

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of mosaicplasty for knee cartilage defects

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2005.

Procedure names

- Autologous osteochondral mosaicplasty
- Cylinder chondrocyte transplant

Specialty societies

- British association for surgery of the knee

Description

Indications

Full thickness cartilage defects of articular surfaces of weight bearing joints may be located to the surface alone (chondral) or involve the underlying bone (osteochondral). These cause symptoms which vary from severe pain, catching, locking and swelling and may lead to early degenerative changes within the joint. These defects usually occur from direct trauma but may also occur in avascular necrosis, osteochondritis dissecans and various cartilage disorders

Current treatment and alternatives

Conventional surgical methods for this condition include Pridies' operation, debridement or abrasion arthroplasty. The aim of these procedures is to lead to fibrocartilagenous scar formation within the defect as opposed to the normal hyaline cartilage. Fibrocartilage has inferior mechanical properties to hyaline cartilage and may not prevent progression to degenerative

arthropathy. Orthopaedic surgeons have struggled to develop techniques which will lead to repair with hyaline cartilage. Historically osteochondral or chondrocyte allografts have been used, but these raise concerns regarding disease transmission and maintaining adequate donors. Techniques using the patient's own tissues (autografts) have been developed. Autologous chondrocyte grafting involves removal of hyaline cartilage from a non-weight bearing portion of the knee, cultivation in vitro and implantation through an open procedure. Similarly autologous periosteal grafts may be utilised using periosteum from the tibia with the lower face containing stem cells turned to face the sub-chondral bone. The periosteal technique may cause morbidity at the operative site and both techniques have difficulty in maintaining the local radius of curvature of the weight bearing joint.

What the procedure involves

Mosaicplasty is a technique of creating an osteochondral autograft by harvesting and transplanting many small cylindrical osteochondral plugs from the less weight-bearing periphery of the patellofemoral area and inserting them into drilled tunnels in the defective section of cartilage.

A local or general anaesthetic may be used. The procedure is commonly undertaken using an arthrotomy technique, but may be carried out via arthroscopy where perpendicular access to the harvesting and implant sites is possible. The implant site is prepared to bring the edges of the defect to good hyaline cartilage, and the base of the lesion ablated to viable subchondral bone in order to encourage production of fibrocartilage between grafts. Tunnels are drilled perpendicular to the condyle surface, to a suitable depth for the graft and at a diameter similar to that of the harvest tool to be used. A cylindrical graft or plug is harvested from the medial rim of the femoral trochlea at an area away from weight-bearing areas. A guide tube is used to at the opening of the implant hole and the cylindrical graft is implanted so that the top of the graft is level with the adjacent cartilage. This process is repeated as necessary until about 70% of the defective area is filled, with a minimal spacing between plugs. Postoperative treatment includes inserting an intra-articular drain for 24 hours, and the patient being instructed not to bear weight on the joint for 4 to 8 weeks depending on the size and location of the treated defect, with gradual mobilisation of the knee.

Efficacy

Comparison of efficacy across studies is made difficult by considerable variation in the outcome measures used in individual studies. In a randomised controlled study of patients undergoing mosaicplasty or autologous chondrocyte implantation (ACI) there was no significant difference in the number of patients having an excellent or good outcome at 1 year based on the Cincinnati rating system – 74% (29/42) and 88% (51/58) respectively. For the subgroup of patients who had repairs to lesions of the medial femoral condyle, significantly more patients having ACI had an excellent or good outcome compared with those having mosaicplasty – 88% (21/24) compared with 74% (21/29) ($p < 0.032$). Arthroscopic evaluation of grafts at 1 year after the procedure found that 82% (31/37) of ACI patients had grafts that rated grade 1 or 2 on International Cartilage Research Society criteria, compared with 34% (8/23) of mosaicplasty patients ($p < 0.01$).

