

Horizon Scanning in Surgery: Application to Surgical Education and Practice

Microwave ablation for lung cancer

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This report is not a comprehensive systematic review. Rather, it is an assessment of an emerging surgical procedure or technology in which the methodology has been limited in one or more areas to shorten the timeline for its completion.

Therefore, this report is a limited evidence-based assessment that is based on a search of studies published in the peer-reviewed literature. This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements in health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

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Objective

This horizon scanning assessment provides short, rapidly completed, 'state of play' documents. These provide current information on technologies to alert clinicians, planners and policy makers of the advent and potential impact of a new or emerging procedure or device. This information can then assist clinicians, planners and policy makers to control and monitor the introduction of new health technologies as well as assist in the prioritization and allocation of resources to promote efficient utilization of available resources.

Introduction

Indications

Microwave ablation is being proposed for the treatment of some lung cancers, and also for other cancers including those of the liver, kidney, breast, bone, pancreas and adrenal gland (Carrafiello et al 2008).

Lung cancer can be defined as uncontrolled cell growth in lung tissues, usually in the cells lining the air passages. Primary lung tumors are classified as small cell lung cancers or non-small cell lung cancers. Small cell lung cancers are aggressive and fast-growing, and are almost exclusively associated with cigarette smoking (Dugdale et al 2009). Non-small cell lung cancers

are more common and usually have a slower rate of growth (Chen 2009). Non-small cell lung cancer is divided into five stages, ranging from stages 0 and I where the cancer is small and has not yet spread to the lymph nodes, to stages III and IV where the cancer has spread to distant lymph nodes and other organs of the body (Chen 2009).

Most patients present with advanced stage lung cancer although approximately 16% of new lung cancers are early stage (stage 0 and I) non-small cell (Abbas et al 2009; Wasser and Dupuy 2008). Surgical resection with the intent to cure is the conventional first line treatment for this latter group of patients and may also be beneficial for some patients with limited pulmonary metastases (Abbas et al 2009). Surgery may involve the removal of a small part of the lung (wedge or segment removal), a lung lobe (lobectomy), or the entire lung (pneumonectomy) (Chen 2009). Patients are generally not eligible for surgery if they present with advanced disease, particularly if they are diagnosed with small cell lung cancer which has a rapid growth rate and tendency to metastasize (Abbas et al 2009; Dugdale et al 2009).

Despite a diagnosis of early stage lung cancer, many patients are not eligible for surgery due to advanced age or cardiorespiratory co-morbidities, and even in patients who are deemed fit for surgery, postoperative mortality occurs (Wasser and Dupuy 2008). Less invasive means of tumor eradication are therefore required for patients who have early stage disease but for whom surgery is not indicated (Wasser and Dupuy 2008). Current alternatives include radiotherapy alone or in conjunction with a cisplatin-based chemotherapeutic agent; however, these therapies have been shown to be less effective in achieving local control when compared with surgery (Wasser and Dupuy 2008).

Other potential alternatives to surgery include a range of tumor ablation techniques that use the direct application of chemical or thermal therapies to a tumor to achieve eradication or substantial tumor destruction (Simon et al 2005). Some ablation techniques use increased heat to induce cancer cell death, as it is known that cancerous tumors are more susceptible to the effects of cell heating than are normal tissues (Wasser and Dupuy 2008). Current thermal ablation techniques available for clinical use include radiofrequency ablation, laser ablation, high-frequency ultrasound ablation, and most recently microwave ablation.

The main objectives of tumor ablation therapy are to eradicate all viable malignant cells in the target (with a safety margin to ensure complete eradication), while minimizing the damage to surrounding tissue (Vogl et al 2009). Potential advantages of local tumor ablation over surgical resection include selective damage, reduced treatment morbidity and mortality, less breathing impairment in patients with borderline lung function (through sparing of healthy lung tissue), repeatability, lower costs, the possibility of good imaging during the procedure and at follow-up, and reduced pain and length of hospitalization (Vogl et al 2009).

Radiofrequency ablation is currently the most studied and widely used ablation technique in lung cancer treatment; however, microwave ablation may offer certain advantages. These potential advantages include higher intratumoral temperatures, larger tumor ablation volumes, faster ablation time and diminished procedural pain (Carrafiello et al 2008).

Burden of disease

Worldwide, lung cancer is the most frequent type of cancer and the leading cause of cancer death (1.3 million deaths annually) (World Health Organization [WHO] 2009). This is followed by worldwide deaths annually from stomach cancer (803 000), colorectal cancer (639 000), liver cancer (610 000) and breast cancer (519 000) (WHO 2009).

In the United States (US) in 2006, about 106,000 men and 90,000 women were diagnosed with lung cancer, and over 80% these numbers died of the disease (89,000 men and 69,000 women) (Centers for Disease Control and Prevention and National Cancer Institute [NCI] 2010). The annual US incidence rate (2007) was about 59 cases per 100,000, with small cell lung cancer accounting for 7 cases per 100,000, and non-small cell lung cancer accounting for 52 cases per 100,000; the rate of death was 51/100,000 (Surveillance Epidemiology and End Results (SEER) 2010).

