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Austrian Institute for
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GmbH

Microwave ablation for liver tumours

Systematic Review

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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.

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Content

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List of abbreviations

AE.....Adverse events
AJCC .....American Joint Committee on Cancer
BCLC .....Barcelona Clinic Liver Cancer Classification
C .....Control
CCA.....Cholangiocarcinoma
CEUS .....Contrast-enhanced ultrasound
CI.....Confidence intervals
CIRSE .....Cardiovascular and Interventional Radiological Society of Europe
CR .....Complete response
CRC.....Colorectal carcinoma
CT.....Computed tomography
EASL.....European Association for the Study of the Liver
ECOG.....The Eastern Cooperative Oncology Group
ESMO.....European Society for Medical Oncology
EORTC .....European Association for Research and Treatment of Cancer
FDG .....Fluorodeoxyglucose
GI.....Gastrointestinal
GRADE .....Grading of Recommendations, Assessment, Development and Evaluations
GHz .....Gigahertz
HCC .....Hepatocellular carcinoma
HRQOL .....Health-related quality of life
Hz .....Hertz
iCCA .....Intrahepatic cholangiocarcinoma
I.....Intervention
ICD .....International Classification of Diseases
INAHTA.....International Network of Agencies for Health Technology Assessment
KLCA.....Korean Liver Cancer Association
KPS .....Karnofsky Performance Score

LRT.....Local regional therapy
MeSH .....Medical subject heading
Min.....Minute/s
mRECIST .....Modified Response Evaluation Criteria in Solid Tumors
MRI .....Magnetic resonance imaging
MWA.....Microwave ablation
N/n .....Number
NA .....Not applicable
NCC .....National Cancer Center
Ng/mL .....Nanograms per milliliter
NICE.....National Institute for Health and Care Excellence
NR.....Not reported
OS.....Overall survival
PD .....Progressive disease
PET .....Positron emission tomography
PMCT .....Percutaneous microwave coagulation therapy
PR.....Partial response
PRISMA.....Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS .....Performance status
Pts.....Participants
QOL .....Quality of life
RCTs .....Randomised controlled trials
RECIST .....Response Evaluation Criteria in Solid Tumors
RFA.....Radiofrequency ablation
RFS .....Recurrence-free survival
RoB.....Risk of bias
RR .....Relative risk/Risk ratio
SBRT.....Stereotactic body radiation therapy
SD.....Stable disease
TACE .....Transcatheter arterial chemoembolisation
TNM.....Primary tumour, Regional lymph nodes, Distant metastases
UICCA.....International Union against Cancer
UK.....United Kingdom
USA.....United States of America
VI.....Vascular invasion
VS .....Versus
Yrs .....Years

Executive Summary

Background: Health Problem & Description of Technology

Globally, liver cancer is a major health problem with poor survival. Whilst resection is considered the gold standard treatment for liver cancer, most patients are ineligible. A range of alternative local treatments for patients with both primary and secondary liver cancer have been developed where surgical intervention is not an option, including ablation therapy. This review evaluated the effectiveness and safety of microwave ablation (MWA) for treating liver tumours: MWA uses electromagnetic energy to heat and destroy tumours. Microwave ablative systems are comprised of a microwave generator, a flexible coaxial cable, and microwave antennae. MWA can be conducted under local or general anaesthesia, either percutaneously, laparoscopically or via open surgery. During the procedure, the antenna is inserted into the tumour under image guidance and then electromagnetic microwaves are generated. Multiple antennae may be used simultaneously when treating a large tumour. At the completion of ablation, the antennae are removed, pressure is applied to stem bleeding. Sutures are rarely required.

liver cancer: major health problem

resection is gold standard

alternative local treatments: ablation therapy

microwave ablation (MWA)

In patients with primary or secondary liver tumours is MWA, in comparison to resection, transcatheter arterial chemoembolisation (TACE) or other ablation techniques, more effective and safe concerning overall survival, tumour recurrence, treatment success, length of hospitalisation, ablation time, resolution of symptoms and adverse events

research question for systematic review on MWA

Methods

A systematic literature search was conducted to evaluate the effectiveness and safety of MWA compared with resection, TACE or other ablation techniques. The following databases were searched: Medline, Embase, The Cochrane Library and the International Network of Agencies for Health Technology Assessment (INAHTA). Two authors independently carried out study selection, data extraction and quality appraisal. Meta-analyses were conducted where more than two studies were available for a particular outcome. The quality of the included studies was assessed using the Cochrane Risk of Bias 2 tool and the strength of the evidence was rated according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

systematic literature search in 4 databases

quality appraisal of literature

meta-analyses

GRADE

The following outcomes were defined as crucial to derive a recommendation on the relative effectiveness of MWA compared to resection, TACE or other ablation techniques, in patients with primary or secondary liver tumours: overall survival, rate of tumour recurrence and resolution of symptoms (for patients undergoing palliative ablation). Additional outcomes considered were: treatment success (i.e. partial ablation, complete ablation), length of hospital stay and ablation time. The following outcomes were defined as crucial to derive a recommendation on the relative safety of MWA compared to resection, TACE or other ablation techniques, in patients with primary or secondary liver tumours: mortality (perioperative and long-term), intra-abdominal bleeding, gastrointestinal bleeding, wound dehiscence, postoperative ascites, intraperitoneal haemorrhage and bile duct injury. Additional outcomes considered were: biliary stenosis, acute respiratory distress syndrome, liver abscess, neoplastic seeding, biliary peritonitis, adjacent vessel thrombosis, collateral thermal injury and postoperative pain.

endpoints for effectiveness: OS, tumour recurrence, resolution of symptoms

endpoints for safety: mortality, bleeding, …

Results: effectiveness and safety

available evidence: 12 RCTs with different comparators and in different patient populations

A total of twelve RCTs that met the predefined inclusion criteria were identified. Five RCTs compared MWA with radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC). One RCT compared MWA with TACE for HCC. One RCT compared MWA plus TACE with standalone TACE for HCC. One RCT compared MWA plus TACE with standalone TACE for patients with HCC, intrahepatic cholangiocarcinoma (iCCA) or mixed HCC. One RCT compared MWA with MWA plus TACE with standalone TACE for HCC. One RCT compared liver resection plus MWA with liver resection only for HCC. One RCT compared MWA with laparoscopic liver resection for HCC. One RCT compared MWA with liver resection for secondary liver tumours (colorectal metastases).

effectiveness: no difference to RFA or resection

advantages vs. TACE

safety: similar to comparators

Overall survival is regarded as the gold standard primary clinical endpoint in cancer trials. This outcome was reported for all MWA comparisons identified. For studies of patients with primary liver cancer (ten RCTs for HCC only and one RCT for HCC, iCCA and mixed HCC), overall survival was not significantly different for MWA versus RFA (at 12 and 24 months) or for MWA versus laparoscopic liver resection (at 12, 24 and 36 months). Survival was significantly improved for MWA compared with TACE. MWA combined with resection or TACE also improved survival compared with resection or TACE alone. In the one RCT comparing MWA with open resection for secondary cancer, overall survival did not significantly differ at three years. Safety outcomes were poorly and inconsistently reported across the included studies. Although not generally statistically analysed, overall complication rates appeared to be similar for most comparisons except MWA versus resection.

upcoming evidence: 34 RCTs ongoing

A total of 34 ongoing RCTs were identified investigating the effectiveness and safety of MWA compared with other invasive and non-invasive treatments for primary (n = 24) and secondary (n = 10) liver tumours.

Discussion

some gaps in the evidence, low quality of evidence

nevertheless MWA seems equally effective and safe as RFA

50% of MWA trials before 2016, ev. better technology now

There are gaps in the evidence with regard to the types of liver cancers included in the studies; these were predominately early-stage HCC with evidence on more advanced HCC and other primary or secondary liver cancers limited. The only comparison represented by more than one study was MWA versus RFA. Results for the remaining comparisons reported in this review are based on one included study each. The results should be interpreted with caution owing to the following factors. The strength of evidence for the critical outcomes for each comparison presented in this report was low to very low owing to the lack of information regarding randomisation, missing data, and uncertainty regarding selective reporting of the results. Further potential applicability issues identified include the location in which trials were undertaken (only one from Europe) and the date which the trials were undertaken. Since half of the studies were published prior to 2016, the MWA technology they used may no longer be representative of current practice. In addition, most studies were conducted at a single-centre and it is uncertain whether they reflect what would be obtained when used widely in clinical practice.

Conclusion

MWA seems comparable to RFA

Based on the evidence, MWA seems comparable to RFA for the treatment of early-stage HCC. Further clinical trials and robust RCTs are needed to evaluate the effectiveness and safety of MWA compared with other treatments in early-stage HCC and on the use of MWA to treat other types of primary and secondary liver cancers.

Zusammenfassung

Hintergrund

Leberkrebs: Resektion ist Goldstandard

alternative lokale Behandlungen: Ablationstherapie

Leberkrebs ist ein weltweites Gesundheitsproblem mit schlechten Überlebensraten. Obwohl die Resektion als Goldstandard für die Behandlung von Leberkrebs gilt, kommen die meisten Patient*innen dafür nicht in Frage. Für Patient*innen mit primärem und sekundärem Leberkrebs, für die eine chirurgische Intervention keine Option darstellt, wurde eine Reihe alternativer lokaler Behandlungen entwickelt, darunter die Ablationstherapie. In dieser Übersichtsarbeit wurden Wirksamkeit und Sicherheit der Mikrowellenablation (MWA) zur Behandlung von Lebertumoren bewertet.

Indikation und therapeutisches Ziel

primärer Leberkrebs: hepatozelluläres Karzinom (HCC) – 90 % aller primären LeberCA

sekundärer Leberkrebs: Fernmetastasen (häufig von KolonCa)

Es gibt mehrere Arten von primärem Leberkrebs, die sich nach der Art der Zellen richten, die zu Krebs werden. Die häufigste Form ist das hepatozelluläre Karzinom (HCC), das etwa 90 % aller primären Leberkrebserkrankungen ausmacht und weltweit die dritthäufigste Ursache für krebsbedingte Todesfälle ist. Das Cholangiokarzinom (CCA) ist der zweithäufigste primäre Leberkrebs und macht 10-25 % aller Leberkrebsfälle aus. Bei den meisten Leberkrebsarten (95 %) handelt es sich um sekundäre Krebsarten, die von einer anderen Stelle in die Leber gestreut haben. Das kolorektale Karzinom (CRC) ist die häufigste Ursache für sekundären Leberkrebs.

Inzidenz von HCC in Österreich 2019:

760 Männer & 265 Frauen

Eine Untersuchung der Inzidenz von HCC in Österreich über einen Zeitraum von 20 Jahren zwischen 1990 und 2009 ergab, dass die altersbereinigte Inzidenz bei Männern in diesem Zeitraum zwischen 3,98 und 7,54 pro 100.000 schwankte. Die Inzidenz bei Frauen war in diesem Zeitraum deutlich niedriger als bei Männern und blieb mit einer Spanne von 1,09 bis 1,61 pro 100.000 stabil. Neuere österreichische Daten zeigen, dass im Jahr 2019 1.025 bösartige Leberkrebserkrankungen diagnostiziert wurden (760 bei Männern und 265 bei Frauen), was 2,5 % der jährlichen Krebserkrankungen in diesem Jahr entspricht. Die altersadjustierte Inzidenzrate liegt bei 11,5 Fällen pro 100.000. Die Inzidenz des sekundären Leberkrebses liegt in Österreich bei 49,2 pro 100.000 Menschen, wobei etwa 25 bis 30 % davon Lebermetastasen entwickeln.

Beschreibung der Technologie

Mikrowellenablation (MWA)

Mikrowellenantennen werden unter Lokalanästhesie in den Tumor eingeführt

Die MWA nutzt elektromagnetische Energie zur Erhitzung und Zerstörung von Tumoren. Mikrowellenablative Systeme bestehen aus einem Mikrowellengenerator, einem flexiblen Koaxialkabel und Mikrowellenantennen. MWA kann unter lokaler oder allgemeiner Anästhesie entweder perkutan, laparoskopisch oder im Rahmen einer offenen Operation angewandt werden. Während des Eingriffs wird die Antenne unter Bildführung in den Tumor eingeführt und es werden anschließend elektromagnetische Mikrowellen erzeugt. Bei der Behandlung eines großen Tumors können mehrere Antennen gleichzeitig eingesetzt werden. Nach Abschluss der Ablation werden die Antennen entfernt und Druck ausgeübt, um die Blutung zu stillen. Nähte sind nur selten erforderlich.

Forschungsfrage für systematischen Review

Ist die MWA bei Patient*innen mit primären oder sekundären Lebertumoren im Vergleich zur Resektion, transkathetergestützten arteriellen Chemoembolisation (TACE) oder anderen Ablationstechniken wirksamer und sicherer im Hinblick auf das Gesamtüberleben, das Wiederauftreten von Tumoren, den Behandlungserfolg, die Dauer des Krankenhausaufenthalts, die Ablationszeit, das Verschwinden von Symptomen und unerwünschte Ereignisse?

Methoden

systematische Literatursuche in 4 Datenbanken

4-Augen-Prinzip bei Selektion, Extraktion, Qualitätsbewertung (RoB, GRADE)

Es wurde eine systematische Literatursuche durchgeführt, um die Wirksamkeit und Sicherheit der MWA im Vergleich zur Resektion, TACE oder anderen Ablationstechniken zu bewerten. Die folgenden Datenbanken wurden durchsucht: Medline, Embase, The Cochrane Library und das International Network of Agencies for Health Technology Assessment (INAHTA). Zwei Personen führten unabhängig voneinander die Studienauswahl, die Datenextraktion und die Qualitätsbewertung durch. Im Falle von Unstimmigkeiten wurde eine dritte Person zur Diskussion und Konsensfindung hinzugezogen. Meta-Analysen wurden durchgeführt, wenn für ein bestimmtes Ergebnis mehr als zwei Studien verfügbar waren. War eine Meta-Analyse nicht möglich, wurden die Ergebnisse narrativ dargestellt. Die Qualität der eingeschlossenen Studien wurde mit dem Cochrane Risk of Bias 2 Tool bewertet und die Stärke der Evidenz gemäß dem Grading of Recommendations, Assessment, Development and Evaluations (GRADE) eingestuft.

wesentliche Endpunkte für Wirksamkeit: Gesamtüberleben, Rate der Tumorrezidive und Abklingen von Symptomen

Die folgenden Endpunkte wurden als entscheidend definiert, um eine Empfehlung zur relativen Wirksamkeit der MWA im Vergleich zur Resektion, TACE oder anderen Ablationstechniken bei Patient*innen mit primärem oder sekundärem Lebertumor abzuleiten: Gesamtüberleben, Rate des Tumorrezidivs und blingen von Symptomen (bei Patient*innen, die sich einer palliativen Ablation unterziehen). Zusätzliche wichtige Endpunkte waren: Behandlungserfolg (d. h. Teilablation, vollständige Ablation), Dauer des Krankenhausaufenthalts und Ablationszeit.

wesentliche Endpunkte für Sicherheit:

Sterblichkeit, Blutungen, Wunddehiszenz

Die folgenden Endpunkte wurden als entscheidend definiert, um eine Empfehlung zur relativen Sicherheit der MWA im Vergleich zur Resektion, TACE oder anderen Ablationstechniken bei Patient*innen mit primären oder sekundären Lebertumoren abzuleiten: Sterblichkeit (perioperativ und langfristig), intraabdominale Blutungen, gastrointestinale Blutungen, Wunddehiszenz, postoperativer Aszites, intraperitoneale Blutungen und Gallengangsverletzungen. Als zusätzliche Endpunkte wurden berücksichtigt: Gallengangsstenose, akutes Atemnotsyndrom, Leberabszess, biliäre Peritonitis, Thrombose benachbarter Gefäße, kollaterale thermische Schädigung und postoperative Schmerzen.

Ergebnisse: Wirksamkeit und Sicherheit

verfügbare Evidenz: 12 RCTs

bei HCC:
5 RCTs: MWS vs. RFA
1 RCT: MWA vs. TACE
1 RCT: MWA+TACE vs. TACE
1 RCT: MWA vs. MWA+ TACE vs. TACE
2 RCTs: MWA vs. Resektion

Insgesamt wurden zwölf RCTs identifiziert, die die vordefinierten Einschlusskriterien erfüllten:

- fünf RCTs verglichen die MWA mit der Radiofrequenzablation (RFA) bei hepatozellulärem Karzinom (HCC).
- ein RCT verglich MWA mit TACE bei HCC.
- ein RCT verglich MWA plus TACE mit einer alleinigen TACE bei HCC.
- ein RCT verglich MWA mit MWA plus TACE mit einer alleinigen TACE bei HCC.

- ein RCT verglich eine Leberresektion plus MWA mit einer alleinigen Leberresektion bei HCC.
- ein RCT verglich MWA mit einer laparoskopischen Leberresektion bei HCC.
- ein RCT verglich MWA plus TACE mit einer alleinigen TACE bei Patient*innen mit HCC, intrahepatischem Cholangiokarzinom (iCCA) oder gemischtem HCC.
- ein RCT verglich MWA mit einer Leberresektion bei sekundären Lebertumoren (kolorektale Metastasen).

bei HCC + iCCA
1 RCT: MWA+TACE vs. TACE
bei sekundären Ca
1 RCT: MWA vs. Resektion

Das Gesamtüberleben gilt als Goldstandard der primären klinischen Endpunkte in Krebsstudien. Dieser Outcome wurde für alle identifizierten MWA-Vergleiche berichtet. Bei Studien mit Patient*innen mit primärem Leberkrebs (zehn RCTs nur für HCC und ein RCT für HCC, iCCA und gemischtes HCC) unterschied sich das Gesamtüberleben nicht signifikant für MWA gegenüber RFA (nach 12 und 24 Monaten) oder für MWA gegenüber laparoskopischer Leberresektion (nach 12, 24 und 36 Monaten). Das Überleben wurde durch MWA im Vergleich zu TACE signifikant verbessert. Die MWA in Kombination mit einer Resektion oder TACE verbesserte ebenfalls das Überleben im Vergleich zur Resektion oder TACE allein. In dem einen RCT, der die MWA mit einer offenen Resektion bei sekundärem Krebs verglich, war das Gesamtüberleben nach drei Jahren nicht signifikant unterschiedlich.

klinische Ergebnisse
Gesamtüberleben:
bei HCC (und iCCA)
kein Unterschied MWA vs. RFA
kein Unterschied MWA vs. Resektion
Unterschied zugunsten von MWA vs. TACE

Zum Endpunkt „Rate der Tumorrezidive" zeigten sich gleiche Ergebnisse wie zum Gesamtüberleben. Zu den Endpunkten Verbesserung der Symptomatik und Lebensqualität konnte keine Evidenz gefunden werden.

Tumorrezidive:
gleiche Ergebnisse
QoL: keine Evidenz

Über die Sicherheitsergebnisse wurde in den eingeschlossenen Studien nur unzureichend und uneinheitlich berichtet. Obwohl sie im Allgemeinen nicht statistisch ausgewertet wurden, schienen die Gesamtkomplikationsraten bei den meisten Vergleichen – mit Ausnahme von MWA versus Resektion – ähnlich zu sein.

Nebenwirkungen und Komplikationen:
uneinheitliche Berichterstattung

Laufende Studien

Insgesamt wurden 34 laufende RCTs identifiziert, in denen die Wirksamkeit und Sicherheit der MWA im Vergleich zu anderen invasiven und nicht-invasiven Behandlungen von primären (n = 24) und sekundären (n = 10) Lebertumoren untersucht werden.

34 laufende RCTs:
24 zu primären Ca
10 zu sekundären Ca

Diskussion

Es gibt Evidenzlücken hinsichtlich der Stadien und Leberkrebsarten, die in die Studien eingeschlossen wurden; es handelte sich überwiegend um HCC im Frühstadium, während die Evidenz zu fortgeschrittenem HCC und anderen primären oder sekundären Leberkrebsarten nur begrenzt vorhanden war. Der einzige Vergleich, der in mehr als einer Studie vertreten war, war MWA versus RFA. Die Ergebnisse für die übrigen in dieser Übersichtsarbeit berichteten Vergleiche beruhen auf jeweils einer eingeschlossenen Studie.

Evidenzlücken zu unterschiedlichen Stadien der LeberCa

Evidenz zu primärem HCC in frühen Stadien, nicht aber zu fortgeschrittenen oder sekundären Ca

Die Ergebnisse sollten aufgrund der folgenden weiteren Faktoren mit Vorsicht interpretiert werden. Die Stärke der Evidenz für die kritischen Endpunkte für jeden in diesem Bericht dargestellten Vergleich war gering bis sehr gering, was auf fehlende Informationen zur Randomisierung, fehlende Daten sowie auf Unsicherheiten aufgrund selektiver Berichterstattung der Er-

viele Studien zu MWA vs. RFA, aber von geringer Qualität

gebnisse zurückzuführen ist. Zu den weiteren potenziellen Problemen bei der Anwendbarkeit gehören der Studienstandort (nur eine Studie aus Europa) und das Studiendatum.

Hälfte der Studien vor 2016, ev. heute andere MWA Technologie

Da die Hälfte der Studien vor 2016 veröffentlicht wurde, ist die darin verwendete MWA-Technologie möglicherweise nicht mehr repräsentativ für die aktuelle Praxis. Darüber hinaus wurden die meisten Studien an einem einzigen Zentrum durchgeführt. Daher ist ungewiss, ob sie die Ergebnisse widerspiegeln, die bei einer breiten Anwendung in der klinischen Praxis erzielt werden würden.

Schlussfolgerung

MWA vs. RFA vergleichbar bez. Wirksamkeit und Sicherheit

Angesichts der vorliegenden Evidenz scheint die MWA für die Behandlung von HCC im Frühstadium mit der RFA vergleichbar zu sein. Weitere klinische Studien und belastbare RCTs sind erforderlich, um die Wirksamkeit und Sicherheit der MWA im Vergleich zu anderen Behandlungen bei HCC im Frühstadium sowie den Einsatz der MWA zur Behandlung anderer Arten von primärem und sekundärem Leberkrebs zu bewerten.

1 Background

1.1 Overview of the disease, health condition and target population[1]

primärer oder sekundärer Leberkrebs

Liver cancer is cancer that affects the cells of the liver. It can be either primary or secondary. Primary liver cancer starts in the liver; secondary liver cancer has spread (metastasised) to the liver from another part of the body [1].[2, 3]

primärer Leberkrebs:

hepatozelluläres Karzinom (HCC)

cholangiozelluläres Karzinom (CCA)

Angiosarkom der Leber

die meisten Leberkrebse sind aber sekundäre Karzinome häufig von ausgehend

There are several types of primary liver cancer, based on the type of cells that become cancerous. The most common form is hepatocellular carcinoma (HCC) which accounts for approximately 90% of all primary liver cancers [2], which is the third leading cause of cancer-related deaths worldwide [3]. Cholangiocarcinoma (CCA), cancer of the bile duct, is the second most common primary liver cancer accounting for 10-25% of liver cancers [4]. There are two forms; intrahepatic cholangiocarcinoma (iCCA) that forms in the bile ducts inside the liver and extrahepatic bile duct cancer, which forms in the bile ducts outside the liver [5]. Another rarer form of primary liver cancer is angiosarcoma (cancer of the liver blood vessels) which accounts for about 0.1 to 2.0% of all primary liver cancers [6]. Most liver cancers (95%) are secondary cancers, having spread to the liver from another site. Colorectal carcinoma (CRC) is the most common origin of secondary liver cancer [7]. Other cancers that spread to the liver include breast, oesophageal, stomach, pancreatic, lung, kidney and melanoma skin cancers [8]. The relevant International Classification of Diseases (ICD)-11 codes for primary and secondary liver cancers are listed in Table 1-1.[3, 4]

Table 1-1: ICD-11 codes for liver cancers

Cancer type	ICD-11 code
Combined hepatocelluar-cholangiocarcinoma	2C12.00
Hepatocellular carcinoma	2C12.02
Other specified malignant neoplasm of the liver	2C12.0Y
Malignant neoplasm of intrahepatic bile ducts	2C12.1
Malignant neoplasms of liver or intrahepatic bile ducts, unspecified	2C12.Z
Malignant neoplasms of perihilar bile duct	2C18
Malignant neoplasm metastasis in liver	2D80.0
Malignant neoplasm metastasis in intrahepatic bile duct	2D80.1
Other specified malignant neoplasm metastasis in liver or intrahepatic bile duct	2D80.Y
Malignant neoplasm metastasis in liver or intrahepatic bile duct, unspecified	2D80.Z

Source: International Classification of Diseases 11th Revision [9]

[1] This section addresses the EUnetHTA Core Model® domain CUR.

[2] **A0001** – For which health conditions, and for what purposes is the technology used?

[3] **A0007** – What is the target population in this assessment?

[4] **A0002** – What is the disease or health condition in the scope of this assessment?

HCC Inzidenz in Ö (1990-2009) Männer: 3,98-7,54 Frauen: 1,09-1,61 pro 100.000

2019: 1.025 (760 bei Männern & 265 bei Frauen)

The incidence of HCC varies globally due to the variation in risk factors in different countries [10]. A review of the incidence of HCC in Austria over a 20-year period between 1990 and 2009 reported the age-adjusted incidence for males fluctuated during this time ranging from 3.98 to 7.54 per 100,000. The incidence in females over this time period was significantly lower than for males and remained stable, ranging from 1.09 to 1.61 per 100,000 [10]. More recent Austrian data indicates 1,025 malignant liver cancers were diagnosed in 2019 (760 in men and 265 in women), accounting for 2.5% of the annual cancer diseases in this year [11]. The age-adjusted incidence rate is 11.5 cases per 100,000 [11]. With respect to secondary liver cancer, in Austria the CRC incidence is about 49.2 per 100,000 people [12] with approximately 25 to 30% of these developing hepatic metastases [13].[5]

Risikofaktoren HCC:

Zirrhose, HepB, Alkohol, Rauchen, Übergewicht, Familiengeschichte

Risk factors for developing HCC include cirrhosis, a condition where healthy liver cells are replaced by scar tissue, long-term infection with hepatitis B or C, heavy alcohol use, non-alcoholic fatty liver disease, smoking tobacco, being overweight and a family history of HCC [14]. Males have a higher risk than females and the risk increases with age [15]. In 2018, 53% of liver cancers in Austria were attributed to both hepatitis B and C combined [16]. Risk factors for CCA include parasitic infections, primary sclerosing cholangitis, biliary-duct cysts, hepatolithiasis and toxins [4].[6]

Symptome: Gelbsucht, Schmerzen im Unterleib, geschwollener Bauch ungeklärte Gewichtsabnahme, Fieber, Müdigkeit

When the cancer is small and in its early stages, liver cancer often has no symptoms. As it grows symptoms of liver cancer can include:

- Yellowing of the skin (jaundice)
- Dark urine and pale faeces
- Pain in abdomen
- A swollen abdomen
- Pain in the right shoulder
- Unexplained weight loss
- Fever
- Fatigue
- Itchy skin [8, 17].[7]

Klassifikation des Schweregrades der Erkrankung

HCC: Barcelona Clinic Liver Cancer Classification (BCLC)

CCA: Tumour-Nodes-Metastasis (TNM)

The effect of liver cancer on the ability of people to function is dependent on its stage.[8] HCC is usually staged using the Barcelona Clinic Liver Cancer Classification (BCLC) and cholangiocarcinoma using the Tumour-Nodes-Metastasis system. For secondary liver cancer it is given a stage using the system for the primary cancer [18]. In the very early stages of primary cancer, where there is only one to three small nodules, people are generally fully active, able to carry on pre-disease performance without restriction. In the later stages of the liver cancer when it has spread outside the liver individuals may be capable of self-care but unable to work. In the final stages of liver cancer people become more and more confined to a bed or chair during waking hours and are eventually unable to perform any self-care [19, 20].

