Intrauterine Ultrasound-Guided Transcervical Radiofrequency Ablation

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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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

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Content

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List of abbreviations

AdHopHTA ..... Adopting Hospital Based Health Technology Assessment
AE ..... Adverse event
CI ..... Confidence interval
CRD ..... Centre for Reviews and Dissemination
CTR ..... Clinical trial registry
DARE ..... Database of Abstracts of Reviews of Effects
DVT ..... Deep vein thrombosis
EMAS ..... European Menopause and Andropause Society
EU ..... European Union
FDA ..... Food and Drug Administration
FIGO ..... International Federation of Gynecology and Obstetrics
GA ..... General anaesthesia
GRADE ..... Grading of Recommendations Assessment, Development and Evaluation
HIFU ..... High Intensity Focused Ultrasound ablation
ICD ..... International Statistical Classification of Diseases
Lap-RFA ..... Laparoscopic radiofrequency volumetric thermal ablation
MIQ ..... Menorrhagia Impact Questionnaire

MP ..... Menstrual pictogram
MRgFUS ..... Magnetic resonance-guided focused ultrasound
MRI ..... Magnetic resonance imaging
NA ..... Not applicable
NHS-EED ..... National Health Service Economic Evaluation Database
NPV ..... Non-perfused volume
NR ..... Not reported
PBAC ..... Pictorial blood loss assessment chart
POP ..... Planned and Ongoing Projects
PRISMA ..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTS ..... Patients
RCT ..... Randomised Controlled Trial
RF ..... Radiofrequency
RFA ..... Radiofrequency ablation
RFVTA ..... Radiofrequency volumetric thermal ablation
ROB ..... Risk of bias
SD ..... Standard deviation
SOGC ..... Society of Obstetricians and Gynaecologists of Canada
TFA ..... Transcervical fibroid ablation
UAE ..... Uterine artery embolization
UAO ..... Uterine artery occlusion
UFS-QOL-HRQL ... Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire
UFS-QOL-SSS ..... Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire Symptom Severity Scale
USD ..... United States Dollar
USgFUS ..... Ultrasound-guided focused ultrasound
USgHIFU ..... Ultrasound-guided high frequency focused ultrasound
UTI ..... Urinary tract infection
VAS ..... Visual analogue scale
WHO-ICTRP ..... World Health Organisation International Clinical Trials Registry Portal

Executive Summary

Introduction

Health Problem

This systematic review is focused on women with symptomatic uterine fibroids who wish to preserve their uterus. Uterine fibroids, also called myomas or leimyomas, are benign tumours that can cause significant symptoms including pain, heavy menstrual bleeding and pelvic pressure. Definitive treatment is hysterectomy, however, less invasive uterine-preserving interventions may be favoured by many women.

uterine fibroids are benign tumours that can cause significant symptoms including pain, heavy menstrual bleeding and pelvic pressure

Description of Technology

Intrauterine ultrasound-guided transcervical radiofrequency ablation (often referred to as transcervical fibroid ablation [TFA]) is a method of delivering radiofrequency (RF) energy to uterine leiomyomas to cause coagulative necrosis of the tissue. There is one marketed TFA device, the Sonata® Sonography-Guided Transcervical Fibroid Ablation System (Gynesonics, Inc.). The technology aims to reduce symptoms through reducing the fibroid volume without requiring a surgical incision. This intervention allows women to retain their uterus.

TFA by RF energy (high frequency energy) is a uterus preserving method for the treatment of myomas

Other uterus preserving interventions which aim to reduce the volume of leiomyomas or remove them, include open, laparoscopic or hysteroscopic myomectomy, uterine artery embolization (UAE), uterine artery occlusion (UAO), magnetic resonance-guided focused ultrasound (MRgFUS), ultrasound-guided focused ultrasound (USgFUS/USgHIFU), and laparoscopic radiofrequency volumetric thermal ablation (laparoscopic RFVTA).

optional interventions: myomectomy, UAE, UAO, MRgFUS, USgFUS/USgHIFU, RFVTA

Methods

The research question was investigated through a systematic review of the current literature on TFA. The EUnetHTA Core Model® for Rapid Assessment of Relative Effectiveness was the main source for selecting relevant assessment elements. The question was whether TFA is more effective and safe or equally effective, but safer with respect to the specified crucial outcomes in the effectiveness and safety domain.

question: is TFA by RF energy vs. other interventions more effective and safer?

The search was executed in four biomedical databases (Medline, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination) on the 4th to 6th of December 2019. Overall, 303 citations were identified from the database searches and one publication was identified through handsearching (overall 304). After removing duplications, 225 citations were identified.

search in 4 databases; 304 hits in total; 225 hits after deduplication

Ongoing and unpublished studies were searched in three clinical trials registries (CTRs: ClinicalTrials.gov; World Health Organisation International Clinical Trials Registry Portal [WHO-ICTRP]; EU Clinical Trials) on the 28th of January 2020 resulting in 20 potential hits (0 relevant). The manufacturer from the most common product (Sonata®, Gynesonics, Inc.) was contacted and provided 23 publications, but no new citations were identified. Study selection, data extraction, and quality appraisal was conducted by two authors (RL, CS).

search in CTRs for ongoing trials, 20 hits (0 relevant); no new publications from the manufacturer

Domain effectiveness

effectiveness outcomes to derive a recommendation

The outcomes used as evidence to derive a recommendation on the effectiveness of TFA included reduction in symptom severity, reduction in menstrual bleeding, rates of surgical reintervention, reduction in fibroid volume, improvement in quality of life, patient satisfaction and fertility following the procedure.

Domain safety

safety outcomes to derive a recommendation

The outcomes used as evidence to derive a recommendation on the safety of TFA included major adverse events and all adverse events.

Results

Available evidence

no comparative studies; 3 single-arm case series studies (FAST-EU, IDE and OPEN Trial) published in 7 publications (234 Pts.)

No comparative studies were identified by the search strategy and therefore the evidence base evaluating TFA comprises of prospective single arm studies. Some outcomes reported were analysed retrospectively. A total of three single-arm case series studies (FAST-EU, IDE and OPEN Trial) published in seven publications [2-8] reporting on three unique cohorts (234 patients) were identified for inclusion.

all 3 case-series: sponsored, max. FU ranged from 6 weeks to 12 months and 2 to 4 pts

All three studies described above were sponsored by Gynesonics, Inc. Patients were followed up for a maximum of 12 months (FAST-EU Trial, IDE Trial) and minimum of 6 weeks (OPEN Trial). Losses to follow-up were reported in each of the studies. In the FAST-EU Trial after 12 months two patients exited the study and two patients were lost-to follow up in the OPEN Trial. Four patients missed the 12 months visit or were withdrawn before the 12 month visit in the IDE trial.

Clinical effectiveness

mean bleeding score reduction (improvement) at 12 months: 53.8% (FAST-EU) and 51.1% (IDE); 64% of patients achieved a >50% reduction in bleeding from baseline at 12 months

Compared to pre-procedure measures TFA resulted in statistically significant reductions in menstrual bleeding three months after the procedure and persisting at 12 months. Two studies reported this outcome and mean reductions in bleeding scores at 12 months were 53.8% in the FAST-EU trial [3] and 51.1% in the IDE trial [2]. In both studies 64% of patients achieved at least a 50% reduction in bleeding from baseline at 12 months.

mean improvement in symptoms at 12 months: UFS-QOL SSS, 35.3 (FAST-EU) and 32.1 (IDE) points; UFS-QOL HRQOL, 45.7 (FAST-EU) and 43.7 (IDE) points

Statistically significant improvements in symptoms were also reported following TFA that were observed by three months post-procedure and remained at 12 months. Two studies reported this outcome and mean improvement in symptoms at 12 months were 35.3 [3] and 32.1 points [2] with respect to the Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire Symptom Severity Scale score (UFS-QOL SSS score). Improvement in health related quality of life at 12 months was documented in two studies with a mean increase in Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QOL HRQOL) score of 45.7 and 43.7 points in the FAST-EU [3] and IDE [2] trial respectively. When measured using the EQ-5D-3L health utility was statistically significantly improved for the cohort as a whole at 12 months compared to baseline. One study reported patient satisfaction with 70.4% of patients being very satisfied [2].

Reintervention was reported with a range of <1% [8] (over 6 weeks of follow-up) to 11.8% [6] (after 5 years of follow-up) of included patients. One pregnancy resulting in the delivery of a term infant by caesarean section was reported in a patient who had received TFA.

reintervention: range <1% to 11.8% of included patients; 1 pregnancy was reported

Reductions in fibroid volume were also demonstrated in two studies with mean percentage reduction in perfused volume at 12 months of 67.4% and 63.9% in the FAST-EU and IDE trial respectively. Mean percentage reductions in total fibroid volume at 12 months were 66.6% (FAST-EU) and 62.4% (IDE).

perfused fibroid volume reduction at 12 months: 67.4% (FAST-EU) and 63.9% (IDE)

The durability of improvements beyond 12 months is unknown.

improvements after 12 months are not known

Safety

Major adverse events (major AE) reported after TFA were one case of deep vein thrombosis (DVT), one case of concurrent leukorrhea, pelvic pain and unconfirmed low-grade fever, and one case of non-specific abdominal pain.

major AEs: DVT (1 case), leukorrhea, pelvic pain and fever (1 case), abdominal pain (1 case)

Furthermore, patients experienced a range of other adverse events with up to 50% of patients experiencing any kind of adverse event. The rate of any specific adverse event was low (typically occurring in less than 10% of patients).

The long-term safety of TFA (beyond 12 months) has not been reported in any prospective studies.

long-term safety (>12 months) is not known

Upcoming evidence

No ongoing relevant randomised controlled trials (RCTs) evaluating the safety or effectiveness of TFA were identified.

no ongoing relevant RCTs

Reimbursement

TFA is not currently reimbursed by the Austrian healthcare system for the treatment of symptomatic uterine fibroids.

TFA is currently not reimbursed in Austria

Discussion

Of the included publications, three were assessed as being at a medium risk of bias [2-4] and four were assessed as being at a high risk of bias [5-8]. The strength of the evidence for effectiveness and safety was rated as low or very low for all outcomes. This was due to the inherent limitations of single arm studies i.e., failure to describe co-interventions/confounding factors and, use of unblinded patient reported outcomes.

Risk of Bias (RoB): 3 publications at medium risk, 4 publications at high risk of bias

Although the strength of the evidence was low to very low, studies consistently reported an improvement in symptoms and reduction in menstrual bleeding following TFA. However, women with symptomatic uterine fibroids currently have access to alternatives to hysterectomy that also reduce symptoms and menstrual bleeding. The performance of TFA relative to any other treatment for symptomatic fibroids is unknown.

strength of evidence is low to very low

Conclusion

The current evidence is not sufficient to prove that TFA is more effective and equally safe or equally effective, but safer than alternative uterine preserving interventions for symptomatic fibroids. Consequently, inclusion in the hospital benefit catalogue is currently not recommended.

currently not recommended to include in the catalogue of benefits

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

uterine Myome sind gutartige Tumore, die Symptome wie starke Menstruationsblutungen, Schmerzen und Druck im Beckenbereich verursachen können

Myome der Gebärmutter sind die häufigsten gutartigen Neubildungen im weiblichen Becken und stellen auch die Hauptindikation für eine Gebärmutterentfernung (Hysterektomie) dar. Die vorliegende systematische Übersicht befasst sich mit symptomatischen Gebärmuttermyomen: Uterusmyome, auch Fibroide oder Leiomyoma genannt, sind gutartige Tumore, die erhebliche Symptome wie Schmerzen, starke Menstruationsblutungen und Druck im Beckenbereich verursachen können. Eine Behandlungsoption ist die Hysterektomie, jedoch bevorzugen viele Frauen weniger invasive, uteruserhaltende Eingriffe.

genaue Aussage über die Prävalenz in der Zielbevölkerung ist schwierig

ca. 15-30 % der Myome können symptomatisch sein; Symptome beeinflussen das körperliche und emotionale Wohlbefinden negativ

Eine genaue Aussage über die Anzahl der betroffenen Frauen ist schwierig, da die Schätzungen über die Prävalenz in der publizierten Literatur eine große Bandbreite aufweisen (4,5 % bis 68,6 %) [9]. Diese Bandbreite ergibt sich durch die unterschiedliche Methodik der untersuchten Population und der Methode zur Diagnoseerhebung in den verschiedenen Studien. Zusätzlich wird berichtet, dass die Myome bei 15-30 % der Frauen symptomatisch sind [10], und es wird angenommen, dass die Symptome mit einer endometrialen und vaskulären Dysfunktion assoziiert sind. Viele der Prävalenzdaten basieren auf Selbsteinschätzungen der Patientinnen zu Symptomen und/oder der Diagnose und können daher unzuverlässig sein. Die Symptome können die Arbeitsfähigkeit und die Ausübung von körperlichen und sozialen Aktivitäten negativ beeinflussen und zu Beeinträchtigung des körperlichen und emotionalen Wohlbefindens führen [11].

insgesamt 5.112 Krankenhausaufenthalte mit der Diagnose Leiomyom in AT, davon 537 tagesklinisch (2018)

In Österreich belief sich die Anzahl der Krankenhausaufenthalte (stationär) von Frauen mit der Diagnose Leiomyom der Gebärmutter im Jahr 2018 auf insgesamt 5.112 [12]. Davon wurden 537 (10,5 %) tagesklinisch behandelt. Für die Altersgruppe 15 bis 44 Jahre beliefen sich die Krankenhausaufenthalte auf 2.035 Fälle, für die Altersgruppe 45 bis 64 Jahre auf 2.914 und für die Altersgruppe 65+ wurden 163 Fälle dokumentiert. Die durchschnittliche Aufenthaltsdauer betrug 4,4 Tage [12].

Beschreibung der Technologie

TFA durch RF-Energie (Hochfrequenzenergie) ist eine uteruserhaltende Methode für die Behandlung von Myomen

Die intrauterine ultraschallgesteuerte transzervikale Radiofrequenzablation (oft als transzervikale Myomablation [TFA] bezeichnet) ist eine uteruserhaltende Methode, bei der unter Verwendung von Radiofrequenzenergie (RF) eine koagulative Nekrose des Gewebes verursacht wird, um somit das Volumen von uterinen Leiomyomen minimal-invasiv zu reduzieren. In der Fachliteratur wird TFA als ein ambulanter Eingriff beschrieben, der von einer/m Gynäkologen/in entweder unter Vollnarkose, Sedierung unter Bewusstsein oder unter regionaler Anästhesie durchgeführt wird. Der Eingriff kann von ÄrztInnen, die eine entsprechende Ausbildung absolviert haben, durchgeführt werden [2].

Ein Gerät zur ultraschallgesteuerten transzervikalen Myomablation mit dem Namen Sonata® wird von dem Hersteller Gynesonics, Inc. vertrieben. Das System hat seit Februar 2019 eine CE-Kennzeichnung [8] und wurde 2018 von der Food and Drug Administration (FDA) für die "diagnostische intrauterine Bildgebung und transzervikale Behandlung von symptomatischen Uterusmyomen, einschließlich solcher, die mit schweren Menstruationsblutungen einhergehen" [13], zugelassen (FDA Cleared).

Sonata®-System hat seit Februar 2019 eine CE-Kennzeichnung und ist seit 2018 durch die FDA zugelassen (FDA Cleared)

Das Sonata®-System besteht aus einem RF-Generator (Signalgenerator), einem Ultraschallsystem mit Führungssoftware und einem Behandlungsgerät (d. h. ein Handstück zur Radiofrequenzablation [RFA] kombiniert mit einer Ultraschallsonde). Das RFA-Handstück ist für den einmaligen Gebrauch bestimmt, weshalb für jeden Eingriff ein neues Handstück erforderlich ist [2, 3].

Komponenten: RF-Generator, Ultraschallsystem inkl. Software, Behandlungsgerät

Die Technologie zielt darauf ab, die Symptome durch eine Verringerung des Myomvolumens zu reduzieren, ohne dass eine chirurgische Inzision erforderlich ist. Dieser Eingriff ermöglicht es, Frauen, ihre Gebärmutter zu erhalten. Optionale uteruserhaltende Eingriffe, die darauf abzielen das Volumen von Leiomyomen zu reduzieren, sind die Myomektomie, die Embolisation der Gebärmutterarterie (UAE), der Verschluss der Gebärmutterarterie (UAO), der magnetresonanzgesteuerte fokussierte Ultraschall (MRgFUS), der ultraschallgesteuerte fokussierte Ultraschall (USgFUS/USgHIFU) und die laparoskopische volumetrische Thermoablation mit Radiofrequenz (laparoskopische RFVTA).

optionale Eingriffe: Myomektomie, VAE, VAO, MRgFUS, USgFUS/USgHIFU, RFVTA

Methoden

Das Ziel dieser systematischen Übersichtsarbeit war es, die Frage zu beantworten, ob TFA wirksamer und sicherer oder ebenso wirksam, aber sicherer in Bezug auf Patientinnen-relevante Endpunkte ist. Die Forschungsfrage wurde durch eine systematische Auswertung der rezenten Literatur zu TFA untersucht. Dabei wurde das EUnetHTA-Core-Modell® für Rapid Assessment of Relative Effectiveness herangezogen.

Forschungsfrage: Ist die TFA durch RF-Energie im Vergleich zu anderen Interventionen wirksamer und sicherer?

Die systematische Suche wurde vom 4. bis 6. Dezember 2019 in vier Datenbanken (Medline via Ovid, Embase, The Cochrane Library, CRD [DARE, NHS-EED, HTA]) durchgeführt. Die Literatursuche beschränkte sich nicht auf ein Publikationsjahr oder Studiendesign, jedoch gab es sprachliche Einschränkungen auf englische und deutsche Artikel. Insgesamt wurden 303 Zitate aus den Datenbankrecherchen und eine Publikation durch Handsuche identifiziert (insgesamt 304). Nach der Deduplikation wurden 225 Zitate identifiziert.

Suche in 4 Datenbanken; insgesamt 304 Treffer; 225 Treffer nach Deduplizierung

Drei klinische Studienregister (ClinicalTrials.gov; World Health Organisation International Clinical Trials Registry Portal [WHO-ICTRP]; EU Clinical Trials) wurden am 28. Januar 2020 nach laufenden oder unveröffentlichten Studien durchsucht. Die Suche ergab 20 potenzielle Treffer von denen 0 als relevant eingestuft wurden. Der Hersteller des gängigsten Produkts (Sonata®, Gynesonics, Inc.) wurde kontaktiert und stellte 23 Publikationen zur Verfügung, wobei keine neuen Publikationen identifiziert werden konnten. Die Studienauswahl, Datenextraktion und Qualitätsbewertung wurde von zwei AutorInnen (RL, CS) durchgeführt.

Suche in CTRs nach laufenden Studien, 20 Treffer (0 relevant); keine neuen Studien durch den Hersteller

Klinische Wirksamkeit

Endpunkte für Empfehlung hinsichtlich der Wirksamkeit

Zur Ableitung einer Empfehlung zur Wirksamkeit von TFA wurden folgende Endpunkte herangezogen: die Verringerung des Schweregrads der Symptome, die Verringerung der Menstruationsblutungen, die Anzahl der chirurgischen Reinterventionen, die Verringerung des Myomvolumens, die Verbesserung der Lebensqualität, die Zufriedenheit der Patientinnen und die Fertilität nach dem Eingriff.

Sicherheit

Endpunkte für Empfehlung hinsichtlich der Sicherheit

Die Endpunkte für die Ableitung einer Empfehlung zur Sicherheit von TFA umfassten schwerwiegende bzw. wesentliche unerwünschte Ereignisse (SAE) und alle unerwünschten Ereignisse bzw. Nebenwirkungen (AE).

Ergebnisse

Verfügbare Evidenz

keine vergleichenden Studien; 3 ein-armige Studien (FAST-EU-, IDE- und OPEN-Trial), in 7 Publikationen (234 Pts.)

Im Rahmen der Suchstrategie wurden keine vergleichenden Studien identifiziert, und daher besteht die Evidenzbasis zur Bewertung der TFA aus prospektiven einarmigen Studien. Insgesamt wurden drei einarmige Studien (FAST-EU-, IDE- und OPEN-Trial), die in sieben Publikationen [2-8] veröffentlicht wurden und über drei Kohorten (234 Patienten) berichteten, identifiziert.

alle 3 Studien wurden gesponsert

Alle drei oben beschriebenen Studien wurden durch den Hersteller Gynesonics, Inc. finanziert. Die Follow-Up-Zeiten der Patientinnen beliefen sich auf maximal 12 Monate (FAST-EU-Studie, IDE-Trial) und 6 Wochen (OPEN-Trial). In jeder der Studien wurde über das Loss-to-Follow-Up berichtet. In der FAST-EU-Studie beendeten zwei Patientinnen nach 12 Monaten die Studie und zwei Patientinnen gingen zur Nachbeobachtung verloren (OPEN-Trial). Vier Patientinnen verpassten den 12-monatigen Besuch oder schieden vor dem 12-monatigen Besuch aus (IDE-Trial).

min./max. FU 6 Wochen bis 12 Monate Loss-to-FU 2 bis 4 Pts.

Klinische Wirksamkeit

Reduktion der Blutungen nach 12 Monaten: 53,8 % (FAST-EU) und 51,1 % (IDE); 64 % Pts. nach 12 Monaten: >50 %-ige Reduktion der Blutungen

Zwei Studien berichteten über den Endpunkt Reduktion der Menstruationsblutungen. Es kam im Vergleich zu den Ausgangswerten vor der Behandlung durch die Intervention zu einer statistisch signifikanten Verringerung nach drei Monaten, die auch nach 12 Monaten noch beobachtet werden konnte. Die durchschnittliche Verringerung der Blutungswerte nach 12 Monaten betrug 53,8 % in der FAST-EU-Studie [3] und 51,1 % in der IDE-Studie [2]. In beiden Studien erreichten 64 % der Patientinnen nach 12 Monaten eine mindestens 50 %-ige Reduktion der Blutungen gegenüber dem Ausgangswert.

Verbesserung der Symptome nach 12 Monaten: UFS-QOL SSS, 35,3 (FAST-EU) und 32,1 (IDE) Punkte

Zwei Studien berichteten über die Veränderung im Schweregrad der Symptome. Es wurden statistisch signifikante Verbesserungen nach drei und 12 Monaten beobachtet. Die durchschnittliche Verbesserung der Symptome wurden anhand des validierten UFS-QOL-SSS-Fragebogens (Uterine Fibroid Symptom and Quality of Life Symptom Severity Score) erhoben und betrugen nach 12 Monaten 35,3 (FAST-EU [3]) bzw. 32,1 Punkte (IDE [2]).

Zwei Studien berichteten die gesundheitsbezogene Lebensqualität: Es wurde nach 12 Monaten ein mittlerer Anstieg des Scores von 45,7 bzw. 43,7 Punkten in der FAST-EU [3] und IDE [2] Studie dokumentiert. Hierbei wurde der Fragebogen zu den uterinen Fibroid-Symptomen und der gesundheitsbezogenen Lebensqualität (UFS-QOL HRQOL) herangezogen. Auch bei der Messung mit dem EQ-5D-3L hat sich der Nutzen hinsichtlich der Gesundheit für die gesamte Kohorte nach 12 Monaten im Vergleich zum Ausgangswert statistisch signifikant verbessert. Eine Studie berichtete über die Patientinnenzufriedenheit, wobei 70,4% der Patientinnen sehr zufrieden waren [2].

