Human dermal allograft for massive rotator cuff tears

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

Decision Support Document No. 117
ISSN online: 1998-0469

Human dermal allograft for massive rotator cuff tears

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, March 2019

Project Team

Project leader: Dr MMag. Sabine Geiger-Gritsch

Authors: 1. Anje Scarfe, BHSc(Hons) Research Officer at Royal Australasian College of Surgeons, Australia
2. Sarah Wolf, BSc, MSc

Project Support

Systematic literature search: Tarquin Mittermayr, BA(Hons), MA

External Review: Prim. Dr Gerald Ch. Loho,
Abteilungsvorstand II. Orthopädische Abteilung Herz Jesu Krankenhaus Wien

Internal Review: Dr MMag. Sabine Geiger-Gritsch

Correspondence

Sarah Wolf, Sarah.Wolf@hta.lbg.ac.at

This report should be referenced as follows:

Scarfe, A, Wolf S. Human dermal allograft for massive rotator cuff tears. Decision Support Document No. 117; 2019. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the LBI-HTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the LBI-HTA.

The HTA Core Model®, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. The following version of the Model was used: HTA Core Model Version 4.2. Use of the HTA Core Model does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

CONTENT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Wien
https://hta.lbg.ac.at/page/imprint

Responsible for content:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
https://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at

Decision Support Document No.: 117

ISSN online: 1998-0469

Content

List of Figures

List of tables

List of abbreviations

AAOS ..... American Academy of Orthopaedic Surgeons
ASES ..... American Shoulder and Elbow Surgeons
CRD ..... Centre for research and development
CS ..... Constant shoulder assessment
DARE..... Database of Abstracts of Reviews of Efficacy
DASH..... Disabilities of the arm, shoulder, and hand score
DNA..... Deoxyribonucleic acid
GRADE..... Grading of Recommendations Assessment, Development and Evaluation
HR-QoL ..... Health-related quality of life
HTA ..... Health Technology Assessment
IHE..... Institute of Health Economics
MRI ..... Magnetic resonance imaging
NHS-EED..... National Health Service – Economic Evaluation Database
N-RCT ..... Non-randomised controlled trial
OSS..... Oxford Shoulder Score
POP ..... Planned Ongoing Projects database
RCT..... Randomised controlled trial
RoB..... Risk of Bias
ROBINS-I ..... Risk Of Bias In Non-randomized Studies – of Interventions
ROM..... Range of Motion score
SCR ..... Superior Capsular Reconstruction
SPADI..... Shoulder Pain and Disability Index score
SSV..... Subjective shoulder value
UCLA..... University of California, Los Angeles
US..... Ultrasound
VAS ..... Visual analogue scale
WORC..... Western Ontario Rotator Cuff Index

Executive Summary

Introduction

Health Problem

This systematic review is focused on patients with irreparable rotator cuff tears. The rotator cuff is comprised of several muscles, with tendons that stabilize the shoulder. When one or more of the rotator cuff tendons are torn, either following trauma or normal wear and tear, the patient experiences pain and restricted movement of the arm. Rotator cuff tear can usually be repaired with surgery. An irreparable rotator cuff tear is defined as large (>3 cm) or massive (>5 cm), involving two or more tendons, or one which has undergone primary surgery without success.

irreparable rotator cuff tears can lead to pain and restricted movement of the arm

Around 30.0% of patients presenting with rotator cuff tears may have massive irreparable tears and post-operative re-tear rates after primary surgical repair of rotator cuff tears range from 20.0 to 90.0%.

estimated re-tear rates after primary surgery: 20.0-90.0%

Description of Technology

Human dermal allograft is a type of augmentation graft which can be incorporated into the musculotendinous bone complex in tendon repair to improve the likelihood of fixation. While grafts are usually derived from animal tissue (xenograft) or artificially manufactured with synthetic materials, this type uses tissue from other humans – in this case cadaveric donors.

human dermal allograft from cadaveric donors

Human dermal allograft is used in the superior capsular reconstruction technique to improve graft consistency and reduce the likelihood of complications or failure of the procedure. The technology is intended for patients with irreparable rotator cuff tears, where there is a high likelihood of poor healing after repair surgery.

technology deemed to improve graft consistency and reduce likelihood of graft failures or complications

Research question

In patients with irreparable rotator cuff tears, how safe and effective is human dermal allograft compared to rotator cuff tear repair without augmentation concerning pain, range of motion, physical functioning, health-related quality of life and patient satisfaction, adverse events, re-tears, re-operations and procedure-related mortality?

efficacy and safety of human dermal allografts compared to rotator cuff repairs without augmentation

Methods

A systematic review was conducted to investigate the safety and effectiveness of human dermal allograft. Four biomedical databases (Medline, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination) were searched from inception to 14 December 2018. After deduplication, overall 455 citations were identified, of which ten studies were included for data extraction and further analysis. Two authors independently conducted the study selection and quality appraisal (AS, SW), the first author conducted study extraction into a pre-define table which was checked by the second author.

systematic literature search in 4 databases, 455 citations after deduplication, 10 studies included, study extraction into pre-defined tables

Domain effectiveness

critical efficacy outcomes: pain, range of motion, physical function, HR-QoL

Critical outcomes used to evaluate the relative efficacy of human dermal allograft included change in pain scores (e.g., VAS, OSS, UCLA), change in range of motion scores (e.g., WORC, CS, ASES, ROM), change in physical function scores (e.g., CS, WORC, OSS, ASES), and change in health-related quality of life (HR-QoL) scores (e.g., WORC, OSS, SF-12).

critical safety outcomes: mortality, failure, re-operation, complications, adverse events

Domain safety

Critical outcomes used to evaluate the relative safety of human dermal allograft included procedure-related mortality, failure/re-tears, re-operation/additional surgery, complications, and adverse events.

Results

Available evidence

1 RCT funded by the manufacturer, 2 N-RCTs and 7 single arm studies (n=42 + 26 + 35 + 277 pts.)

Only prospective studies with 20 or more patients and at least two years of follow-up were considered for inclusion in the assessment of efficacy. Clinical studies with any patient number and follow-up period were considered for inclusion in the assessment of safety. One randomised controlled trial (n=42) was identified which investigated rotator cuff repair using human dermal allograft against the same procedure without human dermal allograft. This randomised control trial was funded by the manufacturer of GraftJacket. In addition, two non-randomised controlled trials (n=26; n=35) and seven single arm studies (total n=277) were identified.

Clinical effectiveness

1 RCT + 2 N-RCTs for efficacy outcomes, only total scores reported

In the included controlled studies **pain**, **range of motion**, **physical function** and **HR-QoL** were assessed via several tools, including the CS, ASES, UCLA, OSS and WORC scores. Of all scores only the total scores have been reported and not the sub-scales, thus only the total scores are reported once for all outcomes.

some significant improvements in efficacy outcomes:

Across the included controlled studies and scores some significant improvements in **pain, range of motion, physical functioning** and **HR-QoL** could be identified.

1 N-RCT: significant improvement in pain in the intervention group measured with VAS score

For example, using the VAS score the mean difference between groups in a non-randomised controlled trial (n=35) was calculated to be 2.7 points lower in the intervention group with the VAS (C: 6.9 [SD 1.1] vs 4.1 [SD 1.1]; I: 6.8 [SD 1.6] vs 1.3 [SD 1.2]; p=0.024), which indicates a significant pain reduction in the treatment group.

1 N-RCT: significant improvement in HR-QoL in the intervention group measured with WORC score

And, using the WORC score the mean difference in the same non-randomised controlled trial (n=35) was calculated to be 22.0 points higher compared to the control group, measured preoperatively and then at last follow-up (C: 58.0 [SD 5.0] vs 66.0 [SD 5.0]; I: 54.0 [SD 8.0] vs 84.0 [SD 4.0]; p=0.0412), indicating a significant improvement in HR-QoL. HR-QoL was measured in the same study (n=35) using SF-12 and a non-significant improvement in the intervention group was reported.

other scores consistent but not significant improvements in intervention groups

Other than the significant improvement in pain as measured using VAS and HR-QoL using WORC, all efficacy outcomes were found to have a consistent, but non-significant improvement across the scores and studies.

Safety

No **procedure-related mortality** was reported in any of the included studies.

no morality cases reported

The relative **failure rates** in the randomised controlled trial (n=42) were 45.0% (9/20) in the control group versus 13.6% (3/22) in the intervention group at mean follow-up of 24 months. Relative failure rates in a non-randomised controlled trial (n=35) were 27.0% (4/15) in the control group versus 10.0% (2/20) in the intervention group at mean follow up of 24.9 months. The failure rate across the seven case series was 19.0% (24/126) with follow up times ranging from 12 to 77 months.

failure rates 27.0-45.0% vs. 10.0-13.6% in 2 controlled studies, failure rate across 7 case series: 19.0%

No **re-operation/additional surgery** was reported in the randomised controlled trial. Re-operation rates in a non-randomised controlled trial (n=35) were 26.0% (3/15) in the control group versus 10.0% (2/20) in the intervention group at mean follow up of 24.9 months. The total re-operation rate across five case series was 18.0% (14/78) with follow up times ranging from 12 to 39 months.

re-operation rate in 1 N-RCT: 26.0 vs. 10.0%, re-operation rate across 5 case series: 18.0%

Complications were reported in six included studies, including a total of 192 patients and mean follow-up times from 12 to 36 months. Only one study reported a complication. It was a non-randomised controlled trial (n=35) which reported one patient had a skin infection after the procedure that was resolved with antibiotics.

1 complication in 192 pts. (6 studies) reported, the 1 complication reported in a N-RCT

Adverse events were reported in five studies. Three single arm studies (n=47) reported none occurred and two studies, the randomized controlled trial (n= 42) and one case series (n=9), reported 22 adverse events in total, resulting in a combined adverse event rate of 19.3% (22/114). Events include re-tears (12), cellulitis (2), shoulder bursitis (2), fibrosis (1), bicep tendon rupture (1), and subsequent shoulder injuries (4). No events were attributed to the presence of the human dermal allograft.

zero adverse events reported in 3 single arm studies (n=47), 22 adverse event cases (19.3%) reported in RCT + 1 single arm study (n= 42 + 9)

Severe adverse events were not reported in the comparative studies. Two single arm studies, with mean follow up times from 12 to 15 months, reported that no serious adverse events occurred, resulting in a combined severe adverse event rate of 0.0% (0/22).

no severe adverse events reported

Quality of evidence

Overall, the quality of evidence for the effectiveness and safety of surgical repair with human dermal allograft in comparison to surgical repair without human dermal allograft is considered “moderate”.

overall, moderate quality of evidence

Upcoming evidence

Ongoing trials include four randomised controlled trials and one non-randomised controlled trial. Completion dates are before mid-2020. Including a total of 244 patients, they investigate rotator cuff repair using human dermal allograft against the same procedure without a graft. Once these have been completed and published results are available, the evidence on human dermal allograft is expected be greatly strengthened.

4 ongoing RCTs + 1 ongoing N-RCT (n=244), completion dates before mid-2020

Reimbursement

Currently, human dermal allografts (GraftJacket™ and Arthrex Inc.) are not included in the Austrian hospital benefit catalogue, thus the device is not reimbursed by the Austrian healthcare system.

human dermal allografts currently not reimbursed in Austria

Discussion

objective, randomised controlled studies lacking

There is a paucity of objective, randomised controlled studies to allow the assessment of the relative risks and benefit of rotator cuff tear repair with human dermal allograft in comparison to rotator cuff tear repair alone.

main limitations: small sample sizes, short follow-up durations, etc.

The main limitations in the evidence base were related to small sample sizes, a lack of comparative data, and short follow-up durations. In addition, the randomised controlled trial was sponsored by the manufacturer of GraftJacket.

Conclusion

based on limited evidence, human dermal allograft more effective and as safe as or safer

At present, the evidence is insufficient to prove the technology is significantly more effective and safer than the comparator. However, from the limited evidence, of "moderate" quality, it appears rotator cuff tear repair with human dermal allograft is more effective, and as safe as or even safer as its comparator. These findings should be considered with caution.

re-evaluation suggested for 2021

It is recommended this technology be re-evaluated in 2021, when some of the ongoing trials have published results.

Zusammenfassung

EinleitungIndikation und therapeutisches Ziel

irreparable Risse der Sehnen in der Rotatorenmanschette führen zu Schmerzen und Bewegungs-einschränkungen der Schulter

Der Fokus der vorliegenden Übersichtsarbeit liegt auf PatientInnenen mit irreparablen Rissen der Rotatorenmanschettensehnen. Die Rotatorenmanschette besteht aus mehreren Muskeln mit Sehnen, die die Schulter stabilisieren. Wenn eine oder mehrere der Sehnen entweder aufgrund eines Traumas oder aufgrund einer normalen Abnutzung gerissen sind, verspürt der Patient/die Patientin Schmerzen und eine eingeschränkte Bewegung des Arms. Ein Sehnenriss in der Rotatorenmanschette kann durch eine Operation repariert werden. Es können jedoch erneute Risse postoperativ auftreten. Ein irreparabler Sehnenriss in der Rotatorenmanschetten wird als groß (>3 cm) bzw. massiv (>5 cm) definiert und umfasst den Riss von zwei bzw. mehreren Sehnen oder ein Sehnenriss bei dem eine primäre Operation erfolglos blieb.

geschätzte Rückfalls-quote nach Primär-operation: 20,0-90,0 %

Ungefähr 30,0 % der PatientInnen mit Rotatorenmanschettensehnenrisse können nach der primären operativen Reparatur schwere irreparable Risse bzw. in 20,0 bis 90,0 % postoperative Risse aufweisen.

Beschreibung der Technologie

Augmentation mittels humaner Dermis von Kadaverspenden

Humane Dermis kann als eine Art Augmentationstransplantat verwendet werden und bei der Sehnenreparatur der Rotatorenmanschette in den muskulotendinösen Knochenkomplex eingebaut werden, wodurch die Fixierung der Sehnenrisse verbessert werden kann. Während Transplantate normalerweise aus tierischen Geweben (Xenograft) stammen oder künstlich mit synthetischen Materialien hergestellt werden, wird für die Augmentation mittels humaner Dermis Gewebe von Menschen – in diesem Fall Kadaverspenden – verwendet.

Technologie scheint Transplantatkonsistenz zu verbessert & Transplantatsversagen bzw. Komplikationen zu verringert

Bei der überlegenen Kapselrekonstruktionstechnik (engl. superior capsular reconstruction, SCR) wird allogene humane Dermis verwendet. Diese Technologie soll eine verbesserte Konsistenz des Transplantats vorweisen und die Wahrscheinlichkeit von Komplikationen oder Misserfolgen des Verfahrens verringern. Die Transplantation von allogener humaner Dermis ist insbesondere für RisikopatientInnen mit Sehnenrissen in der Rotatorenmanschette, für die die Heilungschancen nach einer Reparaturoperation niedrig sind, gedacht,

Forschungsfrage

Wirksamkeit und Sicherheit der Transplantation von allogener humaner Dermis im Vergleich zu Rotatorenmanschetten-reparaturen ohne Augmentation

Wie sicher und wirksam ist die Transplantation von humaner Dermis bei PatientInnen mit irreparablen Rotatorenmanschettensehnenrissen im Vergleich zur Rotatorenmanschettenreparatur ohne Augmentation in Bezug auf Schmerzen, Bewegungsumfang, körperliche Funktionalität, gesundheitsbezogene Lebensqualität und PatientInnenzufriedenheit, sowie bezüglich eingriffsbedingter Mortalität, Fehlerquote, Komplikationen und Nebenwirkungen?

Methoden

systematische Literatursuche in 4 Datenbanken, 455 Zitate nach Deduplizierung, 10 Studien eingeschlossen, Studienextraktion in vordefinierten Tabellen

Eine systematische Literatursuche wurde durchgeführt, um die Sicherheit und Wirksamkeit der Transplantation mittels allogener humaner Dermis zu untersuchen. Bis zum 14. Dezember 2018 wurden vier biomedizinische Datenbanken (Medline, Embase, Cochrane Library, University of York Center für Reviews und Dissemination) durchsucht. Nach Deduplizierung konnten insgesamt 455 Zitate identifiziert werden, von denen zehn Studien für die Datenextraktion und weitere Analyse eingeschlossen wurden. Zwei Autorinnen führten die Studienauswahl und Qualitätsbeurteilung der Studien unabhängig voneinander durch (AS, SW). Die Erstautorin extrahierte die Studiendaten mit Hilfe einer vordefinierten Tabelle, die von der zweiten Autorin überprüft wurde.

Klinische Wirksamkeit

kritische Wirksamkeitsendpunkte: Schmerzen, Bewegungsumfang, körperliche Funktionalität, Lebensqualität

Zu den kritischen Endpunkten, die zur Beurteilung der relativen Wirksamkeit von allogener humaner Dermis verwendet wurden, zählten die Veränderung der Schmerzwerte, gemessen anhand von drei Scores (VAS, OSS, UCLA), die Veränderung des Bewegungsumfanges, gemessen anhand von vier Scores (WORC, CS, ASES, ROM) und die Veränderung der körperlichen Funktionalität, gemessen anhand von vier Scores (CS, WORC, OSS, ASES), sowie Änderung der gesundheitsbezogenen Lebensqualität, gemessen anhand von drei Scores (WORC, OSS, SF-12).

Sicherheit

kritische Sicherheitsendpunkte: Mortalität, Fehlerquote, Re-operationen, etc.

Zu den kritischen Endpunkten, die zur Bewertung der relativen Sicherheit von allogener humaner Dermis verwendet wurden, gehörten die eingriffsbedingte Mortalität, Technologieversagen/Rückfälle (Fehlerquote), Re-operationen/zusätzliche Operationen, Komplikationen und unerwünschte Ereignisse.

Ergebnisse

Verfügbare Evidenz

1 vom Hersteller finanziertes RCT, 2 N-RCTs und 7 einarmige Studien (n=42 + 26 + 35 + 277)

Lediglich prospektive Studien mit 20 oder mehr PatientInnen und einer Nachbeobachtungszeit von mindestens zwei Jahren wurden in die Bewertung der Wirksamkeit einbezogen. Bei der Auswahl der Studien für die Bewertung der Sicherheit wurden keine Restriktionen berücksichtigt. Es wurde eine randomisierte kontrollierte Studie (n=42) identifiziert, in der die Reparatur der Rotatorenmanschettensehne mittels allogener humaner Dermis im Vergleich zu einem Verfahren ohne allogene humane Dermis untersucht wurde. Diese randomisierte Kontrollstudie wurde vom Hersteller der Technologie, GraftJacket, gesponsert. Zusätzlich wurden zwei nicht randomisierte kontrollierte Studien (n=26; n=35) und sieben Einzelarmstudien (insgesamt n=277) identifiziert.

Klinische Wirksamkeit

1 RCT + 2 N-RCTs für Wirksamkeitsergebnisse nur Gesamtpunktezahlen berichtet

In den eingeschlossenen kontrollierten Studien wurden Schmerz, Bewegungsumfang, körperliche Funktionsfähigkeit und gesundheitsbezogene Lebensqualität mit Hilfe von verschiedenen Scores bewertet. Für alle Scores wurden nur die Gesamtwerte und nicht die Subskalen berichtet. Aus diesem Grund wurden lediglich die Gesamtwerte der Scores für die jeweiligen Endpunkte angegeben.

Insgesamt zeigten die eingeschlossenen kontrollierten Studien für alle Scores (teilweise signifikante) Verbesserungen in Bezug auf Schmerzen, Bewegungsumfang, körperliche Funktionalität und gesundheitsbezogene Lebensqualität.

teilweise signifikante Verbesserung der Wirksamkeit

Beispielsweise wurde in einer nicht randomisierten Studie (n=35) signifikante VAS Scores berichtet, die die Berechnung eines durchschnittlichen Unterschieds von 2.7 Punkten zwischen den Studiengruppen ergab (C: 6.9 [SD 1.1] vs. 4,1 [SD 1.1]; I: 6,8 [SD 1.6] vs. 1,3 [SD 1.2]; p = 0.024). Dies bedeutet, dass sich die VAS Werte vom Zeitpunkt null bis zum letzten Follow-up in der Interventionsgruppe um 2,7 Punkte mehr reduziert haben als in Kontrollgruppe. Da niedrigere VAS Werte auf eine Schmerzreduktion verweisen, konnte für die Interventionsgruppe eine signifikante Schmerzverbesserung berichtet werden.

