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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

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ABSTRACT

Background: The aim of the study was to assess the 5-year-follow-up after matrix-associated stem cell transplantation (MAST) 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 that were treated with MAST from April 1, 2009 to May 31, 2012 were included. Size and location of the chondral lesions, method-associated problems and the Visual-Analogue-Scale Foot and Ankle (VAS FA) before treatment and at follow-up were analysed. Stem cell-rich blood was harvested from the ipsilateral pelvic bone marrow and centrifuged (10 min, 1500 RPM). The supernatant was used to impregnate a collagen I/III matrix (Chondro-Gide) that was fixed into the chondral lesion with fibrin glue.
Results: One hundred and twenty patients with 124 chondral lesions were included in the study. Age at the time of surgery was 35 years on average (range, 12–65 years), 74 (62%) were male. VAS FA before surgery was 45.2 on average (range, 16.4–73.5). Lesions were located at medial talar shoulder, n = 55; lateral talar shoulder, n = 58 (medial and lateral, n = 4); tibia, n = 11. Lesion size was 1.7 cm^2 on average (range, .8–6 cm^2). One hundred patients (83%) completed 5-year-follow-up after. VAS FA improved to 84.4 (range, 54.1–100; t-test, $p < 0.01$).
Conclusions: MAST as part of a complex surgical approach led to improved and high validated outcome scores in the mid-term-follow-up. No method related complications were registered. Even though a control group is missing, we conclude that MAST as part of a complex surgical approach is an effective method for the treatment of chondral lesions of the ankle for at least five years.
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1. Introduction

Matrix-associated stem cell transplantation (MAST) is a modification of Autologous Matrix Induced Chondrogenesis (AMIC) with a potentially higher concentration of stem cells in the implanted matrix [1–4]. In the first study, 25 patients were included of which 22 had chondral lesions at the ankle [1]. One of the interpretation was that a cohort of 22 patients is not sufficient to prove effectiveness of a new method and therefore another study with much higher case number and a two-year-follow-up was performed [5]. This study was limited to chondral lesions at the ankle [5]. The conclusions were that MAST is safe and effective, and short-term follow-up of two years is favourable [5]. Hence, longer follow-up was considered to be important [5]. Furthermore, the high percentage of additional procedure and their influence on the outcome should be more considered [5]. Therefore, part of the study cohort was followed until 5-year-follow-up. The aim of this study was to assess the 5-year-follow-up of MAST as part of a complex surgical approach in chondral lesions at the ankle with consideration of additional procedures.

2. Methods

2.1. Technique [1]

MAST was performed as one-stage open procedure associated with other procedures. The indication for surgery was based on