Verbesserung der HRQOL nach 12 Monaten: UFS-QOL, 45,7 (FAST-EU) und 43,7 (IDE) Punkte

Zwei Studien berichteten über die Reinterventionsrate. Sie bewegte sich in einer Bandbreite von <1 % [8] (über 6 Wochen Nachbeobachtung) bis 11,8 % [6] (nach 5 Jahren Nachbeobachtung). Bei einer Patientin wurde über eine Schwangerschaft berichtet, die zu einer Geburt mit Kaiserschnitt führte.

Reinterventionsrate im Bereich <1 % bis 11,8 %; 1 Schwangerschaft wurde dokumentiert

In beiden Studien, die über die Reinterventionsrate berichteten, wurde auch eine Verringerung des Myomvolumens berichtet, wobei die durchschnittliche prozentuale Verringerung des Volumens nach 12 Monaten in dem FAST-EU- bzw. IDE-Trial 67,4 % bzw. 63,9 % betrug. Die durchschnittliche prozentuale Verringerung des Gesamtvolumens der Myome nach 12 Monaten betrug 66,6% (FAST-EU-Trial) bzw. 62,4% (IDE-Trial).

fibroide Volumenreduktion nach 12 Monaten: 67,4 % (FAST-EU) und 63,9 % (IDE)

Die Dauerhaftigkeit der Verbesserungen über 12 Monate hinaus ist unbekannt.

Dauerhaftigkeit der Verbesserungen (>12 Monate): nicht unbekannt

Sicherheit

Die schweren unerwünschten Ereignisse (SAE), die nach einer TFA dokumentiert wurden, waren ein Fall von tiefer Venenthrombose (TVT), ein Fall von gleichzeitiger Leukorrhoe, Beckenschmerzen und unbestätigtem niedriggradigem Fieber sowie ein Fall von unspezifischen Bauchschmerzen.

SAEs: TVT (1 Fall), Leukorrhoe, Beckenschmerzen und Fieber (1 Fall), Bauchschmerzen (1 Fall)

Hinsichtlich anderer unerwünschten Ereignissen (AE) traten bei den Patientinnen eine Reihe von Ereignissen auf, wobei in der größten Studie bis zu 50 % der Patientinnen irgendeine Art von unerwünschtem Ereignis erlebten [2]. Die Rate aller spezifischen unerwünschten Ereignisse war gering (sie trat typischerweise bei weniger als 10 % der Patientinnen auf).

Über die langfristige Sicherheit von TFA (über 12 Monate hinaus) wurde in keiner prospektiven Studie berichtet.

keine Evidenz zur langfristigen Sicherheit (>12 Monate)

Laufende Studien

Es wurden keine laufenden relevanten randomisierten kontrollierten Studien (RCTs) zur Bewertung der Sicherheit oder Wirksamkeit von TFA identifiziert.

es wurden keine laufenden relevanten Studien identifiziert

Kostenerstattung

TFA wird in Österreich derzeit nicht für die Behandlung von symptomatischen Gebärmuttermyomen erstattet.

bisher keine Kostenerstattung in AT

Diskussion

Risk of Bias (RoB): 3 Publikationen mit mittlerem Risiko, 4 Publikationen mit hohem Biasrisiko

Von den eingeschlossenen sieben Publikationen wurden drei mit einem mittleren Biasrisiko [2-4] und vier mit einem hohen Biasrisiko [5-8] bewertet. Die Evidenzstärke (Qualität der Evidenz) für die Wirksamkeit und Sicherheit wurde für alle relevanten Endpunkte als niedrig oder sehr niedrig eingestuft. Zum einen war dies auf die inhärenten Einschränkungen von einarmigen Studien zurückzuführen, d. h. auf das Versäumnis, Kointerventionen/ Störfaktoren zu beschreiben, und zum anderen auf die Verwendung von unverblindeten, von Patientinnen berichteten Endpunkten.

Evidenzstärke (Qualität der Evidenz) ist sehr niedrig bis niedrig

Obwohl die Stärke der Evidenz niedrig bis sehr niedrig war, berichteten die Studien durchwegs über eine Verbesserung der Symptome und eine Verringerung der Menstruationsblutungen nach der Intervention. Frauen mit symptomatischen Uterusmyomen haben jedoch derzeit Zugang zu uteruserhaltenden Alternativen oder Hysterektomie, die ebenfalls die Symptome und die Menstruationsblutungen reduzieren.

Vergleichende Ergebnisse zur Wirksamkeit und Sicherheit der intrauterinen ultraschallgesteuerten transzervikalen Radiofrequenzablation (TFA) bei symptomatischen Myomen zu anderen optionalen Interventionen liegen nicht vor.

Empfehlung

Aufnahme in den Leistungskatalog wird derzeit nicht empfohlen

Die derzeitige Evidenz reicht nicht aus, um zu zeigen, dass die intrauterine ultraschallgesteuerte transzervikale Radiofrequenzablation (TFA) wirksamer und ebenso sicher oder genauso wirksam ist, aber sicherer als optionale uteruserhaltende Interventionen bei symptomatischen Myomen. Daher wird die Aufnahme in den Leistungskatalog derzeit nicht empfohlen.

1 Scope

1.1 PICO question

In patients with symptomatic uterine leiomyoma, is intrauterine ultrasound-guided transcervical radiofrequency ablation more effective and safe than alternative uterine-preserving interventions, concerning reduction in leiomyoma volume, menstrual blood loss, quality of life, need for surgical reintervention, fertility outcomes or adverse events?

PIKO-Frage

1.2 Inclusion criteria

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

Einschlusskriterien für relevante Studien

Table 1-1: Inclusion criteria

Population	Women with symptomatic uterine leiomyomas International classification of diseases (ICD)-10-CM code: D25 Leiomyoma of uterus **Contraindications/exclusions:** Active pelvic infection; cervical dysplasia; endometrial hyperplasia; uterine malignancy. **MeSH Terms:** Leiomyoma [C04.557.450.590.450], Myoma [C04.557.450.590.540] **Rationale:** Recent international guidelines on the place in therapy of transcervical radiofrequency ablation of leiomyomas is not available.Therefore, the population has been defined based on the inclusion criteria for patients treated in clinical trials [3-8, 14].
Intervention	Intrauterine ultrasound-guided transcervical radiofrequency ablation of uterine leiomyoma **Product names**: Sonata®, VizAblate® (previous version of the Sonata® system) **MeSH Term:** Radiofrequency Ablation [E02.808.750], Ultrasonography [E01.370.350.850] The radiofrequency ablation device the Acessa™ was excluded as it requires laparoscopic ultrasound guidance
Control	**Uterine-preserving interventions** for uterine leiomyoma including, but not limited to: myomectomy, uterine artery embolization (UAE), uterine artery occlusion (UAO), magnetic resonance-guided focused ultrasound (MRgFU), and radiofrequency volumentric thermal ablation (RFVTA) **Rationale:** Hysterectomy is a definitive procedure for relief of symptoms and prevention of recurrent leiomyoma-related problems [15]; however, many women would prefer a less invasive treatment and/or wish to preserve their uterus. Comparators to the intervention are presumed to include all alternative uterine-preserving options.
Outcomes	

Efficacy	Clinical endpoints include:
	*Clincial endpoints (**Crucial**):*
	• **Reduction in menstrual blood loss** (pre vs post procedure), measured by but not limited to:
	  ◦ Menorrhagia Impact Questionnaire (MIQ)
	  ◦ Menstrual pictogram (MP) scores
	  ◦ Pictorial blood loss assessment chart (PBAC)
	  ◦ Self report (e.g. symptom free, better, worse)
	  ◦ Quantitative measures
	• Improvement in **quality of life** measures (surrogate measure of pelvic pain and/or bulk related symptoms) including but not limited to the Uterine Fibroid Symptom-Quality of Life (UFS-QOL) questionnaire including the Symptom Severity Score (SSS) subscale
	• **Rates of surgical reintervention** (measure of treatment failure) at any time point

Efficacy *(continuation)*	*Surrogate endpoints (**Important**):*
	• **Reduction in leiomyoma volume**
	• **Recurrence** of uterine leiomyoma at any time point
	• **Fertility outcomes** following the procedure
	  ◦ Pregnancy
	  ◦ Outcome of pregnancy (live birth, miscarriage, complications)
	Rationale: Appropriate clinical outcomes have been informed by clinical studies using the Sonata® device [3, 5, 14] as well as a systematic review protocol addressing interventions for uterine leiomyoma [16].

Safety	• **All adverse events** reported, including but not limited to:
	  ◦ Mortality
	  ◦ Abnormal uterine bleeding
	  ◦ Pain
	  ◦ Urinary tract infection
	  ◦ Other infection
	  ◦ Re-admission
	Rationale: Appropriate clinical outcomes have been informed by clinical studies using the Sonata® device [3, 5, 14] and the EUnetHTA guidelines [17].

Study design	
Efficacy	• Systematic reviews and meta-analyses • Randomised controlled trials • Prospective non-randomised controlled trials • In the absence of comparative evidence, prospective case series with ≥ 10 participants will be included **Excluded:** conference abstracts, narrative reviews, letter to the editor, author response, case reports.
Safety	• Systematic reviews and meta-analyses • Randomised controlled trials • Prospective non-randomised controlled trials • Prospective case-series with ≥ 10 participants **Excluded**: conference abstracts, narrative reviews, letter to the editor, author response, case reports, retrospective case series.

Abbreviations: ***ICD****– International Statistical Classification of Diseases;* ***MIQ****– Menorrhagia Impact Questionnaire;* ***MP****– Menstrual pictogram;* ***MRgFU****– Magnetic resonance-guided focused ultrasound;* ***PBAC****– Pictorial Blood Loss Assessment Chart;* RFVTA *– Radiofrequency volumetric thermal ablation;* ***SSS****– Symptom Severity Score;* ***UAE****– Uterine artery embolization;* ***UAO****– Uterine artery occlusion;* ***UFS-QOL****– Uterine Fibroid Symptom-Quality of Life;* ***VAS****– Visual analogue scale.*

2 Methods

2.1 Research questions

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

Health problem and Current Use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is intrauterine ultrasound-guided transcervical radiofrequency ablation used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition 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 the technologies utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0005	How does intrauterine ultrasound-guided transcervical radiofrequency ablation affect symptoms and outcomes of the disease or health condition?
D0006	How does intrauterine ultrasound-guided transcervical radiofrequency ablation affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of intrauterine ultrasound-guided transcervical radiofrequency ablation on fertility?

Clinical Effectiveness	
Element ID	**Research question**
D0012	What is the effect of intrauterine ultrasound-guided transcervical radiofrequency ablation on generic health-related quality of life?
D0013	What is the effect of intrauterine ultrasound-guided transcervical radiofrequency ablation on disease-specific quality of life?
D0017	Was the use of intrauterine ultrasound-guided transcervical radiofrequency ablation worthwhile?

Safety	
Element ID	**Research question**
C0008	How safe is intrauterine ultrasound-guided transcervical radiofrequency ablation in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying intrauterine ultrasound-guided transcervical radiofrequency ablation?
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 intrauterine ultrasound-guided transcervical radiofrequency ablation?
C0007	Are intrauterine ultrasound-guided transcervical radiofrequency ablation and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of intrauterine ultrasound-guided transcervical radiofrequency ablation and the comparator?

2.2 Sources

verschiedene Quellen herangezogen:

A range of sources were used to identify relevant literature to answer the research questions relating to the description of the technology, health problem and current use, including:

Description of the technology

systematische Suche, Handsuche sowie Informationen des einreichenden Krankenhauses und des Herstellers

- Handsearch in the Planned and Ongoing Projects (POP), Adopting Hospital Based Health Technology Assessment (AdHopHTA) and Centre for Reviews and Dissemination (CRD) databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturers
- Questionnaire completed by the submitting hospitals

Health problem and Current Use

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

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 4th to 6th of December 2019 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (Database of Abstracts of Reviews of Effects [DARE], National Health Service Economic Evaluation Database [NHS-EED], HTA)

The systematic search was not limited by publication year or to study design. Only articles published in English or German were eligible for inclusion. The specific search strategy employed can be found in the Appendix.

Suche nach laufenden Studien in 3 klinischen Studienregistern und Nachfrage beim Hersteller

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; World Health Organisation International Clinical Trials Registry Portal [WHO-ICTRP]; EU Clinical Trials) was conducted on the 28th of January 2020. Searches of the clinical trial registries identified 20 potential relevant hits. However, no relevant ongoing randomised controlled trials (RCTs) evaluating the safety or effectiveness of TFA were identified. The manufacturer from the most common product (Sonata®, Gynesonics, Inc.) was contacted. They submitted 23 publications and no new citations were identified.

2.4 Flow chart of study selection

Literaturauswahl

The search results were screened by two independent researchers (RL, CS), and in case of disagreement a third researcher was involved to resolve the differences. The selection process is displayed in Figure 2-1.

insgesamt wurden 304 Publikationen identifiziert

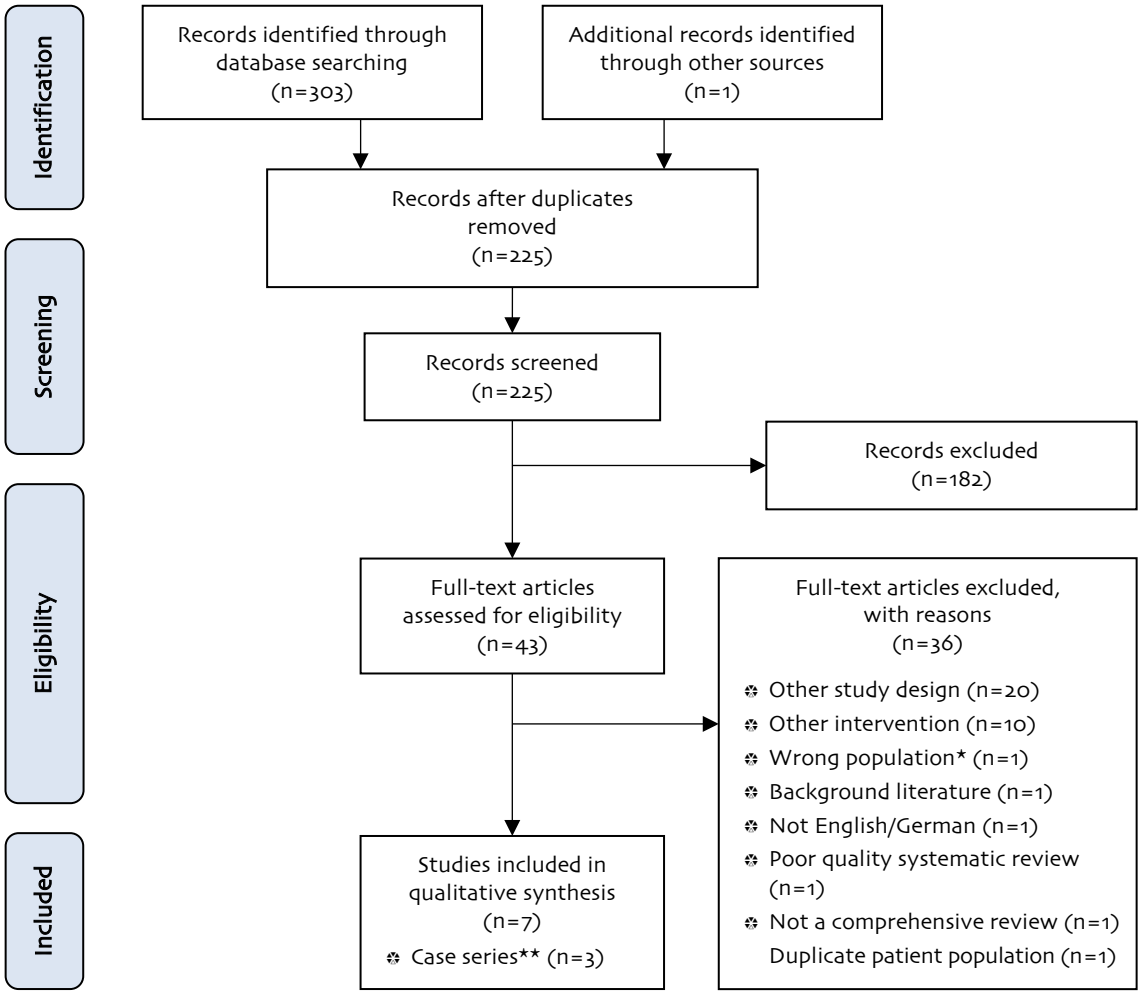
Overall, 303 citations were identified from the database searches and one publication was identified through handsearching (overall 304). After removing duplications, 225 citations were identified.

rezente systematische Übersichtsarbeit wurde ausgeschlossen wegen methodischen Mängeln

One recent systematic review [18] that aimed to assess the clinical performance of radiofrequency ablation of uterine fibroids was identified. This review included literature on transcervical radiofrequency ablation (TFA) but was excluded from this report because the efficacy analysis had significant methodological flaws (i.e., pooling across different study designs) and safety outcomes were not reported.

7 Publikationen mit 3 distinkten Kohorten wurden eingeschlossen

A total of seven publications reporting on three case series studies were identified for inclusion. Multiple studies reporting on the same patient cohort were included only if they contributed new information.



** This study was identified by handsearching; ** Published in 7 Publications*

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

2.5 Analysis

Datenextraktion und Validierung

Relevant data from the included studies were systematically extracted into data extraction tables by one reviewer (RL) (See Appendix Table A-1) based on study design and research question. The extracted data tables were validated for accuracy by a second reviewer (CS). Due to the paucity of available evidence and limited study designs, the safety and effectiveness results are reported narratively.

Bewertung des Bias-Risikos gemäß IHE-Checkliste

Two independent researchers (RL, CS) conducted quality appraisal, including risk of bias assessment, with differences settled via consensus. Quality appraisal was conducted using the Institute of Health Economics (IHE) checklist for single arm studies [19].

2.6 Synthesis

Evidenzsynthese mittels GRADE

The research questions based on the EUnetHTA Core Model® for Rapid Assessment of Relative Effectiveness were answered in plain text format with reference to GRADE (Grading of Recommendations Assessment, Development and Evaluation) evidence tables that are included in the Appendix [20]. The GRADE results are summarised in Table 7-1. No quantitative synthesis for any outcome could be performed due to the limitations of the primary evidence.

wesentliche Endpunkte zur Entscheidungsfindung wurden in Tabellen dargestellt

The outcomes included in the GRADE summary of findings table (Table 7-1) include the outcomes designated as crucial for decision-making, and represent outcomes that are most relevant to patients and decision makers. Several of these outcomes were reported at 3, 6 and 12-month time points. For ease of interpretation, only 12-month outcomes are included in the GRADE tables. This was chosen as the most informative time point as 3-month outcomes do not inform an assessment of effect durability and 6-month outcomes were inconsistently reported.

The 3 and 6-month results (if available) are presented in Table A-1 and are discussed narratively in the results section. The rating (quality) associated with the 12-month results represented in the GRADE tables is directly applicable to the 3 and 6-month results for the respective outcomes.

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What is intrauterine ultrasound-guided transcervical radiofrequency ablation and the comparator(s)?

Intrauterine ultrasound-guided transcervical radiofrequency ablation

TFA mittels Radiofrequenz: uteruserhaltende Methode zur Behandlung von Uterusmyomen

Intrauterine ultrasound-guided transcervical radiofrequency ablation, referred to hereafter as transcervical fibroid ablation (TFA) is a method of delivering radiofrequency (RF) energy to uterine leiomyomas, also called myomas or fibroids[1], to cause coagulative necrosis of the tissue. The technology aims to reduce symptoms through reductions in fibroid volume without requiring surgical incisions. This intervention allows women to retain their uterus.

Sonata®-TFA-System umfasst ein Handgerät mit einer Ultraschallsonde

There is one marketed TFA device, the Sonata® Sonography-Guided Transcervical Fibroid Ablation System (Gynesonics, Inc.). This device was previously marketed as the VizAblate® System. The system is comprised of a single-use RFA handpiece attached to a reusable intrauterine ultrasound probe. The ultrasound probe provides imaging that can be used for guidance during the procedure and for diagnostic purposes (Figure 3-1). The system also includes software which is used for targeting and planning of ablation zones [4]. The system delivers up to 150 W of RF energy for a duration of 2-7 minutes as dictated by the required ablation size. The probe is capable of producing an ablation zone of 4.0 cm x 5.0 cm [4]. Multiple ablations per leiomyoma may be required.

Figure 3-1: Sonata® device: handpiece and console (images supplied by Gynesonics, Inc.)

Comparators

Behandlungsoption ist abhängig von mehreren Faktoren

There are many treatment options for symptomatic uterine leiomyoma that include pharmacological, ablative and minimally invasive therapies, and surgical therapies. The choice of treatment is guided by patient preference, reproductive intentions and history, symptom burden, and the number, size and location of leiomyoma [21].

[1] Note that the terms leiomyoma, myoma and fibroid are used interchangeably within this report.

(uteruserhaltende) Interventionen bei einem symptomatischen Uterusmyom:

The definitive treatment for uterine leiomyoma is hysterectomy. TFA of leiomyoma is intended to provide a uterine-preserving alternative to hysterectomy for women who wish to preserve their uterus. Other interventions which aim to remove or reduce the volume of leiomyomas, whilst preserving the uterus, include:

Myomektomie

- *Myomectomy:* surgical removal of leiomyomas and can be performed via an open, laparoscopic, hysteroscopic or vaginal approach. Robot assisted myomectomy has also been described [21].

Uterusmyom embolisation (UAE)

- *Uterine artery embolisation (UAE):* occlusion of vessels supplying fibroids using microspheres or polyvinyl alcohol particles. The procedure is percutaneous with access via the femoral artery [22].

Verschluss der Gebärmutterarterie (UAO)

- *Uterine artery occlusion (UAO or L [laparoscopic] UAO):* a laparoscopic surgical procedure in which the uterine arteries are occluded using surgical techniques (e.g., ligation, coagulation etc.) [22].

Magnetresonanz-gesteuerter fokussierter Ultraschall (MRgFUS) Ultraschall-gesteuerter fokussierter Ultraschall (USgFUS/USgHIFU)

- *Magnetic resonance-guided focused ultrasound (MRgFUS):* the non-invasive use of ultrasound energy to cause thermal destruction of tissue. Patients undergo the procedure in a magnetic resonance imaging (MRI) machine, with ultrasound delivered via an external transducer [23].
- *Ultrasound-guided high intensity focused ultrasound ablation (USgFUS/USgHIFU)*: the non-invasive use of ultrasound energy to cause thermal destruction of tissue under ultrasound guidance [24].

laparoskopische volumetrische Thermoablation mit Radiofrequenz (laparoskopische RFVTA)

- *Radiofrequency volumetric thermal ablation (Lap-RFA or RFVTA):* radiofrequency ablation of fibroids under ultrasound guidance performed using a laparoscopic approach [21].

A0020 – For which indications has transcervical radiofrequency ablation received marketing authorisation or CE marking?