In a large case series, the proportion of patients having an excellent or good outcome based on standardised clinical scores ranged from 79% to 92% depending on the site of mosaicplasty, at up to 10 years follow-up. In a case series of 57 patients the mean Hospital Special Surgery score at 3 years following mosaicplasty was 90.7 (range 64 to 100). At 3 years 95% (54/57) of cases had returned to their normal level of sport and work activity. An increased level of knee function was achieved in 86% (45/52) of cases undergoing mosaicplasty at 2 years follow-up in another case series.

Safety

Procedure and long-term complications are inadequately reported in the literature and may be influenced by the use of concomitant surgery during the mosaicplasty procedure.

One case series reported postoperative locking of the knee joint in 10% (5/52) of patients. Incidence of haematoma or haemoarthrosis was reported at between 2% (1/52) and 4% (36/831) in case series. Wound infection rates have been recorded ranging from less than 1% (4/831) to 2% (1/52).

There were no serious complications reported at the site of graft harvest. In one case series in patients where six or more plugs of 7 mm were removed there was arthroscopic evidence of crepitation in all 15 cases evaluated, but this was not painful in any case.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to mosaicplasty. Searches were conducted via the following databases, covering the period from their commencement to 24/09/2004: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved

Table 1 Inclusion criteria for identification of relevant studies

| Characteristic | Criteria |
|-----------------------|--|
| Publication type | Clinical studies included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology. |
| Patient | Patients with knee cartilage defects (traumatic and degenerative). |
| Intervention/test | Mosaicplasty. |
| Outcome | Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy. |
| Language | Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base. |

List of studies included in the overview

This overview is based on one comparative trial(1) and four case series(2-5).

Existing reviews on this procedure

There were no systematic reviews or evidence-based guidelines on mosaicplasty for knee cartilage defects found during literature searches.

Table 1 Summary of key efficacy and safety findings on Mosaicplasty for knee cartilage defects

| Abbreviations used: Autologous chondrocyte implantation – ACI, International cartilage research society – ICRS, Hospital Special Surgery – HSS | | | |
|--|---|---|--|
| Study details | Key efficacy findings | Key safety findings | Comments |
| <p>Bentley G (2003)(1)</p> <p>Randomised controlled trial</p> <p>UK</p> <p>n = 100 (mosaicplasty =42, autologous chondrocyte implantation =58)</p> <p>Symptomatic patients with osteochondral or chondral defect > 1cm diameter in joint that is otherwise biomechanically normal</p> <p>Age = 31yrs (mean) (range 16 to 49), Male = 57%</p> <p>Size of defect = 4.66 cm²</p> <p>Post trauma defects = 46%</p> <p>Osteochondritis dissecans = 19%</p> <p>Hondromalacia patellae = 14%</p> <p>Duration of symptoms = 7.2 years</p> <p>Previous surgery = 94%</p> <p>Lesion site: medial femoral condyle = 53% patella = 25% lateral femoral condyle = 18% trochlea = 3% lateral tibial plateau = 1%</p> <p>Open mosaicplasty with 4.5 mm plugs</p> <p>Standardised rehabilitation programme</p> <p>Follow-up = 19 months</p> | <p>Clinical outcomes</p> <p>Regular clinical assessment at one year using the modified Cincinnati rating system, and the Stanmore functional rating system. Rated as excellent (> 80 points), good (55 to 79), fair (30 to 45), poor (< 30).</p> <p>88% (51/58) ACI patients demonstrated an excellent or good clinical outcome compared with 68% (29/42) of mosaicplasty patients (p = 0.277) at 1 year</p> <p>For the subgroup of patients with lesions of the medial femoral condyle 88% (21/24) of ACI patients had an excellent or good outcome vs 74% (21/29) of mosaicplasty patients (p < 0.032)</p> <p>There were no significant differences in the number of good or excellent outcomes following ACI or mosaicplasty for subgroups with lesions in the lateral femoral condyle, or patella</p> <p>All 7 poor results were in the mosaicplasty group. In 10% (4/42) of cases transplanted plugs were in situ but the tissue between them was not covered with continuous fibrous tissue. In 7% (3/42) of cases the plugs had disintegrated, and in 2% (1/42) the articular cartilage at the margins of the defect had broken down</p> <p>Arthroscopic evaluation</p> <p>Arthroscopy was undertaken at 1 year in 60% of patients (no details given of selection).</p> <p>ICRS grade 1 or 2 was found in 82% (31/37) of ACI patients but only 34% (8/23) of mosaicplasty patients (p < 0.01).</p> | <p>Complications</p> <p>Procedure complications were not differentiated between treatment groups</p> | <p>Allocation to study arm by random numbers in sealed opaque envelopes.</p> <p>No comparison of study groups at baseline.</p> <p>No details of blinding of outcome assessors.</p> <p>Inconsistency in clinical outcomes assessment scale (missing range).</p> <p>Inconsistency in scores reported for arthroscopy assessment for ACI patients between report text and table.</p> <p>Authors warn of the possible damage at site of graft or plug harvesting.</p> <p>Non standardised use of periosteum or porcine collagen membrane to cover grafts within the study.</p> |

