FussSprungg 18 (2020) 217—226

Online verfügbar unter www.sciencedirect.com

ScienceDirect

Fuß & Sprunggelenk

www.elsevier.com/locate/fuspru

Original Article

# Matrix-associated stem cell transplantation (MAST) versus autologous matrix induced chondrogenesis plus peripheral blood concentrate (AMIC+PBC) in chondral defects of the first metatarsophalangeal joint — A clinical cohort analysis

# Vergleich Matrix-Assoziierte Stammzelltransplantation (MAST) mit Autologer Matrixinduzierter Chondrogenese mit Peripherem Blutkonzentrat (AMIC+PBC) bei chondralen Defekten am Großzehengrundgelenk — eine klinische Kohortenstudie

**Martinus Richter*, Stefan Zech, Stefan Andreas Meissner, Issam Naef**

*Department for Foot and Ankle Surgery Rummelsberg and Nuremberg, Germany*

Received 9 April 2020; accepted 20 May 2020
Available online 15 June 2020

**KEYWORDS**
Chondral defect;
Matrix-associated stem cell transplantation (MAST);
Autologous matrix induced chondrogenesis (AMIC);

## Summary

*Background:* The aim of the study was to compare matrix-associated stem cell transplantation (MAST) with autologous matrix induced chondrogenesis plus peripheral blood concentrate (AMIC+PBC) in chondral defects at the first metatarsophalangeal joint (MTP1).

*Material and methods:* Patients with chondral defect at MTP1 that were treated with MAST from October 1, 2011 to July 15, 2016 ($n = 623$) or with AMIC+PBC from July 17, 2016 to March 19, 2018 ($n = 230$) were included. 480(89%)/176(89%) patients (MAST/AMIC+PBC) completed follow-up. Size and location of the chondral defects and the Visual-Analogue-Scale Foot and Ankle (VAS FA) and European Foot and Ankle Society Score (EFAS Score) before treatment and at follow-up were compared.

* Corresponding author at: Department for Foot and Ankle Surgery Rummelsberg and Nuremberg, Location Hospital Rummelsberg, Rummelsberg 71, 90592 Schwarzenbruck, Germany.
*E-Mail:* martinus.richter@sana.de (M. Richter).

https://doi.org/10.1016/j.fuspru.2020.05.002

Peripheral blood concentrate (AMIC+PBC);
First metatarsophalangeal joint

*Results:* In 20%/21% (MAST/AMIC+PBC) of patients no deformities in the forefoot were registered. The average were degree of osteoarthritis was 2.1/2.2 (MAST/AMIC+PBC). The chondral defect size was 0.9/1.0 $cm^2$ on average (MAST/AMIC+PBC). The most common location was metatarsal dorsal (31/33%), and in most patients one defect was registered (74/74%)(MAST/AMIC+PBC). Corrective osteotomy of the first metatarsal was performed in 80%/79% (MAST/AMIC+PBC). VAS FA/EFAS Score were preoperatively 53.6/52.6//48.4/46.8 and improved to 72.4/74.1//16.8/17.1 at follow-up (MAST//AMIC+PBC) on average. No parameter significantly differed between MAST and AMIC+PBC cohorts.
*Conclusions:* MAST and AMIC+PBC as treatment for chondral defects at MTP1 as part of a (complex) joint preserving surgery led to improved and high validated outcome scores in 2-year-follow-up. MAST and AMIC+PBC showed similar results.

**SCHLÜSSELWÖRTER**
Knorpeldefekt;
Matrix-Assoziierte Stammzelltransplantation (MAST);
Autologe Matrixinduzierte Chondrogenese mit Peripherem Blutkonzentrat (AMIC+PBC);
Großzehengrundgelenk

## Zusammenfassung

*Hintergrund:* Das Ziel der Studie der Vergleich der Matrix-Assoziierten Stammzelltransplantation (MAST) mit Autologer Matrixinduzierter Chondrogenese mit Peripherem Blutkonzentrat (AMIC+PBC) bei chondralen Defekten am Großzehengrundgelenk (MTP1).
*Material und Methoden:* Eingeschlossen und verglichen wurden Patienten mit chondralen Defekten an MTP1, die 01.10.2011-15.07.2016 mit MAST (n=623) oder 17.07.2016-19.03.2018 mit AMIC+PBC (n=230) behandelt wurden. 480(89%)/176(89%) Patienten (MAST/AMIC+PBC) wurden nachuntersucht. Größe und Lokalisation der chondralen Läsion und Visual Analog-Skala Fuß und Sprunggelenk (VAS FA) European Foot and Ankle Society Score (EFAS Score) wurden präoperativ und zum Nachuntersuchungszeitpunkt verglichen.
*Ergebnisse:* Bei 20%/21% (MAST/AMIC+PBC) der Patienten wurden keine Deformitäten im Vorfuß registriert. Das Arthroseausmaß war 2.1/2.2 (MAST/AMIC+PBC) im Durchschnitt. Die Defektgröße war 0,9/1,0 $cm^2$ (MAST/AMIC+PBC) im Durchschnitt. Die häufigste Defektlokalisation war Metatarsale dorsal (31/33%), und in den meisten Fällen wurde ein Defekt registriert (74/74%)(MAST/AMIC+PBC). Korrekturosteotomien des Metatarsale 1 wurden in 80%/79% (MAST/AMIC+PBC) durchgeführt. VAS FA/EFAS Score waren präoperativ 53.6/52.6//48.4/46.8 und verbesserten sich zum Zeitpunkt der Nachuntersuchung auf 72.4/74.1//16.8/17.1 (MAST//AMIC+PBC) im Durchschnitt. Parameterunterscheide zwischen den MAST/AMIC+PBC Kohorten bestanden nicht.
*Schlussfolgerungen:* MAST und AMIC+PBC als Behandlung von Knorpeldefekten an MTP1 als Teil eines (komplexen) gelenkerhaltenden Eingriff führten zu verbesserten und hohen validierten Nachuntersuchungsscores nach 2 Jahren. MAST und AMIC+PBC zeigten gleiche Ergebnisse.