Sonata®-TFA-System durch FDA zugelassen (2018) und CE-Zertifizierung (2019)

The Sonata® Sonography-Guided Transcervical Fibroid Ablation System was developed to provide a uterus-conserving, transcervical (i.e., incisionless) treatment for International Federation of Gynecology and Obstetrics (FIGO) uterine myoma types 1,2, 3, 4, 5, 6 and 2–5 [8]. Types 1 and 2 refer to myomas located in the lining of the uterine cavity whilst type 3,4 and 5 refer to myomas located within the uterine wall [25]. The system is CE Marked [8] since February 2019 and was approved (FDA cleared) by the Food and Drug Administration (FDA) in 2018 for "diagnostic intrauterine imaging and transcervical treatment of symptomatic uterine fibroids, including those associated with heavy menstrual bleeding" [13].

B0002 – What is the claimed benefit of transcervical radiofrequency ablation in relation to the comparators?

TFA ist als weitere minimalinvasive und inzisionsfreie Therapiemöglichkeit bei gleichzeitigem Erhalt des Uterus und reduzierter Komplikationsrate beabsichtigt

TFA is purported to reduce leiomyoma volume and associated symptoms in women with uterine leiomyoma whilst avoiding or delaying hysterectomy [18]. Compared to other volume-reducing interventions, with the exception of hysteroscopic myomectomy, MRgFUS, and USgFUS/USgHIFU the technology may be considered less invasive as it requires no incisions. Consequently the technology may be associated with a reduced rate of complications (specifically infection, seroma, haematoma, adhesions) relative to open or laparoscopic interventions [3]. Further, it has been claimed that the procedure requires a smaller volume of hypotonic fluid (used for acoustic coupling) and lower intrauterine pressures than hysteroscopic procedures, and may therefore have a reduced risk of fluid intravasion and consequent fluid overload [3].

B0003 – What is the phase of development and implementation of transcervical radiofrequency ablation and the comparators?

Radiofrequency ablation of uterine leiomyoma was first reported in the literature in 2002; however, the combined ultrasound and RFA probe that avoids the need for laparoscopic ultrasound was first reported in 2011 [26]. This study reported on 19 patients who were treated with the VizAblate® device (now called Sonata®) prior to planned hysterectomy. In 2014 the FDA approved an investigational device exemption (IDE) for the SONATA® trial, the results of which informed FDA clearance of the Sonata® system in 2018 [13].

von ultraschallgeführter Radiofrequenzablation ohne laparoskopischen Ultraschall wurde erstmals 2011 berichtet

The rates of hysterectomy for benign conditions in Austria fell by 27% between 2002 and 2014 [27]; which may be in part attributable to the increased availability of uterine-preserving interventions for benign gynaecological conditions, including fibroids. However, it is understood that TFA is less established than other uterine-preserving options including myomectomy, MRgFUS, RFVTA and UAE. The Radiological Gynecological Expert Meeting, which brings together experts from Germany, Switzerland and Austria, has produced position statements on UAE [28] and MRgFUS [23], but to date no position on TFA has been identified. The 2014 European Menopause and Andropause Society (EMAS) position statement on the management of uterine fibroids stated that further studies on the technology were needed [29].

Hysterektomieraten gingen in Österreich zwischen 2002 und 2014 um 27 % aufgrund mehrerer Behandlungsoptionen zurück

TFA ist in Österreich weniger etabliert

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

B0004 – Who administers transcervical radiofrequency ablation and the comparators and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use transcervical radiofrequency ablation and the comparators?

B0009 – What supplies are needed to use transcervical radiofrequency ablation and the comparators?

According to the submitting hospital, intrauterine ultrasound-guided TFA is meant to be conducted in either an inpatient setting or on a day-care basis (Tagesklinik). The planned length of stay in an inpatient setting is typically one day, up to a maximum of two days. The personnel requirements for the intervention comprise of one gynaecologist, one anaesthetist, and two theatre nurses.

in AT: stationäre oder tagesklinische Intervention, geplanter Aufenthalt: 1 Tag

In the peer reviewed literature TFA is described as an outpatient procedure performed by a gynaecologist (or obstetrician-gynaecologist) under either general anaesthesia, conscious sedation or regional anaesthesia provided by an anaesthetist [2]. The literature suggests that the procedure may be safely performed by physicians who have completed training with the system. The training program is reported to include simulation [2].

TFA may be performed in a range of settings. The pivotal trial (i.e., the IDE trial) investigating the technology enrolled 147 patients, of whom 59% were treated in hospital-based operating rooms, 25% in an ambulatory care centre and 15% in procedure rooms of the physician's office [2]. The choice of anaesthesia is individualised, and in the IDE trial included 50% general anaesthesia and 50% conscious sedation [2]. Most patients who undergo TFA will be discharged within three hours of the start of the procedure. The mean length of stay associated with TFA, including procedure time, is 2.5 hours [2].

Literatur: TFA wird als ambulante Intervention durch eine/n Gynäkologin/en unter Allgemeinnarkose, moderaten Sedierung/ Analgetikum oder lokalen Anästhesie durchgeführt

Komponenten des TFA-Systems und weitere Ausstattung

The Sonata® system is comprised of an RF generator, an ultrasound system with guidance software, and a treatment device (i.e., an RFA handpiece combined with an ultrasound probe). The RFA handpiece is single-use and therefore a new handpiece is required for each procedure [2, 3]. Other equipment used to deliver the intervention include surgical supplies common to most healthcare facilities.

Voraussetzungen der Komparatoren sind unterschiedlich

Typically, other uterine-preserving interventions are also considered to be outpatient procedures; however, the specific premises and anaesthesia requirements for them vary according to each intervention. Further, some interventions require special imaging or personnel with specific skills. Key features of the comparators are described in Table 3-1.

Table 3-1: Requirements associated with comparators to TFA [21, 24, 30-33]

	MRgFUS	USgFUS/ USgHIFU	UAE	UAO	RFVTA	Myomectomy
Incisions	No	No	Yes	Yes	Yes	Yes *Hysteroscopic (No)*
Anaesthesia	S/GA	S/GA	S/GA	GA	GA	GA
Laparoscopic surgery	No	No	No	Yes	Yes	Yes
Interventional radiology	Yes	Yes	Yes	No	No	No
Special imaging	MRI	NA	X-ray fluoroscopy	NA	NA	NA
Special supplies	Contrast Specialised ultrasound	Specialised ultrasound	Contrast Embolic agent	Surgical (electrocautery or ligation)	Surgical RFA device	Surgical supplies

Abbreviations: ***GA*** *– general anaesthesia;* ***HIFU*** *– high intensity focused ultrasound;* ***MRI*** *– Magnetic resonance imaging;* ***MRgFUS*** *– Magnetic resonance-guided focused ultrasound;* ***RFA*** *– radiofrequency ablation;* ***RFVTA*** *– Radiofrequency volumetric thermal ablation;* ***S*** *– sedation;* ***UAE*** *– Uterine artery embolization;* ***UAO*** *– Uterine artery occlusion.*

Regulatory & reimbursement status

A0021 – What is the reimbursement status of transcervical radiofrequency ablation?

TFA ist in Österreich nicht erstattungsfähig

Currently, TFA is not included in the Austrian hospital benefit catalogue, and therefore is not reimbursed by the Austrian healthcare system. The device has been cleared by the FDA and is CE marked.

4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is transcervical radiofrequency ablation used?

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

TFA wird eingesetzt, um das Volumen des uterinen Myoms zu reduzieren mit dem Ziel, die damit verbundenen Symptome zu lindern

TFA is used to reduce the volume of uterine leiomyoma with the aim of alleviating associated symptoms, such as heavy menstrual bleeding. The scope of this assessment includes women with symptomatic uterine leiomyoma(s). Uterine leiomyomas (fibroids or myomas) are benign tumours of the uterus. They are derived from smooth muscle cells and may be single or multiple. They are classified according to the FIGO system with eligible types being 1,2, 3, 4, 5, 6 and 2–5 [8]. The FIGO classification system was published and devised by the International Federation of Gynecology and Obstetrics (FIGO). It classifies fibroids by describing the relationship of fibroids to the serosal and mucosal uterine [34]. The Types 1 and 2 refer to myomas located in the lining of the uterine cavity (submucous) whilst type 3,4 and 5 refer to myomas located within the uterine wall [25]. Type 2-5 ("hybrid" type) refer to myomas located in the middle muscle layer, or myometrium (submucosal) and outside of the uterus (subserosal), each with less than half the diameter in the endometrial and peritoneal cavities. Table 4-1 describes the classification system.

TFA wird zur Behandlung von bis zu 10 transmuralen Myomata (FIGO-Klassifikation 0, 1, 2, 3, 4 und 2-5) eingesetzt

The appropriate treatment for leiomyomas depends on the location, size and the number present. TFA is used to treat women with up to ten transmural leiomyomas (FIGO classification 1, 2, 3, 4 and 2- 5), with diameters between 1.0 and 5.0 cm. According to trial investigators type 0 leiomyomas can be treated with TFA [2]; however, this type of leiomyoma can be treated with operative hysteroscopy with resection of the fibroid. Figure 4-1 depicts the type of fibroids treatable by TFA.

The treatment of uterine malignancy and/or suspected malignancy are beyond the scope of this assessment.

Table 4-1: Classification of uterine fibroids [35]

FIGO type		Description
Submucosal	0	Pedunculated intracavitary
	1	>50% intramural
	2	≥50% intramural
Other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Other (parasitic, cervical etc.)
Hybrid leiomyomas	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

Note: When there are two numbers (e.g. 2–5), the first describes the relationship with the endometrium and the second number the relationship with the serosa.

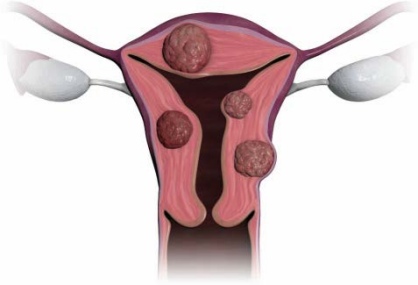


Figure 4-1: Treatable fibroid types (image supplied by Gynesonics Inc.)

A0003 – What are the known risk factors for uterine leiomyoma?

mögliche Risikofaktoren ein Uterusmyom zu entwickeln:

Nulliparität, Ethnizität, Übergewicht, Diabetes mellitus, Bluthochdruck etc.

Uterine fibroids affect a large proportion of women with onset after puberty and increasing incidence rates until the age of 50. Fibroids occur during reproductive years and are often less symptomatic after menopause. Risk factors for development of fibroids include [29, 36]:

- *Nulliparity:* the risk of leiomyoma decreases with the number of term pregnancies, thought to be related to changes in hormones, growth factors, oestrogen receptor levels, and uterine tissue.
- *Early age at first menstruation:* thought to increase risk by increasing the exposure to ovarian steroids.
- *Ethnicity:* leiomyomas are most common in African American women and least common in women of Asian descent; the reason for this is unclear.
- *Older age at first term pregnancy:* increasing age at first term pregnancy is associated with increased risk for leiomyoma; the reason for this is unclear.
- *Obesity and diabetes mellitus:* studies have documented an increased risk of leiomyoma and diabetes mellitus; the relationship between obesity and leiomyoma risk is reported to be inconsistent.
- *Hypertension:* high blood pressure is commonly cited as a risk factor for leiomyoma; however, the causative pathway is unknown.
- *Family history:* twin studies have documented a genetic component to myoma risk.

epidemiologische Daten oft widersprüchlich; klare Identifizierung der Risikofaktoren ist schwierig

A range of risk factors for leiomyoma are cited in the peer reviewed literature; however, epidemiological data is often conflicting and the high prevalence of leiomyoma in women of reproductive age makes identifying contributing factors challenging [36]. Literature on the effect of contraceptive pills and devices is inconclusive, as is literature investigating the effects of dietary factors [36].

A0004 – What is the natural course of uterine leiomyomas?

rezente Literatur: Verlauf des Myoms durch Wachstum und Regression charakterisiert

Historically it was thought that leiomyomas exhibit a linear pattern of growth, appearing after puberty and ceasing at menopause. However, more recent literature reports that the natural course of leiomyoma can include growth and regression, with growth rates varying between 8% and 120% per annum [37]. The factors influencing growth and regression are poorly understood.

individueller Krankheitsverlauf ist schwer vorhersehbar

During pregnancy fibroids are reported to increase rapidly in size in the first half with eventual stabilisation; however, some literature reports that fibroids may remain stable or regress during pregnancy. Consequently, the individual course of disease is difficult to predict [37].

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

A0005 – What is the burden of disease for patients with uterine leiomyomas?

uterine Fibroide können in 50 % der Fälle symptomatisch sein

Fibroids are reported to be symptomatic in 15-30% of women [10], and symptoms are thought to be related to endometrial and vascular dysfunction, and increased bulk. Symptoms include, but are not limited to [29]:

- Heavy menstrual bleeding
- Painful menstruation
- Abdominal discomfort or bloating
- Back ache
- Painful defecation
- Painful sexual intercourse
- Pelvic pressure

Symptome können das körperliche und emotionale Wohlbefinden stark beeinträchtigen

The symptoms most commonly reported as severe or very severe amongst women with fibroids are: menstrual pain, heavy or prolonged bleeding, passing clots during menstruation, fatigue, and abdominal discomfort [38]. Symptoms can impair ability to work, engage in physical and social activities, and impact on a woman's physical and emotional wellbeing [11].

Myome können die Fruchtbarkeit beeinträchtigen oder Komplikationen in der Schwangerschaft hervorrufen

Depending on size and location, fibroids can also impact fertility or cause complications in pregnancy [29]. Uterine leiomyomas, especially FIGO type 0,1 and 2 may contribute to difficulties falling pregnant naturally or through assisted reproductive technologies. Further, women with leiomyomas may have a higher rate of complications during pregnancy, including spontaneous abortion, preterm delivery, and need for caesarean delivery [39].

durchschnittlicher Symptombeginn: 29,7 Jahre

Survey data suggests that the average age of symptom onset is 29.7 years (standard deviation 9.6 years) and that many women initially attempt to self-manage symptoms and/or wait to see if symptoms resolve spontaneously [11]. Most women ultimately diagnosed with fibroids report seeking treatment, and the vast majority have tried at least pharmacologic therapy [11].

A0006 – What are the consequences of uterine leiomyomas for the society?

genaue Schätzungen zu den sozialen Kosten von Uterusmyomen sind schwierig

It is difficult to estimate the societal cost of uterine leiomyoma because of its high prevalence, and individual variation in disease severity and course. Limited available data suggests that the societal consequences of uterine leiomyoma include lost productivity, complications with fertility and pregnancy and, the costs of treatment [39, 40]. One study examining costs associated with uterine fibroids in the United States estimated that the impact of lost productivity may be the largest contributor to the societal cost (in financial terms). This study considered the annual economic burden of uterine fibroids to be substantial at 34.4 billion dollars (2010 USD) [39].

Produktivitätsverlust
Infertilität
Krankenhausaufenthalte

Current clinical management of the disease or health condition

A0024 – How is uterine leiomyoma currently diagnosed according to published guidelines and in practice?

Diagnose umfasst klinische Anamnese, klinische Untersuchung des Beckens und Ultraschall des Beckens

Women with fibroids may present with symptoms prompting investigation or may have fibroids diagnosed as an incidental finding on pelvic ultrasound or other imaging studies. For women presenting with symptoms, diagnosis involves clinical history, pelvic examination and pelvic ultrasound. MRI may also be used in the diagnosis and work-up of a patient with uterine leiomyoma as indicated following pelvic ultrasound [25]. In some rare situations hysteroscopy may be used in diagnosis.

spezifische Überlegungen in der Anamnese sind umfangreich

Specific considerations in patient history suspicious for fibroids include abnormal bleeding and pain related to menstruation, pressure related symptoms (dyspareunia, urinary retention, frequency, hydronephrosis, tenesmus), infertility, miscarriage, obstetric complications, and pelvic pain. Physical examination includes an abdominal and pelvic exam [25].

transvaginaler Ultraschall wird typischerweise bei allen Frauen mit Verdacht auf ein Myom durchgeführt

Transvaginal ultrasound is typically performed in all women with suspected fibroids; it provides information about the location, number and size of tumours. However, submucosal fibroids may be missed on a routine transvaginal ultrasound. Additional ultrasound investigations may include saline infusion sonography that can aid in detection of submucosal fibroids and protrusions into the endometrial cavity [25].

MRT kann für die Behandlungsplanung und zur Unterscheidung von anderen Erkrankungen verwendet werden

Hysteroscopy allows visualisation of the endometrial cavity and may serve diagnostic and therapeutic purposes. If there is any suspicion of malignant disease additional investigations such as MRI and laboratory testing may be required [25]. Further, MRI may be used for treatment planning and to distinguish between leiomyoma and other conditions (e.g., adenomyosis). Biopsy specimens and/or pathology is not necessary for diagnosis and management of uterine leiomyoma [25].

A0025 – How are uterine leiomyomas currently managed according to published guidelines and in practice?

asymptomatische Myome erfordern keine spezielle Behandlung

Asymptomatic fibroids require no specific treatment. For women who do experience symptoms, treatment is highly individualised and may comprise a range of therapies including medical and surgical interventions. Treatment decisions will be influenced by a range of factors including: severity of symptoms, fibroid size and location, age, desire to preserve fertility and/or the uterus, the availability of therapy, and the experience of the treating physician [1, 21, 29].

eine medikamentöse Behandlung von Myomen umfasst ein breites Spektrum von nichtchirurgischen Strategien

Medical management of fibroids includes a wide range of strategies, many of which aim to control heavy menstrual bleeding or bulk related symptoms. Options include: oral contraceptives, intrauterine contraceptive devices, gonadotropin-releasing hormone analogues; gonadotropin-releasing hormone antagonists; selective progesterone receptor modulators; selective oestrogen receptor modulators; aromatase inhibitors; and, androgens [1, 21, 29]. Medical therapy can provide relief of symptoms and may be used as a primary management strategy or to delay surgical intervention [1, 21, 29].

Surgical management of fibroids is varied with hysterectomy representing an efficacious, definitive, treatment [1, 41]. Hysterectomy is currently the prevailing surgical treatment for fibroids; approximately 40% of all hysterectomies are performed for benign indications attributable to leiomyomas [27]. For women who wish to retain their uterus or seek to maintain reproductive capabilities other options are available.

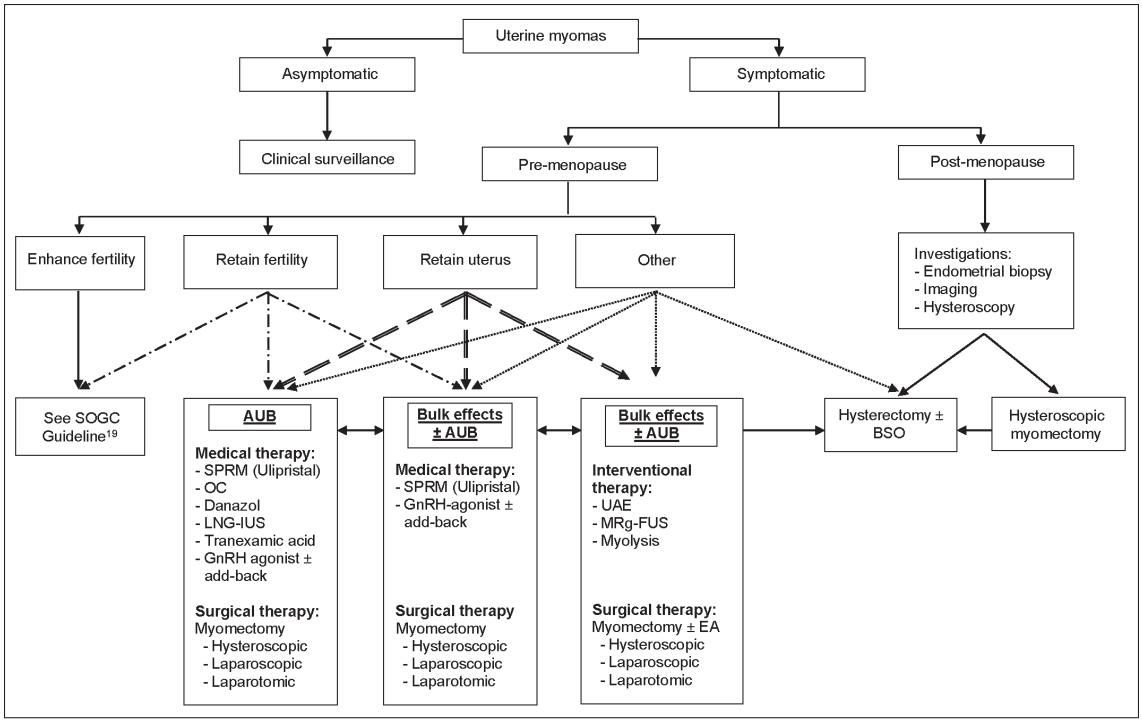
Hysterektomie ist derzeit die vorherrschende chirurg. Behandlung von Myomen

Other interventions which may be performed as an alternative to, or prior to, hysterectomy include: myomectomy; endometrial ablation; ablation procedures with thermal, radiofrequency (RFVTA) or cryoablation; UAO; UAE; USgFUS/USgHIFU and, MRgFU. Of these, UAE, myomectomy, UAO, RFVTA and MRgFU have been shown to reduce symptoms and improve quality of life from baseline [41]. However, there is limited high quality literature available to inform decisions regarding comparative effectiveness of these less invasive surgical options [41]. Further the availability of these alternatives varies according to jurisdiction and treatment choices are ultimately highly individualised.

wenig qualitativ hochwertige Literatur, um Entscheidungen über die vergleichende Wirksamkeit weniger invasiven chirurgischen Optionen zu treffen

Guidelines from the Society of Obstetricians and Gynaecologists of Canada (SOGC) provide a management algorithm, which is reproduced below [1].

Steuerungsalgorithmus zur Myombehandlung



BSO: bilateral salpingo-oophorectomy; MRg-FUS: Magnetic resonance-guided focused ultrasound; OC: oral contraceptives

Figure 4-2: Management of uterine leiomyoma [1]

Target population

A0007 – What is the target population in this assessment?

A0023 – How many people belong to the target population?

A0011 – How much is transcervical radiofrequency ablation utilised?

Zielpopulation des Assessments: Frauen, > 18 Jahre mit symptomatischem uterinen Leiomyom(en), die ihre Gebärmutter erhalten möchten

The target population for this assessment is women at least 18 years of age with symptomatic uterine leiomyoma who wish to preserve their uterus. Accurate estimation of the number of women in the target population is difficult because prevalence estimates in the peer reviewed literature have a wide range (4.5% to 68.6%) [9]. This range is influenced by study methodology, screened population and method of ascertaining diagnosis. Many estimates in the available literature are based on self-reporting of symptoms and/or diagnosis and may therefore be unreliable.

geschätzte Prävalenz: 14,2% (DE); symptomatisch >18 Jahre

One study that reported on symptomatic women with diagnosed uterine fibroids and undiagnosed bleeding symptoms in European countries reported the prevalence of a diagnosis of uterine leiomyoma in women aged 18 or over of 11.7% to 23.6% [42]. The prevalence of diagnosed uterine leiomyoma in Austria was not reported; however, in Germany it was 14.2% [42].

prozentuelle Verteilung der verschiedenen Behandlungsarten in verschiedenen Ländern

This study also reported on the treatment of women with a diagnosis of uterine fibroids in these European countries. Treatment patterns varied according to jurisdiction and are summarised in Table 4-2. In Germany the most common surgical treatment was hysterectomy (28.7% of all procedures). Uterine-preserving procedures that are considered to be comparators to the intervention (i.e., focused ultrasound surgery, hysteroscopic surgery, myolysis; myomectomy; uterine artery/fibroid embolisation) were also reported although only myomectomy comprised >10% of procedures reported (10.2%) [42]. It should be noted that this study included a total of 2,002 women; however, only a small proportion of these symptomatic women had a diagnosis of uterine fibroids (n=108 to 176 with a diagnosis depending on the country). Due to the small sample size in each country, the reported proportions should be interpreted cautiously.

