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Thermal ablation for early-stage breast cancer: cryoablation, microwave, radiofrequency, high-intensity focused ultrasound, and laser ablation

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.

Content

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List of abbreviations

(S)AE ..... (serious) adverse event
AJCC ..... American Joint Committee on Cancer
ASBrS ..... American Society of Breast Surgeons
AWMF ..... Association of the Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*)
BC ..... breast cancer
BCS ..... breast conserving surgery
CEUS ..... contrast enhanced ultrasound
CI ..... confidence interval
CT ..... computed tomography
CYA ..... cryoablation
DCIS ..... ductal carcinoma in situ
DFS ..... disease free survival
ECIBC ..... European Commission Initiative on Breast Cancer
ER ..... oestrogen receptor
ESMO ..... European Society for Medical Oncology
EUnetHTA ..... European Network for Health Technology Assessment
FDA ..... Food and Drug administration
FU ..... follow-up
HER2 ..... human epidermal growth factor receptor 2
HIFU ..... high-intensity focused ultrasound ablation
HR ..... hazard ratio
HTA ..... health technology assessment
IDC ..... invasive ductal carcinoma
INAHTA ..... International Network of Agencies for Health Technology Assessment
LKF ..... Leistungsorientierte Krankenanstaltenfinanzierung
m ..... month(s)
MRI ..... Magnetic resonance imaging
MWA ..... microwave ablation
NA ..... not applicable
NR ..... not reported
NRSI ..... Non-randomised study of intervention
OIS ..... optimal information size
OS ..... overall survival
PICO ..... Population, Intervention Control, Outcome
PR ..... progesterone receptor
RCT ..... randomised controlled trial
RFA ..... radiofrequency ablation
RoB 2 ..... Cochrane Risk of Bias 2.0
ROBINS-I ..... Risk of Bias in Non-Randomised Studies of Interventions
SD ..... standard deviation
SLNB ..... sentinel lymph node biopsy

SR..... systematic review
TNM..... tumour mode metastasis
US..... ultrasound
USA ..... United States of America
VAS..... visual analogue scale
vs..... versus
w ..... week(s)
y..... year(s)

Executive Summary

Introduction

Health Problem

Early-stage breast cancer (BC) refers to invasive malignancies confined to the breast or regional lymph nodes without distant metastasis, classified as stages I to IIA under the TNM system. Diagnosis relies on imaging techniques such as mammography, ultrasound, and magnetic resonance imaging (MRI), along with histopathological and molecular analysis to determine hormone receptor status and genetic markers. In Austria, population-based mammography screening targets women aged 45–69, facilitating early detection and improved prognosis. BC is the most common cancer in women worldwide, with the life-time risk of developing BC being one in eight for women and one in 790 for men. Risk factors for BC include gender, age, genetic predisposition, hormonal influences, and modifiable lifestyle factors such as obesity, physical inactivity, smoking, alcohol consumption, and hormone replacement therapy.

definition, diagnosis & risk factors of early-stage breast cancer (BC)

For early-stage BC, the primary goal is curative treatment. Surgical resection, often followed by radiotherapy is the standard treatment. Breast-conserving surgery (BCS) is preferred, and mastectomy with reconstruction is an alternative when BCS is not feasible. Sentinel lymph node biopsy (SLNB) is used to assess nodal involvement, guiding further management. Adjuvant chemotherapy or endocrine therapy may be administered based on tumour biology and stage. While the five-year survival rate in high-income countries is at least 90%, treatment side effects can significantly impact quality of life.

standard treatment of early-stage BC: surgical resection followed by radiotherapy

Description of Technology

Thermal ablation is a minimally invasive technique using extreme temperatures to destroy tumours cells. In recent years, it has emerged as an alternative to surgical resection for early-stage BC. There are several forms of thermal ablation, including cryoablation (CYA), radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound ablation (HIFU), and laser ablation (LA).

thermal ablation (TA): utilisation of extreme temperatures to destroy tumour cells

Methods

The aim of this systematic review (SR) was to compare the safety and efficacy of different thermal ablation interventions with surgery with or without additional standard care in patients with early-stage BC. A systematic literature search was conducted across four databases for primary studies published in English or German between 2014 and 2024. Study selection and data extraction was performed by one assessor and validated by a second. Evidence quality was assessed according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework.

systematic search in 4 databases,
quality appraisal

GRADE

Domain effectiveness

The following efficacy outcomes were considered critical for formulating a recommendation: Overall survival (OS), disease-free survival (DFS), tumour recurrence and complete tumour ablation.

efficacy outcomes: overall survival (OS), disease-free survival (DFS) , recurrence, complete tumour ablation

Domain safety

Serious adverse events (SAE) and adverse events (AE) were considered critical safety outcomes for decision making.

safety outcomes: (serious) adverse events (S)AE

Results

Available evidence

Nineteen studies in 20 publications were included across all technologies, with 16 single-arm trials classified as having serious risk of bias (RoB) by default. One randomised controlled trial (RCT) on RFA was assessed as having low RoB for mortality, complete tumour ablation, recurrence, and safety. One non-randomised study of intervention (NRSI) on CYA had a critical RoB for AEs, the only comparative outcome from this trial, while a second NRSI on MWA was judged to have serious RoB for OS, DFS and recurrence.

available evidence: 1 RCT, 2 NRSI, 16 single-arm trials

Clinical effectiveness and safety

Cryoablation

Comparative evidence for CYA was limited to one small NRSI (n=20) reporting only AEs and SAEs, with two minor AEs in the intervention group. Complete ablation was achieved in 90% of patients who received CYA. Outcomes such as OS, DFS, and recurrence were not reported.

CYA: 1 NRSI (n=20)

AE: 2 vs 0

Complete tumour ablation: 90%

Eight single-arm trials indicated CYA did not negatively impact OS (n=400) or recurrence (n=279) and achieved complete ablation in all patients (n=192). AE rates varied, with mild to moderate pain and bruising reported most frequently. No SAEs were observed over follow-up periods of two to 60 months (n=129). DFS was not reported in any single-arm trial.

Microwave ablation

A propensity score-matched NRSI, with 33 patients in the intervention group and 99 in the control group, found no significant differences between MWA and surgery for OS and DFS at a median follow-up of 31 months. One patient required re-treatment to achieve complete ablation, and no major differences in recurrence were noted. AEs were reported only in the intervention group, with no events during the follow-up period.

MWA: 1 NRSI (n=132)

no significant difference in OS and DFS at FU 31m

complete ablation: 100%

Additionally, three single-arm trials indicated MWA did not negatively impact OS up to 36 months, with complete ablation achieved in over 90% of cases. Recurrence was reported in one study (n=35) with no cases observed. No SAEs were noted, though pain and swelling were common AEs across studies. DFS was not provided in either study.

no difference in recurrence

Radiofrequency ablation

One RCT (n=40) comparing RFA to surgery found comparable OS and complete ablation in all participants, with no recurrence at a median follow-up of 25 months. Recruitment was halted after an interim analysis due to a higher number of local AEs in the RFA group (8/20 vs. 1/20, p=0.1), though no SAEs were reported.

RFA 1 RCT (n=40)
comparable OS
complete ablation: 100%
no recurrence at FU 25m
>AE in RFA group: 8/20 vs 1/20 (p=0.1)

Additionally, a single-arm trial with 18 patients showed 100% OS and complete ablation at 14 days. Pain levels reported during the administration of anaesthesia and the procedure itself were similar, but increased pain was reported post-procedure. Outcomes such as DFS, recurrence, or SAEs were not reported.

High-frequency ultrasound ablation

No comparative evidence was available for HIFU. Two single-arm trials (n=35) reported 100% OS, with a follow-up of only ten days in one trial and twelve months in the other trial. Complete ablation was achieved in all patients in one trial (n=25), with no recurrences at twelve months. The most common AEs were pain and oedema. DFS and SAEs were not reported.

no comparative data on HIFU

Laser ablation

No comparative evidence was available for LA. One single-arm trial (n=61) reported an 84% complete ablation rate and a 3% recurrence rate at four years for LA. At 43 months, eight mild to moderate AEs (e.g., pain) were observed. The outcomes OS, DFS, and SAEs were not reported.

no comparative data on LA

Upcoming evidence

One ongoing RCT comparing CYA with lumpectomy in T1-stage BC patients was identified, with primary endpoints of treatment-related complications and ipsilateral recurrence at five years. Two NRSIs are comparing CYA and MWA with BCS, alongside several single arm trials.

upcoming evidence:
1 RCT (CYA)
2 NRSIs (CYA, MWA)

Discussion

The standard treatment for early-stage BC is surgery, often combined with neoadjuvant or adjuvant therapies. Surgical approaches have evolved from radical mastectomy to BCS, reflecting a shift towards less invasive procedures. Thermal ablation represents the next step in this progression, offering potential benefits such as lower anaesthesia requirements, faster recovery, and a possible alternative for patients who are either ineligible or unwilling to undergo surgery. However, the evidence supporting thermal ablation for early-stage BC remains limited due to small sample sizes, methodological heterogeneity, and a lack of robust comparative data. A challenge of thermal ablation lies in the precise definition and confirmation of complete tumour ablation. Since the tumour is not resected, no physical specimen is available for traditional histopathological assessment. Margins are inferred using imaging only, which may not provide sufficient sensitivity and specificity. Furthermore, difficulties remain in differentiating post-treatment necrosis from residual or recurrent tumour on imaging and altered tissue properties may hinder precise re-ablation. Most studies performed post-ablation resection, making it difficult to isolate the effects of ablation from subsequent surgery or adjuvant treatments. Variability in treatment protocols and underreporting of patient-relevant outcomes further hinder clinical applicability.

limited comparative evidence

confirmation of tumour ablation challenging

effects of ablation difficult to isolate as most studies performed additional resection

Conclusion

Comparative evidence for thermal ablation interventions relative to surgery is limited to one RCT for RFA and two NRSIs, one for MWA and one for CYA. Low to very low certainty suggests that these treatments have comparable OS, DFS, and recurrence rates, along with mild to moderate AEs, though these outcomes may have been influenced by concurrent tumour resection. Comparative evidence was missing for HIFU and LA. To establish thermal ablation as a viable alternative to surgery, high-quality, long-term RCTs with standardised methodologies and non-inferiority designs are essential.

limited evidence with very low to low certainty on safety and efficacy

further high-quality research needed

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Zielpopulation: Frauen mit Brustkrebs (BK) im Frühstadium (TNM I-IIA)

Brustkrebs (BK) ist weltweit die häufigste Krebserkrankung bei Frauen. Mit 6.096 Neuerkrankungen im Jahr 2022 war BK die häufigste Krebsart bei Frauen in Österreich und machte 30 % aller Krebsfälle aus. BK im Frühstadium umfasst invasive maligne Tumore, die auf die Brust oder regionale Lymphknoten begrenzt sind, jedoch keine Fernmetastasen aufweisen. Dies entspricht den Stadien I bis IIA nach dem TNM-System.

Diagnose durch bildgebende Verfahren und Histopathologie

Früherkennung durch Screening

Die Diagnose basiert auf bildgebenden Verfahren wie Mammographie, Ultraschall und Magnetresonanztomographie (MRT) sowie auf histopathologischen und molekularen Untersuchungen zur Bestimmung des Hormonrezeptorstatus und genetischer Marker. In Österreich trägt das bevölkerungsbasierte Mammographie-Screening für Frauen im Alter von 45 bis 69 Jahren zur frühzeitigen Erkennung von BK bei und verbessert dadurch die Prognose. Zu den Risikofaktoren für BK zählen neben dem biologischen Geschlecht, das Alter, genetische Prädispositionen, hormonelle Einflüsse sowie Lebensstilfaktoren wie Übergewicht, körperliche Inaktivität, Rauchen, Alkoholkonsum und die Einnahme von Hormonersatztherapien.

kuratives Behandlungsziel

Standardtherapie: Resektion ergänzt mit Radio-, Chemo- oder endokriner Therapie

5 Jahre Überlebensrate: >90%

Das primäre Ziel der Behandlung von BK im Frühstadium ist kurativ. Die Standardtherapie umfasst die chirurgische Resektion, die in der Regel durch Radiotherapie ergänzt wird. Dabei wird die brusterhaltende Therapie bevorzugt. Ist diese nicht möglich, erfolgt eine Mastektomie, gegebenenfalls mit Rekonstruktion. Die Durchführung einer Sentinel-Lymphknotenbiopsie (SLNB) ermöglicht die Beurteilung der Lymphknotenbeteiligung und beeinflusst maßgeblich die weitere Therapieplanung. Je nach Tumorbiologie und -stadium können adjuvante Chemotherapie oder endokrine Therapie indiziert sein. Die fünfjährige Überlebensrate liegt in Hocheinkommensländern bei über 90 %, wobei die Nebenwirkungen der Behandlung, wie etwa Müdigkeit, Übelkeit und psychische Belastungen, signifikante Auswirkungen auf die Lebensqualität der betroffenen Patient:innen haben können.

Beschreibung der Technologie

Thermoablation (TA): minimal-invasives Verfahren, bei dem extreme Temperaturen zur Zelldestruktion genutzt werden

Die Thermoablation ist ein minimal-invasives Verfahren, bei dem eine in den Tumor eingeführte Sonde extreme Temperaturen erzeugt und Tumorzellen somit gezielt zerstört. Sie wird bereits zur Behandlung verschiedener benigner und maligner Tumoren eingesetzt, wobei das hepatozelluläre Karzinom zu den Hauptanwendungsgebieten zählt. Verschiedene Ablationstechniken stehen zur Verfügung:

- **Kryoablation (CYA):** Zellzerstörung durch extreme Kälte (≤ -40°C). Zwei aktive Gefrierzyklen mit einem Tauzyklus dazwischen führen zur Dehydrierung und Ruptur der Zellen.
  Kryoablation (CYA): Zellzerstörung durch Kälte (≤ -40°C)
- **Mikrowellenablation (MWA):** Nutzt elektromagnetische Wellen (900 MHz bis 2,45 GHz), die durch Reibung Wärme erzeugen und Gewebe auf über 150°C erhitzen. Diese Technik ermöglicht größere Ablationszonen in kürzerer Zeit.
  Mikrowellenablation (MWA): Zellzerstörung durch Reibung (≥150°C)

- **Radiofrequenzablation (RFA):** Verwendet Radiowellen (350-600 kHz), die über Widerstandserwärmung Gewebe auf Temperaturen von 60 bis 100°C erhitzen. Diese Methode ist in Geweben mit niedriger elektrischer Leitfähigkeit weniger effektiv.
- **Hochintensive fokussierte Ultraschallablation (HIFU):** Non-invasive Technologie, die durch Ultraschallwellen Gewebetemperaturen über 100°C erreicht. Die Effektivität hängt von der Ultraschall-Frequenz und Gewebedichte ab.
- **Laserablation (LA):** Zerstörung von Gewebe durch Wärmeenergie, die durch absorbiertes Licht (Wellenlängen zwischen 800 und 1.064 nm) erzeugt wird. Mehrere Fasern werden eingesetzt, um unregelmäßige Formen oder größere Volumina zu behandeln.

Radiofrequenzablation (RFA): Zellzerstörung durch Widerstandserwärmung (60-100°C)

Hochintensive fokussierte Ultraschallablation (HIFU): komplett noninvasiv (≥150°C)

Laserablation (LA): Zellzerstörung durch Lichtenergie (60-100°C)

Methoden

Ziel des vorliegenden Berichts war es, die Wirksamkeit und Sicherheit von Thermoablationsverfahren im Vergleich zur chirurgischen Resektion mit oder ohne zusätzliche Standardtherapien wie Radio-, Chemo- oder endokriner Therapie bei Patientinnen mit BK im Frühstadium zu bewerten.

Forschungsfrage

Dazu wurde eine systematische Suche nach Primärstudien in englischer oder deutscher Sprache in vier Datenbanken durchgeführt, wobei der Zeitraum auf 2014 bis 2024 begrenzt wurde. Die Studienauswahl und Datenextraktion erfolgten jeweils durch eine Autorin und wurden von einer zweiten verifiziert. Die Studienqualität wurde unabhängig von zwei Autorinnen bewertet – für randomisierte kontrollierte Studien (RCTs) mit RoB 2.0 und für nicht-randomisierte Interventionsstudien (NRSIs) mit

„ROBINS-I. Die Ergebnisse wurden mit dem GRADE-Framework (Grading of Recommendations Assessment, Development and Evaluation) dargestellt.

systematische Suche in 4 Datenbanken

Studienauswahl, Datenextraktion, Bewertung der Evidenz, GRADE

Klinische Wirksamkeit

Die folgenden Endpunkte wurden als entscheidend für die Formulierung einer Empfehlung eingestuft: Gesamtüberleben, krankheitsfreies Überleben, Tumorrezidiv und vollständige Tumorablation.

Wirksamkeitsendpunkte: Gesamtüberleben, krankheitsfreies Überleben, Tumorrezidiv, vollständige Tumorablation

Sicherheit

Schwere unerwünschte Ereignisse (SUE) und andere unerwünschte Ereignisse (UE) wurden als kritisch für die Entscheidungsfindung eingestuft.

Sicherheitsendpunkte: (schwerwiegende) unerwünschte Ereignisse (S)UE

Ergebnisse

Verfügbare Evidenz

Insgesamt wurden 19 Studien in 20 Publikationen zu den verschiedenen Technologien eingeschlossen. Dazu zählen eine nicht-randomisierte Interventionsstudie (n=20) sowie neun einarmige Studien zu CYA, eine nicht-randomisierte Interventionsstudie (n=132) und drei einarmige Beobachtungsstudien zu MWA, ein RCT (n=40) sowie eine einarmige Beobachtungsstudie zu RFA und jeweils zwei bzw. eine einarmige Beobachtungsstudie zu HIFU und LA.

3 Vergleichsstudien & 16 einarmige Studien identifiziert
CYA: 1 NRSI (n=20)
MWA: 1 NRSI (n=132)
RFA: 1 RCT (n=40)

Vertrauenswürdigkeit der Evidenz

Die 16 einarmigen Beobachtungsstudien wurden a priori mit hohem Verzerrungsrisiko bewertet. Die NRSI zu CYA berichtete vergleichende Daten nur zum Endpunkt UE, die mit kritischem Verzerrungsrisiko bewertet wurden. Die NRSI zu MWA wurde für die Endpunkte Gesamtüberleben, krankheitsfreies Überleben und Tumorrezidiv mit schwerwiegendem Verzerrungsrisiko bewertet. Der RCT zu RFA wurde hinsichtlich der Endpunkte Mortalität, vollständige Tumorablation, Rezidiv und Sicherheit als Studie mit geringem Verzerrungsrisiko eingestuft. Insgesamt wurde die Vertrauenswürdigkeit der Evidenz nach GRADE als niedrig bis sehr niedrig bewertet.

RCT (RFA): niedriges ROB

NRSI (CYA): kritisches ROB

NRSI (MWA): schwerwiegendes ROB

GRADE: niedrige - sehr niedrige Vertrauenswürdigkeit

Klinische Wirksamkeit und Sicherheit

Kryoablation

Komparative Evidenz zu CYA beschränkte sich auf eine kleine, nicht-randomisierte Interventionsstudie mit 20 Patientinnen, die ausschließlich UE und SUE vergleichend untersuchte. In der Interventionsgruppe traten zwei geringfügige UEs auf. Vollständige Tumorablation wurde bei 90 % der Patientinnen erreicht, die CYA erhielten. Gesamtüberleben, krankheitsfreies Überleben und Rezidivrate wurden nicht berichtet.

CYA: 1 NRSI (n=20)

AE: 2 vs 0
vollständige Tumorablation 90%

In acht einarmigen Beobachtungsstudien zeigte sich, dass CYA keinen negativen Einfluss auf das Gesamtüberleben (n=400) oder die Rezidivrate (n=279) hatte. In fünf Studien (n=192) wurde eine vollständige Tumorablation berichtet. Die Häufigkeit von Nebenwirkungen variierte, wobei milde bis moderate Schmerzen und Hämatome am häufigsten berichtet wurden. In sechs Studien (n=129) wurden keine SUE in einem Nachbeobachtungszeitraum von zwei bis 60 Monaten erfasst. Krankheitsfreies Überleben wurde in keiner Studie beschrieben.

Mikrowellenablation

Eine propensity-score-abgeglichene, nicht-randomisierte Interventionsstudie (NRSI) mit 33 Patientinnen in der Interventionsgruppe und 99 in der Kontrollgruppe zeigte bei einer medianen Nachbeobachtungszeit von 31 Monaten keine signifikanten Unterschiede zwischen MWA und chirurgischer Resektion hinsichtlich der Endpunkte Gesamtüberleben und krankheitsfreies Überleben. Auch in der Rezidivrate wurden keine nennenswerten Unterschiede festgestellt. Nach einer zusätzlichen Ablationsbehandlung bei einer Patientin erreichten alle Patientinnen der MWA-Gruppe eine vollständige Tumorablation. UE wurden nur für die MWA-Gruppe dokumentiert, und es wurden keine (S)UE in der Nachbeobachtungszeit berichtet.

MWA: 1 NRSI (n=132)

kein signifikanter Unterschied in OS/DFS nach 31 Monaten Nachbeobachtungszeit; vollständige Tumorablation: 100%; kein Unterschied bei Tumorrezidivrate
keine (S)UE (MWA)

Drei einarmige Beobachtungsstudien (n=101) zeigten, dass MWA bei 90 % der Patientinnen zu einer vollständigen Tumorablation führte und das Gesamtüberleben bis zu einer Nachbeobachtungszeit von 36 nicht negativ beeinflusste. Eine Studie (n=35) beschrieb die Rezidivrate und dokumentierte dabei keinen Rezidivfall. Schmerzen und Schwellungen wurden in allen Studien als UE beschrieben, jedoch wurden keine SUE berichtet.

Radiofrequenzablation

Ein RCT mit insgesamt 40 Teilnehmerinnen, der RFA mit chirurgischer Resektion verglich, zeigte vergleichbare Gesamtüberlebensraten, eine vollständige Ablation bei allen Teilnehmerinnen und keine Rezidive während einer medianen Nachbeobachtungszeit von 25 Monaten. Patientinnenrekrutierung wurde nach einer Interim-Analyse gestoppt, nachdem eine höhere Anzahl an

RFA: 1 RCT (n=40)
vorzeitiger Abbruch der Studie wegen höherer UE in Interventionsgruppe

unerwünschten Ereignissen in der Interventionsgruppe beobachtet wurde (8/20 vs. 1/20, p=0.1). Es wurden allerdings keine SUE berichtet.

Zusätzlich zeigte eine einarmige Beobachtungsstudie mit 18 Patientinnen eine Gesamtüberlebensrate von 100 % innerhalb von 14 Tagen Nachbeobachtungzeit, sowie eine vollständige Tumorablation bei allen Patientinnen. Schmerzempfindungen während der Verabreichung des lokalen Anästhetikums und des Eingriffs selbst waren vergleichbar, jedoch wurde nach dem Eingriff eine erhöhte Schmerzintensität festgestellt. Ergebnisse zu den Endpunkten krankheitsfreies Überleben, Tumorrezidiven oder SUE wurden nicht berichtet.

Hochfrequenz-Ultraschall

HIFU: keine komparative Evidenz

Für HIFU wurden zwei einarmige Beobachtungsstudien identifiziert (n=35). Beide Studien berichteten eine Gesamtüberlebensrate von 100 %, jedoch hatte eine Studie eine Nachbeobachtungszeit von nur 10 Tagen. Eine Studie (n=25) berichtete vollständige Tumorablation bei allen Patientinnen und keine Tumorrezidive nach bis zu 12 Monaten Nachbeobachtungszeit. Die häufigsten UE waren Schmerzen und Schwellungen. Krankheitsfreies Überleben und SUE wurden nicht berichtet.

Laserablation

LA: keine komparative Evidenz

Auch für Laserablation lagen keine vergleichenden Daten vor. Eine einarmige Studie (n=61) berichtete vollständige Tumorablation in 84 % der Patientinnen und eine Rezidivrate von 3 % nach vier Jahren. Acht leichte bis mäßige UE (z.B. Schmerzen) wurden beobachtet. Die Endpunkte Gesamtüberleben, krankheitsfreies Überleben und SUE wurden nicht berichtet.

Laufende Studien

laufende Studien:
1 RCT (CYA)
2 NRSIs (CYA, MWA)

Es wurde ein laufender RCT identifiziert, der Kryoablation mit Lumpektomie bei Patientinnen mit BK im T1-Stadium vergleicht. Die primären Endpunkte dieser Studie sind behandlungsbedingte Komplikationen und ipsilaterale Rezidive nach fünf Jahren. Zusätzlich laufen derzeit zwei nicht-randomisierte Interventionsstudien, die Kryoablation und Mikrowellenablation mit BCS vergleichen sowie mehrere einarmige Beobachtungsstudien.

Diskussion

TA als minimal invasive Alternative zu Chirurgie

Die Standardbehandlung für BK im Frühstadium besteht aus einer chirurgischen Resektion, oft in Kombination mit Radiotherapie und adjuvanten Therapien. Das chirurgische Management hat sich von der radikalen Mastektomie hin zu brusterhaltenden Strategien entwickelt, was einen Wandel zu weniger invasiven Verfahren widerspiegelt. Thermoablation stellt einen möglichen nächsten Schritt in dieser Entwicklung dar und verspricht Vorteile wie einen reduzierten Anästhesiebedarf, schnellere Rekuperation und eine Alternative für Patientinnen, die für eine chirurgische Behandlung ungeeignet sind oder den Eingriff ablehnen.

Mangel an hochwertiger Evidenz

Der Vergleich zwischen Thermoablation und chirurgischer Resektion bei Frauen mit BK im Frühstadium weist einen Mangel an hochwertiger, vertrauenswürdiger Evidenz auf. Es konnten nur wenige Vergleichsstudien identifiziert werden. Zudem erschweren die geringe Patientinnenanzahl, methodische Heterogenität, Variabilität in Behandlungsprotokollen sowie die unzureichende Berichterstattung relevanter Endpunkte die Interpretation der Ergebnisse und deren klinische Anwendbarkeit.

Bedenken zur Validierung von vollständiger Tumorablation

Bewertung onkologischer Effizienz durch zusätzliche Resektion & adjuvante Therapien erschwert

Ein Problem der Thermoablation besteht in der präzisen Definition und Validierung einer vollständigen Tumorablation. Im Gegensatz zur chirurgischen Resektion ist eine histopathologische Untersuchung der Tumorränder aufgrund fehlender Gewebeproben nicht möglich. Der Therapieerfolg kann daher ausschließlich durch bildgebende Verfahren überprüft werden, deren Sensitivität und Spezifizität möglicherweise nicht ausreichen. Zudem erschwert die Diagnostik von Tumorresten oder Rezidiven im nekrotischen Gewebe die Beurteilung des Behandlungserfolgs. Darüber hinaus könnten die strukturellen Veränderungen im ablatierten Gewebe die gezielte Nachbehandlung durch eine erneute Ablation limitieren. Der Großteil der inkludierten Studien führte im Anschluss an die Ablation eine Tumorresektion durch, wodurch es schwierig wird, die onkologische Wirksamkeit der Ablation von den Effekten der nachfolgenden Resektion oder adjuvanten Behandlungen zu isolieren.