[5] **A0023** – How many people belong to the target population?

[6] **A0003** – What are the known risk factors for the disease or health condition?

[7] **A0005** – What is the burden of disease for the patients with the disease or health condition?

[8] **A0006** – What are the consequences of the disease or health condition for the society?

Überlebensprognose vom Stadium, aber auch anderen Faktoren (allgemeine Gesundheit) abhängig

längeres Überleben: Fehlen von Aszites und weniger HCC-Nodule, weiblich

Left untreated liver cancer will eventually lead to death, with length of survival depending on the stage of the cancer as well as other factors such as age, fitness and overall health.[9] In a study of 600 Italian patients with untreated HCC, median survival progressively and significantly decreased with worsening BCLC stage as follows; BCLC 0: 38 months, BCLC A: 25 months, BCLC B: ten months, BCLC C: seven months, BCLC D: six months. Overall median survival was nine months with the principal cause of death being tumour progression. Longer survival was significantly associated with female gender, absence of ascites and fewer HCC nodules [21]. Patients with CCA usually present at late stages of the disease as these cancers are difficult to diagnose. As a result, approximately 50% of untreated patients with CCA die within three to four months of presentation from the indirect effects of local tumour progression, bile duct obstruction, liver failure or sepsis from cholangitis and abscesses [22]. A natural history study of Swedish patients with untreated liver metastases from CRC reported a median survival time of 4.5 months (mean of 5.6 months). There was no difference in survival time between patients < 70 years compared with those > 70 years of age. In patients whose tumour occupied less than 25% of their liver the median survival time was 6.2 months whereas in patients whose tumour occupied more than 75% of their liver the median survival time was 3.4 months [23].

1.2 Current clinical practice[10]

Europäische Leitlinien

HCC
CCA (iCCA)
Lebermetastasen

European clinical practice guidelines were identified for the management of HCC [19, 24, 25], intrahepatic CCA [26] and liver metastases [27].

Standards of Practice on thermal ablation of liver tumours were published in 2020 by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Standards of Practice Committee [28]. This involved a review of current literature in consultation with a working group of experts to provide best practice techniques for thermal ablation, including microwave ablation (MWA). These are summarised briefly below.

3 Leitlinien zu HCC:

AWMF 2021
EASL 2018
ESMO 2021

Hepatocellular Carcinoma (HCC): Three guidelines for the management of HCC were identified. They are from the Working Group of the Association of Scientific Medical Societies in Germany (AWMF) [29], European Association for the Study of the Liver (EASL) [24] and the European Society for Medical Oncology (ESMO) [25]. The AWMF guideline was published in 2021. The EASL guideline, published in 2018, is an update of a previous guideline published in conjunction with the European Association for Research and Treatment of Cancer (EORTC) in 2012 [30]. The most recent update to the ESMO guideline was published in March 2021 [19, 25].

These guidelines focus on the surveillance, diagnosis, disease staging and therapeutic strategies for HCC. For the purposes of this report the diagnostic, staging and therapeutic strategies for HCC will be summarised briefly with a focus on the use of microwave (and or other thermal) ablative therapies.

[9] **A0004** – What is the natural course of the disease or health condition?

[10] This section addresses the EUnetHTA Core Model® domain CUR.

Diagnose:

nicht-invasive (CT, MRT, FDG-PET) und invasive (Pathologie) Methoden

Diagnosis[11]*:* The diagnosis of HCC in cirrhotic patients may be based on non-invasive (imaging) criteria alone or in conjunction with pathology, whereas the diagnosis of HCC in non-cirrhotic patients must be confirmed with tumour pathology [24, 25].

Non-invasive criteria (for cirrhotic patients only) are nodule(s) ≥ 1cm based on imaging obtained by multiphasic computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI), or contrast-enhanced ultrasound (CEUS) (in the absence of CT or MRI due to reduced sensitivity) [24]. The use of a fluorodeoxyglucose (FDG) positron emission tomography (PET)-scan is associated with false negatives and is not recommended for early diagnosis of HCC [24]. Pathologic diagnosis should include histological and immunohistological analyses, based on international consensus [24, 25].

Staging HCC: BCLC

Staging Staging of HCC for the purpose of clinical decision making and prognosis should include tumour burden, liver function and performance status (PS) [24]. The BCLC Staging System is validated and recommended for the prognosis and treatment allocation of HCC [24]. The prognostic stages according to the most recent (2022) version of BCLC are presented in Table 1-2.

Table 1-2: Barcelona Clinic Liver Cancer (BCLC) Staging System

BCLC Stage	Tumour burden	Liver function	Performance status (ECOG*)
0 Very early stage	Single nodule ≤2cm	Preserved liver function	0
A Early stage	Single nodule or up to 3 nodules ≤3cm each	Preserved liver function	0
B Intermediate	Multinodular	Preserved liver function	0
C Advanced	Portal invasion and/or extrahepatic spread	Preserved liver function	1-2
D End-stage	Any tumour burden	End-stage liver function	3-4

Source: Reig 2022 [31]

Abbreviations: BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group.

*Notes: * The Eastern Cooperative Oncology Group measures Performance Status on a 6-point scale where 0 = fully active, able to carry on pre-disease performance without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (light housework/office work); 2 = ambulatory and capable of self-care but unable to carry out work activities. Up and about more than 50% of waking hours; 3 = capable of limited selfcare, confined to bed/chair more than 50% of waking hours; 4 = disabled, unable to perform any self-care, and totally confined to bed or chair; 5 = deceased [20].*

Behandlungsoptionen:

thermale Ablation
Resektion
Transplantation
Chemoembolisation
systemische Therapie
Best Supportive Care

Treatment[12]*:* Within the BCLC Staging System, HCC treatment options include ablation, resection, transplant, chemoembolisation, systemic therapy and best supportive care.

According to the AWMF S3 guidelines [29], the following recommendations are applicable for the use of MWA:

- Resection and ablation are equivalent procedures in patients with HCC up to 3cm (strong expert consensus).

[11] **A0024** – How is the disease or health condition currently diagnosed according to published guidelines and in practice?

[12] **A0025** – How is the disease or health condition currently managed according to published guidelines and in practice?

- In patients with HCC smaller than 3cm in an unfavourable location for resection or with impaired or limited liver function, thermoablation of the tumour should be primarily offered (grade of recommendation: A; level of evidence 1).
- Percutaneous ablation of HCC should be performed using RFA or MWA (strong expert consensus).

perkutane Ablation mit Mikrowellen (MWA) oder Radiofrequenz (RFA)

With regards to thermal ablation, the EASL guideline recommended radiofrequency ablation (RFA) be considered the standard of care for patients with BCLC stage 0 and A tumours who are not suitable for surgery (recommendation: strong; level of evidence: high) [24]. The same guideline also stated that thermal ablation of single tumours (2-3cm in size) is considered an alternative to resection in certain circumstances (i.e. based on technical factors such as tumour location, and hepatic and extrahepatic patient conditions). In BCLC stage 0 patients, RFA may be considered the first-line treatment option for tumours in favourable locations even when the patient is not contraindicated for surgery. The only mention of MWA in the EASL guideline is that, based on low quality evidence, MWA showed promising results for local control and survival [24].

SoC bei BCLC stage 0 und A, sofern Resektion nicht möglich ist

The ESMO guideline recommended thermal ablation, via RFA or MWA, as a first-line treatment in BCLC 0 patients (grade of recommendation: A; level of evidence: II) [19]. The guideline also states, in BCLC A patients, RFA has been adopted as a first-line treatment option irrespective of liver function after demonstrating survival benefits compared with surgery (with no mention of MWA in this patient group). With regard to MWA specifically, this guideline states that at the time of writing (2018) MWA had not been adequately compared with RFA, nor had its potential advantage in tumours sized 3-5cm or the impact of the heat-sink effect caused by adjacent large vessels been properly investigated [19].

iCCA: 1 Leitlinie EASL 2014

Intrahepatic cholangiocarcinoma (iCCA): One clinical practice guideline, published in 2014 by EASL, was identified for the diagnosis and management of iCCA [26].

Diagnose: Pathologie WHO-Klassifikation

Diagnosis[11]*:* Definitive diagnosis of iCCA requires pathological testing based on the World Health Organization's classification for biliary tract cancer. Additional testing to differentiate primary iCCA from metastatic adenocarcinoma (i.e. clinical, radiological, or endoscopic evaluation) or mixed HCC tumours (i.e. immunostaining to detect HCC markers) may be needed.

ohne Zirrhose nur radiologische Abklärung

In non-cirrhotic patients who are to undergo surgical resection, a presumed radiological diagnosis of iCCA is sufficient. PET-scan and serological tumour markers (such as CA19-9) are not sufficient for diagnosis of iCCA. CT and/or MRI may be used to assess the resectability of iCCA, intra- and extra-hepatic metastatic disease or venous and arterial invasion.

Staging iCCA: AJCC/UICCA Klassifikation

Staging The preferred staging system for resected iCCA is the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICCA) staging schema which codes the extent of the primary tumour (T), regional lymph nodes (N), and distant metastases (M) and provides a "stage grouping" based on T, N, and M [26, 32]. The prognostic stages according to the AJCC/UICCA are presented in Table 1-3.

Table 1-3: Intrahepatic cholangiocarcinoma stages according to AJCC/UICCA

TNM stage I	Single tumour
TNM stage II	Single or multinodular, vascular invasion (VI)
TNM stage III	Visceral peritoneum perforation, local hepatic invasion
TNM stage IV	Periductal invasion, N1, M1

Source: Sayiner 2019 [26]

Abbreviations: TNM = primary tumour, regional lymph nodes, distant metastases; VI = vascular invasion.

Behandlungsoptionen:

Resektion thermale Ablation (RFA, MWA)

Treatment[13]*:* Surgical resection is the treatment of choice for iCCA. Surgical candidates include those with single nodules and no evidence of disease spread. Surgery is contraindicated in patients with intrahepatic metastases, vascular invasion, lymph node metastases and cirrhotic patients with advanced liver failure. There are no established adjuvant therapies for use after surgical resection [26].

kein Therapiestandard etabliert

For those with non-resectable iCCA there is no established first-line local-regional therapeutic options. This guideline states that ablation approaches may be considered for small, single nodules (<3cm) if surgery is not an option; however, at the time of writing (2014) additional clinical trials were needed to establish its role in this population (evidence quality: C (low); recommendation: 2 (weak)) [26]. The authors noted that although RFA had been the most studied, alternative ablation approaches such as MWA are also feasible [26].

Angiosarkom: keine Leitlinie identifiziert

Liver angiosarcomas: No guidelines for the management of liver angiosarcomas or other rare primary liver cancers were identified.

Lebermetastasen:

NICE Empfehlungen 2016 zu MWA

keine Bedenken gegen MWA Patientenselektion wichtig

Liver metastases: The National Institute for Health and Care Excellence (NICE) published evidenced-based recommendations in 2016 on MWA for the treatment of liver metastases in adults [27]. NICE found no evidence at the time of writing their recommendations that raised any major safety concerns for MWA and its efficacy in terms of tumour ablation was adequate. It was recommended that MWA be used provided standard arrangements for clinical governance, consent and audit were in place. NICE also recommended that patient selection for MWA be carried out by a hepatobiliary cancer multidisciplinary team; however, further research to guide patient selection (in terms of the site and type of primary cancer to be treated, the intention of treatment (curative or palliative), follow-up imaging techniques to measure treatment success, long-term outcomes and survival is needed. The grade and level of evidence of relating to these recommendations were not reported [27].

thermale Ablation für nicht-operable Tumoren, aber auch als Zusatz zur Resektion

The guideline identifies patients who are not suitable for surgery or those with recurrence following surgery as the primary group in which thermal ablation is normally undertaken. Thermal ablation may also be used as an adjunct to resection (prior to, to downstage disease or post-surgery, to ablate small-volume disease in the liver remnant). NICE recognises MWA may be carried out under local or general anaesthesia, via a percutaneous, open or laparoscopic approach, and that a variety of microwave generating devices may be used [27].[13]

[13] **A0025** – How is the disease or health condition currently managed according to published guidelines and in practice?

Of note, an Austrian consensus document on the surgical management of colorectal liver metastases, published in 2009, was identified [33]. Given the age of this document, standalone ablation techniques (namely RFA and thermal ablation) were considered experimental at that time and as such no recommendations on their use were extracted [33].

österr. Konsenspapier aus 2009: Ablationstechniken noch experimentell

International guidelines on MWA

Several non-European guidance documents were identified for the management of liver tumours using MWA specifically and are therefore worth noting; one from the United States [34], one from Korea [35], and one from China [36]. These are summarised briefly below in Table 1-4 with regard to which patient groups are eligible for MWA.

spezifische MWA-Leitlinien zum Management von Leberkrebs

Table 1-4: Summary of international guidance documents for MWA

Organisation/ Author, year	Location	Guidance
KLCA/NCC 2018 [34]	Korea	In this guidance MWA falls under local regional therapy along with percutaneous ethanol injection and cryoablation. LRT is considered one of several alternative treatment options for the following tumour types: single ≤3cm no VI and multiple (≤3 tumours) ≤3cm no VI. In the treatment of HCC, MWA and cryoablation are expected to produce comparable rates of survival, recurrence, and complications to those of RFA (quality of evidence: moderate; strength of recommendation: weak)
American College of Radiology 2015 [37]	USA	HCC solitary tumour <3cm: thermal ablation† usually appropriate. HCC solitary tumour 5cm: thermal ablation† may be appropriate. HCC > one tumour, at least one of them >5cm: thermal ablation* usually not appropriate. iCCA 4cm diameter, no evidence of biliary obstruction: thermal ablation† may be appropriate. Multifocal metastatic neuroendocrine tumour (includes carcinoid tumours as well as islet cell tumours of the pancreas): thermal ablation† usually not appropriate. Multifocal colorectal carcinoma (liver dominant or isolated): thermal ablation† usually not appropriate. Solitary colorectal liver metastasis: thermal ablation† recommended if the tumour is <3-5cm. Use of this procedure depends on local expertise. Note: grade of recommendation and level of evidence not reported
Liang 2013 [36]	China	Indications for curative MWA: single nodule <5cm; maximum three nodules with diameter <3cm; absence of portal vein cancerous thrombus; no extrahepatic spread. Indications for palliative MWA: lesion >5cm; multiple lesions; small extrahepatic tumour burden; unsuitable for other treatment modalities. Note: grade of recommendation and level of evidence not reported

Abbreviations: HCC = hepatocellular carcinoma; iCCA = intrahepatic cholangiocarcinoma; KLCA = Korean Liver Cancer Association; LRT = locoregional therapy; MWA = microwave ablation; NCC = National Cancer Center; RFA = radiofrequency ablation; USA = United States of America; VI = vascular invasion.

*Notes: *Endorsed by Chinese Society of Clinical Oncology, Korean Association for Clinical Oncology, Malaysian Oncological Society, Singapore Society of Oncology and Taiwan Oncology Society. †Where specified, thermal ablation commonly refers to radiofrequency ablation, but other techniques include MWA and cryotherapy.*

Based on information from the submitting hospital, the overall annual utilisation of MWA is estimated to be between 900 and 1,500 treatments.[14]

geschätzter Einsatz von MWA in Ö: ca 900-1.500 mal

[14] **A0011** – How much are the technologies utilised?

1.3 Features of the intervention[15]

thermale Ablation: minimal-invasive Verfahren mit Ziel, Tumor zu zerstören

Thermal ablation is a minimally invasive procedure used for treating liver cancers. As the name indicates, thermal ablation uses high or low temperatures for tumour eradication. The goal of thermal ablation is to destroy a tumour without damaging the surrounding liver tissue. Common types of thermal ablation include MWA, RFA and cryotherapy.

Features of the technology and comparators

bildgestützte Mikrowellenablation (MWA) bedarf 3 Komponenten: Generator, Koaxialkabel, Mikrowellenantennen

Image-guided MWA is a minimally invasive cancer treatment. The technique uses energy from electromagnetic waves to heat and destroy tumours [38].[16] MWA systems are made up of three components: the microwave generator, a flexible coaxial cable, and microwave antennae (also known as the ablation applicator). The coaxial cable connects the antennae to the microwave generator [39]. There are several manufacturers which make MWA systems that are CE marked for liver ablation.[17] Some of these are listed in Table 1-5.

mehrere zugelassene Systeme

MWA can be conducted percutaneously, laparoscopically or via open surgery under local or general anaesthesia [39, 40]. The microwave antenna is inserted into the tumour under image guidance (ultrasound, CT or MRI) and then electromagnetic microwaves generated at a frequency between 900 and 2,450 MHz [40-42]. The intense heat usually ablates (destroys) the tumour within ten minutes [43]. Multiple needles are required to do multiple ablations when treating a large tumour [44]. After the antennae is removed, pressure is applied to stop any bleeding. Sutures are rarely needed. During the MWA procedure patients are continuously monitored with pulse oximetry, electrocardiography, and sphygmomanometry.

MWA: perkutan, laparoskopisch oder in offener OP werden die (gekühlten) Antennen eingeführt

Early-generation MWA devices did not have cooled antennas and so low-power ablation cycles were utilised to prevent skin burns. Low-power, water-cooled systems then emerged followed by high-power, water-cooled systems which allowed for higher frequency ablation treatments of large liver lesions with ablation times between two and five minutes [45].

Komparatoren zur MWA sind:

Resektion oder Hepatektomie TACE, RFA, Kryotherapie

Comparative procedures depend on the type and stage of liver cancer but include resection, TACE and other thermal ablative therapies, namely RFA and cryotherapy.[16] Liver resection, or partial hepatectomy, is an established method of removing both malignant and benign tumours. TACE is used to deliver high doses of chemotherapy directly to tumours. RFA is the most established of the thermal ablative therapies. Cryotherapy is the least commonly used ablation method in the liver (compared with RFA and MWA) due to concerns of increased bleeding risks [46]. According to several clinical practice guidelines, MWA and cryotherapy have the potential to be used in the same clinical settings as RFA [25, 26]. The comparators described in detail here are those used in the included studies.[18]

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[15] This section addresses the EUnetHTA Core Model® domain TEC.

[16] **B0001** – What is the technology and the comparator(s)?

[17] **A0020** – For which indications has the technology received marketing authorisation or CE marking?

[18] **B0003** – What is the phase of development and implementation of the technology and the comparator(s)?

Leberresektion bei primärem wie sekundärem Karzinom,

aber nicht bei allen Pts. möglich

Liver resection involves the surgical removal of the diseased portion of the liver. It can be used to treat both primary and secondary liver tumours but not all patients are candidates for this procedure. It can only be performed if there will be a reasonable amount of liver function left once the tumour is removed and the tumour hasn't spread to other parts of the body where it can't be removed [47, 48]. In patients with healthy livers, regeneration after resection (even when up to 70% has been removed) can occur in just a few weeks [49]. The main risks associated with liver resection are bleeding, postoperative liver failure and cancer recurrence [49].[19]

RFA (ebenso wie MWA): Erhitzung des Tumors, aber mittels elektrischer Wellen

RFA am häufigsten unter den thermalen Ablationen verbreitet

ähnliche Kosten wie MWA

RFA, like MWA, destroys tumours by heating the cancer cells. However, in comparison to MWA, RFA uses an electric current (frequencies of 3 hertz (Hz) to 300 gigahertz (GHz)) delivered through electrodes to produce thermal energy (60-100° centigrade (C)). The electrical circuit is completed via grounding pads attached to the patients thighs or back [39]. Like MWA, RFA is performed under image guidance (ultrasound, CT or MRI) [50, 51].[19] Radiofrequency ablation is currently the most widely used thermal ablation modality for unresectable, early-stage, hepatic malignancy; however, the use of MWA has increased as a result of advancements in this technology [52]. Whilst no comparative costs of MWA with RFA to treat liver tumours could be identified, one US based paper has compared the procedural costs of various percutaneous tumour ablation modalities to treat a 3cm kidney lesion. The procedure and equipment costs (antenna for MWA, ablation probe for RFA) were US$ 8,123 for MWA and US$ 8,289 for RFA, based on 1 MWA antenna and 1 RFA probe to treat a 3cm lesion. This calculation was based on the CT scanner, procedure room personnel and interventional radiologist booked for a fixed time, regardless of ablation modality. It should be noted that the cost of the antenna versus the cost of the probe was the main difference in the cost between the two modalities; however, the number of probes required may depend on the manufacturer and model of the probe [53].

Transarterielle Chemoembolisation (TACE): Chemotherapie

TACE, which is performed under local anaesthetic, involves a small incision in the groin to allow a catheter to enter the hepatic artery [54]. Through this catheter, chemotherapy drugs are delivered directly into the blood vessel which supplies the liver tumour along with small synthetic beads or sponges (known as embolic agents). TACE aims to cut off blood supply to the tumour and trap chemotherapy within the tumour in an effort to shrink or stop its growth [55]. Patients undergoing TACE remain laying down for four hours following the procedure, and follow-up imaging (CT or MRI) is used to measure treatment success approximately six weeks after the procedure [54].[19]

Vorteile von MWA: zeitgleiche multiple Ablationen, größeres Tumorvolumen

The proposed advantages of MWA compared to other ablative techniques include the ability to perform multiple ablations simultaneously, larger tumour ablation volumes, reduced procedural time, as well as reduced perioperative pain [56].[20]

[19] **B0001** – What is the technology and the comparator(s)?

[20] **B0002** – What is the claimed benefit of the technology in relation to the comparators?

Table 1-5: Features of the intervention and comparators

	Intervention/Technology	Comparator	Comparator	Comparator
Name	MWA	RFA	Liver resection	TACE
Proprietary name*	MicroThermX Microwave Ablation System; Acculis®; Emprint™ Ablation System with Thermosphere™ technology; Solero Microwave Tissue Ablation System; MicroBlate™ Fine; MicroBlate™ Flex; MedWaves AveCure™	CRF Radiofrequency Ablation System; KODEX-EPD RF Ablation System; RF3000™ Radiofrequency Ablation System	NA	NA
Manufacturer	Varian, UK ; Angiodynamics, USA and Balmer Medical, Switzerland; Covidien, Ireland; Creo Medical Group, UK; MedWaves, Inc, USA	Cambridge Interventional, USA; EPD Solutions, USA Boston Scientific, USA	NA	NA
Names in other countries	NA	NA	NA	NA
LKF Reference codes	NA	HL010	HL045	ED050
Class/GMDN code	11245	35156	NA	NA

Abbreviations: NA = not applicable; MWA= microwave ablation; RFA= radiofrequency ablation; TACE = transcatheter arterial chemoembolisation; UK = United Kingdom; USA = United States of America.

*Note: *Listed here are the microwave/radiofrequency generator systems with CE marks, the list does not include the associated parts for each system, such as applicators, of which there may be several. This is not an exhaustive list.*

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

thermale Ablation unter Lokalanästhesie

Thermal ablation and TACE are generally performed under local anaesthesia by Interventional Radiologists [51, 54]. Liver resections are performed under general anaesthesia by Hepatobiliary or General Surgeons. General surgeons and Hepatobiliary Surgeons also perform thermal ablation procedures. Anaesthesiologists and operative nursing staff are also needed to carry out MWA, RFA, liver resection and TACE.[21]

Patientenselektion durch multidisziplinäres Team für hepatobiliären Krebs

NICE recommends patient selection for MWA be undertaken by hepatobiliary cancer multidisciplinary teams [27].

MWA + RFA: Bedarf nach OP-Saal mit bildgebenden Modalitäten

For MWA and RFA, apart from the ablation equipment, there are no special premises or equipment required to perform ablation procedures, besides a sterile operating theatre with access to imaging modalities (ultrasound, CT or MRI). Most hospital facilities would have access to this equipment, without the need for additional investment. The same applies for TACE and liver resection.[22] As mentioned, both MWA and RFA systems comprise three components: a generator, flexible coaxial cable and antennae. One-off costs for the purchase of the microwave (or other thermal) generator would be incurred by

[21] **B0004** – Who administers the technology and the comparators and in what context and level of care are they provided?

[22] **B0008** – What kind of special premises are needed to use the technology and the comparator(s)?

facilities wishing to undertake thermal ablation, as well as the ongoing costs of any consumables associated with the ablation system (i.e. catheters).[23]

Leberresektion und TACE Bedarfe

For liver resection, standard surgical equipment including scalpels, clamps, catheters are required.[23] For TACE, the tools needed include x-ray (or other imaging) equipment, a catheter and embolic agents. The most common embolic agents are oil or plastic particles made from polyvinyl alcohol [55].[23]

Regulatory & reimbursement status

Mikrowellenablation derzeit nicht im MEL-Katalog

MWA for liver cancer is currently not included in the Austrian hospital benefit catalogue and, hence, it is not a fully reimbursable service in the Austrian health care system.[24]

[23] **B0009** – What supplies are needed to use the technology and the comparator(s)?

[24] **A0021** – What is the reimbursement status of the technology?

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Is MWA in comparison to resection, TACE, RFA or other ablation techniques, in patients with primary or secondary liver tumours, more or as effective and safe concerning overall survival, tumour recurrence, treatment success, length of hospitalisation, ablation time, resolution of symptoms and adverse events?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 2-1.*

Table 2-1: Inclusion criteria

Population	**Primary liver tumours** 1. Patients with an early stage (single or two to three nodules <3cm) unresectable primary liver tumour (without extrahepatic spread used with curative intent). Primary liver tumours may include any of hepatocellular carcinoma, cholangiocarcinoma, angiosarcoma and hepatoblastoma 2. Patients with a single 2-3cm primary liver tumour or with very early-stage tumour (BCLC-0) as an alternative to surgery 3. Patients undergoing hepatic tumour resection where MWA is used adjuvant to the surgical procedure 4. Patients with intermediate to advanced stage primaries (BCLC B or C) **Note:** "Unresectable" is defined as: patients with inadequate liver reserve or patients with resectable disease who cannot undergo surgery due to medical comorbidities **Secondary liver tumours** 1. Patients with a secondary liver tumour who undergo ablation with curative intent including: a. Patients not indicated for surgery (e.g. those with inadequate liver reserve or patients with resectable disease who cannot undergo surgery due to medical comorbidities) b. As an alternative to surgery c. Adjuvant to surgery – ablate small areas which surgery couldn't resect d. Prior to surgery to downstage to facilitate liver resection 2. Patients with a secondary unresectable neuroendocrine liver metastases who undergo ablation with palliative intent to remove symptoms arising from the tumour **ICD-11 Code:** 2C12.00; 2C12.02; 2C12.0Y; 2C12.1; 2C12.Z; 2C18; 2D80.0; 2D80.1; 2D80.Y; 2D80.Z **MeSH Terms:** Liver neoplasms (Medline and Cochrane); Liver tumor (Embase) **Rationale:** Informed by information of the submitting hospitals, clinical practice guidelines and our expert consultation
Intervention	Microwave ablation (MWA) including any of the following approaches: ■ Percutaneous MWA ■ MWA used during a laparoscopic procedure ■ MWA used during an open procedure **Product names:** MicroThermX Microwave Ablation System, Acculis®, Emprint™ Ablation System with Thermosphere™ technology, Solero Microwave Tissue Ablation System, MicroBlate™ Fine, MicroBlate™ Flex, MedWaves AveCure™ **MeSH terms:** Ablation techniques and Microwaves (Medline and Cochrane); Microwave thermotherapy and MWA device (Embase)
Comparator	Guideline directed standard of care: ■ RFA ■ Percutaneous ethanol ablation ■ Cryotherapy ■ Laser ablation ■ TACE For population 2 and 4b – liver resection should be a comparator **Rationale:** Comparators are based on clinical guidelines, reflecting standard of care.