## Introduction

The optimal treatment for chondral defects at foot and ankle including the first metatarsophalangeal joint (MTP1) is debatable [18]. Principle 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), allologous stem cell transplantation, allograft bone/cartilage transplantation, or matrix-associated stem cell transplantation (MAST) [1,3,4,6–8,11,15,16,24,25]. Most of those options have been used first or even exclusively in the ankle [1,3,4,6–8,11,15,16,24,25]. MAST was described as a modification of AMIC with a potentially higher concentration of stem cells in the implanted matrix, and also as a completely new method [5,16]. MAST was also used at MTP1 with encouraging 2-year-results and later 4–7-year results [12,18]. However, in 2016, the local government authorities re-categorized MAST, i.e. the included BMAC for impregnation of the matrix, as stem call manufacturing and heterologous transplantation [16,21]. Consequently, MAST and all other procedures including BMAC were not "subject to disclosure" as before but "subject to authorization" [21]. Therefore, the authors' institution was not authorized to perform MAST after July 16, 2016, and applied for authorization shortly

after [21]. The authorization process is still pending (status March 2020), and no approval for MAST, or any other procedure involving BMAC has been approved in the entire country [21]. Meanwhile, the authors' institution changed the treatment of chondral defects by replacing BMAC as part of MAST to Peripheral Blood Concentrate (PBC) resulting in AMIC+PBC [21]. The effect of replacing MAST (including BMAC) by AMIC+PBC is unclear [21]. Therefore, we conducted a study to compare MAST with AMIC+PBC [21]. As we used MAST before July 16, 2016, and AMIC+PBC after, we could not conduct a prospective controlled study. Consequently, a cohort comparison analysis was performed.

## Material and methods

### Techniques

The indication for surgery as such with potential inclusion of MAST/AMIC+PBC was based on clinical symptoms and radiographic findings [12,18]. The definite indication for MAST/AMIC+PBC procedures during the surgery was subjectively made by the surgeon for instable, fragmented or missing cartilage [12,18]. MAST was performed as previously described [12,18]. AMIC+PBC was performed in similar fashion except using PBC instead of BMAC for the impregnation of the matrix (detailed description below). The other procedures included joint preserving measures such as corrective osteotomies, cheilectomy, tendon debridement/tenolysis, and others [12,18]. The MAST/AMIC+PBC procedure was performed through a medial approach (Figs. 1—4) [12,18]. The chondral defect was debrided until stable surrounding cartilage was present. Subchondral cysts were cleared out (Fig. 4b) [12,18]. Microfracturing with a 1.6 mm Kirschner wire was performed at intact subchondral bone, and at the ground of subchondral bone defects [17]. Bone defects of more than 3 mm depth (cysts and others) were filled with autologous cancellous bone harvested locally from the resected bone (Fig. 4c).

#### BMAC versus PBC

For MAST including BMAC, 15 cc stem cell-rich blood was harvested during the procedure from the ipsilateral pelvic bone marrow with a Jamshidi needle (10 × 3 mm, Cardinal, Dublin, OH, USA) and a special syringe (Arthrex-ACP, Arthrex, Naples, FL, USA) through a stab incision [17,21]. For AMIC+PBC, 15cc peripheral venous blood was harvested with the same special syringe (Arthrex-ACP, Arthrex, Naples, FL, USA). For both, MAST including BMAC and AMIC+PBC, the syringe was centrifuged (10 min, 1500 rotations per minute) [17,21]. After centrifugation, the supernatant was aspirated including the entire fluid layer directly above the erythrocyte layer. Thus, PBC is a modification of Platelet Rich Plasma (PRP) and Autologous Conditioned Plasma (ACP) [2,9,21,23]. The difference of PBC to PRP is that for PBC no addition of an anticoagulant, such as citrate dextrose A to prevent platelet activation prior to its use as for PRP [2,21]. 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 [21,23].

#### Preparation of the matrix

The supernatant was used to impregnate a collagen I/III matrix (Chondro-Gide, Geistlich, Wollhusen, Switzerland) by submerging the matrix completely into the supernatant for 3 min (impregnation) [12,18]. The matrix was cut to the size of the cartilage defect roughly before and more exact after the impregnation [12,18]. When the chondral defect reached the limit of the chondral region, the matrix was placed 3 mm over this limit (Fig. 1b, plantar; Fig. 4d, dorsal) [12,18]. In chondral defects comprising the entire chondral surface at the sesamoid, the matrix covered the entire previous chondral surface (Fig. 2d). Closure was performed following the local standard with layer wise closure (joint capsule, subcutaneous, skin). The postoperative treatment included full weight bearing without orthosis or splint in cases without corrective osteotomy and with orthosis (Forefoot Relief Shoe, Bort, Weinstadt-Benzach, Germany) and splint (Hallufix Hallux Valgus Schiene, Hallufix AG, Grünwald, Germany) in cases with corrective osteotomies. Motion of the joint with dorsiflexion was started at the day of surgery. Postoperative consultations were performed at 6 weeks, 3, 12 and 24 months.