Spitalsaufenthalte in AT aufgrund eines Myoms: 5.112 Fälle im Jahr 2018, 537 wurden tagesklinisch behandelt

stationär: durchschnittlicher Aufenthalt Ø 4,4 Tage

According to inpatient data from Austrian hospitals the hospital stays of women diagnosed with leiomyoma of the uterus (D25) amounted to 5,112 stays in total in 2018 [12]. Of this number 537 (10.5%) were treated on a day-care basis (Tagesklinik). For the age group 15 to 44 years, hospital stays amounted to 2,035 cases, for the age group 45 to 64, the number was 2,914 and for the age group 65+, 163 cases were reported. The average length of stay was 4.4 days [12]. The number of all uterine-preserving procedures performed for leiomyoma in Austria is not known. According to the submitting hospital, the intervention was carried out 12 times in the year 2018. The submitting hospital expects an annual frequency of 50 procedures and 450 procedures in total at the Austrian level.

Table 4-2: Treatment reported by women with a diagnosis of uterine leiomyoma [42]

Treatment option	Percentage of women by country
No treatment	France: 41.2% Germany: 24.1% Italy: 40.3% Spain: 57.4% United Kingdom: 31.9%
Surgery alone	France: 6.6% Germany: 13.9% Italy: 19.3% Spain: 7.4% United Kingdom: 5.3%
Medication alone	France: 10.3% Germany: 8.3% Italy: 9.7% Spain: 8.6% United Kingdom: 7.1%
Surgery and medication	France: 41.9% Germany: 53.7% Italy: 30.9% Spain: 26.5% United Kingdom: 55.8%

5 Clinical effectiveness

5.1 Outcomes

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

- Reduction in symptom severity
- Reduction in menstrual bleeding
- Surgical reintervention

3 wesentliche Endpunkte, um eine Empfehlung abzuleiten

The outcomes defined as *crucial* to derive a recommendation are considered to be the most relevant to patients. They reflect the key clinical claims that TFA can improve symptoms and reduce rates of surgical intervention.

Improvement in symptoms is a therapeutic goal of TFA. Improvement in/ reduction of symptom burden in women with uterine fibroids is most often assessed using the condition specific Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QOL). Specifically, the 8-item symptom severity scale (SSS)[2] and the 29 item Health-Related Quality of Life (HRQL) domains. Items are scored on a 5-point Likert scale with items ranging from "not at all" to "a great deal" for symptom severity, and "none of the time" to "all of the time" for the HRQL items [43]. The UFS-QOL is a validated questionnaire commonly used in evaluation of treatments of uterine fibroids [43, 44].

Verbesserung der Symptome/Reduktion des Schweregrads:

UFS-QoL-SSS und UFS-QoL-HRQL

Validated minimum clinically important differences for the UFS-QOL and the SSS and HRQL subscales have not been reported in the literature; however:

- Based on expert opinion a difference of ≥ five points represents a clinically meaningful change in UFS-QOL score [45].
- Authors of the FAST-EU trial, one of the initial studies using TFA, defined a 10-point reduction in SSS score as clinically significant [3].
- Literature comparing MRgFUS to hysterectomy defined a 10-point reduction in SSS score as clinically significant [46].

Menstrual bleeding is a common symptom of uterine fibroids and a prominent motivation for seeking treatment. Measures of bleeding used in the evaluation of TFA include the pictorial blood loss assessment chart (PBAC) and the menstrual pictogram (MP). Both have been validated against quantitative reference standards [47]. The PBAC is a semi-quantitative method for evaluating blood loss. Women estimate menstrual blood loss in terms of degrees of saturation of specific sanitary products represented by a specific icon. This is performed for each day of menstruation and is used to generate a score [48]. A score of >100 to 150 is typically considered to define heavy menstrual bleeding [48, 49]. The MP is a modification of the PBAC which includes more products and greater detail.

Menstruationsblutung:

PBAC-Score und MP-Score

[2] A 10-point reduction in SSS was considered clinically significant by authors of the FAST-EU trial [7].

Validated minimum clinically important differences for these scoring systems have not been reported in the literature. However:

- Authors of one large study of TFA considered success with respect to menstrual bleeding to be: ≥50% reduction in PBAC score with the score being <250 at 12 months post-procedure [2].
- The authors of the FAST-EU trial considered a 22% or greater reduction in menstrual blood loss to be clinically meaningful [3]. This was based on a study which used the alkaline haematin method to establish a meaningful improvement of 36 mL/cycle or approximately 22% [50].

chirurgische Reintervention(en)

Surgical reintervention was designated as a crucial outcome because it reflects treatment failure. TFA is intended to avoid the need for more invasive treatments for fibroids and therefore the need for further intervention constitutes treatment failure. Treatment failure may occur with incomplete fibroid ablation, insufficient relief from symptoms and/or worsening, and, fibroid recurrence or growth, or the growth of new fibroids. The rate of reintervention following uterine-preserving interventions that would be considered acceptable is unclear. However, authors of the IDE trial considered success criteria to be met if ≥75% of patients were free from surgical reintervention at 12 months [2].

zusätzlich berücksichtigte wichtige Endpunkte

In addition to the crucial outcomes the following additional *important* outcomes were considered:

- Improvement in quality of life
- Patient satisfaction
- Reduction in fibroid volume
- Fertility following the procedure

Lebensqualität, Zufriedenheit der Patientinnen,

Quality of life and patient satisfaction are important to consider when evaluating the effectiveness of TFA, but they were not considered crucial outcomes as they follow as a consequence of achieving the primary treatment goals (reduced symptom severity and menstrual bleeding).

Reduktion des Fibroidvolumens,

Reduction in fibroid volume measures the direct effect of the procedure and is therefore an important outcome; however, because changes in fibroid volume are not easily correlated with symptom burden this outcome was not considered crucial.

Fertilität

Fertility outcomes were considered relevant to the evaluation as some women may seek uterine-preserving interventions as a means of preserving future fertility. However, the intervention is not intended to preserve fertility (desire for future fertility was an exclusion criterion in most studies) this was not considered a crucial outcome.

5.2 Included studies

eingeschlossene Studientypen

To evaluate the effectiveness and safety of TFA for symptomatic uterine leiomyoma, we considered RCTs and non-randomised studies comparing TFA to uterine-preserving interventions and single arm studies reporting on pre- versus post- procedure outcomes.

keine vergleichenden Studien identifiziert

3 Fallserien (6 Publikationen) wurden eingeschlossen

No comparative studies were identified by the search strategy and therefore the evidence base evaluating TFA comprises of single arm studies. A total of three single-arm case series studies published in seven publications were identified. Of the seven publications identified six contained data on effectiveness and were deemed for inclusion in the effectiveness analysis. All three single-arm studies were prospective, however, publications reporting on subsets of the initial cohort or providing information on data collected as part of a post-hoc protocol amendments may have collected some data retrospectively. Multiple publications reporting on the study population were included because they contributed new information about the patient cohort (Some outcomes reported were analysed retrospectively).

Study characteristics

FAST-EU-Trial: prospektive einarmige Studie, 50 Pts, in 7 Zentren

The FAST-EU trial was a prospective single arm study that enrolled 50 patients from seven sites across Mexico, the Netherlands and the United Kingdom. The primary endpoint was the percentage change in target fibroid perfused volume at three months. Success was defined as a reduction of >30% of mean target fibroid perfused volume in at least 50% of patients. Appropriate sample size was set at 48 patients[3]. Of 50 patients enrolled in the FAST-EU trial 12 month MP scores were available for 48 patients. Additional relevant outcomes collected included reductions in menstrual bleeding (MP score); improvement in symptoms (UFS-QOL SSS); improvements in quality of life (UFS-QOL HRQOL); health status (EQ-5D-3L); reintervention; patient satisfaction; and safety. Patients were followed for 12 months and the study protocol was amended after the study start to add an MRI evaluation at 12 months to provide longer-term information about TFA. This trial was the subject of five publications included in this report:

4 Publikationen zu FAST-EU mit unterschiedlichen Auswertungen

- Brolmann 2016 [3] is the primary reference for the FAST-EU trial providing data for the full patient cohort up to 12 months.
- Bongers 2015 [4] provides supplementary data up to six months concerning non-surgical reintervention for heavy menstrual bleeding as well as a per protocol analysis of selected outcomes reported by Brolmann 2016.
- Garza Leal 2019 [6] included for long term follow-up (>5 year) data on a subset of the trial population enrolled at the site in Mexico.
- Huirne 2018 [7] providing an additional measure of health status in the full trial population at 12 months post-procedure.

6 Monate FU
12 Monate FU
5 Jahre

OPEN-Trial: prospektive einarmige Studie, 37 Pts, in 6 Zentren

The OPEN trial was a prospective single arm study that enrolled 37 patients at six sites in Germany, the Netherlands, Switzerland and the United Kingdom [8]. Patients underwent a baseline hysteroscopy and were included if there was no evidence of adhesions. The primary outcome of the study was

[3] For a power of 82% using a one-group chi-square test with a 0.05 two-sided significance level and assuming a 20% drop-out rate.

to determine the incidence of newly formed adhesions at six weeks post-TFA. Other relevant outcomes included surgical reintervention rates and adverse events. There were no prespecified success criteria. This trial was reported on in one included publication.

IDE-Trial: prospektive einarmige Studie, 147 Pts, in 22 Zentren

The SONATA® Pivotal IDE trial (shortened to IDE trial) was a prospective single arm study that enrolled 147 patients at 22 sites in Mexico and the United States. The study had coprimary endpoints consisting of:

- Menstrual bleeding: "a 50% or greater reduction in pictorial blood loss assessment chart score that was also 250 or less with a 95% lower confidence limit in 45% or greater of patients (i.e., at least 45% of patients must have achieved both a pictorial blood loss assessment chart reduction of at least 50% and a score 250 or less)" [2].
- Reintervention: "the proportion of patients who did not require surgical reintervention for heavy menstrual bleeding with the 95% lower confidence limit of the percentage of patient success 75% or greater" [2].

The prespecified sample size was set at 147[4] and both primary endpoints had to be met for the trial success criteria to be fulfilled. Additional relevant outcomes collected included reductions in fibroid volume, patient satisfaction, and safety. Of 147 patients enrolled in the trial PBAC data at 12 months was available for 142 patients with data for seven patients imputed using the last observation carried forward (PBAC chart missing = 3, withdrawn before 12 months = 3, missed 12 months visit = 1).

alle 3 Studien: gesponsert von Gynesonics

FU: 6 Wochen bis 12 Monate

All three studies described above were sponsored by Gynesonics, Inc. Patients were followed up at 7–14 days, 30 days, 3 months, 6 months, and 12 months (FAST-EU Trial), 6 weeks (OPEN Trial) and 10 days, 30 days, 3 months, 6 months, and at 12 months (IDE Trial). Losses to follow-up were reported in each of the studies. In the FAST-EU Trial after 12 months two patients exited the study and two patients were lost-to follow up in the OPEN Trial. Four patients missed the 12 month visit or were withdrawn before the 12 month visit. Details are provided in Table A-1. The number of patients with data analysed varied according to the outcome and most analyses were per protocol analyses.

Patient characteristics

FAST-EU- und IDE-Trial hatten konsistente Auswahlkriterien hinsichtlich des Fibroidtyps; OPEN-Trial hatte keine speziellen Auswahlkriterien

The FAST-EU trial included women with uterine leiomyomas aged 28 years or older with a three-month history of heavy menstrual bleeding (MP score ≥120) and symptom severity score of at least 20 on the UFS-QOL SSS. The IDE trial included premenopausal women aged 25 to 50 years with a history of heavy menstrual bleeding (PBAC score ≥150 and ≤500). The OPEN trial included women who were at least 18 years of age who elected to undergo TFA for the treatment of symptomatic fibroids.

Across the included trials the eligibility criteria in terms of eligible fibroid types was consistent between the FAST-EU and the IDE trials (Table 5-1) as was the maximum fibroid diameter. However, the FAST-EU trial limited the number of fibroids to five whilst in the IDE trial women could have up to 10. In both trials women were required to have documented heavy menstrual bleeding as assessed by a validated scale but with consistent menstrual

[4] To achieve 90% power with a level equal to 0.05 and an assumed success rate of 60% with a drop-out rate of 15%.

cycles. In the IDE trial an upper limit for menstrual bleeding was specified. Criteria for symptom burden were also specified in the FAST-EU trial although not in the IDE or OPEN trial. The OPEN trial had non-specific eligibility criteria.

Baseline-Charakteristika in den Studien:

Alter, Score für Menstruationsblutung, Symptomstärke und Fibroidcharakteristika

Baseline demographic data provided by study authors included age, menstrual bleeding scores, symptom severity and details of fibroids. No information was provided about patient treatment history in terms of medical management which may be relevant to the assessment. Further, description of co-interventions such as use of the oral contraceptive pill or long acting progestins was only provided in the IDE trial. Detailed 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-6.

Table 5-1: Comparison of eligibility criteria across studies of TFA

Trial	Patient age Eligible fibroid types Number of fibroids	Menstrual bleeding Symptom severity
FAST-EU (n=50) Maximum follow-up: > 5 years (n=17)	✿ ≥28 years ✿ FIGO types 1,2,3,4 and 2-5 of maximum diameter 1-5 cm. At least 1 fibroid indenting the endometrial cavity ✿ 1-5 fibroids	MP score ≥ 120, regular predictable menstrual cycles and heavy menstrual bleeding of ≥3 months. UFS-QOL SSS ≥20
IDE (n=147) Maximum follow-up: 12 months	✿ Premenopausal women aged 25 to 50 ✿ FIGO types 1,2,3,4 and 2-5 of maximum diameter 1-5 cm. At least 1 fibroid indenting/ impinging on the endometrial cavity. ✿ 1-10 fibroids	PBAC score ≥ 150 and ≤500, consistent menstural cycles within normal limits None reported
OPEN (n=37) Maximum follow-up: 6 weeks	✿ ≥18 years ✿ FIGO types 1,2 or 2-5 ✿ ≥1 myoma	NR "symptomatic"

Abbreviations: ***FIGO*** *– Federation of Gynaecology and Obstetrics;* ***MP*** *– menstrual pictogram;* ***NR*** *– not reported;* ***PBAC*** *– pictorial blood loss assessment chart;* ***SD*** *– standard deviation;* ***TFA*** *– transcervical fibroid ablation;* ***UFS-QOL SSS*** *– Uterine Fibroid Symptom-Quality of Life Symptom Severity Score.*

5.3 Results

Morbidity

D0005 – How does transcervical radiofrequency ablation affect symptoms and outcomes of uterine leiomyoma?

3 wesentliche Endpunkte zur Bewertung der Morbidität

The *crucial* outcomes, reduction in menstrual bleeding and reduction in symptoms as well as the outcome reduction in fibroid volume were considered when answering this research question.

Reduction in menstrual bleeding

die Reduktion der Menstruationsblutung war in beiden Studien hinsichtlich des jeweiligen Endpunktes statistisch signifikant

Both the FAST-EU and the IDE trial reported a reduction in menstrual bleeding following TFA. With respect to the IDE trial the study met its menstrual bleeding endpoint with 64.8% of patients (95% Confidence Interval [CI] 56.3–72.6%) experiencing a 50% or greater reduction in menstrual bleeding (measured by the PBAC score) at 12 months. In the FAST-EU trial the proportion of women experiencing a >50% reduction in MP score was 57.1 %, 72.9 % and 64.6% at 3, 6 and 12 months respectively. The proportion of patients achieving >50 % bleeding reduction at 6 months was not significantly different from the proportion at 12 months (p=.095). Using the cut-off point of 22% as a clinically meaningful change, the proportions achieving this at 3, 6 and 12 months were 75.5%, 85.4% and 79.2%, respectively. However, this was not an a priori endpoint of the trial.

IDE-Trial: 64,8 % der Pts. erreichten eine PBAC-Score-Reduktion von ≥50 % bzw. die mittlere prozentuale Verringerung des Scores betrug 51,1 % (nach 12 Monaten)

The mean percentage reduction in menstrual bleeding score at 12 months (relative to baseline) was 51.1% (Standard Deviation [SD] 40.9%) in the IDE Trial.

FAST-EU-Trial: mittlere prozentuale Verringerung des MP-Scores betrug 53,8 % bzw. 64,6 % der Pts. erreichten eine MP-Score-Reduktion von ≥50 % (nach 12 Monaten im Vergleich zum Ausgangswert)

In the FAST-EU trial the mean reduction in menstrual bleeding (measured by the MP score) at 12 months (relative to baseline) was 53.8% (SD 50.5%). Reductions in menstrual bleeding as a mean percentage reduction from baseline were observed at 3, 6 and 12 months and were statistically significant at all time points in both trials (p<0.001). One publication [4] additionally reported a 6 months analysis of this outcome where patients who underwent subsequent procedures or medical reintervention had their data excluded from analysis (i.e., favouring the intervention). This data is provided in Table A-1 but is not discussed here as this data overestimates the treatment effect.

Tabelle gibt eine Übersicht über die Veränderungen der jeweiligen Scores

Table A-1 provides detailed results for this outcome (quantitative reduction in menstrual bleeding score and baseline score). Table 5-2 below provides an overview of the percentage reduction in mean menstrual bleeding score at 3, 6 and 12 months in both cohorts.

Table 5-2: Percentage reduction in menstrual bleeding scores at 3, 6 and 12 months post TFA[5]

Trial	3 months	6 months	12 months
FAST-EU			
mean± SD % reduction in MP score	45.2%±57.9%	51.9%±59.8%	53.8%±50.5%
n	n=49	n=48	n=48
p-value	p<0.001	p<0.001	p<0.001
IDE			
mean± SD % reduction in PBAC score	38.9%±39.1	48.4%±42.9%	51.1%±40.9%
n	n=117	n=142	n=142
p-value	p<0.001	p<0.001	p<0.001

Abbreviations: ***MP*** *– menstrual pictogram;* ***PBAC*** *– pictorial blood loss assessment chart;* ***SD*** *– standard deviation.*
Note: *the p-value relates to a comparison to baseline.*

Reduction in symptoms

Improvement in symptoms as measured by reduction in UFS-QOL SSS score was reported in the FAST-EU and the IDE trials. Neither trial included improvement in symptoms as a primary endpoint. However, change relative to baseline was assessed post-procedure. Both the FAST-EU and the IDE trial documented reductions in mean UFS-QOL SSS from baseline at 3, 6 and 12 months post-procedure that were statistically significant (p<0.001). Table 5-3 summarises the reported results.

In the FAST-EU trial the proportion of patients achieving at least a 10-point reduction in SSS was 82% at 3 months, 86% at 6 months and 78% at 12 months.

der FAST-EU- und auch der IDE-Trial dokumentierten eine statistisch signifikante Verringerung des mittleren UFS-QOL-SSS (Verbesserung) gegenüber dem Ausgangswert nach 3, 6 und 12 Monaten

Table 5-3: Improvement in symptoms (UFS-QOL SSS score) at 3, 6 and 12 months post TFA

Trial	3 months	6 months	12 months
FAST-EU			
mean± SD reduction in score	30.0±22.2	36.7±22.6[6]	35.3±26.9
mean±SD percent reduction in score	46.7%±32.8%	57.6%±31.4%	55.1%±41.0%
n	n=50	n=49	n=49
p-value	p<0.001	p<0.001	p<0.001
IDE			
mean± SD reduction in score	27.9±22.85	31.9±20.98	32.1±21.03
mean±SD percent reduction in score	NR	NR	NR
N	n=141	n=138	n=135
p-value	p<0.001	p<0.001	p<0.001

Abbreviations: ***NR*** *– Not reported;* ***SD*** *– standard deviation;*
UFS-QOL SSS *– Uterine Fibroid Symptom and Health-Related Quality of Life Symptom Severity Subscale.*
Note*: the p-value relates to a comparison to baseline.*

[5] Note that the mean change was a reduction at all time points. The minus sign has not been shown here.

[6] One publication additionally reported a 6 month analysis of this out-come where patients who underwent subsequent procedures or medical re-intervention had their data excluded from analysis (i.e. favouring the intervention). This data is provided in Table A 1 but is not discussed here as this data overestimates treatment effect.

eine Publikation zeigte eine stat. signifikante Verringerung des UFS-QOL-SSS-Scores (Verbesserung) in der langen Frist (FAST-EU)

Garza-Leal 2019 [6] reported long term follow-up of 17 (73.9%) out of 23 patients included at one study site in the FAST-EU trial. The mean follow-up was 64.4 months ±4.5 months (range: 57–73 months). The UFS-QOL SSS scores at long term follow-up were evaluated in this small sample and the authors reported a statistically significant reduction in mean score from baseline (p=0.002). The study reports that the mean SSS score at baseline in these 17 patients was 64.9 (SD 16.9) and that at last follow-up it had reduced to 27.6 (SD 36.1).

IDE-Trial: Pts. berichteten von einer Verbesserung (96,3%), keiner Veränderung (3,0%), Verschlechterung (0,7%) der Symptome

The IDE trial also reported on symptoms at 12 months using the Overall Treatment Effect Scale Questionnaire, which included data for 135 (91.8%) of 147 enrolled patients. Regarding symptoms, patients reported: improvement in symptoms (96.3%); no change in symptoms (3.0%) and worsening of symptoms (0.7%).

Reduction in fibroid volume

FAST-EU- und IDE-Trial: stat. signifikante Verringerung des Gesamtfibroid- und perfundierten Fibroidvolumens zu allen ausgewerteten Zeitpunkten

Reduction in fibroid volume was reported in the FAST-EU trial and the IDE trial; it was the primary endpoint in the FAST-EU trial. In both studies, a statistically significant reduction in both total fibroid volume and perfused fibroid volume were reported for all time points.

The FAST-EU trial met its primary endpoint with 79 (88.7%) of 89 treated fibroids demonstrating a reduction of more than 30% in mean target perfused volume at three months post-procedure. At three months the mean reduction in perfused fibroid volume for all target fibroids was 68.1% (SD 28.6%, p<0.001). The trial also reported 12 month reductions in fibroid volume in a subset (n=28) of patients who consented to an additional MRI at 12 months. The mean reduction in perfused fibroid volume for all target fibroids was 67.4% (SD 31.9%) which was a statistically significant (p<0.001) reduction relative to baseline.

mittlere prozentuale Reduktion des Gesamtvolumens betrug 66,6 % nach 12 Monaten

In terms of total fibroid volume, results reported in the FAST-EU were similar with mean percentage reduction in total fibroid volume at 3 months being 54.7% (SD 37.4%), and at 12 months (in 28 patients) being 66.6% (SD 32.1%). Both were reported to be statistically significant (p<0.001).

IDE-Trial: prozentuale Verringerung des perfundierten Myomvolumens nach 12 Monaten betrug 63,9 %, Gesamtvolumen 62,4 %

The IDE trial did not have fibroid volume as a primary endpoint; however, the mean percentage reduction in total and perfused fibroid volume at 12 months were reported. Results were available for 128 (87%) of 147 enrolled patients. The mean percentage reduction in perfused fibroid volume at 12 months was 63.9%, and for total fibroid volume it was 62.4%. No standard deviations were reported. The authors reported that both changes were statistically significant (p<0.001).