1 N-RCT: signifikante Verbesserung der Schmerzen in der Interventionsgruppe, gemessen mit dem VAS-Score

Für dieselbe nicht randomisierte kontrollierte Studie (n=35) wurde im Hinblick auf die WORC-Scores ein durchschnittlicher Unterschied von +22,0 Punkten im Vergleich zur Kontrollgruppe berechnet (C: 58.0 [SD 5.0] vs. 66,0 [SD 5.0]; I: 54,0 [SD 8.0] vs. 84,0 [SD 4.0]; p = 0.0412). Diese Verbesserung der WORC-Scores in der Interventionsgruppe weist auf eine signifikante Verbesserung der Lebensqualität in dieser Studiengruppe hin. In derselben Studie wurde die Lebensqualität mittels des SF-12 Scores gemessen, welches ebenso eine Verbesserung der Lebensqualität in der Interventionsgruppe – jedoch nicht statistisch signifikant – ergab.

1 N-RCT: signifikante Verbesserung der Lebensqualität in der Interventionsgruppe, gemessen mit dem WORC-Score

Abgesehen von der signifikanten Verbesserung der Schmerzen resultierend aus der VAS-Bewertung und der signifikanten Verbesserung der Lebensqualität gemessen mit dem WORC-Score, ergaben die verbleibenden Messungen keine statistisch signifikanten Verbesserungen in den Interventionsgruppen.

zusätzlich konsistente, aber nicht signifikante Verbesserungen in den Interventionsgruppen

Sicherheit

In keiner der eingeschlossenen Studien wurden Fälle zur eingriffsbedingten Mortalität berichtet.

keine Mortalitätsfälle

Die relativen Fehlerquoten in der randomisierten kontrollierten Studie (n=42) betrugen 45,0 % (9/20) in der Kontrollgruppe versus 13,6 % (3/22) in der Interventionsgruppe bei einer mittleren Nachbeobachtungszeit von 24 Monaten. Die relative Fehlerquote in einer nicht randomisierten, kontrollierten Studie (n=35) betrug 27,0 % (4/15) in der Kontrollgruppe versus 10,0 % (2/20) in der Interventionsgruppe bei einem durchschnittlichen Follow-up von 24,9 Monaten. Die Fehlerquote der sieben Fallserien betrug 19,0 % (24/126) bei einem Nachbeobachtungszeitraum zwischen 12 und 77 Monaten.

Fehlerquoten von 27,0-45,0 % vs. 10,0-13,6 % in 2 kontrollierten Studien, Fehlerquote in 7 Fallserien: 19,0 %

In der randomisierten kontrollierten Studie wurden keine Re-Operationen berichtet. Die Re-Operationsrate in einer nicht randomisierten kontrollierten Studie (n=35) lag in der Kontrollgruppe bei 26.0 % (3/15) gegenüber 10.0 % (2/20) in der Interventionsgruppe bei einer durchschnittlichen Nachbeobachtungszeit von 24.9 Monaten. Die Re-Operationsrate in fünf Fallserien betrug 18.0% (14/78) bei einem Nachbeobachtungszeitraum von 12 bis 39 Monaten.

Re-Operationsrate bei 1 N-RCT: 26.0 vs. 10.0 %, Re-Operationsrate bei 5 Fallserien: 18.0%

In sechs eingeschlossenen Studien mit insgesamt 192 PatientInnen und einer durchschnittlichen Nachbeobachtungszeit zwischen 12 und 36 Monaten wurden über Komplikationen berichtet: Lediglich in einer von den sechs Studien – in der nicht randomisierten kontrollierten Studie (n=35) – trat bei einem Patienten/einer Patientin eine Komplikation auf. Diese Person erlitt postoperativ eine Hautinfektion, die mit Antibiotika behandelt werden konnte.

1 Komplikation in 192 PatientInnen. (6 Studien)

keine unerwünschten Ereignisse in 3 Einarmstudien (n=47), 22 Nebenwirkungen (19,3 %) in 1 RCT + 1 Einarmstudie (n=42 + 9)

In fünf Studien wurde über unerwünschte Ereignisse berichtet. Drei Einarmstudien (n=47) berichteten, dass keine Nebenwirkungen aufgetreten waren, und zwei Studien – die randomisierte kontrollierte Studie (n=42) und eine Fallserie (n=9) – gaben insgesamt 22 unerwünschte Ereignisse an, was in einer kombinierten Nebenwirkungsrate von 19,3 % (22/114) resultiert. Zu den Nebenwirkungen zählten erneute Sehnenrisse nach dem Eingriff (12), Zellulitis (2), Schulter-Bursitis (2), Fibrose (1), Bizepssehnenruptur (1) und nachfolgende Schulterverletzungen (4). Keine der Nebenwirkungen konnte auf die Augmentation mittels allogener humaner Dermis zurückgeführt werden.

keine *schwerwiegenden* Nebenwirkungen

In den inkludierten Studien wurden keine *schwerwiegenden* unerwünschten Ereignisse berichtet.

Qualität der Evidenz

insgesamt moderate Qualität der Evidenz

Insgesamt wird die Qualität der Evidenz für die Wirksamkeit und Sicherheit der chirurgischen Reparatur mittels allogener humaner Dermis im Vergleich zur chirurgischen Reparatur ohne humaner Dermis als „moderat" angesehen.

Laufende Studien

4 laufende RCTs + 1 laufende N-RCT (n=244), Fertigstellungstermine vor Mitte 2020

Die aktuell laufenden Studien umfassen vier randomisierte kontrollierte Studien und eine nicht randomisierte kontrollierte Studie. Fertigstellungstermine werden auf Mitte 2020 geschätzt. Mit insgesamt 244 PatientInnen untersuchen die Studien die Wirksamkeit und Sicherheit der Reparatur der Rotatorenmanschette mittels allogener humaner Dermis im Vergleich zum gleichen Verfahren ohne Transplantat. Die Veröffentlichung der Studiendaten wird weitere relevante Evidenz für die Reparatur von Sehnenrissen in der Rotatorenmanschette mittels allogener humaner Dermis erbringen.

Kostenerstattung

momentan wird nicht erstattet

Derzeit ist die Transplantation von allogener humaner Dermis (GraftJacket™ und Arthrex Inc.) nicht im österreichischen Leistungskatalog enthalten und wird daher vom österreichischen Gesundheitssystem nicht erstattet.

Diskussion

objektive, randomisierte kontrollierte Studien fehlen

Aktuell gibt es keine objektiven, randomisierten kontrollierten Studien, um die relativen Risiken und den Nutzen der Rotatorenmanschettenreparatur mittels allogener humaner Dermis im Vergleich zur Rotatorenmanschettenreparatur ohne Augmentation beurteilen zu können.

Limitationen: kleine Stichprobengrößen, kurze Nachlaufzeiten usw.

Limitationen der vorhandenen Evidenz umfassen kleine Stichprobengrößen, fehlende Vergleichsdaten und kurze Nachbeobachtungszeiträume. Darüber hinaus wurde die randomisierte kontrollierte Studie vom Hersteller von GraftJacket gesponsert.

Zusammenfassung/Empfehlung

gemäß aktueller Evidenz ist Transplantat mittels humaner Dermis wirksamer und gleich sicher oder sicherer

Auf der Grundlage der verfügbaren Evidenz können keine Schlussfolgerungen gezogen werden, ob die Reparatur von Sehnenrissen in der Rotatorenmanschette mittels allogener humaner Dermis wesentlich wirksamer und sicherer ist als eine Reparatur ohne Augmentation. Basierend auf der verfügbaren Evidenz von „mäßiger" Qualität scheint die Reparatur mittels allogener humaner Dermis effektiver und genauso sicher oder sogar sicherer zu sein als ohne Augmentation. Aufgrund der limitierten Evidenz sollten diese Feststellungen jedoch mit Vorsicht betrachtet werden.

erneute Bewertung für 2021 empfohlen

Die erneute Bewertung wird im Jahr 2021 empfohlen, wenn weitere laufende Studien abgeschlossen sind und dadurch zusätzliche Evidenz vorliegt.

1 Scope

1.1 PICO question

PIKO-Frage

In patients with irreparable rotator cuff tears, how safe and effective is human dermal allograft compared to rotator cuff tear repair without augmentation when concerning pain, range of motion, physical functioning, health-related quality of life, patient satisfaction, adverse events, re-tears, re-operations, and procedure-related mortality?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: Inclusion criteria

Population	Patients with irreparable tears of the shoulder rotator cuff tendon. **Contraindications/exclusions:** Presence of subscapular tear, presence of glenohumeral osteoarthritis, Western Ontario Rotator Cuff (WORC) score >70%, uncontrolled diabetes, pregnancy, presence of local or systemic infection, paralysis of the shoulder, poor nutritional state, contracture of the shoulder, presence of cuff tear arthropathy, MRI proven nonvascular surgical sites, and cancer. **MeSH Terms:** Rotator Cuff Injury [C26.761.340, C26.803.063, C26.874.400] **Rationale:** Currently limited international guidelines on the recommended use of human dermal allograft for massive rotator cuff tears are available. Therefore, the population has been informed by a case series,[1] and a review article [2].
Intervention	Reconstruction of the rotator cuff tear with human dermal allograft (athroscopic or open technique), e.g. superior capsular reconstruction (SCR), depending on the size and configuration of the tear.This is conducted in a revision setting after prior failed rotator cuff repairs. **Product names:** GraftJacket (Wright Medical Technology Inc. TN, USA); Arthrex ArthroFLEX Inc. FL, USA) **MeSH Terms:** Acellular dermis [A17.815.180.040] **Rationale:** The relevant intervention has been informed by review articles [3, 4].
Control	Any surgical reconstruction of irreparable rotator cuff tears without use of human dermal allograf, e.g.: ❁ Tendon transfer ❁ Inverse arthroplasty **Rationale:** One randomised study was identified during scoping. In this study, rotator cuff tear repair procedure without human dermal allograft was the control intervention [5].

Outcomes	
Efficacy	*Critical* clinical endpoints include changes between pre- and post-treatment outcomes for: **(A) pain, (B) range of motion, (C) physical function, (D) Health-Related Quality of Life** *Important* clinical endpoints include changes between pre- and post- treatment outcomes for: **(E) patient satisfaction and MRI scan of intact cuffs**. These are measured with the following tools: ❁ Western Ontario Rotator Cuff Index (WORC) questionnaire (B), (C), (D) ❁ Disabilities of the arm, shoulder, and hand (DASH) score (A), (C) ❁ Shoulder Pain and Disability Index (SPADI) score (A), (C) ❁ Range Of Motion (ROM) score (B) ❁ Subjective shoulder value (SSV) score (C)(E) ❁ Constant shoulder (CS) assessment (A), (B), (C) ❁ Oxford Shoulder Score (OSS) (A), (C), (D) ❁ Visual analogue scale (VAS) score (A) ❁ American Shoulder and Elbow Surgeons (ASES) score (A), (B), (C) ❁ SF-12 score (D) ❁ University of California, Los Angeles (UCLA) shoulder score (A), (B), (C), (E) **Rationale:** Efficacy outcomes were informed by a review article,[4] clinical studies, [1, 5] and the EUnetHTA guidelines [6, 7].
Safety	❁ Procedure-related mortality ❁ Failure of repair procedure/re-tears ❁ Re-operation/additional surgery ❁ Complications (procedure-related and device-related) ❁ Adverse events (e.g. bursitis, cellulitis, & fibrosis) **Rationale:** Safety outcomes were informed by a randomised study,[5] and the EUnetHTA guidelines [8].
Study design	
Efficacy	❁ Randomised controlled trials ❁ Prospective non-randomised comparative study designs ❁ In the absence of comparative evidence, prospective case series with ≥ 20 participants and at least 48 months follow up will be included. **Excluded:** case studies, review articles, conference abstracts, letter to the editor, author response, retrospective case series.
Safety	❁ Randomised controlled trials ❁ Prospective non-randomised controlled trials ❁ Prospective case series ❁ Retrospective case series **Excluded:** case studies, review articles, conference abstracts, letter to the editor, author response.

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What is a human dermal allograft and the comparator(s)?
A0020	For which indications has human dermal allograft received marketing authorisation or CE marking?
B0002	What is the claimed benefit of human dermal allograft in relation to the comparators?
B0003	What is the phase of development and implementation of human dermal allograft and the comparator(s)?
B0004	Who administers human dermal allograft and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use human dermal allograft and the comparator(s)?
B0009	What supplies are needed to use human dermal allograft and the comparator(s)?
A0021	What is the reimbursement status of human dermal allograft?

Health problem and Current Use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is human dermal allograft used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for irreparable rotator cuff tears?
A0004	What is the natural course of irreparable rotator cuff tears?
A0005	What is the burden of disease for the patients with irreparable rotator cuff tears?
A0006	What are the consequences of irreparable rotator cuff tears for the society?
A0024	How are irreparable rotator cuff tears currently diagnosed according to published guidelines and in practice?
A0025	How are irreparable rotator cuff tears currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are human dermal allografts utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0005	How does human dermal allograft affect symptoms and findings (severity, frequency) of irreparable rotator cuff tears?
D0006	How does human dermal allograft affect progression (or recurrence) of irreparable rotator cuff tears?
D0011	What is the effect of human dermal allograft on patients' body functions?
D0016	How does the use of human dermal allograft affect activities of daily living?
D0012	What is the effect of human dermal allograft on generic health-related quality of life?
D0013	What is the effect of human dermal allograft on disease-specific quality of life?
D0017	Was the use of human dermal allograft worthwhile?

Safety	
Element ID	**Research question**
D0001	What is the expected beneficial effect of human dermal allograft on mortality?
D0003	What is the effect of human dermal allograft on the mortality due to causes other than irreparable rotator cuff tears?
C0008	How safe is human dermal allograft in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying human dermal allograft?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of human dermal allograft?
C0007	Are human dermal allograft and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of human dermal allograft and the comparator?

2.2 Sources

Description of the technology

Quellen: systematische Suche, Handsuche, Informationen der Einreicher

- Hand-search in the Planned Ongoing Projects database (POP), AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Questionnaire completed by the submitting hospitals

Health problem and Current Use

Quellen: systematische Suche, Handsuche, Informationen der Einreicher

- Hand-search in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Questionnaire completed by the submitting hospitals

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 14.12.2018 in the following databases:

- Medline via Ovid (including PubMed)
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

systematische Suche eingegrenzt nach Sprache und Studiendesign

The systematic literature search was conducted in The Cochrane Library, York CRD, Medline and Embase from inception to 14 December 2018 for only prospective or randomised controlled trials and restricted to articles published in English or German. The specific search strategies employed are presented in the Appendix.

zusätzliche Handsuche, 455 Treffer (nach Deduplizierung)

Following a hand-search, three additional studies were found, resulting in overall 455 hits.

keine Studien von Einreichern

No publications were submitted by the responsible hospitals.

keine Antwort der Hersteller

Both manufacturers have been contacted, however, none of the manufacturers replied. Thus, no additional publication have been submitted.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 11.01.2019. This search identified 67 results of which five trials (4 randomised controlled trials and 1 non-randomised controlled trial) were deemed recent and relevant to this assessment, see Table A-10 & Table A-11.

2.4 Flow chart of study selection

Literaturauswahl

Overall, after removal of duplicates, 455 records were identified. These were screened by two independent researchers and in case of disagreement, they resolve the differences via discussion. The selection process is displayed in Figure 2-1.

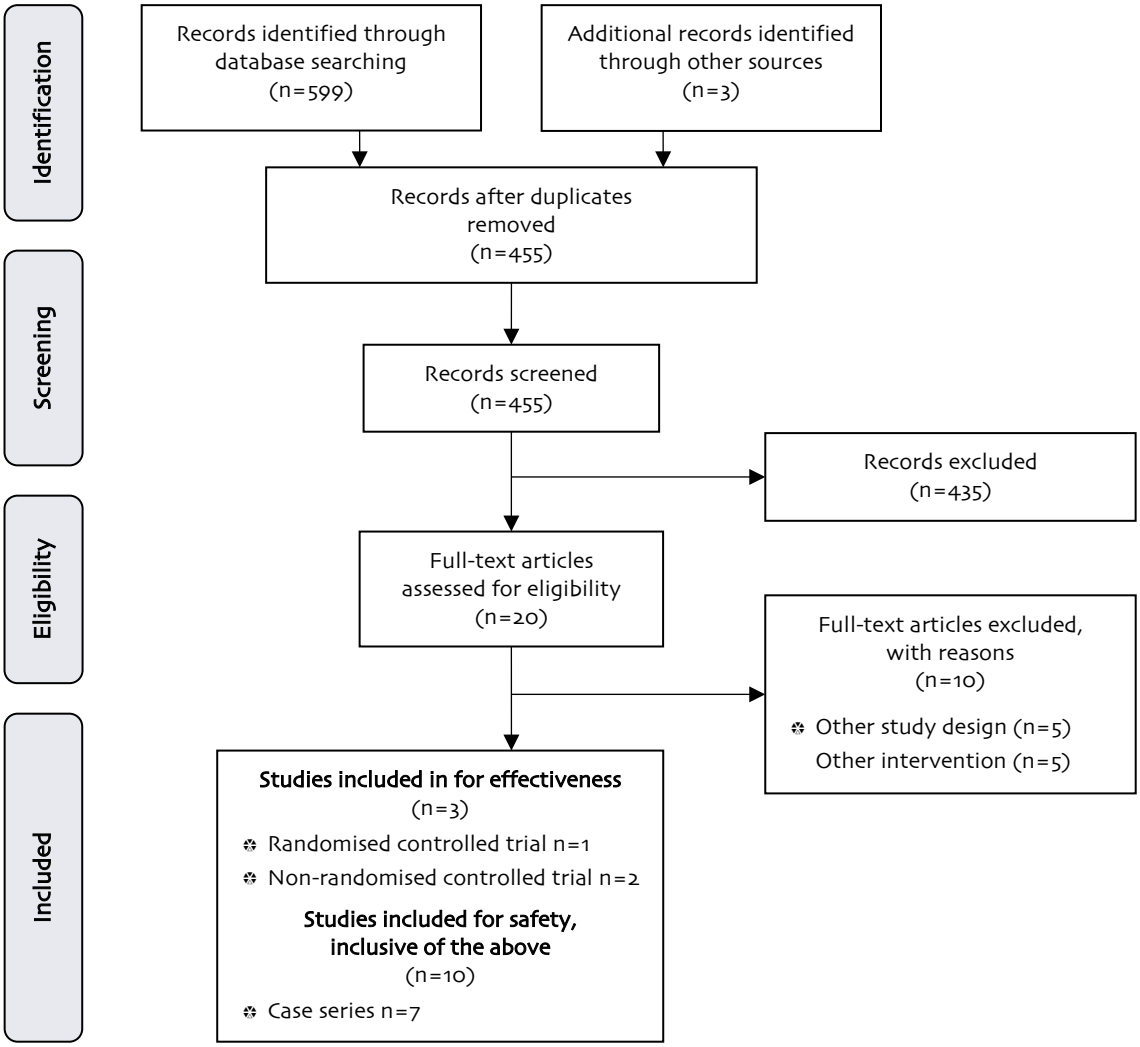

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

Datenextraktion und Bewertung des Bias-Risikos nach Cochrane RoB-Tool, ROBINS-I und IHE Checklist

The data retrieved from the selected studies (see Chapter 2.4) were systematically extracted into data-extraction-tables (see Appendix). Data were extracted by a single author and checked by the second author. No quantitative analysis was conducted due to the limited amount of evidence. Risk of bias was assessed using Cochrane Risk of Bias tool for the randomised controlled trial [9], ROBINS-I for non-randomised controlled trials [10], and the Institute of Health Economics (IHE) Checklist for case series studies [11] (see Table A-3, Table A-4, Table A-5).

2.6 Synthesis

Evidenzsynthese mittels GRADE

The questions were answered in plain text format with reference to Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence tables [12] that are included in Appendix. As comparative studies did not conduct any significant testing between groups, we calculated the mean difference between time points. Results were summarised in Table 7-1.

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What is a human dermal allograft and the comparator (s)?

Technology – Surgical treatment of irreparable rotator cuff tear with human dermal allograft

Rekonstruktion der irreparablen Rotatorenmanschette mittels Anbringung allogener humaner Dermis

Human dermal allografts are most commonly used in the superior capsule reconstruction (SCR) technique [13]. The procedure is a replacement surgery for the torn rotator cuff tendon with incorporation of the human dermal allograft. Patients lie on their side under general anaesthesia and a number of portals are established for inserting of the arthroscope. The human dermal allograft is then arthroscopically secured between the superior glenoid neck, intact rotator cuff, greater tuberosity, and the rotator interval tissue [13, 14].

2 Produkte von 2 unterschiedlichen Herstellern

The products presently available on the market are GraftJacket® which is manufactured by Wright Medical Group Inc. and ArthroFLEX® manufactured by Arthrex. Differences between the two products are outlined in Table 3-1.