### Study design

#### Inclusion criteria

Patients treated with MAST from October 1, 2011 to July 15, 2016 were included (MAST cohort, $n = 623$) [21]. Patients with chondral defect at the ankle that were treated with AMIC+PBC from July 17, 2016 to March 19, 2018 were considered for inclusion prospectively and consecutively ($n = 230$). This data was gathered prospectively and continuously [12,16—19,21].

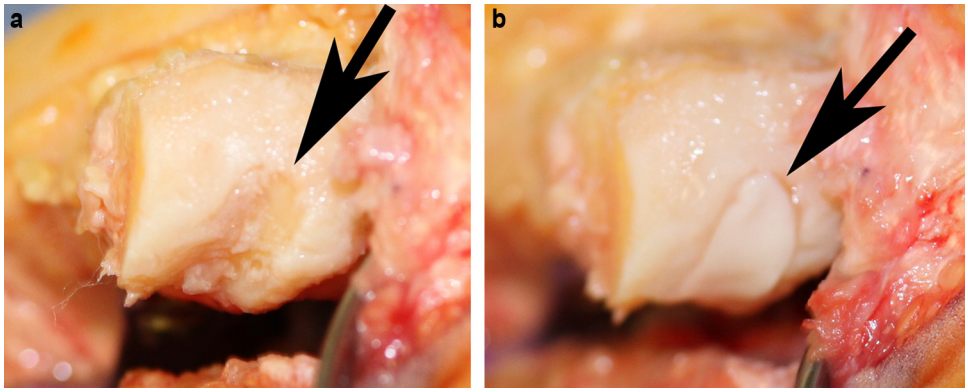


**Figure 1.** (a, b) Case from MAST cohort. Chondral defect at the first metatarsal head (a). The defect (black arrow) was specified as plantarly located, and the size 0.8 cm × 2.7 cm (2.2 $cm^2$) (a). (b) Shows the matrix (black arrow) in place.

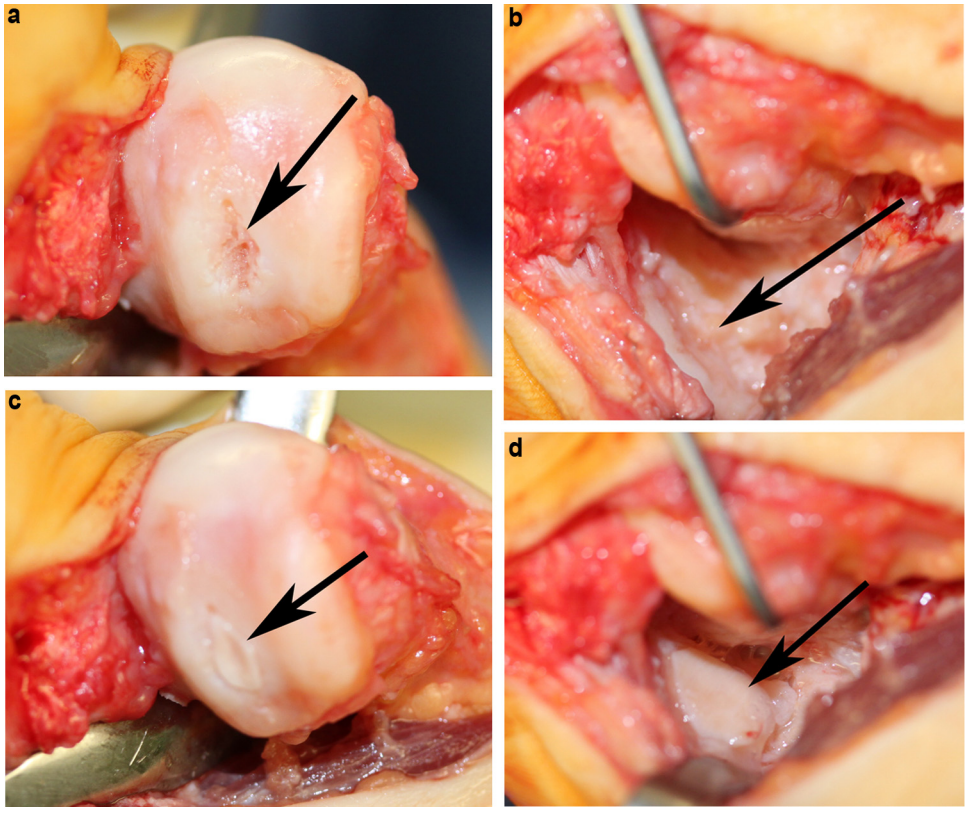


**Figure 2.** (a, d) Case from MAST cohort. Chondral defect at the first metatarsal head (a) and the medial sesamoid (b). The defect at the metatarsal (black arrow) was specified as plantarly located, and the size 0.8 cm × 0.5 cm (0.4 $cm^2$) (a). The defect at the medial sesamoid (black arrow) was specified as size 1.2 cm × 1 cm (1.2 $cm^2$) (b). (c and d) Show the matrix (black arrow) in place.