Schlussfolgerung

minimale Evidenz mit niedriger bis sehr niedriger Vertrauenswürdigkeit

Die komparative Evidenz aus RCTs und nicht-randomisierten Interventionsstudien beschränkt sich auf Studien zu CYA, RFA und MWA. Ergebnisse mit niedriger, bis sehr niedriger Vertrauenswürdigkeit der Evidenz, deuten darauf hin, dass diese Behandlungen vergleichbare Gesamtüberlebensraten, krankheitsfreie Überlebenszeiten und Tumorrezidivraten aufweisen und allgemein sicher sind, mit nur milden bis moderaten unerwünschten Ereignissen. Es besteht jedoch die Gefahr, dass diese Ergebnisse durch eine Tumorresektion und adjuvante Therapien beeinflusst wurden. Um die Thermoablation als tragfähige Alternative zur Chirurgie zu etablieren, sind qualitativ hochwertige, langfristige RCTs mit standardisierten Methoden und Non-Inferiority-Studien unerlässlich.

Re-Evaluierung erst nach 2034 empfohlen

Eine Re-Evaluierung wird vor 2034 nicht empfohlen, da aktuell nur eine Studie zu CYA identifiziert wurde und keine laufenden klinischen Vergleichsstudien zu anderen Ablationsverfahren vorliegen.

1 Background

1.1 Overview of the disease, health condition and target population

Overview of the disease or health condition

HTA CORE MODEL DOMAIN: CUR[1]

Zielpopulation: Frauen mit Brustkrebs (BK) im Frühstadium

The target population of this review are women over the age of 18 with early-stage breast cancer (BC).

Definition BK: maligne, invasive Neubildung der Brust bzw. der Milchdrüsen

BC is defined as malign, invasive neoplasms of the breast or, more specifically, the mammary glands, including ductal carcinoma in situ (DCIS) that have not yet infiltrated the surrounding tissue [1]. It results from masses formed by uncontrollable growing epithelium cells that form in glandular tissue, ducts or lobules [2]. Ductal carcinoma is the most common form of BC (around 70 to 80% of all BC), followed by carcinoma beginning in the lobes or lobules (around 10 to 15% of cases). Further, a less common presentation is inflammatory BC, which is characterised by breast warmth, redness and swelling [1, 3].

TNM-Kriterien: BK-Klassifikation nach Größe des Primärtumors und Ausmaß der Metastasierung

There are several classification systems for BC, which have evolved through continuous advances in knowledge of biology and management of BC and are used to determine management and prognosis [4]. The anatomical staging of BC is accomplished with the tumour node metastasis (TNM) staging system by the American Joint Committee on Cancer (AJCC) and informs treatment decisions. According to the system, BC is classified into stages 0 to IV, depending on the tumour size and area (T), nodular involvement (N) and the presence of metastasis (M). TNM classification of *early-stage BC* encompasses stages I to IIA and can be viewed in Table 1-1. Further, molecular subtypes based on different expressions of the oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), as well as BRCA and PIK3CA gene mutations and PD-L1 expression, inform adjuvant medical treatment [3, 5].

nationale Screeningprogramme zur Früherkennung von BK

BC outcome optimisation relies in many countries on early identification during the asymptomatic stage through population-based screening programmes. Currently, mammography screening is the only screening method proven to reduce BC mortality. It is recommended every two years for average-risk, asymptomatic women between the ages of 50 and 69, according to

[1] This section addresses the following assessment elements:
A0002 – What is the disease or health condition in the scope of this assessment?
A0003 – What are the known risk factors for BC?
A0004 – What is the natural course of BC?
A0005 – What is the burden of disease for patients with BC?
A0006 – What are the consequences of BC for the society?
A0007 – What is the target population in this assessment?
A0024 – How is BC currently diagnosed according to published guidelines and in practice?
A0023 – How many people belong to the target population?

the European Commission Initiative on Breast Cancer (ECIBC) [6]. In Austria, the national BC screening programme invites women aged 45 to 69, while women aged 40 to 44 and over 70 do not receive a formal invitation but can still decide to opt in [7].

Konfirmation der Diagnose anhand Mammographie/Ultraschall

Is BC suspected after an abnormal screening, the diagnosis is confirmed through a bilateral mammogram and ultrasound (US) of both breasts and regional lymph nodes. Magnetic resonance imaging (MRI) may also be used in specific cases. A core biopsy is conducted to determine the presence of cancerous cells and can further be used for genetic analysis. A minimum blood work-up is conducted before surgery and systemic (neo)adjuvant therapy. Additionally, for patients with clinically positive axillary nodes, large tumours, aggressive tumour biology or signs of metastasis, further imaging – such as computed tomography (CT) scans of the chest, abdominal imaging via US, CT or MRI and bone scans - may be performed [5, 6]. Additionally, breast parenchyma is highly heterogeneous and undergoes continuous changes over time, which must be considered when selecting the appropriate diagnostic modality [8].

Table 1-1: TNM classification of early-stage breast cancer

Stage	Primary tumour	Node	Metastasis
I	T1mic (tumour size ≤1 mm)	N0 (no cancer in nearby nodes or only small clusters <2 mm)	M0 (no metastasis)
	T1a (>1-5 mm)		
	T1b (6-10 mm)		
	T1c (11-20 mm)		
IIA	T0, T1mic, T1	N1 (involvement of 1-3 lymph nodes in the armpit and/or in the sentinel lymph nodes)	
	T2 (21- 50 mm)	N0	

Prevalence of breast cancer in the population

BK-Inzidenz 2022: 120 per 100,000 Frauen & 1.5 per 100,000 Männer

BC is the second most diagnosed cancer globally and the most common cancer in women, with approximately 2.3 million new cases in 2022 [2, 9]. BC incidence rates have slightly declined in Austria since 1997, accompanied by improved BC-specific survival rates. However, incidence has risen among women under 45 [10]. In 2022, the annual incidence of BK in Austria was about 120 cases per 100,000 women and 1.5 per 100,000 men, with 6,096 new cases – accounting for 30% of all cancers in women [11]. The median age at diagnosis in Austria is 64, with nearly 80% of cases detected after age 50. In comparison, the median age at death is 77 [10]. The mortality rate is 29.5 per 100,000 women and 0.4 per 100,000 men. Between 2020 and 2022, nearly half of all BC cases were diagnosed at an early, localised stage, while 24% were identified at a regional state (with lymph node involvement) [11]. BC mortality declined between 2011 and 2019 [12]. With current treatment options in Austria, the one-year survival rate was 97% and the five-year survival rate was 87% in 2022 [11].

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

Tumour stage and subtype are key factors in BC prognosis [6, 11]. In high-income countries, prognosis is generally good, with at least 90% of five-year survival after diagnosis. However, BC patients often experience reduced quality of life due to treatment side effects, and effective treatments for metastatic disease remain limited [2]. If left untreated, BC progresses from local abnormal cell growth to invasive disease, spreading into the surrounding breast tissue and from there to regional lymph nodes, which in turn increases the risk of metastasis and, therefore, mortality [13]. Prognosis, therefore, depends on the completeness of surgical tumour removal [1].

5-Jahres-Überlebensrate in Ländern mit hohem Einkommen ≥90 %

The lifetime risk of developing BC is 0.1% (1 in 790) for men and 12.8% (1 in 8) for women. Beyond gender, advanced age is the most important population-based risk factor for BC [14]. In men, genetic factors and hormonal changes are the primary contributors to disease development [1]. Additional risk factors concerning only women include dense breast or mammary gland tissue, early age at menarche, late onset of menopause, fewer or no births, and later age at first childbirth [1, 9]. Further, around a quarter of women with BC have a genetic predisposition involving mutations in the genes BRCA1-, BRCA2-, PALB2 or RAD51C (encompassing a high risk) or in the genes STK11, ATM, PTEN, CHEK-2 (encompassing an intermediate risk) [1, 5]. A family history of BC also increases risk. Modifiable risk factors include overweight, physical inactivity, smoking, alcohol consumption and hormone replacement therapy, including ER/PR combinations [1, 15].

Risikofaktoren u.a. weibliches Geschlecht, Alter, dichtes Brustgewebe, frühe Menarche, späte Menopause, geringere Geburtenzahl, höheres Alter bei der ersten Geburt; modifizierbare Risikofaktoren: Mehrgewicht, Alkohol-, Tabakkonsum, Bewegung

Primary prevention focuses on reducing overweight and alcohol intake while promoting physical activity. Protective factors related to pregnancy include the number of full-term pregnancies, first delivery before age 30, and longer breastfeeding duration [9, 15]. Since few risk factors are modifiable, efforts primarily emphasize early detection through screening programmes (secondary prevention) and timely, comprehensive disease management to reduce late-stage diagnosis and lower mortality rates [9, 14].

Prävention v.a. durch Früherkennung mittels Screeningprogrammen

1.2 Current clinical practice

Current clinical management of the disease or health condition

HTA CORE MODEL DOMAIN: CUR[2]

A multidisciplinary strategy is required for the optimal management of BC, provided by a multidisciplinary team in specialised breast units or centres [3, 15]. Treatment recommendation depends on tumour stage, grade and subtype, prognosis and predictive factors and may include breast-conserving (BCS) or ablative surgery, radiation therapy, chemotherapy, endocrine therapy and antibody therapy [1]. Further, treatment decisions depend on patient preferences and should always be made as part of a shared decision-making process [6].

multidisziplinärer Ansatz bei der Behandlung von BK erforderlich

[2] This section addresses the following assessment elements:

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

For early-stage BC, the primary goal is curative treatment [5]. While neoadjuvant and adjuvant treatments vary by BC subtype and stage, surgery is indicated for around 96% of non-stage IV patients unless contraindicated due to inoperability or advanced age [16]. The preferred approach for most early-stage cases is BCS, followed by adjuvant whole-breast radiotherapy. When BCS is not feasible, nipple- and skin-sparing mastectomy is generally considered oncologically safe, with immediate or delayed breast reconstruction offered to most patients [6]. For patients ineligible for surgery due to multimorbidity, endocrine or radiation therapy may be considered for local tumour control while preserving quality of life [1].

Operation für ca. 96% der Fälle indiziert:

Standardvorgehen: brusterhaltende Therapie (BET), o. Mastektomie (MST)

Sentinel lymph node biopsy (SLNB) is the standard method for evaluating axillar lymph node involvement. No further management of lymph nodes is indicated if sentinel nodes are negative or contain only micro metastases. If macro metastases are present in one to three lymph nodes, three options exist [3, 5]:

Evaluation der Lymphknoten anhand der Sentinel-Lymph-Node Technik (SLNE)

je nach Status der Lymphknoten 3 Optionen

- No axillary dissection is needed if there are less than three macro metastases, the tumour stage is T1 or T2, and adjuvant irradiation and drug treatment are planned.
- Axillary dissection.
- Radiation of the axillary region.

Adjuvant endocrine therapy is indicated for HR+ patients, and treatment with trastuzumab is recommended for patients with HER+ BC. Medical therapy generally decreases recurrence risk and mortality, and chemotherapy is indicated based on the biological characteristics of the tumour and tumour stage.

(neo)adjuvante Therapien, je nach molekularem Subtyp indiziert

A general treatment overview for early-stage BC, as recommended by the European Society for Medical Oncology (ESMO), is shown in Figure 1-1 [6].

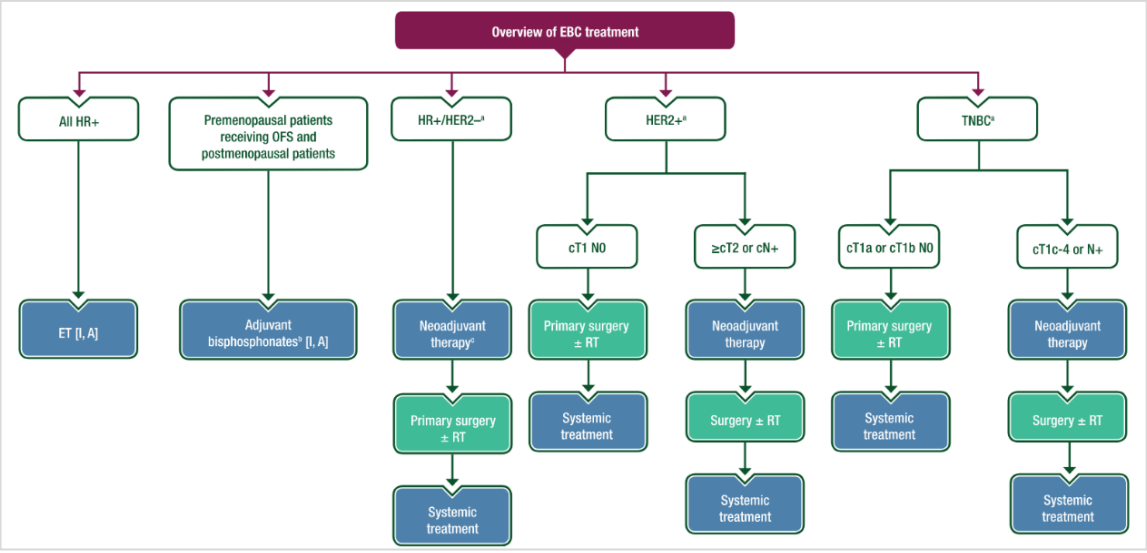

Figure 1-1: Early breast cancer treatment overview (Source: [6])

Demand for physical, social and psychological rehabilitation among BC patients is high. Patients should be informed of rehabilitation options prior to treatment completion, ensuring their preferences are considered. Further anamnesis, physical examinations and advice after treatment are recommended

physische und psychische Beratung bis zu 10 Jahre nach Behandlung

every three months for three years, followed by every six months until the fifth year and every year until the tenth year. Imaging is used every year. The goal of follow-up is early detection of local recurrence, prompt curative intervention, monitoring of treatment side effects, and ongoing psychosocial support [5].

1.3 Features of the intervention and comparator

HTA CORE MODEL DOMAIN: TEC[3]

Features of the interventions

Thermoablation (TA): minimal-invasiver Eingriff, Zerstörung von Tumorgewebe durch sehr hohe/niedrige Temperaturen

Thermal ablation is a percutaneous minimally invasive technique that utilises extreme hyperthermia or hypothermia to induce the targeted destruction of benign or malignant tissue. It is already used for treating various benign and malignant tumours, with hepatocellular carcinoma being one of its hallmark applications [17]. Over the past decade, thermal ablation has gained traction as an alternative to surgical resection in the primary treatment of early-stage BC [18]. The objective of thermal ablation aligns with that of surgical resection: complete eradication of the tumour while preserving a margin of surrounding healthy tissue to minimise recurrence. Therefore, the clinical success of thermal ablation depends on the ability to establish an adequate safety margin around the tumour. Following treatment, the ablated region undergoes coagulative necrosis and is gradually resorbed by the body over several months [19]. A key challenge of thermal ablation is the evaluation of complete ablation when no subsequent resection is performed [20]. Although initial imaging can serve as a good indication of technical success, current imaging techniques' resolution and accuracy preclude identifying residual microscopic foci of malignancy, particularly in the periphery of a treated lesion [21].

verschiedene TA-techniken verfügbar:

Several thermal ablation techniques have been investigated, including cryoablation (CYA), radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound ablation (HIFU) and laser ablation (LA). Following, the different techniques are described in more detail and an overview of identified thermal ablation technologies is provided in Table 1-2.

Cryoablation

Kryoablation (CYA): Zellzerstörung durch Kälte <-40°C

CYA uses cold temperatures (≤ -40°C) either through liquid nitrogen or argon gas to achieve tissue necrosis. The CYA procedure involves two active freezing cycles with one passive thawing cycle in between. The duration of freezing cycles depends on tumour characteristics and the desired ablation margin. During CYA, a needle is inserted percutaneously into the centre of the tumour

[3] This section addresses the following assessment elements:

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

B0001 – What is breast conserving surgery?

B0001 – What is thermal ablation?

B0002 – What is the claimed benefit of the technology in relation to the comparators?

B0003 – What is the phase of development and implementation of thermal ablation?

A0020 – For which indications has thermal ablation received marketing authorization or CE marking?

through its longest axis under US guidance. The cryoprobe is then activated, and an elliptical ice ball expands. During the first freeze, cells are dehydrated due to increased intracellular osmolality. The osmatic gradient is reversed during the thaw cycle, leading to further damage through cell swelling and rupture. During the second freeze, the necrosis area is expanded, as the already affected tissue is freezing faster due to improved conduction of cold temperature [16, 17, 22].

Microwave ablation

MWA involves percutaneously inserting an antenna into the target zone under imaging guidance. The antenna generates an oscillating microwave current (typically 900 MHz to 2.45 GHz), which induces frictional heat through the agitation of water molecules (dielectric hysteresis), directly heating tissue to temperatures exceeding 150°C. Since MWA relies primarily on direct heating rather than thermal conduction, it is capable of larger ablation zones in less time compared to other techniques [23].

Mikrowellenablation (MWA): Anwendung elektromagnetischer Wellen zwischen (zw.) 900 MHz & 2,45 GHz

Radiofrequency ablation

RFA uses high-frequency oscillating current in the range of 350 to 500 kHz. The electrode, which is inserted percutaneously through a needle or probe, does not generate heat itself; instead, RFA relies on resistive heating via an electrically conductive path. This method is less effective in tissues with low electrical conductivity. In monopolar RFA, one or more grounding pads complete the circuit, while in bi- and multipolar RFA, current flows between two or more electrodes within the tissue. Temperatures between 60 and 100°C induce coagulative necrosis in the central zone. At the same time, heat conduction to surrounding tissues causes sublethal temperatures in peripheral areas, leading to cell death by apoptosis and expanding the ablation zone. However, temperatures exceeding 100°C may cause boiling and charring, resulting in increased impedance and diminished efficacy of RFA [24].

Radiofrequenzablation (RFA): Einsatz von Radiowellen zw. 350 & 600 kHz

High-intensity focused ultrasound ablation

HIFU is a non-invasive, hyperthermic ablative technology that induces coagulative necrosis through frequency pressure waves generated by an US transducer (average spatial intensity, 100–10,000 W/cm^2) [22]. As the US waves propagate through tissues with varying densities, a portion of the energy is reflected at each tissue boundary. Minimising these reflections is essential to optimising frictional heating efficiency. The attenuation coefficient, which describes the rate at which ultrasonic energy is absorbed and scattered by tissue, is directly influenced by the frequency of the US waves. Higher frequencies are associated with increased attenuation, resulting in greater energy absorption and thermal deposition; however, this also limits tissue penetration depth. Thus, the optimal treatment frequency depends on the application, and a compromise is required between the desired penetration depth and hyperthermic effect [25].

hochintensive fokussierte Ultraschallablation (HIFU): Tumornekrose durch Ultraschall im Bereich von 100 & 10.000 W/cm^3

Laser ablation

LA destroys targeted tissues by utilising heat energy converted from absorbed light [26]. Under imaging guidance, bare or diffuse tip laser fibres, positioned percutaneously within the tumour via needles or probes, deliver high-density light (wavelengths between 800 to 1,064 nm) into the tissue, resulting in direct and indirect thermal damage. The size and rate of ablation are contingent

Laserablation (LA): Verwendung von Wellenlängen zw. 800 & 1.064 nm

on the wavelength, power, applicator cooling and local perfusion. Lesions are generally ellipsoidal and centric to the fibre tip, so multiple fibres and placements may be needed to conform to an irregular shape or larger volume [27].

Table 1-2: Overview of currently available thermal ablation technologies

Technology	Proprietary name[a]	Manufacturer/ Country	Class /GMDN code	CE mark /indication[b]
CYA	Visica/Visica2 ®	Sanarus/ USA	Class II Code 45738	No
	ProSense Cryosurgical System	IceCure Medical Ltd./ Israel	Class II Code 45738	Yes, BC [28]
	Icefx™	Boston Scientific/ USA	Class II Code 45738	No
MWA	NR	Nanjing Yigao Microwave Electric Institute/ China	NR	NR
	NR	Vision China/ China	NR	NR
RFA	Covidien Cool-tip	Covidien (now Medtronic)/ Ireland	Class II Code 35254	No
	Prototype	Neodynamics/ Sweden	NR	NR
HIFU	Sonalleve-Prototype	Phillips/ Finland	NR	NR
	Therapeutic US	Haifu Medical Technology and Cheng-Cheng Weiye Science and Technology/ China	NR	NR
LA	Novilase Laser Theraphy	Novian Health/ USA	Class II Code 60341	Yes, BC [29]

Abbreviations: BC – breast cancer, CYA – cryoablation, GMDN – Global Medical Device Nomenclature, HIFU – high-intensity focused ultrasound ablation, MWA – microwave ablation, NR – not reported, RFA – radiofrequency ablation, US – ultrasound, USA – United States of America

Comments:

[a] Selection of devices is not exhaustive and limited to products used in included studies.

[b] Some devices are approved for other indications, such as the treatment of soft tissue liver tumours, but only approvals related to BC are listed.

Vorteile TA: geringerer Bedarf an Vollnarkose, geringere Rate an Komplikationen, schnellere Genesung, besseres kosmetisches Ergebnis

The general proposed advantages of percutaneous minimally invasive techniques are a reduced need for general anaesthesia, lower infectious and haemorrhagic complications rates, shorter recovery time (allowing for earlier initiation of adjuvant therapies) and better cosmetic results. The potential for synergizing thermal ablation with immunotherapy has also been a topic of interest, given the potentially favourable microenvironment induced by thermal cell destruction [18]. Currently, none of these techniques has received regulatory approval for the use in malignant breast tumours by the Food and Drug Administration (FDA), and the American Society of Breast Surgeons (ASBrS) have recommended against its use in malignant tumours in their 2018

consensus statement [30]. In addition, the BC treatment guidelines established by the Association of the Scientific Medical Societies in Germany (*AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*) and ESMO do not currently include percutaneous minimally invasive techniques in their treatment modalities [6, 14].

Despite the absence of guidelines or consensus papers on this topic, thermal ablation interventions for BC are generally proposed for tumours smaller than 5 cm, with most applications focusing on tumours no larger than 2 cm along their largest diameter. Given the limited treatment radius of thermal ablation techniques, where complete cell death can be ensured, these interventions have primarily been used for early-stage, small-sized BC tumours [19, 22, 31].

Fokus der TA auf Tumore ≤2 cm durch begrenzten Ablationsradius

Features of the comparator

Surgical excision for early-stage BC typically involves removal of the tumour with BCS or mastectomy in cases where BCS is not possible. While mastectomy involves removing the whole breast, BCS only removes the tumour and tries to keep as much of the breast as possible. As there is a significant correlation between resection margin status and local recurrence rate, it is important to ensure negative margins during surgery. Depending on the source, negative margins are defined as no ink on tumour, or a 2 mm margin, although re-excision decisions in case these margins are not reached, require further considerations [32]. There are different ways to determine the absence of tumour cells in a resected specimens and recent innovations allow for intraoperative assessment [33]. Adjuvant radiation and systemic therapies can influence local recurrence, but only if negative margin status has been achieved. Margin status is assessed through both macroscopic and microscopic assessment [14].

Komparator: BET bzw. MST

Administration, investments, personnel and tools required to use the technology and the comparator(s)[4]

Breast surgery is an intensive procedure that typically requires general anaesthesia, necessitating the presence of an experienced surgical team, as well as specialised surgical tools and consumables. Where available, a multidisciplinary team should provide treatment in specialised breast units, ensuring the ability to refer patients to other specialities and coordinate adjuvant therapies and follow-up care [6]. Tumour resection is performed by surgeons, typically specialised in breast surgery. ESMO recommends that breast surgeons either collaborate with plastic surgeons or be trained in oncoplastic approaches to ensure optimal oncological and cosmetic outcomes. Most BC surgeries are completed in an inpatient setting within a hospital. However, BCS

Operation in spezialisierten Zentren durch Chirurg:innen;

meist stationär

[4] This section addresses the following assessment elements:

B0008 – What kind of special premises are needed to use thermal ablation and surgical excision of breast tumours?

B0009 – What supplies are needed to use surgical excision and thermal ablation of breast tumours?

B0004 – Who administers thermal ablation and surgical excision of breast tumours and in what context and level of care are they provided?

A0021 – What is the reimbursement status of thermal ablation interventions?

A0011 – How much are the technologies utilised?

and SLNB can be performed in outpatient clinics without the need for an overnight stay [3, 6].

TA ambulant durch interventionelle Radiolog:innen o. Chirurg:innen möglich

Thermal ablation interventions are minimally invasive procedures that can be performed in the outpatient setting. They are typically performed by interventional radiologists but can also be performed by breast surgeons certified in using US [34]. Thermal ablation techniques are generally performed under local anaesthesia and mild sedation if required. Their success relies on the availability of US or MRI to accurately guide the application of thermal energy during the procedure and to assess the ablation site during follow-up, ensuring complete tumour ablation. It is of note that conventional breast imaging techniques have not been validated to evaluate the extend of disease or margin analysis. Biopsies of ablated lesions can provide details of tumour viability without excision, but they are limited by the small specimen size. Previous studies have verified the efficacy of MRI and contrast enhanced ultrasound (CEUS) in detecting residual breast lesions after BC treatment [35]. For healthcare facilities considering the adoption of thermal ablation, a one-time investment is required for the purchase of the necessary intervention system. This includes the ablation device and any associated equipment. Ongoing costs are primarily related to consumables, such as ablation probes and materials used for imaging guidance.

Regulatory & reimbursement status

TA derzeit nicht erstattet

The expected annual utilisation of all thermal ablation technologies in Austria is unknown. The submitting hospital estimates approximately 200 CYA interventions per year nationwide, with around 20 interventions annually at their facility. Currently, none of the listed thermal ablation technologies are included in relation to the treatment of BC in the Austrian hospital benefit catalogue (*LKF, leistungsorientierte Krankenanstenfinanzierung*). Thus, they are not fully reimbursable services in the Austrian health care system.

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Is thermal ablation (via RFA, HIFU, MWA, CYA or LA) alone or in conjunction with standard care as effective and as safe or safer than standard care concerning the outcomes mortality, complete ablation rate, residual tumour, recurrence, as well as (serious) adverse events in patients with early-stage BC?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

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

Table 2-1: Inclusion criteria

Population	Adult patients ≥18 years old with early-stage breast cancer **ICD-11 codes:** ■ 2C60-2C6Z - Malignant neoplasm of breast ■ 2E65 - Carcinoma in situ of breast MeSh and Emtree Terms: C04.588.180; C17.800.090.500 **Excluded:** ■ Thermal ablation of benign tumours, such as fibroadenoma ■ Thermal ablation for metastatic tumours or recurrent disease **Rationale:** Informed by the information provided by the submitting hospital and scoping of the literature.
Intervention	**Thermal ablation using any of the following interventions:** ■ Radiofrequency ablation (RFA) ■ High-intensity focused ultrasound (HIFU) ablation ■ Microwave ablation (MWA) ■ Cryoablation (CYA) ■ Laser ablation (LA) ■ **With** immediate/delayed resection OR ■ **Without** immediate/delayed resection AND, if applicable With adjuvant therapy (e.g. +/- radiotherapy, +/- chemotherapy, +/- endocrine therapy, +/- immunotherapy) **Product names:** Various thermal ablation devices, including, but not limited to: ■ Prosense cryosurgical system ■ Cryocare system ■ PulsaBlade ■ Solero MWA ■ AMICA ■ 3 cm Cool-Tip radiofrequency needle electrode MeSH Terms**:** E04.014.180; E02.594; E04.014.520; E02.565.280.945.399; E04.014.380; E02.808.750; E04.014.760

	Excluded: ■ Thermal ablation after standard therapy, e.g. pain management. **Rationale:** Informed by information provided by the submitting hospital and a scoping of the literature.
Control	Conventional management: ■ Surgery alone (e.g., mastectomy, lumpectomy, surgical resection) ■ Surgery with adjuvant therapy (e.g., +/- radiotherapy, +/- chemotherapy, +/- endocrine therapy, +/- immunotherapy)
Outcomes	
Efficacy	■ Mortality (e.g., overall survival, progression-free survival, 5-year survival (rate), 3-year event-free survival) ■ Complete ablation/necrosis rate ■ Recurrence/Recurrence rate (local and distant) ■ Cosmetic results (e.g. with Harvard scale of breast cosmesis, scarring) ■ Quality of life **Rationale:** Informed by a scoping search of the literature.
Safety	■ Adverse events (such as skin burns, local pain, nipple retraction, technical difficulties…) ■ Serious adverse events
Study design	Studies published since 2014 (the last 10 years), that are: ■ Randomised controlled trials (RCT), ■ non-randomised studies of interventions (NRSI), or ■ prospective single-arm case series with at least 10 patients **Excluded:** Non-peer reviewed studies, narrative reviews, letters to the editor and author responses, case reports, conference abstracts.