Survival after diagnosis remains very poor compared with other types of cancer, particularly with a diagnosis of advanced stage cancer (Australian Institute of Health and Welfare 2003). In the US in 1999-2006, the 5-year relative survival after diagnosis of any type of lung cancer was estimated to be 16%; 18% for non-small cell lung cancers and 6% for small cell lung cancers (SEER 2010). Approximately \$9.6 billion is spent in the US each year on lung cancer treatment (NCI 2009).

In patients diagnosed with early stage lung cancer, surgery with a curative intent is the conventional treatment of choice; however, many patients are not eligible for surgery due to age or underlying co-morbidities (Wasser and Dupuy 2008, Bach et al 2009). Of those fit to undergo surgery, postoperative mortality can be around 10% (Ginsberg et al 1983).

Technology

The techniques of radiofrequency ablation, laser ablation, high-frequency ultrasound ablation, and microwave ablation can all be classed as hyperthermal ablation techniques. Treatment temperatures range from 60 to 100°C; at these temperatures, cellular proteins and nucleic acid-histone protein complexes are rapidly denatured, leading to rapid cell death, followed by coagulation necrosis over subsequent days (Wasser and Dupuy 2008). At frequencies from 900 to 2450 MHz microwave radiation heats tissue by agitating water molecules, inducing cellular death via coagulation necrosis (Simon et al 2005). Microwaves produce a large zone of active heating (up to 2 centimeter), allowing more uniform tumor ablation than radiofrequency ablation (several millimeters) (Wasser and Dupuy 2008).

Microwave ablation can be performed as a percutaneous procedure in an out-patient setting or via laparoscopic or open surgery, can often be performed under conscious sedation rather than general anesthetic, and can be guided using ultrasound or computed tomography (CT) (McTaggart and Dupuy 2007, Carrafiello et al 2008, Wasser and Dupuy 2008). Image guidance can be used to localize the tumor, determine the best percutaneous entry route, and the number and type of microwave applicators to be employed (Wolf et al 2008).

Microwave applicators are typically thin 14.5 gauge antennae that are introduced percutaneously into the tumor bed. The antennae are attached to a generator to emit an electromagnetic microwave through their exposed portions. The remaining antennal shafts are insulated to allow cooling (McTaggart and Dupuy 2007). Tumors > 2 centimeter in diameter may require the use of multiple applicators concurrently (Wasser and Dupuy 2008).

Stage of development

Clinical trials for microwave ablation for the treatment of lung cancer have been completed in Italy, the United States and China.

Regulatory approval

A number of microwave ablation devices have received U.S. Food and Drug Administration (FDA) 510(k) approval (Table 1), the earliest device being approved in December 1993 (FDA 2010).

Current clinical trials

No clinical trials on microwave ablation for lung cancer are underway, although clinical trials are being conducted on radiofrequency ablation in lung cancer and on microwave ablation in other cancers (liver and breast) (Clinicaltrials.gov 2010).

Table 1 FDA-approved microwave ablation devices.

Name of device	Manufacturer	FDA approval number	FDA approval date
MicroThermX [®] Microwave Ablation System	BSD Medical Corp.	K100786	08/13/2010
MicroSurgeon Microwave Tissue Ablation Device System	MicroSurgeon Inc.	K082565	02/12/2009
Modification to MedWaves Microwave Coagulation/Ablation System	MedWaves Inc.	K083537	01/15/2009
ValleyLab Microwave Ablation Generator	Covidien LP, formerly known as ValleyLab	K072687	11/25/2008
MicroThermX [®] -100 Microwave Ablation System (MTX-100)	BSD Medical Corp.	K081042	09/03/2008
Microwave Tissue Coagulation System (MTCS)	Foundry Newco X Inc.	K072870	01/14/2008
MedWaves Microwave Coagulation/Ablation System	MedWaves Inc.	K070356	12/18/2007
MicroSurgeon Microwave Soft Tissue Ablation System	MicroSurgeon Inc.	K070023	08/15/2007
VivaWave [™] Microwave Ablation System	ValleyLab	K053535	04/27/2006
VivaWave [™] Microwave Ablation System	Vivant Medical Inc.	K050223	02/24/2005
Guidant Microwave Ablation System	Guidant Corp.	K041340	07/28/2004
VivaRing [™] Microwave Ablation Probe	Vivant Medical Inc.	K040279	03/02/2004
VivaTip [™] Microwave Ablation Probe	Vivant Medical Inc.	K032702	10/03/2003
Tri-Loop [™] Microwave Ablation Probe	Vivant Medical Inc.	K032047	08/06/2003
Loop [™] Microwave Ablation Probe	Vivant Medical Inc.	K023311	04/09/2003
VivaWave [™] Microwave System	Vivant Medical Inc.	K011676	06/18/2002
FLEX 10 Accessory for the AFx Microwave Ablation System	AFx Inc.	K013946	02/27/2002
AFx Microwave Generator Ablation Systems	AFx Inc.	K003978	05/22/2001
Microwave Delivery System (MDS), model MMC-300	Microwave Medical Corp.	K991456	10/25/1999
Microwave Insurg Introducer	Boston Scientific Corp.	K933985	11/12/1993