Table A-1 provides detailed results for this outcome.

Dooo6 – How does transcervical radiofrequency ablation affect progression (or recurrence) of uterine leiomyoma?

The *crucial* outcome surgical reintervention was considered when answering this research question.

alle eingeschlossenen Studien berichteten über chirurgische und medikamentöse Reinterventionsraten nach TFA

All included trials reported reintervention rates following TFA with absence of surgical reintervention considered a coprimary endpoint in the IDE trial. This trial considered the endpoint to have been met successfully if at least 75% of patients did not require reintervention within 12 months of the TFA procedure. The FAST-EU trial reported rates of reintervention across 12 months in the full trial cohort (n=50). The rate of reintervention in a smaller

group (n=17) of patients enrolled at a single site in Mexico with mean follow-up of 64.9 months was also reported. However, this was not a primary endpoint for the FAST-EU trial. The OPEN trial also reported rates of reintervention.

chirurgische Reinterventionsraten:
FAST-EU: 4 Pts. (8%)
IDE: 1 Pt. (<1%)
OPEN: 0 Pts.

In the FAST-EU trial four patients (8%) had surgical reintervention with one patient undergoing hysterectomy. In the smaller subset with longer term follow-up two additional hysterectomies were reported at 3.5 and 4 years post-procedure (2/17, 11.8%) were reported. In the IDE trial 1 patient (<1%) underwent reintervention during 12 months of follow-up. This patient underwent a hysterectomy. In the OPEN trial the rate of reintervention was nil; however, the six week follow-up period limits the usefulness of this data. Table A-1 provides detailed results for this outcome.

medikamentöse Reinterventionsraten (Tranexamsäure):

FAST-EU: 3 Pts. (6%)
IDE: war nicht erlaubt
OPEN: NA

Medical reintervention such as the use of tranexamic acid or other interventions following TFA were poorly reported by the FAST-EU trial. In the six month analysis of the FAST-EU the trial authors reported three patients (6%) requiring tranexamic acid for abnormal uterine bleeding and in the long-term follow-up subset the rate of non-surgical reintervention was reported as nil (0/17). The main publication associated with the FAST-EU trial did not report this data and it is unclear whether additional patients between the 6 and 12-month follow-up required and/or received non-surgical reinterventions. In the IDE trial, introduction of new medical treatment during the trial period was not permitted.

D0011 – What is the effect of transcervical radiofrequency ablation on patients' fertility?

gewünschte Fertilität war ein Ausschlusskriterium, jedoch hatte 1 Patientin nach einer TFA eine Schwangerschaft

The outcome impact on fertility was considered when answering this research question. Desire for future fertility was an exclusion criterion in the two key trials (FAST-EU and the IDE trial); however, in the FAST-EU trial authors reported that one patient (2%) experienced a pregnancy after undergoing TFA. The patient delivered a live term infant by caesarean section.

Health-related quality of life

D0012 – What is the effect of transcervical radiofrequency ablation on generic health-related quality of life?

EQ-5D-3L als generisches Messinstrument

Generic health related quality of life information was available in the form of the EQ-5D-3L tool. As there are validated, disease-specific tools for evaluating quality of life in patients with uterine leiomyoma, generic outcome measures were not the focus of the included studies.

FAST-EU-Trial:
Scores betrugen 0,838; 0,852 bzw. 0,914 nach 3, 6 und 12 Monaten (Ausgangswert: 0,745)

One publication concerning the FAST-EU trial was identified, which contained values from the EQ-5D-3L tool. The data from this tool was used in the study to report the change in health utility for the cohort over 12 months. At baseline the mean EQ-5D-3L score was 0.745 (median 0.811). The mean score at 3, 6 and 12 months was 0.838, 0.852 and 0.914, respectively. The authors concluded that at 12 months the cohort had a statistically significant improvement in health utility (p<0.001).

IDE-Trial: Score:
0,89 nach 12 Monaten (Ausgangswert: 0,72)

Reporting on generic health-related quality of life from the IDE trial was limited with authors reporting only that the mean cohort EQ-5D-3L score increased from 0.72 at baseline to 0.89 at 12 months (p<0.001, n=133 of 147 patients contributing to the analysis).

D0013 – What is the effect of transcervical radiofrequency ablation on disease-specific quality of life?

UFS-QOL HRQOL in FAST-EU- und IDE-Trial

The FAST-EU trial and the IDE trial reported disease specific quality of life using the disease-specific UFS-QOL HRQOL.

beide Studien berichteten über stat. signifikante Verbesserungen zu allen Zeitpunkten

Quality of life was not a primary endpoint in either trial, however, mean scores at 3, 6 and 12 months were compared to baseline. Both studies reported statistically significant improvements in UFS-QOL HRQOL scores at all time points.

The mean increase in score from baseline to 12 months was similar in both studies: 45.7 (SD 30.5, $p<0.001$) in the FAST-EU trial and 43.7 (SD 24.25, $p<0.001$) in the IDE trial. The mean percentage improvement in score was reported only in the FAST-EU trial and was 227% (SD 483%, $p<0.001$) at 12 months. Table A-1 provides detailed results for this outcome.

Patient satisfaction

D0017 – Was the use of transcervical radiofrequency ablation worthwhile?

IDE-Trial: 70,4 % sehr zufrieden, 17,8 % mäßig zufrieden, etc.

The IDE trial reported on patient satisfaction with TFA at 12 months via a questionnaire. The authors report that 70.4% were very satisfied; 17.8% were moderately satisfied; 8.9% were somewhat satisfied; 2.2% were somewhat dissatisfied; and, 0.7% were moderately dissatisfied.

6 Safety

6.1 Outcomes

wesentliche Endpunkte hinsichtlich der Sicherheit

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

- Major adverse events
- All adverse events

TFA ist eine neuartige Intervention → alle unerwünschten Ereignisse wurden für eine Bewertung herangezogen

TFA is a relatively novel treatment for uterine leiomyoma and has an unknown safety profile. Consequently, all data was considered crucial to derive a recommendation.

Additional specific investigations included for safety were reduction in uterine wall thickness and the incidence of adhesions. These events were specifically investigated in two publications:

weitere Endpunkte: Dicke der Uteruswand, neugebildete Adhäsionen

- The rationale for including an evaluation of uterine wall thickness is that uterine rupture during pregnancy, a rare but serious event, has been associated with other interventions in this class of procedure (operative hysteroscopy, myomectomy, UAEs). Reductions in uterine wall thickness of <2.0 to 2.3 mm are purported to indicate an increased risk of uterine rupture [5].
- Similarly, the incidence of new adhesions post-TFA was included in the safety analysis as other transcervical procedures (myomectomy, dilation and curette and endometrial ablation) have been associated with the formation of intrauterine adhesions [8].

6.2 Included Studies

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-6.

3 einarmige Studien (4 Publikationen) eingeschlossen

A total of three single-arm case series trials reported in four publications reporting on 3 unique cohorts (234 patients in total) were identified for inclusion in the safety analysis. Multiple studies reporting on the same patient cohort were included only if they contributed new information about the patient cohort. All studies were single arm studies and describe the same trial cohorts as included for effectiveness. The details of the studies can be found under included studies in section 5.2, the only study not discussed there was a publication concerning the FAST-EU. This study provided information on uterine wall integrity in a subset of the trial population who underwent an elective 12 month MRI in the FAST-EU trial (as per the protocol amendment) [5].

FAST-EU-Trial: eine eigenständige Publikation berichtete über die Unversehrtheit der Uteruswand

6.3 Results

Patient safety

C0008 – How safe is transcervical radiofrequency ablation in comparison to the comparators?

3 einarmige Studien: keine vergleichenden Daten bezüglich der Sicherheit

The crucial outcomes of all adverse events and major adverse events were considered to answer this research question. As only single arm studies were identified no data for comparative safety is available.

Major adverse events

schwerwiegende unerwünschte Ereignisse (SUE):

Adverse events were not reported in a consistent manner across the included studies and therefore are reported separately for each study.

In the largest identified series (the IDE trial, n=147) the authors reported two major adverse events (1.4%) including [2]:

IDE-Trial: 2 SUE, 1 Pt. mit einer tiefen Venenthrombose (TVT) und 1 Pt. mit einer Leukorrhoe, Unterleibsschmerzen und unbestätigtem niedrigem Fieber

- One case of deep vein thrombosis (DVT) at 15 days post-procedure
- One case of a patient who presented with leukorrhea, pelvic pain and unconfirmed low grade fever 28 days post-procedure

The patient with a DVT was managed as an outpatient reportedly without further complication, and the second patient was admitted overnight and managed with broad-spectrum antibiotics. The study publication reports that the event was deemed related to leiomyoma sloughing and leukorrhea with no evidence of infection.

OPEN-Trial: 1 SUE, unspezifische Bauchschmerzen ohne Interventionsbezug

In a small series with six weeks of follow-up (the OPEN trial) one major adverse event (2.7%) was reported in which a patient was admitted to hospital at 18 days post-procedure complaining of non-specific abdominal pain. Imaging studies were normal and the authors considered the event unrelated to the device or procedure [8].

FAST-EU-Trial: keine Unterscheidung zwischen SUE und allen AEs

The FAST-EU trial [3] reported adverse events but did not distinguish between major and minor adverse events. Consequently, all events are considered under all adverse events.

All adverse events

IDE-Trial: verschiedenartige (minderschwere) AEs

In the largest identified series (the IDE trial) adverse events not detailed above were present in 50.3% of patients and included leiomyoma sloughing (30.6%); cramping/pain (7.5%); leukorrhea (6.1%); uncomplicated genitourinary infections (4.8%); nonspecific symptoms (3.4%); expelled leiomyoma (1.4%); flu-like symptoms (1.4%); and, nausea/vomiting (0.7%) [2]. All events were considered minor and were reported as percentages only instead of fractions.

FAST-EU-Trial: 34 AEs gesamt

In the FAST-EU trial adverse events were present in 68% of the study population (in 34 of the 50 enrolled patients) [3]. The events were: dysmenorrhea in 7 patients (14%); abnormal uterine bleeding above baseline in 6 (12%); pelvic pain/cramping in 4 (8%); UTI within 30 days in 2 (4%); fibroid expulsion in 1 (2%); hospital admission in 1(2%); and, bradycardia in 1 (2%).

In addition to the overall rate of adverse events, two publications were identified reporting on specific issues related to procedural safety. Bongers 2019 reported on a subset of women included in the FAST-EU trial who underwent a 12 month MRI and investigated uterine wall patency [8]. This publication reported that all patients evaluated (n=29/29) had a minimum uterine wall thickness > 3.0 mm on their 12 month MRI i.e., no patient met the prespecified criteria for uterine wall thinning or compromise. Bongers 2019b reported that no patients with an evaluable hysteroscopy video at six weeks post-TFA showed evidence of new adhesions [5]. Of the 37 patients enrolled in this trial 34 had an evaluable video.

2 Publikation zum FAST-EU-Trial berichteten zu prozeduralen AEs:

Dicke der Gebärmutterwand und neue Adhäsionen

C0002 – Are there harms related to dosage or frequency of applying transcervical radiofrequency ablation?

No data was identified to answer this research question. No study evaluating the repeatability of TFA for uterine leiomyoma was identified. Further, no investigation regarding the relationship between the length of ablation procedure, number of fibroids ablated, or other variable and safety outcomes was reported in the included studies.

keine Evidenz bzw. offene AE Fragen zu Dauer der Ablation, Anzahl der entfernten Myome etc.

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

No data was identified to answer this research question. All the included studies enrolled patients at multiple sites, used a range of anaesthesia options and performed the procedure in different settings. A breakdown of adverse events as they relate to these variables was not available.

keine Evidenz bzw. offene AE Fragen zu Setting, Anästhesie, Subpopulationen etc.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of transcervical radiofrequency ablation?

No data was identified to answer this research question. The largest cohort of patients treated with TFA was 147 patients and no subgroup analyses of safety outcomes was performed in any publication.

C0007 – Are transcervical radiofrequency ablation associated with user-dependent harms?

No data was identified to answer this research question.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of transcervical radiofrequency ablation and the comparators?

Adverse events associated with TFA beyond 12 months are currently unknown. The available literature reports on a small sample size (total of 234), whereas the eligible population of women with symptomatic fibroids is very large. Long-term follow-up studies including large patient cohorts would be desirable in this setting. Further, the comparative safety of TFA relative to other uterine-preserving interventions for uterine leiomyoma is unknown.

AEs im Zusammenhang mit TFA nach 12 Monaten sind derzeit unbekannt

7 Quality of evidence

RoB bewertet mittels IHE-Checkliste

The risk of bias for individual studies was assessed using the Institute of Health Economics (IHE) checklist for single arm studies. Results of the quality appraisal are presented in Table A-2 in the appendix.

3 Publikationen weisen ein mittleres und 4 ein hohes Biasrisiko auf

Overall there were three single-arm case series studies reported in seven publications reporting on three unique patient cohorts. Of the included publications three were assessed as being at a medium risk of bias and four were assessed as being at a high risk of bias.

5 der eingeschlossenen Publikationen berichteten über alle oder eine Teilmenge der im FAST-EU-Trial teilnehmenden Patientinnen

die Hauptpublikation zum FAST-EU-Trial weist eine mittleres Biasrisiko auf

Five of the included publications reported on all, or a subset of, patients enrolled in the FAST-EU trial. The main 12 month results were presented by Brolmann 2016 [3], which was assessed as having a medium risk of bias. Six month outcomes from this study were reported by Bongers 2015 [4], which was also assessed as having a medium risk of bias. Key limitations identified with the FAST-EU trial included: uncertainty regarding consecutive patient recruitment, failure to describe co-interventions and how these were managed, post-hoc addition of a 12-month MRI, and, lack of blinding of the outcome assessors to the intervention. Three additional publications reporting on a subset of patients enrolled in this trial were assessed as being at a serious risk of bias owing to additional limitations, namely, failure to describe baseline characteristics of patients included in their subset and lack of a statistical analysis plan for analysis results.

der IDE-Trial hat ein mittleres Biasrisiko

The IDE trial was reported by Chudnoff 2019 [2], which was assessed as being at a medium risk of bias. Key limitations contributing to this assessment were: uncertainty regarding consecutive patient recruitment and lack of blinding of the outcome assessors to the intervention.

der OPEN-Trial weist ein hohes Biasrisiko auf

The OPEN trial was reported by Bongers 2019b [8] and was assessed as being at a high risk of bias owing to: uncertainty regarding consecutive patient recruitment; failure to describe co-interventions and how these were managed; short duration of follow-up; partial reporting of safety data; and, lack of blinding of the outcome assessors to the intervention.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to the GRADE Schema [20] for each endpoint individually. Each study was rated by two independent researchers (RL, CS). In case of disagreement a third researcher (TV) was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [20].

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.

Evidenzstärke der jeweiligen wesentlichen Endpunkte ist sehr niedrig (4 Mal) bzw. einmal niedrig

The ranking according to the GRADE scheme for the selected crucial outcomes is as follows:

- The strength of the evidence for the effectiveness of TFA in reducing menstrual bleeding is very low.
- The strength of the evidence for the effectiveness of TFA in improving symptoms is very low.
- The strength of the evidence for the effectiveness of TFA in surgical reintervention is low.
- The strength of the evidence for the safety of TFA with respect to major adverse events is very low.
- The strength of the evidence for the safety of TFA with respect to all adverse events is very low.

For all other outcomes, the strength of the evidence for effectiveness and safety is very low. The summary of findings table below includes the crucial outcomes with all other outcomes summarised in the evidence profile in Appendix Table A-6.

Gesamtstärke der Evidenz für die Wirksamkeit und Sicherheit ist niedrig bis sehr niedrig

It should be noted that observational studies such as case series start with a rating of low in recognition of the inherent limitations and biases introduced by the observational study design. Consequently, further limitations regarding risk of bias, consistency of results, indirectness, imprecision or publication bias typically results in further downgrading of the strength of the evidence to very low. As the evidence base for TFA consists entirely of case series evidence, with significant limitations, the overall strength of evidence for the effectiveness and safety of TFA is low to very low.

Table 7-1: Summary of findings table of transcervical radiofrequency ablation

Outcome	Impact	Number of participants (studies)	Quality	Comments
	EFFECTIVENESS			
Reduction in menstrual bleeding **assessed with: MP or PBAC**	**Mean percentage reduction in menstrual bleeding score at 12 months, mean ± SD at 12 months** FAST-EU (n=49, MP score):-53.8%±50.5% IDE (n=142, PBAC score): -51.1%±40.9% *p<0.001 compared to baseline for both* **Mean reduction in menstrual bleeding score at 12 months, mean ± SD** FAST-EU (n=49, MP score): -243±296 IDE (n=142, PBAC score): -159.7±127.7 *p<0.001 compared to baseline for both*	197 (2 observational studies) [2, 3]	⨁◯◯◯ VERY LOW [a,b,c,d,e]	Reduction indicates improvement
Proportion of patients with ≥50% reduction in menstrual bleeding score **assessed with: MP or PBAC**	**Proportion of patients with ≥50% reduction in menstrual bleeding score at 12 months** FAST-EU: 31/48 (64.6%) IDE: 64.8% (95% CI 56.3–72.6%)	184 (2 observational studies) [2, 3]	⨁⨁◯◯ LOW [a,b,c]	Reduction indicates improvement
Improvement in symptom severity **assessed with: UFS-QOL-SSS**	**Mean percentage reduction in UFS-QOL SSS at 12 months, mean ± SD** FAST-EU (n=49): -55.1%±41.0% IDE (n=135): NR *p<0.001 when compared to baseline in both trials* **Mean reduction in UFS-QOL SSS at 12 months, mean ± SD** FAST-EU (n=49): -35.3±26.9 IDE (n=135): -32.1±21.03 *p<0.001 when compared to baseline in both trials* *The FAST-EU trial reported the proportion of patients with ≥10 point reduction in score was 82% at 3 months, 86% at 6 months and 78% at 12 months.*	197 (2 observational studies) [2, 3]	⨁◯◯◯ VERY LOW [a,c,e]	Reduction indicates improvement
Symptom improvement **assessed with: Overall Treatment Effect Scale**	**In the IDE trial at 12 months patients reported:** Improvement: 130/135 (96.3%) No change: 4/135 (3.0%) Worsening: 1/135 (0.7%)	147 (1 observational study) [2]	⨁◯◯◯ VERY LOW [a,i]	NA
Surgical reintervention rate **assessed with: Rates of surgical reintervention**	**FAST-EU**: 4/50 (8%) of patients underwent surgical reintervention within 12 months *In the long term follow-up of 17 patients enrolled in the FAST-EU trial (> 5 years) 2 patients (11.8%) underwent reintervention at 3.5 and 4 years post treatement.* **IDE:** 1/147 (<1%) of patients underwent surgical reintervention within 12 months **OPEN:** 0/37 (0%) at 6 weeks	234 (3 observational studies) [2, 3, 8]	⨁⨁◯◯ LOW [f,g,h]	NA

Outcome	Impact	Number of participants (studies)	Quality	Comments
	SAFETY			
Major adverse events **assessed with: Rate of major adverse events**	**IDE:** 2/147 (<1%) of patients experienced a serious adverse event comprising of: DVT: 1 (<1%) Leukorrhea, pelvic pain, and unconfirmed low-grade Fever: 1 (<1%) **OPEN** : 1/37 (3%) patient experienced a serious adverse event which was non-specific abdominal pain	184 (2 observational studies) [2, 8]	⨁◯◯◯ VERY LOW [h,j,k]	NA
Overall complications **assessed with: Rate of complications**	**FAST-EU:** 34 events in 50 patients over 12 months of follow-up. **IDE:** 74/147 (50%) experienced an adverse event considered to be non-serious 2/147 (<1%) of patients experienced a serious adverse event the nature of which is reported elsewhere **OPEN :** 1/37 (2%)	234 (3 observational studies) [2, 3, 8]	⨁◯◯◯ VERY LOW [c,j,l]	NA

Abbreviations: ***CI*** *– Confidence interval;* ***DVT*** *– Deep Vein Thrombosis;* ***MP*** *– Menstrual Pictogram;* ***NR*** *– Not reported;* ***PBAC*** *– Pictorial Blood Loss Assessment Chart;* ***SD*** *– Standard Deviation;* ***UFS-QOL-HRQL*** *– Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire;* ***UFS-QOL-SSS*** *– Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire Symptom Severity Scale;* ***UTI*** *– Urinary Tract Infection.*

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.*

Comments:

[a] *Self-reported outcome measures in patients not blinded to treatment status may introduce performance bias; missing data may represent patients who experienced treatment failure.*

[b] *Confounding factors such as the use of medical interventions (i.e. tranexamic acid) in at least three patients may bias in favour of the intervention (FAST-EU trial specific)*

[c] *Quality appraisal of both studies identified a medium risk of bias*

[d] *Reported ranges and standard deviations associated with measures are wide*

[e] *Standard deviations associated with the point estimate exceed clinically meaningful cut-off points*

[f] *Patient cohorts include small sample sizes that represent only a portion of initially enrolled subjects*

[g] *12 month follow-up may not be sufficient to capture treatment failure. Further, outcome assessors were not blinded introducing the possibility of bias – i.e assessors may have favoured avoiding or delaying reintervention during the study period*

[h] *Quality appraisal of the included studies revealed a medium risk of bias for 2 and a high risk of bias for 1*

[i] *Quality appraisal assessed this study as being at a medium risk of bias*

[j] *Reporting of complications was inconsistent across included studies.*

[k] *It is unclear whether 12 months is sufficient to capture all relevant adverse events*

[l] *Criteria for designating an event serious/non-serious were not provided*

8 Discussion

Uterine fibroids are benign tumours that affect many women in their reproductive years. Some women may continue to experience symptoms after menopause. Fibroids can cause significant symptoms including pain, heavy menstrual bleeding and pelvic pressure. They may also have impact on fertility and the risk of miscarriage [41]. Evidence demonstrates that uterine fibroids can significantly affect a woman's quality of life, leading them to seek treatment [11]. Definitive treatment in the form of hysterectomy is efficacious, but less invasive uterine-preserving interventions may be favoured by many women. TFA is a relatively novel procedure which has received market approval in the European Union (CE Mark) in 2019 and in the United States (FDA cleared) in 2018. This review sought to evaluate the safety and effectiveness of TFA compared to alternative uterine-preserving interventions for uterine fibroids.

Uterusfibrome sind gutartige Tumore, die viele Frauen in ihren reproduktionsfähigen Jahren betreffen

Lebensqualität einer Frau kann erheblich beeinträchtigt werden

weniger invasive, uteruserhaltende Eingriffe von vielen Frauen bevorzugt

Summary of evidence from prospective clinical studies

This systematic review included all primary literature available on TFA to treat women with symptomatic uterine fibroids which comprised of seven publications reporting on three unique patient cohorts. The available evidence comparing patients pre- and post-treatment indicates that TFA can reduce fibroid volume, reduce menstrual bleeding, improve symptoms and improve quality of life. Reintervention rates in the included studies were <10% at 12 months. A total of one pregnancy resulting in the delivery of a term infant by caesarean section was reported in a patient who had received TFA. The durability of improvements beyond 12 months is unknown. Although the overall volume of evidence was low, studies were consistent in terms of reporting an improvement following TFA. However, it has to be noted that the single arm study design and use of subjective outcomes is expected to result in overestimation of the treatment effect.

alle Studien (7) berichteten durchwegs über eine Verbesserung der Endpunkte, allerdings ist die Qualität der Evidenz sehr niedrig bis niedrig

Major adverse events reported after TFA in the included studies were one case of DVT, one case of leukorrhea, pelvic pain, and unconfirmed low-grade fever, and one case of non-specific abdominal pain. In terms of other adverse events patients experienced a range of adverse events with up to 50% of patients experiencing any kind of adverse event [2]. The long-term safety of TFA (beyond 12 months) has not been reported in any prospectively conducted studies.

