cm, and MRI-stage 1. The three patients with second surgery before follow-ups did not differ significantly regarding VAS FA / EFAS Score or other parameter from the remaining patients (data not shown).

4. Discussion

This is the first study analysing 5FU after AMIC+PBC in chondral defects of the ankle. An ongoing prospective data acquisition of all surgically treated patients including yearly follow-up at the authors' institution is the basis for this ongoing analysis [13]. The follow-up parameters did not significantly differ between 2FU and 5FU including patient reported outcome measures (VAS FA / EFAS Score) and MRI stage of the chondral lesions (Tables 2 and 3). AMIC+PBC as part of a complex surgical approach allow for stable and favourable results after 2FU until 5FU. No AMIC+PBC related adverse effects have been registered. The comparison with earlier

Table 2

MRI based classification of 129 patients with 136 chondral lesions.

Stage and stage description	Preop n (%)	2FU n (%)	5FU n (%)
1	54 (40)	40 (36)	42 (38)
2a	43 (32)	19 (17)	16 (14)
2b	9 (7)	1 (1)	2 (2)
3	7 (5)	3 (3)	2 (2)
4	7 (5)	1 (1)	2 (2)
5	16 (12)	6 (5)	6 (5)
MRI-stage for chondral or osteo- chondral lesion negative	0 (0)	42 (38)	41 (39)

Preop, preoperatively; 2FU, 2-year follow-up; 5FU, 5-year follow-up.

Lesion-based analysis, preop, n = 136; 2FU, n = 112; 5FU, n = 111. Distribution preop versus 2FU / 5FU; Chi2, $p < 0.01$. Distribution 5FU versus 2FU, Chi2, $p = 0.82$.

Table 3

Additional procedures performed during surgery.

Procedure	n (%)
Arthroscopy	129 (100)
Synovectomy	129 (100)
Debridement / tenolysis peroneal tendons	128 (99)
Lateral ligament reconstruction / augmentation	128 (99)
Gastrocnemius tendon lengthening	120 (93)
Medial malleolus osteotomy	17 (13)
Lateral malleolus osteotomy	1 (1)
Anterior tibial osteotomy	1 (1)
Autologous cancellous bone transplantation (under MAST)	34 (26)
Correction of malalignment	3 (2)
Correction above ankle	0 (0)
Correction below ankle	3 (2)

Patient-based analysis

published 5FU of MAST, confirms equivalency of MAST and AMIC+PBC over five years [1]. Consequently, the main difference of both procedures, i.e. using bone marrow aspirate concentrate (BMAC) or PBC has no influence on 2FU/5FU [1,13]. What does this mean? The use of BMAC and PBC as adjunct might not have an effect on the tissue development and/or the clinical outcome [1,13]. If so, AMIC alone (without BMAC or PBC) would allow for the same results [13]. As we did not perform AMIC without PBC, we tried to find comparable results from the literature [23–31]. The different studies with up to 60 cases and up to 8-year follow-up are difficult to compare because none of the studies included a validated outcome score as our study [13]. Our study includes more cases than all other current studies [23–31]. Our results are best comparable with the results of MAST from Murphy et al [32]. We are again surprised about the low rate of deformities and instabilities from other studies [1,23–33]. Either, these pathologies were not present or were not registered [13]. In our understanding deformity and above all instability is the most important and common prerequisite for chondral lesions at the ankle (see further below) [13]. We are aware that especially the high percentage and extent of additional procedures had influence on the study results and this issue will be discussed extensively below (see below, limitations). We observed a high percentage of lesions limited to the cartilage as before [1,13,33]. We could not detect follow-up score differences between different location, size or MRI-stage of the chondral lesions, as reported before [1,13,33]. We observed only a trend and no significance to higher follow-up scores towards smaller lesions, located at tibia and lower MRI-stages [1,13,33]. The follow-up scores after MRI-stage V (subchondral cyst) were not the lowest as shown in other studies [1,5,13,14,31,33,34]. AMIC+PBC worked also for larger lesions and "higher" MRI-stages for two and for five years [13,33]. We used BMAC before PBC to allow for a high concentration of mesenchymal stem cells [1,13,32,35]. The concentration of mesenchymal stem cells in PBC in comparison with BMAC is questionable [13,35]. We did not

investigate the content of BMAC or PBC cytologically and cannot answer this question [13,35]. Another potential effect could be chemo tactical "attraction" of mesenchymal stem cell from PBC as described for PRP [13,19,35]. This is all unclear and debatable [13,35].

4.1. Limitations

Limitations of the study are: uncomplete follow-up, subjective indication for treatment, unclear influence of associated procedures, missing control group, missing outcome parameter for the created tissue, and matched-patient instead of a "real" control group [13]. More than 80 % of patients completed follow-up which is comparable to other clinical studies and seems therefore to be adequate [13]. One patient that completed 2FU did not complete 5FU. The indication for AMIC+PBC was subjectively made by the surgeon during initial arthroscopy [1,13,33]. This is the typical decision-making process also in other studies but does still not follow objective parameters [1,13,33]. We believe that "surgical" decision-making is still better than indication based on any kind of imaging-based staging with the described limitations [1,13,33]. The indication for AMIC+PBC was not similar to the indication for surgery as such which was based on clinical symptoms and radiographic findings [1,13,33]. The simultaneous additional procedures may confound the results as in all other studies we are aware of (Table 3) [5,13,33,36]. The additional procedures were considered to be necessary to restore joint function (for example lateral ligament reconstruction in 99 % or Gastrocnemius tendon lengthening in 93 %) [13]. Other procedures were performed on a regular basis (for example synovectomy in 100 %) [13]. The percentage of Gastrocnemius lengthening is high and even increasing in comparison with earlier studies [1,13,33]. The indication for gastrocnemius lengthening is not clearly defined and debatable [1,13,33]. This and other studies have shown more advantages like decreased joint load than disadvantages like decreased calf muscle strength as basis for the indication [1,13,33]. Performing AMIC+PBC as single procedure would probably allow for a much more specific study results and conclusions [1,13]. However, we did not notice a single patient with just a chondral lesion and no other pathologies [1,13]. Based on our experience and considering the literature, we doubt that isolated chondral lesions are common [1,13]. We consider instability as the main cause for the chondral lesions [13]. Following this principle, treatment of the chondral lesion alone without treating the cause as for example the ligamentous instability would be inadequate [1,13]. In contrast, our treatment concept was and is still to address all pathologies in addition to the chondral lesion [1,13]. If we would exclude all patients with ligamentous repair and/or Gastrocnemius lengthening from the study, we would exclude 99 % of our patients [13]. This would result in a study cohort that does not reflect the real situation at least in our institution [13]. In conclusion, AMIC+PBC as part of a complex surgical approach led to improved and high validated outcome scores at 2FU/5FU. 2FU and 5FU did not differ. No method related complications were registered.

Conflict of interest

None of the authors or the authors' institution received funding in relation to this study.

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