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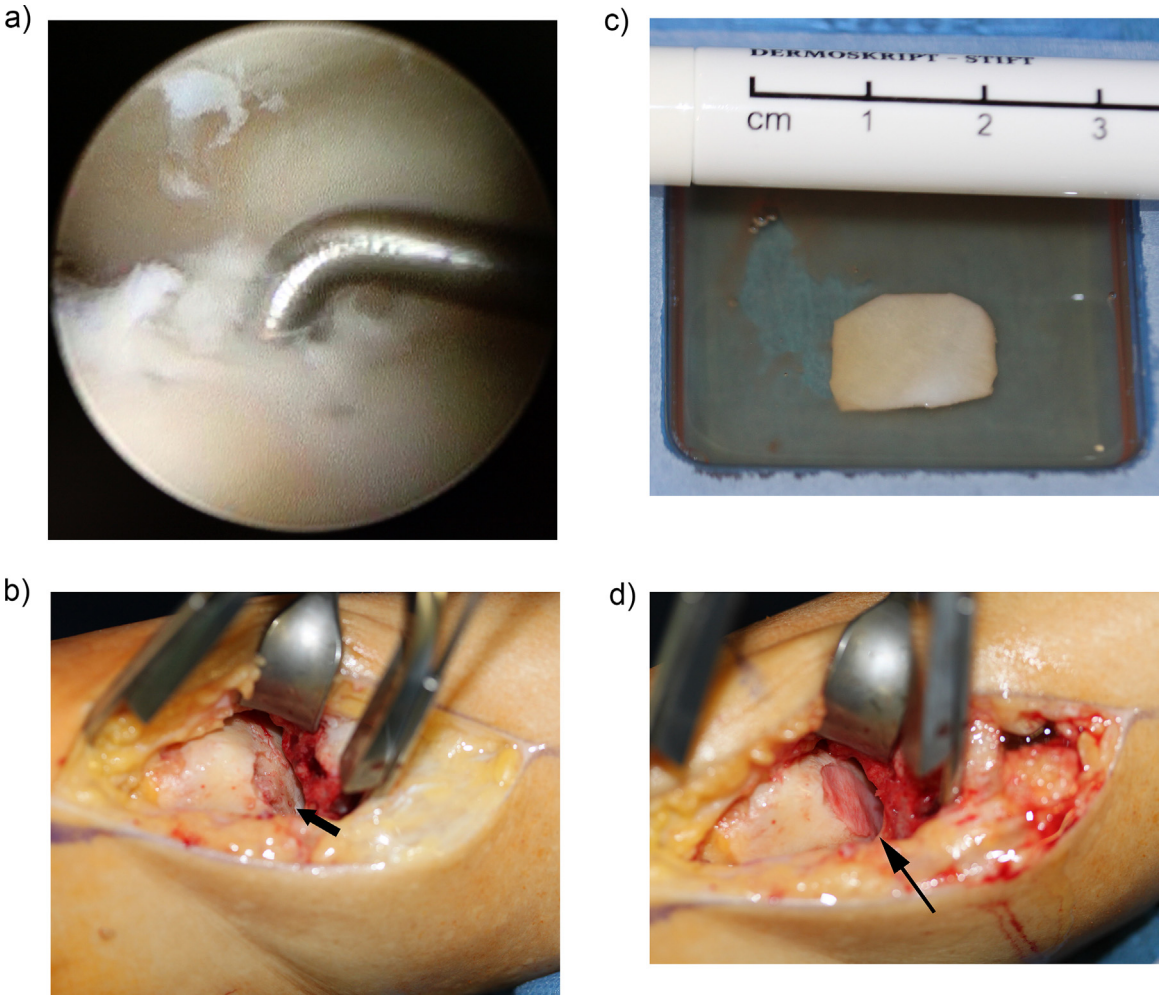

Fig. 1. (a–d) MAST at left medial talar shoulder in a 36-year-old male patient. A distal tibial fracture due to vehicular trauma occurred 4 years ago as potential lesion cause. The VAS FA preoperatively was 45.3. Fig. 1a shows the initial diagnostic arthroscopy with cartilage fragmentation and detachment from the subchondral at the medial talar shoulder. Fig. 1b shows the lesion after debridement and microfracturing. A spreader which was adapted to two 1.6 mm K-wires in tibia and talus was used for better exposure. Fig. 1c shows the Chondro-Gide matrix during impregnation in stem cell-rich fluid. Fig. 1d shows the matrix in the condral lesion. Chondral lesion and matrix measured $1.3 \times 1.5\,cm = 1.95\,cm^2$.

clinical symptoms as for example pain or instability and MRI-findings [6]. The definite indication for MAST was subjectively made by the surgeon during initial arthroscopy (Fig. 1a). MAST was indicated for instable, fragmented or missing cartilage [1]. The other procedures included joint preserving measures such as synovectomy, lateral ligament reconstruction, peroneal tendon debridement/tenolysis, Gastrocnemius tendon lengthening and others [1,7–9]. A gastrocnemius tendon lengthening was performed if ankle dorsiflexion was less than 10° with positive Silverskiöld-test [7–9]. A longitudinal medial 3cm-skin incision was performed above the origin of the gastrocnemius tendon [10]. The fascia was longitudinally incised, and the entire gastrocnemius tendon was cut directly at the origin of the tendon [10]. The lengthened tendon was secured with a single suture in the lengthened position.