### Exclusion criteria

Patients with bilateral treatment ($n = 84$ (13%)/32 (14%) (MAST/AMIC+PBC)) were excluded from the study and 539/198 patients remained (MAST/AMIC+PBC). Patients that did not complete two-year-follow-up (defined as follow-up between 22 and 26 months postoperatively) ($n = 59$(11%)/22 (11%) (MAST/AMIC+PBC)) were excluded from the further analysis. Among those excluded patients, 15(3%)/6(3%) were revised including fusion of MTP1 and 5(1%)/2(1%) were revised including total joint replacement of MTP1. These patients were considered as unsuccessful joint preserving surgery and were excluded from the follow-up study. Patients with revisions including joint preserving procedures were not excluded

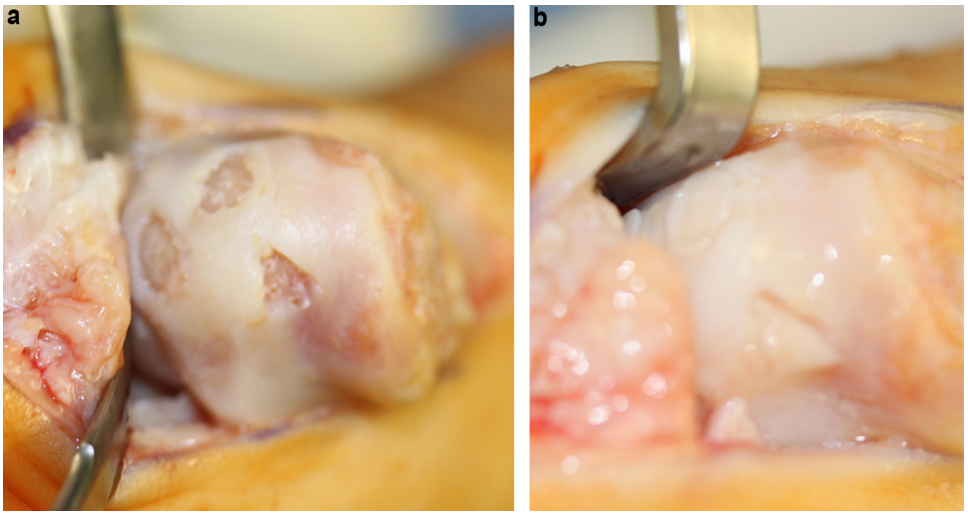


**Figure 3.** (a, b) Case from AMIC/PBC cohort. Three chondral defects at the first metatarsal head (a). One defect was specified as dorsally located, size 1.0 cm × 0.7 cm (1.7 $cm^2$); one as plantarly located, size 0.7 cm × 0.7 cm (0.5 $cm^2$); one as dorsally and plantarly located, size 0.9 cm × 0.6 cm (0.5 $cm^2$); (a). (b) Shows the three matrices in place.