Unterschiede der beiden Produkte

Table 3-1: Features of human dermal allograft products on the market

Product	Features
ArthroFLEX	✿ Available in in 11 shapes/sizes/thicknesses ✿ Sterile, with a Sterility Assurance Level of 10-6 ✿ Decellularized >97% DNA and cellular remnants removed using MatrACELL® process ✿ Intact acellular extracellular matrix ✿ Pre-hydrated, water packed ✿ 3-year shelf life at room temperature
GraftJacket	✿ Available in in 9 shapes/sizes/thicknesses ✿ Sterile, with a Sterility Assurance Level of 10-6 ✿ Decellularized with DNA and cellular remnants removed ✿ Intact acellular extracellular matrix ✿ Pre-hydrated, water packed ✿ 2-year shelf life at room temperature

Comparator – Surgical treatment of irreparable rotator cuff tear* without *human dermal allograft

Reparatur OHNE allogener humaner Dermis, z. B. Sehnentransfer, Arthroplastik, etc.

The comparator for this intervention is surgical reconstruction of irreparable rotator cuff tears without the use of human dermal allograft. This includes:

- ✿ Tendon transfer or inverse arthroplasty
- ✿ The above surgical procedures using augmentation with animal-derived or synthetic grafts

Eingriff ohne Transplantate selten für irreparable Rotatorenmanschette

The procedure for repairing rotator cuff tear without augmentation is described by American Academy of Orthopaedic Surgeons (AAOS) [15], this approach is more common in reparable tears.

offener Eingriff bei langen und komplexen Rissen

Regular rotator cuff tear surgical procedures can be arthroscopic or open. Open surgical incision is required if the tear is long or complex. The surgeon often detaches the deltoid to gain better access, one or more bone spur may be removed from the underside of the acromion; this is also done when additional reconstruction, such as tendon transfers, is being conducted.

bzw. arthroskopischer Eingriff (meist ambulant durchgeführt)

In arthroscopic repair, an arthroscope is inserted into the shoulder joint through small incisions and the repair is carried out. Arthroscopic repair is usually an outpatient procedure.

seltener: minimale offene Reparatur

Another technique is the mini-open repair. This involves a small incision approximately 3-5 cm in length. This approach uses arthroscopy to treat damage and remove bone spurs. However, differences include the deltoid being detached and repair is not being viewed through a screen by the surgeon [15].

umgekehrte Schulterendoprothetik und Sehnentransplantate mit hohen Komplikationsraten

Massive rotator cuff tear have an increased likelihood of re-tear and in recent years newer methods of repair have been sought. Reverse shoulder arthroplasty and tendon transfer have been performed on these rotator cuff tears; however, high complication rates remain and long-term results are uncertain, particularly in younger patients [4].

aktuell beste mögliche Behandlung von irreparablen Rotatorenmanschetten: überlegene Kapselrekonstruktion

Additional approaches include arthroscopic partial repair and arthroscopic debridement; both have success rates of around 50.0% [16].

Irrespective of the advances and the development of novel treatment types the best practice for irreparable rotator cuff tear is agreed to be SCR [4]. Therefore, SCR using fascia lata autograft without human dermal allograft augmentation is seen as the primary comparator in this investigation.

A0020 – For which indications has human dermal allograft received marketing authorisation or CE marking?

keine Marktzulassung der Produkte

The manufacturers of the two human dermal allograft products on the market – Wright Medical Group Inc. and Arthrex Inc. – have not received marketing authorisation for the products in any jurisdictions, including Europe.

Spende von menschlichem Gewebe geregelt unter EUTCD 2004/23/EC

In general, human tissue donation is regulated in the European Union under the European Union Tissue and Cells Directives (EUTCD) 2004/23/EC. The EUTCD outlines the legal framework for the supply of tissues and cells within the EU, to ensure that biological samples meet acceptable safety and quality standards. In this regard, individual suppliers of tissue samples that are licensed to distribute tissue samples under the EUTCD can distribute within the European Union.

B0002 – What is the claimed benefit of human dermal allograft in relation to the comparators?

geringere Rückfallsquote (erneute Risse)

Human dermal allograft is intended to treat patients with massive, irreparable rotator cuff tears, by improving function, reducing pain and preventing re-tears [17-19]. Specifically, human dermal allograft is proposed as a superior technique leading to improvement in pain, range of motion, and strength as well as mechanical improvement in ultrasound imaging at follow up [20].

Einreicher keinen passenden Vergleich geäußert

The submitting hospital did not propose a specific clinical claim in relation to an appropriate comparator, rather that there is no alternative technique that achieves successful, long-lasting, repair in the intended patient group.

B0003 – What is the phase of development and implementation of human dermal allograft and the comparator(s)?

No evidence was identified that could be used in the examination of this question.

keine Evidenz

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers human dermal allograft and the comparator(s) and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use human dermal allograft and the comparator(s)?

Rotator cuff repair using an acellular human dermal allograft should be performed by an orthopaedic surgeon that is fellowship trained in arthroscopic surgery of the shoulder. For the intervention, an orthopaedic surgeon experienced in the use of human dermal allograft will be preferred. Rotator cuff repair with and without human dermal allograft are performed with the patient under general anaesthesia. They should be conducted in a medical centre that is accustomed to performing arthroscopic rotator cuff repair, in a sterile operating theatre.

Eingriff durchgeführt von orthopädischem/r Chirurg/in unter Allgemeinanästhesie in sterilem Operationssaal

B0009 – What supplies are needed to use human dermal allograft and the comparator(s)?

During the procedure, several supplies are needed. The following steps are required to perform the surgical technique; the supplies needed are listed alongside the respective step:

1. Preoperative workup
2. Surgical positioning and diagnostic arthroscopy (padded arm sleeve, an ablation devices or curved scissors, cannulas)
3. Superior glenoid neck preparation (an ablation device or arthroscopic shaver, anchors)
4. Placement of medial anchors (postersuperior anchor)
5. Graft sizing and preparation (acellular human dermal allograft, arthroscopic suture passer)
6. Graft insertion and medial fixation
7. Lateral graft fixation to humerus (corkscrew anchors, lateral-row anchors)
8. Anterior and posterior edge fixation
9. Closure [13].

9 unterschiedliche Operationsschritte und dafür notwendige Materialien, z. B. Schultermanschette, Ablationsvorrichtung, azelluläre allogene humane Dermis, arthroskopisches Nahtführungs-instrument, etc.

Regulatory & reimbursement status

A0021 – What is the reimbursement status of human dermal allograft?

Currently, human dermal allografts (GraftJacket™ and Arthrex Inc.) are not included in the Austrian hospital benefit catalogue. Therefore, the device itself is not reimbursed by the Austrian healthcare system. However, the intervention could be billed under another code, like for reconstruction of the capsule-ligament apparatus of the shoulder joint – arthroscopic (Code ME080 Rekonstruktion des Kapsel-Band-Apparates des Schultergelenks – arthroskopisch).

aktuell keines der Produkte in den Leistungskatalog inkludiert, daher nicht finanziert, jedoch möglicherweise über einen anderen Code abrechenbar

4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is human dermal allograft used?

Human dermal allograft can be used in a range of orthopaedic procedures, including hip & femur, knee, foot, soft tissue, thumb, elbow, shoulder, wrist, hand, or other musculoskeletal system procedures [21].

für orthopädische Eingriffe bei Hüfte, Knie, Fuß, Schulter, etc.

It is proposed that human dermal allograft should be limited to rotator cuff tear patients with a high likelihood of poor healing after repair surgery. The most common indication for human dermal allograft augmentation is tears that are massive and that, while surgically repairable, they have a high risk of not healing [22].

allogene humane Dermis speziell für große und chronische Risse mit geringer Heilungschance

A0002 – What is the disease or health condition in the scope of this assessment?

The rotator cuff is comprised of several muscles, including the supraspinatous muscle, infraspinatus muscle, teres minor muscle, and subscapularis muscle. The tendons of each muscle act together to stabilize the shoulder.

Rotatorenmanschette: eine Gruppe von Muskeln und Sehnen

When one of the rotator cuff muscles are torn, either following trauma or normal wear and tear, the patient experiences pain and restricted movement of the arm [23, 24].

Risse in Sehnen möglich

Rotator cuff tear can usually be repaired with surgery. An irreparable rotator cuff tear is defined as large (>3 cm) or massive (>5 cm), involving two or more tendons, or one which has undergone primary surgery without success [18, 25].

irreparabel = große und massive Risse (>5 cm)

The scope of the present assessment is patients with irreparable rotator cuff tears.

→ PatientInnen-Population des Berichts

A0003 – What are the known risk factors for irreparable rotator cuff tears?

Rotator cuff tears can result from extrinsic trauma, such as falls and sporting injuries, or may be gradually degenerative without any notable trauma. The aetiology is judged purely on patient reported history and is likely to be multi-factorial [26, 27].

Risse durch traumatische Ereignisse oder allmähliche Abnützung

Rotator cuff tears are more common in males, those engaged in heavy labour, and with a history of trauma [28]. Increased age is an important risk factor [22, 26]; indeed, it was reported 51% of individuals aged over 80 years had an asymptomatic rotator cuff tear in a study conducted on 411 German volunteers [29]. High cholesterol, history of smoking and genetics are also known risk factors for rotator cuff tear [27, 30].

Risikofaktoren: männliches Geschlecht, körperliche Arbeit, zunehmendes Alter, Genetik, etc.

A0004 – What is the natural course of massive rotator cuff tears?

Rotator cuff tears have a limited ability to heal without surgical intervention. Tear progression is a significant risk and is correlated with symptom development [27].

gerine Heilungschancen ohne Operation

Symptome: Schmerzen, Einschränkungen in Tätigkeiten des alltäglichen Lebens

A group of 45 asymptomatic patients were observed over a five-year period and 51.0% became symptomatic after 2.8 years. This was associated with increased pain and decreased ability to perform actions of daily life ($P<0.05$) [31].

Anhalten der Symptome nach nicht-operativen Behandlungen

Risks associated with non-operative treatment in symptomatic patients include tear progression without spontaneous healing, increased difficulty with tendon mobilisation, fatty infiltration of the rotator cuff muscles, and progression to arthritis later in life [27].

Effects of the disease or health condition on the individual and society

A0005 – What is the burden of disease for patients with irreparable rotator cuff tears?

Folgen wie Schmerzen, eingeschränkte Schulterfunktion, verminderte Lebensqualität

In general, rotator cuff tears have the potential to cause debilitating shoulder pain, reduced shoulder function, and compromised joint mechanics, leading to degeneration of the glenohumeral joint over time [32], and lowering quality of life.

As stated, symptoms of rotator cuff tear may occur immediately after trauma (acute) or develop over time (chronic).

traumatische Risse vs. chronische Risse

Traumatic tears mostly affect the supraspinatus tendon, or the rotator interval and symptoms include severe pain that radiates through the arm, and limited range of motion, specifically while lifting the shoulder. Symptoms arising from chronic tears include sporadic worsening of pain, debilitation, and atrophy of the muscles, pain during rest, crackling sensations when moving the shoulder, and an inability to move or lift the arm satisfactorily [33].

irreparable Risse aufgrund nicht anschlagender Therapie

Irreparable rotator cuff tears have this same symptom profile, primarily distinguished by failure of repair surgery [34].

A0006 – What are the consequences of irreparable rotator cuff tears for the society?

Prävalenz zwischen 7.0-37.0 %

Cadaveric studies out of Japan and the United States have estimated the incidence of rotator cuff tears in the general population to be between be 13.0% to 37.0% for partial-thickness tears and 7.0% to 27.0% for full-thickness tears [22].

30.0% der Pat. mit massiven, irreparablen Rissen

One case series report that up to 30.0% of patients presenting with rotator cuff tears may have massive irreparable tears; further to that post-operative re-tear rates after primary surgical repair of rotator cuff tears range from 20.0% to 90.0% [34].

zusätzliche gesellschaftliche Kosten

Furthermore, a vast majority of the patients suffering from massive/ irreparable rotator cuff tears are in their productive age. As a result, a part of the patients might be incapacitated for work, which can be assumed to result in additional societal costs.

Current clinical management of the disease or health condition

A0024 – How are irreparable rotator cuff tears currently diagnosed according to published guidelines and in practice?

No guidelines for the diagnosis of irreparable rotator cuff tears could have been identified. According to Thorsness et. al (2016), upon physical examination, the surgeon will assess the presence of scars, range of motion, and conduct comprehensive neurovascular check. Massive tears involving the infraspinatus tendon will usually present with increasing passive internal rotation. Massive tears involving the subscapularis tendon will usually present with increasing passive external rotation. The surgeon will also palpate the long head biceps and conduct strength testing of all rotator cuff muscles.

Diagnose durch körperliche Untersuchung

Imaging for all patient with suspected rotator cuff tear will include true anteroposterior, axillary lateral, and outlet views of the shoulder. Although ultrasound can be used in tear diagnosis, magnetic resonance imaging is preferred as it enables estimation of the size, location, and chronicity of the tear [2].

Diagnose mittels bildgebende Verfahren, MRI bevorzugt

A0025 – How are irreparable rotator cuff tears currently managed according to published guidelines and in practice?

No guidelines for the treatment of irreparable rotator cuff tears could have been identified. According to Thorsness et. al (2016), options after failed repair surgery include simple debridement with biceps tenotomy or tenodesis, revision repair with or without allograft augmentation, or SCR. It is the most popular method for irreparable rotator cuff tears, especially in younger patients [2].

Alternativen nach erfolgloser Operation: Bizepssehnentenodese, SCR, etc.

Target population

A0007 – What is the target population in this assessment?

The population of this assessment includes patients with irreparable tears of the shoulder rotator cuff tendon. See the PICO criteria for further definition.

irreparable Risse der Rotatorenmanschettensehne

A0023 – How many people belong to the target population?

No information on the Austrian or European data for the prevalence or incidence of irreparable rotator cuff tear was identified to inform this research question. Similarly, the frequency of repair surgery conducted for this population in Austria is currently unknown.

keine Evidenz

A0011 – How much are human dermal allografts utilised?

The estimated annual utilisation of the submitting hospitals of human dermal allografts (athroscopic or open technique) in Austria is about 160 [information of submitting hospitals 2018].

geschätzte jährliche Nutzungsrate: 160 Fälle pro Jahr in Österreich

5 Clinical effectiveness

5.1 Outcomes

The following outcomes were defined as *critical* to derive a recommendation on the clinical effectiveness of human dermal allograft repair:

entscheidende Endpunkte für Wirksamkeit ...

- Decrease in pain
- Increase in range of motion
- Increase in physical function
- Increase in health-related quality of life

... Schmerzen gemessen mit 5 Scores

Pain is the primary symptom that is used to measure the effectiveness of surgical repair. It is most often measured using patient reported or observer-reported questionnaire scales, and as such is difficult to measure objectively. Pain can be measured using generic scales, such as a Visual Analogue Scale (VAS), or disease-specific questionnaires, Oxford Shoulder Score (OSS), University of California, Los Angeles (UCLA) Score, American Shoulder and Elbow Surgeons (ASES), and Constant Score (CS) assessment.

... Bewegungsumfang gemessen mit 4 Scores

Range of motion is a typical measure to assess shoulder pathology treatments. It measures patients' ability to raise their arm above shoulder height. There are specific tools with sub-scales to measure it such as UCLA, ASES, CS and Western Ontario Rotator Cuff Index (WORC) assessment.

... körperliche Funktionalität gemessen mit 5 Scores

Physical function is a measure of how the disease impacts daily life and activities. It measures patients' ability to complete tasks of daily life. It can be measured using sub-scales of a range of different scoring tools, including ULCA, ASES, CS, OSS and WORC assessment.

... gesundheitsbezogene Lebensqualität (3 Scores)

Health-related quality of life (HR-QoL) can be measured using generic scales such as SF-12 or with sub-scales of specific shoulder scores, such as OSS and WORC index.

Erklärung der Scores in Extraktionstabellen (Appendix)

The scales of the different scores are explained in more detail in the evidence tables in the Appendix.

weitere (nicht entscheidungsrelevante) Endpunkte zur Beantwortung der Fragen

In addition to the *critical* outcomes, two additional outcomes were considered important but not crucial to the decision:

- Patient satisfaction
- MRI scan of intact cuffs.

5.2 Included studies

kontrollierte Studien für Wirksamkeitsendpunkte

To evaluate the effectiveness of human dermal allograft in rotator cuff repair surgery, we considered randomised controlled trials and prospective non-randomised controlled trials comparing human dermal allograft to any surgical repair without using human dermal allograft.

1 RCT & 2 N-RCTs, 2 Produkte

One randomised controlled trial [35], and two non-randomised controlled trials [17, 18] met the pre-defined inclusion criteria. Investigators in two studies [17, 35] reported outcomes for the GraftJacket, and in one study [18] for the ArthroFLEX.

1 prospektives, multi-zentrisches RCT

The randomised controlled trial was a prospective institutional review board-approved, multicentre series of patients randomised to undergo rotator cuff repair with human dermal allograft, or the same procedure without human dermal allograft.

Hersteller als Sponsor der US-amerikanischen Studie mit 42 (22 vs. 20) PatientInnen, Rehabilitation für alle

This study was supported by grants from the manufacturer, Wright Medical Technology. It was conducted in the United States and enrolled 42 patients with irreparable rotator cuff tear. From the total sample, 22 were randomised to receive human dermal allograft, and 20 to have the repair surgery without augmentation. All patients used an abduction sling for four to six weeks and started supervised physical therapy at four weeks post-operatively.

Ø Alter: 34-72 Jahre, 18,2-35,0 % Frauen, Nachbeobachtungszeit 12-38 Monate

Patients had a mean age of 56 years (range, 34 to 72 years). Most patients were male, with four (18.2%) females in the intervention group, and seven (35.0%) females in the control group. Mean patient follow up was 24 months, ranging from 12 to 38 months. Losses to follow up were not reported.

2 N-RCTs: US-amerikanisch, Arthroflex & UK, GraftJacket

The two non-randomised controlled trials also studied patients undergoing repair with or without human dermal allograft augmentation. One non-randomised prospective blinded trial [18] was conducted in the United States with ArthroFLEX as the intervention. The second non-randomised prospective controlled trial [17] was conducted in the United Kingdom with GraftJacket as the intervention.

insgesamt: 66 PatientInnen (33 vs. 28), Rehabilitation für alle

The trials included a total of 61 patients with irreparable rotator cuff tear. There were 33 patients receiving surgical repair with human dermal allograft and 28 receiving surgical repair with no human dermal allograft, across studies. All groups had an abduction sling for six weeks and started supervised physical therapy at similar time points post-operatively.

Ø Alter: 57-62 Jahre, 30,1-53,0 % Frauen

The mean age of patients ranged from 57 to 59 in the intervention groups and from 59 to 62 in the control groups across studies. Between four (30.1%) and twelve (40.0%) of the patients in the intervention groups and between four (30.1%) and eight (53.0%) of the patients in the control group were females across studies.

Ø Nachbeobachtungszeit 22-60 Monate

The mean follow up time of the studies was 24 and 24.9 months, with ranges from 22 months to 60 months.

Extraktionstabellen im Anhang

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-7.

5.3 Results

Morbidity

D0005 – How does human dermal allograft affect symptoms and findings (severity, frequency) of irreparable rotator cuff tears?

Wirksamkeitsendpunkte anhand mehrerer Scores, nur Gesamtscores berichtet

The critical outcomes for efficacy were pain, range of motion, HR-QoL, and physical function. In the included controlled studies, pain, range of motion and physical function were assessed via several tools, including the CS, ASES, UCLA, OSS and WORC scores. Of all scores only the total scores have been reported and not the sub-scales, thus only the total scores are reported once for all outcomes.

1 RCT: Verbesserung der CS, ASES, ULCA Scores in Interventionsgruppen (nur teilweise statistisch signifikant)

In the RCT [35], the CS mean difference was calculated to be 11.4 points higher in the intervention group, preoperatively versus last follow-up (C: 45.8 vs 85.3 [SD 11.0]; I: 41.0 vs 91.9 [SD 9.2]; p=0.008). The ASES score mean difference was calculated to be 1.6 points higher in the intervention group, preoperatively versus last follow-up (C: 46.0 vs 94.8 [SD 14.2]; I: 48.5 vs 98.9 [SD 4.2]; p=0.035). The UCLA shoulder score mean difference was calculated to be 2.5 points higher in the intervention group, preoperatively versus last follow-up (C: 15.9 vs 28.3 [SD -3.0]; I: 13.3 vs 28.2 [SD 2.1]; p=0.43).