The MAST procedure was performed through a medial approach for medial chondral lesions and through a lateral approach for lateral lesions. When the chondral lesion could not be reached without an additional malleolar osteotomy was performed. Medial malleolar osteotomies were performed as single oblique saw cut. Lateral malleolar osteotomies were performed as anterior window cut with the anterior syndesmotic ligament attached to the cut-out fragment and the central and posterior syndesmotic ligaments attached to the remaining main fragment. The osteotomized fragments were later fixed with lag screws. The chondral lesion was debrided until stable surrounding cartilage was present. Subchondral cysts (MRI-stage 5) were cleared out. Microfracturing with a 1.6 mm Kirschner wire was performed at intact subchondral bone, and at the ground of subchondral bone defects (Fig. 1b). 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. 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. The syringe was centrifuged (10 min, 1500 rotations per minute). 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 (Fig. 1c). The matrix was cut to the size of the cartilage lesion roughly before and more exact after the impregnation. The matrix with stem cells was fixed into the chondral lesion with fibrin glue (Tissucoll, Deerfield, IL, USA, Fig. 1d). Matrix fixation was tested by moving the joint several times. And adequate fixation was approved when the matrix stayed in place in the chondral lesion. A 10 Ch drainage without suction was inserted. Closure was performed following the local

standard with layer wise closure (joint capsule, subcutaneous, skin). The postoperative treatment included partial weight bearing with 15 kg with orthosis (Vacuped, Oped, Valley, Germany). Motion of the joint with MAST 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. Postoperative consultations were performed at 6 weeks, 3, 12 months and yearly.

2.2. Study design

In a prospective consecutive non-controlled clinical follow-up study, all patients with chondral lesion at the ankle that were treated with MAST from April 1, 2009 to May 31, 2012 were analysed. Patients with bilateral treatment (n = 16) or MAST at more than one joint surface, i.e. talus and tibia (n = 9) were excluded from the study. No other exclusion criteria were defined. There were no limitations in terms of patient's age and lesion size defined. Before surgery and at follow-up, radiographs (bilateral views (dorsoplantar and lateral) with full weight bearing) or PedCAT scan based on the availability of PedCAT after July 2012 were obtained [11]. Magnetic resonance imaging (MRI) was also obtained before surgery and at follow-up (Fig. 2a–c). Five-year-follow-up was aimed for and was defined as follow-up between 58 and 62 months postoperatively. Before July 2014, "standard" MRI imaging with slice thickness of 3 mm was obtained (Fig. 2a). From July 2014, MRI with so-called "Cartilage-mapping" with slice thickness of 0.4 mm was obtained (Fig. 2b and c) [5]. Visual Analogue Scale Foot and Ankle (VAS FA) was registered [12,13]. The lesion size and location were registered. The lesions were classified based on MRI [6]. Complications and treatment failure, as for example conversion to ankle joint replacement of arthrodesis were registered. The VAS FA was registered at five-year-follow-up.

2.3. Statistical analysis

The data was analysed with SPSS software (IBM SPSS Statistics 24, IBM, Armonk, NY, USA). An unpaired t-test was used for statistical comparison of VAS FA preoperatively and at follow-up. Before using the paired t-test, the data were investigated regarding the distribution and the data were proven to be normally distributed. Chi^2-test was used to compare the different MRI stages preoperatively versus follow-up. ANOVA (potential Scheffe Post Hoc test) was used to analyse differences of the follow-up scores for different lesion location, size (lesion size $\leq$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

One hundred and twenty patients with 124 chondral lesions were included in the study. The age at the time of surgery was 35 years on average (range, 12–65 years), 74 (62%) were male. The VAS FA before surgery was 45.2 on average (range, 16.4–73.5). In 64 cases (53%), the right foot was affected. Table 1 shows the suspected cause and suspected mechanism of the chondral lesions. Sports-related trauma (47%) was the most common cause, and multiple sprains (62%) the most common suspected mechanism. Forty-five patients (36%) had prior surgery including arthroscopic debridement and microfracturing.

The lesions were located as follows, medial talar shoulder, n = 55; lateral talar shoulder, n = 58 (medial and lateral talar shoulder, n = 4), tibia, n = 11. The lesion size was 1.7 cm^2 on average (range, .8–6 cm^2). Sixty-four (52%) lesions were $\leq$2 cm and 60 (48%) $>$2 cm. Table 2 shows the MRI-stage of the lesions. Most common stages were 1 (cartilage lesion only) in 50 lesions (32%)