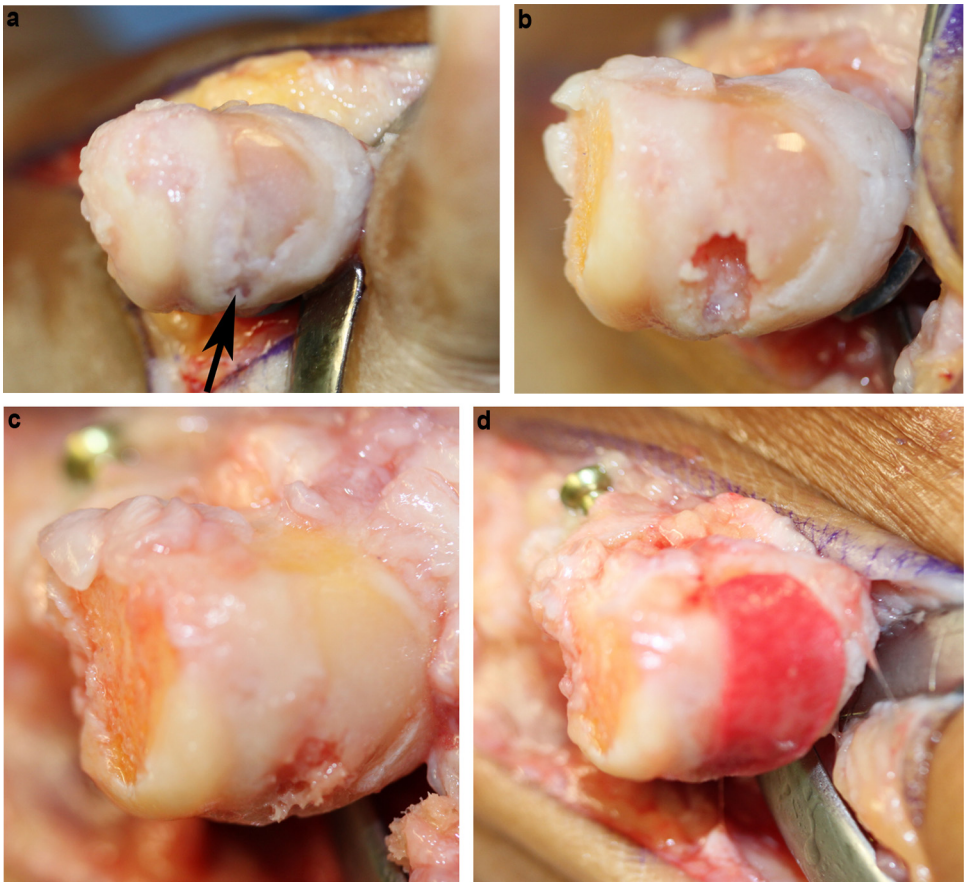


**Figure 4.** (a, d) Case from AMIC/PBC cohort. Chondral defect at the first metatarsal head (a). The defect was specified as dorsally and plantarly located, size 3.2 cm × 1.1 cm (3.5 $cm^2$) (a). A subchondral cyst was detected (black arrow) (a). (b) Shows the status after resection of the medial pseudo-exostosis, limited cheilectomy, debridement of the chondral defect and the subchondral cyst. (c) Shows the status after filling of the subchondral cyst with autologous cancellous bone, microfracturing and distal metatarsal corrective osteotomy. (d) Shows the matrix in place.

and further followed. No other exclusion criteria were defined. 480/176 patients (MAST/AMIC+PBC) completed follow-up and were eligible for the further comparison. The follow-up rate was 89% for both cohorts.

**Parameter**

Before surgery and at follow-up, radiographs (bilateral views (dorsoplantar and lateral) with full weight bearing) or Weightbearing Computed Tomography (WBCT) scan based on the availability of WBCT after July 2012 were obtained [14,21]. Visual Analogue Scale Foot and Ankle (VAS FA) was registered for all patients and the EFAS Score since July 29, 2017 [13,20]. The defect size and location were assessed intraoperatively. The defects were classified as dorsal when located above a virtual horizontal line at 50% of the metatarsal head height or diameter; plantar when located below that line, or both when crossing the line [12]. The degree of osteoarthritis was classified in four degrees [22]. Complications and treatment failure, as for example conversion to joint replacement or arthrodesis were registered.

## 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 preoperatively and at follow-up and between cohorts. Before using the paired t-test, the data were investigated regarding the distribution and the data were proven to be normally distributed. ANOVA (potential Scheffe Post Hoc test) was used to analyse differences of the follow-up scores for different defect location and size and between cohorts. 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).

# Results

Table 1 shows the demographic parameter, preoperative VAS FA and EFAS Score. In 20%/21% (MAST/AMIC+PBC) deformities were registered (considered to be corrected)(Table 1). The average were degree of osteoarthritis was 2.1/2.2 (MAST/AMIC+PBC). Table 2 shows size, location and number (per case) of the chondral defects. The chondral defect size was 0.9/1.0 $cm^2$ on average (MAST/AMIC+PBC). The most common location was metatarsal dorsal (31/33%), and in 74% one defect was registered (74/74%)(MAST/AMIC+PBC). Table 3 shows the additional surgical procedures. Corrective osteotomy of the first metatarsal was performed in 80%/79% (MAST/AMIC+PBC). 58 (12%)/23 (13%) patients (MAST/AMIC+PBC) were revised with joint-preserving surgery including joint debridement and implant removal, and 23 (5%)/5 (3%) including another MAST/AMIC+PBC (Table 3).

## Follow-up

Table 4 shows the follow-up parameter of the entire cohorts and subgroups without correction and with correction of the 1st ray or the 1st and other rays. The highest scores and lowest degree of osteoarthritis occurred in the groups without correction.

## Comparison MAST/AMIC+PBC

The cohorts did not differ in all above listed parameters (each $p > 0.05$).

# Discussion

This is the first study comparing MAST with AMIC+PBC at MTP1. The transition from MAST to AMIC+PBC was enforced by local regulations as described above. The enforced transition was seen very critical at the authors' institution and enormous efforts were undertaken to achieve authorization for performing MAST after July 2016 — without success [21]. However, the transition gave the opportunity to compare MAST with another method (AMIC+PBC) which was not planned before [21]. Based on the good previous results of MAST, we did not expect that AMIC+PBC with potentially less "powerful" cells for matrix impregnation would achieve similar results [17,19,21]. We chose a clinical cohort analysis to compare AMIC+PBC with MAST. An ongoing prospective data acquisition of all surgically treated patients including planned yearly follow-ups at the authors' institution is the basis for this cohort comparison process [21]. The patient cohorts including demographic data, preoperative scores, and all characteristics of the chondral defects were similar in both cohorts (Tables 1 and 2). Except the MAST/AMIC+PBC procedures itself, the additional surgical procedures did not significantly differ between cohorts (Table 3). The follow-up parameters did also not significantly differ between cohorts (Table 4). he highest scores and lowest degree of osteoarthritis occurred in the groups without correction (Table 4). We observed chondral defects in different locations (Table 2). In comparison with the main defect location at the