SAEs:
TVT (1 Fall),
Leukorrhoe,
Beckenschmerzen und Fieber (1 Fall),
Bauchschmerzen (1 Fall)

Patients with uterine fibroids currently have access to a range of uterine-preserving interventions and TFA is proposed as an additional treatment in this class of therapies. However, single arm case series data is insufficient to establish the place of TFA in the treatment of uterine fibroids and therefore no conclusions regarding TFA relative to alternative treatments can be made.

es können keine vergleichenden Schlussfolgerungen bezüglich TFA gezogen werden

Limitations of the evidence

Study quality, validity and overall level of evidence

Evaluation der Wirksamkeit beschränkt sich nur auf Vorher-Nachher-Vergleiche

Daten hinsichtlich der Sicherheit werden nur narrativ berichtet

This systematic review identified 7 publications describing the results of 3 trials (FAST-EU, IDE and the OPEN trials) including a total of 234 patients treated with TFA. No comparative studies were identified by the search and therefore no conclusions regarding the safety or effectiveness of TFA as compared to other interventions for uterine fibroids can be made. Consequently, the evaluation of the effectiveness of TFA for the treatment of uterine fibroids is limited to a before and after comparison of fibroid volume, menstrual bleeding, symptom severity, and quality of life. Similarly, safety data is limited to narrative reporting of events that occurred in patients treated with TFA.

wesentliche Limitationen und Bias: keine Verblindungen aufgrund des Studiendesigns, semi-quantitative und subjektive Ergebnismessung, Performanzbias

A key limitation of the evidence base informing effectiveness of TFA was that study design did not allow for blinding of patients or outcome assessors to treatment status. Both menstrual bleeding scoring systems (MP and PBAC) are semi-quantitative and require patients to self-assess. Similarly, the symptom severity score (UFS-QOL-SSS) is a subjective measure of symptom severity. Knowledge of having received the intervention (TFA) may introduce performance bias. Further, in the IDE trial [2] freedom from surgical reintervention was a co-primary endpoint. However, the criterion for determining when and if reintervention should occur were not reported; it is unclear which factors may have impacted patients' decisions to seek reintervention within the trial period. It is possible that performance bias may have been introduced by investigators.[7]

weitere Limitationen in den Studien:

Ko-Interventionen bei der Interpretation der Ergebnisse wurden in einer Studie nicht beschrieben (FAST-EU)

An additional limitation that should be noted when interpreting the results of the FAST-EU trial was that co-interventions such as the introduction of medical management after TFA, or the continued use of prior treatments such as long acting progestins, were not described. Co-interventions, particularly medical interventions for abnormal bleeding such as tranexamic acid, represent confounding factors because they also influence symptoms and bleeding. Reinterventions also speak to the effectiveness of the intervention (i.e., may indicate treatment failure). From the six month report of the FAST-EU trial it is clear that at least three patients underwent medical intervention (tranexamic acid) during the follow-up period an these patients data were excluded from a per protocol analysis presented in the six month publication [4]. However, the 12 month report [3] does not provide this level of information and it is possible that additional patients received medical intervention after 6 months that were not reported. This limitation does not apply to the IDE study, in which medical reintervention in the trial follow-up period was not allowed. In both studies the use of hormonal contraception was kept stable from three to prior to enrolment through to the end of the trial period.

Unklarheit hinsichtlich des Patientinnenstroms (FAST-EU)

Ambiguity regarding patient flow through the trials also affects confidence in the reporting and quality of the FAST-EU trial. The trial enrolled 50 patients with a total of 118 fibroids that were considered "target" fibroids; however, a total of 92 fibroids were ablated and, of those, baseline data was evaluable for 89. It is assumed that the reason only 92 were treated was because patients could only have a maximum of five fibroids ablated (as per inclusion criteria); however, this was not explicitly stated. Further it is unclear how inclusion of missing volume data from three fibroids would impact on the results.

[7] It should be noted that the trial institutions received support from the sponsor (Gynesonics, Inc) and the primary author (and other authors) had financial ties to the device sponsor.

The OPEN trial contributed limited data to this review as the primary outcomes was the incidence of new adhesions at six weeks post-procedure. There was limited reporting of other outcomes and data from this study did not contribute to an assessment of the crucial effectiveness outcomes and contributed some data to the safety assessment. Importantly, a key limitation of the study was that it reported only serious adverse events. It was unclear whether other events occurred and were not reported or did not occur. Further, although data for surgical reintervention associated with the study is included in this report the six week follow-up period limits the usefulness of this data.

Daten lieferten nur limitierten Beitrag zur Beurteilung der wesentlichen Endpunkte (OPEN)

Long-term follow-up data for any outcome beyond 12 months were limited to a single publication reporting on a subset of patients enrolled in the FAST-EU trial at a study site in Mexico [6]. This report included only 17 patients, was a not-predefined analysis, and did not include safety data. Therefore, it is not possible to assess whether the effects of TFA reported by the included studies are sustained beyond 12 months.

langfristige Ergebnisse (>12 Monate) wurden nur in einer Publikation mit kleiner Stichprobe berichtet

Factors that may influence the external validity

Eligibility criteria for the key trials (FAST-EU and IDE) [2, 3] excluded women with irregular bleeding patterns from the evidence base. Inclusion criteria were heavy menstrual bleeding as defined by semi-quantitative assessment using validated scores. This requirement is likely to be necessary for accurate assessment of the effect over time; however, this requirement excludes women with bleeding between periods, frequent periods or irregular periods. Uterine fibroids are known to be associated both with heavy bleeding and with abnormal patterns of bleeding [51]. Consequently, these women are not represented in the evidence base. To what degree the effect of the intervention may be greater or lesser in women with less predictable bleeding events is unclear.

Externe Validität:

Frauen mit unregelmäßigen Menstruationszyklen wurden ausgeschlossen (FAST-EU und IDE)

Differences in fibroids treated across the trials resulted in uncertainty regarding appropriate patient selection and generalisability of the results. In the FAST-EU trial eligible women had between 1 and 5 fibroids of FIGO types 1, 2, 3, 4 and 2-5 with a maximum diameter between 1-5 cm. In the IDE trial eligible fibroid types and size were the same, however, women could have up to ten fibroids. Consequently, the mean number of target fibroids in the IDE trial was greater than that in the FAST-EU trial (mean 3.0 versus 1.8) as was the total fibroid volume at baseline (mean 71.1 versus 18.8 cm^3). In the OPEN trial eligible fibroid types were poorly characterised (≥1 myoma of FIGO types 1, 2 or 2-5, no size limitations or upper limit of fibroids).

tlw. Unterschiede zwischen den Studien hinsichtlich der Charakteristika (Größe) und Anzahl der Myome

Baseline mean UFS-QOL-SSS scores in the FAST-EU and IDE trial were 61.7 and 54.9, respectively (UFS-QOL-SSS scores range from 0-100, higher scores indicate more severe symptoms). Whilst mean SSS scores were within a similar range for both studies in the FAST-EU study baseline scores ranged from 28.1 to 100 indicating that the study included women across a spectrum of symptom burden. Whilst the range is not provided for women in the IDE trial the standard deviation of 18.7 points suggests a similar distribution from mild/moderate to severe.[8] Similarly, the range of baseline menstrual bleeding scores indicate a wide range of severity in terms of heavy menstrual bleeding. No information on patient's prior treatment history in terms of medical management was provided by any study. Overall, the included studies en-

keine genauen Informationen zur Behandlungshistorie der Patientinnen und tlw. Heterogenität in wichtigen Charakteristika

[8] Classification of severity considered as per Mindjuk (2015) [52].

rolled patients who were heterogenous in some important characteristics. This likely reflects the fact that women with fibroids exhibit a wide range of symptoms and symptom severity. However, extrapolating the results from a heterogenous group to any subpopulations of women with fibroids (i.e. severe symptoms) is challenging.

Unsicherheit bezüglich der Auswahl geeigneter Myome zur Behandlung und der Folgen auf das Ergebnis

An additional consideration regarding the practical applications of TFA is how fibroids were chosen for ablation. In the FAST-EU trial, fibroids that did not contain an edge within the inner half of the myometrium were not counted in this total and were not targeted for ablation, as they were believed to be less likely to contribute to abnormal uterine bleeding. In the IDE trial patients were required to have at least one fibroid that indented or impinged on the endometrial cavity, however, ablation was not restricted only to these fibroids. The IDE trial also allowed a greater number of fibroids per patient. Consequently, there is some uncertainty regarding the appropriate selection of fibroids for treatment and how fibroid selection may affect the performance of TFA in terms of symptoms and bleeding.[9]

Relevance of outcomes assessed to the potential patient-relevant benefits

Ergebnismessungen waren inkonsistent und klinisch relevante Veränderungen in den Endpunkten wurden unterschiedlich berichtet und analysiert

The included studies measured the impact of TFA on direct and indirect measures of effectiveness. However, the measure of success across trials was inconsistent. As none of the included studies had a comparator arm it is challenging to assess the effectiveness of TFA. Pre-specified criterion for success in terms of a certain proportion of the cohort achieving clinically meaningful changes in outcomes can be used to assess effectiveness. Such outcomes were reported and analysed in the included studies variably, with menstrual bleeding being the most consistent between the IDE and FAST-EU trial.

Menstrual bleeding was assessed in the IDE trial menstrual bleeding reduction was considered a co-primary endpoint and authors defined success as a 50% or greater reduction in PBAC score (that was also < 250) in at least 45% of patients. Authors of the FAST-EU trial did not specify a criterion for success in their statistical analysis plan, however, they considered a clinically meaningful reduction to be at least 22% from baseline. The FAST-EU trial also reported the proportion of patients achieving both ≥22% and ≥50% reduction in score. The OPEN trial did not report this outcome.

Symptom severity was measured using the UFS-QOL-SSS with both of the key trials reported mean reductions in SSS score representing an improvement following the procedure. Mean reductions at 12 months in both trials were large (35.3 and 32.1 in the FAST-EU and IDE trial respectively); well in excess of 10 points (commonly cited as a measure of clinically meaningful change). The authors of the FAST-EU trial reported a proportion of patients achieving a ten point reduction from baseline.

[9] Authors of the trial reported no significant differences in success were identified regarding the inclusion qualifying leiomyoma type. However, it is unclear whether the study was powered to detect a difference between groups.

The indirect effectiveness outcome of fibroid volume reduction was measured and reported in a manner inconsistent with other studies of uterine preserving interventions. Studies of other interventions of uterine fibroids have identified the non-perfused volume (NPV) ratio post-treatment as a predictor of clinical success. The measure is typically calculated as the sum of the non-perfused volume of all treated leiomyomata divided by the volume of all uterine leiomyomata (both treated and untreated). In the IDE trial the mean reduction in perfused leiomyoma volume was derived using the treatable fibroid with the *greatest percentage reduction* in total volume from baseline for each patient. This may overestimate percentage reductions if all treated fibroids were considered. Details of the calculation were not provided by authors of the FAST-EU trial. It is unclear whether the way this has been analysed and reported by the FAST-EU and IDE trials is an appropriate measure of the effectiveness of the procedure in causing tissue devascularisation/destruction.

Art der Messung von Volumenreduktion des Myoms, die nicht mit Studien über optionale uteruserhaltende Interventionen übereinstimmt

The translation of reductions in fibroid volume to clinically meaningful changes in symptoms is not well established in the literature. The FAST-EU trial had a primary endpoint of a 3 month reduction in perfused fibroid volume of >30% in 50% of patients. The IDE trial did not specify any criteria for success in terms of fibroid volume. In the broader literature on MRgFUS reductions in fibroid volume have been correlated with clinically meaningful outcomes (i.e., symptom severity and reintervention). However, the threshold for success is not well established with an NPV of more than 20% to more than 80% being quoted in the literature [52-54].

die Überleitung des Endpunktes Volumenreduktion in klinisch bedeutsame Symptomveränderung ist in der Literatur nicht gut begründet

With respect to reintervention, clear thresholds for success are not established. Authors of the IDE trial specified success as freedom from surgical reintervention in ≥75% of patients at 12 months. The rationale for this threshold for success is unclear. Additionally, the appropriate time horizon over which to consider reintervention rates is uncertain. Rates of reintervention within the first year of treatment are reportedly low across many studies of uterine-preserving interventions; however, increase over time with up to 50% at five years in studies of MRgFUS [55] or as little as 19% in studies of myomectomy [56]. The FAST-EU trial did not have reintervention rates as a primary outcome.

es existieren keine klaren Erfolgsschwellenwerte der Intervention in Bezug auf eine Reintervention

Evidence gaps and ongoing studies

No comparative data exists to inform an assessment of comparative effectiveness and safety for TFA. This is a significant limitation of the current evidence base. Similarly, the paucity of data available at time points greater than 12 months post-procedure means that the safety profile of TFA is incomplete and that impacts on fertility and outcomes of pregnancy are poorly understood. Although the intervention is not currently recommended in women who wish to retain their fertility any implications of the procedure for future pregnancy are important research questions. Searches of the clinical trial registries identified 20 potential relevant hits. However, no relevant ongoing randomised controlled trials (RCTs) evaluating the safety or effectiveness of TFA were identified.

keine vergleichenden Daten, unvollständiges Sicherheitsprofil von TFA, Einfluss von TFA auf Fertilität und Schwangerschaft ist nicht bekannt

9 Recommendation

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

Empfehlungsschema

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 is not sufficient to prove that the assessed intervention, intrauterine ultrasound-guided transcervical radiofrequency ablation, is more effective and equally safe or equally effective, but safer than the comparators of best supportive care or other uterine-preserving interventions for uterine leiomyoma including myomectomy, uterine artery embolization (UAE), uterine artery occlusion (UAO), magnetic resonance-guided focused ultrasound (MRgFU), ultrasound-guided focused ultrasound (USgFUS/USgHIFU) and radiofrequency volumetric thermal ablation (RFVTA).

Evidenz unzureichend → TFA wird derzeit für eine Aufnahme in den Leistungskatalog nicht empfohlen

New study results will potentially influence the effect estimate considerably. However, no relevant ongoing randomised controlled trials (RCTs) evaluating the safety or effectiveness of TFA were identified. The re-evaluation is recommended after large and good quality studies are available.

Re-Evaluation nach Verfügbarkeit von qualitativ hochwertigen Studien (RCTs)

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Transcervical radiofrequency ablation results from observational studies[10] (part 1)

Author, year	Brolmann 2016 [3] (FAST-EU)	Bongers 2015 [4] (FAST-EU) *Per protocol, 6 month analysis*	Bongers 2019a [5] (FAST-EU) *Secondary analysis of uterine-wall integrity – INTEGRITY subset*	Garza-Leal 2019 [6] (FAST-EU) *Extended follow-up of patients treated in Mexico – VITALITY subset*
Country	Mexico (1 site) The United Kingdom (2 sites) The Netherlands (4 sites)	See Brolmann 2016	As for Brolmann 2016 – subset of the full patient set	As for Brolmann 2016 – subset of patient enrolled at the site in Mexico
Sponsor	Gynesonics	See Brolmann 2016	See Brolmann 2016	See Brolmann 2016
Intervention/Product	VizAblate System®[11]	See Brolmann 2016	See Brolmann 2016	See Brolmann 2016
Comparator	None	See Brolmann 2016	See Brolmann 2016	See Brolmann 2016
Study design	Case series	See Brolmann 2016	See Brolmann 2016	See Brolmann 2016
Study aim	To establish the effectiveness and confirm the safety of TFA	See Brolmann 2016	To evaluate uterine-wall integrity 12 months after TFA	To learn the long-term (>5 year) clinical outcomes of TFA
Number of pts	50[12]	See Brolmann 2016	29	17
Inclusion criteria	Women with 1-5 uterine fibroids, age ≥28 years, not pregnant, regular predictable menstrual cycles (definition NR) and heavy menstrual bleeding of ≥3 months. MP score ≥ 120, UFS-QOL SSS ≥20	See Brolmann 2016	Patients enrolled in the FAST-EU trial (see Brolmann 2016) who provided consent to undergo an additional 12 month MRI	Patients previously enrolled and treated in the FAST-EU trial (see Brolmann 2016) at the site in Mexico
Fibroid types eligible	FIGO types 1,2,3,4 and 2-5 of maximum diameter 1-5 cm.[13] At least 1 fibroid indenting the endometrial cavity	See Brolmann 2016	See Brolmann 2016	See Brolmann 2016

[10] Please note that data in this table has been standardised to 1 decimal place, original data from peer reviewed publications may differ from the results presented here.

[11] The VizAblate® system is the original version of the Sonata® system.

[12] Note that only 49 women had evaluable baseline data.

[13] Fibroids that did not contain an edge within the inner half of the myometrium were not counted in this total.

Author, year	Brolmann 2016 [3] (FAST-EU)	Bongers 2015 [4] (FAST-EU) *Per protocol, 6 month analysis*	Bongers 2019a [5] (FAST-EU) *Secondary analysis of uterine-wall integrity – INTEGRITY subset*	Garza-Leal 2019 [6] (FAST-EU) *Extended follow-up of patients treated in Mexico – VITALITY subset*
Exclusion criteria	Desire for future fertility, ≥ 1 type o fibroid, cervical dysplasia, endometrial hyperplasia, active pelvic infection, clinically significant adenomyosis[14], ≥ 1 fibroids that were significantly calcified[15]	See Brolmann 2016	See Brolmann 2016	See Brolmann 2016
Co-interventions (e.g. contraceptive devices/agents etc)	NR	See Brolmann 2016	See Brolmann 2016	See Brolmann 2016
Age of patients (yrs), mean ± SD (range)	NR (41–45)[16]	See Brolmann 2016	NR	Most frequent age range: 41–45
Menstrual bleeding score at baseline, mean ± SD (range)	MP score: 423±253 (119–1582)	See Brolmann 2016	NR	NR
UFS-QOL SSS, mean ± SD (range)	61.7±16.9 (28.1–100)	See Brolmann 2016	NR	64.9 ±16.9 (NR)
UFS-QOL- HRQOL score, mean ± SD (range)	34.3±19 (0–73.3)	See Brolmann 2016	NR	27.2±22.4 (NR)
Other baseline Quality of life measures	NA	NA	NA	EQ-5D VAS, mean ± SD: 70.3± 22.2 EQ-5D summary index, mean ± SD: 0.79±0.23
Target/ablated fibroids per patient, mean ± SD (range)	1.8±1.1 (1-5)[17]	See Brolmann 2016	NR	2.1±NR (NR)
Diameter of target/ablated fibroids, mean ± SD (range) cm	3.2±1.4 (1.1–6.9)[18]	See Brolmann 2016	NR	2.5±1.2 (NR)
Perfused fibroid volume, mean ± SD (range) cm³	18.3±20.6 (0.3–77)	See Brolmann 2016	NR	NR
Total fibroid volume, mean ± SD (range) cm³	18.8±21.4 (0.3–77)	See Brolmann 2016	NR	NR

[14] >10 % of the junctional zone measuring more than 10 mm in thickness as measured by MRI.

[15] Defined as <75 % fibroid enhancement by volume on contrast-enhanced MRI.

[16] Note that authors chose to report only the range of patient age owing to concerns regarding patient privacy.

[17] Note the mean number of target fibroids per patient was 2.4±1.7 (1–7) when considering all 50 patients initially included in the trial. Authors report 118 identified target fibroids on MRI of which 92 were ablated but accurate baseline volume measurements were only available for 89 fibroids. Consequently, the numbers reported here are for 92 fibroids ablated. Authors also report two small additional fibroids, beyond the upper limit of five target fibroids/patient, were identified on review of one MRI series after treatment.

[18] Note that the mean diameter of all target fibroids per patient was 2.9±1.4 (1–6.9). The data reported within the extraction tables represents the diameter for 92 ablated fibroids.

Author, year	Brolmann 2016 [3] (FAST-EU)	Bongers 2015 [4] (FAST-EU) *Per protocol, 6 month analysis*	Bongers 2019a [5] (FAST-EU) *Secondary analysis of uterine-wall integrity – INTEGRITY subset*	Garza-Leal 2019 [6] (FAST-EU) *Extended follow-up of patients treated in Mexico – VITALITY subset*
Follow-up	Patients were followed up at: 7–14 days, 30 days, 3 months, 6 months, and 12 months	See Brolmann 2016	Analysis was based on 12 month MRI scans which was a protocol ammendment in the original FAST-EU trial.	Mean ± SD (range): 64.9 ±4.5 (57–73) months
Loss to follow-up, n (%)	Baseline, 3 and 6 months losses to follow-up: NR 12 month MRI: 20 patients did not consent, 2 exited the study[19]	See Brolmann 2016	NR	NA
Exclusions	Baseline: 1 (unusable baseline imaging) 3 months: 2 (quality control) 6 months:1 (pregnancy) 12 months: see losses to follow-up	2 patients were excluded from primary endpoint due to unusable baseline or 3 month imaging. 6 patients were excluded from patient reported outcomes at 6 months due to confounding factors[20]	NA	NR
Missing data	Baseline: 1 (missing HRQOL) 3 months: 1 (missing MP score) 6 months: 1 (missing MP score) 12 months: 1 (missing MP)[21]	See Brolmann 2016	NA	Of 23 patients enrolled at the Mexican site only 17 were able to be contacted regarding enfollment in the VITALITY study
Effectiveness outcomes				
Primary endpoint(s) (descriptive)	Success was defined as >30% reduction in mean target fibroid perfused volume in ≥50% of patients at 3 months[22] The trial met the primary endpoint (79/89 treated fibroids had > 30% reduction in mean target perfused volume)[23]	See Brolmann 2016	NA	NR

[19] No details were provided regarding patients exiting the study.

[20] Two patients (4 %) underwent an ancillary fibroid or polyp resection at the time of RF ablation, and therefore their patient-reported outcomes were excluded from analysis, including baseline MP and UFS-QOL results. Three patients (6 %) underwent medical reintervention (e.g., tranexamic acid) for abnormal uterine bleeding within 6 months of the ablation procedure, resulting in exclusion of their patient-reported outcomes at 6 months.

[21] Note that patient data could be missing from the endpoint analyses due to exclusions and/or missing data. Consequently patient numbers for baseline, 3, 6 and 12 month data (primary endpoint) presented in the results are: 49, 48, 48, 28.

[22] Authors report that a sample of 40 patients was sufficient to detect a difference of 22% in probability of success with a power of 82% using a one-group chi-square test with a 0.05 two-sided significance level. Allowing for an expected dropout rate of 20%at the 12 month follow-up visit, the minimum recommended sample size for the initial trial protocol was 48.