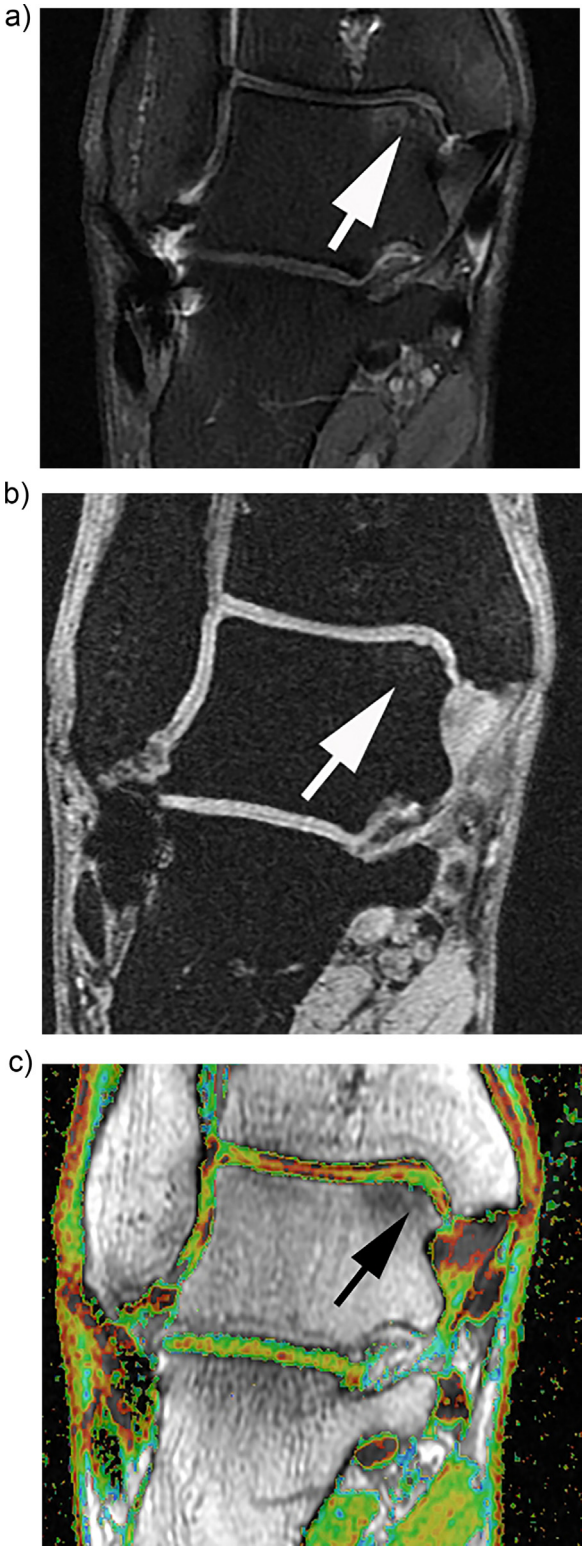

Fig. 2. (a–c) Same patient as Fig. 1. Fig. 2a shows a preoperative coronal MRI reformation of standard T2 specification with 3 mm slice thickness. At the medial talar shoulder (arrow), the cartilage is not clearly visible combined with subchondral oedema (MRI-stage 2b). Fig. 2b shows a coronal MRI reformation of "Cartilage-mapping" T2 specification with 0.4 mm slice thickness at 5-year-follow-up. At the medial talar shoulder (arrow), 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). Fig. 2c shows a colour coded visualization of the cartilage. At the medial talar shoulder (arrow), the fluid percentage/content is not increased (green colour). An increased fluid percentage/content would be a sign for initial chondral damage which often precedes morphologically visible damage.

Table 1
Cause and suspected mechanism of 124 chondral lesions in 120 patients (patient based analysis, i.e. 120 patients in total).

Cause	n (%)
Vehicular accident	10 (8)
Sports-related trauma	56 (47)
Non vehicular/sports-related trauma	41 (34)
Deformity without trauma	4 (3)
Hindfoot/ankle varus	3 (3)
Hindfoot/ankle valgus	1 (1)
Other	3 (3)
Unknown	6 (5)
Mechanism	
Fracture	17 (14)
Single sprain	25 (21)
Multiple sprains	59 (49)
Other	1 (1)
Unknown	18 (15)

Cause and mechanism are independently listed.

and 2a (subchondral fracture with surrounding bone oedema) in 33 (27%). Table 3 shows the additional surgical procedures. Synovectomy was performed in all cases, lateral ligament reconstruction in 93% (n = 112) and Gastrocnemius tendon lengthening in 63% (n = 75).