1 N-RCT: signifikante Verbesserung (CS & OSS) in Interventionsgruppen

One non-randomised controlled trial [17] had a calculated mean difference in CS assessment of 15.0 points higher in the intervention group, preoperatively versus last follow-up (C: 43.1 [SD 3.9] vs 70.8 [SD 5.3]; I: 41.2 [SD 3.1] vs 83.9 [SD 6.0]; p<0.01). Additionally, the mean difference in OSS assessment was calculated to be 9.7 points higher in the intervention group, preoperatively versus last follow-up (C: 17.8 [SD 3.6] vs 37.1 [SD 2.4]; I: 14.9 [SD 3.5] vs 43.9 [SD 2.4]; p=0.01).

1 N-RCT: signifikante Verbesserung (ASES, WORC, VAS) in Interventionsgruppen

The other non-randomised controlled trial [18] had a mean difference calculated to be 12.8 points higher than controls with the ASES scale, preoperatively versus last follow-up (C: 60.3 [SD 9.5] vs 72.6 [SD 11.9]; I: 63.8 [SD 13.8] vs 88.9 [SD 4.8]; p=0.024). Also the mean difference was calculated to be 22.0 points higher for the intervention group in the WORC assessment, preoperatively versus last follow-up (C: 58.0 [SD 5.0] vs 66.0 [SD 5.0]; I: 54.0 [SD 8.0] vs 84.0 [SD 4.0]; p=0.0412). In addition, the mean difference was calculated to be 2.7 points lower in the intervention group with the VAS (C: 6.9 [SD 1.1] vs 4.1 [SD 1.1]; I: 6.8 [SD 1.6] vs 1.3 [SD 1.2]; p=0.024), which indicates a significant pain reduction in the treatment group.

Verbesserungen in Schmerz, Bewegungsumfang & Funktionalität

Overall, across the included controlled studies and scores a partly significant improvement in pain, range of motion and physical functioning could be identified.

Lebensqualität anhand Frage D0012 beantwortet

For results of the assessment of HR-QoL see research question “D0012 – What is the effect of human dermal allograft on generic health-related quality of life?” in this section.

D0006 – How does human dermal allograft affect progression (or recurrence) of irreparable rotator cuff tears?

berichtet im Kapitel 6.3, Frage C0008

For information on device failures see Section 6.3 research question “C0008 – How safe is human dermal allograft in comparison to the comparator(s)?”.

Function

D0011 – What is the effect of human dermal allograft on patients' body functions?

D0016 – How does the use of human dermal allograft affect activities of daily living?

Beantwortung mittels 5 Gesamtscores in 3 Studien

Physical function was assessed by five scores (ULCA, ASES, CS, OSS and WORC) across three studies [17, 18, 35]. For all scores only total scores have been reported in the studies but not the sub-scale for physical functioning.

1 RCT: verbesserte ULCA Scores, jedoch nicht signifikant

The ULCA score was calculated to have a mean difference of 2.5 points higher in the intervention group of the randomised controlled trial [35], preoperatively versus last follow-up (C: 15.9 vs 28.3, [SD -3.0]; I: 13.3 vs 28.2, [SD 2.1]; p=0.43).

1 RCT & 1 N-RCT: signifikant verbesserte ASES Scores in Interventionsgruppen

The ASES score was calculated to have a mean difference of 1.6 points higher for the intervention group in the randomised controlled trial [35], preoperatively versus last follow-up (C: 46.0 vs 94.8 [SD 14.2]; I: 48.5 vs 98.9 [SD 4.2]; p=0.035). The ASES score mean difference was calculated to be 12.8 points higher in the intervention group of a non-randomised controlled trial [18], preoperatively versus last follow-up (C: 60.3 [SD 9.5] vs 72.6 [SD 11.9]; I: 63.8 [SD 13.8] vs 88.9 [SD 4.8]; p=0.024).

1 RCT & 1 N-RCT: signifikante Verbesserung (CS) in Interventionsgruppen

The total CS assessment mean difference was calculated to be 11.4 points higher for the intervention group in the randomised controlled trial [35], preoperatively versus last follow-up (C: 45.8 vs 85.3, [SD 11.0]; I: 41.0 vs 91.9, [SD 9.2]; p=0.008). A mean difference of 15.0 points higher was calculated in the intervention group of a non-randomised controlled trial [17], preoperatively versus last follow-up (C: 43.1 [SD 3.9] vs 70.8 [SD 5.3]; I: 41.2 [SD 3.1] vs 83.9 [SD 6.0]; p<0.01).

1 N-RCT: signifikant verbesserte OSS Scores in Interventionsgruppe

The same non-randomised controlled trial [17] reported the OSS score with the mean difference was calculated to be 9.7 points higher in the intervention group (C: 17.8 [SD 3.6] vs 37.1 [SD 2.4]; I: 14.9 [SD 3.5] vs 43.9 [SD 2.4]; p=0.01).

1 N-RCT: marginal signifikante Verbesserung in Interventionsgruppe

In the other non-randomised controlled trial [18] the mean difference was calculated to be 22.0 points in the WORC assessment in the intervention group, preoperatively versus last follow-up (C: 58.0 [SD 5.0] vs 66.0 [SD 5.0]; I: 54.0 [SD 8.0] vs 84.0 [SD 4.0]; p=0.0412).

insgesamt teilweise signifikante Verbesserung der Funktionalität

Overall, across the studies and the different scores, partly statistically significant improvements in physical functioning in the intervention groups have been reported.

Health-related quality of life

D0012 – What is the effect of human dermal allograft on generic health-related quality of life?

Lebensqualität gemessen mit 3 Scores

Health-related quality of life (HR-QoL) was assessed by three scores across two comparative studies [17, 18].

1 N-RCT: bessere Lebensqualität in Interventionsgruppe gemessen anhand SF-12 und WORC, ...

A non-randomised controlled trial [18], reported outcomes for SF-12 and WORC. Total SF-12 score mean difference was calculated to be 1.4 points higher in the intervention group regarding the mental component and of 5.7 points higher in the intervention group regarding the physical component as measured preoperatively and at last follow-up. The total WORC mean differ-

ence was calculated to be 22.0 points higher compared to the control group, measured preoperatively and then at last follow-up (C: 58.0 [SD 5.0] vs 66.0 [SD 5.0]; I: 54.0 [SD 8.0] vs 84.0 [SD 4.0]; p=0.0412).

... jedoch marginale signifikante Unterschiede lediglich für WORC

The other non-randomised controlled trial [17] reported total OSS including a sub-scale for HR-QoL. The patients were calculated to have a mean difference of 9.7 points higher in the intervention group (C: 17.8 [SD 3.6] vs 37.1 [SD 2.4]; I: 14.9 [SD 3.5] vs 43.9 [SD 2.4]; p=0.01).

1 N-RCT: signifikant verbesserte OSS Scores

Overall, the reported total scores for HR-QoL in the two non-randomised controlled studies indicate an improvement in the intervention groups compared to the control groups, however, the difference was only statistically significant for the WORC score.

insgesamt, verbesserte Lebensqualität in den Interventionsgruppen

D0013 – What is the effect of human dermal allograft on disease-specific quality of life?

No evidence was found to answer this research question.

keine Evidenz

Patient satisfaction

D0017 – Was the use of human dermal allograft worthwhile?

The randomised controlled trial provided patient satisfaction scores using the UCLA tool [35]. A non-statistically significant difference was found between groups, where the UCLA score increased from 15.9 to 28.3 (SD 3.0) in the control group and from 13.3 to 28.2 (SD 2.1) in the intervention group. In the UCLA tool, the patient satisfaction sub-score, a higher score represents better patient satisfaction.

1 RCT: keine statistisch signifikanten Unterschiede (ULCA) zwischen den Studiengruppen

Minimal clinically important differences

Published evidence has reported that the minimal clinically important differences (MCID) for the following shoulder procedure outcomes are: ASES (13.6 ± 2.3), VAS (1.6 ± 0.3), Constant score (5.7 ± 1.9), WORC (245.26) and UCLA (8.7 ± 0.6) [36, 37].

geringster klinisch relevanter Unterschied

Findings in this assessment are compared below to the published MCIDs. ASES has been reported in the randomised controlled trial and in one non-randomised controlled trial with respective mean differences of 1.6 [35] and 12.8 [18], meaning the difference is not clinically significant. VAS has also been reported in one non-randomised controlled trial with a difference of 2.7 [18], meaning the difference is clinically significant. The Constant shoulder assessment was reported in the randomised controlled trial and in one non-randomised controlled trial with respective mean differences of 11.4 [35] and 15.0 [17], meaning differences can be considered clinically significant in both studies. WORC has been reported in one non-randomised controlled trial with a difference of 22.0 [18], showing the difference is not clinically significant. Finally, UCLA was only reported in the randomised controlled trial with a mean difference of 2.5, meaning the difference is not clinically significant. Thus, MDIC may be indicated in VAS and Constant shoulder assessment.

ASES: keine klinisch relevanten Unterschiede,
VAS: klinisch signifikanter Unterschied,
CS: klinisch relevante Unterschiede
WORC & ULCA: keine klinisch signifikanten Unterschiede

6 Safety

6.1 Outcomes

The following outcomes were defined as *critical* to derive a recommendation:

- Procedure-related mortality
- Failure rate/re-tears
- Complications
- Adverse events

entscheidende Endpunkte für Sicherheit: ...

Procedure-related mortality was defined as deaths occurring within 24 months post-operatively or related to a complication incurred in the surgery.

... eingriffsbezogene Mortalität

Failure/re-tears were reported when a shoulder failed to maintain adequate tissue to function as expected, or a re-tear was acknowledged on US or MRI.

... Fehlerquote

Complications were not defined in the studies.

... Komplikationen

Adverse events were all events reported up to final follow up.

... Nebenwirkungen

In addition to the *critical* outcomes, one additional outcome was considered important but not crucial to the decision:

- Re-operation/additional surgery

weiterer (nicht-entscheidungsrelevanter) Endpunkt

Re-operation/additional surgery were not defined in the studies, but must be when another procedure to repair the rotator cuff was needed.

Endpunkt nicht als solche in den Studien definiert

6.2 Included Studies

To evaluate the safety of human dermal allograft in rotator cuff repair surgery, we considered randomised controlled trials, prospective non-randomised controlled trials and single arm studies.

kontrollierte und einarmige Studien für Sicherheit

The same randomised controlled trial and two non-randomised controlled trials used for efficacy were used for safety, as well as, seven single arm studies which met the pre-defined inclusion criteria, including a total of 277 patients [17-20, 34, 35, 38-41]. The comparative trials are described in section 5.2 and the seven single arm studies are described below.

1 RCT, 2 N-RCTs & 7 ein-armige Studien mit 277 PatientInnen

The seven single arm studies were all case series on patients, conducted in the USA, Switzerland, Italy, and Greece [19, 20, 34, 38-41]. One study [19] was supported by grants from Arthrex, and the others did not report any industry funding.

7 einarmige Studien aus Europa oder den USA, 1 Studie gesponsert durch Arthrex

In total, the case series included 174 patients with irreparable rotator cuff tear. All patients received rotator cuff tear repair with human dermal allograft. One study conducted in Switzerland treated three groups of patients with different commercial patches, only data on the patients receiving GraftJacket was extracted [39].

mit insgesamt 174 PatientInnen

4 einarmige Studien mit GraftJacket, 1 mit ArthroFLEX, 2 mit undefinierter Matrix, Rehabilitationsprogramm in allen 7

Ø Alter: 48,0-66,4 Jahre, 0,0-50,0 % Frauen, Ø Nachbeobachtungszeit 12-36 Monate

Extraktionstabellen im Anhang

Four studies used GraftJacket [20, 38, 39, 41], one used ArthroFLEX [19], and the remaining two used a non-identified human dermal matrix [34, 40]. Post-operative treatments included abduction pillow sling for 3-8 weeks, assisted gentle stretching for 3-6 weeks, assisted range of motion at approximately 6 weeks, then strengthening and progression to full activities at approximately 12 weeks.

Mean patient age ranged from 48.0 years to 66.4 years across studies. In these studies, the participants were majority male, with the proportion of female patients ranging from 0.0 to 50.0% across studies. Mean follow up times ranged across studies from 12 to 36 months (range, 29-40).

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-8.

6.3 Results

Mortality

D0001 – What is the expected beneficial effect of human dermal allograft on mortality?

D0003 – What is the effect of human dermal allograft on the mortality due to causes other than irreparable rotator cuff tears?

keine eingriffsbezogenen Todesfälle

No study reported any procedure-related deaths, resulting in a combined procedure-related mortality rate of 0.0% (0/277).

Patient safety

C0008 – How safe is human dermal allograft in comparison to the comparator(s)?

1 RCT: Fehlerquoten 45,0 vs. 13,6 %, 1 N-RCT: 27,0 vs. 10,0 %, 7 einarmige Studien: 19,0 %

At a mean follow up of 24 months the randomised controlled trial [35] reported failure rates were 45.0% (9/20) in the control group versus 13.6% (3/22) in the intervention group, these were not related to the allograft but related to further injuries of the shoulder. Reported failure rates in a non-randomised controlled trial [18] were 27.0% (4/15) in the control group versus 10.0% (2/20) in the intervention group at mean follow up of 24.9 months. The failure rate across the seven case series was 19.0% (24/126) with follow up times ranging from 12 to 77 months [19, 20, 34, 38-41].

1 N-RCT: Re-Operationsrate 26,0 vs. 10,0 %, 5 einarmige Studien: 18,0 %

No reoperation or additional surgery was reported in the randomised controlled trial [35]. Reported reoperation rates in a non-randomised controlled trial [18] were 26.0% (3/15) in the control group versus 10.0% (2/20) in the intervention group at mean follow up of 24.9 months. The total reoperation rate across five case series was 18.0% (14/78) with follow up times ranging from 12 to 39 months [19, 38-41].

1 N-RCT: 1 Komplikation – Hautirritation, behandelt mit Antibiotika

Six included studies reported complications, including a total of 192 patients and mean follow-up times ranging from 12 to 36 months [18, 20, 34, 35, 38, 40]. Within these, only one study reported a complication. It was a non-randomised controlled trial [18] which reported one patient had a complication after the procedure. This patient suffered a superficial skin infection one week post-operatively which was resolved after treatment with antibiotics. In the remaining four studies complications were not reported.

Five studies reported adverse events [19, 20, 35, 38, 40]. Three case series reported none occurred and two studies [19, 35], the randomized controlled trial and one case series, reported 22 adverse events in total, resulting in a combined adverse event rate of 19.3% (22/114). The randomised controlled trial [35] had 14 adverse events in the control group (9 re-tears, 2 cellulitis, 1 shoulder bursitis, 1 fibrosis, 1 bicep tendon rupture) (14/20 [70%]) and four adverse events in the intervention group (3 re-tears, 1 bursitis) (4/22 [18%]). The case series [19] reported four out of nine patients (4/9 [44.4%]) suffered from subsequent shoulder injuries. None of these four subsequent injuries were attributed to the presence of the human dermal allograft. The remaining five studies did not report adverse events.

Nebenwirkungen nicht eingriffsbedingt: 1 RCT: 70,0 vs. 18,0 % 1 einarmige Studie: 44,4 % mit folgenden Schulterverletzungen

Severe adverse events were not reported in any of the comparative studies. Two case series [38, 40], with mean follow up times ranging from 12 to 15 months, did report severe adverse events. They both reported that none occurred, resulting in a combined severe adverse event rate of 0.0% (0/22).

2 einarmige Studien: keine schwerwiegenden Nebenwirkungen

C0002 – Are the harms related to dosage or frequency of applying human dermal allograft?

Not applicable.

keine Relevanz

C0004 – How does the frequency or severity of harms change over time or in different settings?

No evidence was identified to answer this question.

keine Evidenz

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of human dermal allograft?

No evidence was identified to answer this question.

keine Evidenz

C0007 – Are human dermal allograft and comparator(s) associated with user-dependent harms?

No evidence was identified to answer this question.

keine Evidenz

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of human dermal allograft and the comparator?

International, prospective registry data would better inform the long-term safety of human dermal allograft.

internationale, prospektive Registerdaten

7 Quality of evidence

RoB bewertet mit Cochrane Collaborations Tool (RCTs): niedriges Biasrisiko

Risk of bias in the randomised controlled trial was appraised using 'The Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomised Trials' [9] and is presented in Table A-4 (see Appendix). The randomised controlled trial appraised was at low risk of bias. Limited risks of bias were due to patient blinding not being explicitly described, and serious adverse events not being reported.

RoB bewerted mit ROBINS-I (N-RCTs): schwerwiegendes Biasrisiko

Risk of bias in the non-randomised controlled trials was appraised using 'The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool' [10], as presented in Table A-5 (see Appendix). The studies were at serious risk of bias due to a lack of appropriate methods to control for confounding, as well as the risk of time-varying confounding in one study.

RoB bewerted mit IHE Checklist (einarmige Studien): niedriges bis hohes Biasrisiko

Risk of bias in the single arm studies was appraised using the Institute of Health Economics (IHE) appraisal tool for case series studies [11], as presented in Table A-6 (see Appendix). The single arm studies were at low to high risk of bias. The main reasons for increasing the risk of bias were due outcome assessors not being blinded to intervention received (6 studies), uncertainty if patients entered the study at same point in the disease (5 studies), the study being conducted retrospectively (2 studies), follow up not long enough (4 studies), and no reporting of adverse events (4 studies).

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [12] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [12].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

GRADE Tabelle nächste Seite und Appendix

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-7 & Table A-8. Patient satisfaction scores were not seen as critical outcomes in this assessment, and thus were not included in the GRADE analysis.

moderate Evidenzstärke für Wirksamkeit und Sicherheit

Overall, the quality of evidence for the effectiveness and safety of surgical repair with human dermal allograft in comparison to surgical repair without human dermal allograft is considered "moderate".

Table 7-1: Summary of findings table of human dermal allograft

Outcome	Anticipated absolute effects			Relative effect	Number of participants (studies, reference)	Quality	Comments
	Risk with [comparison]	Risk with [intervention]	Difference				
EFFICACY							
Change in pain score Assessed with: UCLA score; scale from: 0 to 35; follow up: range 12 months to 38 months	NR	NR	MD **2.5*** **points higher in I**[1]	Not estimable	42 1 randomised controlled trial [35]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in pain
Change in pain score Assessed with: ASES; scale from: 0 to 100; follow up: mean 24 months	NR	NR	MD **1.6*** **points higher in I**[2]	Not estimable	42 1 randomised controlled trial [35]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in pain
Change in pain score Assessed with: CS assessment; scale from: 0 to 100; follow up: mean 24 months	NR	NR	MD **11.4*** **points higher in I**[3]	Not estimable	42 1 randomised controlled trial [35]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in pain
Change in pain score Assessed with: ASES; scale from: 0 to 100; follow up: mean 24 months	NR	NR	MD **12.8*** **points higher in I**[2]	Not estimable	35 1 non-randomised controlled trial [18]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in pain
Change in pain score Assessed with: CS assessment; scale from: 0 to 100; follow up: range 24 months to 120 months	NR		MD **15.0*** **points higher in I**[3]	Not estimable	26 1 non-randomised controlled trial [17]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in pain
Change in pain score Assessed with: VAS Scale; scale from: 0 to 10; follow up: mean 24.9 months	NR	NR	MD **2.7*** **points lower in I**	Not estimable	35 1 non-randomised controlled trial [18]	⊕⊕⊕◯ MODERATE	Lower scores indicate improvement in pain, significant improvment for intervention group
Change in pain score Assessed with: OSS; scale from: 0 to 60; follow up: range 24 months to 120 months	NR	NR	MD **9.7*** **points higher in I**[4]	Not estimable	26 1 non-randomised controlled trial [17]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in pain
Change in ROM Assessed with: UCLA; scale from: 0 to 35; follow up: mean 24 months	NR	NR	MD **2.5*** **points higher in I**[1]	Not estimable	42 1 randomised controlled trial [35]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in range of motion

[1] Total UCLA score used, not the sub-scores for pain or range of motion.

[2] Total ASES score is used, not sub-scores for pain, range of motion or physical function.

[3] Total Constant shoulder (CS) assessment is used, not sub-scores for pain, range of motion or physical function.

[4] Total OSS score used, not the sub-score for pain, health-related quality of life or physical function.