The PICO was uploaded on OSF before screening:
https://osf.io/jptge/?view_only=4f7374b0d8e541f69caa02294c5ac9aa

Präregistrierung der PIKO auf Open Science Framework

3 Methods

3.1 Research questions

Forschungsfragen nach EUnetHTA

Assessment elements from the European Network for Health Technology Assessment (EUnetHTA) Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [36].

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

systematische Literatursuche in 4 Datenbanken

A preliminary search for SRs published since 2023 was conducted in Embase, resulting in 37 potentially relevant hits. After screening, no SR, which could have been used as the basis for an update, was identified.

A systematic literature search for primary research was conducted on the 15th of December 2024 in the following databases:

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

deutsche und englische Literatur

The systematic search was limited to the years 2014 to 2024 and in Medline and Embase to articles published in English or German. After de-duplication, 1,656 citations remained. The specific search strategy employed can be found in the Appendix.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on 09.01.2025, resulting in 149 potentially relevant hits.

insgesamt 1.656 Publikationen identifiziert

No additional sources were found by hand-search.

3.2.2 Flow chart of study selection

Literaturauswahl

Overall, 1,656 hits were identified. All references were screened by at least two independent researchers, and in case of disagreement, a third researcher was involved in solving the differences. The selection process is displayed in Figure 3-1.

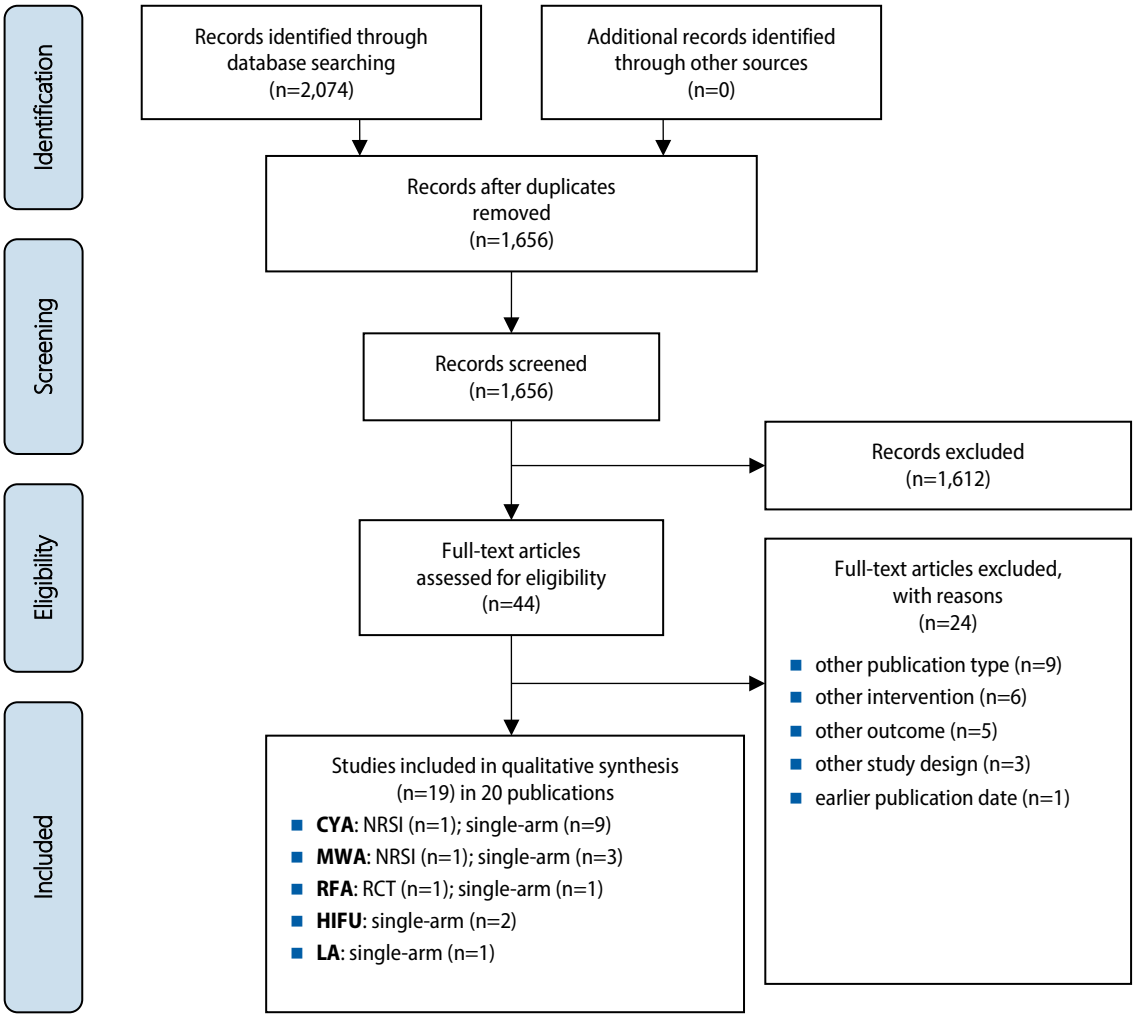

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

Abbreviations: CYA – cryoablation, HIFU – high-intensity focused ultrasound ablation, LA – laser ablation, MWA – microwave ablation, NRSI – non-randomised study of intervention, RFA – radiofrequency ablation,

3.2.3 Analysis

Datenextraktion

One reviewer (DG, JK, or JE) extracted relevant data from the identified studies using standardised extraction tables in Excel, with accuracy validated by a second reviewer (DG, JK, or JE). Two reviewers (DG, JE or JK) independently conducted the risk of bias assessments, and discrepancies were resolved through discussion.

Bewertung des Verzerrungsrisikos (RoB) mit RoB 2 & ROBINS-I

The internal validity of the studies and the certainty of evidence were evaluated using the Cochrane Risk of Bias 2.0 (RoB 2) [37]tool for randomised controlled trials (RCTs) and the Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) [38]tool for non-randomised studies. Results were presented according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) framework [39].

Single-arm trials were classified as having a high risk of bias according to the methodological guidance by the HTA Coordination Group pursuant to the HTA Regulation, and as a result, they were not subject to further assessment [40]. Risk of bias tables are provided in the Appendix (Table A-3 and Table A-4).

automatische Bewertung „hohes Verzerrungsrisiko" von einarmigen Studien

3.2.4 Synthesis

The research questions were answered in plain text format with reference to GRADE evidence tables that are included in Appendix, results were summarised in Table 5-1 to Table 5-5.

Verwendung von GRADE zur Synthese der Evidenz

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

Critical outcomes

Outcomes were selected based on a scoping of the literature and correspondence with external reviewers (an expert in BC surgery). The following outcomes were defined as *critical* to derive a recommendation:

entscheidungs-relevante Endpunkte für die Wirksamkeit:

- **Overall survival (OS):** defined as the time from randomisation (or study entry) to death. It is the most reliable and accessible measure and the gold standard in cancer studies because it uses death from all causes as the endpoint, avoiding the misattribution of death to a specific cause [41].

  Gesamtüberleben
- **Disease-free survival (DFS):** defined as the time from randomisation until disease recurrence [41].

  krankheitsfreies Überleben
- **Recurrence:** defined as the reappearance of the tumour following treatment and complete regression. Following BCS or mastectomy, BC can recur locally, regionally, and/or at distant metastatic sites. A local recurrence is defined as the reappearance of cancer in the ipsilateral preserved breast or chest wall. A regional recurrence denotes a tumour involving the ipsilateral regional lymph nodes, usually the ipsilateral axillary or supraclavicular, and less commonly the infraclavicular and/or internal mammary. The term "locoregional recurrence" indicates a recurrence in either the ipsilateral breast/chest wall or regional nodal basin, as opposed to a distant site [42].

  Rezidivrate
- **Complete tumour ablation:** defined as the destruction of tumour tissue through ablative techniques, where the goal is to eradicate or substantially destroy focal tumours. The term "tumour ablation" refers to the direct application of chemical or energy-based therapies to achieve tumour necrosis, with the outcome confirmed through imaging or histopathological assessment [43].

  vollständige Tumorablation

Additionally, the following outcomes were defined as *important* but not critical for decision-making:

wichtige Endpunkte für die Wirksamkeit: kosmetische Endpunkte, gesundheitsbezogene Lebensqualität

- Cosmetic outcomes.
- Health related quality of life outcomes measured with a validated tool.

These two outcomes are provided in the extraction tables but are not further elaborated on in the results or discussion sections.

4.1.2 Outcomes safety

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

entscheidende Endpunkte für Sicherheit:

- **Serious adverse events (SAE):** defined as 'events that result in death, are life-threatening, lead to (prolonged existing) hospitalisation, result in persistent or significant disability, a birth defect, or any other important medical event that may jeopardise the patient or require medical intervention to prevent any of the outcomes listed above [44].

schwerwiegende unerwünschte Ereignisse (SUE)

- **Adverse events (AE):** defined as 'any unanticipated medical incident, irrespective of severity, in a patient that has received a treatment, which does not have to be causally related to the treatment administered' [44].

unerwünschte Ereignisse (UE)

4.2 Included studies

A total of 19 Studies (in 20 publications) were included in this review:

- CYA: one NRSI [45] and nine single-arm trials in ten publications [46-55]
- MWA: one NRSI [56] and three single-arm trials [57-59]
- RFA: one RCT [60] and one single-arm trial [61]
- HIFU: two single-arm trials [62, 63]
- LA: one single-arm trial [26]

Evidenz:
1 randomisierte kontrollierte Studie (RCT),
2 nicht-randomisierte Interventionsstudien (NRSIs) &
16 einarmige Studien

Included studies are described for each ablation technique separately.

4.2.1 Included studies effectiveness

Study and patient characteristics

Cryoablation

One case-control study [45] and nine single-arm trials in ten publications [46-55] on CYA met our predefined inclusion criteria.

CYA: 1 NRSI & 9 einarmige Studien

Non-randomised studies of interventions (NRSIs)

The case-control study compared CYA to standard surgery was conducted in Italy and published in 2024 [45]. It was sponsored by the European Society of Radiology, the European Institute for Biomedical Imaging Research and GE Health. The primary study endpoints included the presence of necrosis in surgical specimens, the rate of complete tumour ablation, patient satisfaction and the incidence and severity of complications. The ICEfx Cryoablation System and the IceSphere 1.5 were used. A total of 20 patients (ten in each arm) with a solitary invasive BC ≤2 cm were included, who were, on average, 65 years old (range: 47 – 80) in the intervention group and 62 years old (range: 39 – 84) in the control group. In the intervention group, 90% of the participants were menopausal, compared to 60% in the control group. The mean tumour size was 9.9 mm (range: 6 – 18 mm) in the intervention group and 10.5 mm (range: 6 – 13 mm) in the control group. CYA was conducted under local anaesthesia with US guidance. The follow-up lasted a maximum of 21 days until the resection of the ablated tumour in the intervention group. Follow-up duration in the control group was not specified.

1 NRSI:
CYA vs. Operation

20 Patientinnen,
Tumorgröße ≤2 cm

Beobachtungszeit: max. 21 Tage bis zur Resektion in Interventionsgruppe (IG)

Single-arm trials

9 einarmige Studien:

Finanzierung teils durch Hersteller, teils durch Forschungsstipendien

Tumorgrößen ≤1.5 - ≤3cm

The included prospective single-arm trials were published between 2015 and 2024 from China [50], France [46], Japan [54], Spain [52] and the USA [47-49, 51, 53, 55]. Three were multicentric [47, 48, 51, 53], five were conducted in a single centre [46, 50, 52, 54, 55], and one did not report whether it was conducted in one or multiple centres [49]. Out of the eight trials that reported funding sources, one trial reported that the authors had no financial interests to disclose [54]. One trial received funding from a university hospital [52], while the others were financed partly by medical device companies, with further funding such as grants [49-51, 53, 55]. The primary outcome was not reported in three trials [49, 51, 55]. In the remaining trials, the primary outcome was complete tumour ablation [46, 50, 53], ipsilateral breast tumour recurrence at five years [47, 48], presence of residual invasive cancer [52] and cryolesion due to the ablation procedure [54]. The inclusion criteria tumour size varied across the trials. One trial included patients with tumour size ≤3 cm [46], two with tumour size ≤2 cm [52, 53] and five trials with tumour size ≤1.5 cm [47-49, 51, 54, 55]. One trial did not specify the tumour size inclusion criteria, but the median tumour size of included participants was 16 mm (range: 10 to 20 mm) [50]. Only one trial reported participants receiving neoadjuvant treatment [46], while it was not reported in six trials [49, 50, 52-55]. In two trials, neoadjuvant treatment was an exclusion criterion [47, 48, 51]. Adjuvant treatment post-ablation was not reported in three trials [50-52], while in the other trials, between 22% and 100% of patients received adjuvant treatment.

459 Patientinnen

5 Studien ohne Resektion: Nachbeobachtungzeit zw. 14 & 54 Monaten

4 Studien mit Resektion: Nachbeobachtungszeit zw. 21 Tagen & 8 Wochen (jeweils bis zur Resektion)

The total number of patients was 459, with individual study sizes ranging from 12 to 194 patients. Participant's age varied, with a median age between 53 and 85 years. CYA was performed under US guidance in seven trials [47-52, 54, 55]. One trial did not report the type of guidance used [53], and one used CT and US guidance [46]. Anaesthesia during ablation was not reported by two trials [47-49] and the information was not available in another [53]. Most of the remaining trials used local anaesthesia [46, 51, 52, 54, 55] and one study used general anaesthesia [50]. Five trials did not resect the tumour after ablation [46-49, 54, 55]. The follow-up of these trials ranged from 14 to 54 months. Four trials resected the tumour [50-53] between 21 days and eight weeks after ablation, which also defined the follow-up duration in these studies. One study only reported the number of patients who completed follow-ups at <6 months, 6-12 months, 12-24 months and ≥24 months [55].

Study characteristics and results of included studies are displayed in Table A-1 to Table A-4 and in the evidence profile in Table A-13 in the Appendix.

Microwave ablation

MWA:
1 NRSI & 3 einarmige Studien

Four studies, one NRSI [56] and three single-arm trials [57-59] on MWA met the predefined inclusion criteria.

NRSI

1 NRSI:
MWA vs. Operation

Tumorgröße ≤3cm

Ø Alter 79 vs. 77 Jahre

One prospective propensity-score-matched, multicentre cohort study compared MWA with standard surgery [56]. The study was conducted in China and funded by the National Natural Science Foundation and more regional research grants. The study included women with early-stage solitary invasive BC (≤3 cm), clinically negative axillary lymph nodes, and either positive or negative hormone receptor status. Patients self-selected to undergo either MWA with endocrine therapy or standard surgery with standard adjuvant therapies. After propensity score matching for variables including date of

diagnosis, age, histology, tumour size, hormone receptor status, and Ki-67, the study included 33 patients in the MWA group and 99 in the surgery group. All patients were over 70 years, with mean ages of 79.4 (range: 70–94) and 77.4 (range: 70–92), respectively.

keine Resektion in der IG

mediane Nachbeobachtungszeit: 31 Monate

The primary outcomes were OS, DFS and recurrence, with complete ablation and AEs reported for the intervention group only. MWA was performed using a Nanjing Yigao Microwave Electric Institute product under local anaesthesia and US guidance. Surgical options included either mastectomy or BCS with SLNB or axillary lymph node dissection. No resection was performed in the intervention group, so complete tumour ablation was assessed through imaging. All patients in both the intervention and control groups received adjuvant therapy, primarily endocrine therapy, although some patients in the control arm also received radiotherapy or chemotherapy. The median follow-up duration was 31 months (range: 2–74 months).

Case series

3 einarmige Studien:

keine kommerzielle Finanzierung

One of the included single-arm trials was initially designed as a multi-arm RCT [57]; however, only the MWA-arms were considered in our assessment since the other study arm did not meet our PICO criteria. The two MWA-arms were analysed as a single cohort in our assessment. Additionally, two single-arm prospective trials were included [58, 59]. All studies were conducted in China, with two studies being single centre [57, 59] and one being multicentre [58]. All studies were funded by the Natural Science Foundation of China and other more localised research grants, with no commercial funding involved.

101 Patientinnen eingeschlossen

Tumorgröße ≤3 cm

Ø Alter 51 – 59 Jahre

All three studies reported mortality, complete tumour ablation, and safety outcomes. Recurrence was assessed in only one study [58]. A total of 101 (range: 26-40) female patients with early-stage solitary invasive BC were included, with slight variations in other inclusion criteria. One study included tumours ≤2 cm [59], while the other two studies allowed tumours ≤3 cm. All studies required the absence of skin and pectoralis muscle infiltration, with one study specifying a minimum of 1 cm distance between the tumour and chest wall [59]. This study also required radiologically confirmed negative axillary lymph nodes. The mean age of patients ranged from 50.5 (range: 37-65) to 59 (range: 38-87).

Resektion in allen 3 Studien

Nachbeobachtungszeit: direkt, 10 Tage & 31 Monate nach Ablation

MWA was performed under local anaesthesia, guided by US in two studies [57, 58] and MRI in another [59]. All studies performed surgical resection post-ablation, enabling histological confirmation of complete tumour ablation. In one study [58], complete tumour ablation was assessed through imaging studies in patients unsuitable for surgical excision. Adjuvant therapy administration was only described in one study [58], where 93% of patients who underwent MWA without surgery received endocrine therapy; however, data for those who underwent subsequent surgical resection were not provided. No patients were lost to follow-up in two studies: one with up to ten days [57] and one with up to 31 months [58] follow-up. One study [59] did not record the follow-up time specifically but reported outcomes immediately after the intervention.

Study characteristics and results of included studies are displayed in Table A-5 and Table A-6 and the evidence profile is in Table A-14 in the Appendix.

Radiofrequency ablation

Two studies were identified for RFA, one RCT [60] and one single-arm trial [61].

RFA:
1 RCT & 1 einarmige Studie

RCT

The phase II, open-label and single-centre RCT compared RFA followed by resection to lumpectomy [60]. The study was conducted in Spain and did not provide information on funding. A total of 20 women were enrolled, with a mean age of 64 years in each arm. The primary endpoint was intraoperative free margins (histologically assessed distance between the tumour and margin). Eligible participants were females over 40 years old with invasive ductal carcinoma (IDC) ≤2 cm, a maximum intraductal component of 20%, and a minimum distance of 1 cm between the tumour and the skin/chest wall. Tumour size, histological grade, and receptor status were comparable between the groups, although statistical differences in the latter two were not formally analysed. RFA was performed using Covidien (Tyco Healthcare Group, Bolder, USA) under US guidance and general anaesthesia, followed immediately by tumour resection in the intervention group. The control group underwent standard lumpectomy. Most patients received adjuvant therapy, comprising endocrine therapy, chemotherapy, and breast or lymph node irradiation. Statistical analysis revealed that a significantly higher proportion of patients in the intervention group received breast irradiation compared to the control group (p = 0.038), with no other differences detected. Median follow-up time was 26.3 and 23.7 months (p=0.58) for the intervention and control group, respectively, with no losses to follow-up reported in either group.

1 RCT:
RFA vs. Lumpektomie

Resektion direkt nach Ablation

20 Patientinnen

Ø Alter 64 Jahre

Tumorgröße ≤2 cm

mediane Nachbeobachtungszeit:
26 vs. 24 Monate

Case series

The single-arm trial from Sweden was funded by the Swedish Breast Cancer Association, the Capio Research Foundation, AFA Insurance, Bracco Diagnostics and the manufacturer of the device, NeoDynamics AB [61]. The authors reported efficacy and safety outcomes in 18 women with unifocal BC of <2 cm and a maximum of 25% intraductal component. The study did not exclude any hormone receptor status or any tumour grades. The median age of the participants was 67 years (range: 46-84), with the majority (94%) being postmenopausal. The primary outcomes were mortality, complete ablation (verified by imaging and histological assessment), and AEs (specifically pain evaluated with the visual analogue scale). RFA was performed under US guidance and with patients receiving local anaesthesia and light sedation, if necessary. Tumour resection was performed after a median of 14.5 days (range: 6–22 days) post-ablation, which was the maximum follow-up length in this study. The majority of patients (94%) underwent BCS, while one patient required a mastectomy. Adjuvant therapy was administered to all participants; 100% received endocrine therapy, and 94% underwent additional radiation therapy.

1 einarmige Studie:

18 Patientinnen

Ø Alter 67 Jahre

Tumorgröße ≤2 cm

Resektion nach median 14.5 Tagen

Study characteristics and results of included studies are displayed in Table A-7 and Table A-8, and the evidence profile is in Table A-15.

High-intensity focused ultrasound ablation

Two single-arm trials were included for the assessment of HIFU [62, 63].

HIFU: 2 einarmige Studien

One study [62], originally conceptualized as an RCT, was analysed as a single-arm trial in our assessment, focusing only on the study arm treated with HIFU in addition to mastectomy. Although the control arm, which was mastectomy alone, met our PICO criteria, the procedure was performed within two weeks after HIFU. Since mortality, recurrence and AEs were measured only post-mastectomy, it remains uncertain if the results are attributable to HIFU or the mastectomy. Therefore, we disregarded the comparative results of this study due to these uncertainties. The study was conducted in China without a sponsor, and it involved 25 female patients aged 22 to 65 years with various menopausal statuses. The intervention was guided by US and was conducted under general anaesthesia using the JC tumour treatment system. Patients underwent modified radical mastectomy one to two weeks post-HIFU, and all patients received adjuvant therapy. The inclusion criteria specified patients with solitary invasive BC (T1-2, N0-2, M0) ≤5 cm. The study documented no losses to follow-up over a mean duration of 12 months.

1. Studie als RCT konzipiert, jedoch hier als einarmige Studie analysiert

25 Patientinnen, 22-65 Jahre alt

MST 2 Wochen nach Ablation

The other study [63] was a prospective case series from the Netherlands, sponsored by the Center for Translational Molecular Medicine. The aim of the study was to explore the treatment feasibility and safety of HIFU, employing MRI guidance and procedural sedation using a Sonalleve-based prototype. The study included a smaller cohort of 10 female patients with an average age of 54.8 years (SD: ±12.5). Most of the patients (80%) underwent lumpectomies post-ablation, while one patient (10%) did not require surgery post-HIFU. The inclusion criteria were similarly stringent, targeting women with invasive BC (T1-2) ≤1 cm and with specific anatomical requirements for HIFU applicability. The study had a follow-up period of 48 hours to 10 days, and no losses to follow-up were reported.

2. einarmige Studie mit 10 Patientinnen,

Ø Alter 55 Jahre

Tumorgröße ≤1 cm

Lumpektomie nach Ablation durchgeführt

Study characteristics and results of included studies are displayed in Table A-9 and in the evidence profile Table A-16 in the Appendix.

Laser ablation

One prospective, open-label, single-arm trial was included, which assessed the efficacy of percutaneous laser ablation (Novilase Laser Therapy) [26]. The study was conducted in the USA and UK and was sponsored by Novian Health. The study involved 61 female patients, aged between 42 and 77 years, focusing on the rate of complete tumour ablation as its primary endpoint. The patients underwent the procedure under local anaesthesia, using US guidance in 98% of the cases and stereotaxis in 2%.

LA: 1 einarmige Studie

61 Patientinnen, im Alter von 42 bis 77 Jahren

Most patients (90%) had a lumpectomy within 28 days after ablation, and minimal adjuvant therapies were administered due to stringent inclusion criteria that excluded neoadjuvant treatments. All participants had a unifocal IDC ≤2 cm, with less than 25% intraductal components and no prior or concurrent conditions like morbid obesity or renal insufficiency that could impact life expectancy. Tumour characteristics showed a predominance of HER2-, ER+ subtype in 50 patients, varying grades of tumour aggressiveness, and an average tumour size of 11.3 mm as assessed by MRI. The follow-up period averaged 43 months, with a protocol designed for a total follow-up of five years to assess long-term outcomes. There were no losses to follow-up.

bei 90% Lumpektomie innerhalb von 28 Tagen

Tumorgröße ≤2 cm

Study characteristics and results of included studies are displayed in Table A-10 and in the evidence profile in Table A-17 in the Appendix.

4.2.2 Additional included studies safety

No additional studies on safety were included.

4.3 Results

4.3.1 Cryoablation

Mortality[5]

The included NRSI [45] did not report the outcome *OS.*

Eight single-arm trials reported *OS*. During a follow-up between one to 12 months across five studies [46, 50, 51, 53, 55], there were a total of two deaths, resulting in an OS rate of 99% (174/176). The two reported deaths were due to a myocardial infarction in one case [46] and unrelated causes in the second case [55]. During a follow-up between 12 to 60 months, reported by three studies [47-49, 54], the OS rate was 91% (203/224). All deaths (n=21) were reported in one trial [48], of which 16/21 were unrelated to BC, while another three were due to unknown reasons. The remaining two deaths were due to distant metastasis.

CYA:
5 einarmige Studien
Gesamtüberleben <12 Monaten: 99%

3 einarmige Studien
Gesamtüberleben 12-60 Monate: 91%

DFS was not reported in any of the included studies.

krankheitsfreies Überleben nicht berichtet

Morbidity[6]

Complete ablation was reported in one NRSI [45] and was achieved in 9/10 participants (90%) in the intervention group.

Additionally, five single-arm trials reported *complete ablation*, which was achieved in 171/192 patients (89%; range: 53% to 93%) [49, 50, 52, 53].

vollständige Ablation:
1 NRSI: 90%
5 einarmige Studien: 53-93%

The NRSI [45] did not report the outcome *recurrence.*

Five single-arm trials reported the outcome *recurrence [*46, 48, 49, 54, 55*]*. After a follow-up length of 18 to 60 months, there were a total of 14 recurrences (5%; range: 0-22%) in 279 patients.

Rezidivrate in 5 einarmigen Studien: 0-22%

Safety

No *SAEs* occurred in either group (ten patients in each arm) of the NRSI after a follow-up of one week [45].

No *SAEs* occurred in four single-arm trials, with 247 participants after a follow-up of two to 60 months [46, 48, 49, 54].

keine SUEs in 1 NRSI (N=20) & 4 einarmigen Studien (N=247)

The NRSI [45] reported two minor *AEs* post procedure in the intervention group (20%) and none in the control group (0%). The two AEs were small post-ablative hematoma, about 4 cm in size. Pain was assessed in both groups on a scale from one to ten, with higher numbers representing stronger pain. The median pain score was three in the intervention group and five in the

NRSI: 2/10 vs. 0/10 UEs

medianer Schmerz: 3 vs. 5, p=NR

[5] D0001 – What is the expected beneficial effect of CYA on mortality?

[6] D0006 – How does CYA affect progression (or recurrence) of the disease or health condition?

control group, with no p-value reported. After a follow-up of one week, there were no AEs.