Outcomes	
Efficacy	Crucial outcomes ■ Survival ■ Rate of tumour recurrence ■ Treatment success (i.e. partial ablation, complete ablation) ■ Length of hospital stay Other outcomes ■ Ablation time (secondary outcome) ■ Resolution of symptoms (for palliative ablation, population 5) ■ Quality of life **Rationale:** Outcomes are based on previous reports.
Safety	Crucial outcomes ■ Mortality (perioperative and long-term) ■ Intra-abdominal bleeding ■ Gastrointestinal bleeding ■ Wound dehiscence ■ Postoperative ascites ■ Intraperitoneal haemorrhage ■ Bowel perforation ■ Bile duct injury Other adverse events and serious adverse events associated with the intervention and comparator procedures including (but not limited to): ■ Biliary stenosis ■ Acute respiratory distress syndrome ■ Liver abscess ■ Neoplastic seeding ■ Biliary peritonitis ■ Adjacent vessel thrombosis ■ Collateral thermal injury ■ Postoperative pain **Rationale:** Outcomes are based on previous reports.
Study design	
Efficacy	■ Well conducted systematic reviews ■ RCTs Prospective NRCTs A Hierarchical approach to study selection will be taken, with recent, well conducted systematic reviews selected preferentially. If necessary, systematic reviews will be updated with primary studies published subsequent to the review search date. If no systematic reviews are available, then RCTs will be included. If no RCTs are available, then observational studies with control groups will be included. **Excluded:** narrative reviews, letters to the editor and author responses, case reports, retrospective case series, conference abstracts.
Safety	■ Well conducted systematic reviews ■ RCTs ■ Prospective NRCTs ■ Prospective case series studies **Excluded:** narrative reviews, letters to the editor and author responses, case reports, retrospective case series, conference abstracts

Abbreviations: BCLC = Barcelona Clinic Liver Cancer; ICD = international classification of diseases; MeSH = medical subject heading; MWA = microwave ablation; NRCTS = non randomised controlled trials; RCT = randomised controlled trial; RFA = radiofrequency ablation.

*Notes: * The original PICO was modified in consultation with the client and a clinical expert (general surgeon) to include the efficacy outcome 'treatment success' and to include transcatheter arterial chemoembolisation (TACE) as a comparator.*

3 Methods

3.1 Research questions

Please refer to the Appendix (Table A-14 to Table A-17) for the detailed Research questions.

detaillierte Forschungsfragen im Anhang

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

The systematic literature search was conducted on the 13th of December 2021 in the following databases:

systematische Literatursuche in 4 Datenbanken

- Medline via Ovid
- Embase
- The Cochrane Library
- International Network of Agencies for Health Technology Assessment (INAHTA)

The systematic search was not date limited but was restricted to articles published in English or German. After removing duplicates, 1,023 citations were screened by title and abstract. The specific search strategy employed is in the Appendix.

1.023 Zitate nach Entfernung von Duplikaten

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 26th of January 2022 resulting in 113 potential relevant hits; 34 of which are randomised controlled trials and these are reported in the Appendix (Table A-13).

Suche nach laufenden Studien: 113 Studien, davon 34 RCTs

3.2.2 Flow chart of study selection

Literaturauswahl

12 RCTs eingeschlossen

The references (total hits = 1,023) were screened by two independent researchers (JD, AB) and in case of disagreement a third researcher (MVP) was involved to resolve the differences. Owing to the large volume of literature, it was agreed, in consultation with the client, that only randomised controlled evidence would be included. The study selection process is displayed in Figure 3-1.

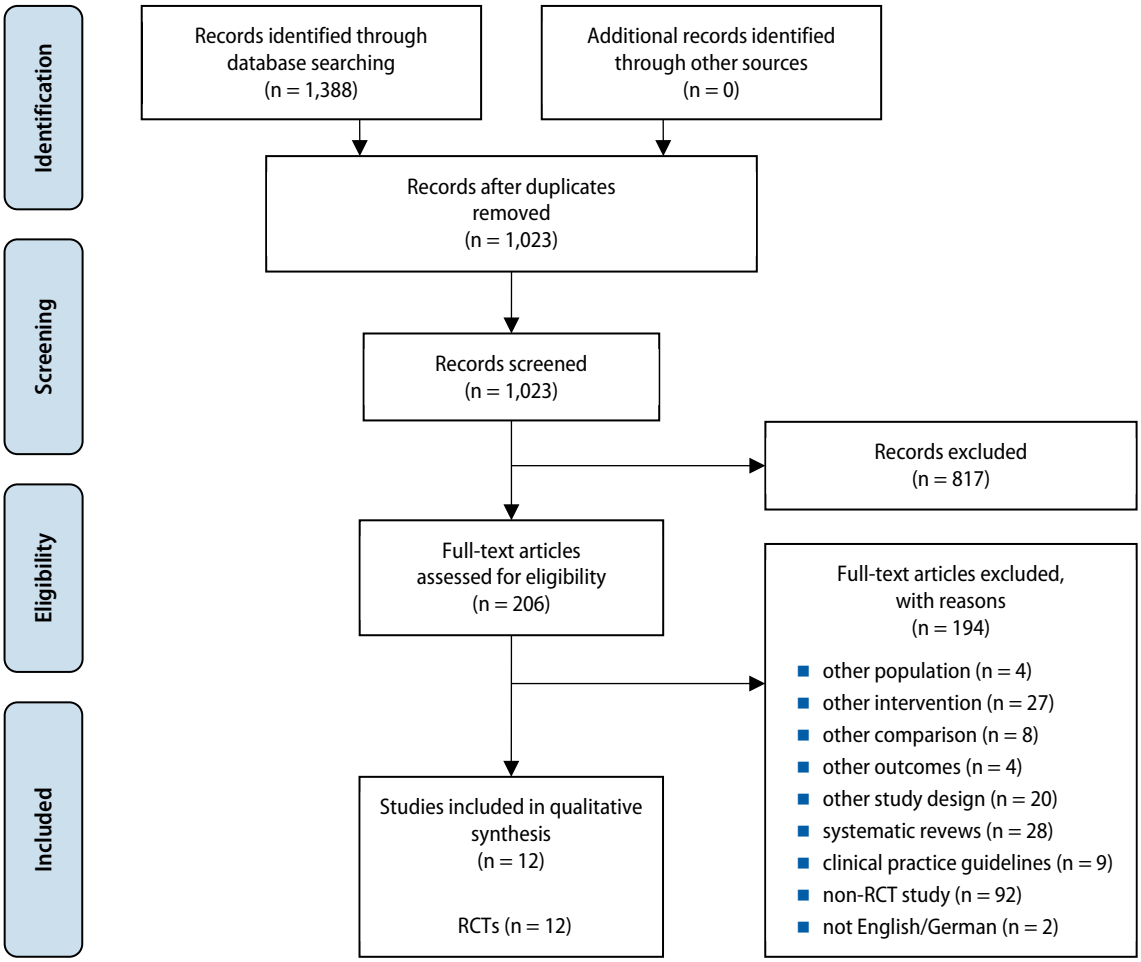

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

Risk of Bias: Cochrane 2 tool

The studies were systematically assessed for internal validity and risk of bias using the Cochrane Risk of Bias 2 tool [62] (see Table A-3).

4-Augen Prinzip bei allen Arbeitsschritten

GRADE

One reviewer (KN) systematically extracted relevant data from the included studies into data extraction tables. A second reviewer (AB) cross-checked the data extraction tables for accuracy. One reviewer (KN) analysed the quality of the data using Grading of Recommendations, Assessment, Development and Evaluations (GRADE), and a second reviewer (JD) validated the analysis. GRADE assessments were unable to be undertaken for individual critical adverse events due to poor reporting; however, the composite outcome of "crucial adverse events" was assessed. Risk of bias (RoB) was conducted by two independent researchers (KN, AB) and differences were settled via consensus.

3.2.4 Synthesis

bei 2 oder mehr RCTs: Metaanalyse

random-effects model

Ergebnisse zum längst verfügbaren Zeitpunkt des jeweiligen Endpunktes

For the crucial effectiveness outcomes, a pairwise meta-analysis was conducted if there were two or more RCTs comparing MWA to any of the comparators. The meta-analyses were performed in R Studio using the meta package [57-60]. All crucial effectiveness outcomes were assessed as dichotomous outcomes, with percentages/rates (e.g. survival rate) converted to number of events within the total sample size at the relevant timepoint or longest follow-up. The meta-analyses were performed using random-effects models. The Mantel-Haenszel method was used to estimate primary study weights. Results were reported as relative risk (RR) with 95% confidence interval (CI). Outcome data were pooled at the longest follow-up for tumour recurrence and treatment response (i.e. complete ablation) and pooled at specific timepoints for survival (e.g. overall survival at 12 months).

MCID in COMET gesucht, aber nicht gefunden

For each outcome included in the meta-analysis, the Core Outcomes Measures in Effectiveness Trial (COMET) Initiative was searched to define the minimum clinically important difference (MCID) that would need to be reached or exceeded to conclude a difference between groups was clinically significant [63]. No MCIDs were able to be defined.

statistische Heterogenitätstests durchgeführt

wenn ungenügend Daten vorhanden: narrative Zusammenfassung

Statistical methods used to measure heterogeneity in meta-analyses of dichotomous outcomes was the Chi^2 test ($p < 0.10$ indicated significant heterogeneity) and I^2. The significance of I^2 were dependent on the strength of the evidence for heterogeneity (i.e. Chi^2) as well as direction and size of the measured effect. It was interpreted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions (version 6.2)* [61]. An I^2 of 0-40% is low (i.e. may not be important), 30-60% is moderate, 50-90% is substantial and 75-100% is considerable heterogeneity [61].

Where there was insufficient data or data that could not be pooled results were synthesised narratively.

Unless otherwise stated results are reported as mean ± standard deviation.

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

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

- Survival; overall survival is the gold standard primary end point in evaluating a procedure in oncologic clinical trials [64]. Survival is of important clinical relevance and is an unbiased way to measure the ability of a procedure to extend the life of a patient [64].
- Rate of tumour recurrence; or time to recurrence is recommended as a primary endpoint for HCC phase 2 and 3 studies that assess local ablation. Evidence of recurrence should follow the Response Evaluation Criteria in Solid Tumours (RECIST). The RECIST criteria define standard methods for converting radiology images to a quantitative framework for measuring the response of tumour size to therapy [65].
- Resolution of symptoms; in the palliative population described in the PICO (patients with a secondary unresectable neuroendocrine liver metastases who undergo ablation with palliative intent to remove symptoms arising from the tumour) resolution of symptoms may improve their quality of life. There are a range of tools to assess the effectiveness of an intervention in providing palliation of symptoms. None were identified that are specific to unresectable neuroendocrine liver metastases [66].

entscheidende Endpunkte für Wirksamkeit:

Überleben

Rate des Wiederauftretens des Tumors

Abklingen der Symptome

weitere wichtige Endpunkte:

Teilablation, vollständige Ablation, Dauer des Krankenhausaufenthalts, Ablationszeit

Selection and rating of crucial outcomes were based on consultation with a clinical expert (general surgeon).

Further outcomes defined as important, but not crucial to derive a recommendation, include treatment success (partial ablation, complete ablation), length of hospital stay and ablation time.

4.1.2 Outcomes safety

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

- Mortality (perioperative and long-term)
- Intra-abdominal bleeding
- Gastrointestinal bleeding
- Wound dehiscence
- Bile duct injury
- Postoperative ascites
- Intraperitoneal haemorrhage
- Bowel perforation

entscheidende Endpunkte für Sicherheit:

Mortalität, Blutungen, Dehiszenz der Wunde, Verletzung des Gallenganges, etc.

These safety outcomes were deemed as crucial based on consultation with a clinical expert (Hepatobiliary Surgeon).

weitere wichtige Endpunkte

Other important adverse events include, but are not limited to, biliary stenosis, acute respiratory distress syndrome, liver abscess, neoplastic seeding, biliary peritonitis, adjacent vessel thrombosis, collateral thermal injury and postoperative pain.

4.2 Included studies

4.2.1 Included studies for effectiveness and safety

12 eingeschlossene RCTs zu unterschiedlichen Patienten-Populationen und mit unterschiedlichen Komparatoren

A total of twelve RCTs met the predefined inclusion criteria [67-78]. Each RCT compared the effectiveness and safety of MWA and its comparators as follows:

PRIMARY LIVER TUMOURS

primäre Lebertumore:

Population 1: patients with early stage (single or 2-3 nodules < 3cm) unresectable primary liver tumour (without extrahepatic spread used with curative intent)

Pop 1: frühes Stadium, wenig + kleine Nodule, nicht-resektierbar

MWA versus (vs) RFA for HCC

MWA vs. RFA:

Five RCTs compared MWA with RFA for HCC [67, 69, 70, 77, 78]. Two of these RCTs were conducted in Egypt [67, 70], and one each in Hong Kong [69], Japan [77], France and Switzerland (multicentre) [78]. The majority of participants across all five studies were male, with HCC, Child-Pugh[25] A or B, with between one to three lesions and lesions no larger than 5cm in diameter.

5 RCTs mit 253 Pts MWA vs. 231 RFA

In total, 253 participants were randomised to receive MWA, while 231 were randomised to receive RFA. MWA was conducted percutaneously in all studies. In one RCT, surgical ablation was used when percutaneous MWA was not suitable [69]. With respect to image guidance two RCTs used ultrasound [67, 77], two used ultrasound or CT [69, 78] and one did not report what image guidance they used [70].

mehrheitlich männlich 42 bis 85 Jahre

FU 2,3 bis 72,7 Monate

The age of participants ranged from 42 to 85 years across four RCTs (one study did not report age range) [69, 70, 77, 78]. Finally, patient follow-up ranged from 2.3 to 72.7 months across all five RCTs [67, 69, 70, 77, 78].

Pop 2: sehr frühes Stadium, einzelner Tumorherd, Alternative zu OP

Population 2: patients with a single 2-3cm primary liver tumour or with very early-stage tumour (BCLC-0) as an alternative to surgery

MWA vs laparoscopic liver resection for HCC

MWA vs. laparoskopische Resektion:

One RCT conducted in China recruited 90 HCC patients; half underwent MWA and the other half laparoscopic resection [74]. Patients with Child-Pugh A or B, lesion ≤5cm in diameter, who had good compliance and no surgical contraindications were included in the study. Patients with extrahepatic metastases, Child-Pugh C, portal hypertension, coagulation disor-

[25] Child-Pugh scoring system: This scoring system uses 5 clinical and laboratory markers and those are: serum bilirubin, serum albumin, ascites, neurological disorder, and prothrombin time to categorise patients into 3 categories: A – good hepatic function; B – moderately impaired hepatic function; C – advanced hepatic dysfunction.

ders, diffuse liver cancer and severe organ insufficiencies were excluded. MWA was performed under local anaesthesia using CT guidance.

Of the total included patients, 73.3% were male. The mean age of patients did not differ between treatment groups. The mean age was years in the MWA group and 58.3 ± 3.1 years in the laparoscopic resection group (p>0.05). Participants were followed-up for 12 to 36 months [74].

1 RCT: 45 vs. 45 Pts
mehrheitlich männlich
57,9 ± 3,4 Jahre
FU 12 bis 36 Monate

Population 3: patients undergoing hepatic tumour resection where MWA used adjuvant to the surgical procedure

Pop 3: resektierbar

MWA plus liver resection vs standalone liver resection for HCC

One RCT conducted in China compared 39 patients who underwent liver resection plus MWA with 40 patients who underwent liver resection only [72]. Patients with HCC were included who had Child-Pugh A or B, a maximum of three lesions, single nodules ≤10cm in diameter or two to three nodules with no more than one lesion >5cm in diameter, no distant metastases and no contraindications for MWA. Patients were excluded if they had incomplete pathology data, previous anticancer treatment prior to surgery, portal or hepatic vein or inferior vena cava invasion, extra-hepatic metastases, other malignancies and who had decompensated cirrhosis. MWA was performed prior to resection, on the same day.

MWA+Resektion vs. Resektion:

1 RCT: 39 vs. 40 Pts.
mehrheitlich männlich
59,3 ± 10,3 Jahre
FU 7 bis 40 Monate

Of the total 79 patients, 75.9% were male. The mean age of the overall cohort was 59.3 ± 10.3 years (age was not reported per treatment group). All patients were followed up for seven to 40 months [72].

Population 4: intermediate and advanced stage primary liver tumours (BCLC B or C)

Pop 4: intermediate und fortgeschrittene Stadien

MWA vs TACE for HCC

One RCT conducted in Egypt included 64 patients with HCC, Child-Pugh A or B, a maximum of three lesions 5-7cm in diameter and with proper coagulation profiles [68]. A total of 76.5% of patients were male. Patients with Child-Pugh C, portal vein thrombosis, distant metastases, lesion outfitting, and unacceptable coagulation profiles were excluded. Patients were also excluded if they had intractable systemic infection, leucopaenia, cardiac/renal insufficiency, hepatic encephalopathy, performance status[26] greater than two, hepatofugal flow, or biliary obstruction. Of the 64 included patients, half received MWA and half received TACE. Ablation was performed under ultrasound guidance.

MWA vs. TACE:

1 RCT: 32 vs. 32 Pts
mehrheitlich männlich

The mean age of patients in the two treatment groups was not statistically different (56.8 ± 5.7 years and 55.5 ± 9.4 years, respectively; p = 0.3). All patients were followed for one to three months post-ablation [68].

56,8 ± 5,7 vs.
55,5 ± 9,4 Jahre
FU 1 bis 3 Monate

[26] Performance Status on a 6-point scale where 0 = fully active, able to carry on pre-disease performance without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (light housework/office work); 2 = ambulatory and capable of self-care but unable to carry out work activities. Up and about more than 50% of waking hours; 3 = capable of limited selfcare, confined to bed/chair more than 50% of waking hours; 4 = disabled, unable to perform any self-care, and totally confined to bed or chair; 5 = deceased.

MWA vs MWA plus TACE vs standalone TACE for HCC

MWA vs. MWA+TACE vs. TACE:

1 RCT: 95 vs. 93 vs. 90 Pts.

One RCT conducted in Egypt compared MWA with MWA plus TACE and with standalone TACE [75]. A total of 278 patients were recruited, 95 patients received MWA, 93 received MWA plus TACE and 90 received TACE only. MWA was performed under ultrasound guidance by interventional radiologists. In the combination group, MWA was performed after 15 days of TACE. Patients with HCC, Child-Pugh A or B, a single lesion >3-5cm in diameter, with no extra-hepatic metastases and no history of encephalopathy or refractory ascites were randomised into one treatment group. Patients with poor compliance, Child-Pugh C, severe coagulation disorders, portal vein thrombosis, renal impairment and those who had previous local ablation therapy of HCC were excluded. The Karnof-sky Performance Score (KPS)[27] instrument was used to measure quality of life.

mehrheitlich männlich
53,8±10,3 vs. 52,1±9,5 vs. 51,3±9,2 Jahre
FU 1 bis 36 Monate

A total of 55.3% of the included patients were male and the mean age did not differ between the three groups (53.8 ± 10.3 years, 52.1 ± 9.5 years and 51.3 ± 9.2 years, respectively; p = 0.177). Patients were followed up at one-month post-ablation and up to 36 months in total. Thirteen patients were lost to follow up [75].

MWA plus TACE vs standalone TACE for HCC

MWA+TACE vs. TACE:

1 RCT: 1.500 vs. 1.500 Pts.

One RCT conducted in China compared MWA plus TACE with standalone TACE for HCC [71]. The study included 3,000 patients; 60.0% were male. Included patients had HCC, BCLC stage B, unresectable lesions 3-6cm in diameter, vascular invasion without distant organ metastases, no history of hepatic encephalopathy and patients with no severe coagulation disorder. Patients received MWA plus TACE (n = 1,500) or TACE only (n = 1,500). After the TACE procedure patients received CT-guided single or multiple MWA treatment.

mehrheitlich männlich
48 vs. 50 Jahre
FU 3,5 bis 24 Monate

The mean age of patients in the MWA plus TACE group was 48 years while the mean age in the TACE only group was 50 years. Age did not differ significantly between the two groups (p > 0.05). Follow-up was conducted one-month post-procedure and between 3.5 to 24 months [71].

MWA+TACE vs. TACE:
(gemischte Pts-Pop)

MWA plus TACE vs standalone TACE for HCC, iCCA and mixed HCC

1 RCT: 80 vs. 80 Pts.

One RCT conducted in China compared MWA plus TACE with standalone TACE in 160 patients (57.0% male) with a mix of different primary liver cancers (including HCC, iCCA and mixed HCC) [76]. Specific BCLC stage and Child-Pugh class were not stated in the inclusion criteria but patients were a mix of Child Pugh class A, B and C and 40% had extrahepatic metastases. Patients were excluded if they had hepatic or renal insufficiencies, coagulation disorders, were allergic to the study drugs, had communication or mental disorders, or had chemotherapy in the last six months and a maximum

mehrheitlich männlich
45,8±8,41 vs. 46,1±7,78 Jahre
FU bis 36 Monate

[27] The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment as follows: 100 – normal no complaints; no evidence of disease; 90 – able to carry on normal activity; minor signs or symptoms of disease; 80 – normal activity with effort; some signs or symptoms of disease; 70 – cares for self; unable to carry on normal activity or to do active work; 60 – requires occasional assistance, but is able to care for most of his personal needs; 50 – requires considerable assistance and frequent medical care; 40 – disabled; requires special care and assistance; 30 – severely disabled; hospital admission is indicated although death not imminent; 20 – very sick; hospital admission necessary; active supportive treatment necessary; 10 – moribund; fatal processes progressing rapidly; 0 – dead.

life expectancy of six months. Treatment allocation was 1:1 (n = 80 received MWA with TACE and n = 80 received TACE only). After four weeks of TACE, patients underwent CT-guided percutaneous MWA under local anaesthesia. The mean age of the patients in each treatment group did not differ; 45.8 ± 8.41 years and 46.1 ± 7.78 years, respectively (p value not reported). All patients were followed up for 36 months [76].

SECONDARY LIVER TUMOURS

No RCTs were identified for populations 5a, 5c, 5d and 6.

sekundäre Lebertumore:

keine RCTs für 4 Patienten Populationen identifiziert

- **Populations 5a**: patients with a secondary liver tumour who undergo ablation with curative intent and who are not indicated for surgery
- **Population 5c**: patients with a secondary liver tumour who undergo ablation with curative intent where MWA is used adjuvant to surgery to ablate small areas which surgery couldn't resect
- **Population 5d**: patients with a secondary liver tumour who undergo ablation with curative intent prior to surgery to downstage to facilitate liver resection
- **Populations 6**: patients with a secondary unresectable neuroendocrine liver metastases who under ablation with palliative intent to remove symptoms arising from the tumour.

Pop 5b: mit kurativer Intention als Alternative zu Resektion

Population 5b: patients with a secondary liver tumour who undergo ablation with curative intent including as an alternative to surgery

MWA vs liver resection for colorectal metastases

MWA vs. Resektion: 1 RCT: 14 vs. 16 Pts.

One RCT conducted in Japan compared MWA with open liver resection [73]. A total of 30 patients were included in this study, 14 received MWA and 16 underwent open resection. Patients with metastases from colorectal carcinoma, less than ten lesions, largest nodule <8cm in diameter, no evidence of periportal/celiac lymph node metastases or extra-hepatic distant metastases or ascites, no sign of liver cirrhosis or chronic hepatitis were included. Under the guide of ultrasonography MWA was performed for a total period of two to 20 minutes.

mehrheitlich männlich 61±10 vs. 61±9 Jahre FU bis 36 Monate

A total of 53.3% of patients were male. The mean age of the included patients was similar in both treatment groups, 61 ± 10 years and 61 ± 9 years, respectively (p = 1.00). Patients were followed up every three months for three years [73].

For further details of each RCT refer to Table A-1 (part 1 and 2) (Appendix).

4.2.2 Additional included studies safety

keine weiteren Studien für Sicherheit inkludiert

No additional studies were identified on safety for inclusion in this report.

4.3 Results

Ergebnisse werden nach Endpunkten berichtet

Results are reported separately for each outcome per comparison.

4.3.1 Mortality (Survival, mortality and procedure-related mortality)[28]

primäre Lebertumore:

PRIMARY LIVER TUMOURS

Pop 1: frühes Stadium, wenig + kleine Nodule, nicht-resektierbar

Population 1: patients with early stage (single or 2-3 nodules < 3cm) unresectable primary liver tumour (without extrahepatic spread used with curative intent)

MWA vs RFA for HCC

MWA vs. RFA: 12-Monats-Überleben (3 RCTs mit 199 Pts.)

24-Monats-Überleben (2 RCTs mit 197 Pts.)

Survival Rates: A pairwise meta-analysis was conducted to compare overall survival between MWA and RFA at 12 and 24 months. Overall survival at 36 and 60 months could not be meta-analysed due to data only being available from a single study (see Table A-1 for details) [69]. At 12 months, data was extracted from three RCTs with a total sample size of 199 patients (Figure 4-1) [67, 69, 70]. At 24 months, data was extracted from two RCTs with a sample size of 197 patients (Figure 4-2) [67, 78].

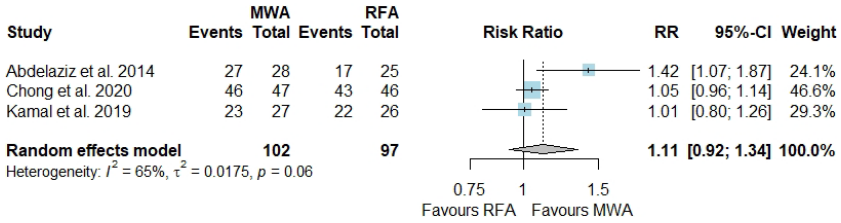

Figure 4-1: Forest plot indicating the relative risk of overall survival when comparing MWA and RFA for treatment of HCC after 12 months

kein s.s. Unterschied nach 12 oder 24 Monaten

There was no statistically significant difference between MWA and RFA (RR 1.11, 95% CI 0.92, 1.34) in overall survival after 12 months. The analysis was associated with substantial heterogeneity (I^2 = 65.0%).

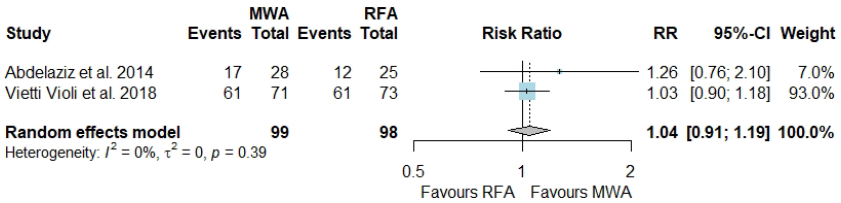

Figure 4-2: Forest plot indicating the relative risk of overall survival when comparing MWA and RFA for treatment of HCC after 24 months

[28] **D0001** – What is the expected beneficial effect of the technology on mortality?

Overall, there was no statistically significant difference between MWA and RFA (RR 1.04, 95% CI 0.91, 1.19) after 24 months. The analysis was associated with low heterogeneity ($I^2 = 0.0\%$).

Long-term mortality: Overall mortality was reported in two RCTs [67, 70]. One reported deaths in five of 28 (17.9%) patients in the MWA group and nine of 25 (36.0%) in the RFA group (the point in follow-up that death occurred was not reported). The causes of death were hepatic failure (n = 6), gastrointestinal haemorrhage (n = 2), spontaneous bacterial peritonitis (n = 2), and pulmonary embolism (n = 1). The cause of death of the remaining three patients was unknown [67]. In the other RCT, deaths in four of 28 (14.3%) patients in both the MWA and RFA treatment groups, respectively, were reported at 12 months. The causes of death in the MWA group were liver decompensation (n = 2), recurrent HCC (n = 1) and de novo HCC (n = 1). The causes of death in the RFA group were pulmonary embolism (n = 1), intracerebral haemorrhage (n = 1) and de novo aggressive HCC (n = 2) [70].