| Abbreviations used: Autologous chondrocyte implantation – ACI, International cartilage research society – ICRS, Hospital Special Surgery – HSS | | | |
|---|---|--|--|
| Study details | Key efficacy findings | Key safety findings | Comments |
| <p>Hangody L (2003)(2)</p> <p>Case series</p> <p>Hungary</p> <p>n = 831 (femoral condyles = 597, patellofemoral joint = 118, and other sites)</p> <p>Two thirds of patients with localised grade III or IV cartilage lesions and one third with osteochondral defects</p> <p>Age < 50 years</p> <p>85% of procedures had concomitant surgical interventions (cruciate ligament reconstruction, realignment osteotomies, meniscal surgery, and patellofemoral realignment)</p> <p>Mosaicplasty through open surgery, miniarthrotomy, or arthroscopically (proportions not specified). Using grafts from 2.7 to 8.5 mm in diameter</p> <p>Follow-up to 10 years</p> <p>Standardised clinical assessment with the modified HSS scoring system, the modified Cincinatti knee rating scale, the Lysholm scale, and the ICRS</p> <p>10% (83/831) of cases had follow-up arthroscopy to assess the quality of the resurfaced area</p> | <p>Clinical outcomes</p> <p>A good to excellent outcome was reported in 92% of patients who had femoral condylar implants, 87% of those who had tibial resurfacings, and 79% of those who had patellar or throchlear mosaicplasty (absolute figures not stated)</p> <p>Arthroscopic assessment</p> <p>83% (69/83) of cases who had follow-up arthroscopy demonstrated good gliding surfaces, and 17% (14/83) had slight or severe degenerative changes at the mosaicplasty site (follow-up period not stated)</p> | <p>Complications</p> <p>Complications were not specified for each treatment site studied, or for concomitant surgery performed. Overall there were < 1% (4/831) deep infections, 4% (36/831) of cases resulted in painful heamarthroses, and < 1% (2/831) of patients had thrombo-embolic complications</p> | <p>Mean or median follow-up period not stated (maximum 10 years).</p> <p>Open or arthroscopic approach not standardised.</p> <p>Concomitant surgery not standardised.</p> <p>No details of baseline patient characteristics.</p> <p>No details provided of clinicians undertaking outcome assessment.</p> <p>Not possible to relate complications to site of mosaicplasty treatment.</p> <p>Outcome measures poorly defines and no details given of validation.</p> <p>Only a selected proportion of cases had arthroscopic assessment, no criteria stated a priori.</p> |