AEs immediately after the procedure were reported in five single-arm trials [46, 49-52] for a total of 129 patients. A total of 39 AEs were reported (30%; range: 0% to 100%). Mild to moderate pain and bruising were described most often and, in some cases, together (bruising: 29/39 AEs, 74%; pain: 16/39 AEs, 41%). Additionally, six single-arm trials [46, 48-51, 54] reported *AEs* after a follow-up period of one week to five years, with a total of 109/282 patients (39%; range: 0% to 50%) experiencing AEs. Most of the patients experiencing AEs were recorded in one trial [48] (97/109 patients, 89%), which reported a total of 187 AEs, the majority of which were mild or moderate cases of bruising, pain and edema.

UEs direkt nach Intervention in 5 einarmigen Studien: 0-100%

UEs nach 1 Woche bis 5 Jahre in 3 Studien: 0-50%

4.3.2 Microwave Ablation

Mortality[7]

At a median follow-up time of 31 months, the NRSI reported an *OS* rate of 100% (33/33) in the intervention group and 99% (98/99) in the control group, with a non-statistically significant hazard ratio (HR) of 0.537 (95% CI: 0.089-3.325, p=0.49) [56]. At the one- and three-year follow-up points, survival rates were 97% vs. 100% and 93 vs. 96% for the intervention and comparator groups, respectively.

MWA_:
Gesamtüberleben:

NRSI: 100% vs. 99%
HR=0.537; p=0.49

No patients in any of the three single-arm trials died during follow-up ranging from immediately post-intervention to 36 months [57-59].

3 einarmige Studien: 100%

DFS was only described by the NRSI, which reported that, at a median follow-up of 31 months, 3% of patients in each group (1 vs. 3 patients) experienced tumour progression. The HR for DFS was 0.536 (95% CI: 0.128–2.249) and statistically not significant (p = 0.38) [56].

krankheitsfreies Überleben nur vom NRSI berichtet; Tumorprogression in 3% in jeder Gruppe

Morbidity[8]

The NRSI reported *complete ablation* in (32/33) 97% of MWA patients. After further treatment in one patient during the one-month follow-up, this was increased to 100% (33/33, 95% CI: 9.4-100) [56].

vollständige Ablation:
NRSI: 97%
3 einarmige Studien: 91% - 100%

Complete ablation ranged from 91 to 100% in the single-arm trials [57-59].

Disease recurrence in the NRSI was 3% (1/33 vs. 3/99) in both the intervention and comparator group during a median follow-up time of 31 months. Recurrence was local in one patient of the intervention group and one patient of the control group, with the two remaining patients in the control group experiencing distant metastasis [56].

Tumorrezidiv:

NRSI: 1/33 vs. 3/99

Only one single-arm trial reported *recurrence* in a subset of patients who received only MWA without resection (due to ineligibility or refusal for surgery), with no recurrence observed after a follow-up of 13 to 47 months [58]. Data on recurrence were unavailable for the remaining patients (20/35) who underwent subsequent resection [58].

1 NRSI: kein Wiederauftreten in 15/35 Patientinnen,
nicht Berichtet für 20/35 Patientinen

[7] D0001 – What is the expected beneficial effect of MWA on mortality?

[8] D0006 – How does MWA affect progression (or recurrence) of the disease or health condition?

Safety

SAEs were not reported in any study.

NRSI: keine UEs in der MWA-Gruppe, keine Daten zur Kontrollgruppe

One NRSI reported no *AEs* in the intervention group; however, AEs in the comparator group were not recorded [56].

UEs in einarmigen Studien: Hautverbrennung, Schwellungen & Schmerzen

Among the single-arm trials, one documented local skin burns in four patients (10%) and local skin necrosis in one patient (2.5%) [57]. Pain during or after the procedure was reported in all three trials, affecting 6 to 16% of patients. Additionally, two trials [58, 59] reported swelling during or after the procedure, with incidence rates ranging from 42% to 100%.

4.3.3 Radiofrequency Ablation

Mortality[9]

Gesamtüberlegen: RCT 100% in beiden Gruppen

In the RCT comparing RFA with subsequent resection to BCS, *OS* was 100% (20/20 vs. 20/20) in both the intervention and control group at a median follow-up of 25 months [60].

einarmige Studie: 100% nach 14 Tagen

In the single-arm trial, 100% (18/18) of patients were alive at the 14-day follow-up [61].

DFS was not reported in any of the included studies.

Morbidity[10]

vollständige Tumorablation: 100% im RCT & in der einarmigen Studie

In the RCT, *complete tumour ablation* was reported in 100% of patients in the intervention group [60].

Complete tumour ablation was 100% in the single-arm trial [61].

kein Wiederauftreten in beiden Gruppen im RCT

No cases of local or distant *tumour recurrence* were reported in either group of the RCT during a mean follow-up time of 25 months [60].

Recurrence was not reported in the single-arm trial [61].

Safety

SAEs were not reported in the studies.

UEs: RCT: 40% vs. 5%, keine statistische Signifikanz

The RCT documented *AEs* after surgical resection in both the intervention and control groups, with 40% (8/20) vs. 5% (1/20) of patients suffering at least one AE [60]. Specifically, breast inflammation was reported in 25% (5/20) of patients in the intervention group as opposed to 5% (1/20) in the control group, and breast infection was observed in 15% (3/20) of patients in the intervention group, with no cases in the control group. However, the differences were not statistically significant.

einarmige Studie: nur medianer Schmerz berichtet

The single-arm trial only reported pain using the visual analogue scale (VAS) [61]. A median pain score of 2 during the administration of the local anaesthetic, compared to a median score of 2.5 during the procedure, was reported.

[9] D0001 – What is the expected beneficial effect of RFA on mortality?

[10] D0006 – How does RFA affect progression (or recurrence) of the disease or health condition?

Additionally, the median pain scores before and after the procedure were 0 and 0.5, respectively. No other AEs were reported.

4.3.4 High-intensity focused ultrasound ablation

Mortality[11]

OS was reported in both included single-arm trials. One trial [63] had a follow-up of ten days and reported that all patients (10/10, 100%) were alive. The other trial [62] measured OS at 12 months post-procedure and reported a 100% survival rate (25/25).

HIFU: Gesamtüberleben 100% in 2 einarmigen Studien

DFS was not reported in any of the included trials.

Morbidity[12]

Complete tumour ablation was reported in one single-arm trial and was achieved in all patients (25/25, 100%) [62].

Recurrence rate was reported in one single-arm trial and measured at 12 months [62]. No recurrences occurred within this period.

vollständige Tumorablation 100% & kein Wiederauftreten in einer einarmigen Studie

Safety

SAEs were not reported in the trials. Milder *AEs* were reported in both included single-arm trials. One trial [62] reported edema in 25/25 (100%) of patients at twelve months, pain in 11/25 (44%), and mild fever in 3/25 (12%). The other trial [63] had only a 10-day follow-up period and reported five minor AEs, including nausea and vomiting, pain and skin changes. The two pain-related AEs reported a pain score of 4 and 5 out of 10.

UEs in 2 einarmigen Studien: Ödem, Schmerzen, leichtes Fieber, Übelkeit & Hautveränderungen

4.3.5 Laser ablation

Mortality[13]

OS and *DFS* were not reported in the included single-arm trial [26].

LA: 1 einarmige Studie

Morbidity[14]

Complete tumour ablation was achieved in 51/61 patients (84%) [26].

Recurrence rate was measured at four years, 2/61 patients (3%) had a recurrence [26].

vollständige Tumorablation in 84% der Patientinnen & Wiederauftreten in 3%

[11] D0001 – What is the expected beneficial effect of HIFU on mortality?

[12] D0006 – How does HIFU affect progression (or recurrence) of the disease or health condition?

[13] D0001 – What is the expected beneficial effect of LA on mortality?

[14] D0006 – How does LA affect progression (or recurrence) of the disease or health condition?

Safety

The single-arm trial [26] reported only eight mild and six moderate *AEs* at 43 months. The moderate events included pain in four cases, one lump and one seroma. The mean pain score was 4.2 from a maximum of 10. *SAEs* were not reported.

8 milde & 6 moderate UEs: Schmerzen, Klumpen & Serom

5 Certainty of evidence

Verzerrungspotential mit Cochrane RoB V2 & mit ROBINS-I V2 bewertet, einarmige Studien automatisch mit hohem Verzerrungspotential

The RoB of individual outcomes in the RCT was assessed using the Cochrane RoB 2.0 tool. NRSIs were evaluated using the Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I, version 2) tool. Single-arm trials were not formally assessed and were considered to have a high risk of bias by default. The risk of bias assessment tables are presented in Table A-3 and Table A-4 in the Appendix.

NRSI zu CYA: kritisches Verzerrungspotential

A *critical risk of bias* was identified in the domain "bias due to confounding" for the outcome AEs in the included NRSI on CYA [45]. The outcome AEs was the only outcome with available comparative data. Consequently, the RoB was not assessed for other outcomes.

NRSI zu MWA: hohes Verzerrungspotential

The included NRSI on MWA was assessed to have a *serious risk of bias* due to confounding factors and missing data concerns for the outcomes OS, DFS and recurrence. There was an imbalance in the number of patients receiving adjuvant therapies, and no patients in the control group underwent axillary resection or SLNB, which are important aspects of managing disease progression. In addition, the loss to follow-up was not clearly described and no information on management of missing data was available. No comparative data was available for complete tumour ablation and safety.

RCT zu RFA: niedriges Verzerrungspotential

The included RCT on RFA [60] was assessed to have a *low risk of bias* for the following critical outcomes: mortality, complete tumour ablation, recurrence and safety.

Vertrauenswürdigkeit der Evidenz nach GRADE

The strength of evidence for each endpoint was assessed according to the GRADE framework. Each study was independently evaluated by two researchers and any disagreements were resolved by a third reviewer. Further details on the applied criteria are available in the GRADE Working Group recommendations [39].

GRADE uses four categories to rank the strength of evidence:

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

The ranking according to the GRADE scheme for the research question can be found in the summary of findings tables below and in the evidence profiles in the Appendix Table A-5 to Table A-9.

Vertrauenswürdigkeit der Evidenz zur Wirksamkeit & Sicherheit niedrig für RFA & sehr niedrig für CYA & MWA

Comparative evidence for the effectiveness and safety of the different thermal ablation techniques was only available for CYA, RFA and MWA.

Overall, the strength of evidence for the effectiveness and safety of the different thermal ablation interventions compared to surgery with or without standard care was:

- very low for CYA

- very low for MWA
- low for RFA

keine Vergleichende Evidenz zu HIFU & LA verfügbar

No comparative evidence was identified for HIFU and LA.

Table 5-1: Summary of findings table of cryoablation

Outcome	Anticipated absolute effects (CYA vs. surgery)	Number of participants (studies)	Certainty	Comments
Efficacy				
Overall survival	FU 1 - 12 m: 174/176 (99%) FU >12 - 60 m: 203/224 (91%)	400 (8 single-arm trials)	⨁◯◯◯ Very low	Most deaths (n=21) reported in one study with the longest FU [Fine, 2024], of which 16 were unrelated to BC and 3 for unknown reasons,
Disease-free survival	See comment.	See comment.	See comment.	No study reported this outcome.
Complete ablation	9/10 (90%) vs NA	10 vs 10 (1 NRSI)	⨁◯◯◯ Very low	Very low sample size.
	171/192 (89%; median 92%; range: 53% to 93%)	192 (5 single-arm trials)	⨁⨁◯◯ Low	-
Recurrence	FU 18 m – 60 m: 14/279 (5%; median: 3%; range: 0% to 22%)	279 (5 single-arm trials)	⨁⨁◯◯ Low	-
Safety				
Adverse events FU: immediate/post procedure	Minor AE: 2*/10 vs 0/10 *small post-ablative hematoma (about 4 cm in size) Pain (assessed on a scale from 1-10): Median score: 3 vs 5, p=NR	10 vs 10 (1 NRSI)	⨁◯◯◯ Very low	No adjustment for confounding factors, low sample size.
	39/129 (30%; median 22%; range: 0 to 100) Mild to moderate pain and bruising was most often described, in some cases together: (Bruising: 29/39 AEs, 74%; Pain: 16/39 AEs, 41%)	129 (5 single-arm trials)	⨁◯◯◯ Very low	Only non-comparative evidence, low sample size, inconsistency in occurrence.
Adverse events FU: 1 w to 5 y	FU 1 w: 0 vs 0	10 vs 10 (1 NRSI)	⨁◯◯◯ Very low	No adjustment for confounding factors, low sample size.
	FU 1 w - 5 y: 109 (39%; median 5%; range: 0% to 50%)	282 (6 single-arm trials)	⨁◯◯◯ Very low	Only non-comparative evidence, small sample size, inconsistent occurrence.
Serious adverse events	FU 1 w: 0 vs 0	10 vs 10 (1 NRSI)	⨁◯◯◯ Very low	No adjustment for confounding factors, low sample size.
	FU 2 m – 60 m: 0 (0)	247 (4 single-arm trials)	⨁◯◯◯ Very low	Only non-comparative evidence.

Abbreviations: AE – adverse event, BC – breast cancer, CI – confidence interval, CYA – cryoablation, FU– follow-up, m – month(s), NA – not applicable, NRSI – nonrandomized study of intervention, NR– not reported, NA – not applicable, vs – versus, w – week(s)

Table 5-2: Summary of findings table of microwave ablation

Outcome	Anticipated absolute effects (MWA vs. surgery)	Number of participants (studies)	Certainty	Comments
Efficacy				
Overall survival	At median FU: 31 m (2-74) 33 (100) vs 98 (99) HR: 0.537 (95%CI: 0.089-3.325), p=0.49 At 1 y: 97% vs 100% At 3 y: 93% vs 96%	33 vs 99 (1 NRSI)	⨁◯◯◯ Very low	Concerns regarding missing data and confounding factors (no lymph node dissection and SLNB in comparator group).
	Post ablation - 36 m FU: 100%	101 (3 single-arm trials)[a]	⨁◯◯◯ Very low	Only non-comparative evidence. One study had extremely short follow-up.
Disease-free survival	At median FU: 31 m (2-74) HR: 0.563 (95% CI: 0.128-2.240, p=0.38)	33 vs 99 (1 NRSI)	⨁◯◯◯ Very low	Concerns regarding missing data and confounding factors (no lymph node dissection and SLNB in comparator group.
Complete ablation	FU 1 w: 32 (97) FU 1m: 33 (100) 95% CI: 89.4-100)	33[b] (1 NRSI)	⨁◯◯◯ Very low	-
	Post ablation - 36 m FU: 91-100%	101 (3 single-arm trials)[c]	⨁◯◯◯ Very low	-
Recurrence	At median FU 31 m (2-74): Total recurrence: 1 (3) vs 3 (3) Local recurrence: 1(3) vs 1(1) Distant recurrence: 0 (0) vs 2 (2)	33 vs 99 (1 NRSI)	⨁◯◯◯ Very low	Concerns regarding missing data and confounding factors (no lymph node dissection and SLNB in comparator group.
	At median FU 13-47 m MWA: 0/15 (0) MWA+resection: NR	35 (1 single-arm trials)	⨁◯◯◯ Very low	Only noncomparative evidence, low rate of events.
Safety				
Adverse events	At median FU 31 m (2-74): 0 (0) vs NR	33 vs 99 (1 NRSI)	⨁◯◯◯ Very low	No details on AE expected or observed.
	All studies reported pain during and/or after procedure: 6-18% of patients 2 studies reported swelling during and/or after procedure: 42-100% of patients 1 study: reported skin burns 10% (4/40) and skin necrosis 2.5% (1/40)	101 (3 single-arm trials)	⨁◯◯◯ Very low	FU time not specified for observation of AE.
Serious adverse events	At median FU 31 m (2-74): 0 (0) vs NR	33 vs 99 (1 NRSI)	⨁◯◯◯ Very low	No details on expected SAE.
	0	35 (1 single-arm trial)	⨁◯◯◯ Very low	No details on expected SAE.

Abbreviations: AE – adverse event, CI – confidence interval, FU– follow-up, m – months, HR – hazard ratio, MWA – microwave ablation, NA – not applicable, NR – not reported, NRSI – non-randomised study of intervention, SAE – serious adverse event, SNLB- sentinel lymph node biopsy, vs – versus, y – years, w –weeks

Comments:

[a] One study was designed as a multi-arm RCT but due to the control groups not matching our PICO, we include noncomparative data for patients of two arms receiving MWA, treating it like a single arm study.

[b] Complete ablation only assessable in the intervention group.

[c] One study was designed as a multi-arm RCT but due to the control groups not matching our PICO, we include noncomparative data for patients of two arms receiving MWA, treating it like a single arm study.

Table 5-3: Summary of findings table of radiofrequency ablation

Outcome	Anticipated absolute effects (RFA vs. surgery)	Number of participants (studies)	Certainty	Comments
Efficacy				
Overall survival	At 25 m (1-83): 20/20 (100) vs 20/20 (100)	20 vs 20 (1 RCT)	⨁⨁◯◯ Low	This study was prematurely stopped due to higher number of local AEs in the intervention group; hence OIS was not reached. Further, there is a low number of events.
	At 14 d: 18/18 (100)	18 (1 single-arm trial)	⨁◯◯◯ Very low	Extremely short FU.
Disease-free survival	See comment.	See comment.	See comment.	No studies reported this outcome.
Complete ablation	20/20 (100)	20 vs NA[a] (1 RCT)	⨁⨁◯◯ Low	-
	MRI: 18/18 (100) Histology: 15/18 (83) - 16/18 (85)	18 (1 single-arm trial)	⨁◯◯◯ Very low	-
Recurrence	At 25 m (1-83): Local: 0 (0) vs 0 (0) Distant: 0 (0) vs 0 (0)	20 vs 20 (1 RCT)	⨁⨁◯◯ Low	Concerns regarding missing data during FU.
Safety				
Adverse events	Total AE: 8 (40) vs 1 (5), p=0.1 Breast inflammation: 5 (25) vs 1 (5), p=0.18 Breast infection: 3 (15) vs 0 (0), p=0.23	20 vs 20 (1 RCT)	⨁⨁⨁◯ Moderate	AE were assessed post surgical resection in both groups hence cannot necessarily be clearly attributed to the intervention itself in the group receiving RFA
	VAS pain score: administration of anaesthetic vs during RFA: 2 vs 2.5, p=0.512 before RFA vs post RFA: 0 vs 1.5, p=0.042	18 (1 single-arm trial)	⨁◯◯◯ Very low	-
Serious adverse events	See comment.	See comment.	See comment.	No studies assessed this outcome.

Abbreviations: AE – adverse event, d – day(s), FU – follow-up, m – month(s), MRI- magnetic resonance imaging, NA – not applicable, RCT – randomized controlled trial, RFA – radiofrequency ablation, VAS – visual analogue scale, vs – versus

Comments:

[a] *Complete ablation was only assessable in the intervention group.*

Table 5-4: Summary of findings table of high-intensity focused ultrasound ablation

Outcome	Anticipated absolute effects	Number of participants (studies)	Certainty	Comments
Efficacy				
Overall survival	At 10 d [63]: 10/10 (100%) At 12 m [62]: 25/25 (100%)	35 (2 single-arm trials)	⨁◯◯◯ Very low	Only non-comparative evidence, follow-up too short in one study to assess OS.
Disease-free survival	See comment.	See comment.	See comment.	No studies assessed this outcome.
Complete ablation	25/25 (100%)	25 (1 single-arm trial)	⨁◯◯◯ Very low	-
Recurrence	At 12 m: 0/25 (0%)	25 (1 single-arm trial)	⨁◯◯◯ Very low	Only non-comparative evidence.
Safety				
Adverse events	At 10 d [63]: Minor AEs: 5 Nausea and vomiting: 2, pain: 2 (4 and 5 score out of 10), skin changes: 1 At 12 m [62]: Edema: 25/25 (100%) Pain: 11/25 (44%) Mild fever: 3/25 (12%)	35 (2 single-arm trials)	⨁◯◯◯ Very low	Only non-comparative evidence, one study had extremely short follow-up. Only minor or mild AEs were reported. One study reported the number of patients with AE, the other study reported the number of AEs only.
Serious adverse events	See comment.	See comment.	See comment.	No studies assessed this outcome.

Abbreviations: (S)AE – (serious) adverse event, d – day(s), m – month(s)

Table 5-5: Summary of findings table of laser ablation

Outcome	Anticipated absolute effects	Number of participants (studies)	Certainty	Comments
Efficacy				
Overall survival	See comment.	See comment.	See comment.	No studies assessed this outcome.
Disease-free survival	See comment.	See comment.	See comment.	No studies assessed this outcome.
Complete ablation	51/61 (84%)	61 (1 single-arm trial)	⨁◯◯◯ Very low	-
Recurrence	At 4 years: 2/61 (3%)	61 (1 single-arm trial)	⨁◯◯◯ Very low	Only non-comparative evidence.
Safety				
Adverse events	At 43 months: Mild: 8 Moderate: 6 pain: 4 (mean score 4.2) lump: 1 seroma: 1	61 (1 single-arm trial)	⨁◯◯◯ Very low	Only non-comparative evidence.
Serious adverse events	See comment.	See comment.	See comment.	No studies assessed this outcome.

6 Discussion

6.1 Summary of findings

The aim of the current review was to compare the efficacy and safety of different available thermal ablation interventions with surgery with or without additional standard care in patients with early-stage breast cancer (BC). We identified 19 studies in 20 publications, of which one was an RCT, two were NRSIs, and 16 were single-arm trials.

Ziel: Thermoablation (TA) vs. Standardoperation
Einschluss 1 RCT, 2 NRSIs & 16 einarmige Studien

Cryoablation (CYA)

Comparative evidence for CYA was limited to one small non-randomised study of intervention (NRSI) with 20 participants comparing CYA with standard surgery [45]. Only the outcomes serious adverse events (SAEs) and adverse events (AEs) were described for both groups, with only two minor AEs reported in the intervention group. Overall survival (OS), disease-free survival (DFS) and recurrence were not reported. Complete ablation was achieved in 90% of patients treated with CYA.

CYA: 1 NRSI
wenige UEs als einziges vergleichend berichtet

keine Information zu anderen Endpunkten

In addition, evidence from eight prospective single-arm trials [46-51, 53-55] with a total of 427 participants suggested that CYA did not adversely affect OS (eight studies) or recurrence (five studies) and was able to completely ablate the tumour (five studies). AE rates, reported with immediate (five studies) and longer-term (one week to five years) follow-up (six studies) varied widely, potentially due to differences in reporting. The most reported AEs were mild to moderate pain and bruising. There were no SAEs (six studies) during a follow-up period of two to 60 months. The outcome DFS was not recorded in any of the included single-arm trials.

8 einarmige Studien:
keine negativen Effekte von TA zu Gesamtüberleben o. Wiederauftreten, generell vollständige Ablation

Microwave ablation (MWA)

A propensity score-matched NRSI with a total of 33 patients in the intervention group and 99 in the control group [56] found no statistically significant differences between MWA and surgery for the outcomes OS and DFS at a median follow-up of 31 months. Only one patient failed to achieve complete ablation with MWA. This patient was treated and achieved complete ablation at the one-month follow-up. There were no major differences in recurrence, although the p-value was not reported. AEs were only described for the intervention group, with no events reported during the median follow-up period.

MWA: 1 NRSI
keine Gruppenunterschiede beim Gesamtüberleben, krankheitsspezifischem Überleben, o. Tumorrezidiv

Furthermore, three single-arm trials with a total of 101 included patients [57-59] provided evidence that MWA did not adversely affect OS up to 36 months of follow-up and complete ablation was generally achieved in more than 90% of patients. Recurrence was reported in only one study for a subset of the sample (n = 15), with no recurrences recorded. In addition, no SAEs were reported (one study), and there were varying numbers of AEs per study, with the most common AEs being pain or swelling (three studies). The outcome DFS was not reported.

3 einarmige Studien:
generell gutes Gesamtüberleben, vollständige Ablation, kein Wiederauftreten, Heterogenität bei UEs

Radiofrequency ablation (RFA)

RFA: 1 RCT
vorzeitiger Abbruch der Studie

One small RCT comparing RFA to surgery was included, comprising 20 patients in each arm [60]. It showed comparable OS, complete ablation in all 20 participants of the intervention group and no recurrence in either group at a median follow-up of 25 months. Recruitment to the study was prematurely stopped with 20 participants in each arm after a preplanned interim analysis due to a higher number of local AEs in the intervention group (8/20 vs 1/20, p=0.1), although no SAEs were reported.

1 einarmige Studie, vollständige Tumorablation & Gesamtüberleben

In addition, one single-arm trial [61] with 18 patients showed 100% OS at 14 days and 100% complete ablation. Patients experienced no difference in pain levels during the administration of anaesthesia or the RFA procedure itself; however, they reported increased pain following the procedure. Outcomes OS, DFS, recurrence or SAEs were not reported.

High-intensity focused ultrasound ablation (HIFU)

HIFU: 2 einarmige Studien
Ablationsrate 100% in einer Studie

No comparative evidence was available for HIFU, and only two single-arm trials [62, 63] with a total of 35 participants were included. OS was 100% in both, but the follow-up period was only ten days in one of trials. Complete ablation was achieved in all patients (n=25) with no recurrences at twelve months. The most common AEs were pain and edema. DFS and SAEs were not reported.

Laser ablation (LA)

LA: 1 einarmige Studie
84% Ablationsrate

There was also no comparative evidence available for LA, and only one single-arm trial [26] with 61 participants showed a complete ablation rate of 84% and a recurrence rate of 3% at four years. At 43 months, a total of eight mild to moderate AEs, such as pain, were reported. The outcomes OS, DFS and SAEs were not reported.

6.2 Interpretation of findings

BK-Operation – Entwicklung zu weniger invasiven Verhalten

TA als mögliche Option für Patientinnen, für die eine Operation nicht in Frage kommt

The current gold-standard treatment for early-stage BC is surgery, often complemented by neoadjuvant or adjuvant therapies based on tumour characteristics. Over time, BC surgery has evolved from radical mastectomy to breast-conserving surgery (BCS), reflecting a trend toward less invasive procedures [64]. Minimally invasive percutaneous treatments, such as thermal ablation interventions, could represent the next step in this progression. These interventions promise reduced invasiveness, lower anaesthesia requirements, faster recovery, and improved cosmetic outcomes [22]. Additionally, they provide an alternative for patients who are unsuitable for surgery due to old age, comorbidities, or unwilling to undergo surgery due to personal preference. However, the current body of evidence for thermal ablation interventions remains limited, primarily consisting of single-arm trials with relatively small sample sizes and short follow-up durations. The lack of high-quality RCTs or NRSIs restricts robust comparisons with surgery.

Evidenz aus rezenten SRs mit ähnlichen Erkenntnissen: kaum vergleichende Evidenz, häufige Resektion & kurze Nachbeobachtungszeiten

Our findings align with those from recent SRs. A 2024 SR on CYA for tumours up to 2 cm reported comparable local recurrence rates between CYA and those reported for BCS but highlighted the lack of comparative evidence and limited follow-up periods [65]. The authors also suggest adjuvant radiation for managing subclinical foci outside the ablation zone. Similarly, an SR on RFA from 2021 noted high complete ablation rates and low rates of AEs but

emphasized the potential impact of resection post-ablation on local recurrence [66]. The evidence has improved only marginally over the last decade, as the 2012 AIHTA review on RFA in BC could not yet identify any comparative studies [67]. Recent SRs on HIFU found it to be a safe procedure for BC, with promising effectiveness in histopathological response, immunological reactivity, and vascular damage, but they did not assess the patient-relevant endpoints defined in our assessment [68]. Moreover, concerns remain about the consistency of coagulation necrosis and the reliability of imaging modalities for assessment [69]. Finally, a SR on LA concluded that LA should be used in the context of clinical trials until further validation for early BC is obtained [70]. No SR on MWA for early-stage BC could be identified, which is in line with other SRs on all thermal ablation interventions on BC, usually only finding limited evidence on MWA [20, 31].