Mortalität (im FU Zeitraum):

1 RCT: MWA 5/28 (17,9 %) vs. RFA 9/25 (36 %) verstarben

1 RCT: 4/28 (14,3 %) vs. 4/28 (14,3 %)

Procedure-related mortality[29]*:* Procedure-related mortality was reported by five RCTs [67, 69, 70, 77, 78]. No cases of procedure-related mortality were reported in these; however, one RCT reported that 2/28 (7.1%) patients died in the MWA group in the 30 days following the procedure (and none in the RFA group; p = not significant). The cause of death in these patients was not specifically reported [70].

Verfahrensbedingte Sterblichkeit:

5 RCTs: keine aber 1/28 Todesfälle in 30 Tagen nach MWA

Population 2: patients with a single 2-3cm primary liver tumour or with very early-stage tumour (BCLC-0) as an alternative to surgery

Pop 2: sehr frühes Stadium, einzelner Tumorherd, Alternative zu OP

MWA vs laparoscopic liver resection for HCC

Survival Rates: Survival rates for the 45 MWA patients compared with the 45 resection patients at 12, 24 and 36 months were 88.9% versus 91.1%, 66.7% versus 68.9% and 33.3% versus 37.8%, respectively [74]. No significant difference was observed between treatments at any time point (12 months, p = 0.600; 24 months, p = 0.736; 36 months, p = 0.510).

MWA vs. laparoskopische Resektion: 1 RCT: 12-, 24-, 36-Monats-Überleben: kein s.s. Unterschied

Long-term mortality: Not reported [74].

Procedure-related mortality[29]*:* No procedure-related mortality was reported in either treatment group [74].

Mortalität & Verfahrensbedingte Sterblichkeit: nicht berichtet

Population 3: patients undergoing hepatic tumour resection where MWA is used adjuvant to the surgical-procedure

Pop 3: resektierbar

MWA plus liver resection vs standalone liver resection for HCC

MWA+Resektion vs. Resektion:

Survival Rates: The survival rate at 36 months for the 39 patients who underwent liver resection plus MWA was significantly higher (66.7%) compared with 40 patients who underwent liver resection only (47.5%) (p = 0.044) [72].

1 RCT: 36-Monats-Überleben: s.s. Unterschied zugunsten MWA+Resektion

Long-term mortality: Not reported [72].

Procedure-related mortality[29]*:* No procedure-related mortality was reported in either treatment group [72].

Mortalität & Verfahrensbedingte Sterblichkeit: nicht berichtet

[29] **D0003** – What is the effect of the technology on the mortality due to causes other than the target disease?

Pop 4: intermediate und fortgeschrittene Stadien

Population 4: intermediate and advanced stage primary liver tumours (BCLC B or C)

MWA vs TACE for HCC

MWA vs. TACE: 1 RCT: 12-, 18- Monats-Überleben kein s.s. Unterschied, aber durchschnittlich länger mit MWA

Survival Rates: Overall mean survival in the one RCT comparing MWA to TACE was significantly longer in the MWA group (21.7 months) compared with the TACE group (13.7 months) ($p = 0.04$). Survival at 12 and 18 months, whilst not statistically compared, was also higher in the MWA group (78.2% and 68.4%, respectively) compared with 52.4% and 28.6%, respectively in the TACE group [68].

Mortalität (im FU Zeitraum): MWA 5/32 (15,6 %) vs. TACE 21/32 (65,6 %)

Long-term mortality: All patients were followed for 18 months. During the follow up period, 5/32 patients (15.6%) died in the MWA group and 21/32 patients (65.6%) died in the TACE group (p value not reported). The causes of death in the MWA group were haematemesis ($n = 3$, hepatorenal syndrome ($n = 1$) and sepsis ($n = 1$). The causes of death in the TACE group were liver failure ($n = 15$), spontaneous bacterial peritonitis ($n = 3$), hepatorenal syndrome ($n = 2$) and haematemesis ($n = 1$) [68].

Verfahrensbedingte Sterblichkeit: nicht berichtet

Procedure-related mortality[29]*:* Not reported [68].

MWA plus TACE vs standalone TACE for HCC

MWA+TACE vs. TACE: 1 RCT: 6-, 12-, 18-, 24-Monats-Überleben s.s. zugunsten von MWA+TACE

Survival Rates: Survival rates were reported at 6-, 12-, 18- and 24-months for 1,500 MWA plus TACE patients and 1,500 TACE only patients. At 6 months, survival was 88.1% in the MWA plus TACE group versus 76.2% in the standalone TACE group, at 12 months 73.8% versus 57.1%, at 18 months 52.3% versus 30.9% and at 24 months 33.3% versus 9.5%. Overall survival rate was significantly higher for the MWA plus TACE group ($p = 0.011$) [71].

Mortalität: nicht berichtet

Long-term mortality: Not reported [71].

Verfahrensbedingte Sterblichkeit: keine

Procedure-related mortality[29]*:* The one RCT on MWA plus TACE vs standalone TACE reported that none of its included patients died after their procedure [71].

MWA plus TACE vs standalone TACE for HCC, iCCA and mixed HCC

MWA+TACE vs. TACE (gemischte Pts-Pop):

1 RCT 12-, 24-, 36-Monats-Überleben s.s. zugunsten von MWA+TACE

Survival Rate: Survival rates were reported at 12-, 24- and 36- months for 80 MWA plus TACE patients and 80 TACE only patients. At 12 months, survival was 82.5% in the MWA plus TACE group versus 63.8% in the standalone TACE group, at 24 months 51.3% versus 25.0% and at 36 months 27.5% versus 5.0%. The overall survival rate was significantly higher in the MWA plus TACE group at all three timepoints ($p < 0.05$) [76].

Mortalität & Verfahrensbedingte Sterblichkeit: nicht berichtet

Long-term mortality: Not reported [76].

Procedure-related mortality[29]*:* Not reported [76].

MWA vs MWA plus TACE vs standalone TACE for HCC

MWA vs. MWA+TACE vs. TACE:

1 RCT: 24-, 36- Monats-Überleben s.s. zugunsten von MWA+TACE

Survival Rates: Median survival differed significantly among the three treatments varying from 21 months for the 95 MWA patients, 24 months for the 93 MWA plus TACE patients and 19 months for the 90 TACE only patients ($p = 0.02$). Overall survival rate at 36 months also differed significantly between treatments with 54.3% (50/92) reported for the MWA group, 69.6% (62/89) for the MWA plus TACE group and 54.8% (46/84) reported for the TACE only group ($p = 0.02$). Mean progression free survival which was 16.7%, 22.3% and 15.4% in the three treatment groups, respectively, also differed significantly ($p < 0.001$) [75].

Long-term mortality: A significant difference in mortality was observed between the three treatment groups at follow-up with 29/92 (31.5%) deaths in the MWA group, 17/89 (19.1%) deaths in the MWA plus TACE group and 28/84 deaths (33.3%) in the TACE only group (p = 0.02). The causes of the deaths were not reported [72].

Mortalität: s.s. zugunsten von MWA+TACE

Procedure-related mortality[29]*:* Not reported [75].

Verfahrensbedingte Sterblichkeit: nicht berichtet

SECONDARY LIVER TUMOURS

sekundäre Lebertumore:

Population 5b: patients with a secondary liver tumour who undergo ablation with curative intent as an alternative to surgery

Pop 5b: mit kurativer Intention als Alternative zu Resektion

MWA vs liver resection for colorectal metastases

Survival Rates: The estimated cumulative survival rates, survival rate at three years, and disease-free survival time did not differ between the 14 MWA patients and 16 liver resection patients (p = 0.83, 0.65 and 0.47, respectively). The mean survival time was 27 months for patients who underwent MWA and 25 months for patients who underwent resection. The overall survival rates at 12 months, 24 months and 36 months for MWA versus resection were 71.0% versus 69.0%, 57.0% versus 56.0% and 14.0% versus 23.0%, respectively. The disease free survival time was 11.3 months for the MWA group and 13.3 months for the resection group [73].

MWA vs. Resektion:

1 RCT: 36-Monats Überleben kein s.s. Unterschied

Long-term mortality: During the follow-up a total of 9/14 (64.3%) patients died in the MWA group compared with 12/16 (75.0%) in the liver resection group. Hepatic failure was the cause of 6/9 deaths (66.7%) in the MWA group and 7/12 deaths (58.3%) in the resection group. Mortality due to hepatic failure did not differ significantly between the two groups (p = 0.95) [73].

Mortalität: kein s.s. Unterschied

Verfahrensbedingte Sterblichkeit: keine

Procedure-related mortality[29]*:*No procedure-related mortality was reported in either treatment group [73].

4.3.2 Morbidity (Tumour recurrence, symptoms, treatment success)[30, 31]

No data on the effect of MWA on liver cancer symptoms were identified.

keine Evidenz zur Symptomkontrolle

PRIMARY LIVER TUMOURS

primäre Lebertumore

Population 1: patients with early stage (single or 2-3 nodules < 3cm) unresectable primary liver tumour (without extrahepatic spread used with curative intent)

Pop 1: frühes Stadium, wenig + kleine Nodule, nicht-resektierbar

MWA vs RFA for HCC

Tumour recurrence: A pairwise meta-analysis was conducted to investigate local recurrence after MWA compared with RFA. Data were extracted from four RCTs providing information on 492 nodules (Figure 4-3, see Table A-1 for details) [67, 70, 77, 78].

MWA vs. RFA: 4 RCTs: Wiederauftreten des Tumors 12-, 14 Monate

[30] **D0005** – How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?

[31] **D0006** – How does the technology affect progression (or recurrence) of the disease or health condition?

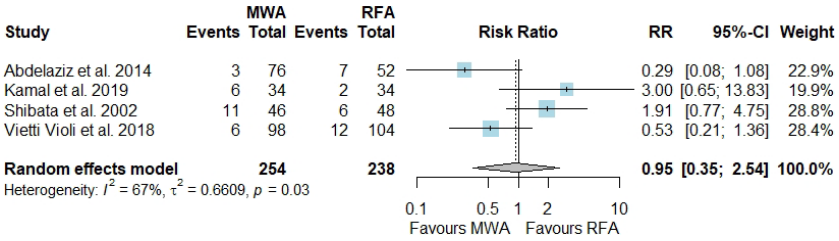

Figure 4-3: Forest plot indicating the relative risk of local recurrence when comparing MWA and RFA after 12 to 24 months

kein s.s. Unterschied

Overall, there was no statistically significant difference in local recurrence between MWA and RFA (RR 0.95, 95% CI 0.35, 2.54) between 12 to 24 months. The analysis was associated with substantial heterogeneity (I^2 = 67.0%).

Pop 2: sehr frühes Stadium, einzelner Tumorherd, Alternative zu OP

Population 2: patients with a single 2-3cm primary liver tumour or with very early-stage tumour (BCLC-0) as an alternative to surgery

MWA vs laparoscopic liver resection for HCC

MWA vs. lap.Resektion: 1 RCT: Lokalrezidiv: s.s. zuungunsten MWA; Gesamtrezidivrate: kein Unterschied

Tumour recurrence: Local tumour recurrence rate was significantly higher among the patients who underwent MWA (9/45; 20.0%) compared with patients who underwent laparoscopic resection (4/45; 8.9%) (p = 0.025). The authors state this is probably due to large tumour size in some cases. However, total tumour recurrence rates did not differ between the two groups (48.9% [22/45] for MWA versus 44.4% [20/45] for resection; p = 0.528)[74].

Pop 3: resektierbar

Population 3: patients undergoing hepatic tumour resection where MWA is used adjuvant to the surgical-procedure

MWA+Resektion vs. Resektion:

MWA plus liver resection vs standalone liver resection for HCC

1 RCT: Rezidivrate s.s. geringer unter MWA+Resektion

Tumour recurrence: Tumour recurrence was significantly lower among patients who underwent liver resection with MWA (4/39; 10.2%) compared with patients who underwent liver resection only (11/40; 27.5%) (p = 0.047) [72].

Pop 4: intermediate und fortgeschrittene Stadien

Population 4: intermediate and advanced stage primary liver tumours (BCLC B or C)

MWA vs TACE for HCC

MWA vs. TACE:

Tumour recurrence: A pairwise meta-analysis was conducted to compare local recurrence in MWA compared with TACE. Data were extracted from two RCTs providing information on 213 patients (Figure 4-4, see Table A-1 for details) [68, 75].

2 RCTs:

kein s.s. Unterschied

Overall, there was no statistically significant difference between MWA and TACE (RR 0.84, 95% CI 0.65, 1.09) after 12 months (one study did not report length of follow-up) [68]. The analysis was associated with low heterogeneity (I^2 = 0.0%).

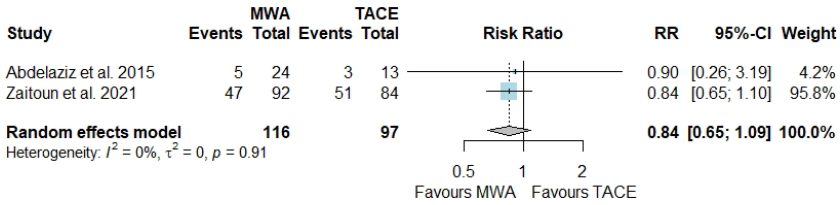

Figure 4-4: Forest plot indicating the relative risk of local recurrence when comparing MWA and TACE after 12 months

MWA plus TACE vs standalone TACE for HCC

MWA+TACE vs. TACE: keine Rezidive

No tumour recurrence occurred in either treatment group [71].

MWA plus TACE vs standalone TACE for HCC, iCCA and mixed HCC

MWA+Tace vs. TACE (gemischte Pat.Pop) Rezidive nicht berichtet

Not reported [76].

MWA vs MWA plus TACE vs standalone TACE for HCC

MWA vs. MWA+TACE vs. TACE:

s.s. zugunsten von MWA+TACE

Tumour recurrence: The rate of tumour recurrence was 51.1%, 22.5% and 60.7% for the MWA, MWA plus TACE and TACE only groups, respectively, with a significant difference reported among the three groups (p = 0.0001) [75].

SECONDARY LIVER TUMOURS

sekundäre Lebertumore:

Population 5b: patients with a secondary liver tumour who undergo ablation with curative intent as an alternative to surgery

Pop 5b: mit kurativer Intention als Alternative zu Resektion

MWA vs liver resection for colorectal metastases

MWA vs. Resektion: keine Rezidive in 3 Monaten FU

Tumour recurrence: Tumour recurrence was not observed for at least three months in either treatment group [73].

PRIMARY LIVER TUMOURS

primäre Lebertumore:

Population 1: patients with early stage (single or 2-3 nodules < 3cm) unresectable primary liver tumour (without extrahepatic spread used with curative intent)

Pop 1: frühes Stadium, wenig + kleine Nodule, nicht-resektierbar

MWA vs RFA for HCC

Treatment success: A pairwise meta-analysis was conducted to compare complete ablation in MWA compared with RFA. Data was extracted from four RCTs providing information on 492 nodules (Figure 4-5) [67, 70, 77, 78]. One study was excluded from the analysis due to results being reported per patient rather than per nodule (see Table A-1 for details) [69].

MWA vs. RFA: 4 RCTs: Behandlungserfolg

Overall, there was no statistically significant difference between MWA and RFA (RR 1.00, 95% CI 0.98, 1.02). The analysis was associated with low heterogeneity (I^2 = 0.0%).

kein s.s. Unterschied

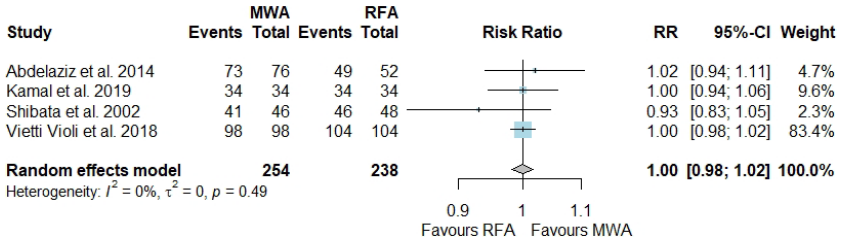

Figure 4-5: Forest plot indicating the relative risk of complete ablation when comparing MWA and RFA

Pop 2: sehr frühes Stadium, einzelner Tumorherd, Alternative zu OP

MWA vs. lap. Resektion: Behandungserfolg nicht berichtet

Population 2: patients with a single 2-3cm primary liver tumour or with very early-stage tumour (BCLC-0) as an alternative to surgery

MWA versus laparoscopic liver resection for HCC

Treatment success: Not reported [74].

Pop 3: resektierbar

MWA+Resektion vs. Resektion: Behandungserfolg nicht berichtet

Population 3: patients undergoing hepatic tumour resection where MWA is used adjuvant to the surgical-procedure

MWA plus liver resection vs standalone liver resection for HCC

Treatment success: Not reported [72].

Pop 4: intermediate und fortgeschrittene Stadien

Population 4: intermediate and advanced stage primary liver tumours (BCLC B or C)

MWA vs TACE for HCC

MWA vs. TACE: s.s. zugunsten von MWA

Treatment success: CT scans[32] were performed four weeks after the procedure to examine treatment responses. Complete ablation was achieved in significantly more MWA patients 75.0% (24/32) compared with TACE patients 40.6% (13/32) (p = 0.005) [68].

MWA plus TACE vs standalone TACE for HCC

MWA+TACE vs. TACE: Ansprechraten s.s. zugunsten von MWA+TACE

Treatment success was not reported however treatment response among 84 patients (42 in each group) in terms of the Response Evaluation Criteria in Solid Tumors (RECIST)[33] criteria were reported by one study [71]. Complete remission was achieved in 45.2% of patients in the MWA plus TACE group compared with 23.8% of patients in the TACE only group. Partial remission was achieved in 26.2% of patients in the MWA plus TACE group compared with 19.0% of patients in the TACE only group. Disease stability was achieved in 16.7% of patients in the MWA plus TACE group compared with 21.4% of

[32] When no contrast enhancement inside the lesion in the arterial phase was seen in the CT scan, response to treatment was rated as complete. However, when areas of enhancement within the boundaries of the original lesion in the arterial phase was apparent, response to treatment was rated as partial.

[33] RECIST criteria: complete response (CR): disappearance of all target lesions; partial response (PR): at least a 30% decrease in the sum of the longest diameter of the target lesions; progressive disease (PD): at least a 20% increase in the sum of the longest diameter of the target lesions; stable disease (SD): neither sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD.

patients in the TACE only group. Progressive disease was reported in 11.9% of patients in the MWA plus TACE group compared with 35.7% of patients in the TACE only group. Effective response remission was achieved in 71.4% of patients in the MWA plus TACE group compared to 42.8% of patients in the TACE only group. The overall treatment response was significantly higher among the MWA plus TACE group compared with the TACE only group (p value = < 0.05) [71].

MWA plus TACE vs standalone TACE for HCC, iCCA and mixed HCC

MWA+TACE vs TACE (gemischte Pat.Pop):

Ansprechraten höher bei MWA+TACE

Treatment success: MWA plus TACE group had higher cases of complete remission (55.0%) compared to the TACE only group (35.0%). Cases of partial remission were also higher among the MWA plus TACE group (32.5%) compared with the TACE only group (25.0%). Cases with stable disease and progressive disease were higher in the TACE only group compared to the MWA plus TACE group (26.3% versus 8.8% and 17.8% versus 8.8%, respectively). However, overall response rate of the treatment was significantly higher among the MWA plus TACE group (87.5%) compared with the TACE only group (60.0%) (p < 0.001) [76].

MWA vs MWA plus TACE vs standalone TACE for HCC

MWA vs. MWA+TACE vs. TACE:

Ansprechraten höher bei MWA+TACE

Treatment success: The Modified Response Evaluation Criteria in Solid Tumors (mRECIST)[34] criteria were used to evaluate treatment response after one month of the procedure. The overall treatment response differed significantly among the three treatment groups (p = 0.0002). Complete remission was achieved in 56.5%, 86.5% and 54.8% in the MWA, MWA plus TACE and TACE only groups, respectively. Partial remission was achieved in 27.2%, 3.3% and 32.1% in the MWA, MWA plus TACE and TACE only groups, respectively. Stable disease was achieved in 6.5%, 5.6% and 6.0% of the patients in the MWA, MWA plus TACE and TACE only groups, respectively. Progressive disease was identified in 9.8%, 4.5% and 7.1% of the patients in the MWA, MWA plus TACE and TACE only groups, respectively [75].

SECONDARY LIVER TUMOURS

sekundäre Lebertumore:

Population 5b: patients with a secondary liver tumour who undergo ablation with curative intent as an alternative to surgery

Pop 5b: mit kurativer Intention als Alternative zu Resektion

MWA vs liver resection for colorectal metastases

MWA vs. Resektion: kein s.s. Unterschied

Treatment success: Serum carcinoembryonic antigen concentration was estimated four weeks prior and four weeks post-procedure to assess treatment success. It decreased significantly from a mean of 18.5 ± 21.6 ng/mL to 5.8 ± 6.3 ng/mL (p = 0.05) in the MWA group and from 13.5 ± 11.4ng/mL to 4.1 ± 3.9 ng/mL (p < 0.01) in the liver resection group. Therefore treatment success, as measured by serum carcinoembryonic antigen concentration, was similar between the two treatment groups [73].

[34] mRECIST criteria: complete response (CR): absence of enhanced tumour areas during the arterial phase, reflecting complete tissue necrosis; partial response (PR): at least a 30% decrease; progressive disease (PD): at least a 20% increase in the sum of the longest diameter in the enhanced tumour areas; stable disease (SD): neither sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD.

4.3.3 Function[35, 36]

keine Evidenz zum Einfluss auf Alltagstätigkeiten

No data on the effect of MWA on patient's body functions or activities of daily living were identified.

4.3.4 Health-related quality of life[37, 38]

Evidenz zur QoL nur in 1 RCT

Quality of life was only reported for Population 4 (primary liver tumours) by one study which compared MWA plus TACE with standalone TACE in patients with HCC, iCC or mixed HCC.

PRIMARY LIVER TUMOURS

Pop 4: intermediate und fortgeschrittene Stadien

Population 4: intermediate and advanced stage primary liver tumours (BCLC B or C)

s.s. besser MWA+TACE

Quality of life was measured 30 days after discharge. A greater improvement in quality of life was reported, measured 30 days after discharge, was reported by the 80 patients in the MWA plus TACE group (92.5%) compared with the 80 patients in the TACE only group (72.5%) ($p < 0.001$) [76].

No data on disease-specific quality of life was identified.

4.3.5 Patient satisfaction[39]

keine Evidenz zur Patienten-Zufriedenheit

No data on the effect of MWA on patient satisfaction were identified.

[35] **D0011** – What is the effect of the technology on patients' body functions?

[36] **D0016** – How does the use of technology affect activities of daily living?

[37] **D0012** – What is the effect of the technology on generic health-related quality of life?

[38] **D0013** – What is the effect of the technology on disease-specific quality of life?

[39] **D0017** – Was the use of the technology worthwhile?

4.3.6 Patient safety (Procedure-related morbidity, serious adverse events)[40, 41, 42, 43, 44]

PRIMARY LIVER TUMOURS

primäre Lebertumore:

Population 1: patients with early stage (single or 2-3 nodules < 3cm) unresectable primary liver tumour (without extrahepatic spread used with curative intent)

Pop 1: frühes Stadium, wenig + kleine Nodule, nicht-resektierbar

MWA vs RFA for HCC

Procedure-related morbidity: Procedure-related complications were reported in five RCTs [67, 69, 70, 77, 78]. Where statistical comparisons were made, no significant difference was reported between the MWA and RFA groups for overall complication rates (see Table A-2 in the Appendix).

MWA vs. RFA: 5 RCTs: kein s.s. Unterschied

Population 2: patients with a single 2-3cm primary liver tumour or with very early-stage tumour (BCLC-0) as an alternative to surgery

Pop 2: sehr frühes Stadium, einzelner Tumorherd, Alternative zu OP

MWA vs laparoscopic liver resection for HCC

Procedure-related morbidity: Overall complication rate was significantly lower in the MWA group (3/45 (6.7%)) compared with the laparoscopic liver resection group (8/45 (17.8%)) (p = 0.016) [74]. Of the 45 patients who underwent MWA, bile leakage, pleural effusion, and postoperative blood loss each occurred in 2.2% (1/45) of patients. Of the 45 patients who underwent laparoscopic resection, bile leakage and pleural effusion each occurred in 6.7% (3/45) of patients, and 4.4% (2/45) of patients had postoperative blood loss [74]. No data on the following was identified: harms related to dosage or frequency of MWA, frequency or severity of harms changing over time or in different settings, susceptible patient groups at greater risk of harms, evidence of user-dependent harms.

MWA vs. lap. Resektion: s.s. weniger Komplikationen unter MWA

Population 3: patients undergoing hepatic tumour resection where MWA is used adjuvant to the surgical-procedure

Pop 3: resektierbar

MWA plus liver resection vs standalone liver resection for HCC

Procedure-related morbidity: Rates of overall complications did not differ between the two treatment groups (7.7% for MWA with resection versus 10.0% for liver resection only; p = 0.718). The number of patients with postoperative fever was not significantly different between treatments (20.5% versus 30.0%; p = 0.331) but postoperative blood loss was significantly lower in patients who underwent MWA with resection compared with those who underwent resection only (25.6% versus 70.0% respectively; p = <0.001). Late postoperative morbidities (e.g. chronic liver failure, ascites, and postoperative incisional hernias) did not differ significantly between the treatment groups (5.1% versus 10.0%; p = 0.409) [72].

MWA+Resektion vs. Resektion: generell kein s.s. Unterschied,

aber weniger Blutverlust unter MWA+Resektion

[40] **C0008** – How safe is the technology in comparison to the comparator(s)?

[41] **C0002** – Are the harms related to dosage or frequency of applying the technology?

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

[43] **C0005** – What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

[44] **C0007** – Are the technology and comparator(s) associated with user-dependent harms?

Pop 4: intermediate und fortgeschrittene Stadien

Population 4: intermediate and advanced stage primary liver tumours (BCLC B or C)

MWA vs TACE for HCC

MWA vs. TACE: kein s.s. Unterschied mit Ausnahme von Aszites (zuungunsten von TACE)

Procedure-related morbidity: The RCT stated that no major procedure-related complications occurred with either treatment. Significantly more patients had post-treatment ascites in the TACE group (15/32, 46.9%) compared with the MWA group (4/32, 12.5%) ($p = 0.003$). No significant difference was observed between the groups with the number of patients who experienced portal vein thrombosis, 3/32 (9.4%) and 1/32 (3.1%) in the TACE and MWA groups, respectively [68].

MWA plus TACE vs standalone TACE for HCC

MWA-TACE vs. TACE: kein Unterschied

Procedure-related morbidity: Procedure-related complications (including fever, abdominal pain, abdominal distension, vomiting, and embolism syndrome) were present in all patients (specific number per complication not reported). Whilst transient, increased aminotransferase levels were also reported in a few patients in both groups (number not reported) [71].

MWA plus TACE vs standalone TACE for HCC, iCCA and mixed HCC

MWA+TACE vs. TACE (gemischte Pat.Pop): kein s.s. Unterschied

Procedure-related morbidity: No significant difference in the number of procedure-related adverse events between the MWA plus TACE group (38/80; 47.5%) and the TACE only group (41/80; 51.2%) ($p = 0.625$). Of the 80 patients in each treatment group 10.0% versus 13.0% had nausea, 12.5% versus 10.0% had vomiting, 2.5% versus 5.0% had fever, 8.8% versus 7.5% had abdominal pain, 2.5% versus 2.5% had bone marrow suppression, 11.3% versus 8.8% had diarrhoea and 0.0% and 3.8% had hepatic injury in the MWA plus TACE group and the TACE only group, respectively [76].