No complications (Neuropraxia, stiffness, wound healing problems, thrombosis, infection) were registered until follow-up. Three patients (3%) underwent another joint preserving ankle surgery after 36, 39, and 48 months including another MAST procedure. Each patient reported subsequent ankle sprains during sports activity before the second surgery before follow-up. All three patients completed follow-up.

One hundred patients (83%) completed the defined 5-year-follow-up after 60.2 months on average (range, 58–62 months). VAS FA improved to 84.4 (range, 54.1–100; t-test, $p < 0.01$). The MRI stage improved (Table 2; Chi^2, $p < 0.01$). In 49 of the previous lesion locations (48%), no lesion was visible in the MRI at follow-up (Fig. 2b and c). Table 4 shows the mean VAS FA differentiated for different chondral lesion specification at time of surgery. Different lesion location (medial/lateral talar shoulder, tibia), lesion size ($\leq$2 cm or >2 cm) or MRI-stage did not lead to different VAS FA at follow-up (ANOVA, all $p > 0.05$, Post Hoc test not applicable). Highest scores were registered in lesions located at the Tibia, size $\leq$2 cm, and MRI-stage 1. The three patients with second surgery before follow-up did not differ significantly regarding VAS FA or other parameter from the remaining 97 patients (data not shown).

4. Discussion

Our 5-year-follow-up results after MAST at the ankle 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).

We compared our findings with our own two-year-follow-up results [5]. The foot and ankle specific validated follow-up scores remained stable after two years until five years [5,12]. Again, we observed a high percentage of lesions limited to the cartilage [5]. Again, we could not detect follow-up score differences between different location, size or MRI-stage of the chondral lesions, as reported before [5]. Again, there was only a trend and no significance to higher follow-up scores towards smaller lesions, located at tibia and lower MRI-stages [5]. Again, the follow-up scores after MRI-stage V (subchondral cyst) were not the lowest as shown in other studies [5,6,14,15]. MAST worked also for larger lesions and "higher" MRI-stages for two and for five years [5]. However, we found differences after five years in comparison with the two-year-follow-up results [5]. When comparing the MRI-stages, we did *not* observe non visible chondral lesions after two years but in almost half of the previous lesion locations after five years [5]. This means that approximately half of the "repaired" lesions were still visible as lesions after two years but not any more after five years. This implies that something happened with the "repaired" lesions between two and five years postoperatively which changed the visibility in the MRI. However, based on the questionable visibility of lesions limited to the cartilage in the MRI (see below under limitations), this finding should not be over-estimated.

Comparison with other studies with MAST as part of a complex surgical approach is not possible based on the lack of other publications. Comparison with other studies with different methods is difficult or also not possible, because we are not aware of a single study using a validated foot and ankle specific outcome score as performed in our study [12,13]. When ignoring the lack of validated outcome score, the comparison with other studies show similar or better results especially after five years in our study [2,3,14–58]. The main difference of the different study cohorts is a higher percentage of lesions limited to the cartilage in our study in contrast to higher percentages of lesion involving the subchondral bone in most other studies [2,3,14–57]. Based on our findings that the MRI-stage does not influence the outcome, this might not explain potential outcome differences anyhow. We were especially interested in a comparison with the latest AMIC results since MAST is a modification of AMIC [2,56,57]. D'Ambrosi et al. investigated eleven patients with a maximum follow-up of two years and reported favourable score results and no adverse effects [59]. Walther et al. reported 30 months follow-up in 14 patients favourable score results and no adverse effects [2]. Also based on these results, a guideline from the group "Clinical Tissue Regeneration" of the German Society of Orthopaedics and Traumatology (DGOU) recommends AMIC for chondral lesions in the ankle [58]. Usuelli et al. reported a two-year-follow-up in 20 patients, also with good score results [57]. These recent AMIC publications included also MRI based interpretation [2,56–58]. Our study shows also favourable results but in contrast to the above described studies with a foot and ankle specific validated outcome [12,13]. Then, we report five-year-follow-up in comparison with a maximum follow-up of 30 months in the other studies [2,56,57]. Above all, we present a follow-up of a much higher case number of 100 patients which is more than all other recent studies together [2,56,57].