Internal, external validity and evidence gaps

niedriges RoB im RCT, jedoch vorzeitiger Abbruch, relativ hohes RoB von NRSIs, fehlende komparative Evidenz von single-arm Studien

Although the included RCT on RFA had a relatively low RoB, it fundamentally lacked the power to detect significant differences between the intervention and control group due to its premature termination during the recruitment phase. Comparative evidence from NRSIs was restricted to certain outcomes, for which there was generally a lack of control of confounding and, therefore, a high risk of bias. Further, single-arm trials lacked a comparison group to adequately gauge the efficacy of thermal ablation interventions as compared to surgery.

vollständige Ablation: negativer Vorhersagewert von MRT 81%

Imaging prior to ablation or surgery is essential to assess tumour size and location. Since the different thermal ablation interventions vary in their treatment capacity – typically up to 5 cm depending on the intervention [22] - the included studies focused on tumours ranging from ≤1 cm to ≤5 cm. However, a significant challenge remains in confirming complete tumour ablation. Unlike surgical excision, thermal ablation raises concerns about margin assessment and definitive histopathology, which is one of the most critical quality control measures in oncologic surgery [71]. In trials without resection, assessment was primarily conducted through imaging, i.e. US or magnetic resonance imaging (MRI). While MRI is considered to be more reliable, with one study on CYA reporting a negative predictive value of 81% [53], the accuracy could potentially be further improved by incorporating additional imaging modalities for confirmation [22].

Resektion & adjuvante Behandlungen verzerren die Ergebnisse von Thermoablation

Since imaging techniques alone do not guarantee complete ablation, most of the included studies (13 out of 19 studies), resected the tumour after ablation immediately or within eight weeks post-ablation. In these cases, it becomes unclear whether outcomes, such as OS, DFS and recurrence, are affected by the ablative intervention or the subsequent surgery. In addition, there was variation in whether adjuvant treatment was reported and to the extent that patients received adjuvant treatment. Adjuvant treatment, such as whole breast radiation, is generally indicated post-surgery for early-stage BC and has likely an influence on recurrence and local tumour control. As with surgery, without comparative evidence, it is unclear to what extent adjuvant treatments, or the lack thereof, influenced the results.

unterschiedliche BK Subtypen erschweren vollständige Ablation

Another challenge in evaluating ablation rates without resection is that BC subtypes differ significantly in morphology, influencing their response to imaging, ablation techniques, and treatment strategies. Ductal carcinomas, for example, frequently have stellate extensions, complicating precise ablation. This challenge is further compounded by cases with intraductal spread, where

the tumour extends along the ductal system, making precise ablation even more difficult [72]. In contrast, lobular carcinomas, due to E-cadherin deficiency, infiltrate in an amorphous pattern, making radiological and interventional standardisation difficult [73]. These concerns are already being recognised by experts as important factors to determine future clinical indications for the use of thermal ablation interventions. An expert panel supported the following tumour characteristics for ablation without resection: well defined lesion, maximum diameter of 1 cm, negative axilla and luminal-A-like. While they propose to exclude invasive lobular cancers [18]. Only when effectiveness and safety are confirmed for this indication, applications of thermal interventions should be expanded.

Erfassung vom Tumorrezidiv mit Bildgebenden Verfahren schwieriger nach Ablation als nach Resektion

Finally, there are further difficulties with the identification of local tumour recurrence after thermal ablation. Post-ablation necrosis may mimic malignancy on imaging, complicating differentiation between benign post-ablation changes and residual/recurrent tumour. This is particularly challenging in cases of trauma-induced fat necrosis. Identifying local recurrence in an amorphous fat necrosis area is more difficult than detecting it within structured surgical scars following excision. Breast MRI does not have a clear advantage in assessing recurrence post-ablation, and false positives remain a concern [22]. As breast tissue consistency, density, and its thermal conductivity likely influence the penetration and hence the effectiveness of ablative techniques, the tumour morphology must be carefully considered when selecting the appropriate minimally invasive ablation techniques [74]. In case of further treatments required, the altered conductive and physical properties of previously ablated tissue may limit the feasibility of precise re-ablation, as scar tissue can unpredictably affect the thermal effect.

Generalisierbarkeit der Ergebnisse: kleine Teilnehmerinnenanzahlen, wenig komparative Evidenz, fehlende Angabe von Patientinnenrelevanten Endpunkten

Regarding external validity, the patient characteristics and study settings generally align with the intended use of these interventions. However, the relatively small sample sizes and limited study quality reduce the generalisability of the findings. Furthermore, the extent to which thermal ablation compares to surgery remains unclear due to the lack of direct comparative evidence. Only one RCT, which was stopped early due to increased cases of AEs in the intervention group, was identified for RFA, while there was only one NRSI for CYA and one for MWA. Comparative evidence for HIFU and LA was missing entirely. Additionally, patient-relevant endpoints were often underreported, further limiting the applicability of findings to clinical practice. This was especially the case for the outcome DFS, which was only reported by one study. Further, the included studies had a relatively short follow-up period, making it hard to assess longer-term outcomes, such as mortality and recurrence.

Entwicklung von weniger invasiven Verfahren auch bei der Bewertung der Lymphknoten notwendig

Furthermore, although thermal ablation is being explored as a less invasive alternative to surgery for early-stage BC tumours, some patients with positive lymph node involvement will still require to undergo axillary lymph node dissection in case of positive lymph nodes. As axillary lymph node dissection is associated with various side effects and has a negative effect on postoperative quality of life, other, less invasive options of axillary lymph node management need to be explored in the future [31].

hochqualitative RCTs & NRSIs sind zur Bewertung der Effektivität & Sicherheit von TA notwendig

To close the knowledge gap about the routine clinical use of thermal ablation techniques in BC treatment, high-quality, long-term RCTs and NRSIs are needed. A non-inferiority study design would be appropriate to demonstrate whether these minimally invasive technologies are at least as effective and safe as the standard intervention, surgical excision, which is the most invasive treatment option. Existing studies, even when evaluating the same thermal

ablation technology, have applied heterogeneous protocols, particularly in device application and procedural standardisation. One key challenge remains the confirmation of complete ablation, which should be standardised across studies. Further, standardisation is required for the reporting of patient-relevant outcomes. Health-related quality of life and cosmetic outcomes were only reported in a few studies and mostly in a variety of ways.

To date, the number of RCTs or NRSIs assessing thermal ablation is very limited. A major barrier to patient enrolment is that, even when randomised to the thermal ablation study arm, surgical excision is required to confirm total ablation. As a result, patient participation largely depends on altruism. Safety and undertreatment concerns can be mitigated through rigorous study design, including clear stopping rules to prevent the continuation of an insufficient technique [75].

Sicherheitsbedenken bei Studien zu TA, könnten durch rigorosen Studiendesign teilweise aufgehoben werden

Ongoing clinical trials

A search of clinical trial registries identified one RCT in the USA comparing CYA with lumpectomy in 256 patients with T1-stage BC. The primary endpoints include treatment-related complications within one month and ipsilateral recurrence at the five-year follow-up, while secondary outcomes assess DFS and OS at five years. Recruitment began in April 2024, with a projected primary completion date of April 2034. No further RCTs were identified.

laufende Studien:
1 RCT (n=256)
Vergleich: CYA mit Lumpektomie
vsl. Ende: 2034

We also identified two NRSIs comparing CYA and MWA, respectively, with BCS and 24 single-arm trials (nine for CYA, six for MWA, four for RFA, three for HIFU and one for LA). Notably, many trials had not reported results despite exceeding their primary completion date, in some cases, by several years. Additionally, several trials were withdrawn, often citing funding limitations or patient recruitment challenges. However, in many cases, no clear explanation for termination was provided. It further remains a question of why no RCTs on the different ablation techniques are conducted.

1 NRSI für CYA
1 NRSI für MWA

fehlende Ergebnisse, obwohl schon lange abgeschlossen

6.3 Limitations

Some limitations of this review should be acknowledged. First, we included only studies published in the last ten years, excluding evidence prior to 2014. This decision was based on two key factors: First, multiple recent SRs have already summarised evidence from the last 25 years, providing a comprehensive overview of earlier findings. Second, non-established interventions evolve rapidly, and focusing on more recent studies ensures that the latest advancements receive appropriate attention. Further, only peer-reviewed literature in English or German was considered for this review. As a result, relevant findings from grey literature and articles in other languages may have been missed. However, our review includes studies from China, Japan and various European countries, mitigating some of these risks.

Limitationen:
nur Studien der letzten 10 Jahre eingeschlossen

In addition, we chose to present the evidence for each thermal ablation intervention separately rather than as a combined analysis. While these interventions share a common mechanism of tumour destruction, the different modalities may vary in their effects on tumour necrosis and associated AEs. Moreover, each technique has distinct ablation size capabilities potentially making some more suitable for specific tumour types than others.

Evidenz der TA-Interventionen nur separat dargestellt

durch Formulierung der PIKO, einige Studien als einarmig analysiert

Due to the formulation of our PICO and the way results were presented in some studies, some trials initially labelled as RCTs were analysed as single-arm trials, focusing on the study arm that evaluated the intervention specified in our PICO. In these cases, the outcomes relevant for us were only reported for the intervention group, preventing direct comparison. Additionally, one study distinguished treatment MWA alone and MWA combined with the immune checkpoint inhibitor Camrelizumab. Since our PICO did not differentiate between thermal ablation treatment alone or in combination with other treatments, we merged these two arms into a single group.

6.4 Conclusion

Fazit: niedrige bis sehr niedrige Vertrauenswürdigkeit der komparativen Evidenz für RFA, CYA & MWA

The current comparative evidence for thermal ablation interventions relative to surgery is limited to one RCT for RFA and two NRSIs, one for CYA and one for MWA. Recruitment to the RCT was stopped early due to a higher number of AEs in the intervention group. Overall, low to very low certainty evidence indicates that these three interventions have comparable OS, DFS and recurrence rates, albeit with a limited follow-up duration and low sample sizes.

niedrige bis sehr niedrige Vertrauenswürdigkeit der Evidenz der einarmigen Studien

Low to very low certainty evidence from single-arm trials indicates that thermal ablation interventions can generally be considered safe, with only mild to moderate AEs reported. Still, it is unclear whether outcomes in most included studies are due to the ablation interventions themselves or due to the often-conducted subsequent resection of the tumour.

7 Evidence-based conclusions

In Table 7-1 the scheme for evidence-based conclusion is displayed and the according choice is highlighted.

Table 7-1: Evidence based conclusions

	1	Strong evidence for added benefit in routine use.
	2a	Evidence indicates added benefit only in specific indications.
	2b	Less robust evidence indicating an added benefit in routine use or in specific indications
X	3	No evidence or inconclusive evidence available to demonstrate an added benefit of the intervention of interest.
	4	Strong evidence indicates that intervention is ineffective and or harmful.

Reasoning:

The current evidence is not sufficient to prove that thermal ablation interventions (cryoablation, microwave ablation, radiofrequency ablation, high-intensity ultrasound ablation or laser ablation) alone or in conjunction with standard care are as effective and equally safe or safer than surgery with or without standard care. New study results will potentially influence the effect estimates.

derzeit unzureichende Evidenz, um Effektivität und Sicherheit von Thermoablation im Vergleich zur Operation nachzuweisen

Based on one identified ongoing clinical trial of cryoablation compared to lumpectomy, and no ongoing trials for other thermal ablation interventions, a re-evaluation of thermal ablation interventions is not recommended before the year 2034.

Reevaluierung: frühestens 2034

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Cryoablation: Results from non-randomised studies of interventions

Author, year	Galati, 2024 [45]
Country	Italy
Sponsors	European Society of Radiology, European Institute for Biomedical Imaging Research, GE Healthcare
Intervention, Product	CYA, ■ ICEfx Cryoablation System and IceSpehere 1.5 (Boston Scientific, Marlborough, Massachusetts, USA)
Comparator	Surgery, standard surgery
Study design	NRSI, prospective, case-control, pilot
Primary study endpoint	■ Presence of necrosis in surgical specimens, ■ Rate of complete tumour ablation, ■ Patients' satisfaction, ■ Incidence and severity of complications
Guidance, n (%)	ultasound
Resection, n (%)	**Yes,** within 21 days from enrollment, ■ quadrantectomy: 10 (100) vs 9 (90) ■ MST: 0 (0) vs 1 (10)
(Neo)Adjuvant Therapy, n (%)	NR
Anesthesia during ablation, n/N (%)	local
Inclusion criteria	**Intervention:** ■ ≥ 18 years ■ solitary invasive BC (T1 N0) ≤2 cm ■ ≥ 1.5 cm tumour to skin surface distance and ≥2cm tumour edge to nipple distance ■ not eligible for neoadjuvant therapy **Control**: ■ ≥ 18 years ■ early-stage invasive BC (T1 N0) ≤2 cm ■ without a cryo-feasible cancer location
Exclusion criteria	■ pure DCIS lesions (microcalcifications only on mammogram) ■ Hx of previous BC ■ breast implants

Author, year	Galati, 2024 [45]
	■ C/I to use of contrast ■ non-suitability for cryoablation Tx ■ pregnancy or breastfeeding
Recruitment period	07.2022 - 01.2023
Number of patients	20 (10 vs 10)
Number of tumours	20 (10 vs 10)
Age of patients, mean/median±SD (range)	mean: 65 (47-80) vs 62 (39-84)
Sex, menopausal status	female: 10 vs 10, ■ menopausal: 9 (90) vs 6 (60) ■ regular menstrual cycle: 1 (10) vs 4 (40)
BC type, n (%)	**Histology** ■ No special type: 8 (80) vs 7 (70) ■ ILC: 2 (20) vs 1 (10) ■ Apocrine carcinoma: 0 (0) vs 1 (10) ■ Mucinous carcinoma: 0 (0) vs 1 (10) **Tumour grade** ■ G1: 1 (10) vs 2 (20) ■ G2: 8 (80) vs 4 (40) ■ G3: 1 (10) vs 4 (40)
Size of tumour (mm), mean/median±SD (range) / n (%)	mean: 9.9 (6-18) vs 10.5 (6-13)
Number of sessions in number of patients	N sessions per patient NR; Procedure time ca. 25 min, 2 freeze cycles (10/5/10 min)
Length of follow-up	Max. 21 days
Loss to follow-up, n (%)	0
Outcomes	
Efficacy	
Overall survival	**≤21 days**: 0 vs NR
Complete ablation, n (%)	**≤21 days:** 9 (90) vs NA
Determination of complete ablation	histologic
Residual tumour, n (%)	**≤21 days**: 1 (10) vs NA
Recurrence, n (%)	NR
Cosmetic results, n (%)	**Cosmetic satisfaction** (on a scale of 1-10): ■ 8: 5 (50) ■ 9: 2 (20) ■ 10: 3 (30)
Quality of life	NR
Safety	

Author, year	Galati, 2024 [45]
Adverse events (overall), n (%)	**Post procedure**: **minor complications**: 2 (20) vs 0 ■ small post-ablative hematoma (about 4 cm in size): 2 (20) vs 0 **Pain during cryoablation vs after surgery** (1-10)[a]: ■ 1: 2 (20) vs 0 ■ 2: 3 (30) vs 0 ■ 3: 3 (30) vs 4 (40) ■ 4: 1 (10) vs 0 ■ 5: 0 vs 1 (10) ■ 6: 0 vs 2 (20) ■ 7: 1 (10) vs 3 (30) median: 3 (mild pain) vs 5 (moderate pain) **1 week:** 0 vs 0 **Pain**: ■ 1: 2 (20) vs NR ■ 2: 8 (80) vs NR
Serious adverse events	0

Abbreviations: BC – breast cancer, C/I – contraindication, CYA – cryoablation, DCIS – ductal carcinoma in situ, Hx – history, ILC – invasive lobular carcinoma, MST – mastectomy, n – number, NR – not reported, NRSI – non-randomised study of intervention, SD – standard deviation, Tx – therapy

Comments:

[a] *Higher scores signify more pain.*

Table A-2: Cryoablation: Results from single-arm trials (1/3)

Author, year	Cazzato, 2015 [46]	Poplack, 2015 [51]	Simmons, 2016 [53]
Country	France	USA	USA
Sponsor	NR	Sanarus Medical, Norris Cotton Cancer Center at the Dartmouth Hitchcock Medical Center (grant No. CA23108)	National Cancer Institute (grant No. U10CA180821 and U10CA180882), Alliance for Clinical Trials in Oncology, Sanarus Technologies
Intervention, Product	RFA, IceSphere (Galil Medical Ltd., Israel), IceRod (Boston Scientific, Marlborough, Massachusetts, USA)	RFA, Visica (n = 15) or Visica 2 (n=5) treatment system (Sanarus Technologies Inc., Pleasanton, CA).	RFA, Visica 2TM Treatment System (Sanarus Technologies Inc., Pleasanton, CA)
Comparator	none	none	none
Study design	Single-arm, prospective, single-centre	Single-arm, prospective, multicenter	Single-arm, non-randomised, multicenter
Primary study endpoint	Rate of complete tumour ablation	NR	Rate of complete tumour ablation
Guidance, n (%)	ultrasound/computed tomography	ultrasound	NR
Resection, n (%)	**No**	**Yes,** CE-MRI 25–40 days after ablation, followed within 1–5 days by surgical resection, ■ Lumpectomy: 19 (95) ■ MST: 1 (5)	**Yes**, within 28 days after ablation. ■ Partial MST: 85 (98) ■ Full MST: 2 (2)
(Neo)Adjuvant Therapy, n (%)	■ neoadjuvant: 11 (47) ■ endocrine: 11 (47) ■ adjuvant: 5 (22) ■ endocrine: 5 (22)	■ neoadjuvant: 0 (0) (exclusion criteria) ■ adjuvant: NR	■ neoadjuvant: NR ■ adjuvant: 86 (100)
Anesthesia during ablation, n/N (%)	local: 18/23 (78.3) local + conscious sedation: 5/23 (21.7)	local	■ NR (described in protocol, which couldn't be located)
Inclusion criteria	unifocal BC ≤3.0 cm ■ tumour to skin surface, nipple and chest wall ≥0.5 cm ■ patients declining (1/23) or unsuitable for surgery (19/23)	unifocal IDC ≤1.5cm (with DCIS component ≤ 25%) ■ tumour to skin surface ≥0.5cm ■ enhancement on CE-MRI	unifocal IDC ≤2.0 cm <25% intraductal component ■ tumour enhancement visible on MRI
Exclusion criteria	multi-focal tumours ■ tumours undetectable with DCE-MRI ■ local/systemic infections and/or coagulopathies	planned neoadjuvant Tx ■ current use of immunosuppressive medications ■ breast implants ■ angiolymphatic invasion* * additional exclusion criterion added midway through the study.	lobular histology: 2 ■ lacking tumour enhancement: 1 ■ wrong MRI study: 1 ■ did not undergo cryablation: 2 ■ surgery instead: 1 ■ non credentialed surgeon: 1 ■ benign lesion: 1 ■ withdrew consent: 1 ■ probe failure: 1 ■ treatment prior study start: 1

Author, year	Cazzato, 2015 [46]	Poplack, 2015 [51]	Simmons, 2016 [53]
Recruitment period	01.2013 - 01.2015	NR	03.2009 - 06.2013
Number of patients	23	20	86
Number of tumours	23	20	87* *one patient had bilateral tumours
Age of patients, mean/median±SD (range)	median: 85 (56-96)	median: 61 (36-91)	mean: 61.1±9.3 (42-81) median: 62
Sex, menopausal status	female, postmenopausal	female, NR	female, NR
BC type, n (%)	**Histology** ■ IDC: 21 (91.3) ■ ILC: 2 (8.7) **Tumour grade** ■ Grade 1: 7 (30.4) ■ Grade 2: 10 (43.5) ■ Grade 3: 4 (17.4)	**Histology** ■ IDC: 10 (50) ■ IDC and ≤25% DCIS: 10 (50) ■ ER+, PR+, HER2−*: 17 (85) ■ ER+, PR−, HER2− : 2 (10) ■ ER+, PR+, HER2+ : 1 (5) *in the original paper the authors used the alternative name for the HER2 receptor - ERBB2, but we changed it to HER2 to improve understanding and readability	**Histology** ■ IDC: 86 (98.9) other: 1 (1.1) **Tumour grade** ■ G1: 30 (38.0) ■ G2: 35 (44.3) ■ G3: 14 (17.7) ■ unkwown: 8 **Receptor status** ■ HER2+: 11(12.6) ■ HER2-, HR+: 75 (86.2) ■ Triple negative: 1 (1.2)
Size of tumour (mm), mean/median±SD (range) / n (%)	median: 14 (5-28)	median: ■ mammo: 10 ■ MRI: 11 ■ US: 9	mean: ■ US: 10±4 (0-2) ■ mammo: 11±4 (0-19) median: ■ US: 10 ■ mammo: 11
Number of sessions in number of patients	freeze-thaw cycles in patiens: ■ 2: 10 (43%); (10/10/10) ■ 3: 13 (57%); (3/3/7/7/7)	1 session per patient, 2 freeze cycles, time dependent on tumour size and used system: **Viscia:** ■ <10 mm: 8/10/8 min ■ 10-15 mm: 10/10/10 min	NR *couldn't locate protocol

Author, year	Cazzato, 2015 [46]	Poplack, 2015 [51]	Simmons, 2016 [53]
		Viscia 2: ■ <10 mm: 6/10/6 min ■ 10-15 mm: 8/10/8 min	
Length of follow-up	3, 12, 18, 28 months median: 14.6 months	1 day 7-10 d 2 week CE-MRI was performed 25–40 days after ablation, followed within 1–5 days by surgical resection.	max 28 days
Loss to follow-up, n (%)	NR	0	0
Outcomes			
Efficacy			
Overall survival	**2 months**: 1 (4)* *death due to myocardial infarction, un related to intervention	**<2 months**: 0 (0)	**≤28 days**: 0
Complete ablation, n (%)	NR	**<1-2 months**: 17 (85)	**≤28 days:** 80 (92) including cancer tissue identified >2cm of ablation zone with necrosis of ablated cancer: 66 (76)
Determination of complete ablation	imaging	histologic	histologic
Residual tumour, n (%)	NR	**<1-2 months**: 3 (15)	**≤28 days**: 21 (24)
Recurrence, n (%)	**≤24 months**: 5 (22)	NR	NR
Cosmetic results, n/N (%)	NR	NR	NR
Quality of life	NR	NR	NR
Safety			
Adverse events (overall), n (%)	**Immediate complications**: 5 (22) ■ hematomas: 4 (17) ■ skin retraction: 1 (4) ■ skin burn: 1 (4) **3 months**: 1 (4) ■ skin retraction: 1 (4)	**1 day**: ■ Slight ecchymosis and swelling, no pain: 8 (40) ■ Minor ecchymosis, pain not requiring analgesics: 4 (20) ■ Moderate ecchymosis, swelling at cryoablation site, pain requiring over-the-counter analgesics: 8 (40) **7-10 days**: ■ Slight ecchymosis and swelling, no pain: 12 (60)	NR

Author, year	Cazzato, 2015 [46]	Poplack, 2015 [51]	Simmons, 2016 [53]
		■ Minor ecchymosis, pain not requiring analgesics: 6 (30) ■ Moderate ecchymosis, swelling at cryoablation site, pain requiring over-the-counter analgesics: 2 (10) **2 weeks**: ■ Slight ecchymosis and swelling, no pain: 5 (74) ■ Minor ecchymosis, pain not requiring analgesics: 4 (21) ■ Moderate ecchymosis, swelling at cryoablation site, pain requiring over-the-counter analgesics: 1 (5)	
Serious adverse events	0	NR	NR

Abbreviations: BC – breast cancer, CA – California, CE-MRI – contrast-enhanced magnetic resonance imaging; DCE-MRI – dynamic contrast-enhanced magnetic resonance imaging, DCIS – ductal carcinoma in situ, ER – estrogen receptor, G1, G2, G3 – tumor grades 1, 2, 3, HER2 – human epidermal growth factor receptor 2, HR – hormone receptor, IDC – invasive ductal carcinoma, ILC – invasive lobular carcinoma, MRI – magnetic resonance imaging, MST – mastectomy, n/N – number of cases / total cases, NR – not reported, PR – progesterone receptor, RFA – radiofrequency ablation, Tx – treatment, US – ultrasound

Table A-3: Cryoablation: Results from single-arm trials (2/3)

Author, year	Fine, 2021 [47]; Fine, 2024 [48]	Habrawi, 2021 [49]	Kwong, 2023 [50]
Country	USA	USA	China
Sponsor	IceCure Medical Ltd.	ASCO Endowment for Excellence in Women's Health, Sanarus Technologies, Inc.	Li Shu Pui Medical Foundation, the University of Hong Kong Li Ka Shing Faculty of Medicine, the Hong Kong SAR Government (grant No. 0617656), ICeCure Medical Ltd.
Intervention, Product	RFA, ■ ProSense Cryosurgical System (IceCure Medical Ltd, Caesarea, Israel)	RFA, ■ Visica® 2 Treatment System (Sanarus Technologies Inc., Pleasanton, CA)	RFA, ■ ProSense Cryoablation System (IceCure Medical, Caesarea, Israel)
Comparator	none	none	none
Study design	Single-arm, prospective, multicentre, single-arm, non-randomised	Single-arm, prospective, longitudal	Single-arm, prospective, single arm
Primary study end-point	■ Ipsilateral breast tumour recurrence at 5 years, as defined by biopsy	■ NR	■ Rate of complete tumour ablation
Guidance, n (%)	ultrasound	ultrasound	ultrasound
Resection, n (%)	**No**	**No**	**Yes**, 8 weeks after ablation, ■ lumpectomy: 15 (8)
(Neo)Adjuvant Therapy, n (%)	■ **neoadjuvant:** 0 (0) (exclusion criteria) ■ **adjuvant**: 153 (79)	■ **neoadjuvant:** NR ■ **adjuvant:** 12 (100)	NR

Author, year	Fine, 2021 [47]; Fine, 2024 [48]	Habrawi, 2021 [49]	Kwong, 2023 [50]
	▪ endocrine only: 124 (64) ▪ whole-breast radiation only: 3 (2) ▪ endocrine + radiation: 25 (13) ▪ endocrine + radiation + chemo: 1 (1)	▪ radiation: 1 (8) ▪ endocrine: 12 (100)	
Anesthesia during ablation, n/N (%)	NR	NR	general
Inclusion criteria	▪ female, ≥60 years ▪ unifocal IDC ≤1.5 cm ▪ ER+, PR+, HER2- ▪ low to intermediate histology grade (B2) ▪ clinically confirmed negative axillary status (US and palpation)	▪ patients ≥50 years ▪ unifocal IDC ≤1.5 cm (without extensive in situ component visible on US) ▪ ER+, PR+, HER2-	▪ solitary T1 BC ▪ tumour to skin surface distance ≥0.5 cm ▪ any immunohistotype
Exclusion criteria	▪ multifocal and/or multicentric tumours ▪ ≥25% intraductal component ▪ prior surgical biopsy ▪ neoadjuvant Tx ▪ coagulopathy or thrombocytopenia ▪ non-suitability for cryoablation Tx	NR	▪ invasive lobular carcinoma ▪ lobular carcinoma in situ ▪ retro areolar tumour ▪ pregnancy or breastfeeding
Recruitment period	10.2014 - 02.2019	01.2017 - 02.2020	2018 - NR
Number of patients	194	12	15
Number of tumours	194	12	15
Age of patients, mean/median±SD (range)	mean: 74.9±6.9 (55-94)	mean: 74.1±10.3 (55-93) median: 75	median: 53 (40-67)
Sex, menopausal status	female, NR	female, NR	NR, NR
BC type, n (%)	**Tumour grade** ▪ Grade 1: 98 (51) ▪ Grade 2: 96 (49) **Receptor status** ▪ ER+: 194 (100) ▪ PR+: 184 (92.8) ▪ HER2–: 194 (100)	**TNM Staging** ▪ Stage 1A: 7 (58.3) ▪ Stage 2B: 4 (33.3)	**Histology** ▪ DCIS: 5 (33.3) ▪ IDC: 10 (66.6) **Receptor status**[a] ▪ HR+, HER2-: 3 (30) ▪ HR+, HER2+: 2 (20) ▪ HER2 enriched: 3 (30) ▪ Triple negative: 2 (20) [a]receptor status only reported on 10 IDC patients
Size of tumour (mm),	mean: US:	mean: 9.9±2.9 (5-15) median: 10	median: ▪ MRI: 16 (10-20)