MWA vs MWA plus TACE vs standalone TACE for HCC

MWA vs. MWA+TACE vs. TACE: Unterschiede zugunsten von MWA+TACE

Procedure-related morbidity: Postoperative major and minor adverse events were reported for all three treatment groups. Severe hepatic dysfunction was observed in one patient (1.1%) in the MWA plus TACE group and three patients (3.6%) in the TACE only group. Tumour seeding was reported in two patients (2.2%) who received MWA only (no cases were reported in the other two treatment groups). Minor *adverse events* included nausea/vomiting, abdominal pain and low grade fever. Nausea and vomiting occurred in 7.6% (7/92), 4.5% (4/89) and 6.0% (5/84) of patients in the MWA, MWA plus TACE and TACE only group, respectively. Abdominal pain was prevalent in 21.7% (20/92), 16.9% (15/89) and 28.6% (24/84) in the MWA, MWA plus TACE and TACE only group, respectively. Low grade fever was reported in 8.7% (8/92), 3.4% (3/89) and 15.1% (11/84) of patients, respectively [75].

sekundäre Lebertumore:

SECONDARY LIVER TUMOURS

Pop 5b: mit kurativer Intention als Alternative zu Resektion

Population 5b: patients with a secondary liver tumour who undergo ablation with curative intent as an alternative to surgery

MWA vs liver resection for colorectal metastases

MWA vs. Resektion: s.s. Unterscheid zugunsten von MWA

Procedure-related morbidity: Blood loss was significantly greater in the liver resection compared with the MWA group ($p < 0.05$) and blood transfusion was needed for 6/14 patients (42.8%) in the liver resection group and none in the MWA group ($p < 0.05$) [73]. The following postoperative complications were

reported: intestinal obstruction (1/16 resection patient (6.3%)), bile duct fistula (1/14 MWA patient (7.1%) and 1/16 resection patient (6.3%)), hepatic abscess (1/14 MWA patient (7.1%)) and wound infection (1/16 resection patient (6.3%)) [73].

4.3.7 Other effectiveness outcomes (Ablation/procedural time, lengths of stay)

PRIMARY LIVER TUMOURS

primäre Lebertumore:

Population 1: patients with early stage (single or 2-3 nodules < 3cm) unresectable primary liver tumour (without extrahepatic spread used with curative intent)

Pop 1: frühes Stadium, wenig + kleine Nodule, nicht-resektierbar

MWA vs RFA for HCC

Ablation/procedural time: Ablation time was reported in three RCTs. In all three studies, it was significantly shorter for MWA compared with RFA [69, 70, 77]. In the first RCT ablation time was 4.41 ± 1.7 minutes for MWA versus 14.21 ± 9.1 minutes for RFA ($p < 0.001$) [70]. The second RCT reported ablation times of 12 minutes for MWA and 24 minutes for RFA (standard deviation not reported) [69] whilst the third RCT reported 33 ± 11 minutes for MWA and 53 ± 16 minutes for RFA [77].

MWA vs. RFA:

3 RCTs zu Verfahrensdauer: kürzer mit MWA

Length of stay: One RCT reported postoperative length of stay. Patients in both the MWA and RFA groups remained in hospital for a mean duration of four days, ranging from one to ten days in the MWA group, and one to 13 days in the RFA group. The difference was not significant ($p = 0.543$) [69].

1 RCT: Dauer des Krankenhausaufenthalts: kein s.s. Unterschied

Population 2: patients with a single 2-3cm primary liver tumour or with very early-stage tumour (BCLC-0) as an alternative to surgery

Pop 2: sehr frühes Stadium, einzelner Tumorherd, Alternative zu OP

MWA vs laparoscopic liver resection for HCC

Ablation/procedural time: Mean procedural time was significantly shorter for the MWA group (96.7 ± 27.8 minutes) compared to the laparoscopic resection group (134.2 ± 34.3 minutes) ($p < 0.001$) [74].

MWA vs. lap. Resektion: Verfahrensdauer: kürzer mit MWA

Population 3: patients undergoing hepatic tumour resection where MWA is used adjuvant to the surgical-procedure

Pop 3: resektierbar

MWA plus liver resection vs standalone liver resection for HCC

MWA+Resektion vs. Resektion:

Ablation/procedural time: No difference in ablation/procedural time among the two treatment groups was observed ($p = 0.914$). In 48.7% of patients who underwent liver resection with MWA, and in 47.5% of patients who underwent liver resection alone, the surgery time was no more than 180 minutes [72].

Verfahrensdauer: kein Unterschied in der Ablationszeit

Length of stay: Patients who underwent MWA plus liver resection were significantly more likely to have postoperative stays longer than ten days in duration compared with those who had liver resection only (33.3% versus 82.5%, respectively; $p < 0.001$) [72].

Dauer des Krankenhausaufenthalts: s.s. Unterschied zuungunsten MWA + Resektion

Pop 4: intermediate und fortgeschrittene Stadien

Population 4: intermediate and advanced stage primary liver tumours (BCLC B or C)

MWA vs TACE for HCC

MWA vs. TACE: Verfahrensdauer: weniger Sessions mit MWA

Ablation/procedural time: A significantly lower number of sessions was required to achieve complete ablation in the MWA group (1.2 ± 0.4 sessions) compared with the TACE group (2.9 ± 0.9 sessions) (p = 0.001) [68].

Length of stay: no evidence was reported

sekundäre Lebertumore:

SECONDARY LIVER TUMOURS

Pop 5b: mit kurativer Intention als Alternative zu Resektion

Population 5b: patients with a secondary liver tumour who undergo ablation with curative intent as an alternative to surgery

MWA vs liver resection for colorectal metastases

MWA vs. Resektion: Verfahrensdauer: kein s.s. Unterschied; Dauer des Krankenhaus-aufenthalts: kein s.s. Unterschied

Ablation/procedural time: There was no difference in the MWA and liver resection groups with respect to procedural time (mean 180 ± 20 minutes versus 200 ± 50 minutes, respectively (p = 0.20) [73].

Length of stay: There was no difference in the mean length of stay between the MWA (20 ± 7 days) and liver resection groups (25 ± 12 days) (p = 0.23) [73].

5 Quality of evidence

RoB mit Cochrane RoB 2

Risk of Bias in the RCTs included in this review was assessed by the Cochrane Risk of Bias 2 tool [62], and presented in Table A-3 (Appendix).

RoB Bewertung auf Endpunkt-Ebene

Überleben, Rezidive, schwere Nebenwirkungen/ Komplikationen

Study quality was assessed for crucial outcomes: survival, tumour recurrence and serious adverse events. With respect to overall survival, one of the twelve RCTs [77] did not evaluate survival rates, two RCTs have low RoB [69, 78], seven RCTs [68, 70, 72-76] have some RoB and two RCTs [67, 71] have a high RoB. With respect to tumour recurrence, one RCT [76] did not evaluate tumour recurrence, two RCTs have low RoB [69, 78], five RCTs [68, 70, 72, 74, 75] have some RoB and four have a high RoB [67, 71, 73, 77]. With respect to serious adverse events, two RCTs have low RoB [69, 78], seven RCTs [68, 70, 72-76] have some RoB and three have a high RoB [67, 71, 77].

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [1] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [1].

GRADE uses four categories to rank the strength of evidence:

Stärke der Evidenz: sehr niedrig bis hoch

- **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.

The ranking according to the GRADE scheme for the various comparisons can be found in the summary of findings tables below and in the evidence profile in Table A-4 to Table A-11 (Appendix). Results are summarised below per population.

PRIMARY LIVER TUMOURS

primäre Lebertumore:

Pop 1: frühes Stadium, wenig + kleine Nodule, nicht-resektierbar

Population 1: patients with early stage (single or 2-3 nodules < 3cm) unresectable primary liver tumour (without extrahepatic spread used with curative intent)

MWA vs. RFA: sehr niedrige Stärke der Evidenz

- For MWA versus RFA for the treatment of HCC, the strength of the evidence for overall survival, tumour recurrence, mortality (perioperative and at longest follow-up) and crucial adverse events is very low.

Pop 2: sehr frühes Stadium, einzelner Tumorherd, Alternative zu OP

Population 2: patients with a single 2-3cm primary liver tumour or with very early-stage tumour (BCLC-0) as an alternative to surgery

MWA vs. lap. Resektion: sehr niedrige Stärke der Evidenz

- For MWA versus laparoscopic liver resection, the strength of the evidence for overall survival, tumour recurrence, mortality (perioperative and at longest follow-up) and crucial adverse events is very low.

Pop 3: resektierbar

Population 3: patients undergoing hepatic tumour resection where MWA is used adjuvant to the surgical-procedure

MWA+Resektion vs. Resektion: sehr niedrige Stärke der Evidenz

- For MWA plus liver resection versus standalone liver resection for HCC, the strength of the evidence for overall survival, tumour recurrence, mortality (perioperative) and crucial adverse events is very low.

Pop 4: intermediate und fortgeschrittene Stadien

Population 4: intermediate and advanced stage primary liver tumours (BCLC B or C)

niedrige bis sehr niedrige Stärke der Evidenz

- For MWA versus TACE for HCC, the strength of the evidence for overall survival, tumour recurrence, mortality (at longest follow-up) and crucial adverse events is very low.
- For MWA plus TACE versus standalone TACE for HCC, the strength of the evidence for overall survival, tumour recurrence and mortality (at longest follow-up) and crucial adverse events is very low.
- For MWA plus TACE versus standalone TACE for HCC (BCLC stage B), the strength of the evidence for overall survival, tumour recurrence and mortality (perioperative) and crucial adverse events is low.
- For MWA plus TACE versus standalone TACE for mixed primary tumours (HCC, iCCA and mixed HCC), the strength of the evidence for overall survival, mortality (perioperative) and crucial adverse events is very low.

sekundäre Lebertumore:

SECONDARY LIVER TUMOURS

Pop 5b: mit kurativer Intention als Alternative zu Resektion

Population 5b: patients with a secondary liver tumour who undergo ablation with curative intent as an alternative to surgery

MWA vs. Resektion: sehr niedrige Stärke der Evidenz

- For MWA versus liver resection for colorectal metastases, the strength of the evidence for overall survival, tumour recurrence and mortality (perioperative and at longest follow-up) and crucial adverse events is very low.

Table 5-1: Summary of findings table of MWA compared to RFA for the treatment of HCC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with RFA	Risk with MWA				
Tumour recurrence **follow-up: range 12 months to 24 months**	113 per 1,000	**108 per 1,000** (40 to 288)	**RR 0.95** (0.35 to 2.54)	492 (4 RCTs)	⨁◯◯◯ Very low[a,b,c]	
Overall survival **follow-up: 12 months**	845 per 1,000	**955 per 1,000** (786 to 1,000)	**RR 1.13** (0.93 to 1.38)	199 (3 RCTs)	⨁◯◯◯ Very low[a,b,c]	
Overall survival **follow-up: 24 months**	745 per 1,000	**775 per 1,000** (678 to 886)	**RR 1.04** (0.91 to 1.19)	197 (2 RCTs)	⨁◯◯◯ Very low[a,b,c,d]	
Overall survival (follow up: 36 months) – not reported	-	-	-	-	-	
Mortality (perioperative) **follow-up: 30 days**	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 5.00** (0.25 to 99.59)	431 (5 RCTs)	⨁◯◯◯ Very low[a,b,c]	
Mortality (long-term) **follow-up: 12 months**	245 per 1,000	**157 per 1,000** (74 to 336)	**RR 0.64** (0.30 to 1.37)	109 (2 RCTs)	⨁◯◯◯ Very low[a,b,d]	One study [67] did not report follow-up duration
Crucial adverse events **follow-up: 34 months**	Subcapsular hepatic hematoma= MWA: 3/164 (1.8%), RFA: 9/149 (6.0%) [67, 78] Ascites= MWA: 1/145 (0.7%), RFA: 2/150 (1.3%) [69, 78] Bleeding requiring embolisation= MWA: 4/126 (3.2%), RFA: 0/132 (0%) [70, 78] Hematemesis= MWA: 1/28 (3.6%), RFA: 0/28 (0%), p = 1.000 Segmental hepatic infarction= MWA: 0/36 (0%), RFA: 1/36 (2.7%), p = NR Cholangitis with intrahepatic bile duct dilation = MWA: 1/36 (2.7%), RFA: 0/36 (2.7%), p = NR			534 (5 RCTs)	⨁◯◯◯ Very low[a,b]	

Abbreviations: CI = confidence interval; MWA = microwave ablation; NR = not reported; RFA = radiofrequency ablation; RR = risk ratio

*Notes: *** The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).*
a = Bias arising from the randomisation process/missing outcome data/selection of the reported result, b = Unclear applicability of trial population to Austrian context,
c = 95% CI overlap line of no effect, d = moderate sample size (100-199).

Table 5-2: Summary of findings table of MWA compared to TACE for treatment of HCC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TACE	Risk with MWA				
Tumour recurrence **follow-up: 12 months**	557 per 1,000	**468 per 1,000** (362 to 607)	**RR 0.84** (0.65 to 1.09)	213 (2 RCTs)	⨁◯◯◯ Very low[a,b,c]	
Overall survival **follow-up: 12 months**	531 per 1,000	**781 per 1,000** (537 to 1,000)	**RR 1.47** (1.01 to 2.14)	64 (1 RCT)	⨁◯◯◯ Very low[a,b,d]	
Overall survival (follow-up: 24 months) – not reported	-	-	-	-	-	
Overall survival **follow-up: 36 months**	548 per 1,000	**542 per 1,000** (422 to 728)	**RR 0.99** (0.77 to 1.33)	176 (1 RCT)	⨁◯◯◯ Very low[a,b,e]	
Mortality (perioperative) – not reported	-	-	-	-	-	
Mortality (long-term) **follow-up: 36 months**	422 per 1,000	**211 per 1,000** (55 to 824)	**RR 0.50** (0.13 to 1.95)	240 (2 RCTs)	⨁◯◯◯ Very low[a,b,c,f]	
Crucial adverse events **follow-up: 36 months**	Post-treatment ascites= TACE 15/32 (46.9%) vs MWA 4/32 (12.5%), p = 0.003			64 (1 RCT)	⨁◯◯◯ Very low[a,b,d]	

Abbreviations: CI = confidence interval; MWA = microwave ablation; RR = risk ratio; TACE = transcatheter arterial chemoembolisation

*Notes: * **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).*
a = Bias arising from randomisation process/selection of reported outcome, b = Unclear applicability of trial population to Austrian context, c = 95% CI overlaps line of no effect,
d = Small sample size (1-99), e = Moderate sample size (100-199), f = Heterogeneity assessed by I^2 statistic above 75%.

Table 5-3: Summary of findings table of MWA plus TACE compared to standalone TACE for treatment of HCC (BCLC stage B)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TACE	Risk with MWA + TACE				
Recurrence **follow-up: range 3.5 months to 24 months**	'No recurrence after long-term follow-up'			3000 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Overall survival **follow-up: 12 months**	571 per 1,000	**737 per 1,000** (697 to 777)	**RR 1.29** (1.22 to 1.36)	3000 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Overall survival **follow-up: 24 months**	95 per 1,000	**334 per 1,000** (281 to 396)	**RR 3.50** (2.95 to 4.15)	3000 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Overall survival (follow-up: 36 months) – not reported	-	-	-	-	-	
Mortality (perioperative) **follow-up: 30 days**	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	3000 (1 RCT)	⨁⨁◯◯ Low[a,b]	
Mortality (long-term) (follow up: 24 months) – not reported	-	-	-	-	-	
Crucial adverse events **follow-up: 36 months**	"No fatal complications such as severe liver and kidney function damage and massive haemorrhage were found"			3000 (1 RCT)	⨁⨁◯◯ Low[a,b]	

Abbreviations: CI = confidence interval; RR = risk ratio.

*Notes: * **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).*
a = bias arising from randomisation process/missing outcome data/selection of reported results, b = Unclear applicability of trial population to Austrian context.

Table 5-4: Summary of findings table of MWA plus TACE compared to standalone TACE for treatment of mixed primary liver tumours (HCC, iCCA, mixed HCC)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TACE	Risk with MWA + TACE				
Recurrence – not reported	-	-	-	-	-	
Overall survival follow-up: 12 months	638 per 1,000	**822 per 1,000** (682 to 1,000)	**RR 1.29** (1.07 to 1.57)	160 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Overall survival follow-up: 24 months	250 per 1,000	**513 per 1,000** (333 to 793)	**RR 2.05** (1.33 to 3.17)	160 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Overall survival follow-up: 36 months	50 per 1,000	**275 per 1,000** (99 to 762)	**RR 5.50** (1.98 to 15.24)	160 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Mortality (perioperative) follow-up: 30 days	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	160 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Mortality (long-term) (follow up: 36 months) – not reported	-	-	-	-	-	
Crucial adverse events follow-up: 36 months	Hepatic injury= MWA + TACE 0/80 (0%) vs TACE 3/80 (3.75%), p = NR			160 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	

Abbreviations: CI = confidence interval; MWA = microwave ablation; NR = not reported; RR = risk ratio; TACE = transcatheter arterial chemoembolisation

*Notes: *** The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).*
a = bias arising from randomisation process/selection of reported results, b = Unclear applicability of trial population to Austrian context, c = Moderate sample size (100-199).

Table 5-5: Summary of findings table of MWA plus TACE compared with standalone TACE for treatment of HCC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TACE	Risk with MWA + TACE				
Tumour recurrence follow-up: 12 months	607 per 1,000	**225 per 1,000** (146 to 340)	**RR 0.37** (0.24 to 0.56)	173 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	An additional study [71] also reported 'No recurrence after long-term follow-up'
Overall survival (follow-up: 12 months) – not reported	-	-	-	-	-	
Overall survival (follow-up: 24 months) – not reported	-	-	-	-	-	
Overall survival follow-up: 36 months	548 per 1,000	**695 per 1,000** (548 to 882)	**RR 1.27** (1.00 to 1.61)	173 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Mortality (perioperative) (follow-up: 30 days) – not reported	-	-	-	-	-	
Mortality (long-term) follow-up: 36 months	333 per 1,000	**190 per 1,000** (113 to 323)	**RR 0.57** (0.34 to 0.97)	173 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Crucial adverse events follow-up: 36 months	Severe hepatic dysfunction= TACE 3/84 (3.6%), TACE + MWA 1/89 (1.1%), p = NR			173 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	

Abbreviations: CI = confidence interval; MWA = microwave ablation; NR = not reported; RR = risk ratio; TACE = transcatheter arterial chemoembolisation

*Notes: *** The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).*
a = bias arising from randomisation process/selection of reported results, b = Unclear applicability of trial population to Austrian context, c = Moderate sample size (100-199).

Table 5-6: Summary of findings table of MWA plus liver resection compared to standalone liver resection for HCC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with liver resection without MWA	Risk with Liver resection using MWA				
Tumour recurrence **follow-up: median 18 months**	275 per 1,000	**102 per 1,000** (36 to 294)	**RR 0.37** (0.13 to 1.07)	79 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Overall survival (follow up: 12 months) – not reported	-	-	-	-	-	
Overall survival (follow up: 24 months) – not reported	-	-	-	-	-	
Overall survival **follow-up: 36 months**	475 per 1,000	**665 per 1,000** (451 to 988)	**RR 1.40** (0.95 to 2.08)	79 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Mortality (perioperative) **follow-up: 30 days**	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	79 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Mortality (long-term) – not reported	-	-	-	-	-	
Crucial adverse events **follow-up: median 18 months**	"Both groups had similar postoperative morbidity and late postoperative morbidity (e.g. chronic liver failure, ascites, and postoperative incision hernias)"			79 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	

Abbreviations: CI = confidence interval; RR = risk ratio.

*Notes: *** The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).*
a = Bias arising from randomisation process/selection of the reported result, b = Unclear applicability of trial population to Austrian context, c = Small sample size (1-99)

Table 5-7: Summary of findings table of MWA compared to laparoscopic resection for HCC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with laparoscopic resection	Risk with MWA				
Tumour recurrence **follow-up: range 1 years to 3 years**	89 per 1,000	**200 per 1,000** (67 to 603)	**RR 2.25** (0.75 to 6.78)	90 (1 RCT)	⨁◯◯◯ Very low[a,b]	
Overall survival **follow-up: 12 months**	911 per 1,000	**893 per 1,000** (774 to 1,000)	**RR 0.98** (0.85 to 1.12)	90 (1 RCT)	⨁◯◯◯ Very low[a,b]	
Overall survival **follow-up: 24 months**	689 per 1,000	**668 per 1,000** (503 to 889)	**RR 0.97** (0.73 to 1.29)	90 (1 RCT)	⨁◯◯◯ Very low[a,b]	
Overall survival **follow-up: 36 months**	378 per 1,000	**332 per 1,000** (193 to 582)	**RR 0.88** (0.51 to 1.54)	90 (1 RCT)	⨁◯◯◯ Very low[a,b]	
Mortality (perioperative) **follow-up: 30 days**	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	90 (1 RCT)	⨁◯◯◯ Very low[a,b]	
Mortality **follow-up: 36 months**	622 per 1,000	**666 per 1,000** (492 to 908)	**RR 1.07** (0.79 to 1.46)	90 (1 RCT)	⨁◯◯◯ Very low[a,b]	
Crucial adverse events **follow-up: 36 months**	Bile leakage= MWA: 1/45 (2.22%), Laparoscopic resection: 3/45 (6.67), p = 0.13 Postoperative blood loss= 1/45 (2.22%), Laparoscopic resection: 2/45 (4.44%), p = 0.83			90 (1 RCT)	⨁◯◯◯ Very low[a,b]	

Abbreviations: CI = confidence interval; MWA = microwave ablation; RR = risk ratio

*Notes: *** The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).*
a = Unclear applicability of trial population to Austrian context, b = Small sample size (1-99)

Table 5-8: Summary of findings table of MWA compared to resection for colorectal metastases

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with resection	Risk with MWA				
Tumour recurrence **follow-up: NR**	'Recurrence was not found for at least 3 months in all patients'			30 (1 RCT)	⨁◯◯◯ Very low[a,b,c]	
Overall survival **follow-up: 12 months**	688 per 1,000	**715 per 1,000** (447 to 1,000)	**RR 1.04** (0.65 to 1.66)	30 (1 RCT)	⨁◯◯◯ Very low[b,c]	
Overall survival **follow-up: 24 months**	563 per 1,000	**574 per 1,000** (304 to 1,000)	**RR 1.02** (0.54 to 1.90)	30 (1 RCT)	⨁◯◯◯ Very low[b,c]	
Overall survival **follow-up: 36 months**	188 per 1,000	**143 per 1,000** (28 to 735)	**RR 0.76** (0.15 to 3.92)	30 (1 RCT)	⨁◯◯◯ Very low[b,c]	
Mortality (perioperative) **follow-up: 30 days**	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	30 (1 RCT)	⨁◯◯◯ Very low[b,c]	
Mortality (long-term) **follow-up: NR**	750 per 1,000	**645 per 1,000** (398 to 1,000)	**RR 0.86** (0.53 to 1.39)	30 (1 RCT)	⨁◯◯◯ Very low[b,c]	
Crucial adverse events **follow-up: NR**	Bile duct fistula= MWA: 1/14 (7.14%), Resection: 1/16 (6.25%), p = NR			30 (1 RCT)	⨁◯◯◯ Very low[b,c]	

Abbreviations: CI = confidence interval; MWA = microwave ablation; NR = not reported; RR = risk ratio

*Notes: *** The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).*
a = Bias due to missing outcome data/selection of the reported result, b = Unclear applicability of trial population to Austrian context, c = small sample size (1-99)

6 Discussion

Liver cancer is a major health problem with poor survival rates. Generally, patients are diagnosed in the advanced stages of the disease, resulting in poor prognosis. The preferred curative treatment for primary and secondary liver tumour is resection (partial hepatectomy) [79]. However, resection is often only an option for a small number of people with liver cancer. This may be due to the tumour being too large or in a position which makes it difficult to remove safely, or if there are several tumours, or if the remaining part of the liver is unhealthy [47]. For HCC, the most common form of primary liver cancer, fewer than 40% of patients are candidates for surgery, and the rate of recurrence after curative surgery is high [80]. As a result of the ineligibility of many patients for resection, alternative treatments for patients with primary and secondary liver cancer have been investigated. These include TACE and also local ablative therapies, such as MWA, RFA, ethanol injection and cryoablation. Whilst RFA is the most widely used ablative treatment, MWA has reported advantages including higher temperatures, faster heating, shorter ablation times, larger ablation volumes and less heat sink effect [79]. As a result, the use of MWA to treat liver cancer has recently increased [79]. This review summarised the effectiveness and safety of MWA compared to other treatments for patients with liver cancer.

Leberkrebs hat schlechte Überlebensraten

Therapie 1. Wahl: Resektion

Diagnosestellung häufig spät, Resektion nicht möglich

Ablationsverfahren als Alternative RFA häufiger, zunehmend aber auch MWA

Summary of findings

A total of twelve RCTs were included [67-78]. Of these, eleven RCTs included patients with primary liver cancer [67-72, 74-78]; ten of these exclusively with HCC [67-72, 74, 75, 77, 78], and one with mixed primary cancers (HCC, iCCA and mixed HCC) [76]. The other RCT was on patients with secondary liver cancer from colorectal metastases [73].

Zusammenfassung der Ergebnisse

12 RCTs: davon 11 zu primären (HCC), nur 1 zu sekundären Karzinomen

The current evidence indicates that the assessed technology, MWA, is as effective and safe as the comparator, RFA, for the treatment of early-stage HCC only. This is consistent with the most recent ESMO guideline which recommended thermal ablation, via RFA or MWA, as a first-line treatment in BCLC 0 patients [19]. Evidence for other primary cancers, more advanced HCC or secondary cancers is not available for this comparison.

Evidenz sagt aus, dass WMA ebenso wirksam und sicher ist wie RFA

The current evidence is not sufficient to determine if the assessed technology, MWA, is more or less effective and safe than the comparators, resection and TACE, in primary or secondary liver cancers.

Evidenz ist insuffizient für Aussagen im Vergleich zu anderen Komparatoren

Internal and external validity

Results of this review should be interpreted cautiously due to concerns with both the internal and external validity of the studies. For internal validity, the main concerns were a lack of information regarding randomisation, missing data and the unavailability of the study protocol resulting in uncertainty regarding selective reporting of the results.

verschiedene Faktoren, warum Evidenz vorsichtig zu beurteilen ist: Qualitätsmängel der Studien

For external validity, there are applicability concerns for the included populations, the age of the studies and the geographical location and setting of the studies.

Übertragbarkeit auf "normale" Pts. im klinischen Alltag?

Leitlinien empfehlen MWA nur für inoperable Pts.

In the studies comparing RFA to MWA in patients with early-stage HCC, it was not clear that the patients were assessed and considered unsuitable for surgical resection. Published guidelines recommend ablation for patients in this group who cannot undergo resection. Inclusion of patients suitable for resection may result in study outcomes not representative of what would be achieved in clinical practice, for example, due to differences in underlying liver function. Four studies were conducted in patients with intermediate or advanced stage HCC who were suitable for treatment with TACE [68, 71, 75, 76]. Patients eligible for TACE are not a group currently recommended for ablative treatments in guidelines and this use of MWA should therefore be considered experimental.