| Abbreviations used: Autologous chondrocyte implantation – ACI, International cartilage research society – ICRS, Hospital Special Surgery – HSS | | | |
|---|--|--|---|
| Study details | Key efficacy findings | Key safety findings | Comments |
| <p>Christel P (1998)(3)</p> <p>Case series - Abstract</p> <p>France</p> <p>n = 21</p> <p>July 1996 to April 1998</p> <p>Osteochondritis dissecans = 12 cartilage or osteochondral tears = 9</p> <p>Age = 17 to 41 years (range) Male = 86% Size of defect = 4.6cm² Number of grafts = 1 to 12</p> <p>29% (6/21) of cases had previously undergone surgery for cartilage lesion, and 29% (6/21) of cases had undergone stabilising ligamentoplasty</p> <p>Mosaicplasty by arthroscopy = 6, or arthrotomy = 15 (more common for treatment of lateral condyles and trochlea). Grafts of 2.7 mm, 3.5 mm, or 4.5 mm</p> <p>Concomitant surgery: tibial osteotomy = 2 reconstruction of anterior cruciate ligament = 3</p> | <p>Clinical outcomes For the 8 cases that have reached 6 months follow-up excellent results were achieved in 38% (3/8) of cases, a good result in 50% (4/8), and a poor result in 1 case. Method of assessment not described</p> <p>Structural outcomes MRI evaluation was undertaken in 3 cases. Consistent cartilage coverage was seen in 67% (2/3) of cases, and the cartilage was detached in 1 case at 6 months</p> <p>6 month follow-up arthroscopy found that cartilage coverage was achieved in all 6 cases that were assessed</p> | <p>Procedural complications No postoperative complications were reported, and no morbidity reported relating to harvest of grafts</p> | <p>Full baseline demographic and clinical characteristics of the cases are not provided.</p> <p>Follow-up period not well described.</p> <p>Case selection for outcome evaluation by MRI or arthroscopy not described.</p> <p>Short follow-up period.</p> <p>Results not grouped for site of mosaicplasty treatment or by arthroscopic or arthrotomy method.</p> <p>Concomitant surgical therapy not standardised.</p> <p>Not clear whether study report is from a peer-reviewed source</p> |

| Abbreviations used: Autologous chondrocyte implantation – ACI, International cartilage research society – ICRS, Hospital Special Surgery – HSS | | | |
|---|--|---|--|
| Study details | Key efficacy findings | Key safety findings | Comments |
| <p>Hangody L (1998)(4)</p> <p>Case series</p> <p>Hungary</p> <p>n = 57</p> <p>Diagnosis of chondral or osteochondral lesions as confirmed by arthroscopy. 61% (35/57) cases had condylar cartilage defects, 12% (7/57) patients had grade III to IV chondromalacia, and 26% (15/57) patients had osteochondral defects</p> <p>Age = 31 years Male = 46% Duration of symptoms = 5 months Area of cartilage defect = 1 to 8.5 cm²</p> <p>Mosaicplasty by miniarthrotomy for lesions >15 mm or arthroscopy for lesions < 15 mm. Grafts 2.7 to 4.5 mm, mean 8 grafts, range 3 to 17</p> <p>68% (39/57) of cases required some form of concomitant surgery during mosaicplasty</p> <p>Follow-up = 3 years</p> | <p>Clinical outcomes A standardised physical examination including range of motion and strength assessment was carried out and cases evaluated using the modified HSS knee scoring system</p> <p>At three years following mosaicplasty the mean HSS score was 90.7 (range 64 to 100). The use of concomitant surgical procedure during mosaicplasty did not significantly influence the result</p> <p>95% (54/57) of cases had returned to their normal activity level in sports and work at 3 years follow-up</p> <p>Arthroscopic evaluation 19 patients had a repeat arthroscopy examination. The transplanted cartilage remained hyaline in character and bonding had occurred at the treatment site. 84% (16/19) of cases demonstrated smooth solid surface of cartilage, but 16% (3/19) cases were found to display grade II chondromalacia</p> | <p>Procedure complication There was no clinical or radiographic evidence of graft loosening, protuberance, or subsidence</p> <p>Painful haemarthrosis = 4%(2/57)</p> | <p>Patients are likely to be from the same study population as Hangody (2003), more detailed outcomes are reported here.</p> <p>Case series represents 95% (57/60) of cases through to 3-year follow-up. Characteristics of those lost to follow-up not stated.</p> <p>No baseline clinical assessment made for comparison.</p> <p>No quantification of assessment of cartilage character in arthroscopic evaluation.</p> <p>No reasons given for the selection of patients for follow-up arthroscopy.</p> |