Author, year	Fine, 2021 [47]; Fine, 2024 [48]	Habrawi, 2021 [49]	Kwong, 2023 [50]
mean/median±SD (range) / n (%)	■ Sagittal: 8.0±2.9 (2.5-14.9) ■ Transverse: 7.4±2.7 (2.8–14) ■ Anterior-posterier: 6.3±2.6 (1-14) median: US: ■ Sagittal: 8.1 ■ Transverse: 7.0 ■ Anterior-Posterior: 6.3		■ US: 13 (8.6-18)
Number of sessions in number of patients	1 session per patient, 2 freeze cycles, (9/8/9)	1 session per patient, freeze cycles depending on tumour size: ■ <10 mm: 6/10/6 min ■ 10-20 mm: 8/10/8 min	Median procedure time: 75 (25-101) min, freeze-thaw cycles in patients: ■ 2: 10 (67) ■ ≥3: 5 (33)
Length of follow-up	6, 12, 24, 36, 48, 60 months **interim**: mean: 34.8±18 months **main:** mean: 54±13.07 months	24-48 hours, 2 weeks, 6, 12, 18, 24 months	6 weeks (MRI scans), 8 weeks (lumpectomy procedure)
Loss to follow-up, n (%)	3 years (interim): 18 (9) 5 years: 32 (16)	6 months: 1 (8) 12 months: 4 (33) 24 months: 8 (67)	0
Outcomes			
Efficacy			
Mortality	**3 years**: ■ unrelated to BC*: 10 (5) * reasons unrelated to the device, procedure, or BC **5 years**: 21 (11) ■ distant metastasis: 2 (1) ■ unknown reasons: 3 (2) ■ unrelated to BC*: 16 (8) *due to heart failure, respiratory failure, myocardial infarction, cardiac arrest, non-traumatic intracerebral hemorrhage, and renal failure leading to multiorgan failure ■ BC survival rate: 96.7 (95% CI 92.2-98.6%) ■ Overall survival rate: 88.6% (82.9-92.5%)	**6 months**: 0 (0) **12 months**: 0 (0) **24 months:** 0 (0)	**8 weeks**: 0 (0)
Complete ablation, n (%)	NR	**6 months**: 11 /11 **12 months**: 8/8 **24 months**: 4/4	**8 weeks:** 8 (53)

Author, year	Fine, 2021 [47]; Fine, 2024 [48]	Habrawi, 2021 [49]	Kwong, 2023 [50]
Determination of complete ablation	NA	imaging/histologic* *mammo+US+MRI and 5 /patiens had biopsy	histologic
Residual tumour, n (%)	NR	**6 months**: 0 (0) **12 months**: 0 (0) **24 months:** 0 (0)	**8 weeks**: 7 (47)
Recurrence, n (%)	**mean fu: 34.83±17.96 months:** (0.07–67.55): ■ local recurrence: 4 (2.06, 95% CI, 0.56–5.19) **36 months**: ■ local recurrence: 1 (0.6, 95% CI 0.1–3.9) **48 months**: ■ local recurrence: 3 (1.7, 95% CI 0.6–5.3) **mean fu: 54.16±13.07 months**: ■ local recurrence: 7 (3.61) **5 years (60 months):** ■ local recurrence: 8 (4.3, 95% CI 2.1–8.7)	**6 months**: 0 (0) **12 months**: 0 (0) **24 months**: 0 (0)	NR
Cosmetic results, n/N (%)	**Cosmetic satisfaction** (on a scale of 1-5, but given as % of follow-up patients/physicians who were satisfied with the results) **6 months:** ■ patients (n=177/194): 99.3% ■ physicians (n=176/194*): 98,6% ■ *patients/procedures **3 years**: ■ patients (n=NR): 95% ■ physicians (n=NR): 98% **5 years:** ■ patients (n=111/194): 100% ■ physicians (n=102/194): 100%	No cosmetic deficits in any patient	NR
Quality of life	NR	NR	NR
Safety			
Adverse events (overall), n (%)	**3 years (interim):** 43 AEs in 23 (12) patients ■ Mild: 38 ■ Moderate: 5 ■ Severe: 0	**Post procedure:** **minor complication**: 10 (83) ■ bruising: 5 (42) ■ edema: 2 (16)	None

Author, year	Fine, 2021 [47]; Fine, 2024 [48]	Habrawi, 2021 [49]	Kwong, 2023 [50]
	5 years:187 AEs in 97 (50) patients **Mild**: 165 ■ Bruising: 48 (25.7) ■ Pain: 39 (20.9) ■ Edema: 36 (19.3) ■ Hematoma: 8 (4.3) ■ Tenderness: 8 (4.3) ■ Pruritus and rash: 4 (2.1) ■ Erythema multiforme: 3 (1.6) ■ Injection site reaction: 3 (1.6) ■ Burn: 3 (1.6) ■ Fatigue: 2 (1.1) ■ Drainage: 2 (1.1) ■ Flushing: 1 (0.5) ■ Skin infection: 1 (0.5) ■ Breast twitches: 1 (0.5) ■ Heat sensation: 1 (0.5) ■ Breast warm to the touch: 1 (0.5) ■ Tethering: 1 (0.5) ■ Dimpling: 1 (0.5) ■ Hemorrhage: 1 (0.5) ■ Induration at cryo site: 1 (0.5) **Moderate:** 18 ■ Bruising: 10 (5.3) ■ Edema: 3 (1.6) ■ Burn: 2 (1.1) ■ Pain: 2 (1.1) ■ Hematoma: 1 (0.5) **Severe:** 4 ■ Bruising: 4 (2.1)	■ mild to moderate pain: 3 (12) **2 weeks**: 0	
Serious adverse events	0	0	NR

Abbreviations: AE – adverse event, BC – breast cancer, CI – confidence interval, ER – oestrogen receptor, fu – follow-up, HER2 – human epidermal growth factor receptor 2, IDC – invasive ductal carcinoma, MRI – magnetic resonance imaging, n – number, NA – not applicable, NR – not reported, PR – progesterone receptor, RFA – radiofrequency ablation, SD – standard deviation, US – ultrasound, USA – United States of America

Table A-4: Cryoablation: Results from single-arm trials (3/3)

Author, year	Khan, 2023 [55]	RocaNavarro, 2024 [52]	Kawamoto, 2024 [54]
Country	USA	Spain	Japan
Sponsor	ASCO Equipment Endowment for Excellence in Women's Health, Sanarus technologies Inc. and ICECure Medical (donation of probes)	La Paz University Hospital	None
Intervention, Product	RFA, ■ Visica 2 treatment system (Sanarus Technologies, Inc. Pleasanton, CA, USA, now acquired by ICECure Medical, Caesarea, Israel)	RFA, ■ ICEfx Cryoablation System (Boston Scientific, Marlborough, Massachusetts, USA), ■ Needles: IceSphere 17G (n=40) or IcePearl 14G (n=20)	RFA, ■ ProSense Cryosurgical System (IceCure Medical Ltd, Caesarea, Israel)
Comparator	none	none	none
Study design	Single-arm, prospective, single centre, longitudinal	Single-arm, prospective, observational	Single-arm, single centre
Primary study endpoint	NR	Presence of residual invasive cancer	Cryolesion due to ablation procedure
Guidance, n (%)	ultrasound	ultrasound	ultrasound
Resection, n (%)	**No**	**Yes,** after mean 21.8±13.8 (6-78) days after ablation, BCS: 60 (100)	**No**
(Neo)Adjuvant Therapy, n (%)	■ **aeoadjuvant:** NR ■ **adjuvant:** ■ endocrine: 31 (97) ■ radiation: 6 (19)	NR	■ **neoadjuvant**: NR ■ **adjuvant:** 18 (100) ■ radiation: 18 (100) ■ endocrine: 18 (100)
Anesthesia during ablation, n/N (%)	local	local	local
Inclusion criteria	■ ≥50 years ■ unifocal IDC ≤1.5 cm (without extensive in situ components) ■ ER+, PR+, HER2-	■ ≥18 years ■ IDC ≤2 cm ■ ER+, HER2- ■ radiologically confirmed negative axillary status (US) ■ suitable for BCS, with no requirement for primary systemic therapy	■ female, 20-85 years ■ unifocal IDC ≤1.5 cm ■ ER+, PR+, HER2-, ≤20% Ki67+ ■ negative SLN biopsy ■ ECOG performance status 0/1
Exclusion criteria	NR	■ Tumours ≥2.0 cm with extensive intraductal component ■ HER2 + luminal tumours ■ axillary involvement ■ distant metastasis ■ pregnancy or breastfeeding	■ invasive lobular carcinoma ■ invasive microcapillary carcinoma ■ intraductal lesions ■ tumour to skin surface and pectoralis <0.5 cm
Recruitment period	01.2017 - 05.2023	03.2021 - 06.2023	NR

Author, year	Khan, 2023 [55]	RocaNavarro, 2024 [52]	Kawamoto, 2024 [54]
Number of patients	32	59	18
Number of tumours	33* *one patient had bilateral tumours	60* *one patient had 2 tumours ablated in the same breast	18
Age of patients, mean/median±SD (range)	mean: 71±10.5 (50-91) median: 70	mean: 63±8 (31-81)	mean: 59±9.0 (43-72) median: 60.3
Sex, menopausal status	female, NR	female, NR	female, NR
BC type, n (%)	**TNM Staging** ■ Stage T1: 34 (100) ■ 1A: 9 (27.3) ■ 1B: 13 (39.4) ■ 1C: 11 (33.3) **Tumour grade** ■ Grade 1/2: 34 (100)	**Tumour grade** ■ G1: 23 (38) ■ G2: 37 (62) **Rezeptor status** ■ ER+: 60 (100) ■ PR+: 53 (88) ■ HER2-: 60 (100)	**Histology** ■ IDC: 17 (94.4) ■ Mucinous carcinoma: 1 (5.6) **Receptor status** ■ ER+: 18 (100) ■ PR+: 17 (94.4) ■ HER2-: 18 (100)
Size of tumour (mm), mean/median±SD (range) / n (%)	mean: ■ US: 8.7±3.5 (4.0-15) median: ■ US: 8.0	mean: ■ US: 10.1±3.6 (4-20)	mean: ■ MRI: 9.8±2.3 (6-14.5) median: ■ MRI: 9.9
Number of sessions in number of patients	NR	N session per patient NR, 2 freeze-cycles: 10/10/10 min	N session per patient NR
Length of follow-up	6, 12, 18, 24 months ■ <6 months: 3 (9.4) ■ 6-12 months: 2 (6.3) ■ 12-24 months: 8 (25.0) ■ ≥24 months: 20 (62.5)	mean: 21.8±13.8 (6-78) days	1, 6, 12, 24, 36, 60 months mean: 34.5±16.2 (18-68) median: 44.3
Loss to follow-up, n (%)	NR	0	0
Outcomes			
Efficacy			
Mortality	**1 year:** 1 (3)* *death due to unrelated causes	NR	mean FU 34.5 months: 0

Author, year	Khan, 2023 [55]	RocaNavarro, 2024 [52]	Kawamoto, 2024 [54]
Complete ablation, n (%)	NR	mean fu: 55 (92)	NR
Determination of complete ablation	NA	histologic	Imaging
Residual tumour, n (%)	NR	mean fu: 5/60	0 (0)
Recurrence, n (%)	**18 months**: ■ local recurrence: 0 (0) ■ distant metastasis: 1 (3)	NR	**5 years**: ■ local recurrence: 0 (0) ■ distant metastasis: 0 (0)
Cosmetic results, n/N (%)	NR	NR	Visual assessment (by Moire topography): excellent results with no nipple positions distortion, breast deformity or assymetry observed (no numerical results)
Quality of life	NR	NR	**EQ-VAS** (mean baseline: 84) **36m**: 85 **60m**: 82.5 **EQ-5D-5L** (mean baseline: 0.9): **6m**: 0.89 **12m**: 0.87 **24m**: 0.94 **36m**: 0.94 **60m**: 0.93
Safety			
Adverse events (overall), n (%)	NR	**Post procedure**: **mild AEs**: 4 (7)* ■ mild discomfort: 6 (10) ■ moderate to severe pain: 1 (2) ■ small (5 mm) skin vesicle: 1 (2) *authors did not define what the mild AEs were and reported 8 AEs in text	**1 week:** **Overall:** 1 (5.5) ■ skin redness grade 1 (CTCAE classification): 1 (5.5) *varying degrees of burns in the pectoralis muscle were observed by MRI 1 month post intervention in all patients but were symptomless and resolved after 6 months
Serious adverse events	NR	NR	0

Abbreviations: AE – adverse event, ASCO – American Society of Clinical Oncology, BC – breast cancer, BCS – breast-conserving surgery, CTCAE – common terminology criteria for adverse events, ECOG – Eastern Cooperative Oncology Group, ER – estrogen receptor, EQ-5D-5L – euroqol 5-dimension 5-level questionnaire, EQ-VAS – euroqol visual analogue scale, FU – follow-up, G1, G2, G3 – tumor grades 1, 2, 3, HER2 – human epidermal growth factor receptor 2, IDC – invasive ductal carcinoma, MRI – magnetic resonance imaging, NA – not applicable, NR – not reported, PR – progesterone receptor, RFA – radiofrequency ablation, SD – standard deviation, SLN – sentinel lymph node, TNM – tumor-node-metastasis staging system, Tx – treatment, US – ultrasound

Table A-5: Microwave ablation: Results from non-randomised studies of interventions

Author, year	Zhong, 2023 [56]
Country	China
Sponsor	National Natural Science Foundation of China (grant No. 81771953 and 82172683), the Natural Science Foundation of Jiangsu Province (grant No. BK20180108), the Priority Academic Program Development of Jiangsu Higher Education Institutions
Intervention, Product	MWA, ■ Nanjing Yigao Microwave Electric Insitute, China
Comparator	Surgery, MST or BCS and axillary lymph node dissection or SLNB with adjuvant therapy
Study design	Propensity score matched NRSI, prospective, non-randomised, multicentre controlled
Primary study endpoint	■ DFS, ■ OS, ■ LOS
Guidance, n (%)	ultrasound
Resection, n (%)	No
(Neo)Adjuvant Therapy, n (%)	■ **neoadjuvant**: 0 (0) (exclusion criteria) ■ **adjuvant**: 33 (100) vs 99 (100) ■ endocrine: 33 (100) vs 99 (100) ■ radiation: 0 (0) vs 8 (8), p=0.20 ■ chemo: 0 (0) vs 8 (8), p=0.20
Anesthesia during ablation, n/N (%)	local
Inclusion criteria	■ female, >70 years ■ single invasive BC ≤3.0 cm ■ HR+/- ■ clinically negative axillary LN (US) ■ tumour outside the nipple/areola area with any distance to the skin and chest wall but not infiltrated to skin and pectoralis muscle
Exclusion criteria	■ previous surgery, ■ radiotherapy or systemic antitumour Tx ■ distant metastasis
Recruitment period	01.2016 - 07.2021
Number of patients	132 (33 vs 99)
Number of tumours	132 (33 vs 99)
Age of patients, mean/median±SD (range)	mean: 77.9±7.6 (70-94) vs 77.4±5.5 (70-92)
Sex, menopausal status	female, postmenopausal
BC type, n (%)	**Histology**, p=0.147 ■ IDC: 31 (94) vs 80 (81) ■ ILC: 1 (3) vs 4 (4) ■ other: 1 (3) vs 15 (15)

Author, year	Zhong, 2023 [56]
	ER, p=1.000 ■ <90%: 2 (6.1) vs 8 (8.1) ■ ≥90%: 31 (93.9) vs 91 (91.9) **PR,** p=0.619 ■ <20%: 8 (24.2) vs 19 (19.2) ■ ≥20%: 25 (75.8) vs 80 (80.8) **Ki67 status**, p=0.681 ■ ≤14%: 13 (39.4) vs 35 (35.4) ■ >14%: 20 (60.6) vs 64 (64.6)
Size of tumour (mm), mean/median±SD (range) / n (%)	■ <1cm: 2 vs 7, ■ 1-2cm: 18 vs 5, ■ >2cm: 13 vs 35, p=0.948 **Intervention group** (mm): mean: 18.9±5.9 (7-30) median: 18
Number of sessions in number of patients	Sessions per patients: ■ 1: 32 (97) ■ 2: 1 (3)* *one week after first ablation, due to residual tumour on US mean ablation time: 2.64±0.59 (1.67-4.5) min
Length of follow-up	median: 31 (2-74) months
Loss to follow-up, n (%)	0
Outcomes	
Efficacy	
Mortality	**OS median fu**: ■ MWA: 0/33 died ■ Control: 1/99 died HR: 0.537 95%CI: 0.089-3.325, p=0.49 **OS rate 1 year**: ■ MWA: 97% ■ Control: 100% **OS rate 3 year**:

Author, year	Zhong, 2023 [56]
	■ MWA: 92.6% ■ Control: 96.1%
Complete ablation, n (%)	**1 week:** 32 (97) **1 month:** 33 (100) (95% CI, 89.4-100%)
Determination of complete ablation	imaging
Residual tumour, n (%)	**1 week**: 1 (3)* vs NR **1 month:** 0 vs NR *patient received second ablation
Recurrence, n (%)	**Overall tumour progression, median fu**: 1 (3) vs 3 (3) HR: 0.536; 95%,CI 0.128-2.249 p=0.38 ■ Local recurrence: 1 (3) vs 1 (1) ■ Distant metastasis: 0 (0) vs 2 (2)
Cosmetic results, n/N (%)	NR
Quality of life	NR
Safety	
Adverse events (overall), n (%)	0 vs NR
Serious adverse events	0 vs NR

Abbreviations: AE – adverse event, BC – breast cancer, BCS – breast-conserving surgery, CI – confidence interval, DFS – disease-free survival, ER – estrogen receptor, FU – follow-up, HR – hazard ratio, HR+/- – hormone receptor positive/negative, IDC – invasive ductal carcinoma, ILC – invasive lobular carcinoma, Ki67 – proliferation marker Ki-67, LN – lymph node, LOS – length of stay, MWA – microwave ablation, MST – mastectomy, NRSI – non-randomized study of interventions, NR – not reported, OS – overall survival, PR – progesterone receptor, SD – standard deviation, SLNB – sentinel lymph node biopsy, Tx – treatment, US – ultrasound

Table A-6: Microwave ablation: Results from single-arm trials

Author, year	Ji, 2024 [59]	Zhou, 2021 [58]	Pan, 2024 [57]
Country	China	China	China
Sponsor	National Natural Science Foundation of China (grant No.12090024, 81972872), Science and Technology Innovation Project of Shanghai Science and Technology Commission (grant No.17441900700)	National Natural Science Foundation of China (grant No. 81771953), the Six Kinds of Outstanding Talent Foundation of Jiangsu Province (garnt No. WSW-014), the Natural Science Foundation of Jiangsu Province (grant No. BK20180108), the Priority Academic Program Development of Jiangsu higher Education Institutions	Natural Science Foundation of Jiangsu Province, the Jiangsu Province Capability Improvement Project, the Jiangsu Province Excellent Postdoctoral Program, Jiangsu Provincial Science and Technology Department, Jiangsu Provincial Science and Technology Department, Jiangsu Postgraduate Practice and Innovation Plan, Priority Academic Program Development of Jiangsu HIgher Education Institutions
Intervention, Product	MWA,	MWA,	MWA,

Author, year	Ji, 2024 [59]	Zhou, 2021 [58]	Pan, 2024 [57]
	■ Microwave probe: Vision China Medical Devices R&Dm, Najing, China; ■ MR-guideded PMC: DynaCAD Version 2.0 (Invivo Corporation, FL, USA)	■ Nanjing Yigao Microwave Electric Institute, China	■ Nanjing Yigao Microwave Electric Institute, China
Comparator	Single-arm, prospective, single centre, observational	Single-arm, prospective, observational, single arm, multicentre	Single-arm, RCT, single centre, open label, three arms - Cohort
Study design	Treatment efficacy	Rate of complete tumour ablation, (secondary: MWA-induced immune response 1 week after ablation)	Treatment feasibility and safety (secondary: complete ablation rate)
Primary study end-point	MRI	US	US *Based on information that they followed protocol of their centre (Zhong, 2023)
Guidance, n (%)	**Yes**, immediately after ablation, MST: 26 (100)	Yes, 1 week after ablation, surgery: 20 (57) declined surgery/unsuitable for surgery after ablation: 15 (43)	Yes, 7-10 days after ablation, MST: 16 (40) BCS: 23 (57.5)
Resection, n (%)	NR	■ neoadjuvant: NR ■ adjuvant: ■ 15 patients who underwent MWA without surgery received: ■ endocrine: 14 (93) ■ anti-HER2 treatment: 1 (7) ■ 20 patients with MWA + surgery: NR	■ neoadjuvant: 1 (5) ■ adjuvant: NR
(Neo)Adjuvant Therapy, n (%)	local	local	local *based on information that they followed the protocol of their centre (Zhong, 2023)
Anesthesia during ablation, n/N (%)	none	NA	none
Inclusion criteria	■ unifocal BC ≤2.0 cm ■ tumour to skin surface and pectoralis ≥1.0 cm ■ radiologically confirmed negative axillary status (US) and free from distant metastasis (CT staging)	■ solitary invasive BC ≤3.0 cm (without extensive intraductal component) ■ no infiltration of skin or pectoralis muscle	■ ≥18 years ■ invasive solitary BC ≤3.0 cm ■ no infiltration of the skin and pectoralis muscle ■ no systemic therapy ■ adequate organ and bone marrow function
Exclusion criteria	■ multifocal lesions ■ preference to undergo BCS ■ pregnancy or breastfeeding	NR	■ inflammatory BC ■ prior radiotherapy or use of other ■ immunosuppressive agents ■ Hx of autoimmune disease ■ recent vaccination
Recruitment period	05.2018 - 12.2019	07.2016 - 06.2019	03.2021 - 08.2022

Author, year	Ji, 2024 [59]	Zhou, 2021 [58]	Pan, 2024 [57]
Number of patients	26	35	40 (20, 20)
Number of tumours	26	35	40 (20, 20)
Age of patients, mean/median±SD (range)	mean: 52.0±12.2 (31–75)	median: 59 (38-87)	mean: **MWA:** 52.6 (37-65) **MWA+cam**: 50.5 (32-64)
Sex, menopausal status	female, NR	female, NR	female, NR
BC type, n (%)	**Histology** IDC: 20 (77) Invasive lobular carcinoma: 1 (3.8) Solid papillary carcinoma: 1 (3.8) Mucinous carcinoma: 2 (7.7) DCIS: 2 (7.7) **Receptor status** ER+, PR+/HER2-: 12 (46.2) ER+, HER2- : 6 (23.1) ER+, HER2+: 5 (19.2) HER2 enriched: 1 (3.8) Triple negative: 2 (7.7)	**Receptor status** HR+, HER2-: 20 (57) HER2+: 7 (20) Triple negative: 8 (23) **TNM staging** T1: 20 (57) T2: 15 (43) N0: 29 (83) N1: 4 (11) N2: 2 (6)	**Receptor status** HR+, HER2-: 25 (62.5) HER2+: 8 (20) Triple negative: 7 (17.5)
Size of tumour (mm), mean/median±SD (range) / n (%)	mean: MRI: long axis: 14.88±2.55 (11–19) short axis: 12.19±3.25 (5–19)	**MWA:** 18.8 **MWA+surgery:** 19.6 T1: 20 (57.1) T2: 15 (42.9)	US ≤20 mm: 29 (72.5) >20 mm: 11 (27.5)
Number of sessions in number of patients	1 session per patient, mean ablation time: 4.2±0.5 (3.3–5.2) min mean procedure time: 104.231±13.468 (90–130) min Prolonged ablation: 14 (54) Antenna repositioned: 1 (4)	mean treatment time: 2.5 (2-5) min	NR
Length of follow-up	NR (reported outcomes immediately post ablation)	median: 36 (13–47) months	7-10 days
Loss to follow-up, n (%)	NA	0	0
Outcomes			
Efficacy			
Mortality	0	0	0

Author, year	Ji, 2024 [59]	Zhou, 2021 [58]	Pan, 2024 [57]
Complete ablation, n (%)	**Directly after procedure:** 26 (100)	**Total:** 32 (91.4) **MWA:** 15/15 (100) **MWA+surgery:** 17/20 (85)	**Total:** 34/37* (91.9) (95%CI: 78.1-98.3) **MWA:** 18/19 (94.7) **MWA+cam**: 16/18 (8.8) *reasons for not being able to assess whether complete ablation had been achieved included preoperative treatment (n = 1) and absence of intraoperative specimen analysis (n = 2)
Determination of complete ablation	histologic	**MWA :** imaging-based **MWA+surgery:** histologic	histological
Residual tumour, n (%)	0 (0)	**Total:** 3 (9) **MWA:** 0 (0) **MWA+surgery**: 3 (15)	**Total**: 3/37* (8.1) **MWA:** 1/19 (5.2) **MWA+cam:** 2/18 (1.1) *reasons for not being able to assess whether complete ablation had been achieved included preoperative treatment (n = 1) and absence of intraoperative specimen analysis (n = 2)
Recurrence, n (%)	NR	Local recurrence: **median fu: 13-47m** **MWA:** 0 (0) **MWA+surgery**: NR	NR
Cosmetic results, n/N (%)	**Cometic satisfaction**: patients satisfied: 26 (100)	NR	NR
Quality of life	NR	NR	NR
Safety			
Adverse events (overall), n (%)	**During procedure:** ■ slight pain requiring administration of lidocaine mixed with saline: 3 (12) ■ subtle heat/swelling: 11 (42) **Post procedure:** ■ moderate pain: 1 (4) ■ Postoperative oozing/other complication: 0 ■ induration due to swelling and fibrosis around ablation area: 16 (62)	**During procedure:** ■ 35 (100) showed local swelling at the treatment site about 2–3 days after ablation which then disappeared in 1 week ■ 2 (5.7) suffered moderate pain in the procedure of ablation, and the prescheduled ablation was completed after additional local anaesthesia.	**MWA-related AEs** **Total** (n=40): ■ pain during MWA: 7 (17.5) ■ local skin burn: 4 (10) ■ local skin necrosis: 1 (2.5) ■ poor incision healing after surgery: 2 (5) **Grade 1**: ■ pain during MWA: 1 (2.5) ■ Local skin burn: 4 (10) **Grade 2**: ■ pain during MWA: 6 (15) ■ local skin necrosis: 1 (2.5)