Hälfte der RCTs vor 2016 publiziert: ev. heute bessere MWA Technologie

Half of the RCTs were published in 2016 or earlier. In recent years there has been advancement in MWA technology with newer devices and generators designed to increase the size of ablation zones, achieve larger ablation margins and minimise tumour progression [67, 69, 70, 77, 78]. These earlier studies may therefore have used technology which is now outdated and does not reflect the results that could be achieved using current MWA technology.

die meisten der RCTs bei HCC nicht in Europa durchgeführt

Except for one RCT comparing MWA to RFA for HCC, which was conducted in France and Switzerland, the other RCTs were conducted in China, Japan, Egypt and Hong Kong. The applicability of the results from these populations to Austrian people is uncertain [81].

die meisten Studien waren single-center RCTs = Ergebnisse sehr abhängig von Erfahrung des Operateurs

All but one included study was conducted at a single centre and all but one included study used CT or ultrasound guidance. It is reported that the success of visualisation with ultrasound guidance is strongly dependent on the experience of the operator [82]. Given that many of the comparisons included in this review included a single RCT, in addition to being conducted at a single centre, it is uncertain how well the results reflect the average outcomes that could be achieved in clinical practice.

Gaps in the Evidence and ongoing studies

meiste Evidenz liegt zu primären HCC vor, hier im Vergleich MWA vs. RFA

kaum Evidenz zu MWA bei sekundären Karzinomen

keine RCTs identifiziert zum Vergleich mit Ethanol Ablation, Kryotherapie, Laserablation

Most of the evidence on MWA (all but one RCT) was on the treatment of primary liver tumours, mainly HCC. In addition, most of these studies compared MWA with RFA in patients with early-stage HCC only. The comparative effectiveness and safety of MWA to RFA for the treatment of other primary liver tumours is unknown. The other comparisons on primary liver cancer were only reported in one RCT each which makes it difficult to draw conclusions. Similarly, there was only one study investigating the use of MWA for treatment of secondary liver cancers, also leading to uncertainty regarding the effectiveness and safety of MWA in this population. This RCT compared MWA to resection for colorectal metastases. The comparative effectiveness and safety of MWA to other treatment modalities and for other types of secondary liver cancers is unknown.

No RCTs were identified comparing MWA to ethanol ablation, cryotherapy or laser ablation, other comparators listed in the PICO, for any type of liver cancer.

auch die Mehrheit der laufenden Studien ist zu HCC (24/34)

There are 34 ongoing RCTs on MWA for treatment of liver cancer, the majority are on HCC, while ten are on patients with metastatic cancer. Comparators include stereotactic body radiation therapy, resection, TACE, RFA, ethanol injection, chemotherapy, and variations of MWA.

Limitations

wegen der Fülle der RCTs wurden keine Studien außer RCTs eingeschlossen

einige eingeschlossene RCTs sehr klein: ausreichend gepowert?

Due to the volume of RCT evidence identified, this report did not include lower levels of evidence. While randomised studies are the best way to establish comparative safety and effectiveness of an intervention, this limitation may have resulted in rare safety events not being captured due to the relatively small number of patients include in each study. Further, the report was not able to identify emerging uses of RFA, for which single arm or non-randomised comparative studies may have been conducted. Only three of the studies pre-specified effectiveness thresholds and conducted power calculations to ensure recruitment was adequate [69, 73, 78]. It is therefore uncertain whether the studies were adequately powered to detect any difference in the technologies. In general, studies in this area are limited by a lack of standardised published MCIDs which limits the assessment of clinical significance of results.

Conclusion

MWA scheint RFA gleichwertig in den relevanten Endpunkten bei primären HCC zu sein

From the included studies, MWA appears to be comparable with RFA for the treatment of early-stage HCC, in terms of survival, tumour recurrence, treatment success, and procedure-related mortality. There is not enough evidence to draw conclusions on the safety and effectiveness of MWA compared with other treatments for HCC, or for treatment of other types of primary liver tumours. In addition, there is not enough evidence to draw conclusions regarding its safety and effectiveness for the treatment of secondary liver tumours.

7 Recommendation

In Table 7-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 7-1: Evidence based recommendations

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

Reasoning:

gleichwertig zu RFA bei primärem HCC in frühen Stadien

With respect to the treatment of early-stage (BCLC 0 or A) HCC, the current evidence indicates that the assessed technology, MWA, is as effective and safe as the comparator RFA. Previously, RFA had been compared to resection and no difference in outcomes was found [83, 84]. This led to RFA being recommended as an effective treatment for early-stage HCC. While this review could not conclude that MWA is superior to RFA; there is consistent evidence, albeit low quality, that the techniques lead to equivalent outcomes. Therefore, given RFA is the recommended standard of care for early-stage HCC, it seems reasonable to recommend MWA use in the same populations for which RFA is established, noting this does not consider other factors such as relative costs.

d. h. für dieselbe Patient*innen-Population wie RFA empfohlen

nicht empfohlen für fortgeschrittene Stadien des HCC, andere Leberkarzinome oder sekundäre Karzinome

The inclusion in the catalogue of benefits is only recommended for the treatment of this specific population. It is not recommended for the treatment of other stages of HCC, other types of primary liver tumours or for the treatment of secondary liver tumours owing to a lack of evidence.

Re-Evaluation für diese Indikationen: 2025

A total of 34 ongoing clinical trials (all RCTs) investigating the safety and effectiveness of MWA to a range of other treatments for either primary or secondary liver cancer were identified. All should be completed by the end of 2024. Based on this, the re-evaluation of MWA for the treatment of secondary liver cancer is recommended in 2025.

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: MWA: Results from randomised controlled trials (part 1)

Author, year	Li 2016 [71]	Abdelaziz 2015 [68]	Zaitoun 2021 [75]	Zhu 2021 [76]	Abdelaziz 2014 [67]	Chong 2020 [69]	Kamal 2019 [70]
Country	China	Egypt	Egypt	China	Egypt	Hong Kong	Egypt
Sponsor	Nil	Nil	Nil	Nil	Nil	Shun Tak District Min Yuen Tong of Hong Kong	Nil
Intervention/ Product	MWA with TACE	MWA	I1: MWA I2: MWA with TACE	MWA with TACE	MWA	MWA	MWA
Comparator	TACE	TACE	C: TACE	TACE	RFA	RFA	RFA
Study design	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Number of pts	3000 (I: 1500, C: 1500)	64 (I: 32, C: 32)	278 (I1: 95, I2: 93, C: 90)	160 (I: 80, C: 80)	111 (I: 66, C: 45)	93 (I: 47, C: 46)	56 (I: 28, C: 28)
Inclusion criteria	HCC, BCLC stage B, lesion 3-6cm in diameter, unresectable, vascular invasion without distant organ metastases, no history of hepatic encephalopathy, no severe coagulation disorder	HCC, Child-Pugh A or B, ≤3 lesions, largest lesion 5-7cm in diameter, proper coagulation profile (platlet count >50,000/cm^3 and prothrombin concentration >60%)	HCC, Child-Pugh A or B, single lesion >3–<5cm in diameter, no extra-hepatic metasteses, no history of encephalopathy or refractory ascites	Primary liver cancer (HCC, cholangiocelluar carcinoma, mixed HCC), good complaince, complete clinical data	HCC, Child-Pugh A or B, ≤3 lesions, largest lesion ≤5cm in diameter, performance status 0, proper coagulation profile (platlets >50.000/mm^3, prothrombin concentration >60%)	>18 years, HCC, Child-Pugh A or B, ≤3 lesions, largest lesion ≤5cm in diameter, no extra-hepatic metastases, no evidence of major vasular or bile duct invasion, Karnofsky performance status ≤70%	HCC, liver cirrhosis related to hepatitis C, Child-Pugh A or B, ≤3 lesions, ≤5cm in diameter, no extra-hepatic metastases, no evidence of vasular invasion
Exclusion criteria	NR	Child-Pugh C, portal vein thrombosis, distant metastases, unacceptable coagulation profile, patients with intractable systemic infection, leucopenia, cardiac/renal insufficiency, hepatic encephalopathy, performance status >2, hepatofugal flow, and biliary obstruction. Patients were also excluded if lesions could be managed with MWA or TACE but not both	Poor compliance, Child-Pugh C, severe coagulation disorders, portal vein thrombosis, renal impairment, previous local ablation therapy of HCC	Hepatic/renal insufficiencies, coagulation disorders, allergic to study drugs, communication/mental disorders, chemotherapy in the last 6 months, life expectancy ≤6 months	Child-Pugh C, portal vein thrombosis, distant metastases, unacceptable coagulation profile, technically difficult tumours (near portal vein or interior vena cava)	Informed consent not available, pregnant, unfavourable tumour location, chronic renal failure,concomitant hepatectomy, HCC with history of rupture	History of alcohol consumption, positive hepatitis C surface antigen, other known cause of liver disease, direct-acting antiviral medication for hepatitis C, other locoregional treatment for HCC
Age of patients (yrs) [mean±SD (range)]	I: 48 (35-67) C: 50 (35-67) P > 0.05	I: 56.8 ± 5.7 (NR) C: 55.5 ± 9.4 (NR) P = 0.5	I1: 53.8 ± 10.3 (38-72) I2: 52.1 ± 9.5 (48-76) C: 51.3 ± 9.2 (41-75) P = 0.177	I: 45.8 ± 8.41 (NR) C: 46.12 ± 7.78 (NR) P > 0.05	I: 53.6 ± 5 (NR) C: 56.8 ± 7.3 (NR) P = 0.01	I: 63 (50-80) C: 64.5 (42-85) P = 0.726	I: ~55 (42-80) C: ~55 (42-80)
Gender, male n (%)	I: 929 (61.9) C: 857 (57.1) P > 0.05	I: 26 (81.2) C: 23 (71.9) P = 0.3	I1: 50 (54.3) I2: 52 (58.4) C: 52 (61.9) P = 0.596	I: 49 (61.3) C: 42 (52.5) P = 0.264	I: 48 (72.7) C: 31 (68.9) P = 0.6	I: 30 (63.8) C:38 (82.6) P = 0.041	I: 21 (75.0) C: 22 (78.6)

Author, year	Li 2016 [71]	Abdelaziz 2015 [68]	Zaitoun 2021 [75]	Zhu 2021 [76]	Abdelaziz 2014 [67]	Chong 2020 [69]	Kamal 2019 [70]
Follow-up (months)	1 month post operation up to 3.5-24 months	1 month post ablation and every 3 months (mean follow-up NR)	1 month post ablation up to 36 months	Every 3 months up to 36 months	Every 3 months (mean follow-up NR)	I: 38.3 (2.3-78) C: 33.9 (4.9-72.7)	12 months
Loss to follow-up, N (n)	NR	0 (0)	13 (I1: 3, I2: 4, C: 6)	NR	58 (I: 38, C: 20)	NR	12 (I: 6, C: 6)
MWA Instrument	ECO-100A1, Eco	AMICA GEM	AMICA GEM	NR	AMICA GEM	Microsulis Medical	AMICA GEN AGN-H-1.2
MWA guidance	CT	US	US	CT	US	CT or US	NR
Outcomes							
Efficacy							
Recurrence, n (%)	'No recurrence after long-term follow-up'	I: 5/24 (20.8) C: 3/13 (23.0) P = 0.02	**12 months:** I1: 47/92 (51.1) I2: 20/89 (22.5) C: 51/84 (60.7) P = 0.0001	NR	I: 3/76 (3.9) C: 7/52 (13.5) P = 0.04	NR	**3 months:** I: 2/26 (7.7) C: 0/28 (0.0) P = 0.227 **6 months:** I: 2/24 (8.3) C: 0/26 (0.0) P = 0.225 **12 months:** I: 2/22 (9.1) C: 2/22 (9.1) P = 1.000
De novo lesions, n (%)		I: 6/32 (18.8) C: 14/32 (43.8) P = 0.03			I: 9 (13.6) C: 10 (22.2) P = 0.2		**3 months:** I: 2/26 (7.7) C: 4/28 (14.3) P = 0.670 **6 months:** I: 2/24 (8.3) C: 2/26 (7.7) P = 0.670 **12 months:** I: 4/22 (18.2) C: 4/22 (18.2) P = 1.000
Malignant vascular invasion, n (%)							**3 months:** I: 0/26 (0.0) C: 2/28 (7.1) P = 0.491 **6 months:** I: 1/24 (4.2) C: 0/26 (0.0) P = 0.480 **12 months:** I: 0/22 (0.0) C: 2/22 (9.1) P = 0.488

Author, year	Li 2016 [71]	Abdelaziz 2015 [68]	Zaitoun 2021 [75]	Zhu 2021 [76]	Abdelaziz 2014 [67]	Chong 2020 [69]	Kamal 2019 [70]
Survival rate (%)	***Overall survival rate:*** **6 months:** I: 88.1 C: 76.2 **12 months:** I: 73.8 C: 57.1 **18 months:** I: 52.3 C: 30.9 **24 months:** I: 33.3 C: 9.5 P = 0.011	***Overall mean survival of total (n=64) patients:*** 15.4 months **12 months:** 63.6 **18 months:** 38.7 ***Mean survival:*** I: 21.7 months C: 13.7 months P = 0.04 ***Overall survival rate:*** **12 months:** I: 78.2 C: 52.4 **18 months:** I: 68.4 C: 28.6	***Median survival time (months):*** I1: 21 I2: 24 C: 19 P = 0.02 ***Overall survival rate:*** **36 months:** I1: 50/92 (54.3) I2: 62/89 (69.6) C: 46/84 (54.8) P = 0.02 **Mean progression-free survival (months):** I1: 16.7 I2: 22.3 C: 15.4 P < 0.001	***Overall survival rate:*** **12 months:** I: 66/80 (82.5) C: 51/80 (63.8) P < 0.05 **24 months:** I: 41/80 (51.3) C: 20/80 (25.0) P < 0.05 **36 months:** I: 22/80 (27.5) C: 4/80 (5.0) P < 0.05	***Overall median survival of total (n=53) patients:*** 27 months ***Overall survival rate of total (n=53) patients:*** **12 months:** 91.6 **24 months:** 86.1 ***Overall survival rate:*** **12 months:** I: 96.4 C: 67.6 **24 months:** I: 62.0 C: 47.4 P = 0.49	***Overall survival rate:*** **12 months:** I: 97.9 C: 93.5 **36 months:** I: 67.1 C: 72.7 **60 months:** I: 42.8 C: 56.7 P = 0.899 ***Disease-free survival:*** **12 months:** I: 51.1 C: 58.7 **36 months:** I: 24.1 C: 22.7 **60 months:** I: 19.3 C: 0.0 P = 0.912	***Overall survival rate:*** **12 months:** I: 23/27 (85.2) C: 22/26 (84.6) P = 0.496 ***Local tumour recurrence-free survival:*** **12 months:** I: 92.3 C: 90.9 P = 0.932 ***Estimated mean local recurrence-free time (months):*** I: 11.3 C: 11.7
Treatment success, n (%)	NR	**Complete ablation:** I: 24/32 (75.0) C: 13/32 (40.6) P = 0.005 **Partial ablation:** I: 8/32 (25.0) C: 19/32 (59.4)	NR	NR	**Complete ablation:** I: 73/76 (96.1) C: 49/52 (94.2) P = 0.6 **Partial ablation:** I: 3/76 (3.9) C: 3/52 (5.8)	**Complete ablation:** I: 45/47 (95.7) C: 45/46 (97.8) P > 0.999 **Residual disease at one month:** I: 2/47 (4.3) C: 1/46 (2.2) P > 0.999	**Complete ablation:** I: 34/34 (100) C: 34/34 (100)
Treatment response	***RECIST criteria*** **Complete remission, n (%)** I: 19/42 (45.2) C: 10/42 (23.8) P < 0.05 **Partial remission, n (%)** I: 11/42 (26.2) C: 8/42 (19.0) **Stable disease, n (%)** I: 7/42 (16.7) C: 9/42 (21.4) **Progressive disease, n (%)** I: 5/42 (11.9) C: 15/42 (35.7)	NR	***mRECIST criteria at one month*** **Complete remission, n (%)** I1: 52/92 (56.5) I2: 77/89 (86.5) C: 46/84 (54.8) P = 0.0002 **Partial remission, n (%)** I1: 25/92 (27.2) I2: 3/89 (3.3) C: 27/84 (32.1) **Stable disease, n (%)** I1: 6/92 (6.5) I2: 5/89 (5.6) C: 5/84 (6)	***RECIST criteria*** **Complete remission, n (%)** I: 44/80 (55.0) C: 28/80 (35.0) **Partial remission, n (%)** I: 26/80 (32.5) C: 20/80 (25.0) **Stable disease, n (%)** I: 7/80 (8.8) C: 21/80 (26.3) **Progressive disease, n (%)** I: 3/80 (8.8) C: 11/80 (17.8)	NR	NR	NR

Author, year	Li 2016 [71]	Abdelaziz 2015 [68]	Zaitoun 2021 [75]	Zhu 2021 [76]	Abdelaziz 2014 [67]	Chong 2020 [69]	Kamal 2019 [70]
Treatment response *(continuation)*	**Effective response remission, n (%)** I: 30/42 (71.4) C: 18/42 (42.8)		**Progressive disease, n (%)** I1: 9/92 (9.8) I2: 4/89 (4.5) C: 6/84 (7.1)	**Overall response rate, n (%)** I: 70/80 (87.5) C: 48/80 (60.0) P < 0.001			
HRQOL	NR	NR	NR	***KPS Instrument*** **Improved:** I: 45/80 (56.3) C: 26/80 (32.5) P < 0.05 **Stable:** I: 29/80 (36.3) C: 32/80 (40.0) **Worsen:** I: 6/80 (7.5) C: 22/80 (27.5)	NR	NR	NR
Length of hospital stay (days)	NR	NR	NR	NR	NR	I: 4 (1-10) C: 4 (1-13) P = 0.543	NR
Ablation time (min) [mean±SD (range)]	NR	NR **Number of sessions:** I: 1.2 ± 0.4 C: 2.9 ± 0.9 P = 0.001	NR	NR	NR	**Ablation time:** I: 12 (6-30) C: 24 (12-72) P < 0.001 **Operation time:** I: 100 (0-195) C: 105 (0-200) P = 0.850	**Ablation time:** I: 4.41±1.7 (3-10) C: 14.21±9.1 (4-31) P < 0.001 **Number of sessions per lesion:** I: 1 session = 32 (94.1%) 2 sessions = 2 (5.9%) C: 1 session = 30 (88.2%) 2 sessions = 4 (11.8%) P = 0.673
Resolution of symptoms	NR	NR	NR	NR	NR	NR	NR
Safety							
Mortality, n (%)	NR	I: 5/32 (15.6) C: 21/32 (65.6) **Causes:** I: hematemesis (n=3), hepatorenal syndrome (n=1), sepsis (n=1) C: liver failure (n=15), spontaneous baterial peritonitis (n=3), hepatorenal syndrome (n=2), haematemesis (n=1)	I1: 29/92 (32) I2: 17/89 (19.1) C: 28/84 (34.5) P = 0.02	NR	I: 5/28 (17.9) C: 9/25 (36.0) **Causes (not separated per treatment group):** Hepatic failure (n=6), GI haemorrhage (n=2), spontaneous bacterial peritonitis (n=2), pulmonary embolism (n=1), unknown (n=3)	NR	**12 months:** I: 4/27 (14.8) C: 4/26 (15.3) P = 0.496

Author, year	Li 2016 [71]	Abdelaziz 2015 [68]	Zaitoun 2021 [75]	Zhu 2021 [76]	Abdelaziz 2014 [67]	Chong 2020 [69]	Kamal 2019 [70]
Procedure-related mortality, n (%)	**Postoperative mortality:** 0 (0.0)	NR	NR	NR	NR	**30-day mortality:** 0 (0.0)	**30-day mortality:** I: 2/28 (7.1) C: 0/28 (0.0) P = 0.491
Precedure-related complications/AEs, n (%)	'Postoperative fever, abdominal pain, abdominal distension, vomiting, embolism syndrome found in all patients.' All resolved within 3-5 days of symptomatic treatment. 'Transient increase of aminotrasferase observed in some patients of both groups' Levels back to normal in 5-7 days after symptomatic treatment.	'No major procedure-related complications evidenced by either procedure' **Portal vein thrombosis:** I: 1/32 (3.1) C: 3/32 (9.4) P = 0.3 **Post-treatment ascites:** I: 4/32 (12.5) C: 15/32 (46.9) P = 0.003	***Major AEs:*** **Severe hepatic dysfunction:** I1: 0/92 (0.0) I2: 1/89 (1.1) C: 3/84 (3.6) **Tumour seeding:** I1: 2/92 (2.2) I2: 0/89 (0.0) C: 0/84 (0.0) ***Minor AEs:*** **Nausea/vomiting:** I1: 7/92 (7.6) I2: 4/89 (4.5) C: 5/84 (6.0) **Abdominal pain:** I1: 20/92 (21.7) I2: 15/89 (16.9) C: 24/84 (28.6) **Low grade fever:** I1: 8/92 (8.7) I2: 3/89 (3.4) C: 11/84 (15.1)	***Total incidence of AEs:*** I: 38/80 (47.5) C: 41/80 (51.3) P = 0.625 **Nausea:** I: 8/80 (10.0) C: 11/80 (13.8) **Vomiting:** I: 10/80 (12.5) C: 8/80 (10) **Fever:** I: 2/80 (2.5) C: 4/80 (5.0) **Abdominal pain:** I: 7/80 (8.8) C: 6/80 (7.5) **Bone marrow supression:** I: 2/80 (2.5) C: 2/80 (2.5) **Diarrhea:** I: 9/80 (11.3) C: 7/80 (8.8) **Hepatic injury:** I: 0/80 (0.0) C: 3/80 (3.8)	***Total complications:*** I: 2/66 (3.2) C: 5/45 (11.1) P = 0.09 **Subcapsular hematoma:** I: 1/66 (1.5) C: 2/45 (4.4) **Thigh burn:** I: 0/66 (0.0) C: 1/45 (2.2) **Abdominal wall burn:** I: 1/66 (1.5) C: 0/45 (0.0) **Pleural effusion:** I: 0/66 (0.0) C: 2/45 (4.4) **Portal vein thrombosis:** I: 2/66 (3) C: 0/45 (0) P = 0.2 **Abdominal lymph nodes:** I: 1/66 (1.5) C: 2/45 (4.4) P = 0.3	**Ileus:** I: 1/47 (2.1) C: 0/46 (0.0) **Ascites:** I: 0/47 (0.0) C: 1/46 (2.1) **Operative blood loss:** I: 10ml (1-726ml) C: 10ml (1-600ml) P = 0.415	**Pain at site of intervention:** I: 12/28 (42.9) C: 12/28 (42.9) P = 1.000 **Right shoulder pain:** I: 4/28 (14.3) C: 2/28 (7.1) P = 0.669 **Low grade fever:** I: 8/28 (28.6) C: 6/28 (21.4) P = 0.537 **Bleeding requiring embolisation:** I: 1/28 (3.6) C: 0/28 (0.0) P = 1.000 **Hematemesis within 24 hours of procedure:** I: 1/28 (3.6) C: 0/28 (0.0) P = 1.000

Abbreviations: AEs = adverse events; BCLC = Barcelona Clinic Liver Cancer; C = comparator; CT = computed tomography; GI = gastrointestinal; HCC = hepatocellular carcinoma; HRQOL = health-related quality of life; I = intervention; KPS = Karnofsky Performance Score; min = minute/s; mRECIST = Modified Response Evaluation Criteria in Solid Tumours; MWA = microwave ablation; n = number; NR = not reported; pts = participants; RCT = randomised controlled trial; RECIST = Response Evaluation Criteria in Solid Tumours; RFA = radiofrequency ablation; ± = standard deviation; TACE = transcatheter arterial chemoembolization; US = ultrasound; yrs = years.

Table A-1: MWA: Results from randomised controlled trials (part 2)

Author, year	Shibata 2002 [77]	Vietti Violi 2018 [78]	Shen 2018 [72]	Shibata 2000 [73]	Xu 2015 [74]
Country	Japan	France & Switzerland	China	Japan	China
Sponsor	Nil	Microsulis & Aculis grant	Nil	NR	Hebei Science and Technology Science and Technology Support Program
Intervention/ Product	MWA	MWA	Liver resection plus MWA	MWA	MWA
Comparator	RFA	RFA	Liver resection without MWA	Liver resection	Lapraroscopic liver resection
Study design	RCT	RCT	RCT	RCT	RCT
Number of pts	72 (I: 36, C: 36)	152 (I: 76, C: 76)	79 (I: 39, C:40)	30 (I: 14, C: 16)	90 (I: 45, C: 45)
Inclusion criteria	HCC, single nodule <4cm in diameter or 2-3 nodules ≤3cm in diameteter	≥18 years, HCC, Child-Pugh A or B, ≤3 lesions, ≤4cm in diameter, chronic liver disease or cirrhosis	HCC, Child-Pugh A or B, ≤3 lesions, largest single nodule ≤10cm in diameter or 2-3 nodules with no more than one lesion >5cm in diameter, no distant metastases, no contraindications for MWA	Colorectal carcinoma (adeno-carcinoma), <10 lesions, largest nodule <8cm, no evidence of periportal/celiac lymph node metastases or extra-hepatic distant metastases or ascites, no sign of liver cirrhosis or chronic hepatitis	HCC, Child-Pugh A or B, lesion ≤5cm in diameter, good compliance, no surgical contraindications
Exclusion criteria	NR	Chronic renal failure with creatinine clearnance <30 ml/min, existing concomitant tumour, contraindication to percutaneous treatment (BCLC criteria), previous systemic treatment or liver treatment by transarterial chemoembolisation or radioembolisation	Incomplete pathology data, previous anticancer treatment prior to surgery, portal/hepatic vein or inferior vena cava in-vasion, extrahepatic metastases, other malignancies, decompensated cirrhosis		Extrahepatic metastases, Child-Pugh C, portal hypertension, coagulation disorders, diffuse liver cancer, severe organ insufficiencies
Age of patients (yrs) [mean±SD (range)]	I: 62.5 (52-74) C: 63.6 (44-83)	I: 68 (60-72) C: 65 (59-73)	Combined: 59.32 ± 10.34	I: 61 ± 10 (42-81) C: 61 ± 9 (46-71) P = 1.0	I: 57.9 ± 3.4 (27-76) C: 58.3 ± 3.1 (26-78) P > 0.05
Gender, male n (%)	I: 24 (66.6) C: 26 (72.2)	I: 59 (83.0) C: 62 (85.0)	I: 31 (79.5) C: 29 (72.5) P = 0.467	I: 6 (42.9) C: 10 (62.5) P = NR	I: 32 (71.1) C: 34 (75.6) P > 0.05
Follow-up (months)	Mean 18 months (range: 6-27 months)	I: Median 26 (IQR 18-29) C: Median 25 (IQR 18-34)	Median 18 months (range: 7-40 months)	Every 3 months (mean follow-up NR)	12-36 months
Loss to follow-up, N (n)	NR	2 (I: 1, C: 1)	0 (0)	NR	NR
MWA Instrument	Microtaze	Acculis Sulis VpMTA	ECO-100A	HSD-20M	MTC-3-type microwave generator
MWA guidence	US	US	NR	US	CT