Current treatment and alternatives

Current treatments available for early stage lung cancer include:

- Surgery (lobectomy, wedge or segment removal, pneumonectomy)
- Radiotherapy
- Chemotherapy
- Ablation (radiofrequency, laser, high-frequency ultrasound, microwave, cryo)
- Combination therapy, e.g. radiotherapy + cisplatin-based chemotherapy

Surgical resection with curative intent is the traditional gold standard of treatment for early stage lung cancer (Wasser and Dupuy 2008). In patients ineligible for surgical resection, minimally invasive alternatives include radiotherapy (alone, or in conjunction with chemotherapy) or ablation techniques. Hyperthermal ablative techniques differ mainly in the method of heat generation and thus the tissue damage achieved (Vogl et al 2009).

Literature review

Search criteria

Keywords utilized:

Lung cancer, lung tumor*, lung tumour*, cancer, tumor*, tumour*, microwave ablation

MeSH terms utilized:

Lung neoplasm, Neoplasm, Tumor

Databases utilized:

PubMed, OVID (EMBASE)

Study inclusion criteria

Table 2 Inclusion criteria for identification of relevant studies.

Characteristic	Criteria
Publication type	Systematic reviews, randomized controlled trials (RCTs), non-randomized comparative studies, case series studies
Patient	Patients with lung cancer
Intervention	Minimally invasive microwave ablation
Comparators	Surgical resection, radiotherapy, chemotherapy, other ablative techniques
Outcomes	Treatment success, disease recurrence, patient survival, complications
Language	English only

Included studies

Three case series studies were identified for inclusion in this report. These studies examined the use of microwave ablation in a total of 71 patients with lung cancer.

Given the limited evidence available for microwave ablation in lung cancer, higher quality studies reporting outcomes in patients with other common cancer types treated with microwave ablation were also examined. Studies comparing different methodologies of microwave ablation (e.g. straight versus looped antennae) were not eligible for inclusion.

Critical appraisal

All three lung cancer studies were case series (Carrafiello et al 2010; Wolf et al 2008; He et al 2006) (see Table 3 for study profiles). Comparative evidence and one review were available for microwave ablation in liver cancers¹ (Hompes et al 2010; Ong et al 2009; Ohmoto et al 2009; Wang et al 2008; Shibata et al 2002).

¹ The annual incidence rate of liver cancer in the US in 2007 was 6.9 cases per 100,000, and the rate of death was 5.4 individuals per 100,000 (about 10% of that of lung cancer); 5-year survival after diagnosis (1999-2006) was similar to that of lung cancer at about 14% (SEER 2010).

Lung cancer

Case series evidence

In Italy, Carrafiello et al (2010) retrospectively reviewed the outcomes of nine patients with 10 histologically confirmed non-small cell lung cancers who underwent percutaneous microwave ablation. The tumours were squamous cell carcinoma (n=5), adenocarcinoma (n=4), and neuroendocrine carcinoma (n=1) and in two cases patients had lung metastases from tumors in the opposite lung. Ablative procedures were performed under local anesthesia and moderate sedation using CT fluoroscopy guidance (n=7 lesions) or XperGuide (n=3 lesions). The microwave antenna was inserted within the lesions and maintained at a power of 45 watts for a total ablation time of 10 minutes; lesions with a maximum diameter ≤ 3 centimeter (n=8) were treated using a single antenna while those > 3 centimeter (n=2) were treated using two antennae simultaneously (positioned 1 centimeter apart). Immediate follow-up included CT to confirm treatment success, followed by chest radiography to evaluate the presence of immediate complications. Further CT examination occurred at 1, 3 and 6 months. Technical success was defined as correct positioning of the antennae within the lesion. Safety included occurrence of intra-, peri- and post-ablation complications, which were classified as either major or minor based on the Society of Interventional Radiology classification system.² Treatment effectiveness was defined as complete absence of enhancement within the ablation zone on contrast-enhanced images.