Outcome	Anticipated absolute effects			Relative effect	Number of participants (studies, reference)	Quality	Comments
	Risk with [comparison]	Risk with [intervention]	Difference				
Change in ROM score Assessed with: CS assessment; scale from: 0 to 100; follow up: mean 24 months	NR	NR	MD **11.4*** **points higher in I**[3]	Not estimable	42 1 randomised controlled trial [35]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in range of motion
Change in ROM score Assessed with: ASES; scale from: 0 to 100; follow up: mean 24 months	NR	NR	MD **1.6*** **points higher in I**[2]	Not estimable	42 1 randomised controlled trial [35]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in range of motion
Change in ROM score Assessed with: CS assessment; scale from: 0 to 100; follow up: range 24 months to 120 months	NR	NR	MD **15.0*** **points higher in I**[3]	Not estimable	26 1 non-randomised controlled trial [17]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in range of motion
Change in ROM score Assessed with: ASES; scale from: 0 to 100; follow up: mean 24.9 months	NR	NR	MD **12.8*** **points higher in I**[2]	Not estimable	35 1 non-randomised controlled trial [18]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in range of motion
Change in ROM score Assessed with: WORC; scale from: 0 to 100; follow up: mean 24.9 months	NR	NR	MD **22.0*** **points higher in I**[5]	Not estimable	35 1 non-randomised controlled trial [18]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in range of motion
Change in physical function Assessed with: ASES; scale from: 0 to 100; follow up: mean 24 months	NR	NR	MD **1.6*** **points higher in I**[2]	Not estimable	42 1 randomised controlled trial [35]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in physical function
Change in physical function Assessed with: CS assessment; scale from: 0 to 100; follow up: median 24 months	NR	NR	MD **11.4*** **points higher in I**[3]	Not estimable	42 1 randomised controlled trial [35]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in physical function
Change in physical function Assessed with: ASES; scale from: 0 to 100; follow up: mean 24.9 months	NR	NR	MD **12.8*** **points higher in I**[2]	Not estimable	35 1 non-randomised controlled trial [18]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in physical function
Change in physical function Assessed with: CS assessment; scale from: 0 to 100; follow up: range 24 months to 120 months	NR	NR	MD **15.0*** **points higher in I**[3]	Not estimable	26 1 non-randomised controlled trial [17]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in physical function
Change in physical function Assessed with: OSS; scale from: 0 to 100; follow up: range 24 months to 120 months	NR	NR	MD **9.7*** **points higher in I**[4]	Not estimable	26 1 non-randomised controlled trial [17]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in physical function
Change in health-related quality of life Assessed with: WORC; scale from: 0 to 100; follow up: mean 24.9 months	NR	NR	MD **22.0*points higher in I**[6]	Not estimable	35 1 non-randomised controlled trial [18]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in range of motion

[5] Total WORC used, not sub-score for range of motion, health-related quality of life.

Outcome	Anticipated absolute effects			Relative effect	Number of participants (studies, reference)	Quality	Comments
	Risk with [comparison]	Risk with [intervention]	Difference				
Change in health-related quality of life Assessed with: SF-12; scale from: 0 to 100; follow up: mean 24.9 months	NR	NR	Physcial: MD **5.7* points higher in I** Mental: **1.4 points higher in I**	Not estimable	35 1 non-randomised controlled trial [18]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in health-related quality of life
Change in health-related quality of life Assessed with: OSS; scale from: 0 to 60; follow up: range 24 months to 120 months	NR	NR	MD **9.7* points higher in I**[4]	Not estimable	26 1 non-randomised controlled trial [17]	⊕⊕⊕◯ MODERATE	Higher scores indicate improvement in health-related quality of life
SAFETY							
Procedure-related mortality follow up: mean 24 months, range 12-38	Overall deaths: C: 0/20 (0.0%), I: 0/22 (0.0%)			RR: NR	42 1 randomised controlled trial [35]	⊕⊕⊕⊕ HIGH	No procedure-related mortality
Procedure-related mortality follow up: range 22-120 months	Overall deaths: 0/61 (0.0%)			RR: NR	61 2 non-randomised controlled trials [17, 18]	⊕⊕◯◯ LOW	No procedure-related mortality
Procedure-related mortality follow up: range 12-77 months	Overall deaths: 0/174 (0.0%)			RR: NR	174 7 case series [19, 20, 34, 38-41]	⊕◯◯◯ VERY LOW	No procedure-related mortality
Failure of repair procedure/re-tears follow up: mean 24 months, range 12-38	Overall failures: C: 9/20 (45.0%), I: 3/22 (12.6%)			RR: NR	42 1 randomised controlled trial [35]	⊕⊕⊕⊕ HIGH	Failures include nine rotator cuff re-tears (C) and three (I), not attributed to the presence of graft
Failure of repair procedure/re-tears follow up: range 22-120 months	Overall failures: 10/61 (16.4%)			RR: NA	61 2 non-randomised controlled trials [17, 18]	⊕⊕◯◯ LOW	In one trial, two patients needed revision surgery after six months, one had reverse should arthroplasty after one year
Failure of repair procedure/re-tears follow up: range 12-77 months	Overall failures: 24/174 (13.8%)			RR: NA	174 7 case series [19, 20, 34, 38-41]	⊕◯◯◯ VERY LOW	Patients experienced failures in all seven case series. Causes include falls, MVA, re-tears, and glenohumeral fusion.
Complications follow up: mean 24 months, range 12-38	Overall complications: C: 0/20 (0.0%), I: 0/22 (0.0%)			RR: NR	42 1 randomised controlled trial [35]	⊕⊕⊕⊕ HIGH	No device- or procedure-related complications occurred/reported

[6] Total WORC used, not sub-score for range of motion, health-related quality of life.

Outcome	Anticipated absolute effects			Relative effect	Number of participants (studies, reference)	Quality	Comments
	Risk with [comparison]	Risk with [intervention]	Difference				
Complications follow up: mean 24.9 months, range 22-26	Overall complications: 1/35 (2.8%)			RR: NR	35 1 non-randomised controlled trial [18]	⊕⊕◯◯ LOW	Procedure-related complication, patient had a superficial skin infection one week after surgery
Complications follow up: range 12-77 months	Overall complications: 0/137 (0.0%)			RR: NR	137 4 case series [20, 34, 38, 40]	⊕◯◯◯ VERY LOW	No device- or procedure-related complications occurred/reported
Adverse events follow up: mean 24 months, range 12-77	Overall adverse events: 18/42 (42.8%) C: 14/20 (70.0%) , I: 4/22 (18.0%)			RR: NR	42 1 randomised controlled trial [35]	⊕⊕⊕⊕ HIGH	Control group = 14 AEs, including 9 re-tears, 2 cellulitis, 1 shoulder bursitis, 1 post-traumatic fibrosis and 1 biceps tendon rupture. Intervention group = 4 AEs, including 3 re-tears and 1 bursitis. None were allograft-related.
Adverse events follow up: range 12 40 months	Overall adverse events: 4/55 (7.3%)			RR: NR	55 4 case series [19, 20, 38, 40]	⊕◯◯◯ VERY LOW	Four subsequent shoulder injuries (not attributed to the human dermal allograft).

***Abbreviations: AEs** = adverse events; **C** = control group; **I** = intervention group; **MVA** = motor vehicle accidents; **NA** = not applicable; **NR** = not reported; **ROM** = Range of Motion; **RR** = relative risk.*

**Self-calculated.*

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

8 Discussion

Patients with rotator cuff tear experience debilitating shoulder pain, reduced shoulder function, and compromised joint mechanics [32]. Rotator cuff tear can usually be repaired with surgery. An irreparable rotator cuff tear is defined as large (>3cm) or massive (>5cm), involving two or more tendons, and one which has undergone primary surgery without success [18, 25].

(irreparable) Risse in der Rotatorenmanschette einhergehend mit Schmerzen und verminderter Funktion

Several surgical techniques have been proposed, yet irreparable rotator cuff tear procedures are complicated by structural failure and other poor outcomes. Various xenografts and synthetic allografts have also been proposed, to little success [2].

bisher keine erfolgreichen Behandlungen

In patients under 65 years who do not have glenohumeral arthritis SCR using human dermal allograft for augmentation is the most common form of repair [2]. This form of repair was first reported in a case series in 2007. The study showed good clinical outcomes at short follow up [42]. There has since been growing interest in the human dermal allograft for rotator cuff tear repair.

Evidenz zur Reparatur mit allogener humaner Dermis bei Pat. unter 65 Jahren ohne Arthritis im Schultergelenk

The aim of this systematic review was to evaluate the safety and effectiveness of rotator cuff tear repair surgery augmented with human dermal allograft in comparison to rotator cuff tear repair surgery without human dermal allograft.

Ziel: Bewertung Wirksamkeit & Sicherheit von allogener humaner Dermis

Available evidence

Three studies, two non-randomised and one randomised, thus one being industry sponsored, were used to ascertain the efficacy of human dermal allograft [17, 18, 35]. They assessed patients preoperatively and at last follow-up using seven scores which cover a range of patient specific factors.

Wirksamkeit untersucht in 1 RCT & 2 N-RCTs

ASES, VAS, Constant shoulder assessment, WORC, and UCLA are used to assess all the critical outcomes: changes in pain, range of motion, physical function, and health-related quality of life. In the included studies, significant clinically important differences have been found in VAS and Constant shoulder assessment. Although, small patient study sizes make this not meaningful.

geringste klinisch relevante Unterschiede für VAS und CS Score nicht bedeutend

The three studies showed a slight improvement in pain, range of motion, physical functioning and health-related quality of life in the intervention groups across the different scores. However, this improvements were only partly statistically significant. Health-related quality of life was reported by the two non-randomised controlled trials as improved in the human dermal allograft groups, but as the studies are non-randomised these results should be viewed with caution.

verbesserte Schmerzen, Bewegungsmobilität, Funktionalität und Lebensqualität in Interventionsgruppen, jedoch nur teilweise signifikant

The safety evidence is made up of the same randomised controlled trial, two non-randomised controlled trials and additional seven case series [17-20, 34, 35, 38-41].

… für Sicherheit zusätzlich 7 einarmige Studien

All trials found human dermal allograft comparatively safe, with very few complications reported. The most commonly reported safety outcome was failure/re-tear. The randomised controlled trial reported failures rates were 45.0% (9/20) in the control group versus 13.6% (3/22) in the intervention group, at mean 24 months follow-up. Failure rates in a non-randomised controlled trial were slightly lower, 27.0% (4/15) in the control group versus 10.0% (2/20) in the intervention group, at mean follow up of 24.9 months. No procedure-related deaths were reported in any study.

Reparatur mit allogener humaner Dermis vergleichsweise sicher, Fehlerquote 27,0-45,0 % vs. 10,0-13,6 %, keine Mortalitätsfälle

Ø Nebenwirkungsrate 19,3 % über 5 Studien

Out of the five studies that reported adverse events, three reported none had occurred and two reported a total of 22, giving a combined adverse event rate of 19.3% (22/114).

Evidenzstärke moderate für Wirksamkeit und Sicherheit

Overall, the strength of evidence for the clinical effectiveness and safety of rotator cuff tear repair surgery augmented with human dermal allograft in comparison to rotator cuff tear repair surgery without human dermal allograft was determined as "moderate". The strength of evidence of the identified studies was mainly downgraded due to risk of time-varying confounding.

Interpretation of study results

Schwächen der Evidenz

There are several weaknesses in the evidence base around human dermal allograft.

2 leicht unterschiedliche Interventionen → Effekt auf Resultate möglich

There are two products on the market fitting the definition of human dermal allograft for rotator cuff tear. GraftJacket which is produced by Wright Medical Technology Inc. and Arthrex produced by Arthroflex Inc., both are companies based in the United States. Table 3-1 outlines the features of these two products. As they are not the same product, there could be slight differences between the interventions assessed which might influence the results.

limitierte Wirksamkeitsresultate aufgrund geringer Pat.-Anzahl und Nachbeobachtungszeit

The studies identified for assessing the intervention had low patient numbers and short follow-up periods, which can diminish the strength of the evidence. Efficacy was assessed with one randomised controlled trial, and two non-randomised controlled trials with sample sizes ranging from 26 to 42 patients. The low patient numbers and relatively short follow-up periods can prevent true efficacy outcomes from being identified.

PatientInnen-berichtete Wirksamkeitsendpunkte

The efficacy outcomes also relied on patient reported measures which leads to a level of subjectivity, which was taken into account in the RoB assessment.

inkonsistente Berichterstattung der Daten

Some of these studies suffered from confusion in the reporting of outcomes in the published article. For example, inconsistencies were found in scores reported in the tables to the text.

nur Gesamtscores berichtet – Interpretation schwierig klinisch relevante minimale Unterschiede bedeutend bei größerer Pat.-Anzahl

The efficacy outcomes were measured with various different scores within and across studies. Only overall scores and not specific sub-scores were reported meaning that the interpretation of the effect of the intervention on a specific outcome was more difficult. However, it was calculated that in the included studies, significant clinically important differences may be indicated in VAS and Constant shoulder assessment. This would have more power if the studies included more patients.

Probleme mit Adjustierung nach Störgrößen

There were also issues around confounding adjustment, where study authors had not used an appropriate method for controlling for confounding in the non-randomised studies.

niedrige Pat.-Anzahl & kurze Nachbeobachtungszeit problematisch bezügl. seltene, schwere Nebenwirkungen

The reported safety evidence had low strength of evidence due to the study designs. Safety was assessed the same two non-randomised controlled trials, and one randomised controlled trial and additional seven single arm studies. The low patient numbers and short follow-up periods of the studies can be particularly problematic for identifying possible serious/rare adverse events.

... Intervention scheint trotzdem gleich sicher bzw. sicherer

Despite weaknesses of the evidence, human dermal allograft seem to have equal or better safety to the comparator intervention.

Additional discussion on available evidence

Studien zur Wirksamkeit repräsentieren nicht optimale Vergleichsinterventionen

As the target population of the present report are patients with irreparable rotator cuff tears, the included studies for effectiveness do not present the most suitable comparators. In fact, for rotator cuff reconstruction surgeries with human dermal allograft, reconstruction surgeries without human dermal allograft, like tendon transfer or inverse arthroplasty, would have been the appropriate comparators.

Angaben zur gleichzeitigen bzw. nachfolgenden Medikation limitiert

It was very rarely reported whether patients received additional medication after the surgical procedure or not. Furthermore, information on longer term medication use and symptom control was lacking. For example, the consumption of pain relievers during the trial and up to final follow-up could have impacted the assessment of outcomes such as pain and health-related quality of life. Reporting of this measure in the trials would improve understanding of the effect of the intervention.

mögliches Confounding durch postoperative Maßnahmen

All included studies reported on post-operative rehabilitation programmes. However, the effects of these post-operative therapies on the overall efficacy and safety outcomes were not considered. Thus, there is a possible confounding effect on the reported findings.

v.a. PatientInnen im berufsfähigen Alter → Arbeitsunfähigkeit → zusätzliche gesellschaftliche Kosten

In general, the population of the included studies were patients who are still of working age. This could indicate additional costs to society as massive rotator cuff tear impacts an individual's quality of life and therefore their ability to work. The patients are likely to experience extended leave from work and less productivity at work. They may require more sick leave and need to change to another work role (requiring retraining), or even need to enter into retirement early.

vollständige Anwendungstabelle im Appendix

For a summary of the applicability of the included studies to the population likely to receive the intervention, see the Applicability table in the Appendix.

Upcoming evidence

4 laufende RCTs + 1 N-RCT, Fertigstellungstermin Mitte des Jahres 2020

Four randomised controlled trials and one non-randomised controlled trial are reportedly underway with completion dates before mid-2020. They are being conducted in Canada, the United States and Europe. All studies compare rotator cuff repair using augmentation with a human dermal allograft with the same procedure without any graft. They are reported to include a total of 244 patients, with follow-up of 12 months in one trial, where the other trials did not report follow-up. Once these have been completed and published results are available, the evidence on human dermal allograft is expected be greatly strengthened.

Limitations to our study

Ausschluss retrospektiver Studien für Wirksamkeit

We excluded retrospective studies for assessment of efficacy – even controlled studies with a retrospective control group – because the sources of error due to confounding and bias are more common in retrospective studies than in prospective ones.

keine Antwort der Hersteller

The manufacturers did not respond to communication around the publication, so further information could not be obtained. In addition, it is possible that not all manufacturers were identified.

unterschiedliche Begrifflichkeiten – Möglichkeit der Nicht-Identifikation relevanter Studien

Moreover, different terminologies for the surgery with human dermal allograft in patients with irreparable rotator cuff tears, ranging from rotator cuff repair/reconstruction and replacement to superior capsular reconstruction may have precluded identification of all appropriate studies. In the present report, the repair of irreparable rotator cuff tears with human dermal allograft was used as an overall term for the reconstruction of irreparable rotator cuff tears.

Aussagekraft der GRADE Analyse evtl. limitiert

In all included studies efficacy outcomes were measured with various different scores within and across the studies. Therefore and because of the different study designs, for most of the scores only one study was available for performing the GRADE analysis. This could have had an impact on the explanatory power of the strength of evidence resulted from the analysis.

Interpretation der Resultate unter Berücksichtigung aller Limitationen

Overall, the results of this review should be interpreted in light of the limitations. We only included one randomised study and it was industry funded. We did include seven single arm studies with no limits to follow up or sample size. This may have invited low quality studies into the assessment.

Conclusion

klare Aussage limitiert, Intervention jedoch scheinbar wirksamer und gleich sicher oder sicherer

In the absence of objective, randomised studies it is difficult to ascertain the relative risks and benefit of rotator cuff tear repair with human dermal allograft in comparison to rotator cuff tear repair alone. However, from the limited evidence, of moderate quality, it appears rotator cuff tear repair with human dermal allograft might be more effective, and equally safe or safer as its comparator.

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence indicates, that the assessed technology reconstruction of the rotator cuff tear with human dermal allograft (when restricted to cases where there is a high likelihood of poor healing after rotator cuff tear repair) is more effective and equally safe or safer compared with the comparator, surgical rotator cuff tear repair without use of human dermal allograft.

allogene humane Dermis scheint vergleichsweise wirksamer und gleich sicher oder sicherer

However, due to the limited strength of evidence, these results should be interpreted with caution. As a result, the reconstruction of irreparable rotator cuff tears with human dermal allograft is currently not recommended for the inclusion in the Austrian hospital benefit catalogue.

moderate Evidenzqualität
→ aktuell, Refundierung nicht empfohlen

There are four randomised controlled trials which all expect to be completed by mid-2020, the results from these should add value to the evidence base on human dermal allograft (see List of ongoing randomised controlled trials in the Appendix).

4 laufende RCTs
→ Fertigstellung 2020

The re-evaluation is recommended in 2021, when some of these trials have published results.

Re-Evaluierung für 2021 empfohlen

10 References

[1] Kokkalis ZT, Mavrogenis AF, Scarlat M, Christodoulou M, Vottis C, Papagelopoulos PJ, et al. Human dermal allograft for massive rotator cuff tears. Orthopedics. 2014;37(12):e1108-16.

[2] Thorsness R, Romeo A. Massive rotator cuff tears: Trends in surgical management. Orthopedics. 2016;39(3):145-51.

[3] Moore MA, Samsell B, Wallis G, Triplett S, Chen S, Jones AL, et al. Decellularization of human dermis using non-denaturing anionic detergent and endonuclease: A review. Cell and tissue banking. 2015;16(2):249-59.

[4] Petri M, Greenspoon JA, Moulton SG, Millett PJ. Patch-augmented rotator cuff repair and superior capsule reconstruction. The open orthopaedics journal. 2016;10:315-23.

[5] Barber FA, Burns JP, Deutsch A, Labbe MR, Litchfield RB. A prospective, randomized evaluation of acellular human dermal matrix augmentation for arthroscopic rotator cuff repair. Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association. 2012;28(1):8-15.

[6] EUnetHTA Joint Action 2. Endpoints used for relative effectiveness assessment: Health-related quality of life and utility measures. 2015.

[7] EUnetHTA Joint Action 2. Therapeutic medical devices 2015.

[8] EUnetHTA Joint Action 2. Endpoints used in relative effectiveness assessment: Safety. 2015.

[9] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. British Medical Journal. 2011;343:d5928.

[10] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. British Medical Journal. 2016;355:i4919.

[11] Moga C, Guo B, Schopflocher D, Harstall C. Development of a quality appraisal tool for case series studies using a modified Delphi technique Edmonton AB: Institute of Health Economics; 2012 [cited 19 January 2019]. Available from: http://www.ihe.ca/advanced-search/development-of-a-quality-appraisal-tool-for-case-series-studies-using-a-modified-delphi-technique.

[12] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology. 2011;64(4):383-94.

[13] Tokish JM, Beicker C. Superior capsule reconstruction technique using an acellular dermal allograft. Arthroscopy Techniques. 2015;4(6):e833-9.

[14] Cabarcas BC, Garcia GH, Gowd AK, Liu JN, Romeo AA. Arthroscopic superior capsular reconstruction and over-the-top rotator cuff repair incorporation for treatment of massive rotator cuff tears. Arthroscopy Techniques. 2018;7(8):e829-37.