Author, year	Ji, 2024 [59]	Zhou, 2021 [58]	Pan, 2024 [57]
			■ poor incision healing after surgery: 2 (5)
Serious adverse events	0	0	0

Abbreviations: AE – adverse event, BC – breast cancer, BCS – breast-conserving surgery, CAM – complementary and alternative medicine, CI – confidence interval, DCIS – ductal carcinoma in situ, ER – estrogen receptor, FU – follow-up, HER2 – human epidermal growth factor receptor 2, HR – hazard ratio / hormone receptor, Hx – history, IDC – invasive ductal carcinoma, ILC – invasive lobular carcinoma, MWA – microwave ablation, MST – mastectomy, MRI – magnetic resonance imaging, NA – not applicable, NR – not reported, PR – progesterone receptor, RCT – randomized controlled trial, SD – standard deviation, TNM – tumor-node-metastasis staging, Tx – treatment, US – ultrasound

Table A-7: Radiofrequency ablation: Results from randomised controlled trials

Author, year	Garcia-Tejedor, 2018 [60]
Country	Spain
Sponsor	NR
Intervention, Product	RFA, ■ Covidien (Tyco Healthcare Group, Bolder, USA)
Comparator	Surgery, lumpectomy
Study design	phase II RCT, prospective, single centre, open label
Primary study endpoint	Intraoperative free margins (distance between the tumour and the margin in order to indicate if extensions are mandatory)
Guidance, n (%)	US
Resection, n (%)	Yes, immediately after ablation, ■ lumpectomy: 20 (100) vs 20 (100)
(Neo)Adjuvant Therapy, n (%)	■ **Neoadjuvant:** 0 (0) vs 0 (0) (exclusion criteria) ■ **Adjuvant:** ■ Endocrine: 19 (95) vs 18 (90), p=0.99 ■ Chemo: 8 (40) vs 5 (25), p=0.31 ■ Partial breast irradation: 3 (15) vs 9 (45), **p=0.038** ■ Lymph node irradiation: 3 (15) vs 1 (5), p=0.61
Anesthesia during ablation, n/N (%)	general
Inclusion criteria	■ female, >40 years ■ IDC ≤2.0 cm ■ ≤20% intraductal component ■ tumour to skin and chest wall surface ≥1.0 cm
Exclusion criteria	■ male gender ■ <40 years

Author, year	Garcia-Tejedor, 2018 [60]
	■ multifocal tumours ■ extensive intraductal component neoadjuvant Tx ■ previous surgery or radiation of the ipsilateral breast ■ pregnancy or breast feeding
Recruitment period	09.2013 - 02.2017
Number of patients	40 (20 vs 20)
Number of tumours	40 (20 vs 20)
Age of patients, mean/median±SD (range)	overall: 64 (46-86) mean: 64 vs 64 median: 64 vs 64
Sex, menopausal status, n (%)	female: 20 vs 20 ■ postmenopausal: 18/20 (90) vs 18/20 (90) ■ premenopausal: 2/20 (10) vs 2/20 (10)
BC type, n (%)	**Tumour grade** ■ G1: 10 (50) vs 11 (55) ■ G2: 7 (35) vs 5 (25) ■ G3: 3 (15) vs 4 (20) **Receptor status** ■ ER+/PR+: 11 (55) vs 11 (55) ■ HER2-: 7 (35) vs 6 (30) ■ HER2+: 1 (5) vs 1 (5) ■ HER2 enriched: 1 (5) vs 1 (5) ■ Triple negative: 0 (0) vs 1 (5)
Size of tumour (mm), mean/median±SD (range) / n (%)	median: ■ radio: 13 vs 10.5, p=0.33 ■ pathology: 11.5 (5-20) vs 10.5 (6-16), p=0.07
Number of sessions in number of patients	1 session per patient, 8-10 min
Length of follow-up	immediately after surgery, 15 days, 6, 12, 18 months, 2 years median: 26.3 vs 23.7 months, p=0.58
Loss to follow-up, n (%)	0 (0) vs 0 (0)
Outcomes	
Efficacy	
Mortality	median FU of 25 months (range 1-83): 0/20 (0) vs 0/20 (0)
Complete ablation, n (%)	RFA: 20 (100)
Determination of complete ablation	histologic
Residual tumour, n (%)	NR
Recurrence, n (%)	**after median FU of 25 months** (range 1-83):

Author, year	Garcia-Tejedor, 2018 [60]
	■ local recurrence: 0 vs 0 ■ distant metastasis: 0 vs 0
Cosmetic results, n/N (%)	Cosmetic satisfaction: Good or very good: 17 (85) vs 17 (85), p=0.56
Quality of life	NR
Safety	
Adverse events (overall), n (%)	**Local adverse effects after surgery**: 8 (40) vs 1 (5), **p<0.01** ■ Breast inflammation: 5 (25) vs 1 (5), p=0.18 ■ Breast infection**:** 3 (15) vs 0 (0), p=0.23 * Recruitment was stopped with 20 participants in each group after the pre planned interim analysis because of the higher amount of local adverse effects observed in the RFA arm.
Serious adverse events	NR

Abbreviations: BC – breast cancer, ER – estrogen receptor, FU – follow-up, G1, G2, G3 – tumor grades 1, 2, 3, HER2 – human epidermal growth factor receptor 2, IDC – invasive ductal carcinoma, NR – not reported, PR – progesterone receptor, RCT – randomized controlled trial, RFA – radiofrequency ablation, Tx – treatment, US – ultrasound

Table A-8: Radiofrequencyablation: Results from single-arm trials

Author, year	Schassburger, 2014 [61]
Country	Sweden
Sponsor	Swedish BC Association, Capio Research Foundation, AFA Insurance, NeoDynamics AB, Bracco Diagnostics
Intervention, Product	RFA, ■ Neodynamics, AB, Sweden
Comparator	none
Study design	Single-arm
Primary study endpoint	■ Treatment efficacy and safety
Guidance, n (%)	Ultasound
Resection, n (%)	■ Yes, median days after ablation: 14.5 (6-22), BCS: 17 (94) MST: 1 (6)
(Neo)Adjuvant Therapy, n (%)	■ neoadjuvant: NR ■ adjuvant: 18 (100) ■ radiation: 17 (94) ■ endocrine: 18 (100)
Anesthesia during ablation, n/N (%)	■ local: 18/18 (100) ■ addtional light sedation: 2/18 (11)

Author, year	Schassburger, 2014 [61]
Inclusion criteria	■ unifocal BC ≤2.0 cm ■ ≤25% intraductal component ■ ER+, PR+, HER2+, tumour grade 3
Exclusion criteria	■ multifocal tumours ■ diffuse growth pattern ■ DCIS ■ lobular cancer
Recruitment period	NR
Number of patients	18
Number of tumours	18
Age of patients, mean/median±SD (range)	median: 67 (46-84)
Sex, menopausal status, n (%)	female, ■ postmenopausal: 17/18 (94) ■ premenopausal: 1/18 (6)
BC type, n (%)	**Histology** ■ Ductal: 15 (83) ■ Ductal/Tubular: 1 (6) ■ Tubular: 2 (11) **Tumour grade** ■ G1: 5 (28) ■ G2: 13 (72) ■ G3: 0 (0) Receptor status ■ ER+: 18 (100) ■ PR+: 16 (89), PR- 2 (11) ■ HER2-: 15 (83) ■ HER2+: 3 (17)
Size of tumour (mm), mean/median±SD (range) / n (%)	median: ■ MRI: 11 (5-20) ■ US : 10 (6-15) ■ mammography: 10 (6-15) ■ pathology: 10 (5-16)
Number of sessions in number of patients	1 session per patient, median time: 10 (8-14) min
Length of follow-up	median: 14.5 (6-22) days
Loss to follow-up, n (%)	0
Outcomes	
Efficacy	
Mortality	0
Complete ablation, n (%)	MRI: median FU of 13 days: 18 (100) Resection: median: 14.5 (6-22) days: 15/18 (83); 16/18 (85); 18 (100) with at least one histological staining method

Author, year	Schassburger, 2014 [61]
Determination of complete ablation	imaging and histologic
Residual tumour, n (%)	median FU of 13 days: 0 (0)
Recurrence, n (%)	NR
Cosmetic results, n/N (%)	NR
Quality of life	NR
Safety	
Adverse events (overall), n (%)	**Own pain assessment/management protocol using VAS** (0=no pain, 10= unbearable pain): ■ pain during administration of anestethics: 2 VAS ■ pain during procedure: 2.5 VAS, p=0.512 ■ median pain before procedure: 0 ■ median pain after procedure: 0.5, p=0.042
Serious adverse events	NR

Abbreviations: BC – breast cancer, BCS – breast-conserving surgery, DCIS – ductal carcinoma in situ, ER – estrogen receptor, FU – follow-up, G1, G2, G3 – tumor grades 1, 2, 3, HER2 – human epidermal growth factor receptor 2, MST – mastectomy, MRI – magnetic resonance imaging, NR – not reported, PR – progesterone receptor, RCT – randomised controlled trial, RFA – radiofrequency ablation, Tx – treatment, US – ultrasound, VAS – visual analog scale

Table A-9: High-intensity focused ultrasound ablation: Results from single-arm trials

Author, year	Guan, 2016 [62]	Merckel, 2016 [63]
Country	China	Netherlands
Sponsor	None	Center for Translational Molecular Medicine
Intervention - Product	HIFU, ■ JC tumour treatment system (Haifu Medical Technology co., Ltd, Chongqing, China); ■ PZT-4 piezo-ceramic ultrasound transducer (Beijing Cheng-Cheng Weiye Science and Technology Co., Ltd, Beijing, China); ■ AU3 ultrasound imaging device (Esaote, Genoa, Italy)	HIFU, ■ Sonalleve-based prototype (Philips Healthcare, Vantaa, Finland)
Comparator	Surgery, modified radical mastectomy without any other treatment before surgery	None
Study design	Single-arm - prospective* *originally an RCT	Single-arm - prospective
Primary study endpoint	■ Damage effect of HIFU on BC tissues and their vascularities	■ Treatment feasibility and safety
Guidance	US	MRI
Resection, n (%)	**Yes,** 1-2 weeks after ablation, ■ modified radical mastectomy: 25 (100)	**Yes**, 48h-10 days after ablation, ■ lumpectomy: 8 (80) ■ MST: 1 (10) ■ No surgery: 1 (10)

Author, year	Guan, 2016 [62]	Merckel, 2016 [63]
(Neo)Adjuvant Therapy, n (%)	■ **neoadjuvant:** NR ■ **adjuvant:** 25 (100) vs 25 (100)	■ **neoadjuvant:** 0 (0) (exclusion criteria) ■ **adjuvant:** NR
Anesthesia during ablation, n/N (%)	general	procedural sedation
Inclusion criteria	■ solitary invasive BC (T1-2, N0-2, M0) ≤5.0 cm ■ tumour to skin surface/ribcage ≥1.0 cm ■ tumour to nipple ≥2.0 cm	■ female, ≥18 years ■ invasive BC (T1-2) ≤1.0 cm ■ tumour to skin surface and pectoralis ≥1.0 cm and within reach of the ■ HIFU transducers with the patient in prone position ■ WHO performance status ≤2, weight ≤80 kg
Exclusion criteria	■ multifocal tumours or tumours with undefined margins ■ coagulation disorders, myocardial disease or diabetes	■ neoadjuvant Tx ■ C/I for MRI ■ macro-calcifications scar tissue or surgical clips in path of the ultrasound beams
Recruitment period	02.2014 - 08.2014	09.2012 - 06.2014
Number of patients	50 (25 vs 25)	10
Number of tumours	50 (25 vs 25)	10
Age of patients, mean/median±SD (range)	mean: 48 (22-63) vs 45 (25-65)	mean: 54.8±12.5
Sex, menopausal status	**female,** ■ Premenopausal: 5 (20) vs 4 (16) ■ Peri-menopausal: 5 (20) vs 4 (16) ■ Postmenopausal: 16 (64) vs 16 (64)	female, NR
BC type, n (%)	**Histology,** p=NS ■ IDC: 13 (52) vs 14 (56) ■ ILC: 7 (28) vs 5 (20) ■ other: 5 (20) vs 6 (24) **TNM Staging,** p=NS ■ Stage 1: 6 (24) vs 7 (28) ■ Stage 2A: 4 (16) vs 5 (20) ■ Stage 2B: 15 (60) vs 13 (52) **Tumour grade** ■ G1: 10 (40) vs 12 (48) (p=NS) ■ G2: 12 (48) vs 9 (36) ■ G3: 3 (12) vs 4 (16) **Receptor status,** p=NS ■ ER+, PR+: 13 (52) vs 14 (56) ■ ER+, PR–: 4 (16) vs 2 (8)	**Histology** ■ IDC: 8 (80) ■ ILC: 2 (20)

Author, year	Guan, 2016 [62]	Merckel, 2016 [63]
	■ ER-, PR–: 7 (28) vs 8 (32)	
Size of tumour (mm), mean/median±SD (range) / n (%)	(21-48) vs (23-45)	mean: pathology: 20.0±5.6
Number of sessions in number of patients	NR	mean treatment time: 145 min actual sonification time: 1.7 min
Length of follow-up	**2 weeks, 12 months** ■ median: 368 days ■ mean: 12 months	48h-10 days
Loss to follow-up, n (%)	**2 weeks**: 0 (0) vs 0 (0) **12 months**: 0 (0) vs 0 (0)	0
Outcomes		
Efficacy		
Mortality	0 vs 0	0
Complete ablation, n (%)	**1-2 weeks:** 25 (100)	NA *only reported on the extent of tumour necrosis, not evident whether the extend describes full ablation
Determination of complete ablation	histologic	histologic
Residual tumour, n (%)	0 (0)	NA
Recurrence, n (%)	**12 months**: 0 vs 0	NR
Cosmetic results, n/N (%)	NR	NR
Quality of life	NR	NR
Safety		

Adverse events (overall), n (%)	**post procedure:**
	■ edema in the mammary tissue circumjacent the ablated tumour: 25 (100)
	■ pain, tenderness, discomfort: 11 (44)
	■ mild fever: 3 (12)
		48 hours - 10 days:
		■ **Minor AEs**: 5
		  ■ nausea and vomiting: 2 (20)
		  ■ pain: 2 (20)*
		  ■ skin changes: 1 (10)
		
		*Scores 4 and 5 out of 10

Serious adverse events	**NR**	**0**

Abbreviations: AE – adverse event, BC – breast cancer, C/I – contraindication, DCIS – ductal carcinoma in situ, ER – estrogen receptor, FU – follow-up, G1, G2, G3 – tumor grades 1, 2, 3, HIFU – high-intensity focused ultrasound, IDC – invasive ductal carcinoma, ILC – invasive lobular carcinoma, MST – mastectomy, MRI – magnetic resonance imaging, NA – not applicable, NR – not reported, NS – not significant, PR – progesterone receptor, RCT – randomised controlled trial, RFA – radiofrequency ablation, SD – standard deviation, TNM – tumor, node, metastasis (staging system), Tx – treatment, US – ultrasound, WHO – World Health Organization

Table A-10: Laser ablation: Results from single-arm trials

Author, year	Schwartzberg, 2018 [26]
Country	USA, UK
Sponsor	Novian Health
Intervention, Product	LA, ■ Novilase Laser Therapy (Novian Health, Chicago, IL, USA)
Comparator	None
Study design	Single-arm - prospective, multicenter, open label
Primary study endpoint	■ Rate of complete tumour ablation
Guidance, n (%)	■ ultrasound : 60 (98) ■ stereotaxis: 1 (2)
Resection, n (%)	**Yes**, within 28 days after ablation: ■ lumpectomy: 55 (90) ■ MST: 6 (10)
(Neo)Adjuvant Therapy, n (%)	■ neoadjuvant: 0 (0) (exclusion criteria) ■ adjuvant: 1 (2) ■ chemo + radiation: 1 (2)
Anesthesia during ablation, n/N (%)	local
Inclusion criteria	■ female, 18-80 years ■ unifocal IDC ≤2.0 cm ■ ≤25% intraductal components ■ tumour to skin and chest wall surface ≥0.5 cm
Exclusion criteria	■ benign tumours and DCIS ■ BRCA + ■ neoadjuvant treatment ■ Hx of PLA BC Tx ■ recurrent BC ■ morbid obesity, renal insufficiency and other cobmorbidities affecting life expectancy ■ pacemakers/metallic implants ■ pregnancy or breast feeding
Recruitment period	06.2012 - 05.2015
Number of patients	61
Number of tumours	61
Age of patients, mean/median±SD (range)	mean: 64 (42-77)
Sex, menopausal status	female, NR
BC type, n (%)	**Histology** ■ IDC: 47 (77) ■ Infiltrating ductal /ductal in situ: 9 (14.7) ■ DCIS: 1 (1.6)

Author, year	Schwartzberg, 2018 [26]
	■ other: 3 (4.9) **Tumour grade** ■ G1: 24 (39.3) ■ G2: 31 (50.8) ■ G3: 6 (9.8) **Tumour subtype** ■ HER2-, ER+: 50 (81.9) ■ HER2+, ER+: 4 (6.5) ■ HER2+, ER-: 2 (3.3) ■ HER2 equivocal: 2 (3.3) ■ HER2-, ER-: 1 (1.6) ■ unkown: 2 (3.3)
Size of tumour (mm), mean/median±SD (range) / n (%)	mean: MRI: 11.3 (4.0-19.0)
Number of sessions in number of patients	1 session per patient; Mean laser time: 15.8 (14.5-36.5) min; average time of total procedure <1 hour
Length of follow-up	surgical excision within 28 days, FU up to 5 years mean: 43 (34-65) months
Loss to follow-up, n (%)	NR
Outcomes	
Efficacy	
Mortality	NR
Complete ablation, n (%)	**28 days**: 51 (84)
Determination of complete ablation	histology
Residual tumour, n (%)	**28 days**: 10 (16)
Recurrence, n (%)	**4 years**: 2 (3)
Cosmetic results, n/N (%)	**28 days**: Cosmetic satisfaction (measured by questionnaire): ■ Excellent: 27/58 (64) ■ Good: 19/58 (33) ■ <Good: 12/58 (21) ■ Missing: 3/61 (5) significant scar: 1 (2)
Quality of life	Health-related quality-of-life (EORTC QLQ-BR23 and QLQ-C30 surveys): change of ≥5 points compared with reference mean for early stage BC: 100% of patients
Safety	

Author, year	Schwartzberg, 2018 [26]
Adverse events (overall), n (%)	**mean fu: 43 (34-65) months**: **mild AEs**: 8 ■ lump: 1 (2) ■ blister: 2 (3) ■ hematoma: 1 (2) ■ erythema: 1 (2) ■ fat necrosis: 3 (5) **moderate AEs**: 6 ■ pain: 4 (7) ■ lump: 1 (2) ■ seroma: 1 (2) Average maximum pain during treatment: 4.2±2.9 (0-10)
Serious adverse events	0

Abbreviations: AE – adverse event, BC – breast cancer, BRCA+ – mutation in BRCA gene (breast cancer susceptibility gene), DCIS – ductal carcinoma in situ, ER – estrogen receptor, EORTC QLQ-BR23 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer Module, EORTC QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30, FU – follow-up, G1, G2, G3 – tumor grades 1, 2, 3, HER2 – human epidermal growth factor receptor 2, Hx – history, IDC – invasive ductal carcinoma, ILC – invasive lobular carcinoma, LA – laser ablation, MST – mastectomy, MRI – magnetic resonance imaging, NR – not reported, NS – not significant, PLA – percutaneous laser ablation, PR – progesterone receptor, QLQ – quality of life questionnaire, Tx – treatment, UK – United Kingdom, USA – United States of America

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 and in the Guidelines of EUnetHTA [36].

Table A-11: ROB2 [37] of RCTs comparing thermal ablation techniques with surgical resection

Trial	Endpoints	Bias arising from the randomization 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
CYA							
No RCTs identified							
MWA							
No RCTs identified							
RFA							
Garcia-Tejedor, 2018 [60]	Mortality	Low	Low	Low	Low	Low	Low
	Complete tumour ablation	Low	Low	Low	Low	Low	Low
	Recurrence	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low
HIFU							
No RCTs identified							
LA							
No RCTs identified							

Abbreviations: CYA – cryoablation, HIFU – high-intensity focused ultrasound ablation, LA – laser ablation, MWA – microwave ablation, RCT– randomized controlled trial, RFA – radiofrequency ablation, RoB – risk of bias

Table A-12: Outcome-specific ROBINS-I [38] of NRSI comparing thermal ablation techniques with surgical resection

Study reference/ID	Outcome	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
CYA										
Galati, 2024 [45]	Adverse events	Critical[a]	-	-	-	-	-	-	Critical	Only adverse events were described for both groups.
MWA										
Zhong, 2023 [56]	Mortality	Serious[b]	Low	Low	Low	Serious[c]	Low	Low	Serious	Only OS, DFS and recurrence were described for both groups.
	Disease free survival	Serious[b]	Low	Low	Low	Serious[c]	Low	Low	Serious	
	Recurrence	Serious[b]	Low	Low	Low	Serious[c]	Low	Low	Serious	
No NRSI identified										
HIFU										
No NRSI identifid										
LA										
No NRSI identified										

Abbreviations: CYA – cryoablation, DFS – disease free survival, HIFU – high-intensity focused ultrasound ablation, LA – laser ablation, MWA – microwave ablation, NRSI –non-randomised study of intervention, OS – overall survival, RFA – radiofrequency ablation, RoB – Risk of Bias

Comments:

[a] *According to the guideline of the newest ROBINS-I tool, no further assessment was conducted after finding the domain "bias due to confounding" critical.*

[b] *Only patients in the surgery group underwent axillary management (p=0.001). This could have influenced tumour recurrence rates and overall survival.*

[c] *Concerns regarding missing patients at later follow-up dates without details on the management of missing data.*

Table A-13: Evidence profile: efficacy and safety of cryoablation in early-stage breast cancer

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYA	Surgery	Relative (95% CI)	Absolute (95% CI)	
EFFICACY											
Overall survival (follow-up: 1 month to 60 months)											
8 [46-51, 53-55]	Single-arm	Serious[a]	Not serious	Not serious	Serious[b]	None	400	NA	FU 1 m - 60 m: 377/400 (94%; median: 100%; range: 89% to 100%) FU 1 - 12 m: 174/176 (99%) FU >12 - 60 m: 203/224 (91%)		⨁◯◯◯ Very low
Disease-free survival – not reported											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Complete tumour ablation/necrosis*											
1 [45]	NRSI	Very serious[c]	Not serious	Not serious	Not serious	None	10	NA	9/10 (90%) vs NA		⨁◯◯◯ Very low
5 [49-53]	Single-arm	Serious[a]	Not serious	Not serious	Not serious	None	192	NA	171/192 (89%; median 92; range: 53 to 93)		⨁⨁◯◯ Low
Recurrence/local and distant (follow-up: 18 to 60 months)											
5 [46-49, 54, 55]	Single-arm	Serious[a]	Not serious[d]	Not serious	Not serious	None	279	NA	FU 18 m – 60 m: 14/279 (5%; median: 3%; range: 0% to 22%)		⨁⨁◯◯ Low
SAFETY											
Adverse events (Immediate/post procedure)											
1 [45]	NRSI	Very serious[c]	Not serious	Not serious	Serious[e]	None	10	10	Minor AE: 2/10* vs 0/10		⨁◯◯◯ Very low

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CYA	Surgery	Relative (95% CI)	Absolute (95% CI)	
									*small post-ablative hematoma (about 4 cm in size) Pain (assessed on a scale from 1-10): Median score: 3 vs 5, p=NR		
5 [46, 49-52]	Single-arm	Serious[a]	Serious[f]	Not serious	Serious[e]	None	129	NA	39/129 (30%; median 22%; range: 0 to 100) Mild to moderate pain and bruising was most often described, in some cases together: (Bruising: 29/39 AEs, 74%; Pain: 16/39 AEs, 41%)		⨁◯◯◯ Very low
Adverse events (follow-up: 1 week to 5 years)											
1 [45]	NRSI	Very serious[c]	Not serious	Not serious	Serious[e]	None	10	10	FU 1 w: 0 vs 0		⨁◯◯◯ Very low
6 [46-51, 54]	Single-arm	Serious[a]	Serious[f]	Not serious	Not serious	None	282	NA	109 (39%; median 5; range: 0 to 50)		⨁◯◯◯ Very low
Serious adverse events (follow-up: 1 week to 60 months)											
1 [45]	NRSI	Very serious[c]	Not serious	Not serious	Serious[e]	None	10	10	FU 1 w: 0 vs 0		⨁◯◯◯ Very low
4 [46-49, 54]	Single-arm	Serious[a]	Not serious	Not serious	Not serious	None	247	NA	FU 2 m – 60 m: 0 (0)		⨁◯◯◯ Very low

Abbreviations: AE – adverse event, CI – confidence interval, CYA – cryoablation, FU– follow-up, m – months, NA – not applicable, NRSI –- non-randomized study of intervention, RoB – Risk of Bias, vs – versus

Comments:

[a] *According to the HTA-Guidelines and LATITUDES recommended risk of bias tools, single-arm trials were considered to have a high risk of bias.*

[b] *Most deaths (n=21) reported in one study with the longest FU [Fine, 2024], of which 16 were unrelated to BC and 3 for unknown reasons.*

[c] *Assessed as having a critical risk of bias, confounding factors were not adjusted for.*

[d] *High recurrence rate in study with 23 patients, tumour sizes bigger than in other studies and included patients, who were "unsuitable for surgery" [46].*

[e] *Very low sample size, OIS not reached.*

[f] *High variation in what and how adverse events were reported.*

Table A-14: Evidence profile: efficacy and safety of microwave ablation in early-stage breast cancer

Quality assessment							Summary of findings			
							Number of patients		Effect (I vs C)	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MWA	Surgical Resection		
EFFICACY										
Overall survival/Mortality (follow-up: immediately post ablation to 36 months)										
1 [56]	Propensity score matched NRSI	Serious[a]	Not serious	Serious[b]	Serious[c]	None	33	99	OS mean FU 31 m (2-74): 33 (100) vs 98 (99) HR: 0.537 95%CI: 0.089-3.325, p=0.49 OS rate 1 y: 97% vs 100% OS rate 3 y: 93% vs 96%	⨁◯◯◯ Very low
3 [57-59]	Single-arm	Serious[d]	Not serious	Not serious	Serious[e]	None	101	NA	FU immediately post ablation to 36 m: 100 (100%)	⨁◯◯◯ Very low
Disease-free survival										
1 [56]	Propensity score matched NRSI	Serious[a]	Not serious	Serious[b]	Serious[c]	None	33	99	median FU 31m (2-74): HR: 0.536 95%CI: 0.128-2.249, p=0.38	⨁◯◯◯ Very low
0	Single-arm	NA	NA	NA	NA	NA	NA	NA	NA	NA
Complete tumour ablation/necrosis										
1 [56][f]	Propensity score matched NRSI	Serious[d]	Not serious	Serious[b]	Serious[e]	None	33	NA	FU 1 w: 32 (97) FU 1 m: 33 (100), 95%CI: 89.4-100%)	⨁◯◯◯ Very low
3 [57-59]	Single-arm	Serious[d]	Not serious	Not serious	Serious[e]	None	101	NA	FU immediately post ablation to 36 m: 91-100%	⨁◯◯◯ Very low
Recurrence/local and distant										
1 [56]	Propensity score matched NRSI	Serious[g]	Not serious	Serious[b]	Serious[c]	None	33	99	median FU: 31 m (2-74) Local recurrence: 1 (3) vs 1 (1) Distant metastasis: 0 (0) vs 2 (2)	⨁◯◯◯ Very low
1 [58]	Single-arm	Serious[d]	Not serious	Not serious	Very serious[e]	None	35	NA	Median FU 13-47m MWA: 0/15 (0) MWA+surgery: NR	⨁◯◯◯ Very low

Quality assessment							Summary of findings			
							Number of patients		Effect (I vs C)	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MWA	Surgical Resection		
SAFETY										
Adverse events										
1 [56][f]	Propensity score matched NRSI	Serious[d]	Not serious	Not serious	Serious[e]	None	33	NA	Median FU 31 m (2-74): 0 vs NR	⨁◯◯◯ Very low
3 [57-59]	Single-arm	Serious[d]	Not serious	Not serious	Serious[e]	None	101	NA	Pain during or after the procedure was reported in all studies in 6-18% of patients Ji, 2024 [59] and Zhou 2021 [58] reported swelling during or after the procedure in 42% and 100% of patients Pan, 2024 [57] reported skin burn in 10% and skin necrosis in 3% of patients	⨁◯◯◯ Very low
Serious adverse events										
1 [56][f]	Propensity score matched NRSI	Serious[d]	Not serious	Not serious	Serious[e]	None	33	NA	0 vs NR	
3 [57-59]	Single-arm	Serious[d]	Not serious	Not serious	Serious[e]	None	101	NA	0	

Abbreviations: AE – adverse event, CI – confidence interval, DFS – disease free survival, FU– follow-up, m – months, HR – hazard ratio, HTA – health technology assessment, MRI- magnetic resonance imaging, MWA – microwave ablation, NA – not applicable, NR – not reported, NRSI – non-randomised study of intervention, OIS – optimal information size, OS – overall survival, RoB – Risk of Bias, vs – versus

Comments:

[a] Concerns regarding missing data and confounding factors (no lymph node dissection/SLNB in intervention group).