In the U.S., Wolf et al (2008) retrospectively evaluated 50 patients with primary or secondary lung malignancies without chest wall involvement who underwent CT-guided percutaneous microwave ablation. All tumours were deemed to be inoperable or patients refused surgery. CT and/or positron emission tomographic (PET)/CT images were undertaken preoperatively to determine lesion histology. Treated were primary lung cancers (27 non-small cell; 3 small cell [initially interpreted as non-small cell at biopsy]) and metastases ≤ 5 centimeter (primaries included nine colorectal; three breast; two hepatocellular; two head and neck; one rhabdomyosarcoma; and one each of bladder, renal cell, and uterine). All procedures were carried out by one of two experienced, board-certified radiologists under local (n=48) or general (n=2) anesthesia. Tumors < 2 centimeter were treated with a single antenna (n=35) and those ≥ 2 centimeter were treated with multiple antennae (two antennae n=3, three antennae n=18, four antennae n=6, multitine deployable ring n=4). Ablation took place in accordance with the manufacturer's recommendations (10 minutes for 3.7 centimeter active tip and 5 to 10 minutes for 1.6 centimeter active tip) if the patient could tolerate the ablation time. Immediate complications were assessed by chest radiography 2 hours post-ablation; if patients were considered stable without complications they were discharged home. Follow-up CT was performed at 1, 3 and 6 months. Reablation was performed in patients with local tumor progression on follow-up CT scans. Technical success was defined as tumors treated per protocol with no detectable enhancement on initial (1 to 30 day post-ablation) CT scans. The Common Terminology Criteria for Adverse Events (CTCAE³) system was used to grade severity of complications.

² Society of Interventional Radiology classification system: **Minor Complications:** A. No therapy, no consequence; B. Nominal therapy, no consequence; includes overnight admission for observation only. **Major Complications:** C. Require therapy, minor hospitalization (<48 hours); D. Require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 hours); E. Permanent adverse sequelae; F. Death.

³ Common Terminology Criteria for Adverse Events: Grade 1: mild adverse event, Grade 2: moderate adverse event, Grade 3: severe adverse event, Grade 4: life-threatening or disabling adverse event, Grade 5: death related adverse event.

In China, He et al (2006) reported the use of ultrasound-guided percutaneous microwave ablation in 12 patients with 16 peripheral (in contact with the visceral pleura) cytologically proven, malignant lung tumors. Five patients had primary lung tumours (squamous cell, adenocarcinoma and large cell) and seven had metastatic lung tumors (liver, kidney, stomach and glioma). Patients were not surgical candidates due to: patient preference (n=5), poor previous experience with chemo- or radiotherapy (n=4) and poor cardiopulmonary reserve (n=3). Percutaneous microwave ablation was carried out under local anaesthesia by attending radiologists. For tumors < 3 centimeter, treatment started with 60 watts for 100 seconds and then changed to 30-40 watts for 300-600 seconds. For tumors \geq 3 centimeter, treatment started with 70-80 watts for 100 seconds then changed to 40-60 watts for 300-600 seconds. Additional three-dimensional microwave ablation took place simultaneously in tumors \geq 3 centimeter. Patients remained in hospital for 6 to 24 hours. Follow-up involved chest x-ray immediately post-ablation to assess presence of pneumothorax. Ultrasound and CT were used to assess changes in the size, echogenicity/ attenuation and vascularity of the ablated tumors. Tumors were considered to have remarkable, moderate or mild shrinkage if area reductions were 70% to 100%, 50% to 70% and 30% to 50%, respectively. Repeat ablation was employed if: tumor size increased, tumor blood flow existed or increased on Color Doppler Flow Imaging (CDFI⁴) or tumor enhancement was observed on a contrast-enhanced CT scan.

⁴ CDFI of tumor blood flow: Grade 0: none; Grade I: 1-2 tiny branch vessels (<2 mm in diameter); Grade II: 3-4 tiny branch vessels or 1-2 feeding vessels (>2 mm in diameter); Grade III: >2 feeding vessels.

Table 3 Profile of studies reporting microwave ablation for lung cancer (Level IV evidence).

Author, year	Level of evidence	Location	Study period	Selection criteria	n	Patient characteristics	Tumor characteristic	Follow-up (mean)
Carrafiello et al, 2010	Level IV case series	Italy (Single centre)	11/2008 to 08/2009	Inclusion: Retrospective review of patients with neoplastic lung disease judged to be inoperable on the basis of tumor stage, co-morbidities, advanced patient age and/or patient refusal to undergo surgery. Exclusion: NR	9	Age: mean 78 (range 69-88) years M/F: 7/2	Number: 10 (mean 1.1 lesions/patient) Diagnosis: squamous cell carcinoma (n=5), adenocarcinoma (n=4), neuroendocrine carcinoma (n=1) Diameter: mean 29.5 (range 14-69) mm	3.6 (range 1-9) months
Wolf et al, 2008	Level IV case series	United States (Single centre)	11/2003 to 08/2006	Inclusion: Retrospective review of patients considered medically inoperable, or those who refused surgery. Exclusion: Patients with radiographic evidence of nodal disease, index tumor abutting the main-stem bronchi, main pulmonary artery branches, esophagus, or trachea, or all of these structures; parietal pleural transgression into the chest wall; or an international normalized ratio greater than 1.8; or all of these.	50	Age: mean 70 years M/F: 28/22	Number: 82 (mean 1.42 lesions/ patient) Diagnosis: Lung cancer primary (n=30 patients) and secondary (n=20 patients: primaries of colorectal, breast, liver, head and neck, rhabdomyosarcoma, bladder, kidney and uterus) Diameter: mean 3.5 (SD 1.6) cm	10 (SD 6.8) months
He et al, 2006	Level IV case series	China (Single centre)	12/2002 to 09/2003	Inclusion: Patients who refused surgery, had poor cardiopulmonary reserve and those who experienced severe side effects from previous chemo/radiotherapy (including vomiting, diarrhea, renal failure). Exclusion: NR	12	Age: mean 47.5 (range 31-69) years M/F: 12/5	Number: 16 Diagnosis: Lung cancer primary (n=6 lesions) and secondary (n=10 lesions [liver, kidney, stomach and glioma]) Diameter: mean 4.18 cm	20 (range 6-40) months

M/F: male/female; NR: not reported; SD: standard deviation.