Author, year	Brolmann 2016 [3] (FAST-EU)	Bongers 2015 [4] (FAST-EU) *Per protocol, 6 month analysis*	Bongers 2019a [5] (FAST-EU) *Secondary analysis of uterine-wall integrity – INTEGRITY subset*	Garza-Leal 2019 [6] (FAST-EU) *Extended follow-up of patients treated in Mexico – VITALITY subset*
Percentage reduction (improvement) in perfused fibroid volume, mean ± SD (median, range)	**3 months** (n=49) -68.1%±28.6% (-76.9%,-100%–33.3%) **12 months** (n=28) -67.4%±31.9% (-73.3%,-100–32.7%) *P<0.001 at both time points*	Additional per protocol analysis at 3 months (n=48) -68.8%±27.8% (-77.1%, -100–33.3%) *P<0.0001*	NA	NR
Percentage reduction (improvement) in total fibroid volume, mean ± SD (median, range)	**3 months** (n=49) -54.7%±37.4% (-62.5%, -100–85.7%) **12 months** (n=28) -66.6%±32.1% (-73.3%,-100–32.7%) *P<0.001 at both time points*	Additional per protocol analysis at 3 months (n=48) -55.3%±37.2% (-63.1%,-100–85.7%) *P<0.0001*	NA	NR
Perfused fibroid volume, mean ± SD (median, range) cm³	**3 months** (n=49) 5.8±9.6 (1.6, 0 –45.7) **12 months** (n=28) 6.6±11.3 (1, 0–56.1) *P<0.001 at both time points*	Additional per protocol analysis at 3 months (n=48) 5.5±9.2 (1.6, 0–45.7) *P<0.0001*	NA	NR
Total fibroid volume, mean ± SD (median, range) cm³	**3 months** (n=49) 8±12 (1.9, 0–56.3) **12 months** (n=28) 6.8±11.4 (1.2, 0–56.1) *P<0.001 at both time points*	Additional per protocol analysis at 3 months (n=48) 7.7±11.8 (1.9, 0–56.3) *P<0.0001*	NR	NR
Reduction (improvement) in menstrual bleeding score, mean ± SD (median, range)	**3 months** (n=49) -221±290 (-191, -1265–700) **6 months** (n=48) -244±302 (-191,-1307–700) **12 months** (n=48) -243±296 (-217,-1543–343) *P<0.001 at all time points*	NR	NA	NR

[23] Of 118 fibroids identified on baseline MRI imaging there were 92 fibroids treated (maximum per patient = 5). However, accurate baseline data regarding volume was available for 89 fibroids (49 patients) only.

Author, year	Brolmann 2016 [3] (FAST-EU)	Bongers 2015 [4] (FAST-EU) *Per protocol, 6 month analysis*	Bongers 2019a [5] (FAST-EU) *Secondary analysis of uterine-wall integrity – INTEGRITY subset*	Garza-Leal 2019 [6] (FAST-EU) *Extended follow-up of patients treated in Mexico – VITALITY subset*
Percentage reduction (improvement) in menstrual bleeding score, mean ± SD (median, range)	**3 months** (n=49) -45.2%±57.9% (-56.9%,-100–225%) **6 months** (n=48) -51.9%±59.8% (-68.6%,-100–225%) **12 months** (n=48) -53.8%±50.5% (-72.3%, -100%–103%) *P<0.001 at all time points*	Additional per protocol analysis at 6 months (n=43) -60.8%±38.2% (-70.8%, -73.1–100%) *P<0.0001*	NA	NR
Proportion of patients with ≥50% reduction in score, n/N (%) or % (95% CI)	MB score **3 months** 28/49 (57.1%) **6 months** 35/48 (72.9%), **12 months** 31/48 (64.6%)	Additional per protocol analysis at 6 months (n=43) 33/43 (76.7%) *The median reduction in MP score at 6 months was 70.8 %.*	NA	NR
Reduction (improvement) in UFS-QOL SSS, mean ± SD (median, range)	**3 months** (n=50) -30 ±22.2 (-31.3,-84.4–18.8) **6 months** (n=49) -36.7±22.6 (-37.5,-75–6.3) **12 months** (n=49) -35.3±26.9 (-37.5,-93.8–18.8) *P<0.001 at all time points* *Patients with ≥10 point reduction in score was 82% at 3 months, 86% at 6 months and 78% at 12 months.*	NR	NA	Reduction from mean ± SD at baseline (64.9±16.9) to 27.6±36.1 at long term follow-up (p=0.002)
Percentage reduction (improvement) in UFS-QOL SSS, mean ± SD (median, range)	**3 months** (n=50 -46.7%±32.8% (-52.5%, -100–33.3%) **6 months** (n=49) -57.6%±31.4% (-66.7%,-100–22.2%) **12 months** (n=49 -55.1%±41% (-62.5%,-100–66.7%) *P<0.001 at all time points*	Additional per protocol analysis at 6 months (n=44) -59.7%±30.4% (-66.7%, -100–22.2%) *P<0.0001*	NA	NR

Author, year	Brolmann 2016 [3] (FAST-EU)	Bongers 2015 [4] (FAST-EU) *Per protocol, 6 month analysis*	Bongers 2019a [5] (FAST-EU) *Secondary analysis of uterine-wall integrity – INTEGRITY subset*	Garza-Leal 2019 [6] (FAST-EU) *Extended follow-up of patients treated in Mexico – VITALITY subset*
Increase (improvement) in UFS-QOL HRQOL score, mean ± SD (median, range)	**3 months** (n=49) 42.1±25.6 (40.5,-7.8–95.7) **6 months** (n=48) 44.5±26.7 (45.3,-5.2–96.6) **12 months** (n=48) 45.7±30.5 (45.7,-33.6–96.6) *P<0.001 at all time points*	Not reported	NA	Increase from mean ± SD at baseline (27.2±22.4) to 76 ±32.6 at long term follow-up (p=0.0001)
Percentage increase (improvement) in UFS-QOL HRQOL HRQOL score, mean ± SD (median, range)	**3 months** (n=49) 336%±846% (123%, -11.1–5550%) **6 months** (n=48) 266%±475% (118%, -28.6–2800%) **12 months** (n=48) 277%±483% (127%, -54.2–2800%) *P<0.001 at all time points*	Additional per protocol analysis at 6 months (n=43) 263%±468% (126%, -28.6–2800%) *P<0.0001*	NA	NR
Improvement in quality of life as measured by the EQ-5D-3L	NA	See Brolmann 2016	NA	Increase (improvement) in mean ± SD EQ-5D VAS score at baseline (70.3±22.2) to 79.8±25.5 at long term follow-up (p=0.042). The mean ± SD EQ-5D summary index increased from 0.79±0.23 to 0.83±0.26 (p=0.599)
Overall Treatment Effect Scale change in symptoms, n/N (%)	NR	See Brolmann 2016	NA	NR
Patient satisfaction, descriptive %	NR	See Brolmann 2016	NA	NR
Surgical reintervention, n/N (%)	4/50 (8%)	None < 6 months	NA	2/17 (11.8%)[24]
Non-surgical reintervention, n/N (%)	NR	3/50 (6%)	NA	0/17 (0%)
Subsequent pregnancy, n/N (%)	1/50 (2%)	See Brolmann 2016	NA	1/17 (6%) – no additional preganacy beyond that reported by Brolmann 2016
Fertility outcomes, descriptive	One patient became pregnant and delivered a live term infant by cesarean section	See Brolmann 2016	NA	See Brolmann 2016

[24] Two patients had hysterectomies for abnormal uterine bleeding at 3.5 and 4 years post procedure.

Author, year	Brolmann 2016 [3] (FAST-EU)	Bongers 2015 [4] (FAST-EU) *Per protocol, 6 month analysis*	Bongers 2019a [5] (FAST-EU) *Secondary analysis of uterine-wall integrity – INTEGRITY subset*	Garza-Leal 2019 [6] (FAST-EU) *Extended follow-up of patients treated in Mexico – VITALITY subset*
Safety outcomes				
Overall complications, n/N (%)	NR 34 events over 12 months	See Brolmann 2016	NA	NR
Major AE, n/N (%)	NR	See Brolmann 2016	NA	NR
Minor AE, n/N (%)	NR	See Brolmann 2016	NA	NR
Procedure-related mortality, n/N (%)	NR (presumed nil)	See Brolmann 2016	NA	NR
Complications, n (%)	Dysmenorrhea: 7 (14%) Abnormal uterine bleeding above baseline: 6 (12%) Pelvic pain/cramping: 4 (8%) UTI within 30 days: 2 (4%) Fibroid expulsion: 1 (2%) Hospital admission: 1(2%)[25] Bradycardia: 1 (2%)[26]	As for Brolmann 2016 except dysmenorrhea (n=6)	NA	NR
Other	NA	NA	29/29 (100%) of patients had minimum uterine wall thickness > 3 mm on 12 month MRI[27] No patient had new myometrial scars	NA

Abbreviations: ***CI****– confidence interval;* ***DVT****– deep vein thrombosis;* ***FIGO****– Federation of Gynaecology and Obstetrics;* ***MP****– menstrual pictogram;* ***MRI****– magnetic resonance imaging;* ***NA****– not applicable;* ***NR****– not reported;* ***PBAC****– pictorial blood loss assessment chart;* ***SD****– standard deviation;* ***TFA****– transcervical fibroid ablation;* ***UAE****– uterine artery embolization;* ***UAO****– uterine artery occlusion;* ***UFS-QOL-SSS****– Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire Symptom Severity Scale;* ***UFS-QOL-HRQL****– Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire;* ***UTI****– urinary tract infection*

[25] Postprocedure day 9 to receive parenteral antibiotics for lower abdominal pain believed secondary to cystitis (patient also had UTI) discharged on the following day.

[26] Treated successfully with atropine and observation.

[27] Evaluated by T1-weighted MRI with a minimum uterine-wall threshold set at > 2.5 mm. If any 12 month MRI scans showed a measured uterine-wall thickness < 2.5 mm radiologist review would be required to verify thinning or compromise of the uterine wall, compared to baseline.

Table A-1: Transcervical radiofrequency ablation results from observational studies[28] (part 2)

Author, year	Huirne 2018 [7] (FAST-EU) Health utiliity as measured by the EQ-5D-3L system	Bongers 2019b [8] (OPEN)	Chudnoff 2019 [2] (IDE)
Country	See Brolmann 2016	6 Academic centres/community hospitals in the United Kingdom, the Netherlands, Switzerland and Germany	Mexico (1 site) The United States (21 sites)
Sponsor	See Brolmann 2016	Gynesonics	Gynesonics
Intervention/Product	See Brolmann 2016	Sonata® system	Sonata® system
Comparator	See Brolmann 2016	None	None
Study design	See Brolmann 2016	Case series	Case series
Study aim	To establish the improvement in patient health utilities following TFA	To document the incidence of de novo uterine adhesions after TFA	To evaluate the 12 month safety and effectiveness of TFA
Number of pts	49[29]	37	147
Inclusion criteria	See Brolmann 2016	Women ≥18 years, selecting TFA with the Sonata® system for the treatment of symptomatic fibroids	Premenopausal women aged 25 to 50 with up to 10 uterine fibroids, PBAC score ≥ 150 and ≤ 500, consistent menstural cycles within normal limits (definition NR)
Fibroid types eligible	See Brolmann 2016	≥1 myoma of FIGO types 1,2 or 2-5	FIGO types 1,2,3,4 and 2-5 of maximum diameter 1-5 cm. At least 1 fibroid indenting/ impinging on the endometrial cavity
Exclusion criteria	See Brolmann 2016	Preexisting adhesions within the endometrial cavity (European Society of Hysteroscopy score ≥1), type 0 fibroids and/or endometrial polyps	Desire for future pregnancy, ≥ 1 type 0 fibroid 1 cm or greater, endometrial polyps ≥ 1.5 cm or multiple polyps, bulk symptoms attributable to subserous leiomyoma, uterine volume ≥ 1,000 cm^3, presence of tubal implants, clinically significant adenomyosis, positive cervical cancer screening test in the last 12 months, pregancy, prior: endometrial ablation/UAE/UAO/hyperthermic ablation
Co-interventions (e.g. contraceptive devices/agents etc)	See Brolmann 2016	NR	Women on oral contraceptive pills had stable regimens from 6 months prior to the end of the trial period. Introduction of medical therapy for heavy menstrual bleeding throughout the trial period was not permitted.[30]
Age of patients (yrs), mean ± SD (range)	See Brolmann 2016	42.2±7.2 (NR)	Median (range): 43 (31–50)

[28] Please note that data in this table has been standardised to 1 decimal place, original data from peer reviewed publications may differ from the results presented here.

[29] This study included only the 49 women with evaluable baseline data.

[30] Washout periods applied for: intrauterine systems, long acting progestins and medical therapy for heavy bleeding.

Author, year	Huirne 2018 [7] (FAST-EU) Health utiliity as measured by the EQ-5D-3L system	Bongers 2019b [8] (OPEN)	Chudnoff 2019 [2] (IDE)
Menstrual bleeding score at baseline, mean ± SD (range)	NR	NR	PBAC score (all patients): 300.6±98.5 (150.2–499.0) Analysis subset (n=142): 303.6±98.6 (150.2–499)
UFS-QOL SSS, mean ± SD (range)	See Brolmann 2016	NR	Analysis subset (n=143: 54.9±18.65 (NR)
UFS-QOL- HRQOL score, mean ± SD (range)	See Brolmann 2016	NR	Analysis subset (n=142): 40.3±20.5 (NR)
Other baseline Quality of life measures	EQ-5D-3L score mean (median): 0.745 (0.811)	NA	EQ-5D-3L mean overall score: 0.72
Target/ablated fibroids per patient, mean ± SD (range)	NR	1.4±0.6 (NR)	3±2.1 (1–9)[31]
Diameter of target/ablated fibroids, mean ± SD (range) cm	NR	3.4±1.76 (1–8)	2.5±1.2 (0.3–6.5)
Perfused fibroid volume, mean ± SD (range) cm³	NR	NR	NR
Total fibroid volume, mean ± SD (range) cm³	NR	3.3±1.71 (1–8) Visualised fibroid volume	71.1±84.7 (0.8–522.9)
Follow-up	Analysis of EQ-5D-3L scores at 3, 6 and 12 months	6 weeks (baseline versus 6 week hysteroscopy)	Patients were followed up at: 10 days, 30 days, 3 months, 6 months, and at 12 months (longer term follow-up planned for 24 and 36 months)
Loss to follow-up, n (%)	NR	2 (5%)	4 (2.7%) missed the 12 month visit (n=1) or were withdrawn (reason NR) < 12 months (n=3)
Exclusions	NR	One patient did not have an evaluable hysteroscopy video	4 patients were excluded from the analysis set due to reaching menopause. One patient was excluded from the menstrual bleeding endpoint due to surgical reintervention.
Missing data	Six missing values were imputed by last observation carried forward	2 patients did not return for follow-up hysteroscopy	PBAC assessments were missing for 7 patients at 12 months
Effectiveness outcomes			
Primary endpoint(s) (descriptive)	NA	NA	Menstrual bleeding: success required both ≥ 50% reduction in PBAC score that was also ≤ 250 in at least 45% of patients. Surgical reintervention: The proportion of patients who did not require surgical reintervention for heavy menstrual bleeding ≥75% of patients.

[31] Total number of leiomyomas per patient had mean± SD (range) of: 3.5±2.2 (1–10).

Author, year	Huirne 2018 [7] (FAST-EU) Health utiliity as measured by the EQ-5D-3L system	Bongers 2019b [8] (OPEN)	Chudnoff 2019 [2] (IDE)
Primary endpoint(s) (descriptive) *(continuation)*			Trial success required satisfing both criteria.[32] The trial met the coprimary endpoints with: 64.8% of patients (95% CI 56.3–72.6%) experienced 50% or greater reduction in menstrual bleeding and 99.3% of patients (95% CI 95.1–99.9%) were free from surgical reintervention.
Percentage reduction (improvement) in perfused fibroid volume, mean ± SD (median, range)	NA	NA	**12 months** (n=128) -63.9% (NR) *p<0.001*
Percentage reduction (improvement) in total fibroid volume, mean ± SD (median, range)	NA	NA	**12 months** (n=129) -62.4% (NR) *p<0.001*
Perfused fibroid volume, mean ± SD (median, range) cm³	NA	NA	NR
Total fibroid volume, mean ± SD (median, range) cm³	NR	NR	NR
Reduction (improvement) in menstrual bleeding score, mean ± SD (median, range)	NA	NA	**3 months** (n=117) -119.3±116 (-113,-395.2–445.1) **6 months** (n=142) -144.1±180 (-143.4,-469–1,549.2) **12 months** (n=142) -159.7±127.7 (-147.8,-494.3–679.4) *P<0.001 at all time points*
Percentage reduction (improvement) in menstrual bleeding score, mean ± SD (median, range)	NA	NA	**3 months** (n=117) -38.9%±-39.1 (-44.4%,-96.5–219.6) **6 months** (n=142) -48.4%±42.9% (-56.6%,-95.7–313.4%) **12 months** (n=142) -51.1%±40.9% (-58.3%,-100 –304.9%) *P<0.001 at all time points*
Proportion of patients with ≥50% reduction in score, n/N (%) or % (95% CI)	NA	NA	**PBAC score** **12 months** 64.8% (95% CI 56.3–72.6%)

[32] Authors report that a sample size of 125 treated patients was needed to achieve 90% power with an a level equal to 0.05 and an assumed success rate of 60%. Including a conservative estimate for "lost to followup" of 15%, the number of patients needed to treat was calculated to be 147.

Author, year	Huirne 2018 [7] (FAST-EU) Health utiliity as measured by the EQ-5D-3L system	Bongers 2019b [8] (OPEN)	Chudnoff 2019 [2] (IDE)
Reduction (improvement) in UFS-QOL SSS, mean ± SD (median, range)	NA	NA	**3 months** (n=141) -27.9±22.85 (NR) **6 months** (n=138) -31.9±20.98 (NR) **12 months** (n=135) -32.1±21.03 *P<0.001 at all time points*
Percentage reduction (improvement) in UFS-QOL SSS, mean ± SD (median, range)	NA	NA	NR
Increase (improvement) in UFS-QOL HRQOL score, mean ± SD (median, range)	NA	NA	**3 months** (n=139) 37.3±24.30 (NR) **6 months** (n=136) 43.3±25.07 (NR) **12 months** (n=134) 43.7±24.25 *P<0.001 at all time points*
Percentage increase (improvement) in UFS-QOL HRQOL HRQOL score, mean ± SD (median, range)	NA	NA	NR
Improvement in quality of life as measured by the EQ-5D-3L	**Eq-5D-3L score** **3 month** Mean: 0.838 Median: 0.848 **6 months** Mean: 0.852 Median: 0.848 **12 months** Mean: 0.914 Median: 1 *At 12 months health utility was statistically significantly improved (p<0.001)* *The overall cohort experienced, on average, 0.85 quality-adjusted life years*	NA	**12 months** (n=133) Mean increase: 0.17 (from 0.72 to 0.89) *p<0.001*
Overall Treatment Effect Scale change in symptoms, n/N (%)	NA	NA	**12 months** (n=135) Improvement: 130/135 (96.3%) No change: 4/135 (3 %) Worsening: 1/135 (0.7%)
Patient satisfaction, descriptive %	NA	NA	**12 months** (n=NR) Very satisfied: 70.4% Moderately satisfied: 17.8% Somewhat satisfied: 8.9% Somewhat dissatisfied: 2.2% Moderately dissatisfied: 0.7%

Author, year	Huirne 2018 [7] (FAST-EU) Health utiliity as measured by the EQ-5D-3L system	Bongers 2019b [8] (OPEN)	Chudnoff 2019 [2] (IDE)
Surgical reintervention, n/N (%)	NA	0/37 (0%)	1/147 (<1%)[33]
Non-surgical reintervention, n/N (%)	NA	NA	NR
Subsequent pregnancy, n/N (%)	NA	NA	NR (presumed nil)
Fertility outcomes, descriptive	NA	NA	NA
Safety outcomes			
Overall complications, n/N (%)	NR	NR	NR
Major AE, n/N (%)	NR	1/37 (3%)[34]	2/147 (<1%)[35]
Minor AE, n/N (%)	NR	NR	74/147 (50%)
Procedure-related mortality, n/N (%)	NR	NR (presumed nil)	NR (presumed nil)
Complications, n (%)		Non-specific abdominal pain: 1 (3%)	**Serious** All: 2/147 (<1%) DVT: 1 (<1%) Leukorrhea, pelvic pain, and unconfirmed low-grade Fever: 1 (<1%) **Nonserious** All: 74/147, 50.3%) Leiomyoma sloughing: NR (30.6%) Cramping/pain: NR (7.5%) Leukorrhea: NR (6.1%) Uncomplicated genitourinary infections: NR (4.8%) Nonspecific symptoms: NR (3.4%) Expelled leiomyoma: NR (1.4%) Flu-like symptoms: NR (1.4%) Nausea/vomiting: NR (0.7%) Other: NR (5.4%) *e.g. high blood pressure, constipation etc*
Other	NR	No patient with an evaluable hysteroscopy videa (n=34/37) had evidence of new adhesions at 6 weeks post procedure	NA

Abbreviations: *see Table A-1 (part 1), page 71*

[33] Elective hysterectomy for heavy menstrual bleeding. 99.3% of patients (95% CI 95.1–99.9%) did not undergo surgical reintervention.

[34] Nature of the event was unclear, the patient was admitted 18 days post ablation with non-specific abdominal pain. The investigators deemed the event unrelated to the procedure.

[35] Both were procedure-related consisting of: one deep venous thrombosis at 15 days post procedure and one case of leukorrhea, pelvic pain and unconfirmed low grade fever 28 days post-procedure.

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 [57] and in the Guidelines of EUnetHTA [58].

Table A-2: Risk of bias – study level (case series), using the Institute for Health Economics appraisal tool [19]

Study reference/ID	Brolmann 2016 [3] (FAST-EU)	Bongers 2015 [4] (FAST-EU)	Bongers 2019a [5] (FAST-EU)	Garza-Leal 2019 [6] (FAST-EU)	Huirne 2018 [7] (FAST-EU)	Bongers 2019b [8] (OPEN)	Chudnoff 2019 [2] (IDE)
Study objective							
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study design							
2. Was the study conducted prospectively?	Yes	Yes	Yes[36]	No	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	Yes	Yes	Yes	No	Yes	Yes	Yes
4. Were patients recruited consecutively?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Study population							
5. Were the characteristics of the patients included in the study described?	Yes	Yes	No	Yes	No	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	Yes	Yes
7. Did patients enter the study at a similar point in the disease?[37]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Intervention and co-intervention							
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	No	No	No	No	No	No	Yes
10. Were relevant outcome measures established a priori?	Partial[38]	Partial	No	Partial[39]	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	No	No	No

[36] Patients were enrolled and followed prospectively, however, the addition of the 12-month MRI that enabled evaluation of uterine wall integrity was a post-hoc addition to the study.

[37] Within studies there was a range of fibroid type, number, baseline menstrual bleeding and symptom burden. However, this question was scored yes as the target population for the intervention is understood to encompass a range of disease severity (both physiological – ie. Fibroid type and number and clinical – symptom burden etc).

[38] The protocol was amended to include a 12-month endpoint with MRI evaluation of fibroid volume, 58.3% of patients (n=28) provided consent to an additional 12-month post-ablation MRI.

[39] Scored partial as long-term follow-up with specified outcome measures was not considered a priori.