[b] This study included only participants >70 years.

[c] Certainty in evidence lowered because of a small number of events leading to wide confidence intervals.

[d] According to the HTA-Guidelines and LATITUDES recommended risk of bias tools, single-arm trials were considered to have a high risk of bias.

[e] Small sample size, OIS not reached.

[f] Zhong et al. compared only the outcomes of mortality, OS, DFS and recurrence between the groups, other outcomes are described only for the intervention group, therefore we utilize this data like findings from a single-arm trial.

[g] Concerns regarding missing data and confounding factors (no lymph node dissection/SLNB in intervention group).

Table A-15: Evidence profile: efficacy and safety of radiofrequency ablation in early-stage breast cancer

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)	
EFFICACY											
Overall survival (FU immediately post surgery-2 years)											
1 [60]	RCT	Not serious	Not serious	Not serious	Very serious[a]	None	20	20	median FU of 25 m (range: 1 to 83): 20/20 (100) vs 20/20 (100)		⊕⊕◯◯ Low
1 [61]	Single-arm	Serious[b]	Not serious	Not serious	Serious[c]	None	18	NA	median FU 14.5 d 18/18 (100)		⊕◯◯◯ Very low
Disease free survival											
0	RCT	NA	NA	NA	NA	NA	NA	NA	NA		NA
0	Single-arm	NA	NA	NA	NA	NA	NA	NA	NA		NA
Complete tumour ablation/necrosis											
1 [60]	RCT	Not serious	Not serious	Not serious	Serious[c]	None	20	NA	Immediately after ablation: 20 (100)		⊕⊕◯◯ Low
1 [61]	Single-arm	Serious[b]	Not serious	Not serious	Serious[c]	None	18	NA	MRI: Median FU of 13 d 18 (100) Histology: Median FU of 14.5 days (range: 6-22): 15/18 (83) – 16/18 (85)[d]		⊕◯◯◯ Very low
Recurrence/local and distant (FU immediately post surgery-2 years)											
1 [60]	RCT	Not serious	Not serious	Not serious	Very serious[a]	None	20	20	median FU of 25 m (range: 1-83): local: 0 vs 0 distant metastasis: 0 vs 0		⊕⊕◯◯ Low
0	Single-arm	NA	NA	NA	NA	NA	NA	NA	NA		NA
SAFETY											
Adverse events											
1 [60]	RCT	Not serious	Not serious	Not serious	Serious[a]	None	20	20	Total AE after surgery[e]: 8 (40) vs 1 (5), p=0.1 Breast inflammation: 5 (25) vs 1 (5), p=0.18 Breast infection:		⊕⊕⊕◯ Moderate

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)	
									3 (15) vs 0 (0), p=0.23		
1 [61]	Single-arm	Serious[b]	Not serious	Not serious	Serious[c]	None	18	NA	pain during (administration of anaesthetics vs procedure): 2 vs 2.5 VAS, p=0.512 median pain (before vs after procedure): 0 vs 0.5, p=0.042		⨁◯◯◯ Very low
Serious adverse events											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA

Abbreviations: AE – adverse event, CI – confidence interval, FU– follow-up, m – months, MRI- magnetic resonance imaging, NA – not applicable, OIS – optimal information size, RCT – randomized controlled trial, RFA – radiofrequency ablation, RoB – Risk of Bias, HTA – health technology assessment, VAS – visual analogue scale, vs – versus
Comments:
[a] This study was prematurely stopped due to higher number of local adverse events in the intervention group; hence OIS was not reached. Further, there is a low number of events.
[b] According to the HTA-Guidelines and LATITUDES recommended risk of bias tools, single-arm trials are considered to have a high risk of bias.
[c] Small sample size (n=18); IOS not met.
[d] Complete ablation was assessed with MRI and histological staining. Complete tumour devitalization was indicated in 15/18 (83%) of patients as judged by H&E staining and in 16/18 (89%) of patients as judged by CK8 staining.
[e] Tumour was immediately resected after ablation in the intervention group.

Table A-16: Efficacy and safety of high-intensity focused ultrasound in early breast cancer

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)	
EFFICACY											
Overall survival (follow-up 10 days to 12 months)											
2 [62, 63]	Single-arm	Serious[a]	Not serious	Not serious	Serious[b]	None	35	NA	At 12 m [62]: 25/25 (100%) At 10 d [63]: 10/10 (100%)		⨁◯◯◯ Very low
Disease free survival											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)	
Complete tumour ablation/Necrosis/Residual tumour											
1 [62]	Single-arm	Serious[a]	Not serious	Not serious	Serious[b]	None	25	NA	25/25 (100%)		⨁◯◯◯ Very low
Recurrence/local and distant (follow-up 12 months)											
1 [62]	Single-arm	Serious[a]	Not serious	Not serious	Serious[b]	None	25	NA	0/25 (0%)		⨁◯◯◯ Very low
SAFETY											
Adverse events (from 10 days post-intervention up to 12 months)											
2 [62, 63]	Single-arm	Serious[a]	Not serious	Not serious	Serious[b]	None	35	NA	At 12 m [62]: edema: 25/25 (100%) Pain: 11/25 (44%) Mild fever: 3/25 (12) At 10 d [63]: Minor AEs: 5 Nausea and vomiting: 2, pain: 2 (4 and 5 score out of 10), skin changes: 1		⨁◯◯◯ Very low
Serious adverse events											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA

Abbreviations: AE – adverse event, CI – confidence interval, FU– follow-up, HIFU – high-intensity focused ultrasound ablation, HTA – health technology assessment, m – months, NA – not applicable

Comments:

[a] According to the HTA-Guidelines and LATITUDES recommended risk of bias tools, single-arm trials are considered to have a high risk of bias.

[b] Small sample size, low number of events.

Table A-17: Efficacy and safety of laser ablation in early-stage breast cancer

Quality assessment							Summary of findings				
							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)	
EFFICACY											
Overall survival											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA
Disease free survival											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA
Complete tumour ablation/necrosis*											
1 [26]	Single-arm	Serious[a]	Not serious	Not serious	Serious[b]	None	61	NA	51/61 (84%)		⨁◯◯◯ Very low
Recurrence/local and distant (follow-up 4 years)											
1 [26]	Single-arm	Serious[a]	Not serious	Not serious	Serious[b]	None	61	NA	2/61 (3%)		⨁◯◯◯ Very low
SAFETY											
Adverse events (follow-up 43 months)											
1 [26]	Single-arm	Serious[a]	Not serious	Not serious	Serious[b]	None	61	NA	Mild AEs: 8 Moderate AEs: 6 pain: 4 (mean score 4.2) lump: 1 seroma: 1		⨁◯◯◯ Very low
Serious adverse events											
0	NA	NA	NA	NA	NA	NA	NA	NA	NA		NA

Abbreviations: AE – adverse event, CI – confidence interval, FU– follow-up, LA – laser ablation, m – months, NA – not applicable
Comments:
[a] *According to the HTA-Guidelines and LATITUDES recommended risk of bias tools, single-arm trials are considered to have a high risk of bias.*
[b] *Small sample size, low number of events.*

Applicability table

Table A-18: Summary table characterising the applicability of the body of studies

Domain	Description of applicability of evidence
Population	Overall, the study participants comprised patients with unifocal early-stage invasive BC, with no evidence of lymph node involvement or distant metastases. Tumour sizes varied, though most studies included patients with tumours up to 2 cm. The predominant histological subtype was invasive ductal carcinoma, though there was considerable heterogeneity across studies regarding tumour grade and hormone receptor status as well as some variation in the administration of adjuvant therapies. The RCT on RFA included female patients older than 40 with early-stage BC and tumour sizes below 2 cm, the NRSI on CYA included female patients older than 18 with early-stage BC and tumour sizes below 2 cm and the NRSI on MWA included only patients older than 70 with a tumour size up do 3 cm. This aligns with our PICO criteria and represents the target population for thermal ablation therapies in Austria. The inclusion of older patients in one NRSI remains relevant, as comorbidities in this age might prevent surgery. The heterogeneity between the studies regarding hormone receptor status and adjuvant therapy administration is unlikely to affect the safety outcomes and complete ablation, but these factors are significant prognostic factors and thus likely to affect long-term prognosis and therefore the outcomes OS, DFS and recurrence.
Intervention	CYA was used in ten studies, MWA in four, RFA in two, HIFU in one, and LA in one. Provision of neoadjuvant and adjuvant treatments was heterogenous, with twelve studies reporting different rates of adjuvant treatments in their participants, while neoadjuvant treatment was either not reported or an exclusion criterion. To the authors' knowledge, only one cryotherapy device and the device used for laser ablation have received CE marking for the indication of malignant BC. Some other devices have CE marking for different indications but were used off-label for BC in these studies. For several devices, no information on approval or certification status was available.
Comparators	In comparative studies, the comparator was surgical resection, most often breast conserving surgery, which is in line with the standard of care routinely used to treat early-stage BC in Austria.
Outcomes	Adverse events were consistently reported across all included studies. Mortality data were also presented by the majority of studies; however, the follow-up periods were generally too short in a significant proportion of studies to demonstrate a clear benefit. One comparative NRSI reported mortality at the shortest follow-up of ≤ 21 days, while another documented this outcome up to 3 years post-intervention. The RCT provided mortality data after a 5-month follow-up. Cancer-specific outcomes, such as OS and DFS, were only reported by two studies, one of which was a comparative NRSI. Complete ablation was also reported by most studies, although there was notable heterogeneity in how it was assessed. Most studies confirmed complete tumour destruction histologically following subsequent surgical resection, whereas four studies relied solely on imaging (US or MRI) to ascertain this outcome. In real-world applications, where thermal ablation may replace surgery, imaging or biopsy of the ablated area would likely be utilized to confirm treatment success. Thus, the conditions in most studies do not fully reflect typical clinical practice. Tumour recurrence was also reported by the majority of studies, and the concern regarding short follow-up periods similarly limits the interpretability of this outcome.
Setting	Studies were conducted in Europe, the USA, Japan, and China. Therefore, the applicability of the results is unlikely to be limited by geographic factors. However, there was limited information on the specific clinical setting, such as whether radiologists or surgeons performed the procedure or details like length of hospital stay. Nevertheless, it is presumable that the procedure was performed by specialized staff in tertiary hospitals, which aligns with its expected use in the Austrian healthcare system.

Abbreviations: BC – breast cancer, CYA – cryoablation, DFS – disease-free survival, HIFU – high-intensity ultrasound ablation, LA – laser ablation, MWA – microwave ablation, NRSI – non-randomised, OS – overall survival, RCT – randomised controlled trial, RFA – radiofrequency ablation, US – ultrasound, USA – United States of America

List of ongoing randomised controlled trials

Table A-19: List of ongoing randomised controlled trials of thermal ablation for early-stage breast cancer

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT05505643 COOL-IT	Women with T1 breast cancer	Cryoablation	Lumpectomy	Safety IBTR at 5 years	30/04/34	Washington University School of Medicine

Research questions

Table A-20: 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-21: 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-22: Clinical Effectiveness

Element ID	Research question
D0001	What is the expected beneficial effect of the technology on mortality?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?

Table A-23: Safety

Element ID	Research question
C0008	How safe is the technology in comparison to the comparator(s)?

Literature search strategies

Search strategy for Cochrane

Search Name: Thermoablation for breast cancer	
Search date: 15.12.2024	
ID	Search
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	((breast* OR mamma*) NEAR (cancer* OR tumo?r* OR carcinom* OR adenom* OR adeno?c* OR sarcoma* OR neoplasm* OR malignan*)) (Word variations have been searched)
#3	#1 OR #2
#4	(thermo?ablat*) (Word variations have been searched)
#5	(thermo-ablat*) (Word variations have been searched)
#6	MeSH descriptor: [Radiofrequency Ablation] explode all trees
#7	(RFA*)
#8	(laser*) (Word variations have been searched)
#9	(PLA):ti,ab,kw
#10	(micro?wave*) (Word variations have been searched)
#11	(micro-wave*) (Word variations have been searched)
#12	MWA*
#13	MeSH descriptor: [Laser Therapy] explode all trees
#14	MeSH descriptor: [Cryotherapy] explode all trees
#15	MeSH descriptor: [Microwaves] explode all trees
#16	#13 OR #14 OR #15
#17	MeSH descriptor: [Ablation Techniques] explode all trees
#18	#16 AND #17
#19	MeSH descriptor: [High-Intensity Focused Ultrasound Ablation] explode all trees
#20	(high-intensity NEXT focus?ed NEXT ultra?sound*) (Word variations have been searched)
#21	(HIFU*) (Word variations have been searched)
#22	MeSH descriptor: [Cryosurgery] explode all trees
#23	(cryo?ablat*) (Word variations have been searched)
#24	(cryo-ablat*) (Word variations have been searched)
#25	((radio?frequenc* OR radio-frequenc* OR thermal OR thermic OR laser* OR micro?wave* OR micro-wave* OR ultra?sound* OR cryo*) NEAR (ablat* OR irridat* OR hyper?therm* OR hyper-therm* OR hypo?therm* OR hypo-therm*)) (Word variations have been searched)
#26	(Prosense*) (Word variations have been searched)
#27	(Cryocare*) (Word variations have been searched)
#28	(PulsaBlade*) (Word variations have been searched)
#29	(Solero*) (Word variations have been searched)
#30	(AMICA)
#31	(Cool-Tip*) (Word variations have been searched)
#32	(Cool?Tip*) (Word variations have been searched)
#33	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 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
#34	#3 AND #33
#35	#3 AND #33 with Cochrane Library publication date Between Jan 2014 and Jan 2024
#36	#3 AND #33 with Publication Year from 2014 to 2024, in Trials
#37	#35 OR #36
#38	English:la

#39	German:la
#40	#38 OR #39
#41	#37 AND #40
#42	(conference proceeding):pt
#43	(abstract):so
#44	(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
#45	#42 OR #43 OR #44
#46	#41 NOT #45
Total hits: 122	

Search strategy for Embase

Search Name: Thermoablation for breast cancer		
Search date: 15.12.2024		
No.	Query Results	Results
#1	'breast tumor'/exp	730,379
#2	(breast* OR mamma*) NEAR/2 (cancer* OR tumo*r* OR carcinom* OR adenom* OR adeno*c* OR sarcoma* OR neoplasm* OR malignan*)	823,436
#3	#1 OR #2	829,354
#4	'thermal ablation'/exp	1,578
#5	thermo*ablat*	1,142
#6	'thermo-ablat*'	158
#7	'radiofrequency ablation'/exp	50,381
#8	rfa*	26,679
#9	pla:ti,ab	28,879
#10	'laser surgery'/exp	75,208
#11	'cryoablation'/exp	12,203
#12	'microwave thermotherapy'/exp	7,667
#13	mwa*	24,592
#14	'high intensity focused ultrasound'/exp	7,446
#15	'high-intensity focus*ed ultra*sound*'	8,668
#16	hifu*	9,546
#17	cryo*ablat*	15,056
#18	'cryo-ablat*'	372
#19	(radio*frequenc* OR 'radio frequenc*' OR thermal OR thermic OR laser* OR micro*wave* OR 'micro-wave*' OR ultra*sound* OR cryo*) N EAR/2 (ablat* OR irridat* OR hyper*therm* OR 'hypertherm*' OR hypo*therm* OR 'hypo-therm*')	94,735
#20	'prosense'/exp	17
#21	prosense*:dn	21
#22	'cryotherapy device'/exp	231
#23	'cryosurgery device'/exp	2,476
#24	cryocare:dn	81
#25	pulsablade*	
#26	'solero'/exp	22
#27	solero:dn	25
#28	'amica'/exp	30

#29	amica:dn	78
#30	'cool tip rf ablation system'/exp	14
#31	'cool tip rf system'/exp	12
#32	'radiofrequency ablation device'/exp	4,162
#33	'cool-tip*'	747
#34	'cool*tip*'	946
#35	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #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 OR #34	244,947
#36	#3 AND #35	3,886
#37	#36 AND [2020-2024]/py	1,316
#38	#37 AND [2020-2024]/py AND ([english]/lim OR [german]/lim)	1,283
#39	#38 AND 'Conference Abstract'/it	224
#40	#38 NOT #39	1,059
Total hits: 1,059		

Search strategy for Medline via Ovid

Search Name: Ovid MEDLINE(R) ALL <1946 to December 17, 2024>	
Search date: 15.12.2024	
ID	Search
#1	exp Breast Neoplasms/ (362254)
#2	((breast* or mamma*) adj3 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or sarcoma* or neoplasm* or malignan*)).mp. (530925)
#3	1 or 2 (530933)
#4	thermo?ablat*.mp. (610)
#5	thermo-ablat*.mp. (81)
#6	exp Radiofrequency Ablation/ (43823)
#7	RFA*.mp. (11281)
#8	PLA.mp. (19145)
#9	exp Laser Therapy/ (69199)
#10	exp Cryotherapy/ (28289)
#11	exp Microwaves/ (20709)
#12	9 or 10 or 11 (117240)
#13	exp Ablation Techniques/ (136295)
#14	12 and 13 (64626)
#15	MWA*.mp. (3372)
#16	exp High-Intensity Focused Ultrasound Ablation/ (2987)
#17	high-intensity focus?ed ultra?sound*.mp. (5105)
#18	HIFU*.mp. (3433)
#19	exp Cryosurgery/ (14579)
#20	cryo*ablat*.mp. (5448)
#21	cryo-ablat*.mp. (106)
#22	((radio?frequenc* or radio-frequenc* or thermal or thermic or laser* or micro?wave* or micro-wave* or ultra?sound* or cryo*) adj3 (ablat* or irridat* or hyper*therm* or hyper-therm* or hypo?therm* or hypo-therm*)).mp. (53601)
#23	Prosense*.mp. (42)
#24	Cryocare*.mp. (20)
#25	PulsaBlade*.mp. (0)

#26	Solero*.mp. (16)
#27	AMICA.mp. (92)
#28	Cool-Tip*.mp. (136)
#29	Cool?Tip*.mp. (7)
#30	4 or 5 or 6 or 7 or 8 or 14 or 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 (172220)
#31	3 and 30 (1866)
#32	limit 31 to yr="2014 - 2024" (921)
#33	limit 32 to (english or german) (896)
#34	remove duplicates from 33 (893)
Total hits: 893	

Search strategy for HTA-INATHTA

Search Name: Thermoablation for breast cancer	
Search date: 15.12.2024	
ID	Search
#1	"Breast Neoplasms" [mhe],"708","2024-12-15T03:59:17.000000Z"
#2	(breast* OR mamma*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR sarcoma* OR neoplasm* OR malignan*),"867","2024-12-15T04:02:23.000000Z"
#3	((breast* OR mamma*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR sarcoma* OR neoplasm* OR malignan*)) OR ("Breast Neoplasms" [mhe]),"929","2024-12-15T04:02:32.000000Z"
#4	thermoablat*,"3","2024-12-15T04:03:04.000000Z"
#5	thermo-ablat*,"0","2024-12-15T04:03:09.000000Z"
#6	"Radiofrequency Ablation" [mhe],"238","2024-12-15T04:03:46.000000Z"
#7	RFA*,"70","2024-12-15T04:04:19.000000Z"
#8	laser*,"347","2024-12-15T04:04:50.000000Z"
#9	PLA,"3","2024-12-15T04:05:54.000000Z"
#10	microwave*,"53","2024-12-15T04:06:24.000000Z"
#11	micro-wave*,"0","2024-12-15T04:06:29.000000Z"
#12	MWA*,"6","2024-12-15T04:06:52.000000Z"
#13	"Cryotherapy" [mhe],"59","2024-12-15T04:07:48.000000Z"
#14	"Laser Therapy" [mhe],"218","2024-12-15T04:08:14.000000Z"
#15	"Microwaves" [mhe],"28","2024-12-15T04:09:00.000000Z"
#16	("Microwaves" [mhe]) OR ("Laser Therapy" [mhe]) OR ("Cryotherapy" [mhe]),"304","2024-12-15T04:09:40.000000Z"
#17	"Ablation Techniques" [mhe],"564","2024-12-15T04:10:03.000000Z"
#18	("Ablation Techniques" [mhe]) AND (("Microwaves" [mhe]) OR ("Laser Therapy" [mhe]) OR ("Cryotherapy" [mhe])),"228","2024-12-15T04:10:11.000000Z"
#19	"High-Intensity Focused Ultrasound Ablation" [mhe],"54","2024-12-15T04:11:03.000000Z"
#20	high-intensity focused ultrasound*,"63","2024-12-15T04:11:32.000000Z"
#21	high-intensity focussed ultrasound*,"3","2024-12-15T04:11:45.000000Z"
#22	HIFU*,"27","2024-12-15T04:12:40.000000Z"
#23	"Cryosurgery" [mhe],"45","2024-12-15T04:13:01.000000Z"
#24	cryoablat*,"35","2024-12-15T04:13:19.000000Z"
#25	cryo-ablat*,"0","2024-12-15T04:13:31.000000Z"
#26	(radiofrequenc* OR radio-frequenc* OR thermal OR thermic OR laser* OR microwave* OR micro-wave* OR ultrasound* OR ultra-sound* OR cryo*) AND (ablat* OR irridat* OR hypertherm* OR hyper-therm* OR hypotherm* OR hypo-therm*),"301","2024-12-15T04:17:05.000000Z"

#27	((radiofrequenc* OR radio-frequenc* OR thermal OR thermic OR laser* OR microwave* OR micro-wave* OR ultrasound* OR ultra-sound* OR cryo*) AND (ablat* OR irridat* OR hypertherm* OR hyper-therm* OR hypotherm* OR hypo-therm*)) OR (cryo-ablat*) OR (cryoablat*) OR ("Cryosurgery" [mhe]) OR (HIFU*) OR (high-intensity focussed ultrasound*) OR (high-intensity focused ultrasound*) OR ("High-Intensity Focused Ultrasound Ablation" [mhe]) OR (("Ablation Techniques" [mhe]) AND (("Microwaves" [mhe]) OR ("Laser Therapy" [mhe]) OR ("Cryotherapy" [mhe]))) OR (MWA*) OR (micro-wave*) OR (microwave*) OR (PLA) OR (laser*) OR (RFA*) OR ("Radiofrequency Ablation" [mhe]) OR (thermo-ablat*) OR (thermoablat*),"795","2024-12-15T04:19:42.000000Z"
#28	(((radiofrequenc* OR radio-frequenc* OR thermal OR thermic OR laser* OR microwave* OR micro-wave* OR ultrasound* OR ultra-sound* OR cryo*) AND (ablat* OR irridat* OR hypertherm* OR hyper-therm* OR hypotherm* OR hypo-therm*)) OR (cryo-ablat*) OR (cryoablat*) OR ("Cryosurgery" [mhe]) OR (HIFU*) OR (high-intensity focussed ultrasound*) OR (high-intensity focused ultrasound*) OR ("High-Intensity Focused Ultrasound Ablation" [mhe]) OR (("Ablation Techniques" [mhe]) AND (("Microwaves" [mhe]) OR ("Laser Therapy" [mhe]) OR ("Cryotherapy" [mhe]))) OR (MWA*) OR (micro-wave*) OR (microwave*) OR (PLA) OR (laser*) OR (RFA*) OR ("Radiofrequency Ablation" [mhe]) OR (thermo-ablat*) OR (thermoablat*)) AND (((breast* OR mamma*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR sarcoma* OR neoplasm* OR malignan*)) OR ("Breast Neoplasms" [mhe])),"15","2024-12-15T04:20:24.000000Z"
#29	(((radiofrequenc* OR radio-frequenc* OR thermal OR thermic OR laser* OR microwave* OR micro-wave* OR ultrasound* OR ultra-sound* OR cryo*) AND (ablat* OR irridat* OR hypertherm* OR hyper-therm* OR hypotherm* OR hypo-therm*)) OR (cryo-ablat*) OR (cryoablat*) OR ("Cryosurgery" [mhe]) OR (HIFU*) OR (high-intensity focussed ultrasound*) OR (high-intensity focused ultrasound*) OR ("High-Intensity Focused Ultrasound Ablation" [mhe]) OR (("Ablation Techniques" [mhe]) AND (("Microwaves" [mhe]) OR ("Laser Therapy" [mhe]) OR ("Cryotherapy" [mhe]))) OR (MWA*) OR (micro-wave*) OR (microwave*) OR (PLA) OR (laser*) OR (RFA*) OR ("Radiofrequency Ablation" [mhe]) OR (thermo-ablat*) OR (thermoablat*)) AND (((breast* OR mamma*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR sarcoma* OR neoplasm* OR malignan*)) OR ("Breast Neoplasms" [mhe])),"15","2024-12-15T04:22:37.000000Z"
#30	((((radiofrequenc* OR radio-frequenc* OR thermal OR thermic OR laser* OR microwave* OR micro-wave* OR ultrasound* OR ultra-sound* OR cryo*) AND (ablat* OR irridat* OR hypertherm* OR hyper-therm* OR hypotherm* OR hypo-therm*)) OR (cryo-ablat*) OR (cryoablat*) OR ("Cryosurgery" [mhe]) OR (HIFU*) OR (high-intensity focussed ultrasound*) OR (high-intensity focused ultrasound*) OR ("High-Intensity Focused Ultrasound Ablation" [mhe]) OR (("Ablation Techniques" [mhe]) AND (("Microwaves" [mhe]) OR ("Laser Therapy" [mhe]) OR ("Cryotherapy" [mhe]))) OR (MWA*) OR (micro-wave*) OR (microwave*) OR (PLA) OR (laser*) OR (RFA*) OR ("Radiofrequency Ablation" [mhe]) OR (thermo-ablat*) OR (thermoablat*)) AND (((breast* OR mamma*) AND (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR adeno-c* OR sarcoma* OR neoplasm* OR malignan*)) OR ("Breast Neoplasms" [mhe]))) FROM 2014 TO 2024,"0","2024-12-15T04:22:51.000000Z"
Total hits: 0	

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