Note on study quality: The lack of comparative evidence available for microwave ablation of lung cancer is a major limitation. Case series studies are more susceptible to bias than are comparative trials and RCTs (although their data provides preliminary information about safety and efficacy). At least two of the three included studies were retrospective reviews (Carrafiello et al 2010; Wolf et al 2010); the remaining study did not report whether patients were selected prospectively (He et al 2006). Selection bias may therefore have confounded results. Patient numbers were also very small in two studies (Carrafiello et al 2010; He et al 2006). The mix of tumor types (particularly primary and secondary) also meant that patient groups were quite disparate. Finally, in one of the included studies (Carrafiello et al 2010), a manufacturer of microwave ablation devices (ValleyLab) provided the microwave generators and antennae used to treat all of the included patients; however, it was reported that *“those authors who were not consultants for ValleyLab had control of the inclusion of any data and information that might present a conflict of interest for those authors who are consultants for this industry.”*

Liver cancer

A quasi-systematic literature review examined microwave ablation for liver cancer (Ong et al 2009). In addition, four studies compared the use of microwave ablation with either radiofrequency ablation (n=3 studies) or surgical resection (n=1 studies) (Hompes et al 2010; Ohmoto et al 2009; Wang et al 2008; Shibata et al 2002). (See Table 4 for study profiles.) Only one of these comparative studies used random allocation to assign patients to a treatment group (Shibata et al 2002).

Review evidence

Ong et al (2009) reviewed the efficacy and safety of microwave ablation for primary and secondary liver cancers. A literature search of a single database (PubMed) was conducted, using a broad range of search terms to retrieve literature published in English between 1975 and January 2008. Included studies reported on outcomes of interest (technical success of microwave ablation, local tumor recurrence rate, and patient survival). Additional studies were identified via the bibliographies of included studies. Data collection and analysis were conducted by a single researcher and 25 clinical studies (n=1598 total) published between 1996 and 2007 were selected for inclusion. The majority of lesions treated were hepatocellular carcinoma (HCC). Reported in 21 of the 25 studies (84%) were: microwave frequency (2450 MHz); the power at which each ablation took place (50-90 watts), and duration of ablation (30-1500 seconds).

Comparative evidence

Microwave ablation versus radiofrequency ablation:

In Belgium, Hompes et al (2010) compared single-probe ultrasound-guided microwave ablation of liver metastases in 6 patients with a historical control group (matched for tumor size and localization) of 13 patients treated with ultrasound-guided radiofrequency ablation. Microwave ablation was performed laparoscopically in five patients and percutaneously in one patient. Microwave ablation was delivered according to manufacturer guidelines (915 MHz microwaves, 10 minutes, 40 watts). Radiofrequency ablation was performed via laparoscopy (n=7), laparotomy (n=4) and percutaneously (n=2). Pre- and post- ablative tumor diameters were measured using dual-phase contrast enhanced helical CT liver scans. Postoperative analysis was performed within 1 week and 3 months of treatment. Irregular peripheral contrast enhancement and a multilobular shape at the ablation margin were considered to indicate residual tumor, and local

recurrence was defined as cancer recurrence at the site of the ablated liver metastasis. Microwave ablation and radiofrequency ablation were compared with respect to the increase in lesion diameters measured before and after treatment, the variability between the lesions after ablation, and the variability within the lesion diameters.

A study by Ohmoto et al (2008) took place at a single institution in Japan where outcomes for 49 patients treated with microwave ablation for small (≤ 2 centimeter) HCC nodules were compared with those for 34 patients treated with radiofrequency ablation. There were no significant differences between patient groups at baseline. All patients undergoing thermal ablation had opted to do so over surgery and the modality by which thermal ablation was achieved (i.e. microwave versus radiofrequency) also depended on patient preference. All procedures were performed under local anaesthesia and sedation using ultrasound guidance. Microwave ablation was performed using 2450 MHz microwaves for a duration of 60 seconds at 60 watts followed by the application of dissociated current for 30 seconds. Radiofrequency ablation took place for 12 minutes at 200 watts.