4.1. Limitations

Limitations of the study are: subjective indication for treatment, unclear influence of associated procedures, missing control group, questionable visibility of lesions limited to the cartilage in the MRI, and missing outcome parameter for the created tissue.

The indication for MAST was subjectively made by the surgeon during initial arthroscopy [5]. This is the typical decision-making process also in other studies but still does not follow objective parameters [5]. We believe that "surgical" decision-making is still better than indication based on any kind of imaging based staging with the described limitations [5]. The indication for MAST was not similar to the indication for surgery as such which was based on clinical symptoms as usual [5].

The simultaneous additional procedures (Table 3) confound the results as in all other studies we are aware of [5,14,24]. As stated this above, we consider this as a main limitation of this study. These procedures were considered to be necessary to restore joint

Table 2
MRI based classification of 124 chondral lesions in 120 patients preoperatively (preop; lesion based analysis, i.e. 124 lesions in total), and of 102 chondral lesions in 10 patients at 5-year-follow-up (FU; lesion based analysis, i.e. 102 lesions in total).

Stage and stage description	Preop n (%)	FU n (%)
1. Cartilage lesion only	50 (40)	37 (36)
2a. Subchondral fracture with surrounding bone oedema	33 (27)	8 (8)
2b. Subchondral fracture with no surrounding bone oedema	11 (9)	2 (2)
3. Detached but undisplaced fragment	7 (6)	2 (2)
4. Displaced fragment	6 (5)	1 (1)
5. Subchondral cyst	17 (14)	3 (3)
MRI-stage for chondral or osteochondral lesion negative	0 (0)	49 (48)

Distribution preop versus FU; Chi^2, $p < 0.01$.

function (for example lateral ligament reconstruction in 93% or Gastrocnemius tendon lengthening in 63%). Other procedures were performed on a regular basis (for example synovectomy in 100%). The percentage of Gastrocnemius lengthening is high [5]. The indication for gastrocnemius lengthening is not clearly defined and highly debatable [5]. We see more advantages than disadvantages, or higher positive benefit than risk, and this is the main reason for indication [5]. Doing MAST as single procedure would allow for a much more specific study result and allow much stronger conclusions. However, we did not notice a single patient with just a chondral defect and no other pathologies. Based on our experience and considering the literature, we doubt that isolated chondral defects are common. In our cohort, the main cause for the chondral defect might have been post traumatic and/or ligamentous instability. If this would be true, treatment of the chondral defect alone without treating the cause as for example the ligamentous instability would be suboptimal. In contrast, our treatment concept was and is still to address all pathologies in addition to the chondral defect. If we would exclude all patients with ligamentous repair and/or Gastrocnemius lengthening from the study, we would exclude more than 90%. This would result in study cohort that does not reflect the real situation at least in our institution.

A missing control group is always a methodological shortcoming as in many other studies that we cannot invalidate.

We utilized MRI for diagnostics including classification [5,6]. Giannini et al. suggested to use special MRI protocols (T2) for the ankle for evaluation of the tissue at follow-up and created a score from that was used later for other studies [32,57,59]. Based on our experience, we would like to discuss the diagnostic value of MRI for chondral defects even if we did not investigate the imaging as such [5]. In our earlier studies and other studies, a high incoherence was noticed between MRI findings and intraoperative (arthroscopic) findings when focusing on the cartilage and not on the subchondral bone situation [1,5,22,60]. So, it seems clear that MRI is able to detect subchondral bone abnormalities but it is much less clear why the investigation of the cartilage is not optimal [6,22,60]. After having changed from “standard” MRI imaging with slice thickness of 3 mm to so-called “Cartilage-mapping” with slice thickness of 0.4 mm, we immediately realized the reason is simply technical [5]. The normal cartilage thickness at the ankle is around 1 mm [5]. Using an investigating method with a larger slice thickness (“standard” MRI with 3 mm slice thickness) is technically not able to correctly picture cartilage [5]. The created pictures show a full image but the displayed structures between the slices are calculated means from the neighbouring slices [5]. This might be sufficient for subchondral bone structure with a diameter of

Table 3
Additional procedures performed during surgery in 120 cases.