| Abbreviations used: Autologous chondrocyte implantation – ACI, International cartilage research society – ICRS, Hospital Special Surgery – HSS | | | | | | | | | | | |
|--|---|---|---------------------|------------|------------------|-----------|---------------------------------|-----------|-----------------|-----------|---|
| Study details | Key efficacy findings | Key safety findings | Comments | | | | | | | | |
| <p>Jakob R (2002)(5)</p> <p>Case series (prospective)</p> <p>Switzerland</p> <p>n = 52</p> <p>Patients with cartilaginous defects: post traumatic lesions = 16 osteochoondritis dissecans = 13 femoropatellar arthrosis = 10 femoropatellar maltracking = 5 acute trauma = 5 localised degeneration = 3</p> <p>Age = 34 years (mean) Male = 56% Surface lesion = 4.9 cm² Concomitant surgery = 58%</p> <p>Mosaicplasty by arthrotomy or arthroscopy (4% 2/52), with plugs of 4.6 to 7.4mm, and a mean 6 plugs transplanted. A 70 to 85% coverage of the defect was achieved</p> <p>Follow-up = 3 years</p> | <p>Clinical outcomes Standardised evaluation was based on the ICRS criteria.</p> <p>At 2 years follow up there was an increased level of knee function and activity in 86% (45/52) of cases. For patients who had mosaicplasty alone (without concomitant surgery) there was improved knee function in 91% (20/22) of cases</p> <p>There was no statistically significant correlation between outcome and lesion size or defect aetiology</p> <p>Arthroscopic evaluation In 10 patients a secondary arthroscopy was carried out (at 4 to 41 months), patients were selected according to symptoms of catching, secondary surgery, and evaluation of return to sport</p> <p>The grafted cartilage had a smooth or slightly fibrillated surface, and histological examination showed that transplanted cartilage retained its hyaline character</p> <p>Subjective assessment A self-administered questionnaire was completed by 81% (42/52) of cases 18 months postoperatively</p> <p>The subjective evaluation of the function of the treated knee compared with the healthy knee on a visual analogue scale was found to improve from 37.5 points at baseline to 82.5 points (p < 0.0001)(SD of scores not presented)</p> <p>At 18 months after surgery 93% (39/42) of patients had no or slight limitations in normal life, and 52% (22/42) of cases had an increased level of sporting activity compared to baseline</p> <p>Length of stay The average length of hospital stay was 10 days (range 6 to 21)</p> | <p>Complications</p> <table border="0"> <tr> <td>Symptoms of locking</td> <td>10% (5/52)</td> </tr> <tr> <td>Severe infection</td> <td>2% (1/52)</td> </tr> <tr> <td>Haematoma requiring reoperation</td> <td>2% (1/52)</td> </tr> <tr> <td>Joint stiffness</td> <td>2% (1/52)</td> </tr> </table> <p>In cases with more than six grafts of 6 to 7mm harvested, some degree of crepitation was observed in all cases (15/15) but this was not painful</p> <p>88% (37/42) of patients were satisfied with the outcome, while 12% (5/42) regretted the operation</p> | Symptoms of locking | 10% (5/52) | Severe infection | 2% (1/52) | Haematoma requiring reoperation | 2% (1/52) | Joint stiffness | 2% (1/52) | <p>Consecutive cohort of patients.</p> <p>Baseline and follow-up clinical outcome assessment using different criteria in some cases.</p> <p>Cases selected for secondary arthroscopy may tend to be non responders.</p> <p>Reasons for non responders to subjective evaluation are given.</p> <p>No details of number of operators.</p> |
| Symptoms of locking | 10% (5/52) | | | | | | | | | | |
| Severe infection | 2% (1/52) | | | | | | | | | | |
| Haematoma requiring reoperation | 2% (1/52) | | | | | | | | | | |
| Joint stiffness | 2% (1/52) | | | | | | | | | | |

Validity and generalisability of the studies

- A variety of clinical outcome measures for knee function are used across the studies, no details are given as to whether these have been validated.
- Little long term follow up, where the aim of treatment is to limit progression of osteo-arthritis.
- Many cases had concomitant surgical treatment during the mosaicplasty procedure.
- Open or arthroscopic approach not standardised across or within studies, and outcomes for these subgroups not reported separately.