**Table 1** Demographic parameter, preoperative VAS FA and EFAS Score, and concomitant forefoot pathology.

| | MAST | AMIC+PBC | Test, *p* |
|---|---|---|---|
| *Age (average (range))* | 53.6 (8–83) | 52.6 (13–78) | *t*-test, 0.51 |
| *Gender (male; n (%))* | 70 (15) | 28 (16) | $Chi^2$, .81 |
| *VAS FA (average (range))* | 48.4 (0–80.4) | 46.8 (8.7–79.8) | *t*-test, 0.18 |
| *EFAS score (average (range))*[a] | 11.6 (2–22) | 11.9 (2–22) | *t*-test, 0.37 |
| *Concomitant pathology* | | | |
| No deformity (*n* (%)) | 94 (20) | 37 (21) | |
| HV plus lesser ray deformity (*n* (%)) | 288 (60) | 107 (61) | |
| Degree osteoarthritis (average (range)) | 2.1 (1–4) | 2.2 (1–4) | $Chi^2$, 0.43 |

[a] EFAS score not available for entire MAST cohort.

**Table 2** Size, location and number (per case) of chondral defects.

| MAST | | AMIC+PBC | Test, *p* |
|---|---|---|---|
| *Size ($cm^2$) (average, range)* | 0.9 (0.3–6.0) | 1.0 (0.2–6.4) | *t*-test, $p = 0.73$ |
| *Location* | | | |
| Metatatarsal head dorsal (*n* (%)) | 198 (31) | 78 (33) | |
| Metatatarsal head plantar (*n* (%)) | 145 (23) | 54 (23) | |
| Metatatarsal head dorsal/plantar (*n* (%)) | 101 (16) | 30 (13) | $Chi^2$, $p = 0.39$ |
| Medial sesamoid (*n* (%)) | 146 (23) | 56 (24) | |
| Lateral sesamoid (*n* (%)) | 45 (7) | 16 (7) | |
| Phalanx (*n* (%)) | 12 (2) | 4 (2) | |
| *Number of defects* | | | |
| 1 (*n* (%)) | 354 (74) | 131 (74) | |
| 2 (*n* (%)) | 93 (19) | 31 (18) | |
| 3 (*n* (%)) | 26 (5) | 11 (6) | $Chi^2$, $p = 0.73$ |
| 4 or more (*n* (%)) | 7 (1) | 3 (2) | |
| In total (*n*) | 647 | 238 | |

dorsal part of the metatarsal in cases without deformity (comparable to Hallux rigidus), we found a lot of defects at the plantar part of the metatarsal and the sesamoids in cases with deformity (Hallux valgus) [12,18]. Furthermore, we found chondral defects at the sesamoids without chondral defect at the opposite surface of the metatarsal and vice versa and defects at both corresponding surfaces (so called "kissing-lesions"). The principal result of our study is that MAST and AMIC+PBC did not differ. Consequently, the main difference of both procedures, i.e. using BMAC or PBC had no influence on the results of this study. 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 [21]. If so, AMIC alone (without BMAC or PBC) would allow for the same results [21]. As we did not perform AMIC, we tried to find comparable results from the literature. We did not find any. Also no significant difference between PBC and BMAC as adjunct might exist [21]. We used BMAC before to allow for a high concentration of mesenchymal stem cells [10,17,19,21]. The concentration of mesenchymal stem cells in PBC in comparison with BMAC is questionable [21]. We did not investigate the content of BMAC or PBC cytologically and cannot answer this question [21]. Another potential effect could be chemo-tactical "attraction" of mesenchymal stem cell from PBC as described for PRP [2]. This is all unclear and debatable. We earlier reported about anecdotal histological investigations after MAST at the ankle showing chondrocytes, and we suspect that the same would be observed after AMIC+PBC which is also debatable [19]. Our 2-year-follow-up results after MAST and AMIC+PBC MTP1 as part of a complex surgical approach are favourable and no adverse effects have been registered. 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).

## Limitations

Limitations of the study are: subjective indication for treatment, unclear influence of associated procedures, missing control group, missing outcome

**Table 3** Additional procedures performed during initial surgery and later revision surgery (Cohorts with completed follow-up).

| | MAST | AMIC+PBC |
|---|---|---|
| *Patients in total* | 480 | 176 |
| *Additional procedure during initial surgery* | *n* (%) | *n* (%) |
| *Synovectomy* | 480 (100) | 176 (100) |
| *Debridement/tenolysis Extensor et flexor hallucis longus et brevis,* | | |
| Abductor/adductor hallucis | 480 (100) | 176 (100) |
| Cheilectomy (limited) | 480 (100) | 176 (100) |
| Corrective osteotomy 1st metatarsal | 386 (80) | 139 (79) |
| Corrective osteotomy 1st phalanx | 5 (1) | 2 (1) |
| Arthrodesis 1st tarsometatarsal joint | 12 (3) | 4 (2) |
| Corrective osteotomy 2nd—5th metatarsal | 288 (60) | 107 (61) |
| Correction arthrodesis PIP 2-3 | 288 (60) | 107 (61) |
| Autologous cancellous bone transplantation (under MAST) | 34 (7) | 12 (7) |
| *Revisions* | | |
| Joint-preserving surgery | 58 (12) | 23 (13) |
| including MAST | 18 (4) | — |
| Including AMIC+PBC | 5 (1) | 5 (3) |
| MTP1 fusion | 0 | 0 |
| MTP1 joint replacement | 0 | 0 |

Case (patient) based analysis. Multiple procedures possible. MTP1, 1st tarso-phalangeal joint. PIP, proximal interphalangeal joint.