Study reference/ID	Brolmann 2016 [3] (FAST-EU)	Bongers 2015 [4] (FAST-EU)	Bongers 2019a [5] (FAST-EU)	Garza-Leal 2019 [6] (FAST-EU)	Huirne 2018 [7] (FAST-EU)	Bongers 2019b [8] (OPEN)	Chudnoff 2019 [2] (IDE)
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	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?	Yes	Yes	Unclear	Unclear[40]	Yes	Unclear	Yes
Results and Conclusions							
15. Was follow-up long enough for important events and outcomes to occur?	Unclear[41]	Unclear	Yes	Yes	Unclear	Yes	Unclear
16. Were losses to follow-up reported?[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	Yes	Yes	No	Yes	Yes
18. Were the adverse events reported?	Yes	Yes	No	No	No	Partial	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Unclear[43]	Yes	Yes	Yes
Competing interests and sources of support							
20. Were both competing interests and sources of support for the study reported?	Yes	Yes	Yes	Yes	Partial	Yes	Yes
Overall Risk of bias	Medium	Medium	High	High	High	High	Medium

[40] Small sample size (n=17) and no a priori definition of success for these endpoints was provided.

[41] 12 months of follow-up data is not available for all patients.

[42] This question was scored as a yes if the study reported patient numbers associated with the clinical outcomes. For example if the study reported missing data at a specific time point, withdrawals or exclusions this was scored as a yes even if there was no explicit statement regarding losses to followu-up.

[43] Conclusions do not contextualise potential for limited generalisability of the results beyond the small included sample.

Table A-3: Evidence profile: efficacy and safety of TFA

Quality assessment							Impact	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Effectiveness								
Reduction in menstrual bleeding (assessed with: Menstrual pictogram or pictorial blood loss assessment chart)								
2 [2, 3]	observational studies	serious [a,b,c]	not serious	not serious	serious [d,e]	all plausible residual confounding would suggest spurious effect, while no effect was observed	**Mean percentage reduction (improvement) from baseline in menstrual bleeding score, mean ± SD (median, range) at 12 months** **FAST-EU (n=48) measured with MP score:** -53.8%±50.5% (-72.3%, -100%–103%) **IDE (n=142) measured with PBAC score:** -51.1%±40.9% (-58.3%,-100.0–304.9%) *p<0.001 compared to baseline for both* **Mean reduction (improvement) from baseline in menstrual bleeding score, mean ± SD (median, range) at 12 months** **FAST-EU (n=48) measured with MP score:** -243±296 (-217,-1543–343) **IDE (n=142) measured with PBAC score:** -159.7±127.7 (-147.8,-494.3–679.4) *p<0.001 compared to baseline for both*	⊕◯◯◯ VERY LOW
Proportion of patients with ≥50% reduction in menstrual bleeding score (assessed with: Menstrual pictogram or pictorial blood loss assessment chart)								
2 [2, 3]	observational studies	serious [a,b,c]	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	**Proportion of patients with ≥50% reduction in menstrual bleeding score at 12 months** FAST-EU: 31/48 (64.6%) IDE: 64.8% (95% CI 56.3–72.6%)	⊕⊕◯◯ LOW CRITICAL
Improvement in symptom severity (assessed with: UFS-QOL-SSS)								
2 [2, 3]	observational studies	serious [a,c]	not serious	not serious	serious [e]	all plausible residual confounding would suggest spurious effect, while no effect was observed	**Mean percentage reduction (improvement) from baseline in UFS-QOL SSS at 12 months, mean ± SD (median, range)** **FAST-EU (n=49):** -55.1%±41.0% (-62.5%,-100–66.7%) **IDE (n=135):** NR *p<0.001 when compared to baseline in both trials* **Mean reduction (improvement) from baseline in UFS-QOL SSS at 12 months, mean ± SD (median, range)** **FAST-EU (n=48):** -35.3±26.9 (-37.5,-93.8– 18.8) **IDE (n=135):** -32.1±21.03 (NR) *p<0.001 when compared to baseline in both trials* *The FAST-EU trial reported the proportion of patients with ≥10 point reduction in score was 82% at 3 months, 86% at 6 months and 78% at 12 months.*	⊕◯◯◯ VERY LOW CRITICAL

Quality assessment							Impact	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Symptom improvement (assessed with: Overall Treatment Effect Scale)								
1 [2]	observational studies	serious [a,m]	not serious	not serious	not serious	none	At 12 months patients reported: Improvement: 130/135 (96.3%) No change: 4/135 (3.0%) Worsening: 1/135 (0.7%)	⊕◯◯◯ VERY LOW IMPORTANT
Surgical reintervention rate (assessed with: Rates of surgical reintervention)								
3 [2, 3, 8]	observational studies	serious [h,i,j]	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	**FAST-EU:** 4/50 (8%) of patients underwent surgical reintervention within 12 months In the long term follow-up of 17 patients enrolled in the FAST-EU trial (> 5 years) 2 patients (11.8%) underwent reintervention at 3.5 and 4 years post treatement. **IDE:** 1/147 (<1%) of patients underwent surgical reintervention within 12 months **OPEN**: 0/37 (0%)	⊕⊕◯◯ LOW CRITICAL
Non-surgical reintervention rate (assessed with: reintervention rate)								
1 [4]	observational studies	serious [l,m]	not serious	not serious	not serious	none	3/50 (6%) of patients required tranexamic acid for abnormal uterine bleeding during 6 months of follow-up	⊕◯◯◯ VERY LOW IMPORTANT
Reduction in fibroid volume (assessed with: Perfused fibroid volume)								
2 [2, 3]	observational studies	serious [b,c]	not serious	serious [f]	serious [d]	none	**Mean percentage reduction in perfused fibroid volume, mean ± SD (median, range)** **FAST-EU 3 months (n=49):** -68.1%±28.6 (-76.9%,-100%–33.3%) **12 months (n=28):** -67.4%±31.9 (-73.3%,-100–32.7%) *The primary endpoint of the FAST-EU was >30% reduction in mean target fibroid perfused volume in ≥50% of patients at 3 months.The trial met its primary endpoint (79/89 treated fibroids had > 30% reduction in mean target perfused volume at 3 months).* **IDE 12 months (n=128): -**63.9% (NR) *p<0.001 relative to baseline*	⊕◯◯◯ VERY LOW IMPORTANT
Reduction in total fibroid volume (assessed with: Mean percentage reduction in total fibroid volume)								
2 [2, 3]	observational studies	serious [c,f,k]	not serious	not serious	serious [d]	none	**Reduction in total fibroid volume, mean ± SD percentage reduction (median, range)** **FAST-EU 3 months (n=49):** -54.7%±37.4% (-62.5%, -100– 85.7%) **12 months (n=28):** -66.6%±32.1%(-73.3%,-100–32.7%) *p<0.001 at both time points* compared to baseline **IDE 12 months (n=129):** 62.4% (NR) *p<0.001 for 12 month results compared to baseline*	⊕◯◯◯ VERY LOW IMPORTANT

Quality assessment							Impact	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Patient satisfaction (assessed with: Questionnaire)								
1 [2]	observational studies	serious [a,m,t]	not serious	not serious	not serious	none	**Responses reported at 12 months** (n=NR): Very satisfied: 70.4% Moderately satisfied: 17.8% Somewhat satisfied: 8.9% Somewhat dissatisfied: 2.2% Moderately dissatisfied: 0.7%	⊕◯◯◯ VERY LOW IMPORTANT
Improvement in health related quality of life (disease specific) (assessed with: UFS-QOL HRQOL)								
2 [2, 3]	observational studies	serious [a,c]	not serious	not serious	serious [d]	all plausible residual confounding would suggest spurious effect, while no effect was observed	**Increase (improvement) in UFS-QOL HRQOL score from baseline at 12 months, mean ± SD (median, range)** **FAST-EU** (n=48): 45.7±30.5 (45.7,-33.6–96.6) **IDE** (n=134): 43.7±24.25 (NR) *p<0.001 relative to baseline in both* **Percentage increase (improvement) in UFS-QOL HRQOL score from baseline at 12 months, mean ± SD (median, range)** **FAST-EU** (n=48): 277%±483% (127%,-54.2–2800%), p<0.001 **IDE** (n=134): NR >5 year follow-up of a subset of the FAST-EU trial (n=17): Statistically significant increase from mean ± SD at baseline (27.2±22.4) to 76.0±32.6 at long term follow-up (p=0.0001)	⊕◯◯◯ VERY LOW IMPORTANT
Improvement in quality of life (generic measures) (assessed with: Euro-Qol or EQ-5D-3L)								
2 [2, 3]	observational studies	serious [a,c]	not serious	not serious	serious [d,g]	all plausible residual confounding would suggest spurious effect, while no effect was observed	**IDE** Mean increase in the cohort health status as measured by the Euro-Qol questionairre at 12 months was 0.17 points. The mean cohort Euro-Qol score improved from 0.72 at baseline to 0.89 at 12 months (measured in 133 of 147 enrolled patients at 12 months) **FAST-EU** **Changes in the EQ-5D-3L from baseline, mean (median)**: **Baseline:** 0.745 (0.811) (0.848) **12 months** : 0.914 (1.000) *At 12 months health utility was statistically significantly improved (p<0.001) compared to baseline*	⊕◯◯◯ VERY LOW IMPORTANT
Pregnancy after transcervical radiofrequency ablation (assessed with: Rate of reported pregnancy during follow-up)								
1 [3]	observational studies	not serious [n]	not serious	not serious	not serious	none	1/50 (2%) with the patient delivering a live term infant by cesarean section Note: in long term follow-up (mean 64.9 months) of a subset of patients (n=17) no additional pregnancies were recorded.	⊕⊕◯◯ LOW IMPORTANT

Quality assessment							Impact	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Safety								
Overall complications (assessed with: Rate of complications)								
3 [2, 3, 8]	observational studies	serious [j]	serious [o]	serious [p]	not serious	none	**FAST-EU:** 34 events in 50 patients over 12 months of follow-up. Events comprised: Dysmenorrhea: 7 (14%) Abnormal uterine bleeding above baseline: 6 (12%) Pelvic pain/cramping: 4 (8%) UTI within 30 days: 2 (4%) Fibroid expulsion: 1 (2%) Hospital admission: 1(2%) Bradycardia: 1 (2%) **IDE:** 74/147 (50%) experienced an adverse event considered to be non-serious. Events comprised: Leiomyoma sloughing: NR (30.6%) Cramping/pain: NR (7.5%) Leukorrhea: NR (6.1%) Uncomplicated genitourinary infections: NR (4.8%) Nonspecific symptoms: NR (3.4%) Expelled leiomyoma: NR (1.4%) Flu-like symptoms: NR (1.4%) Neausea/vomiting: NR (0.7%) Other: NR (5.4%) *e.g. high blood pressure, constipation etc* 2/147 (<1%) of patients experienced a serious adverse event the nature of which is reported elsewhere **OPEN :** 1/37 (2%) patient experienced a serious adverse event the nature of which is reported elsewhere	⨁◯◯◯ VERY LOW CRITICAL
Major adverse events (assessed with: Rate of major adverse events)								
2 [2, 8]	observational studies	serious [c,q]	serious [o]	not serious	not serious	none	**IDE:** 2/147 (<1%) of patients experienced a serious adverse event comprising of: DVT: 1 (<1%) Leukorrhea, pelvic pain, and unconfirmed low-grade Fever: 1 (<1%) **OPEN** : 1/37 (3%) patient experienced a serious adverse event which was non-specific abdominal pain	⨁◯◯◯ VERY LOW CRITICAL
Impact on uterine wall thickness (assessed with: MRI)								
1 [5]	observational studies	serious [h,k,r]	not serious	not serious	not serious	none	Of 29 patients enrolled in the FAST-EU trial who consented to an MRI at 12 months 29/29 (100%) of patients had minimum uterine wal thickness > 3.0 mm on 12 month MRI. i.e. no evidence of uterine wall thinning or compromise was identified.	⨁◯◯◯ VERY LOW IMPORTANT
Incidence of adhesions (assessed with: Hysteroscopy)								
1 [8]	observational studies	serious [h,k,r]	not serious	serious [s]	not serious	none	No patient with an evaluable hysteroscopy video (n=34/37) had evidence of new adhesions at 6 weeks post procedure .	⨁◯◯◯ VERY LOW IMPORTANT

Abbreviations: ***CI****– confidence interval;* ***DVT****– deep vein thrombosis;* ***MP****– menstrual pictogram;* ***NA****– not applicable;* ***NR****– not reported;* ***PBAC****– pictorial blood loss assessment chart;* ***SD****– standard deviation;* ***UFS-QOL-SSS****– Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire Symptom Severity Scale;* ***UFS-QOL-HRQL****– Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire;* ***UTI****– urinary tract infection.*

Comments

[a] *Self-reported outcome measures in patients not blinded to treatment status may introduce performance bias; missing data may represent patients who experienced treatment failure*
[b] *Confounding factors such as the use of medical interventions (i.e. tranexamic acid) in at least 3 patients may bias in favor of the intervention (FAST-EU trial specific)*
[c] *Quality appraisal of both studies identified a medium risk of bias*
[d] *Reported ranges and standard deviations associated with measures are wide*
[e] *Standard deviations associated with the point estimate exceed clinically meaningful cut-off points*
[f] *Details of the method for evaluating reductions in target fibroid volume were not provided and the relationship between reductions in fibroid volume and symptom burden is unclear*
[g] *Measures of variance such as standard deviations and ranges were not provided*
[h] *Patient cohorts include small sample sizes that represent only a portion of initially enrolled subjects*
[i] *12 month follow-up may not be sufficient to capture treatment failure. Further, outcome assessors were not blinded introducing the possibility of bias – i.e assessors may have favoured avoiding or delaying reintervention during the study period*
[j] *Quality appraisal of the included studies revealed a medium risk of bias for 2 and a high risk of bias for 1*
[k] *Missing data from withdrawals and exclusions may favor the intervention*
[l] *Outcome assessors were not blinded and may have influenced participant decisions regarding reintervention*
[m] *Quality appraisal assessed this study as being at a medium risk of bias*
[n] *Although the included study was assessed as being at a medium risk of bias the risk of bias associated with study design was considered to have minimal impact on the reporting of pregnancy*
[o] *Reporting of complications was inconsistent across included studies.*
[p] *It is unclear whether 12 months is sufficient to capture all relevant adverse events*
[q] *Criterion for designating an event serious/non-serious were not provided*
[r] *Quality appraisal assessed this study as being at a high risk of bias*
[s] *Short follow-up duration*
[t] *Denominator not provided*

Applicability table

Table A-4: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The target population is broad, comprising women with symptomatic uterine fibroids. Women in this population are heterogenous in that they may have many or few fibroids, fibroids of varying sizes, mild to severe symptoms, and normal to extremely heavy menstrual bleeding. Symptomatic fibroids affect both young and older women and the course of disease may change over the course of a womans life. The included studies recruited women with heterogenous baseline characteristics, all of whom reported symptomatic uterine fibroids. Consequently, the broad spectrum of disease represented in the included studies is largely representative of the target population. There is uncertainty regarding the maximal number of fibroids that can or should be treated in any individual, and women not represented in the included studies are those with inconsistent menstrual cycles and/or a with a desire for future fertility.
Intervention	All studies reported the same intervention using the same device. Different study sites within the same studies utilised different types of anaesthesia (general, conscious sedation or regional) and the procedures conducted in different facilities (i.e. hospital-based, procedural rooms etc.) were varied. Proceduralists were gyneacologists or obstetricians. This reflects the minimally invasive nature of the procedure and no evidence was identified to suggest that the clinical performance of the procedure would be affected by the choice of setting, anaesthesia or proceduralist provided that the provider and facility are appropriately credentialled and trained.
Comparators	The included literature were single arm studies. Consequently, no comparative data is available to inform a judgement of effectiveness and safety relative to alternative treatments for uterine fibroids. Currently, women with symptomatic uterine fibroids have access to uterine-preserving interventions that have been compared in RCTs to hysterectomy or to alternative uterine-preserving interventions. Hence, the lack of comparative data regarding TFA is not reflective of the treatment landscape for uterine fibroids.
Outcomes	The included studies reported on important, patient-relevant outcomes. Specifically menstrual bleeding, symptom severity and reintervention rates. These outcomes are consistent with those reported in literature on comparator interventions. Whilst the choice of outcomes facilitates application of the evidence to the real life clinical problems of reducting heavy menstrual bleeding and symptom burden, there were important limitations in terms of study quality that must be considered. Follow-up duration was short (12 months), important outcome measures were unblinded patient reported outcomes, and some ambiguity exists regarding the methods used to calculate and report certain outcomes (reductions in perfused and total fibroid outcomes). Safety outcomes were reported; however, the short follow-up periods and small patient numbers limit the comprehensiveness of a safety assessment.
Setting	Patients in the included studies were recruited from Mexico, The United Kingdom, the Netherlands, Switzerland, German and the United States. The procedure was performed in a range of settings acording to the facilities of the participating site. Within Austria the submitting hospital has clarified that TFA is intended to be conducted in the full inpatient setting or on a day-care basis. The settings described in the included studies are considered applicable to the use of TFA in an inpatient or day-care setting, noting that the procedure is typically considered an outpatient procedure.

List of ongoing randomised controlled trials

No ongoing randomised controlled trials were identified. One trial record (ChiCTR-INR-17010471) referred to a comparative study of microwave ablation, radiofrequency, laser, high intensity focused ultrasound and anhydrous alcohol for uterine leiomyoma. The study is being conducted in Beijing and the available information in English was not sufficient to determine whether the study is a randomised controlled trial and further whether the radiofrequency ablation technology refers to TFA or RFVTA.

Literature search strategies

Search strategy for Cochrane

Search Name: Transcervical RFA of uterine leiomyoma	
Last Saved: 06/12/2019 16:04:38	
Comment: MEL2020 RL/CS	
Search date: 6.12.2019	
ID	Search
#1	MeSH descriptor: [Leiomyoma] explode all trees
#2	(Leiomyoma*) (Word variations have been searched)
#3	(Leio-myoma*) (Word variations have been searched)
#4	MeSH descriptor: [Myoma] explode all trees
#5	(Myoma*) (Word variations have been searched)
#6	(Fibroid*) (Word variations have been searched)
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6 (Word variations have been searched)
#8	MeSH descriptor: [Radiofrequency Ablation] explode all trees
#9	((radiofrequenc* OR radio-frequenc* OR thermal OR heat*) NEAR (ablat* OR therap* OR treatment* OR intervention* OR program* OR procedure* OR regimen* OR transcervi* OR trans-cervi* OR current* OR wave*)) (Word variations have been searched)
#10	(RFA):ti,ab,kw (Word variations have been searched)
#11	(Myolys*) (Word variations have been searched)
#12	(Sonata*) (Word variations have been searched)
#13	(VizAblate*) (Word variations have been searched)
#14	(Viz-Ablate*) (Word variations have been searched)
#15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 (Word variations have been searched)
#16	#7 AND #15 (Word variations have been searched)
70 Hits	

Search strategy for CRD

Search Name: Transcervical RFA of Leiomyomas (MEL 2020) RL/CS 061219	
Search date: 6.12.2019	
ID	Search
#1	MeSH DESCRIPTOR Leiomyoma EXPLODE ALL TREES
#2	(Leiomyoma*)
#3	(Leio-myoma*)
#4	MeSH DESCRIPTOR Myoma EXPLODE ALL TREES
#5	(Myoma*)
#6	(Fibroid*)
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	MeSH DESCRIPTOR Catheter Ablation EXPLODE ALL TREES
#9	(Radiofrequenc*)
#10	(Radio-frequenc*)
#11	(thermal)
#12	(heat*)
#13	(RFA)

#14	(Myolys*)
#15	(Sonata*)
#16	(VizAblate*)
#17	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#18	#7 AND #18
13 Hits	

Search strategy for Embase

Search Name: Transcervical RFA of Leiomyomas (MEL 2020) RL/CS 061219	
Search date: 6.12.2019	
ID	Search
#1	'leiomyoma'/exp
#2	leiomyoma*:ti,ab,de,kw
#3	'leio myoma*':ti,ab,de,kw
#4	'uterus myoma'/exp
#5	myoma*:ti,ab,de,kw
#6	'fibroids'/exp
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	'radiofrequency ablation'/exp
#10	((radiofrequenc* OR 'radio frequenc*' OR thermal OR heat*) NEAR/2 (ablat* OR therap* OR treatment* OR intervention* OR program* OR procedure* OR regimen* OR transcervi* OR 'trans cervi*' OR current* OR wave*)):ti,ab,de,kw
#11	rfa:ti,ab
#12	'myolysis'/exp
#13	myolys*:ti,ab,de,kw
#14	sonata*:dn,ti,ab,de,kw
#15	vizablate*:dn,ti,ab,de,kw
#16	'viz ablate*':dn,ti,ab,de,kw
#17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	#8 AND #17
#19	#18 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)
#20	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti
#21	#18 AND #20
#22	#19 OR #21
#23	#18 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)
#24	#18 AND ('meta analysis'/de OR 'meta analysis (topic)'/de OR 'systematic review'/de)
#25	#23 OR #24
#26	#22 OR #25
121 Hits	

Search strategy for Medline

Search Name: Transcervical RFA of Leiomyomas (MEL 2020) RL/CS 061219		
Search date: 6.12.2019		
ID	Search	Hits
#1	exp Leiomyoma/	22,878
#2	leiomyoma*.mp.	26,825
#3	leio-myoma*.mp.	5
#4	exp Myoma/	2,927
#5	myoma*.mp.	7,128
#6	fibroid*.mp.	7,585
#7	1 or 2 or 3 or 4 or 5 or 6	34,224
#8	exp Radiofrequency Ablation/	39,267
#9	((radiofrequenc* or radio-frequenc* or thermal or heat*) adj3 (ablat* or therap* or treatment* or intervention* or program* or procedure* or regimen* or transcervi* or trans-cervi* or current* or wave*)).mp.	66,966
#10	RFA.ti,ab.	7,675
#11	myolys*.mp.	309
#12	sonata*.mp.	319
#13	VizAblate*.mp.	3
#14	8 or 9 or 10 or 11 or 12 or 13	90,375
#15	7 and 14	377
#16	limit 15 to clinical trial, all	36
#17	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)	4,633,325
#18	15 and 17	84
#19	16 or 18	97
#20	limit 15 to (meta analysis or "systematic review" or systematic reviews as topic)	17
#21	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt.	556,096
#22	15 and 21	38
#23	20 or 22	38
#24	19 or 23	122
#25	remove duplicates from 24	99
99 Hits		

Search strategy for ClinicalTrials.gov

Date of search: 28.01.2020

(radiofrequency OR radio-frequency OR RFA OR ablation OR ablative OR Myolysis OR sonata OR vizablate OR exablate) AND AREA[ConditionSearch] (Leiomyoma OR Myoma OR Fibroid Uterus OR fibroid)

52 Studies identified

Search strategy for WHO-ICTRP

Date of search: 28.01.2020

(Leiomyoma OR Myoma OR Uterine Fibroid OR fibroid) **in the Condition**

(radiofrequency OR radio-frequency OR RFA OR ablation OR ablative OR Myolysis OR sonata OR vizablate OR exablate) **in the Intervention**

43 (17 further) studies identified

Search strategy for EU Clinical Trials (EUdraCT)

Date of search: 28.01.2020

(Leiomyoma OR Myoma OR fibroid) AND (radiofrequency OR radio-frequency OR RFA OR ablation OR ablative OR Myolysis OR sonata OR vizablate OR exablate)

8 studies identified*

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Health Technology Assessment