[15] American Academy of Orthopaedic Surgeons. Rotator cuff tears: Surgical treatment options 2018 [cited 21 January 2019]. Available from: https://orthoinfo.aaos.org/en/treatment/rotator-cuff-tears-surgical-treatment-options/.

[16] Berth A, Neumann W, Awiszus F, Pap G. Massive rotator cuff tears: Functional outcome after debridement or arthroscopic partial repair. Journal of Orthopaedics and Traumatology. 2010;11(1):13-20.

[17] Pandey R, Tafazal S, Shyamsundar S, Modi A, Singh HP. Outcome of partial repair of massive rotator cuff tears with and without human tissue allograft bridging repair. Journal Shoulder and Elbow. 2016;9(1):23-30.

[18] Gilot GJ, Alvarez-Pinzon AM, Barcksdale L, Westerdahl D, Krill M, Peck E. Outcome of large to massive rotator cuff tears repaired with and without extracellular matrix augmentation: A prospective comparative study. The Journal of Arthroscopic Related Surgery. 2015;31(8):1459-65.

[19] Hirahara AM, Andersen WJ, Panero AJ. Superior capsular reconstruction: Clinical outcomes after minimum 2-Year follow-up. American Journal of Orthopedics. 2017;46(6):266-78.

[20] Gupta AK, Hug K, Berkoff DJ, Boggess BR, Gavigan M, Malley PC, et al. Dermal tissue allograft for the repair of massive irreparable rotator cuff tears. Am J Sports Med. 2012;40(1):141-7.

[21] Wright Medical Group. GraftJacket Tennessee, USA2018 [cited 19 January 2019]. Available from: http://www.wright.com/healthcare-professionals/graftjacket.

[22] Aurora A, McCarron J, Iannotti JP, Derwin K. Commercially available extracellular matrix materials for rotator cuff repairs: State of the art and future trends. Journal of shoulder and elbow surgery. 2007;16(5 Suppl):S171-8.

[23] John M. AHRQ Comparative effectiveness reviews treatment options for rotator cuff tears: A guide for adults. Comparative Effectiveness Review Summary Guides for Consumers. Rockville (MD): Agency for Healthcare Research and Quality (US); 2005.

[24] Wall KC, Toth AP, Garrigues GE. How to use a graft in irreparable rotator cuff tears: A literature review update of interposition and superior capsule reconstruction techniques. Current Reviews in Musculoskeletal Medicine. 2018;11(1):122-30.

[25] Warner JJP, Higgins L, Parsons IM, Dowdy P. Diagnosis and treatment of anterosuperior rotator cuff tears. Journal of shoulder and elbow surgery. 2001;10(1):37-46.

[26] Kukkonen J, Joukainen A, Itälä A, Äärimaa V. Operatively treated traumatic versus non-traumatic rotator cuff ruptures: A registry study. Upsala Journal of Medical Sciences. 2013;118(1):29-34.

[27] Tashjian RZ. Epidemiology, Natural History, and Indications for Treatment of Rotator Cuff Tears. Clinics in Sports Medicine. 2012;31(4):589-604.

[28] Yamamoto A, Takagishi K, Osawa T, Yanagawa T, Nakajima D, Shitara H, et al. Prevalence and risk factors of a rotator cuff tear in the general population. Journal of shoulder and elbow surgery. 2010;19(1):116-20.

[29] Tempelhof S, Rupp S, Seil R. Age-related prevalence of rotator cuff tears in asymptomatic shoulders. Journal of shoulder and elbow surgery. 1999;8(4):296-9.

[30] Baumgarten KM, Gerlach D, Galatz LM, Teefey SA, Middleton WD, Ditsios K, et al. Cigarette smoking increases the risk for rotator cuff tears. Clinical Orthopaedics and Related Research. 2010;468(6):1534-41.

[31] Yamaguchi K, Tetro AM, Blam O, Evanoff BA, Teefey SA, Middleton WD. Natural history of asymptomatic rotator cuff tears: A longitudinal analysis of asymptomatic tears detected sonographically. Journal of shoulder and elbow surgery. 2001;10(3):199-203.

[32] Dalton SE, Snyder SJ. Glenohumeral instability. Baillière's Clinical Rheumatology. 1989;3(3):511-34.

[33] Guckel C, Nidecker A. Diagnosis of tears in rotator-cuff-injuries. European journal of radiology. 1997;25(3):168-76.

[34] Varvitsiotis D, Papaspiliopoulos A, Antipa E, Papacharalampous X, Flevarakis G, Feroussis J. Results of reconstruction of massive irreparable rotator cuff tears using a fascia lata allograft. Indian Journal of Orthopaedics. 2015;49(3):304-11.

[35] Barber FA, Burns JP, Deutsch A, Labbe MR, Litchfield RB. A prospective, randomized evaluation of acellular human dermal matrix augmentation for arthroscopic rotator cuff repair. Arthroscopy: The Journal of Arthroscopic and Related Surgery. 2012;28(1):8-15.

[36] Simovitch R, Flurin P-H, Wright T, Zuckerman JD, Roche CP. Quantifying success after total shoulder arthroplasty: the minimal clinically important difference. Journal of shoulder and elbow surgery. 2018;27(2):298-305.

[37] Wright RW, Baumgarten KM. Shoulder outcomes measures. The Journal of the American Academy of Orthopaedic Surgeons. 2010;18(7):436-44.

[38] Burkhead Jr WZ, Schiffern SC, Krishnan SG. Use of Graft Jacket as an augmentation for massive rotator cuff tears. Seminars in Arthroplasty. 2007;18(1):11-8.

[39] Leuzinger J, Sternberg C, Smolen D, Jakob R. [Patch augmentation in rotator cuff repair surgery with elder patients]. J Zeitschrift fur Orthopadie & Unfallchirurgie. 2016;154(5):504-12.

[40] Rotini R, Marinelli A, Guerra E, Bettelli G, Castagna A, Fini M, et al. Human dermal matrix scaffold augmentation for large and massive rotator cuff repairs: preliminary clinical and MRI results at 1-year follow-up. Musculoskeletal surgery. 2011;95(1):13.

[41] Sharma N, El Refaiy A, Sibly TF. Short-term results of rotator cuff repair using GraftJacket as an interpositional tissue-matched thickness graft. Journal of Orthopaedics. 2018;15(2):732-5.

[42] Dopirak R, Bond JL, Snyder SJ. Arthroscopic total rotator cuff replacement with an acellular human dermal allograft matrix. International Journal of Shoulder Surgery. 2007;1(1):7.

[43] EUnetHTA Joint Action 2. Internal validity of non-randomised studies (NRS) on interventions 2015 [cited 20 February 2019]. Available from: https://www.eunethta.eu/internal-validity-of-non-randomised-studies-nrs-on-interventions-guideline-final-jul-2015/.

[44] EUnetHTA Joint Action 2 WP. Levels of evidence: Internal validity (of randomized controlled trials) 2015 [cited 20 February 2019]. Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/16_WP7-SG3-GL-int_val_RCTs_amend2015.pdf.

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Human dermal allograft for irreparable rotator cuff tears: Results from randomised controlled trials

Author, year [Reference]	Barber, 2012 [35]
Country	USA/Canada
Sponsor	Wright Medical Technologies
Intervention/Product	GraftJacket: 3-dimensional human dermal tissue scaffold from native collagen structure
Comparator	Rotator cuff tear repair without augmentation
Study design	Prospective, multicentre, randomised controlled trial
Number of pts	42: C: 20 I: 22
Inclusion criteria	Large (3-5cm), 2-tendon rotator cuff tear that could be repaired arthroscopically, age 18-75 years, good preoperative movement of the non-operative arm (>90°), ability to perform post-operative exercises, ability to conduct patient reported outcomes
Exclusion criteria	Irreparable massive rotator cuff tear (>5 cm), subscapularis tendon disruptions, revision surgery, inflammatory or autoimmune diseases, evidence of active infection, cancer or highly communicable diseases, smokers, pts. not expected to be able to participate in the protocol-required post-operative follow up examination.
Mean age of patients (yrs, range)	C: 56 (34-72) I: 56 (43-69)
Female sex, n (%)	C: 7 (35*) I: 4 (18.18*)
Post-operative treatment(s)	Use of abduction sling for 4-6 weeks, allowing daily pendulum motion exercises, start of supervised physical therapy at 4 weeks, with strengthening allowed starting at 12 weeks
Follow up (months)	24 (range, 12-38)
Loss to follow up, n (%)	Not reported
Primary endpoint(s)	Presence of residual tendon defects on MRI at 1 year
Outcomes	
Efficacy	
Pain, scores	
ULCA (pre-operatively vs last follow up)[1]	C: 15.9 vs 28.3 (SD 3.0) I: 13.3 vs 28.2 (SD 2.1) (*P*=0.43)
ASES (pre-operatively vs last follow up)[2]	C: 46.0 vs 94.8 (SD 14.2) I: 48.5 vs 98.9 (SD 4.2) (*P*=0.035)
CS (pre-operatively vs last follow up)[3]	C: 45.8 vs 85.3 (SD 11.0) I: 41.0 vs 91.9 (SD 9.2) (*P*=0.008)

Author, year [Reference]	Barber, 2012 [35]
❁ OSS	Not reported
❁ DASH	Not reported
❁ SPADI	Not reported
❁ VAS	Not reported
ROM, scores	
❁ ULCA (pre-operatively vs last follow up)[1]	C: 15.9 vs 28.3 (SD 3.0) I: 13.3 vs 28.2 (SD 2.1) (*P*=0.43)
❁ WORC	Not reported
❁ CS (pre-operatively vs last follow up)[3]	C: 45.8 vs 85.3 (SD 11.0) I: 41.0 vs 91.9 (SD 9.2) (*P*=0.008)
❁ ASES (pre-operatively vs last follow up)[2]	C: 46.0 vs 94.8 (SD 14.2) I: 48.5 vs 98.9 (SD 4.2) (*P*=0.035)
❁ ROM	Not reported
Physical function, scores	
❁ SSV	Not reported
❁ WORC	Not reported
❁ DASH	Not reported
❁ SPADI	Not reported
❁ ASES (pre-operatively vs last follow up)[2]	C: 46.0 vs 94.8 (SD 14.2) I: 48.5 vs 98.9 (SD 4.2) (*P*=0.035)
❁ CS (pre-operatively vs last follow up)[3]	C: 45.8 vs 85.3 (SD 11.0) I: 41.0 vs 91.9 (SD 9.2) (*P*=0.008)
❁ OSS	Not reported
Health-related quality of life, scores	
❁ OSS	Not reported
❁ SF-12	Not reported
❁ WORC	Not reported
Patient satisfaction, scores	
❁ ULCA (pre-operatively vs last follow up)[1]	C: 15.9 vs 28.3 (SD 3.0) I: 13.3 vs 28.2 (SD 2.1) (*P*=0.43)
❁ SSV	Not reported
❁ MRI scan of intact cuffs, n (%)	C: 17 (85) I: 6 (40[7]) (*P*<0.01)
Safety	
Procedure-related mortality	0/42 (0.0)
Failure of repair procedure, re-tear-rate (%)	C: 9/20 (45.0*) I: 3/22 (13.6*)
Additional surgery, re-operation-rate (%)	Not reported
Complications	
❁ Procedure-related	Not reported
❁ Device-related	0/22 (0.0)

[7] In the intervention group only 15 out of 22 pts. underwent MRI.

Author, year [Reference]	Barber, 2012 [35]
Adverse events	C: 14[8]/20 I: 4[9]/22
Severe adverse events	Not reported

Abbreviations: ***ASES*** *= American Shoulder and Elbow Surgeons;* ***C*** *= control group;* ***CS*** *= Constant shoulder assessment;* ***DASH*** *= Disabilities of the arm, shoulder, and hand;* ***I*** *= intervention group;* ***MRI*** *= magnetic resonance imaging;* ***OSS*** *= Oxford Shoulder Score;* ***ROM*** *= Range Of Motion;* ***SD*** *= standard deviation;* ***SPADI*** *= Shoulder Pain and Disability Index;* ***SSV*** *= Subjective shoulder value;* ***UCLA*** *= University of California, Los Angeles;* ***USA*** *= United States of America;* ***VAS*** *= Visual analogue scale;* ***WORC*** *= Western Ontario Rotator Cuff Index.*

** Self-calculated.*

Table A-2: Human dermal allograft for irreparable rotator cuff tears: Results from non-randomised controlled studies

Author, year [Reference]	Gilot, 2015 [18]	Pandey, 2017 [17]
Country	USA	UK
Sponsor	Not reported	None
Intervention/Product	ArthroFLEX: Acellular dermal extracellular matrix (ECM) of collagen, elastin and growth factors providing supplemental support and covering for soft tisue repair	GraftJacket: Human dermal cell-free tissue with an intact matrix to retain collagen, proteoglycans and elastin
Comparator	Rotator cuff tear repair without augmentation with ECM graft	Partial repair without GraftJacket graft
Study design	Non-randomised, prospective, blinded, single-centre, controlled trial	Prospective non-randomised controlled trial
Number of pts	35 C: 15 I: 20	26: C: 13 I: 13
Inclusion criteria	Patient with large (3.0-5.0 cm) or masssive rotator cuff tear (>5 cm) as seen on MRI, scheduled to undergo primary rotator cuff tear repair, aged 18-85 years, and willing to provide scores for the study	Massive rotator cuff tear (>5 cm) not amenable to complete repair
Exclusion criteria	Known allergy to ECM material, addiction to illegal drugs and involved in a treatment program, infection, pregnant or breast feeeding, history of autoimmune disease, and beliefs prohibiting the use of grafts	Previous shoulder surgeries with established glenohumeral osteoarthritis, cuff tears, which could be completely repaired
Mean age of patients (yrs, SD)	C: 62.0 (SD4.6) I: 58.9 (SD6.2) (*P*=0.683)	C: 59 (range, 45-67) I: 57 (range, 45-68)
Female sex, n (%)	C: 8.0 (53.0) I: 12.0 (40.0) (p=0.514)	C: 4 (30.77*) I: 4 (30.77*)
Post-operative treatment(s)	First 6 weeks: sling immobilisation, additional 6 weeks passive motion, additional 6 weeks active motion, after 18 weeks strengthening exercises	Use of polysling for 6 weeks to immobilise the shoulder, initiation of strenghtening exercises at 3 months
Follow up (months)	24.9 (22-26)	Min. 24 (2-5 years)
Loss to follow up, n (%)	0/35 (0.0)	0/26 (0.0)
Primary endpoint(s)	Precence or abscene of a re-tear as noted on MRI or US examination	Not reported

[8] The 14 AEs include the 9 cases of re-tears and additionally, cellulitis, shoulder bursitis, post-traumatic fibrosis and a biceps tendon rupture.

[9] The 4 AEs include the 3 cases of re-tears and an additional case of bursitis.

Author, year [Reference]	Gilot, 2015 [18]	Pandey, 2017 [17]
Outcomes		
Efficacy		
Pain, scores		
❁ ULCA	Not reported	Not reported
❁ ASES (pre-operatively vs last follow up)[2]	C: 60.3 (SD 9.5) vs 72.6 (11.9) [improvement +9.9 (SD 24.7)] I: 63.8 (SD 13.8) vs 88.9 (SD 4.8) [improvement +29.9 (SD 18.6)] Significant better improvement for I at 96 week (*P*=0.024)	Not reported
❁ CS (pre-operatively vs last follow up[3]	Not reported	C: 43.1 (SD 3.9) vs 70.8 (SD 5.3) (P=0.01) I: 41.2 (SD 3.1) vs 83.9 (SD 6.0) (*P*=0.005)) Significant better improvement for I at 24 months (*P*<0.01)
❁ OSS[4]	Not reported	C: 17.8 (SD 3.6) vs 37.1 (SD 2.4) (P =0.009) I: 14.9 (SD 3.5) vs 43.9 (SD 2.4) (P =0.005)) Significant better improvements for I at 24 months (P=0.01)
❁ DASH	Not reported	Not reported
❁ SPADI	Not reported	Not reported
❁ VAS (pre-operatively vs last follow up)	C: 6.9 (SD 1.1) vs 4.1 (SD 1.1) [improvement + 2.1 (SD 2.0)] I: 6.8 (SD 1.6) vs 1.3 (SD 1.2) [improvement +5.9 (SD 1.1)] Significant better improvements for I (*P*=0.024)	Not reported
ROM, scores		
❁ ULCA	Not reported	Not reported
❁ WORC (percentage pre-operatively vs last follow up)[5]	C: 58.0 (SD 5.0) vs 66.0 (SD 5.0) [improvement +13.0 (SD 10.0)] I: 54.0 (SD 8.0) vs 84.0 (SD 4.0) [improvement +30.0* (SD 12.0)] Significant better improvement for I (*P*=0.0412)	Not reported
❁ CS (pre-operatively vs last follow up)[3]	Not reported	C: 43.1 (SD 3.9) vs 70.8 (SD 5.3) (P=0.01) I: 41.2 (SD 3.1) vs 83.9 (SD 6.0) (P=0.005)) Significant better improvement for I for 24 months (P<0.01)
❁ ASES (pre-operatively vs last follow up)[2]	C: 60.3 (SD 9.5) vs 72.6 (11.9) [improvement +9.9 (SD 24.7)] I: 63.8 (SD 13.8) vs 88.9 (SD 4.8) [improvement +29.9 (SD 18.6)] Significant better improvement for I at 96 week (*P*=0.024)	Not reported
❁ ROM	Not reported	Not reported
Physical function, scores		
❁ SSV	Not reported	Not reported
❁ WORC	Not reported	Not reported
❁ DASH	Not reported	Not reported
❁ SPADI	Not reported	Not reported
❁ ASES (pre-operatively vs last follow up)[2]	C: 60.3 (SD 9.5) vs 72.6 (11.9) [improvement +9.9 (SD 24.7)] I: 63.8 (SD 13.8) vs 88.9 (SD 4.8) [improvement +29.9 (SD 18.6)] Significant better improvement for I at 96 week (*P*=0.024)	Not reported

Author, year [Reference]	Gilot, 2015 [18]	Pandey, 2017 [17]
❁ CS (pre-operatively vs last follow up)[3]	Not reported	C: 43.1 (SD 3.9) vs 70.8 (SD 5.3) (P=0.01) I: 41.2 (SD 3.1) vs 83.9 (SD 6.0) (P=0.005)) Significant better improvement for I at 24 months (*P*<0.01)
❁ OSS (pre-operatively vs last follow up)[4]	Not reported	C: 17.8 (SD 3.6) vs 37.1 (SD 2.4) (*P*=0.009) I: 14.9 (SD 3.5)vs 43.9 (SD 2.4) (P=0.005) Significant better improvements for I at 24 months (*P*=0.01)
Health-related quality of life, scores		
❁ OSS (pre-operatively vs last follow up)[4]	Not reported	C: 17.8 (SD 3.6) vs 37.1 (SD 2.4) (*P* =0.009) I: 14.9 (SD 3.5)vs 43.9 (SD 2.4) (*P*=0.005) Significant better improvements for I at 24 months (*P*=0.01)
❁ SF-12 (pre-operatively vs last follow up)	C: 43.1 (SD 8.2) vs. 42.9 (SD 10.8) difference 3.7 (SD 12.7) I: 42.2 (SD 12.1) vs. 64.1 (9.3) difference 5.1 (SD 11.7)	Not reported
❁ WORC (Percantage pre-operatively vs last follow up)[5]	C: 58.0 (SD 5.0) vs 66.0 (SD 5.0) [improvement +13.0 (SD 10.0)] I: 54.0 (SD 8.0) vs 84.0 (SD 4.0) [improvement +30.0* (SD 12.0)] Significant better improvement for I (P=0.0412)	Not reported
Patient satisfaction, scores		
❁ ULCA	Not reported	Not reported
❁ SSV	Not reported	Not reported
❁ MRI scan of intact cuffs, n (%)	C: 11/15 (73.3*) I: 18/20 (90.0*)	Not reported
Safety		
Procedure-related mortality	0/35 (0.0)	0/26 (0.0)
Failure of repair procedure, re-tear-rate (%)	C: 4/15 (26.8) I: 2/20 (10) (p=0.0483)	C: 0/13 (0.0) I: 4/13 (30.0)
Additional surgery, re-operation-rate (%)	C: 3/15 (26.0)[10] I: 2/20 (10.0)	Not reported
Complications		
❁ Procedure-related	C: 0/15 (0.0) I: 1/20 (5.0)[11]	Not reported
❁ Device-related	C: 0/15 (0.0) I: 0/15 (0.0)	Not reported
Adverse events	Not reported	Not reported
Severe adverse events	Not reported	Not reported

Abbreviations: ***ASES*** *= American Shoulder and Elbow Surgeons;* ***C*** *= control group;* ***CS*** *= Constant shoulder assessment;* ***DASH*** *= Disabilities of the arm, shoulder, and hand;* ***ECM*** *= extracellular matrix;* ***I*** *= intervention group;* ***OSS*** *= Oxford Shoulder Score;* ***ROM*** *= Range Of Motion;* ***SD*** *= standard deviation;* ***SPADI*** *= Shoulder Pain and Disability Index;* ***SSV*** *= Subjective shoulder value;* ***UCLA*** *= University of California, Los Angeles;* ***UK*** *= United Kingdom;* ***USA*** *= United States of America;* ***VAS*** *= Visual analogue scale;* ***WORC*** *= Western Ontario Rotator Cuff Index.*

* *Self-calculated.*

[10] Of the 4 pts. with a re-tear, 2 pts. needed revision surgery after 6 months and 1 pt. required a reverse shoulder arthroplasty after 1 year.