In an RCT in Japan conducted by Shibata et al (2002), 72 consecutive patients with biopsy-proven HCCs received ablation therapy. Patients were randomly assigned (using the sealed envelope method) to microwave ablation (n=36) or radiofrequency ablation (n=36). There were no significant differences between the two treatment groups at baseline, including the proportion of patients with one (28 versus 25), two (6 versus 10) or three (2 versus 1) nodules to be treated. One author performed all ablative procedures using either 460 kHz radiofrequency or 2450 MHz microwaves. The power and duration of ablation varied between the treatment groups and depended on the size of the antennae used. In addition to pretreatment imaging (abdominal ultrasound and CT), dynamic CT was performed 1 week and 1 month after the initial treatment, and every two months thereafter (these scans were interpreted by a single author). Complete tumor necrosis, or treatment success, was defined by a non-enhancing area with a diameter equal to or greater than that of the treated nodule on follow-up CT. Additional ablation was performed 1 week after the initial treatment when incomplete tumor necrosis was detected.

Microwave ablation versus surgical resection:

In China, Wang et al (2008) retrospectively compared outcomes for patients with nodular HCC treated with either microwave ablation (n=114) or hepatic resection (n=80). There were no significant differences between the patient groups at baseline in regards to age, sex, co-morbidities or tumor characteristics. Microwave ablation was performed with a microwave frequency of 2450 MHz and a power output range of 10-80 watts. A single or multiple puncture technique was used to ablate each nodule depended on its size; tumors < 1.7 centimeter in diameter were treated with a single puncture technique and tumors > 1.7 centimeter in diameter were treated with a multiple (simultaneous) puncture technique. In general, an output setting of 60 watts for 300 seconds was used during ablation. Radiation was stopped when the measured temperature outside the tumor reached 60°C or maintained a level of 54°C for 1 minute. The treatment protocol for those patients treated with hepatic resection was not reported.

Table 4 Profile of studies reporting microwave ablation for liver cancer (Level III evidence).

Author, year	Level of evidence	Location	Study period	Selection criteria	n	Comparator (n)	Patient characteristic	Tumor characteristics	Blinding	Follow-up
<i>Microwave ablation versus radiofrequency ablation</i>										
Hompes, 2010	Level III-3 comparative evidence	Belgium (Single centre)	08/2008 to 11/2008	Inclusion: Patients with liver metastases (< 3 cm in diameter) without underlying liver disease who were considered ineligible for surgical resection based on high clinical risk score, no or minimal response to systemic chemotherapy and severe systemic disease. Exclusion: NR	16	RFA (13)	<i>MWA</i> Age: median 64 (range 47-82) years M/F: 2/4 <i>RFA</i> Age: median 58 (range 35-70) years M/F: 7/6	Number: NR Diagnosis: metastases Diameter: (median transverse) MWA = 12 (range 6-18) mm; RFA = 12 (range 7-24) mm	NR	Median 6.3 (range 4.9-7.8) months
Ohmoto, 2009	Level III-3 comparative evidence	Japan (Single centre)	06/1998 to 08/2006	Inclusion: NR Exclusion: NR	49	RFA (34)	<i>MWA</i> Age: mean 64 (range 38-75) years M/F: 41/8 <i>RFA</i> Age: mean 67 (range 44-78) years M/F: 25/9	Number: MWA = 56 nodules; RFA = 37 nodules Diagnosis: HCC Diameter: MWA = mean 1.7 (range 0.8-2.0) cm; RFA = mean 1.6 (range 0.7-2.0) cm	NR	MWA: mean 1019 days RFA: Mean 787 days
Shibata, 2002	Level II randomized controlled trial evidence	Japan (Single centre)	03/1999 to 10/2000	Inclusion: Patients with a solitary hepatocellular nodule with a diameter < 4 cm or, two or three nodules ≤ 3 cm in diameter. Exclusion: NR	36	RFA (36)	<i>MWA</i> Age: mean 62.5 (range 52-74) years M/F: 24/12 <i>RFA</i> Age: mean 63.6 (range 44-83) years M/F: 26/10	Number: MWA = 46 lesions; RFA = 48 lesions Diagnosis: HCC Diameter: MWA = mean 2.2 (range 0.9-3.4) cm; RFA = mean 2.3 (range 1.0-3.7) cm	NR	Mean 18 (range 6-27) months

Microwave ablation versus surgical resection										
Wang, 2008	Level III	China	01/1995 to 12/2004	<p>Inclusion: Patients with a single HCC < 5 cm in diameter and the absence of portal vein thrombosis or extrahepatic metastases.</p> <p>Exclusion: NR</p>	114	Resection (80)	<p><i>MWA</i></p> <p>Age: mean 54.82 (range 25-81) years</p> <p>M/F: 99/15</p> <p><i>Resection</i></p> <p>Age: mean 57.66 (range 18-78) years</p> <p>M/F: 72/8</p>	<p>Number: 194 (1 lesion/ patient)</p> <p>Diagnosis: HCC</p> <p>Diameter: MWA = mean 2.9 (range 1.1-4.9) cm; resection = mean 3.0 (range 1.2-4.8) cm</p>	Pre-ablation biopsy specimens assessed by two blinded pathologists.	NR

HCC: hepatocellular carcinoma; M/F: male/female; MWA: microwave ablation; NR: not reported; RFA: radiofrequency ablation.