Specialist Advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

- The intended benefit of this procedure is to provide good knee function without catching, locking, swelling, and without pain.
- Advisors report anecdotal adverse event to include, little integration with, and degeneration of the adjacent cartilage, fracture of femoral condyle, and occasional technical problems. Theoretical complications may be incomplete repair of the defect, long term loss of functional benefit, infection, and pain at the donor site.
- Future audit should include evaluation of osteo-arthritis progression.
- Efficacy may vary depending on the size of the area of defected cartilage to be repaired, and consequently the amount of donor cartilage required. This may also effect whether the procedure can be carried out arthroscopically or by open procedure.

Issues for consideration by IPAC

- The committee should be aware of the technology appraisal on autologous cartilage transplantation <http://www.nice.org.uk/pdf/guidanceactknee.pdf>

References

- (1) Bentley G, Biant LC, Carrington RW, Akmal M, Goldberg A, Williams AM et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee.[see comment]. *Journal of Bone & Joint Surgery - British Volume* 2003; 85(2):223-230.
- (2) 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. *Journal of Bone & Joint Surgery - American Volume* 2003; 85-A Suppl 2:25-32.
- (3) Christel P, Versier G, Landreau Ph, Dijan P. Osteochondral Grafting usign the Mosaicplasty Technique. *Maitrise Otrhopedique* . 1998.
Ref Type: Abstract
- (4) Hangody L, Kish G, Karpati Z, Udvarhelyi I, Szigeti I, Bely M. Mosaicplasty for the treatment of articular cartilage defects: Application in clinical practice. *Orthopedics* 1998; Vol. 21(7):-756.
- (5) Jakob RP, Franz T, Gautier E, Mainil-Varlet P. Autologous osteochondral grafting in the knee: indication, results, and reflections. *Clinical Orthopaedics & Related Research* 2002;(401):170-184.

Appendix A: Additional papers on mosaicplasty for knee cartilage defects not included in the summary tables

| Article title | Number of patients/ follow-up | Comments | Direction of conclusions |
|---|----------------------------------|--|---|
| Berlet GC, Mascia A, Miniaci A. Treatment of unstable osteochondritis dissecans lesions of the knee using autogenous osteochondral grafts (mosaicplasty). <i>Arthroscopy</i> 1999; 15(3):312-316. | n=1 FU=9 months | One case only where series are available | Age =15 years with osteochondritis dissecans and trauma to knee. Mosaicplasty and anterior cruciate ligament reconstruction. MRI documented healing of the transplanted plugs and a continuous layer of cartilage at the plug-articular interface |

Appendix B: Literature search for mosaicplasty for knee cartilage defects

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PreMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

| Procedure Name: | | | |
|--|------------------------------|---------------------------------|-------------------------|
| Database name: medline, premedline and embase | | Date searched 24/09/2004 | |
| Search History (paste from search engine) | | | |
| 1 | mosaicplasty.tw. | 5 | Display |
| 2 | cartilage restoration.tw. | 1 | Display |
| 3 | cylinder autograft.tw. | 0 | - |
| 4 | cartilage transfer.tw. | 0 | - |
| 5 | hangody l.au. | 0 | - |
| 6 | osteocondritis dissecans/ | 0 | - |
| 7 | ocd.tw. | 77 | Display |
| 8 | osteocondritis dissecans.tw. | 9 | Display |
| 9 | osteocondral defect\$.tw. | 17 | Display |
| 10 | cartilage, articular/ | 0 | - |
| 11 | or/6-10 | 101 | Display |
| 12 | or/1-5 | 6 | Display |
| 13 | 11 and 12 | | |