Procedure	n (%)
Arthroscopy	120 (100)
Synovectomy	120 (100)
Debridement/tenolysis peroneal tendons	112 (93)
Lateral ligament reconstruction/augmentation	112 (93)
Gastrocnemius tendon lengthening	75 (63)
Medial malleolus osteotomy	12 (10)
Lateral malleolus osteotomy	1 (1)
Autologous cancellous bone transplantation (under MAST)	16 (13)
Correction of malalignment	4 (3)
Correction above ankle	1 (1)
Correction below ankle	3 (3)

Table 4
VAS FA at 5-year follow-up for different chondral lesion specifications at time of surgery in 100 patients.

Location	n (%)	VAS FA (mean)	ANOVA, p
Medial talar shoulder	46 (46)	84.1	
Lateral talar shoulder	44 (44)	86.6	
Medial *plus* lateral talar shoulder	2 (2)	79.8	
Tibia	10 (10)	86.3	0.23
Size	**n (%)**	**VAS FA (mean)**	**ANOVA, p**
≤2 cm	55 (54)	86.3	
>2 cm	47 (46)	82.4	0.28
MRI-stage	**n (%)**	**VAS FA (mean)**	**ANOVA, p**
1	33 (32)	86.4	
2a	28 (27)	85.3	
2b	10 (10)	83.2	
3	8 (8)	81.2	
4	9 (9)	79.3	
5	14 (14)	81.5	0.38

Lesion location at the time of surgery was counted as medial *or* lateral talar shoulder or tiba, i.e. 102 lesions in total. Consequently, 1 patient that completed follow-up with lesions at the medial *and* lateral at the time of surgery was counted *twice*. The potential Post Hoc test was not applicable due to ANOVA not reaching significance level.

3 mm or more but not for cartilage with thickness of less than 2 mm [5]. When we obtained "slices" of 0.4 mm after modifying the MRI at our institution, we immediately noticed the difference (Fig. 2a and b). The cartilage was clearly pictured with the thinner slices (Fig. 2b) which was not visible with thicker slices (Fig. 2a) [5]. Furthermore, fluid content could be measured and displayed (Fig. 2c) [5]. Even lacking a scientific investigation, the qualitative interpretation of changed MRI methods with smaller slice thickness implies that the modified technique is much better [5]. We conclude again, that only MRI with slice thickness of 1 mm or less is able to correctly picture ankle cartilage [5]. Furthermore, it calls again into question if the current MRI based classification looking at the subtalar bone has prognostic value as proposed [5,6,22].

Except the questionable MRI based "parameters", we as all others cannot provide adequate parameter for the created tissue [5,32] We would still be interested in histological specimens of the transplants [1,5]. Earlier histological assessment from specimens from the talus gave anecdotal but clear evidence that the transplanted cells could develop or better determine into chondrocytes, and that the implanted collagen matrix stayed in place and acts as a scaffold for the chondrocytes as in "real" cartilage [1,5]. The same was observed in all specimens that were taken during surgeries in three patients that underwent surgery until 5-year-follow-up. We would like to point out that all surgeries were performed after repeated trauma.