Note on study quality: The evidence base available for microwave ablation of liver cancer is of higher quality than that available for lung cancer in that some comparative evidence exists. However, only one RCT has been carried out (and allocation concealment was not employed) and the comparative study by Ohmoto et al (2008) allowed patients to select treatment modality. Patients were generally well matched at baseline, and inclusion/exclusion criteria and outcomes of interest were well defined. Bias may have been further reduced in the studies that involved a single surgeon/assessor.

Safety and efficacy

Safety

Complications such as postablation syndrome, skin burns and pain may be associated with ablative treatment. The safety profile of microwave ablation is investigated below for its use in lung and liver cancer, respectively.

Lung cancer

All of the complications reported in the studies included for this indication (Carrafiello et al 2010; Wolf et al 2008; He et al 2006) are presented below in Table 5. Common adverse events were pneumothorax, skin burns and pain.

Pneumothorax

Low-grade, asymptomatic, pneumothorax was reported in all three case series studies. Wolf et al (2008) reported the highest incidence at 39% of ablation sessions (26/66). Of these, 69% (18/26) were graded mild (CTCEA grade 1) and 31% (8/26) were graded moderate to severe (CTCEA grade 2-3). In Carrafiello et al (2010), asymptomatic grade 1 pneumothorax was recorded in three patients. In the sole affected patient in the study by He et al (2006), spontaneous absorption occurred.

Skin burns

All three included studies reported the incidence of intra-procedural skin burns. Occurrence rate ranged from 0% to 8% and the majority of cases were mild and resolved with conservative therapies. However, in the study by Wolf et al (2008) one burn was considered severe (CTCEA grade 3) and required plastic surgery and another was classified as CTCEA grade 2, requiring topical therapy.

Pain

All patients reported some degree of pain during treatment and follow-up periods. He et al (2006) stated that all patients experienced mild to moderate pain in the site at which the microwave probe was inserted, which usually resolved within 1 week. The proportion of patients experiencing significant pain necessitating analgesic usage appeared to be low; with only one patient (pain score of 5 out of 10 on the visual analogue scale) receiving narcotic analgesia (Wolf et al 2008).

Other

- Postablative syndrome: Wolf et al (2008) reported that 1 patient (2%) experienced postablative syndrome, defined as a constellation of a productive cough with or without minor hemoptysis, residual soreness in the treated area and fever which occurred for several days after ablation. All signs and symptoms resolved within 3 to 4 days in this patient.
- Fever: Low-grade fever was reported in 7 patients (58%) in the study by He et al (2006); in all cases fever subsided with conservative treatment.
- Readmission to hospital: This occurred in 20% (10/50) of patients in the study by Wolf et al (2008). The majority (9/10) were admitted for continued monitoring or pneumothorax and were discharged home after 1 to 2 days. The remaining patient was admitted to the intensive

care unit due to acute respiratory distress syndrome and seizure activity. After 1 week this patient was moved to a regular ward and discharged home shortly thereafter.

- 30-day death rates: Two of the included studies reported on this outcome; in both cases the rate was 0% (Carrafiello et al 2010; Wolf et al 2008). The same two studies reported one death each at longer term follow-up (3 months and 8 months, respectively). In the study by Carrafiello et al (2010) it was noted that the death was only 'relatively related to the ablation therapy' and in the study by Wolf et al (2008) the death was due to a delayed complication (fatal hemoptysis as a result of an eroding abscess).

Table 5 Complications reported in lung cancer studies.

Complication	Author, year		
	Carrafiello, 2010	Wolf, 2008	He, 2006
Pneumothorax	3/9 patients (33%)	26/66 ablation sessions (39%)	1/12 patient (8%)
Skin burns	0/9 patients (0%)	2/50 patients (4%)	1/12 patient (8%)
Postablative syndrome	0/9 patients (0%)	1/50 patients (2%)	NR
Pain	No patient with VAS score indicating pain relief needed	1/50 patients (2%)	12/12 patients (100%)
Fever	NR	NR	7/12 patients (58%)
Re-admission	0/9 patients (0%)	10/50 patients (20%); 10/66 ablations (15%)	NR
Death (30-day rate)	0/9 patients (0%)	0/50 patients (0%)	NR

NR: not reported; VAS: visual analogue scale

Liver cancer

Safety was reported in three of the four comparative studies (Ohmoto et al 2009; Wang et al 2008; Shibata et al 2002). Safety was also detailed in the review by Ong et al (2009) for 20 of the 25 included studies (n=995 patients). The most common complications were pain and fever.