[11] 1 pt. Had a superficial skin infection 1 week after surgery.

Table A-3: Human dermal allograft for irreparable rotator cuff tears: Results from observational studies

Author, year [Reference]	Burkhead, 2007 [38]	Rotini, 2011 [40]	Gupta, 2012 [20]	Varvitsiotis, 2015 [34]	Leuzinger, 2016 [39]	Hirahara, 2018 [19]	Sharma, 2018 [41]
Country	USA	Italy	USA	Greece	Switzerland	USA	UK
Sponsor	Not reported	Not reported	Not reported	None	Not reported	Arthrex	None
Intervention/Product	GraftJacket	AHDM: Acellular human dermal matrix	GraftJacket	Fascia lata allograft	GraftJacket: human dermal cell-free tissue with an intact matrix to retain collagen, proteoglycans and elastin	ArthroFLEX	GraftJacket
Study design	Case series retrospective[12]	Case series	Case series	Case series	Case series	Case series	Case series retrospective[13]
Number of pts	17	6	24	68	28	9	22
Inclusion criteria	Massive or failed rotator cuff tear involving two or more tendons	Large/massive rotator cuff lesions with high risk of recurrence in healthy patients aged <55 years, lesions involving infraspinatus and supraspinatus tendons, tendon retraction ≤3 accord-ing to Thomazeau, fatty degeneration ≤3 according to Goutallier, possibility of surgery for tendon reduction, follow up >1 year	Patients with massive irreparable rotator cuff tear (>5 cm), failure of a minimum 6 months' non-operative management, inability to reduce residual cuff to anatomic footprint (after full mobilisation of tendon), ability to fully participate in post-operative rehabilitation protocol	Patients with massive rotator cuff tear symptomatic with nocturnal pain and decreased functioning, irreparable by simple suture, at least 2 ruptured tendons, >5 in maximal diameter, proven by MRI, and confirmed at surgery	Massive rotator cuff tear involving 2 or more tendons	Patients with irreparable massive rotator cuff tear	Rotator cuff tear with pain and where direct repair is not possible

[12] Indicated by no reporting of inclusion/exclusion criteria.

[13] Indicated by change of procedure after study start .

Author, year [Reference]	Burkhead, 2007 [38]	Rotini, 2011 [40]	Gupta, 2012 [20]	Varvitsiotis, 2015 [34]	Leuzinger, 2016 [39]	Hirahara, 2018 [19]	Sharma, 2018 [41]
Exclusion criteria	Irreparable tendon for stable repair, active infection	Arthritic degeneration even mild according to Samilson, frozen shoulder, symptomatic acromioclavicular arthritis, inability to cope with an a post-operative rehabilitation regime, autoimmune connective disease tissue, pork and penicillin alleriges	Glenohumeral arthritis/rotator cuff tear arthropathy >50% fatty infiltration of the supraspinatus muscle, prior RC repair, RC reducible to lateral footprint during arthroscopy	Advanced glenohumeral arthritis	Osteoarthritis, fatty degeneration >2 according to Goutallier	Not reported	Not reported
Mean age of patients (yrs, range)	56.9	48.0 (37-55)	63 (45-83)	64.9 (43-81)	66.4 (SD 7.9)	61.3 (47-78)	64.6 (39-87)
Female sex, n (%)	5 (29.41*)	0 (0.0)	12 (50*)	30 (44.1*)	8 (28.6)	2 (25*)	4 (20*)
Post-operative treatments (s)	Immobilisation with an abduction pillow 45° with no motion for 3 weeks, passive motion above the pillow for additional 3 weeks or conversion to an Ultra-Sling, active assisted range of motion initiated at 6 weeks, strengthening delayed until at least 12 weeks	Use of abduction pillow sling for 30 days after surgery, following gentle rehabilitation with gradual strengthening exercises after 3 months	Pain free passive range of motion until week 8, progressive active assisted range of motion until week 12, progressive isometric strengthening exercises start week 12, progression to full activities of daily living start after 4 months	Use of standard abduction pillow for first 6 weeks with starting pendulum exercises after 3 weeks, passive motion continued for 6 additional weeks, strengthening started at 12 weeks, resistance exercises at 16 weeks, return to activity as tolerated at 24 weeks	Not reported	Not reported	Pendulum exercises and passive movement during first 3 weeks, gentle stretching and active assisted movements from week 3 to 6, full ROM together with proprioceptive stretching was permitted after 6 weeks
Follow up (months)	Mean 15*	12 for all	Mean 36 (range, 29-40)	12 for all, mean 43 (31-77)	36	Mean 32.4 (range, 25-39)	24.5 and 18 for two groups[14]
Loss to follow up, n (%)	0/17 (0.0)	1/6 (16.7)	0/24 (0.0)	0/68 (0.0)	3/92 (3.3*)[15]	1/9 (11.1)	2/22 (9.1)
Primary endpoint(s)	Not reporded	Safety and efficacy of the membrane	Not reported	Not reported	Not reported	Not reported	Not reported

[14] Group 1 included 2 pts. Treated with a single interpositional GraftJacket repair. In group 2, 18 pts. were treated with a doubled GraftJacket.

[15] Loss- to follow-up due to non-specific foreign body reaction 2 weeks after the implantation.

Author, year [Reference]	Burkhead, 2007 [38]	Rotini, 2011 [40]	Gupta, 2012 [20]	Varvitsiotis, 2015 [34]	Leuzinger, 2016 [39]	Hirahara, 2018 [19]	Sharma, 2018 [41]
Outcomes							
Efficacy							
Pain, scores							
❁ ULCA (pre- vs post-operatively)[1]	9.1 vs 26.1 (*P*<0.001)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
❁ ASES (pre-operatively vs last follow up)[2]	Not reported	Not reported	66.6 vs 88.7 (*P*<0.001)	Not reported	Not reported	41.8 (SD 12.7)vs 86.5 (SD 12.7) (*P*<0.001)	Not reported
❁ CS (pre- vs post-operatively)[3]	Not reported	64.0 (range, 55-75) vs 88.0 (range, 77-95) Avegage increase of 24 (range 20-30)	Not reported	32.5 vs 88.7	t=6 months[16]: 47.3 (SD 7.3) vs. 81.4 (SD 11.4) (p=0.002)	Not reported	Not reported
❁ OSS[4]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	22 (SD 4.5) vs 45.5 (SD 2.5) at 17 months (P<0.001)[17]
❁ DASH	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
❁ SPADI	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
❁ VAS	Not reported	Not reported	Not reported	Not reported	Not reported	6.3 (SD 1.6) vs 0.4 (SD 1.1) (*P*<0.001)	Not reported
ROM, scores							
❁ ULCA (pre- vs post-operatively)[1]	9.1 vs 26.1 (*P*<0.001)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
❁ WORC	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
❁ CS (pre- vs post-operatively)[3]	Not reported	64.0 (range, 55-75) vs 88.0 (range, 77-95) Avegage increase of 24 (range 20-30)	Not reported	32.5 vs 88.7	t=6 months 47.3 (SD 7.3) vs. 81.4 (SD 11.4) (p=0.002)	Not reported	Not reported
❁ ASES (pre-operatively vs last follow up)[2]	Not reported	Not reported	66.6 vs 88.7 (*P*<0.001)	Not reported	Not reported	41.8 (SD 12.7) vs 86.5 (SD 12.7) (*P*<0.001)	Not reported
❁ ROM	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

[16] Mean CS score for all pts. was only reported for the follow-up of 6 months.

[17] OSS scores were only extracted for group 2 (n=18). However, scores were only available of 13/18 pts (72.2%).

Author, year [Reference]	Burkhead, 2007 [38]	Rotini, 2011 [40]	Gupta, 2012 [20]	Varvitsiotis, 2015 [34]	Leuzinger, 2016 [39]	Hirahara, 2018 [19]	Sharma, 2018 [41]
Physical function, scores							
❁ SSV	Not reported	Not reported	Not reported	Not reported	t= 6 months: 4.3 (SD 0.8) vs. 8.2 (SD 1.1) (p=0.002) t= 36 months: 4.3 (SD 0.8) vs. 9.1 (SD 1.2) (p=0.002)	Not reported	Not reported
❁ WORC	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
❁ DASH	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
❁ SPADI	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
❁ ASES (pre-operatively vs last follow up)[2]	Not reported	Not reported	66.6 vs 88.7 (*P*<0.001)	Not reported	Not reported	41.8 (SD 12.7) vs 86.5 (SD 12.7) (*P*<0.001)	Not reported
❁ CS (pre- vs post-operatively)[3]	Not reported	64.0 (range, 55-75) vs 88.0 (range, 77-95) Avegage increase of 24 (range 20-30)	Not reported	32.5 vs 88.7	t=6 months: 47.3 (SD 7.3) vs. 81.4 (SD 11.4) (p=0.002)	Not reported	Not reported
❁ UCLA (pre- vs post-operatively)[1]	9.1 vs 26.1 (*P*<0.001)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
❁ OSS[4]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	22 (SD 4.5) vs 45.5 (SD 2.5) (P<0.001)[17]
Health-related quality of life, scores							
❁ OSS[4]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	22 (SD 4.5) vs 45.5 (SD 2.5) (*P*<0.001)[17]
❁ SF-12 (pre-operatively vs last follow up)	Not reported	Not reported	48.8 vs 56.8 (*P*=0.03)	Not reported	Not reported	Not reported	(Post-operative) Physical 47.4 (SD 9.19); Mental 56.6 (SD 5.48)
❁ WORC	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Patient satisfaction, scores							
❁ ULCA (pre- vs post-operatively)[1]	9.1 vs 26.1 (*P*<0.001)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Author, year [Reference]	Burkhead, 2007 [38]	Rotini, 2011 [40]	Gupta, 2012 [20]	Varvitsiotis, 2015 [34]	Leuzinger, 2016 [39]	Hirahara, 2018 [19]	Sharma, 2018 [41]
✿ SSV		Not reported	Not reported	Not reported	t= 6 months: 4.3 (SD 0.8) vs. 8.2 (SD 1.1) (p=0.002) t= 36 months: 4.3 (SD 0.8) vs. 9.1 (SD 1.2) (p=0.002)	Not reported	Not reported
✿ MRI scan of intact cuff, n (%)	9/11 (81.8*)	3/5 (60*)	14/19 (74)	27/30 (90*)[18]	14/16 (87.5*)	7/8 (87.5)	Not reported
Safety							
Procedure-related mortality	0/17 (0.0)	0/5 (0.0)	0/24 (0.0)/ Not reported	0/68 (0.0)	0/89 (0.0)	0/8 (0.0)	0/22 (0.0)
Failure of repair procedure, re-tear-rate (%)	3/11 (27.3*) re-tears—no action (n=2), glenohumeral fusion (n=1)	2/5 (40.0) re-tears – no action	1/24 (4.2*)[19]	3/30 (10.0*)	12/28 (42.9*)	2/8 (12.5) caused by a fall/motor vehicle accident – no actions	1/20 (5.0)
Additional surgery, re-operation-rate (%)	0/17 (0.0)	0/5 (0.0)	0/24 (0.0)/ Not reported	Not reported	12/28 (42.9*)	1/8 (12.5) Pt with MRI-confirmed rupture – revision SCR or RTSA considered	1/20 (5.0)
Complications							
Procedure-related	0/17 (0.0)	0/5 (0.0)	0/24 (0.0)	0/68 (0.0)	Not reported	Not reported	Not reported
Device-related	0/17 (0.0)	0/5 (0.0)	0/24 (0.0)	0/68 (0.0)	Not reported	Not reported	Not reported
Adverse events	0/17 (0.0)	0/5 (0.0)	0/24 (0.0)	Not reported	Not reported	4/9 (44.4)	Not reported
Severe adverse events	0/17 (0.0)	0/5 (0.0)	0/24 (0.0)/ Not reported	Not reported	Not reported	Not reported	Not reported

Abbreviations: ***AHDM*** *= Acellular Human Dermal Matrix;* ***ASES*** *= American Shoulder and Elbow Surgeons;* ***CS*** *= Constant shoulder assessment;* ***DASH*** *= Disabilities of the arm, shoulder, and hand;* ***OSS*** *= Oxford Shoulder Score;* ***RC*** *= rotator cuff;* ***ROM*** *= Range Of Motion;* ***SD*** *= standard deviation;* ***SPADI*** *= Shoulder Pain and Disability Index;* ***SSV*** *= Subjective shoulder value;* ***UCLA*** *= University of California, Los Angeles;* ***UK*** *= United Kingdom;* ***USA*** *= United States of America;* ***VAS*** *= Visual analogue scale;* ***WORC*** *= Western Ontario Rotator Cuff Index.*

***** *Self-calculated.*

[18] 10 pts. underwent follow-up MRI, resulting in confusing results. However, 30 pts underwent ultrasound showing clearer results.

[19] 1 partial graft re-tear occurred because of patient noncompliance with postoperative rehabilitation.

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement, a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [2] and in the Guidelines of EUnetHTA [43]. The single randomised controlled trial was appraised using the Cochrane Collaboration's Risk of Bias Tool [9]. The non-randomised controlled trials were appraised using The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool [10]. Single arm studies were appraised according to the IHE appraisal tool for case series studies [11].

Table A-4: Risk of bias – study level (randomised studies), see [44]

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
Barber, 2012, [35]	Yes	Yes	Unclear[20]	No[21]	No[22]	No	Low

Table A-5 Risk of bias of non – randomised studies comparing human dermal allograft rotator cuff tear repair versus RCT repair without human dermal allograft and reporting results on [ASES, CS, OSS, VAS, WORC, and SF-12], see [43]

Trial	Bias due to confounding			Baseline confounding			baseline and time-varying confounding		Risk of bias judgement
	Confounding of effect	Time-varying confounding	Time-varying factoras likely to effect outcome	Appropriate analysis method used	Valid and reliable measurement	Control for post-intervention variables	Appropriate methis for all the important confounding domains and for time-varying confounding	Valid and reliable measurement of domains controlled for	
Gilot, 2015, [18]	N	N	NA	N	NA	N	N	N	Serious risk of bias
Pandey, 2017, [17]	Y	Y	PY	NA	NA	NA	PN	N	Serious risk of bias

Abbreviations: ***NA*** *= not applicable;* ***NI*** *= no information;* ***N*** *= no;* ***PN*** *= probably no;* ***PY*** *= probably yes;* ***Y*** *= yes.*

[20] Patient blinding was not explicitly described.

[21] Blinding of surgeon is not possible in this intervention, but radiologist was blinded for interpretation of MRIs.

[22] Severe adverse events were not described.

Table A-6: Risk of bias – study level (case series), see [4]

Study reference/ID	Burkhead, 2007 [38]	Rotini, 2011 [40]	Gupta, 2012 [20]	Varvitsiotis, 2015 [34]	Leuzinger, 2016 [39]	Hirahara, 2017 [19]	Sharma, 2018 [41]
Study objective							
1. Was the hypothesis/aim/objective of the study clearly stated?	Partial	Yes	Partial[23]	Partial[24]	Yes	Yes	Partial[23]
2. Was the study conducted prospectively?	No	Yes	Yes	Yes	Yes	Yes	No
3. Were the cases collected in more than one centre?	Unclear[25]	Unclear	No	No	Unclear	No	No
4. Were patients recruited consecutively?	Yes	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Partial	Yes	Partial	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Partial	Partial
7. Did patients enter the study at a similar point in the disease?	Yes	Yes	Yes	Yes	Unclear[26]	Yes	Unclear
Intervention and co-intervention							
8. Was the intervention of interest clearly described?	Yes	Partial	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Partial[27]	Partial[20]	Partia[20]	Partial[20]	No	No	Partial[20]
Outcome measures							
10 Were relevant outcome measures established a priori?	No	Partial[28]	Yes	Yes	Yes	Yes	Yes
11 Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	Yes[29]	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Partial[30]	Yes	Yes	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statistical Analysis							
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes

[23] Only patients and outcomes were included in the hypothesis.

[24] Only indication and intervention were described.

[25] Unclear if the senior author performed all open rotator cuff repairs of the study.

[26] Preoperative tests were reported but not described.

[27] Yes the postoperative care programme was described.

[28] Safety assessment was stated a priori, while the efficacy measures, e.g. Constant shoulder assessment was not.

[29] Yes radiographer blinded for reading MRI in postoperative assessment.

[30] Pain, function, flexion was reported with unknown scores, whereas the postoperative MRI evaluation and the ULCA state appropriate methods.

Study reference/ID	Burkhead, 2007 [38]	Rotini, 2011 [40]	Gupta, 2012 [20]	Varvitsiotis, 2015 [34]	Leuzinger, 2016 [39]	Hirahara, 2017 [19]	Sharma, 2018 [41]
Results and Conclusions							
15. Was follow up long enough for important events and outcomes to occur?[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. Were losses to follow up reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	No	Partial	Yes	No	Yes	Yes	Yes
18. Were the adverse events reported?	Yes	Yes	Yes	No	No	Partial[32]	No
19. Were the conclusions of the study supported by results?	Yes	Yes	Unclear[33]	Yes	Unclear[27]	Unclear[27]	Yes
Competing interests and sources of support							
20. Were both competing interests and sources of support for the study reported?	No	Partial[34]	Partial[34]	Yes	Partial[34]	Yes	Yes
Overall Risk of bias	**High**	**High**	**Moderate**	**Low**	**Moderate**	**Low**	**Low**

[31] Twelve months was considered appropriate.

[32] No severe adverse events were reported.

[33] Did not consider the limitations of the study (study design) for the conclusion.

[34] Only competing interests of the authors was reported.

*Table A-7: Evidence profile: **efficacy** of human dermal allograft for massive rotator cuff tears*

Quality assessment							Summary of findings			
							Number of patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgical repair with human dermal allograft	Surgical repair without human dermal allograft	Absolute mean difference	
Pain										
Pain measured with UCLA, N=42 (follow up: mean 24 months, range 12-38) Scale 0-35 (higher better)										
1	Randomised controlled trial	Not serious	N/A (only one trial)	Not serious	Not serious	None	22	20	MD 2.5* points higher in I[1]	⊕⊕⊕◯ MODERATE
Pain measured with ASES, N = 42 (follow up: mean 24 months, range 12-38) Scale 0-100 (higher better)										
1	Randomised controlled trial	Not serious	N/A (only one trial)	Not serious	Not serious	None	22	20	MD 1.6* points higher in I[2]	⊕⊕⊕◯ MODERATE
Pain measured with CS, N = 42 (follow up: mean 24 months, range 12-38) Scale 0-100 (higher better)										
1	Randomised controlled trial	Not serious	N/A (only one trial)	Not serious	Not serious	None	22	20	MD 11.4* points higher in I[3]	⊕⊕⊕◯ MODERATE
Pain measured with ASES, N = 35 (follow up: mean 24.9 months, range 22-26) Scale 0-100 (higher better)										
1	Non-randomised controlled trial	Serious[36]	N/A (only one trial)	Not serious	Not serious	None	20	15	MD 12.8* points higher in I[2]	⊕⊕⊕◯ MODERATE
Pain measured with CS, N = 26 (follow up: mean 24 months, range 2-5 years) Scale 0-100 (higher better)										
1	Non-randomised controlled trial	Serious[35]	N/A (only one trial)	Not serious	Not serious	None	13	13	MD 15.0* points higher in C[3]	⊕⊕⊕◯ MODERATE
Pain measured with VAS, N=35 (follow up: mean 24.9 months, range 22-26) Scale 0-10 (lower better)										
1	Non-randomised controlled trial	Serious[36]	N/A (only one trial)	Not serious	Not serious	None	20	15	MD 2.7* points lower in I	⊕⊕⊕◯ MODERATE
Pain measured with OSS, N=26 (follow up: mean 4 months, range 2-5 years) Scale 0-60 (higher better)										
1	Non-randomised controlled trial	Serious[35]	N/A (only one trial)	Not serious	Not serious	None	13	13	MD 9.7* points higher in I[4]	⊕⊕⊕◯ MODERATE
Range of motion										
Range of motion with UCLA, N=42 (follow up: mean 24 months, range 12-38) Max score 35 (higher better)										
1	Randomised controlled trial	Not serious	N/A (only one trial)	Not serious	Not serious	None	22	20	MD 2.5* points higher in I[1]	⊕⊕⊕◯ MODERATE

[35] Risk of time-varying confounding.