Author, year	Shibata 2002 [77]	Vietti Violi 2018 [78]	Shen 2018 [72]	Shibata 2000 [73]	Xu 2015 [74]
Outcomes					
Efficacy					
Recurrence, n (%)	***Rate of residual foci of untreated disease:*** **12 months:** I: NR (10) C: NR (4) **24 months:** I: NR (24) C: NR (12) P = 0.20	***Local tumour progression:*** **24 months:** I: 6/98 (6.0) C: 12/104 (12.0) RR 1.62, 95%CI 0.66 to 3.94, p = 0.27 ***Median time to local progression:*** I: 12 months (95%CI 5-28) C: 16 months (95% CI 4-24) P = 0.28	I: 4/39 (10.2) C: 11/40 (27.5)	'Recurrence of the coagulated tumors was not found for at least 3 months in all the patients in whom the tumors were judged to be coagulated completely'.	**Local recurrence:** I: 9/45 (20.0) C: 4/45 (8.9) P = 0.0254 **Total recurrence:** I: 22/45 (48.9) C: 20/45 (44.4) P = 0.5282
Survival rate (%)	NR	***Overall surival rate:*** **24 months:** I: 61/71 (86.0) C: 61/73 (84.0) P = 0.87	***Overall survival rates (combined):*** **12 months:** Combined: 93.7 **36 months:** Combined: 57 ***Comparative surival rates:*** **36 months:** I: 66.7 C: 47.5	***Mean survival time:*** I: 27 months C: 25 months ***Overall survival rate:*** **12 months:** I: 71 C: 69 **24 months:** I: 57 C: 56 **36 months:** I: 14 C: 23 P = 0.83 ***Disease-free survival time:*** I: 11.3 months C: 13.3 months P = 0.47	***Overall survival rates:*** **12 months:** I: 40/45 (88.9) C: 41/45 (91.1) P = 0.6007 **24 months:** I: 30/45 (66.7) C: 31/45 (68.9) P = 0.7369 **36 months:** I: 15/45 (33.3) C: 17/45 (37.8) P = 0.5109
Treatment success, n (%)	**Complete ablation:** I: 41/46 (89.0) C: 46/48 (96.0)	**Complete ablation:** I: 98/98 (100) C: 104/104 (100)	NR	NR	NR
Treatment response	NR	NR	NR	***Serum carcinoemryonic antigen concentration:*** **4 weeks prior:** I: 18.5 ± 21.6 C: 13.5 ± 11.4 **4 weeks post:** I: 5.8 ± 6.3 C:4.1 ± 3.9 Significant reduction for MWA (P < 0.05) and resecton (P < 0.01)	NR

Author, year	Shibata 2002 [77]	Vietti Violi 2018 [78]	Shen 2018 [72]	Shibata 2000 [73]	Xu 2015 [74]
HRQOL	NR	NR	NR	NR	NR
Length of hospital stay (days)	NR	NR	**>10 days:** I: 13/39 (33.3) C: 33/40 (82.5)	I: 20 ± 7 C: 25 ± 12 P = 0.23	NR
Ablation time (min) [mean±SD (range)]	**Ablation time:** I: 33±11 C: 53±16 **Number of sessions per lesion:** I: 1 session = 11/46 (24.0%) 2 sessions = 12/46 (26.0%) 3 sessions = 18/46 (39.0%) 4 sessions = 4/46 (9.0%) 5 sessions = 1/46 (2.0%) C: 1 session = 43/48 (90.0%) 2 sessions = 3/48 (6.0%) 3 sessions = 2/48 (4.0%) **Mean number of treatments per lesion** I: 2.4 ± 1.0 C: 1.1 ± 0.46 P < 0.001	**Operation time:** I: 81±13 C: 84±11	**Operation time (>180min):** I: 19/39 (48.7) C: 19/40 (47.5)	**Operation time:** I: 180 ± 20 C: 200 ± 50 P = 0.20	**Operation time:** I: 96.7 ± 27.8 C:134.2 ± 34.3 P = 0.0000
Resolution of symptoms	NR	NR	NR	NR	NR
Safety					
Mortality, n (%)	NR	**24 months mortality:** I: 10/71 (14) C: 12/73 (16) P = 0.87	NR	I: 9/14 (64.3) C: 12/16 (75.0)	See survival rates
Procedure-related mortality, n (%)	0 (0)	0 (0)	**30-day mortality:** 0 (0)	0 (0)	0 (0)
Procedure-related complications/AEs, n (%) *(continuation)*	***Overall complications:*** I: 4/36 (3.0) C: 1/36 (2.0) P = 0.36 **Segmental hepatic infarctional:** I: 0/36 (0) C: 1/36 (2.7) **Liver abscess:** I: 1/36 (2.7) C: 0/36 (0) **Cholangitis with intrahepatic bile ducy dilation:** I: 1/36 (2.7) C: 0/36 (0)	***Note: Analysed per lesion*** ***Grade 1 (Overall):*** I: 3/98 (3.0) C: 9/104 (9.0) **Subcapsular hepatic haematoma** I: 2/98 (2.0) C: 7/104 (6.7) **Peritoneal fluid effusion** I: 1/98 (1.0) C: 1/104 (0.9) **Minor hepatic blood test perturbation** I: 0/98 (0.0) C: 1/104 (0.9)	***Overall complications:*** I: 3/39 (7.7) C: 7/40 (10.0) **Fever:** I: 8/39 (20.5) C: 12/40 (30.0) **Late postoperative morbidities (eg, chronic liver failure, ascites, and post-operative incision hernias:** I: 2/39 (5.1) C: 4/40 (10.0)	**Intestinal obstruction:** I: 0/14 (0.0) C: 1/16 (6.3) **Bile duct fistula:** I: 1/14 (7.1) C: 1/16 (6.3) **Hepatic abscess:** I: 1/14 (7.1) C: 0/16 (0.0) **Wound infection:** I: 0/14 (0.0) C: 1/16 (6.3)	**Bile leakage:** I: 1/45 (2.2) C: 3/45 (6.7) P = 0.1268 **Pleural effusion:** I: 1/45 (2.2) C: 3/45 (6.7) P = 0.1268 **Intraoperative blood loss:** I: 231.9 ± 74.2ml C: 320.5 ± 89.4 P = 0.0000

Author, year	Shibata 2002 [77]	Vietti Violi 2018 [78]	Shen 2018 [72]	Shibata 2000 [73]	Xu 2015 [74]
Procedure-related complications/AEs, n (%)	**Subcutaneous abscess with skin burn:** I: 1/36 (2.7) C: 0/36 (0) **Subcapsular hematoma:** I: 1/36 (2.7) C: 0/36 (0)	***Grade 2 (Overall):*** I: 2/98 (2.0) C: 3/104 (3.0) **Pain requiring medication** I: 1/98 (1.0) C: 3/104 (3.0) **Infection of the puncture site** I: 2/98 (2.0) C: 0/104 (0.0) ***Grade 3 (Overall):*** I: 0/98 (0.0) C: 3/104 (3.0) **Pneumothorax requiring drainage** I: 0/98 (0.0) C: 1/104 (0.9) **Umbilical vein lesion requiring surveillance** I: 0/98 (0.0) C: 1/104 (0.9) **Intrahepatic segmental necrosis** I: 0/98 (0.0) C: 1/104 (0.9) ***Grade 4 (Overall):*** I: 2/98 (2.0) C: 0/104 (0.0) **Arterial bleeding requiring embolisation** I: 2/98 (2.0) C: 0/104 (0.0) **Grade 5 (Overall):** I: 0/98 (0.0) C:0/104 (0.0)	**Blood loss:** I: 10/39 (25.6) C: 28/40 (70.0)	**Intraoperative blood loss:** I: 360 ± 230ml C: 910 ± 490ml P = 0.027 **Pts requiring blood transfusion:** I:6/14 (42.8) C: 0/16 (0.0) P = 0.035	**Postoperative blood loss:** I: 1/45 (2.2) C: 2/45 (4.4) P = 0.3816 ***Total complication rate:*** I: 3/45 (6.7) C: 8/45 (17.8) P = 0.0164

Abbreviations: AEs = adverse events; BCLC = Barcelona Clinic Liver Cancer; C = comparator; CI = confidence interval; HCC = hepatocellular carcinoma; HRQOL = health-related quality of life; I = intervention; IQR = interquartile range; min = minute/s; MWA = microwave ablation; n = number; NR = not reported; pts = participants; RCT = randomised controlled trial; RFA = radiofrequency ablation; ± = standard deviation; yrs = years; RR = risk ratio.

Procedure-related morbidity for MWA compared with RFA for HCC

Table A-2: Summary of procedure-related morbidity for MWA compared with RFA for HCC

Study	Abdelaziz 2014 [67] n/N(%)	Chong 2020 [69] n/N(%)	Kamal 2019 [70] n/N(%)	Shibata 2002 [77] n/N(%)	Vietti Violi 2018 [78], n/N(%) Results reported per lesion
Total complications	MWA: 2/66 (3.2); RFA: 5/45 (11.1) p = 0.09	MWA: 1/47 (2.1); RFA: 1/46 (2.2) p > 0.999	NR	MWA: 4/36 (3.0); RFA: 1/36 (2.0) p = NR	Grade 1 MWA: 3/98 (3.0); RFA: 9/104 (9.0) Grade 2 MWA: 2/98 (2.0); RFA: 3/104 (3.0) Grade 3 MWA: 0/98 (0.0); RFA: 3/104 (3.0) Grade 4 MWA: 2/98 (2.0); RFA: 0/104 (0.0) p > 0.05
Subcapsular haematoma	MWA: 1/66 (1.5); RFA: 2/45 (4.4) p = NR	NR	NR	MWA: 1/36 (2.7); RFA: 0/36 (0) p = NR	MWA: 2/98 (2.0); RFA: 7/104 (6.7) p = NR
Thigh burn/skin burn	MWA: 0/66 (0.0); RFA: 1/45 (2.2) p = NR	NR	NR	MWA: 1/36 (2.7); RFA: 0/36 (0) p = NR	NR
Abdominal wall burn	MWA: 1/66 (1.5); RFA: 0/45 (0.0) p = NR	NR	NR	NR	NR
Pleural effusion	MWA: 0/66 (0.0); RFA: 2/45 (4.4) p = NR	NR	NR	NR	NR
Ileus	NR	MWA: 1/47 (2.1); RFA: 0/46 (0.0) p = NR	NR	NR	NR
Ascites	NR	MWA: 0/47 (0.0); RFA: 1/46 (2.2) p = NR	NR	NR	MWA: 1/98 (1.0); RFA: 1/104 (0.9) p = NR
Pain at site of intervention	NR	NR	MWA:12/28 (42.9); RFA: 12/28 (42.9) p = 1.00	NR	MWA: 1/98 (1.0); RFA: 3/104 (3.0) p = NR
Right shoulder pain	NR	NR	MWA: 4/28 (14.3); RFA: 2/28 (7.1) p = 0.669	NR	NR
Low grade fever	NR	NR	MWA: 8/28 (28.6); RFA: 6/28 (21.4) p = 0.537	NR	NR
Bleeding requiring embolisation	NR	NR	MWA: 1/28 (3.6); RFA: 0/28 (0.0) p = 1.00	NR	MWA: 2/98 (2.0); RFA: 0/104 (0.0) p = NR
Haematemesis within 24 hours of procedure	NR	NR	MWA: 1/28 (3.6); RFA: 0/28 (0.0) p = 1.00	NR	NR
Segmental hepatic infarction	NR	NR	NR	MWA: 0/36 (0); RFA: 1/36 (2.7) p = NR	NR
Liver abscess	NR	NR	NR	MWA: 1/36 (2.7); RFA: 0/36 (0) p = NR	NR

Study	Abdelaziz 2014 [67] n/N(%)	Chong 2020 [69] n/N(%)	Kamal 2019 [70] n/N(%)	Shibata 2002 [77] n/N(%)	Vietti Violi 2018 [78], n/N(%) Results reported per lesion
Cholangitis with intra-hepatic bile duct dilation	NR	NR	NR	MWA: 1/36 (2.7); RFA: 0/36 (0) p = NR	NR
Minor hepatic blood test perturbation	NR	NR	NR	NR	MWA: 0/98 (0.0); RFA: 1/104 (0.9) p = NR
Infection of the puncture site	NR	NR	NR	NR	MWA: 2/98 (2.0); RFA: 0/104 (0.0) p = NR
Pneumothorax	NR	NR	NR	NR	MWA: 0/98 (0.0); RFA: 1/104 (0.9) p = NR
Umbilical vein lesion requiring surveillance	NR	NR	NR	NR	MWA: 0/98 (0.0); RFA: 1/104 (0.9) p = NR
Intrahepatic segmental necrosis	NR	NR	NR	NR	MWA: 0/98 (0.0); RFA: 1/104 (0.9) p = NR

Abbreviations: MWA = microwave ablation; NR = not reported; RFA = radiofrequency ablation.

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 AIHTA [2] and in the Guidelines of EUnetHTA [3].

Table A-3: Risk of bias – study level (randomised studies), see [1]

Trial	Endpoints	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Abdelaziz 2014 [67]	Survival	Low	Low	High	Low	Some concern	**High**
	Tumour recurrence	Low	Low	High	Low	Some concern	
	Serious adverse events	Low	Low	Low	Low	Some concern	
Abdelaziz 2015 [68]	Survival	Some concern	Low	Low	Low	Some concern	**Some concern**
	Tumour recurrence	Some concern	Low	Low	Low	Some concern	
	Serious adverse events	Some concern	Low	Low	Low	Some concern	
Chong 2020 [69]	Survival	Low	Low	Low	Low	Low	**Low**
	Disease free survival	Low	Low	Low	Low	Low	
	Serious adverse events	Low	Low	Low	Low	low	
Kamal 2019 [70]	Survival	Some concern	Low	Low	Low	Some concern	**Some concern**
	Tumour recurrence	Some concern	Low	Low	Low	Some concern	
	Serious adverse events	Some concern	Low	Low	Low	Some concern	
Li 2016 [71]	Survival	Some concern	Low	High	Low	Some concern	**High**
	Tumour recurrence	Some concern	Low	High	Low	High	
	Serious adverse events	Some concern	Low	High	Low	Some concern	
Shen 2018 [72]	Survival	Some concern	Low	Low	Low	Some concern	**Some concern**
	Tumour recurrence	Some concern	Low	Low	Low	Some concern	
	Serious adverse events	Some concern	Low	Low	Low	Some concern	
Shibata 2000 [73]	Survival	Low	Low	Low	Low	Some concern	**Some concern**
	Tumour recurrence	Low	Low	High	Low	High	**High**
	Serious adverse events	Low	Low	Low	Low	Some concern	**Some concern**

Trial	Endpoints	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Shibata 2002 [77]	Survival	Not reported					
	Tumour recurrence	Low	Low	High	Low	High	**High**
	Serious adverse events	Low	Low	High	Low	Some concern	
Vietti Violi 2018 [78]	Survival	Low	Low	Low	Low	Low	**Low**
	Disease free survival	Low	Low	Low	Low	Low	
	Serious adverse events	Low	Low	Low	Low	Low	
Xu 2015 [74]	Survival	Low	Low	Low	Low	Some concern	**Some concern**
	Tumour recurrence	Low	Low	Low	Low	Some concern	
	Serious adverse events	Low	Low	Low	Low	Some concern	
Zaitoun 2021 [75]	Survival	Some concern	Low	Low	Low	Low	**Some concern**
	Tumour recurrence	Some concern	Low	Low	Low	Low	
	Serious adverse events	Some concern	Low	Low	Low	Low	
Zhu 2021 [76]	Survival	Some concern	Low	Low	Low	Some concern	**Some concern**
	Tumour recurrence	Not reported					
	Serious adverse events	Some concern	Low	Low	Low	Some concern	**Some concern**

Table A-4: Evidence profile: efficacy and safety of MWA compared to RFA for the treatment of HCC

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With RFA	With MWA		Risk with RFA	Risk difference with MWA
Tumour recurrence (follow-up: range 12 months to 24 months)											
492 (4 RCTs) [67, 70, 77, 78]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	27/238 (11.3%)	26/254 (10.2%)	**RR 0.95** (0.35 to 2.54)	113 per 1,000	**6 fewer per 1,000** (from 74 fewer to 175 more)
Overall survival (follow-up: 12 months)											
199 (3 RCTs) [67, 69, 70]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	82/97 (84.5%)	96/102 (94.1%)	**RR 1.13** (0.93 to 1.38)	845 per 1,000	**110 more per 1,000** (from 59 fewer to 321 more)
Overall survival (follow-up: 24 months)											
197 (2 RCTs) [67, 78]	serious[a]	not serious	serious[b]	serious[c,d]	none	⨁◯◯◯ Very low	73/98 (74.5%)	78/99 (78.8%)	**RR 1.04** (0.91 to 1.19)	745 per 1,000	**30 more per 1,000** (from 67 fewer to 142 more)
Overall survival (follow up: 36 months) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mortality (perioperative) (follow-up: 30 days)											
431 (5 RCTs) [67, 69, 70, 77, 78]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	0/206 (0.0%)	2/225 (0.9%)	**RR 5.00** (0.25 to 99.59)	0 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)
Mortality (long-term) (follow-up: 12 months)											
109 (2 RCTs) [67, 70]	serious[a]	not serious	serious[b]	serious[d]	none	⨁◯◯◯ Very low	13/53 (24.5%)	9/56 (16.1%)	**RR 0.64** (0.30 to 1.37)	245 per 1,000	**88 fewer per 1,000** (from 172 fewer to 91 more)
Crucial adverse events (follow-up: 34 months)											
534 (5 RCTs) [67, 69, 70, 77, 78]	serious[a]	not serious	serious[b]	not serious	none	⨁◯◯◯ Very low	Subcapsular hepatic hematoma= MWA: 3/164 (1.8%), RFA: 9/149 (6.0%) [67, 78] Ascites= MWA: 1/145 (0.7%), RFA: 2/150 (1.3%) [69, 78] Bleeding requiring embolisation= MWA: 4/126 (3.2%), RFA: 0/132 (0%) [70, 78] Hematemesis= MWA: 1/28 (3.6%), RFA: 0/28 (0%), p = 1.000 Segmental hepatic infarction= MWA: 0/36 (0%), RFA: 1/36 (2.7%), p = NR Cholangitis with intrahepatic bile duct dilation = MWA: 1/36 (2.7%), RFA: 0/36 (2.7%), p = NR				

Sources: Abdelaziz 2014 [67], Chong 2020 [69], Kamal 2019 [70], Shibata 2002 [77], Vietti Violi 2018 [78]

Abbreviations: CI = confidence interval; RR = risk ratio.

Notes:

a = Bias arising from the randomisation process/missing outcome data/selection of the reported result

b = Unclear applicability of trial population to Austrian context

c = 95% CI overlap line of no effect

d = moderate sample size (100-199)

Comments:

Crucial adverse events were defined as intra-abdominal bleeding, gastrointestinal bleeding, wound dehiscence, bile duct injury, postoperative ascites, intraperitoneal haemorrhage and bowel perforation

Table A-5: Evidence profile: efficacy and safety of MWA compared to TACE for treatment of HCC

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With TACE	With MWA		Risk with TACE	Risk difference with MWA
Tumour recurrence (follow-up: 12 months)											
213 (2 RCTs) [68, 75]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	54/97 (55.7%)	52/116 (44.8%)	**RR 0.84** (0.65 to 1.09)	557 per 1,000	**89 fewer per 1,000** (from 195 fewer to 50 more)
Overall survival (follow-up: 12 months)											
64 (1 RCT) [68]	serious[a]	not serious	serious[b]	very serious[d]	none	⨁◯◯◯ Very low	17/32 (53.1%)	25/32 (78.1%)	**RR 1.47** (1.01 to 2.14)	531 per 1,000	**250 more per 1,000** (from 5 more to 606 more)
Overall survival (follow-up: 24 months) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Overall survival (follow-up: 36 months)											
176 (1 RCT) [75]	serious[a]	not serious	serious[b]	serious[e]	none	⨁◯◯◯ Very low	46/84 (54.8%)	50/92 (54.3%)	**RR 0.99** (0.77 to 1.33)	548 per 1,000	**5 fewer per 1,000** (from 126 fewer to 181 more)
Mortality (perioperative) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mortality (long-term) (follow-up: 36 months)											
240 (2 RCTs) [68, 75]	serious[a]	serious[f]	serious[b]	serious[c]	none	⨁◯◯◯ Very low	49/116 (42.2%)	34/124 (27.4%)	**RR 0.50** (0.13 to 1.95)	422 per 1,000	**211 fewer per 1,000** (from 368 fewer to 401 more)
Crucial adverse events (follow-up: 36 months)											
64 (1 RCTs) [68]	serious[a]	not serious	serious[b]	very serious[d]	none	⨁◯◯◯ Very low	Post-treatment ascites= TACE 15/32 (46.9%) vs MWA 4/32 (12.5%), p = 0.003				

Sources: Abdelaziz 2015 [68], Zaitoun 2021 [75]

Abbreviations: CI = confidence interval; MWA = microwave ablation; RR = risk ratio; TACE = transcatheter arterial chemoembolisation

Notes:

a = Bias arising from randomisation process/selection of reported outcome
b = Unclear applicability of trial population to Austrian context
c = 95% CI overlaps line of no effect
d = Small sample size (1-99)
e = Moderate sample size (100-199)
f = Heterogeneity assessed by I2 statistic above 75%

Comments: Crucial adverse events were defined as intra-abdominal bleeding, gastrointestinal bleeding, wound dehiscence, bile duct injury, postoperative ascites, intraperitoneal haemorrhage and bowel perforation

Table A-6: Evidence profile: efficacy and safety of MWA plus TACE compared to standalone TACE for treatment of HCC (BCLC stage B)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With TACE	With MWA + TACE		Risk with TACE	Risk difference with MWA + TACE
Recurrence (follow-up: range 3.5 months to 24 months)											
3,000 (1 RCT) [71]	serious[a]	not serious	serious[b]	not serious	none	⨁⨁◯◯ Low	'No recurrence after long-term follow-up'				
Overall survival (follow-up: 12 months)											
3,000 (1 RCT) [71]	serious[a]	not serious	serious[b]	not serious	none	⨁⨁◯◯ Low	857/1,500 (57.1%)	1,107/1,500 (73.8%)	**RR 1.29** (1.22 to 1.36)	571 per 1,000	**166 more per 1,000** (from 126 more to 206 more)
Overall survival (follow-up: 24 months)											
3,000 (1 RCT) [71]	serious[a]	not serious	serious[b]	not serious	none	⨁⨁◯◯ Low	143/1,500 (9.5%)	500/1,500 (33.3%)	**RR 3.50** (2.95 to 4.15)	95 per 1,000	**238 more per 1,000** (from 186 more to 300 more)
Overall survival (follow-up: 36 months) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mortality (perioperative) (follow-up: 30 days)											
3,000 (1 RCT) [71]	serious[a]	not serious	serious[b]	not serious	none	⨁⨁◯◯ Low	0/1,500 (0.0%)	0/1,500 (0.0%)	not estimable	0 per 1,000	
Mortality (long-term) (follow up: 24 months) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Crucial adverse events (follow-up: 36 months)											
3,000 (1 RCT) [71]	serious[a]	not serious	serious[b]	not serious	none	⨁⨁◯◯ Low	*"No fatal complications such as severe liver and kidney function damage and massive haemorrhage were found"*				

Sources: Li 2016 [71]

Abbreviations: CI = confidence interval; RR = risk ratio.

Notes:

a = bias arising from randomisation process/missing outcome data/selection of reported results

b = Unclear applicability of trial population to Austrian context

Comments: Crucial adverse events were defined as intra-abdominal bleeding, gastrointestinal bleeding, wound dehiscence, bile duct injury, postoperative ascites, intraperitoneal haemorrhage and bowel perforation

Table A-7: Evidence profile: efficacy and safety of MWA plus TACE compared to standalone TACE for treatment of mixed primary liver tumours (HCC, iCCA, mixed HCC)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With TACE	With MWA + TACE		Risk with TACE	Risk difference with MWA + TACE
Recurrence – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Overall survival (follow-up: 12 months)											
160 (1 RCT) [76]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	51/80 (63.7%)	66/80 (82.5%)	**RR 1.29** (1.07 to 1.57)	638 per 1,000	**185 more per 1,000** (from 45 more to 363 more)
Overall survival (follow-up: 24 months)											
160 (1 RCT) [76]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	20/80 (25.0%)	41/80 (51.2%)	**RR 2.05** (1.33 to 3.17)	250 per 1,000	**262 more per 1,000** (from 83 more to 543 more)
Overall survival (follow-up: 36 months)											
160 (1 RCT) [76]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	4/80 (5.0%)	22/80 (27.5%)	**RR 5.50** (1.98 to 15.24)	50 per 1,000	**225 more per 1,000** (from 49 more to 712 more)
Mortality (perioperative) (follow-up: 30 days)											
160 (1 RCT) [76]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	0/80 (0.0%)	0/80 (0.0%)	not estimable	0 per 1,000	
Mortality (long-term) (follow up: 36 months) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Crucial adverse events (follow-up: 36 months)											
160 (1 RCT) [76]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	Hepatic injury= MWA + TACE 0/80 (0%) vs TACE 3/80 (3.75%), p = NR				

Sources: Zhu 2021 [76]

Abbreviations: CI = confidence interval; MWA = microwave ablation; NR = not reported; RR = risk ratio; TACE = transcatheter arterial chemoembolisation

Notes:

a = bias arising from randomisation process/selection of reported results

b = Unclear applicability of trial population to Austrian context

c = moderate sample size (100-199)

Comments: Crucial adverse events were defined as intra-abdominal bleeding, gastrointestinal bleeding, wound dehiscence, bile duct injury, postoperative ascites, intraperitoneal haemorrhage and bowel perforation

Table A-8: Evidence profile: efficacy and safety of MWA plus TACE compared to standalone TACE for treatment of HCC

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With TACE	With MWA + TACE		Risk with TACE	Risk difference with MWA + TACE
Tumour recurrence (follow-up: 12 months)											
173 (1 RCT) [75]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	51/84 (60.7%)	20/89 (22.5%)	**RR 0.37** (0.24 to 0.56)	607 per 1,000	**382 fewer per 1,000** (from 461 fewer to 267 fewer)
Overall survival (follow-up: 12 months) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Overall survival (follow-up: 24 months) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Overall survival (follow-up: 36 months)											
173 (1 RCT) [75]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	46/84 (54.8%)	62/89 (69.7%)	**RR 1.27** (1.00 to 1.61)	548 per 1,000	**148 more per 1,000** (from 0 fewer to 334 more)
Mortality (perioperative) (follow-up: 30 days) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Mortality (long-term) (follow-up: 36 months)											
173 (1 RCT) [75]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	28/84 (33.3%)	17/89 (19.1%)	**RR 0.57** (0.34 to 0.97)	333 per 1,000	**143 fewer per 1,000** (from 220 fewer to 10 fewer)
Crucial adverse events (follow-up: 36 months)											
173 (1 RCT) [75]	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	Severe hepatic dysfunction= TACE 3/84 (3.6%), TACE + MWA 1/89 (1.1%), p = NR				

Source: Zaitoun 2021 [75]

Abbreviations: CI = confidence interval; MWA = microwave ablation; NR = not reported; RR = risk ratio; TACE = transcatheter arterial chemoembolisation

Notes:

a = bias arising from randomisation process

b = Unclear applicability of trial population to Austrian context

c = moderate sample size (100-199)

Comments: Crucial adverse events were defined as intra-abdominal bleeding, gastrointestinal bleeding, wound dehiscence, bile duct injury, postoperative ascites, intraperitoneal haemorrhage and bowel perforation

Table A-9: Evidence profile: efficacy and safety of MWA plus liver resection compared to liver resection alone for HCC

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With liver resection without MWA	With liver resection using MWA		Risk with liver resection without MWA	Risk difference with liver resection using MWA
Tumour recurrence (follow-up: median 18 months)											
79 (1 RCT) [72]	serious[a]	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	11/40 (27.5%)	4/39 (10.3%)	**RR 0.37** (0.13 to 1.07)	275 per 1,000	**173 fewer per 1,000** (from 239 fewer to 19 more)
Overall survival (follow up: 12 months) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Overall survival (follow up: 24 months) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Overall survival (follow-up: 36 months)											
79 (1 RCT) [72]	serious[a]	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	19/40 (47.5%)	26/39 (66.7%)	**RR 1.40** (0.95 to 2.08)	475 per 1,000	**190 more per 1,000** (from 24 fewer to 513 more)
Mortality (perioperative) (follow-up: 30 days)											
79 (1 RCT) [72]	serious[a]	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	0/40 (0.0%)	0/39 (0.0%)	not estimable	0 per 1,000	
Mortality (long-term) – not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Crucial adverse events (follow-up: median 18 months)											
79 (1 RCT) [72]	serious[a]	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	*"Both groups had similar postoperative morbidity and late postoperative morbidity (e.g. chronic liver failure, ascites, and postoperative incision hernias)"*				

Source: Shen 2018 [72]

Abbreviations: CI = confidence interval; RR = risk ratio.