**Table 4** Follow-up parameter and values.

| | MAST | AMIC+PBC | Test, *p* |
|---|---|---|---|
| *Overall* | | | |
| VAS FA (average, range) | 72.4 (0—100) | 74.1 (19.1—100) | *t*-test, 0.30 |
| EFAS Score (average, range)[a] | 16.8 (11—24) | 17.1 (11—24) | *t*-test, 0.51 |
| Degree osteoarthritis (average, range) | 0.9 (0—3) | 0.8 (0—3) | $Chi^2$, 0.48 |
| *Without correction* | | | |
| *n* | 94 | 36 | |
| VAS FA (average, range) | 83.5 (10.3—100) | 81.2 (15.6—100) | *t*-test, 0.45 |
| EFAS Score (average, range)[a] | 17.7 (13—24) | 18.2 (14—24) | *t*-test, 0.67 |
| Degree osteoarthritis (average, range) | 0.5 (0—3) | 0.5 (0—3) | $Chi^2$, 0.67 |
| *Including Hallux valgus correction* | | | |
| *n* | 98 | 35 | |
| VAS FA (average, range) | 67.3 (5.6—100) | 68.1 (18.2—100) | *t*-test, 0.42 |
| EFAS score (average, range)[a] | 17.1 (12—24) | 17.0 (12—24) | *t*-test, 0.45 |
| Degree osteoarthritis (average, range) | 1.0 (0—3) | 0.9 (0—3) | $Chi^2$, 0.34 |
| *Including Hallux valgus and lesser ray correction* | | | |
| *n* | 288 | 105 | |
| VAS FA (average, range) | 64.4 (0—94.5) | 63.1 (19.1—92.3) | *t*-test, 0.25 |
| EFAS Score (average, range)[a] | 15.9 (11—23) | 16.0 (11—24) | *t*-test, 0.38 |
| Degree osteoarthritis (average, range) | 1.1 (0—3) | 1.0 (0—3) | $Chi^2$, 0.25 |

[a] EFAS Score not available for entire MAST cohort.

parameter for the created tissue, and comparison of cohorts instead of a "real" control group.

The indication for MAST/AMIC+PBC was subjectively made by the surgeon [12,18]. This is the typical decision-making process also in other studies but does still not follow objective parameters [12,18]. We believe that "surgical" decision-making is still better than indication based on any kind of imaging-based staging with the described limitations [17,19]. The indication for MAST/AMIC+PBC was not similar to the indication for surgery as such which was based on clinical

symptoms as usual [12,18]. The simultaneous additional procedures (Table 3) confound the results. As stated above, we consider this as a main limitation of this study. These procedures were considered to be necessary to restore joint function (for example corrective osteotomies of the first metatarsal in 80%/79% (MAST/AMIC+PBC)). Other procedures were performed on a regular basis (for example synovectomy in 100%). Performing MAST or AMIC+PBC as single procedure would allow for a much more specific study results and would allow for much stronger conclusions [21]. However, we did not notice a single patient with just a chondral defect and no other pathologies [12,18]. Based on our experience and considering the literature, we doubt that isolated chondral defects are common [17]. In our cohorts, the main cause for the chondral defect might have been Hallux valgus deformity. Following this principle, treatment of the chondral defect alone without treating the cause as for example the deformity would be inadequate [17]. In contrast, our treatment concept was and is still to address all pathologies in addition to the chondral defect [17]. If we would exclude all patients with deformities from the study, we would exclude 80% of all patients. This would result in study cohort that does not reflect the real situation at least in our institution. In addition, we have analysed cases without deformity before [12,18]. A cohort comparison study design is not as good as a prospective study with control group and at best randomized. However, we are not aware of any other prospective controlled (randomized) study. The presented cohort comparison study design is adequate. Based our results, we do proceed with AMIC+PBC instead of MAST. We are not sure if we would return to MAST even if we would achieve approval again. Another task is fixation of the matrix in the chondral defect without fibrin-glue to reduce cost, complexity and risk of infection since fibrin-glue is an allologous blood product [17]. We are working on different fixation possibilities beyond suture and glue.

In conclusion, MAST and AMIC+PBC as treatment for chondral defects at MTP1 as part of a (complex) joint preserving surgery led to improved and high validated outcome scores in 2-year-follow-up. MAST and AMIC+PBC showed similar results. No method related complications were registered.

## Conflict of interest

None of the authors or the authors' institution received funding in relation to this study. Martinus Richter is consultant for Geistlich Pharma AG.