4.2. Technical issues – how to do it and why [5]

Despite an earlier almost similar publication of this text part, we decided to include the text again instead of just citing for direct approach and convenience of the reader [5]. MAST is a combination of stem cell transplantation and AMIC [1]. The advantage in comparison with AMIC which uses peripheral blood is the higher concentration of pluripotent cells or stem cells. No one knows the exact concentration of stem cells which varies for different age and location [1,5,61]. Rough estimations name 0.1% stem cells as concentration in the peripheral blood and 3% in the pelvic bone marrow in young adults [1,5,61,62]. This deduces that the cells should be harvested from the pelvic bone marrow which is part of MAST [1,5]. Centrifugation is a useful method to double the concentration of the cells, and the MAST includes a typical centrifugation (1500 RPM for 10 min) that potentially doubles the concentration of stem cells in the supernatant to 6% [1,5]. As in MACI, MAST uses a carrier or scaffold for the cells [1]. Different scaffold are available, some with hyaluronic acid, and others with collagen [1]. The introduced method includes a collagen matrix (Chondro-Gide, Geistlich, Wollhusen, Switzerland Fig. 1b–d) [1,5]. This scaffold is manufactured out of denaturated collagen from the pig, and contains collagen I and III [5]. The matrix has two layers (bilayer) [5]. The superficial layer is water proof, and the deep layer is porous [1,5]. The superficial, water proof layer should maintain the cell fluid in the lesion, and the deep, porous layer should contain and maintain the cells, and should integrate in part with the underlying subchondral bone [1,5]. The microfracturing is added to add cells and to allow for perfusion from the underlying bone (marrow) [1,5]. The fibrin glue is added to give sufficient initial stability for early functional after treatment [1]. Our strategy is to fit the matrix as exact and as stable as possible [1,5]. The main advantage of MAST in comparison with ACI and MACI is the single procedure methodology and lower cost [1,5]. The advantage in comparison with AMIC is the potential higher concentration of stem cells [1,5]. The advantage of the Chondro-Gide in comparison with other scaffolds/matrices used (hyaluronic acid) is the more physiological content and structure [1,5]. This matrix gives the initial stability to allow the early stimulation of the transplanted cells by cyclic motion and loading which induces the determination of the transplanted stem cells into chondrocytes [1,5]. Furthermore, it gives the collagen scaffold which seems to be extremely difficult to determine from stem cells by an in vivo stimulation [1,5]. The necessity of vivo stimulation and determination calls the adequate aftertreatment into question [5]. It is unknown how much load and motion is needed [5]. Based on generally questionable compliance, we protect the operated foot and ankle with an orthosis [5]. In cases without ligament reconstruction (8 of 120) an orthosis would not have been necessary to protect the reconstructed ligaments [5]. Our hypothesis was that the possible motion *in* the orthosis is adequate [5]. The score results and anecdotal histological assessment imply supports this hypothesis [1,5].

4.3. Consequences and developments

Based on our results, we do not limit primary surgery to microfracturing as others and question microfracturing alone as gold-standard [58]. Adding scaffold and more potent "cells" seems to be advantageous without increased risk. Therefore, our primary treatment for chondral lesions in the ankle currently is MAST. As further development, we are working on a complete MAST system or set with inclusion of all needed materials/instruments/devices such as matrix, syringe, fibrin-glue, Jamshidie-needle, and centrifuge. Another task is fixation of the matrix in the chondral lesion without fibrin-glue to reduce cost, complexity and risk of infection since fibrin-glue is an allologous blood product. We are working on different fixation possibilities beyond suture and glue. Then we want to modify the complete arthroscopic procedure as already described to be as simple, fast and safe as the open procedure [63].

Looking in the further future, it seems to be a question of time until complete cartilage containing chondrocytes and collagen scaffold could be "manufactured" and implanted in the ankle as in other joints [1,5]. There are promising concepts that could even show good initial clinical results for the ankle joint [1,62,64–66]. However, no real breakthrough could be observed in the last years [5]. It seems clear that autologous stem cells would be more acceptable than allologous stem cells [5]. In the current stage, just injecting stem cells whatever kind into joints would not create new cartilage whereas real implantation in combination with a matrix works as histologically proven [1,5]. Additionally, the determination of stem cells into cells like chondrocytes is much easier to induce and much faster to complete than to create more complex structures like collagen scaffold [1,5]. The logical solution of this problem would be to create the entire cartilage in vitro with autologous stem cells [1,5]. This looks technically demanding but not impossible [66]. The questionable issues are the environment (for example temperature or pH), the stimulation (motion and load), the dose and especially the control of the stem cells [1,5]. The high potential of the stem cells does also include the risk that undesirable cells and tissues are created, as for example cancer [1,5]. Facing the fact that all cancer cells have also been stem cells earlier derives this concern [1,5]. However, if these issues could be resolved not only cartilage but also complete joints could be "manufactured" from autologous stem cells which might then replace the joint replacements techniques that are actually used [1–3,5,14–58].

MAST as part of a complex surgical approach led to improved and high validated outcome scores in the mid-term-follow-up. No method related complications were registered. Even though a control group is missing, we conclude that MAST as part of a complex surgical approach is an effective method for the treatment of chondral lesions of the ankle for at least five years. However, the effect of MAST alone and/or other surgical procedures on the outcome remains unclear.

Conflict of interest

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