Notes:

a = Bias arising from randomisation process/selection of the reported result

b = Unclear applicability of trial population to Austrian context

c = Small sample size (1-99)

Comments: Crucial adverse events were defined as intra-abdominal bleeding, gastrointestinal bleeding, wound dehiscence, bile duct injury, postoperative ascites, intraperitoneal haemorrhage and bowel perforation

Table A-10: Evidence profile: efficacy and safety of MWA compared to laparoscopic resection for HCC

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With laparoscopic resection	With MWA		Risk with laparoscopic resection	Risk difference with MWA
Tumour recurrence (follow-up: range 1 years to 3 years)											
90 (1 RCT) [74]	not serious	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low	4/45 (8.9%)	9/45 (20.0%)	**RR 2.25** (0.75 to 6.78)	89 per 1,000	**111 more per 1,000** (from 22 fewer to 514 more)
Overall survival (follow-up: 12 months)											
90 (1 RCT) [74]	not serious	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low	41/45 (91.1%)	40/45 (88.9%)	**RR 0.98** (0.85 to 1.12)	911 per 1,000	**18 fewer per 1,000** (from 137 fewer to 109 more)
Overall survival (follow-up: 24 months)											
90 (1 RCT) [74]	not serious	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low	31/45 (68.9%)	30/45 (66.7%)	**RR 0.97** (0.73 to 1.29)	689 per 1,000	**21 fewer per 1,000** (from 186 fewer to 200 more)
Overall survival (follow-up: 36 months)											
90 (1 RCT) [74]	not serious	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low	17/45 (37.8%)	15/45 (33.3%)	**RR 0.88** (0.51 to 1.54)	378 per 1,000	**45 fewer per 1,000** (from 185 fewer to 204 more)
Mortality (perioperative) (follow-up: 30 days)											
90 (1 RCT) [74]	not serious	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low	0/45 (0.0%)	0/45 (0.0%)	not estimable	0 per 1,000	
Mortality (follow-up: 36 months)											
90 (1 RCT) [74]	not serious	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low	28/45 (62.2%)	30/45 (66.7%)	**RR 1.07** (0.79 to 1.46)	622 per 1,000	**44 more per 1,000** (from 131 fewer to 286 more)
Crucial adverse events (follow-up: 36 months)											
90 (1 RCT) [74]	not serious	not serious	serious[a]	very serious[b]	none	⨁◯◯◯ Very low	Bile leakage= MWA: 1/45 (2.22%), Laparoscopic resection: 3/45 (6.67), p = 0.13 Postoperative blood loss= 1/45 (2.22%), Laparoscopic resection: 2/45 (4.44%), p = 0.83				

Source: Xu 2015 [74]

Abbreviations: CI = confidence interval; MWA = microwave ablation; RR = risk ratio.

Notes:

a = Unclear applicability of trial population to Austrian context

b = Small sample size (1-99)

Comments: Crucial adverse events were defined as intra-abdominal bleeding, gastrointestinal bleeding, wound dehiscence, bile duct injury, postoperative ascites, intraperitoneal haemorrhage and bowel perforation

Table A-11: Evidence profile: efficacy and safety of MWA compared to resection for colorectal metastases

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With hepatectomy	With MWA		Risk with resection	Risk difference with MWA
Tumour recurrence (follow-up: NR)											
30 (1 RCT) [73]	serious[a]	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	'Recurrence was not found for at least 3 months in all patients'				
Overall survival (follow-up: 12 months)											
30 (1 RCT) [73]	not serious	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	11/16 (68.8%)	10/14 (71.4%)	**RR 1.04** (0.65 to 1.66)	688 per 1,000	**28 more per 1,000** (from 241 fewer to 454 more)
Overall survival (follow-up: 24 months)											
30 (1 RCT) [73]	not serious	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	9/16 (56.3%)	8/14 (57.1%)	**RR 1.02** (0.54 to 1.90)	563 per 1,000	**11 more per 1,000** (from 259 fewer to 506 more)
Overall survival (follow-up: 36 months)											
30 (1 RCT) [73]	not serious	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	3/16 (18.8%)	2/14 (14.3%)	**RR 0.76** (0.15 to 3.92)	188 per 1,000	**45 fewer per 1,000** (from 159 fewer to 548 more)
Mortality (perioperative) (follow-up: 30 days)											
30 (1 RCT) [73]	not serious	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	0/16 (0.0%)	0/14 (0.0%)	not estimable	0 per 1,000	
Mortality (long-term) (follow-up: NR)											
30 (1 RCT) [73]	not serious	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	12/16 (75.0%)	9/14 (64.3%)	**RR 0.86** (0.53 to 1.39)	750 per 1,000	**105 fewer per 1,000** (from 353 fewer to 292 more)
Crucial adverse events (follow-up: NR)											
30 (1 RCT) [73]	not serious	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	Bile duct fistula= MWA: 1/14 (7.14%), Resection: 1/16 (6.25%), p = NR				

Source: Shibata 2000 [73]

Abbreviations: CI = confidence interval; MWA = microwave ablation; NR = not reported; RR = risk ratio.

Notes:

a = Bias due to missing outcome data/selection of the reported result

b = Unclear applicability of trial population to Austrian context

c = small sample size (1-99)

Comments: Crucial adverse events were defined as intra-abdominal bleeding, gastrointestinal bleeding, wound dehiscence, bile duct injury, postoperative ascites, intraperitoneal haemorrhage and bowel perforation

Applicability table

Table A-12: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	There is uncertainty regarding the applicability of the size of the tumours treated in the included studies for populations one and two. The tumour sizes were slighty larger than defined in the PICO. Population one in the PICO includes single or two to three primary nodules < 3cm whilst Population two includes a single 2-3cm primary tumour. Three of the five RCTs included for population one and the one RCT on population two stipulated that they included lesions up to 5cm. In the ESMO clinical practice guidelines for the treatment of HCC it lists thermal ablation as one of the standard treatments for BCLC stage 0-A; however, it lists the following constraints – tumour size ≤ 3cm and not adjacent to vessels or bile duct [25]. Similary in the EASL guidelines it states that thermal ablation in single HCC tumours 2 to 3cm in size is an alternative to surgical resection based on technical factors (location of the tumour), hepatic and extrahepatic patient conditions [2].Thus the studies included for populations one and two treated tumours larger than that defined in the PICO and larger than what is recommended in clinical guidelines. In addition to uncertainty regarding the appliability of the size of the patient's tumours in the studies included for Population one, there is uncertainty regarding the applicability of the health of the patient's liver. Population one, as defined in the PICO, are patients with unresectable primary liver tumours. It was not reported in the studies included for Population one that the patients had to have unresectable liver tumours. Four studies were inlcuded that treated patients with intermediate to advanced stage primary liver cancer. This is not a recommended indiation for ablation in any of the guidelines identified and is unlikely to represent current stand of care.
Intervention	The intervention in this review was MWA. It is not known whether the devices used in the included studies are reflective of those currently being used in hospitals to treat liver cancer. Six of the twelve RCTs were published in 2016 or earlier. In recent years there has been advancement in MWA technology with the development of newer devices and generators designed to increase treatment efficacy and safety. It is possible these earlier studies may have used technology which is now outdated and does not reflect the results that could be achieved with current MWA technology. Where reported in the studies MWA was generally performed percutaneously using CT or ultrasound guidance. This is reflective of what would occur in clinical practice.
Comparators	The comparators used in the studies included in this review, resection, TACE and RFA, are reflective of those currently used to treat liver cancer as reported in European guidelines [24-27, 30].
Outcomes	Overall survival is regarded as the gold standard primary clinical endpoint in cancer trials [85]. This outcome was reported for all MWA comparisons identified: MWA versus RFA for the treatment of HCC at 12 and 24 months, MWA versus TACE for the treatment of HCC at 12 and 18 months, MWA plus TACE versus TACE alone for the treament of HCC at 12, 24 and 36 months, MWA plus resection versus resection alone for the treatment of HCC at 36 months, MWA versus laparoscopic resection for the treatment of HCC at 12, 24 and 36 months and MWA versus liver resection for the treatment of colorectal metastases at 36 months.
Setting	Eleven of the twelve RCTs were conducted in either China, Japan, Egypt or Hong Kong. The applicability of results from these populations to the Austrian population is not known.

List of ongoing randomised controlled trials

Table A-13: List of ongoing randomised controlled trials of MWA for liver cancer

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT02820194	Patients with secondary malignant neoplasm of liver	MWA	SBRT	Evaluation of proportion of patients free from progression from starting radiotherapy	February, 2022	Istituto Clinico Humanitas
NCT04081168	Liver metastasis colon cancer	MWA	SBRT	One-year local tumour progression-free survival	September, 2024	VU University Medical Center
NCT03674073	HCC	Neoantigen vaccines + MWA	MWA	Safety of neoantigen-based DC vaccine as measured by the number of subjects experiencing each type of adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events	October, 2020	Chinese PLA General Hospital
NCT04106453	Liver cancer	Navigated MWA	Ultrasound guided navigation	Time to complete ablation	January, 2020	Universitätsklinikum Köln
NCT02866344	Colorectal neoplasms Hepatic neoplasms	MWA	Hepatic resection	Local disease control at the site of intervention [Time Frame 2 years]	February, 2018	Atrium Health
NCT03609268	Recurrent HCC	MWA	SBRT	Progression free survival [Time Frame 3 years]	May, 2021	Second Affiliated Hospital, School of Medicine, Zhejiang University
NCT04721470	HCC	MWA MWA +TACE	TACE	Adverse events [Time Frame Up to three years after procedure] Treatment Response [Time Frame One month] RR [Time Frame 12 months after procedure] Overall mortality rate [Time Frame Three years after procedure] Progression-free survival [Time Frame 3 years after procedure] AFP variation rate [Time Frame Baseline and 1-2 months after procedure]	May, 2020	Zagazig University
NCT01340105	HCC	MWA	RFA	Complete ablation rate [Time Frame 1 month]	October, 2015	Chinese University of Hong Kong
NCT02646137	HCC	RFA + TACE MWA + TACE	TACE	Number of patients with successful ablation [Time Frame 3 months]	December, 2023	Sherief Abd-Elsalam
NCT03402607	HCC	Percutaneous Local Abalation (MWA)	Hypofractionated Image Guided Radiation Therapy	Change in QOL [Time Frame Baseline to 1 month]	July, 2019	Duke University

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT03654131	Colorectal carcinoma liver metastases	MWA	SBRT	Freedom from local lesion progression (analysed on patient-level) [Time Frame 3 years]	July 25, 2023	Rigshospitalet, Denmark
NCT03766555	HCC	MWA	Resection	OS [Time Frame 5 years]	July, 2023	Chinese University of Hong Kong
NCT03636620	HCC	TACE + MWA/RFA	TACE	OS [Time Frame up to 46 months]	August, 2018	Fudan University
NCT03088150	Liver metastasis colon cancer	MWA/RFA	Resection	OS [Time Frame 5 years]	July, 2022	VU University Medical Center
NCT03168152	HCC	MWA	SBRT	Time to local tumour progression [Time Frame 2 years]	April, 2022	University of Michigan Rogel Cancer Center
NCT02859753	HCC	PMCT	RFA	Time to disease progression according to American Society of Interventional Radiology criteria [Time Frame Through study completion up to 5 years]	October, 2019	Centre Hospitalier Universitaire Dijon
NCT02886104	Secondary malignant neoplasm of liver	MWA	Resection	OS [Time Frame 3 years]	July, 2021	Sixth Affiliated Hospital, Sun Yat-sen University
NCT02728193	HCC, very-early Stage	MWA and RFA	Percutaneous ethanol injection	RR [Time Frame 3 years]	December, 2014	Eastern Hepatobiliary Surgery Hospital
NCT02630108	HCC	RFA + TACE MWA + TACE	TACE	OS [Time Frame From the date of randomisation until the date of death from any cause, assessed up to 26 months]	December, 2017	Shanghai Zhongshan Hospital
NCT01867918	Metastatic colorectal cancer	Chemotherapy+ MWA/RFA	Chemotherapy	OS from time of randomisation [Time Frame 6 months]	December, 2016	Oslo University Hospital
NCT02964260	HCC	TAE combined MWA/RFA simultaneously	TACE combined MWA/ RFA sequentially	OS [Time Frame 3 years]	December, 2022	Sun Yat-sen University
NCT04224636	HCC non-resectable	Atezolizumab and Roche Bevacizumab (Atezo/Bev) followed by on-demand selective TACE (sdTACE) * RFA or MWA are permitted as alternative to TACE	Initial Synchronous Treatment With TACE and Atezo/Bev	24-months survival rate [Time Frame 24 months]	March, 2025	Ludwig-Maximilians – University of Munich
NCT03864211	HCC non-resectable	MWA/RFA plus toripalimab	Toripalimab monotherapy	Progression free survival [Time Frame Up to approximately 3 years]	February, 2022	Xiangya Hospital of Central South University
NCT05129787	Colorectal cancer metastatic	MWA/RFA	Surgical resection	Local tumour progression [Time Frame 12 months]	December, 2024	Oslo University Hospital
NCT04665609	HCC	MWA + Anlotinib and TQB2450 solution	MWA+ TQB2450 Solution	Objective response rate [Time Frame 2-year]	December, 2022	Chinese PLA General Hospital

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT04931420	Metastatic cancer Foregut carcinoid tumour Gastric adenocarcinoma Gallbladder adenocarcinoma Liver cancer GI cancer GI carcinoma Lung cancer	Video-assisted thoracic surgery or lobectomy or consolidative radiation or MWA/RFA or resection or excision peritonectomy transarterial radioembolisation	Standard of care chemotherapy	Progression free survival [Time Frame 12 months]	May, 2024	University of Chicago
JPRN-UMIN000036206	Colorectal liver metastasis	MWA	RFA	Modified RECIST evaluated by the CT scan taken after the first session of MWA or RFA	March, 2019	Juntendo University
JPRN-UMIN000035442	HCC	New generation MWA	New generation RFA	Technical success rate evaluated by the CT scan taken after the first session of new-generation MWA or RFA	November, 2018	Juntendo University
JPRN-UMIN000033297	HCC	MWA	RFA	CR rate [Time Frame 2-year from treatment]	July, 2018	Tokyo Medical University
ChiCTR-IOR-17013743	Intermediate-stage HCC	TACE + MWA	MWA	Safety and efficacy	December, 2021	Beijing You'an Hospital, Capital Medical University
ChiCTR-ICR-15006187	HCC	MWA	None	Regulatory T cells	March, 2016	401th Hospital of People's Liberation Army
ChiCTR-TRC-09000550	Primary liver cancer	RFA/cryoablation/MWA	Surgical resection	Survival rate	October, 2016	Chinese PLA General Hospital
2017-002755-29	HCC who are at high risk of recurrence	Nivolumab after MWA/RFA or resection	Placebo after MWA/RFA or resection	RFS	NR	Bristol-Myers Squibb International Corporation
2018-004800-20	HCC	Pembrolizumab (MK-3475) after MWA/RFA or resection	Placebo after MWA/RFA or resection	RFS; OS [Time Frame 4-6 years]	NR	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Abbreviations: CR = complete response; EORTC C-30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; GI = gastrointestinal; HCC = hepatocellular carcinoma; MWA = microwave ablation; OS = overall survival; PMCT = percutaneous microwave coagulation therapy; QOL = quality of life; RFA = radiofrequency ablation; RFS = recurrence-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; RR = recurrence rate; SBRT = stereotactic body radiation therapy; TACE = transcatheter arterial chemoembolization.

Research questions

Table A-14: Health problem and Current Use

Element ID	Research question
A0001	For which health conditions, and for what purposes is the technology 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?

Table A-15: Description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology 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 the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Table A-16: Clinical Effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0003	What is the effect of the technology on the mortality due to causes other than the target disease?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?
D0017	Was the use of the technology worthwhile?

Table A-17: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying the technology?
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 the technology?
C0007	Are the technology and comparator(s) associated with user-dependent harms?

Literature search strategies

Search strategy for Cochrane

Search Name: Microwave ablation for liver tumours	
Last saved: 13/12/2021 18:36:03	
Comment: MEL 2022 (ASERNIP-S/GG) 131221	
ID	Search
#1	MeSH descriptor: [Liver Neoplasms] explode all trees
#2	((liver OR hepatic OR hepato*cellular OR hepato-cellular) NEAR (cancer* OR tumo?r* OR carcinom* OR adenom* OR adeno?c* OR neoplasm* OR sarcoma* OR h?emangioma* OR malignan* OR lump* OR mass* OR metasta*)) (Word variations have been searched)
#3	#1 OR #2
#4	MeSH descriptor: [Ablation Techniques] explode all trees
#5	(ablation*) (Word variations have been searched)
#6	#4 OR #5
#7	MeSH descriptor: [Microwaves] explode all trees
#8	(micro?wave*) (Word variations have been searched)
#9	(micro-wave*) (Word variations have been searched)
#10	#7 OR #8 OR #9
#11	#6 AND #10
#12	((micro?wave* OR micro-wave*) NEAR (ablation* OR thermo?ablat* OR thermo-ablat* OR thermo?destruc* OR thermo-destruc* OR "thermal destruc*" OR thermo?coag* OR thermo-coag* OR "thermal coag*")) (Word variations have been searched)
#13	(MWA):ti,ab,kw
#14	#11 OR #12 OR #13
#15	#3 AND #14
#16	(conference abstract):pt (Word variations have been searched)
#17	(abstract):so (Word variations have been searched)
#18	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so (Word variations have been searched)
#19	#16 OR #17 OR #18
#20	#15 NOT #19
Total: 85 Hits	

Search strategy for Medline

Database: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to December 10, 2021>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2017 to December 10, 2021	
Search date: 13.12.2021	
ID	Search
#1	exp Liver Neoplasms/
#2	((liver or hepatic or hepato*cellular or hepato-cellular) adj3 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or adeno-c* or neoplasm* or sarcoma* or h?emangioma* or malignan* or lump* or mass$2 or metasta*)).mp.
#3	1 or 2
#4	exp Ablation Techniques/
#5	ablation*.mp.
#6	4 or 5
#7	exp Microwaves/
#8	micro*wave*.mp.
#9	micro-wave*.mp.

#10	7 or 8 or 9
#11	6 and 10
#12	((micro*wave* or micro-wave*) adj5 (ablation* or thermo?ablat* or thermo-ablat* or thermo?destruc* or thermo-destruc* or thermal destruc* or thermo?coag* or thermo-coag* or thermal coag*)).mp.
#13	MWA.ti,ab.
#14	11 or 12 or 13
#15	3 and 14
#16	limit 15 to (meta analysis or "systematic review")
#17	(((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.
#18	15 and 17
#19	limit 15 to randomized controlled trial
#20	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.) (1659870)
#21	15 and 20
#22	limit 15 to observational study
#23	exp epidemiologic studies/ or exp clinical trial/ or comparative study/
#24	((control and study) or program).mp.
#25	23 or 24
#26	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
#27	history.fs. or case report.mp.
#28	26 or 27
#29	25 not 28
#30	15 and 29
#31	16 or 18 or 19 or 21 or 22 or 30
#32	limit 31 to (english or german)
#33	remove duplicates from 32
Total: 610 Hits	

Search strategy for Embase

Search Name: Microwave ablation for liver tumours		
Comment: Embase Search results		
Search date: 13.12.2021		
No.	Query Results	Results
#54	#52 NOT #53	686
#53	#52 AND 'Conference Abstract'/it	238
#52	(#10 OR #11 OR #13 OR #14 OR #50) AND ([english]/lim OR [german]/lim)	924
#51	#10 OR #11 OR #13 OR #14 OR #50	969
#50	#9 AND #49	697
#49	#34 NOT #48	5,004,417
#48	#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47	3,856,564
#47	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)	2,383,591
#46	(rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de	1,135,842

#45	(databases NEAR/5 searched):ab	50,211
#44	'update review':ab	119
#43	'we searched':ab AND (review:ti,tt OR review:it)	39,146
#42	review:ab AND review:it NOT trial:ti,tt	930,922
#41	('random cluster' NEAR/4 sampl*):ti,ab,tt	1,508
#40	'random field*':ti,ab,tt	2,570
#39	nonrandom*:ti,ab,tt NOT random*:ti,ab,tt	17,427
#38	'systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt)	192,658
#37	'case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt)	19,135
#36	'cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt)	310,981
#35	((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt)	2,772
#34	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	5,639,564
#33	trial:ti,tt	351,042
#32	'human experiment'/de	563,500
#31	volunteer:ti,ab,tt OR volunteers:ti,ab,tt	264,524
#30	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt	402,159
#29	assigned:ti,ab,tt OR allocated:ti,ab,tt	433,272
#28	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt	406,031
#27	crossover:ti,ab,tt OR 'cross over':ti,ab,tt	114,038
#26	(parallel NEXT/1 group*):ti,ab,tt	28,519
#25	'double blind procedure'/de	190,864
#24	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt	253,014
#23	(open NEXT/1 label):ti,ab,tt	92,610
#22	(evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)	2,406,406
#21	compare:ti,tt OR compared:ti,tt OR comparison:ti,tt	575,180
#20	placebo:ti,ab,tt	334,113
#19	'intermethod comparison'/de	279,822
#18	'randomization'/de	92,369
#17	random*:ti,ab,tt	1,730,087
#16	'controlled clinical trial'/de	435,746
#15	'randomized controlled trial'/de	688,302
#14	#9 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	111
#13	#9 AND #12	280
#12	('meta analysis'/exp OR 'systematic review'/exp OR ((meta NEAR/3 analy*):ab,ti) OR metaanaly*:ab,ti OR review*:ti OR overview*:ti OR ((synthes* NEAR/3 (literature* OR research* OR studies OR data)):ab,ti) OR (pooled AND analys*:ab,ti) OR (((data NEAR/2 pool*):ab,ti) AND studies:ab,ti) OR medline:ab,ti OR medlars:ab,ti OR embase:ab,ti OR cinahl:ab,ti OR scisearch:ab,ti OR psychinfo:ab,ti OR psycinfo:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti OR cinhal:ab,ti OR cancerlit:ab,ti OR cochrane:ab,ti OR bids:ab,ti OR pubmed:ab,ti OR ovid:ab,ti OR (((hand OR manual OR database* OR computer*) NEAR/2 search*):ab,ti) OR ((electronic NEAR/2 (database* OR 'data base' OR 'databases')):ab,ti) OR bibliograph*:ab OR 'relevant journals':ab OR (((review* OR overview*) NEAR/10 (systematic* OR methodologic* OR quantitativ* OR research* OR literature* OR studies OR trial* OR effective*)):ab)) NOT ((((retrospective* OR record* OR case* OR patient*) NEAR/2 review*):ab,ti) OR (((patient* OR review*) NEAR/2 chart*):ab,ti) OR rat:ab,ti OR rats:ab,ti OR mouse:ab,ti OR mice:ab,ti OR hamster:ab,ti OR hamsters:ab,ti OR animal:ab,ti OR animals:ab,ti OR dog:ab,ti OR dogs:ab,ti OR cat:ab,ti OR cats:ab,ti OR bovine:ab,ti OR sheep:ab,ti) NOT ('editorial'/exp OR 'erratum'/de OR 'letter'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) NOT (('animal'/exp OR 'nonhuman'/exp) AND 'human'/exp))	1,399,356

#11	#9 AND ('meta analysis'/de OR 'meta analysis topic'/de OR 'systematic review'/de OR 'systematic review topic'/de)	148
#10	#3 AND #8 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	116
#9	#3 AND #8	2,785
#8	#4 OR #5 OR #6 OR #7	7,000
#7	mwa:ti,ab	2,095
#6	(microwave* OR 'micro-wave*') NEAR/5 (ablation* OR thermoablation* OR 'thermo-ablat*' OR thermodestruc* OR 'thermo-destruc*' OR 'thermal destruc*' OR thermocoag* OR 'thermo-coag*' OR 'thermal coag*')	4,443
#5	'microwave ablation device'/exp	290
#4	'microwave thermotherapy'/exp	5,286
#3	#1 OR #2	387,901
#2	(liver OR hepatic OR hepato*cellular OR 'hepatocellular') NEAR/3 (cancer* OR tumor* OR tumor* OR carcinom* OR adenom* OR adenoc* OR 'adeno c*' OR neoplasm* OR sarcoma* OR hemangioma* OR haemangioma* OR malignan* OR lump* OR mass* OR metasta*)	379,900
#1	'liver tumor'/exp	326,060

Search strategy for INAHTA

Search Name: Microwave ablation for liver tumours	
Search date: 13.12.2021	
ID	Search
#15	((((microwave* OR micro-wave*) AND (ablation* OR thermoablat* OR thermo-ablat* OR thermodestruc* OR thermo-destruc* OR "thermal destruc*" OR thermocoag* OR thermo-coag* OR "thermal coag*")) OR (((micro-wave*) OR (microwave*) OR ("Microwaves"[mhe])) AND ((ablation*) OR ("Ablation Techniques"[mhe])))) AND (((liver OR hepatic OR hepatocellular OR hepatocellular) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR neoplasm* OR sarcoma* OR hemangioma* OR haemangioma* OR malignan* OR lump* OR mass* OR metasta*)) OR ("Liver Neoplasms"[mhe]))) AND (English OR German)[Language]
#14	(((microwave* OR micro-wave*) AND (ablation* OR thermoablat* OR thermo-ablat* OR thermodestruc* OR thermo-destruc* OR "thermal destruc*" OR thermocoag* OR thermo-coag* OR "thermal coag*")) OR (((micro-wave*) OR (microwave*) OR ("Microwaves"[mhe])) AND ((ablation*) OR ("Ablation Techniques"[mhe])))) AND (((liver OR hepatic OR hepatocellular OR hepatocellular) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR neoplasm* OR sarcoma* OR hemangioma* OR haemangioma* OR malignan* OR lump* OR mass* OR metasta*)) OR ("Liver Neoplasms"[mhe]))
#13	((microwave* OR micro-wave*) AND (ablation* OR thermoablat* OR thermo-ablat* OR thermodestruc* OR thermo-destruc* OR "thermal destruc*" OR thermocoag* OR thermo-coag* OR "thermal coag*")) OR (((micro-wave*) OR (microwave*) OR ("Microwaves"[mhe])) AND ((ablation*) OR ("Ablation Techniques"[mhe])))
#12	(microwave* OR micro-wave*) AND (ablation* OR thermoablat* OR thermo-ablat* OR thermodestruc* OR thermo-destruc* OR "thermal destruc*" OR thermocoag* OR thermo-coag* OR "thermal coag*")
#11	((micro-wave*) OR (microwave*) OR ("Microwaves"[mhe])) AND ((ablation*) OR ("Ablation Techniques"[mhe]))
#10	(micro-wave*) OR (microwave*) OR ("Microwaves"[mhe])
#9	micro-wave*
#8	microwave*
#7	"Microwaves"[mhe]
#6	(ablation*) OR ("Ablation Techniques"[mhe])
#5	ablation*
#4	"Ablation Techniques"[mhe]
#3	((liver OR hepatic OR hepatocellular OR hepatocellular) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR neoplasm* OR sarcoma* OR hemangioma* OR haemangioma* OR malignan* OR lump* OR mass* OR metasta*)) OR ("Liver Neoplasms"[mhe])
#2	(liver OR hepatic OR hepatocellular OR hepatocellular) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR neoplasm* OR sarcoma* OR hemangioma* OR haemangioma* OR malignan* OR lump* OR mass* OR metasta*)
#1	"Liver Neoplasms"[mhe]
Total: 7 Hits	

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Austrian Institute for
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