Quality assessment							Summary of findings			
							Number of patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgical repair with human dermal allograft	Surgical repair without human dermal allograft	Absolute mean difference	
Range of motion with CS, N = 42 (follow up: mean 24 months, range 12-38) Scale 0-100 (higher better)										
1	Randomised controlled trial	Not serious	N/A (only one trial)	Not serious	Not serious	None	22	20	MD 11.4* points higher in I[3]	⊕⊕⊕◯ MODERATE
Range of motion with measured with ASES, N = 42 (follow up: mean 24 months, range 12-38) Scale 0-100 (higher better)										
1	Randomised controlled trial	Not serious	N/A (only one trial)	Not serious	Not serious	None	22	20	MD 1.6* points higher in I[2]	⊕⊕⊕◯ MODERATE
Range of motion with CS, N = 26 (follow up: mean 24 months, range 2-5 years) Scale 0-100 (higher better)										
1	Non-randomised controlled trial	Serious[35]	N/A (only one trial)	Not serious	Not serious	None	13	13	MD 15.0* points higher in I[3]	⊕⊕⊕◯ MODERATE
Range of motion with measured with ASES, N = 35 (follow up: mean 24.9 months, range 22-26) Scale 0-100 (higher better)										
1	Non-randomised controlled trial	Serious[36]	N/A (only one trial)	Not serious	Not serious	None	20	15	MD 12.8* points higher in I[2]	⊕⊕⊕◯ MODERATE
Range of motion with WORC, N=35 (follow up: mean 24.9 months, range 22-26) Scale 0-100 (higher better)										
1	Non-randomised controlled trial	Serious[36]	N/A (only one trial)	Not serious	Not serious	None	20	15	MD 22.0* points higher in I[5]	⊕⊕⊕◯ MODERATE
Physical function										
Physical function with ASES, N = 42 (follow up: mean 24 months, range 12-38) Scale 0-100 (higher better)										
1	Randomised controlled trial	Not serious	N/A (only one trial)	Not serious	Not serious	None	22	20	MD 1.6* points higher in I[2]	⊕⊕⊕◯ MODERATE
Physical function with CS, N = 42 (follow up: mean 24 months, range 12-38) Scale 0-100 (higher better)										
1	Not serious	Not serious	N/A (only one trial)	Not serious	Not serious	None	22	20	MD 11.4* points higher in I[3]	⊕⊕⊕◯ MODERATE
Physical function with ASES, N = 35 (follow up: mean 24.9 months, range 22-26) Scale 0-100 (higher better)										
1	Non-randomised controlled trial	Serious[36]	N/A (only one trial)	Not serious	Not serious	None	20	15	MD 12.8* points higher in I[2]	⊕⊕⊕◯ MODERATE
Physical function with CS, N = 26 (follow up: mean 4 months, range 2-5 years) Scale 0-100 (higher better)										
1	Non-randomised controlled trial	Serious[35]	N/A (only one trial)	Not serious	Not serious	None	13	13	MD 15.0* points higher in I[3]	⊕⊕⊕◯ MODERATE

[36] Appropriate method controlling for confounding not used.

Quality assessment							Summary of findings			
							Number of patients		Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgical repair with human dermal allograft	Surgical repair without human dermal allograft	Absolute mean difference	
Physical function with OSS, N = 26 (follow up: mean 24 months, range 2-5 years) Scale 0-60 (higher better)										
1	Non-randomised controlled trial	Serious[35]	N/A (only one trial)	Not serious	Not Serious	None	13	13	MD 9.7* points higher in I[4]	⊕⊕⊕◯ MODERATE
Health-related quality of life										
Health-related quality of life with WORC, N=35 (follow up: mean 24.9 months, range 22-26) Scale 0-100 (higher better)										
1	Non-randomised controlled trial	Serious[36]	N/A (only one trial)	Not serious	Not serious	None	20	15	MD 22.0* points higher in I[5]	⊕⊕⊕◯ MODERATE
Health-related quality of life with OSS, N = 26 (follow up: mean 24 months, range 2-5 years) Scale 0-60 (higher better)										
1	Non-randomised controlled trial	Serious[35]	N/A (only one trial)	Not serious	Not serious	None	13	13	MD 9.7* points higher in I[4]	⊕⊕⊕◯ MODERATE
Health-related quality of life with SF-12, N=35 (follow up: mean 24.9 months, range 22-26) Scale 0-100 (higher better)										
1	Non-randomised controlled trial	Serious[36]	N/A (only one trial)	Not serious	Not serious	None	20	15	*Physical* MD 5.7* points higher in I *Mental* MD 1.4* points higher in I	⊕⊕⊕◯ MODERATE

Abbreviations: ***ASES*** *= American Shoulder and Elbow Surgeons;* ***CI*** *= confidence interval;* ***CS*** *= Constant shoulder assessment;* ***DASH*** *= Disabilities of the arm, shoulder, and hand;* ***MD*** *= mean difference;* ***OSS*** *= Oxford Shoulder Score;* ***ROM*** *= Range Of Motion;* ***SF-12*** *= 12-item Short Form questionnaire;* ***SPADI*** *= Shoulder Pain and Disability Index;* ***SSV*** *= Subjective shoulder value;* ***UCLA*** *= University of California, Los Angeles;* ***VAS*** *= Visual analogue scale;* ***WORC*** *= Western Ontario Rotator Cuff Index.*

** Self-calculated.*

*Table A-8: Evidence profile: **safety** of human dermal allograft for massive rotator cuff tears*

Quality assessment							Summary of findings	
							Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proportion (range)	
Safety								
Procedure-related mortality, N = 42 (follow up: mean 24 months, range 12-38, number deaths reported)								
1	Randomised controlled trial	Not serious	N/A (only one trial)	Not serious	Not serious	None	Overall deaths: 0/42(0.0%)	⊕⊕⊕⊕ HIGH
Procedure-related mortality, N = 61 (follow up: range 22 months to 120 months, number deaths reported)								
2	Non-randomised controlled trials	Serious[35,36]	Not serious	Not serious	Serious[36,35]	None	Overall deaths: 0/61 (0.0%)	⊕⊕◯◯ LOW
Procedure-related mortality, N = 174 (follow up: range 12 months to 77 months, number deaths reported)								
7	Case series	Moderate[20,23,34]	Not serious	Not serious	Not serious	None	Overall deaths: 0/174 (0.0%)	⊕◯◯◯ VERY LOW
Failure of repair procedure/re-tears, N = 42 (follow up: mean 24 months, range 12-38, number re-tears reported)								
1	Randomised controlled trial	Not serious	N/A (only one trial)	Not serious	Not serious	None	Overall failures: C: 9/20 (45.0%*) I: 3/22 (12.6%*)	⊕⊕⊕⊕ HIGH
Failure of repair procedure/re-tears, N = 61 (follow up: range 22 months to 120 months, number re-tears reported)								
2	Non-randomised controlled trials	Serious[35,36]	Not serious	Not serious	Serious[35,36]	None	Overall failures: 10/61 (16.4%*)	⊕⊕◯◯ LOW
Failure of repair procedure/re-tears, N = 174 (follow up: range 12 months to 77 months, number re-tears reported)								
7	Case series	Moderate[20,23,34]	Not serious	Not serious	Not serious	None	Overall failures: 24/174 (13.8%*)	⊕◯◯◯ VERY LOW
Complications (procedure-related and device-related), N = 42 (follow up: mean 24 months, range 12-38, number complications reported)								
1	Randomised controlled trial	Not serious	N/A (only one trial)	Not serious	Not serious	None	Overall complications: 0/42 (0.0%)	⊕⊕⊕⊕ HIGH
Complications (procedure-related and device-related), N = 35 (follow up: mean 24.9 months, range 22-26, number complications reported)								
1	Non-randomised controlled trial	Serious[36]	N/A (only one trial)	Not serious	Seriou[s35,36]	None	Overall complications: 1/35 (2.8%*)	⊕⊕◯◯ LOW
Complications (procedure-related and device-related), N = 137 (follow up: range 12 months to 77 months, number complications reported)								
4	Case series	Moderate[20,34]	Not serious	Not serious	Not serious	None	Overall complications: 0/137 (0.0%)	⊕◯◯◯ VERY LOW

Quality assessment							Summary of findings	
							Effect	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proportion (range)	
Adverse events, N = 42 (follow up: mean 24 months, range 12-77 months, number adverse events reported)								
1	Randomised controlled trial	Not serious	N/A (only one trial)	Not serious	Not serious	None	Overall adverse events: 18/42 (42.8%*): C: 14/20 (70.0%*) I: 4/22 (18.0%*)	⊕⊕⊕⊕ HIGH
Adverse events, N = 55 (follow up: range 12 months to 40 months, number adverse events reported)								
4	Case series	Moderate[20,34]	Not serious	Not serious	Not serious	None	Overall adverse events: 4/55 (7.3%*)	⊕◯◯◯ VERY LOW

Abbreviation: CI *= confidence interval.*

** Self-calculated.*

Nomenclature for GRADE tables:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

Applicability table

Table A-9: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The patient population (n=277) did not appear to differ significantly between studies. Surgeons consider this procedure only in patients who are young (<65 years), with a massive rotator cuff tear where healing is unlikely. The included studies were conducted primarily in the United States/Canada, followed by the United Kingdom and locations in Europe. Though they are all from developed Western countries, it cannot be known for sure if the practice represents that in Austria. Patient demographics may be reflective of practice in terms of gender where mostly males have been treated, and post-operative treatments.
Intervention	The intervention, rotator cuff surgery using human dermal allograft, is well defined in the literature. Techniques may vary between surgeons, but the use of the dermal allograft to augment the repair appears consistent across studies.
Comparators	Due to our stringent inclusion criteria, all comparative studies included had the same comparator of rotator cuff surgery without using human dermal allograft. The randomised controlled trial stated rotator cuff tears without human dermal allograft was the comparator. The surgical technique is not described, it is assumed to be the currently agreed best technique, which is superior capsular reconstraction (SCR). Pandey et al. reported patients received the same procedure, partial repair, with or without the addition of human dermal allograft. Gilot et al. reported the surgical technique for both groups differed only in the use of the allograft. It is expected this is representative of clinical practice.
Outcomes	The three studies used for efficacy all reported pain, range of motion, and physical function using a range of scores. These studies had mean follow up of 2 years, ranging from one to five years. As the biggest impact of rotator cuff tear is pain and limited movement, these outcomes over the time period reported seem appropriate.
Setting	The efficacy studies were carried out in the United States, the United Kingdom, and Canada. The safety studies were in the United States, the United Kingdom, Greece, Itali and Switzerland. Settings were hospitals and universitis affiliated with hospitals.

List of ongoing randomised controlled trials

There were four randomised controlled trials and one non-randomised controlled trial on human dermal allograft for massive rotator cuff tears identified in trial databases.

Table A-10: List of ongoing randomised controlled trials of human dermal allograft for massive rotator cuff tears

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome, FU	Primary completion date	Sponsor
NCT03551509 LifeNet: Extracellular Matrix Graft in Rotator Cuff Repair	Large (3-5 cm) or massive (>5 cm) rotator cuff tear proven on MRI (N=70)	RC repair augmented with ArthroFLEX ECM scaffold graft	RC repair using standard practice, no ECM graft	Tendon healing, FU=12 months	June 2020 * Recruiting	The Cleveland Clinic, USA
NCT03617562 Superior Capsule Reconstruction vs Partial Repair of Massive Rotator Cuff Tears	Massive (>4 cm) rotator cuff tear proven on MRI (N=44)	RC repair augmented with dermal allograft	Partial RC repair using standard practice	ASES, FU=NR	May 2020 * Recruiting	Sunnybrook Health Sciences Centre, Canada
NCT01987973 Allograft Reconstruction of Massive Rotator Cuff Tears vs Partial Repair Alone	Large or massive (>3 cm) rotator cuff tear proven on MRI (N=30)	Partial RC repair with Allopatch HD patch allograft	Partial RC repair	WORC FU=NR	February 2017 * Status unknown	Ivan Wong, Nova Scotia Health Authority, Canada
NCT03425500 Massive Rotator Cuff Tear Reconstruction	Large or massive (>3 cm) rotator cuff tear proven on MRI (N=60)	RC repair augmented with the GraftJacket	RC repair	Maintenance of the Acromiohumeral distance shown on xray	June 2019 * Not yet recruiting	Ivan Wong, Nova Scotia Health Authority, Canada

***Abbreviations: ASES** = The American Shoulder and Elbow Surgeons Shoulder Score; **ECM** = extracellular matrix; **FU** = follow-up; **NR** = not reported; **MRI** = magnetic resonance imaging; **RC** = rotator cuff; **RC** = rotator cuff; **WORC** = Western Ontario Rotator Cuff Index.*

Table A-11: List of ongoing non-randomised controlled trials of human dermal allograft for massive rotator cuff tears

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome, FU	Primary completion date	Sponsor
NCT03739749 Arthroscopic Superior Capsular Reconstruction (SCR) – Study of Different Types of Grafts	Rotator cuff tear arthropathy, Hamada stage 1 or 2 proven on MRI (N=40)	6 arms for SCR with grafts, of which one used fascia lata allograft	Fascia lata autograft, achilles tendon allograft, bovine pericardium xenograft, swine dermal xenograft, or collagen graft	Constant Score assessment FU=NR	October 2020 * Recruiting	Hospital de Egas Moniz, Portugal

***Abbreviations: FU** = follow-up; **NR** = not reported; **MRI** = magnetic resonance imaging; **SCR** = superior capsular repair.*

Literature search strategies

Search strategy for The Cochrane Library

Search Date: 14/12/2018	
ID	Search
#1	MeSH descriptor: [Rotator Cuff Injuries] explode all trees
#2	(("rotator cuff*" or supraspinat* or infraspinat* or supra-spinat* or infra-spinat*) NEAR (tear* or rupture* or injur* or damage* or defect*)) (Word variations have been searched)
#3	(supraspinat*) (Word variations have been searched)
#4	("supraspinatus tendon") (Word variations have been searched)
#5	(infraspinatus) (Word variations have been searched)
#6	((massive NEAR (tear* or rupture* or injur* or damage* or defect*) NEAR ("rotator cuff*" or supraspinat* or infraspinat* or supra-spinat* or infra-spinat*))) (Word variations have been searched)
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6 (Word variations have been searched)
#8	(capsul* NEAR (reconstruct* or augment* or repa*)) (Word variations have been searched)
#9	((superior NEAR (capsul* NEAR (reconstruct* or augment* or repa*)))) (Word variations have been searched)
#10	(SCR):ti,ab,kw (Word variations have been searched)
#11	MeSH descriptor: [Fascia Lata] explode all trees
#12	("fascia lata") (Word variations have been searched)
#13	#11 OR #12 (Word variations have been searched)
#14	MeSH descriptor: [Autografts] explode all trees
#15	(autograft*) (Word variations have been searched)
#16	#14 OR #15 (Word variations have been searched)
#17	#13 AND #16 (Word variations have been searched)
#18	("fascia lata" NEAR autograft*) (Word variations have been searched)
#19	MeSH descriptor: [Allografts] explode all trees
#20	(allograft*) (Word variations have been searched)
#21	MeSH descriptor: [Acellular Dermis] explode all trees
#22	("regenerative tissue matrix") (Word variations have been searched)
#23	(GraftJacket*) (Word variations have been searched)
#24	(Graft Jacket*) (Word variations have been searched)
#25	(Arthro Flex) (Word variations have been searched)
#26	(ArthroFLEX*) (Word variations have been searched)
#27	#8 OR #9 OR #10 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 (Word variations have been searched)
#28	#7 AND #27 (Word variations have been searched)
Total: 15 Hits	

Search strategy for CRD (DARE, NHS-EED, HTA)

No.	Search terms	Results
1	(capsul* NEAR (reconstruct* OR augment* OR repa*))	5

Search strategy for Embase

No.	Query Results	Results	Date
#30	#8 AND #29	359	13 Dec 2018
#29	#9 OR #10 OR #11 OR #12 OR #13 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	19,507	13 Dec 2018
#28	arthroflex*:ti,ab,de	13	13 Dec 2018
#27	graftjacket*:ti,ab,de	64	13 Dec 2018
#26	'graftjacket'/exp	12	13 Dec 2018
#25	'regenerat* tissue* matri*':ti,ab,de	33	13 Dec 2018
#24	'acellular dermal matrix'/exp	1,660	13 Dec 2018
#23	'skin allograft'/exp	2,141	13 Dec 2018
#22	'derm* allograft*':ti,ab,de	210	13 Dec 2018
#21	('fascia lata' NEAR/5 autograft*):ti,ab,de	107	13 Dec 2018
#20	#16 AND #19	208	13 Dec 2018
#19	#17 OR #18	24,665	13 Dec 2018
#18	'autograft*':ti,ab,de	24,665	13 Dec 2018
#17	'autograft'/exp	13,129	13 Dec 2018
#16	#14 OR #15	3,403	13 Dec 2018
#15	'fascia lata':ti,ab,de	3,403	13 Dec 2018
#14	'fascia lata'/exp	1,838	13 Dec 2018
#13	'fascia lata graft'/exp	39	13 Dec 2018
#12	(superior NEAR/5 (reconstruct* OR augment* OR repa*)):ti,ab,de	3,252	13 Dec 2018
#11	(capsul* NEAR/5 (reconstruct* OR augment* OR repa*)):ti,ab,de	1,882	13 Dec 2018
#10	scr:ti,ab	10,446	13 Dec 2018
#9	'superior capsular reconstruction'/exp	17	13 Dec 2018
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	12,661	13 Dec 2018
#7	(massive NEAR/5 ('rotator cuff*' OR supraspinat* OR infraspinat*)):ti,ab,de	854	13 Dec 2018
#6	(('rotator cuff*' OR supraspinat* OR 'supraspinat*' OR infraspinat* OR 'infra spinat*') NEAR/5 (tear* OR rupture* OR injur* OR damage* OR defect*)):ti,ab,de	10,905	13 Dec 2018
#5	'infraspinatus tendon'/exp	52	13 Dec 2018
#4	'supraspinatus tendon rupture'/exp	11	13 Dec 2018
#3	'supraspinatus tear'/exp	22	13 Dec 2018
#2	'supraspinatus tendon tear'/exp	26	13 Dec 2018
#1	'rotator cuff injury'/exp	10,048	13 Dec 2018

Search strategy for Medline

Database: Ovid MEDLINE(R) <1946 to December Week 1 2018>, Ovid MEDLINE(R) Epub Ahead of Print <December 12, 2018>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 12, 2018>, Ovid MEDLINE(R) Daily Update <December 12, 2018>	
Search Strategy:	
1	exp Rotator Cuff Injuries/
2	((rotator cuff* or supra?spinat* or infra?spinat*) adj5 (tear* or rupture* or injur* or damage* or defect*)).mp.
3	exp Rotator Cuff
4	supra?spinat*.mp.
5	infra?spinat*.mp.
6	3 or 4 or 5
7	injuries.fs.
8	6 and 7
9	(massive adj5 ((tear* or rupture* or injur* or damage* or defect*) adj5 (rotator cuff* or supra?spinat* or infra?spinat*))).mp.
10	1 or 2 or 8 or 9
11	(capsul* adj5 (augment* or reconstruct* or repa*)).mp.
12	(superior adj5 (capsul* adj5 (augment* or reconstruct* or repa*))).mp.
13	SCR.ti,ab.
14	exp Fascia Lata/
15	fascia lata.mp.
16	14 or 15
17	exp Autografts/
18	autograft*.mp.
19	17 or 18
20	16 and 19
21	(fascia lata adj5 autograft*).mp.
22	exp ALLOGRAFTS/
23	allograft*.mp.
24	exp Acellular Dermis
25	regenerat* tissue* matri*.mp
26	GraftJacket*.mp.
27	Graft Jacket*.mp
28	ArthroFLEX*.mp
29	11 or 12 or 13 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30	10 and 29
Search date: 14/12/2018	
Hits: 220	

Ludwig Boltzmann Institut
Health Technology Assessment