## References

[1] Benthien JP, Behrens P. Autologous matrix-induced chondrogenesis (AMIC): combining microfracturing and a collagen I/III matrix for articular cartilage resurfacing. Cartilage 2010;1(1):65—8.
[2] Dhurat R, Sukesh M. Principles and methods of preparation of platelet-rich plasma: a review and author's perspective. J Cutaneous Aesthetic Surg 2014;7(4):189—97.
[3] Giannini S, Buda R, Battaglia M, Cavallo M, Ruffilli A, Ramponi L, et al. One-step repair in talar osteochondral lesions: 4-year clinical results and t2-mapping capability in outcome prediction. Am J Sports Med 2013;41(3):511—8.
[4] Giannini S, Buda R, Grigolo B, Bevoni R, Di Caprio F, Ruffilli A, et al. Bipolar fresh osteochondral allograft of the ankle. Foot Ankle Int 2010;31(1):38—46.
[5] Giannini S, Buda R, Vannini F, Cavallo M, Grigolo B. One-step bone marrow-derived cell transplantation in talar osteochondral lesions. Clin Orthop Relat Res 2009;467(12):3307—20.
[6] Giza E, Sullivan M, Ocel D, Lundeen G, Mitchell ME, Veris L, et al. Matrix-induced autologous chondrocyte implantation of talus articular defects. Foot Ankle Int 2010;31(9):747—53.
[7] Gobbi A, Francisco RA, Lubowitz JH, Allegra F, Canata G. Osteochondral lesions of the talus: randomized controlled trial comparing chondroplasty, microfracture, and osteochondral autograft transplantation. Arthroscopy 2006;22(10):1085—92.
[8] Hangody L, Fules P. Autologous osteochondral mosaicplasty for the treatment of full-thickness defects of weight-bearing joints: ten years of experimental and clinical experience. J Bone Joint Surg Am 2003;85-A(Suppl. 2):25—32.
[9] Mei-Dan O, Carmont MR, Laver L, Mann G, Maffulli N, Nyska M. Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus. Am J Sports Med 2012;40(3):534—41.
[10] Murphy EP, Fenelon C, Egan C, Kearns SR. Matrix-associated stem cell transplantation is successful in treating talar osteochondral lesions. Knee Surg Sports Traumatol Arthrosc 2019;27(9):2737—43.
[11] Niemeyer P, Salzmann G, Schmal H, Mayr H, Sudkamp NP. Autologous chondrocyte implantation for the treatment of chondral and osteochondral defects of the talus: a meta-analysis of available evidence. Knee Surg Sports Traumatol Arthrosc 2011;20(9):1696—703.
[12] Richter M. Mid-term (4—7 years) results of matrix-associated stem cell transplantation (MAST) in chondral defects of the first metatarsophalangeal joint. Fuss Sprungg 2019;17:11—20.
[13] Richter M, Agren PH, Besse JL, Coster M, Kofoed H, Maffulli N, et al. EFAS Score — multilingual development and validation of a patient-reported outcome measure (PROM) by the score committee of the European Foot and Ankle Society (EFAS). Foot Ankle Surg 2018;24(3):185—204.

[14] Richter M, Seidl B, Zech S, Hahn S. PedCAT for 3D-imaging in standing position allows for more accurate bone position (angle) measurement than radiographs or CT. Foot Ankle Surg 2014;20:201—7.
[15] Richter M, Zech S. 3D-imaging (ARCADIS) based computer assisted surgery (CAS) guided retrograde drilling in osteochondritis dissecans of the Talus. Foot Ankle Int 2008;29(12):1243—8.
[16] Richter M, Zech S. Matrix-associated stem cell transplantation (MAST) in chondral defects of foot and ankle is effective. Foot Ankle Surg 2013;19(2):84—90.
[17] Richter M, Zech S. Matrix-associated stem cell transplantation (MAST) in chondral lesions at the ankle as part of a complex surgical approach-5-year-follow-up in 100 patients. Foot Ankle Surg 2019;25(3):264—71.
[18] Richter M, Zech S, Andreas Meissner S. Matrix-associated stem cell transplantation (MAST) in chondral defects of the 1st metatarsophalangeal joint is safe and effective-2-year-follow-up in 20 patients. Foot Ankle Surg 2017;23(3):195—200.
[19] Richter M, Zech S, Andreas Meissner S. Matrix-associated stem cell transplantation (MAST) in chondral defects of the ankle is safe and effective — 2-year-followup in 130 patients. Foot Ankle Surg 2017;23(4):236—42.
[20] Richter M, Zech S, Geerling J, Frink M, Knobloch K, Krettek C. A new foot and ankle outcome score: questionnaire based, subjective, Visual-Analogue-Scale, validated and computerized. Foot Ankle Surg 2006;12(4):191—9.
[21] Richter M, Zech S, Meissner S, Naef I. Comparison Matrix-Associated Stem Cell Transplantation (MAST) with Autologous Matrix Induced Chondrogenesis plus Peripheral Blood Concentrate (AMIC+PBC) in chondral lesions at the ankle — a clinical matched-patient analysis. Foot Ankle Surg 2020.
[22] Shereff MJ, Baumhauer JF. Hallux rigidus and osteoarthrosis of the first metatarsophalangeal joint. J Bone Joint Surg Am 1998;80(6):898—908.
[23] Smith PA. Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis: an FDA-sanctioned, randomized, double-blind placebo-controlled clinical trial. Am J Sports Med 2016;44(4):884—91.
[24] Tay LX, Ahmad RE, Dashtdar H, Tay KW, Masjuddin T, Ab-Rahim S, et al. Treatment outcomes of alginate-embedded allogenic mesenchymal stem cells versus autologous chondrocytes for the repair of focal articular cartilage defects in a rabbit model. Am J Sports Med 2012;40(1):83—90.
[25] van Roermund PM, Marijnissen AC, Lafeber FP. Joint distraction as an alternative for the treatment of osteoarthritis. Foot Ankle Clin 2002;7(3):515—27.