Pain

Intraprocedural or post-procedural pain (lasting between hours and days) occurred in a total of 93% of patients included in the review. Similarly, all of the patients in the study by Ohmoto et al (2008) reported pain to varying degrees; the incidence of postoperative pain was significantly higher in the microwave ablation group compared with the radiofrequency ablation group ($P=0.035$). Wang et al (2008) reported that most patients in the microwave ablation group experienced mild to severe pain at the insertion site or diaphragm irritation with right shoulder tip pain during the procedure, which lasted 1-7 days following the procedure. In the majority of these patients (n=70) pain resolved spontaneously but in 13% (15/114), analgesics were required. In the same study, mild pain was reported in 73% (58/80) of patients in the resection group (statistical comparisons were not made). The RCT by Shibata et al (2002) reported the need for analgesics during or immediately after treatment in 15 of 36 patients in the microwave ablation group compared with 10 of 36 patients in the radiofrequency group. Three of the 15 patients in the microwave ablation group who experienced procedural pain could not continue treatment owing to the severity of that pain and underwent subsequent ablative sessions under general anesthesia.

Fever

Transient fever was the second most common complication reported in the review, occurring in 70% of patients. In Ohmoto et al (2008), the incidence of fever was significantly higher in the microwave ablation group compared with the radiofrequency ablation group ($P=0.016$). Fever also occurred commonly in the study by Wang et al (2008); an elevated temperature ranging between 37.2 to 39.7°C and beginning the day of ablation and persisting for approximately 3 to 5 days was apparent in 68% (78/114) of patients in the microwave ablation group, compared with 20% of patients in the radiofrequency ablation group.

Mortality

Across all studies in the Ong et al (2009) review, the total mortality rate was 0.002% (two deaths). Wang et al (2008) (n=194 patients) also reported mortality outcomes after 5 years of follow-up; a total of 30 and 24 patients in the microwave ablation and hepatic resection groups died of HCC and its complications and an additional 9 deaths (microwave ablation group n=5; hepatic resection n=4) occurred from non-hepatic diseases. Differences between treatment groups were not significant.

Other

- In the Ong et al (2009) review, other complications included bile duct injury (0-26% of patients), pleural effusion (6%), wound infection (5%), liver abscess (3%), skin burns (3%), liver failure (2%), hemorrhage (3%), portal vein thrombosis (2%) and seeding of tumor cells along the needle track (rate not reported). The authors noted that increased complication rate may be associated with a higher number of tumors per patient, larger tumors and a higher number of microwave antenna insertions.
- Ohmoto et al (2008) reported that the incidence rates of bile duct injury ($P=0.025$), plural effusion ($P=0.043$) and ascites ($P=0.026$) were significantly higher in the microwave ablation group compared with the radiofrequency ablation group. In the same study it was reported that serious complications, such as liver abscess, hemorrhage, hepatic infarction and portal thrombus, only occurred in the microwave ablation group.
- In the RCT by Shibata et al (2002), major complications were reported in one patient in the radiofrequency ablation group compared with four patients in the microwave ablation group (difference not significant). Also reported were liver abscess, cholangitis, skin burn and subsupilar hematoma in one patient each in the microwave ablation group, and segmental hepatic infarction in one patient in the radiofrequency ablation group. Conservative therapies were sufficient in resolving all of the complications encountered in this study.

Efficacy

Common efficacy outcomes included treatment success (e.g., complete absence of enhancement within the ablation zone on contrast-enhanced CT images), disease recurrence, and patient survival. Technical success rate (correct positioning of the antennae within the lesion) was reported but is of less interest here.

Lung cancer

Treatment success

All three studies reported the occurrence of complete tumor ablation. Two studies reported technical success rate (Carrafiello et al 2010; Wolf et al 2010) and one study reported the need for reablation of residual disease (Wolf et al 2008) (Table 6).

Table 6 Complete tumor ablation rate following microwave ablation.

Author, year	Mean length of follow-up	Complete tumor ablation	Need for reablation of residual disease
Carrafiello, 2010 (n=10)	3.6 (range 1–9) months	Complete necrosis in 9/10 ablations (90%)	None
Wolf, 2008 (n=50)	10 ± 6.8 months	37/50 patients (74%); i.e., 13/50 (26%) patients had residual disease at the ablation site at follow-up	Re-ablation within 6 months = 4 / 66 ablations (6%)
He, 2006 (n=12)	20 (range 6-40) months	4 / 12 patients as proven by biopsy, (remaining patients did not undergo biopsy)	NR

NR: not reported.

A common finding upon postablation CT examination reported in the studies by Carrafiello et al (2010) and Wolf et al (2008) was areas of ground-glass attenuation⁵ within the ablated lesion, which extended to the areas surrounding the antennae tracks. Carrafiello et al performed further diagnostic evaluation at 1, 3 and 6 month follow-up in 9, 8 and 3 patients, respectively. An initial increase (0.67 centimeter) in the maximum tumor diameter was observed, followed by a persistent reduction in the diameter of the ablated area, consistent with consolidation of the pulmonary parenchyma. Wolf et al reported similar findings, with an initial increase (0.65 centimeter) in tumor diameter followed by a persistent reduction.

Carrafiello et al (2010) noted the presence of a cavitation in 50% (5/10) of lesions, along with minor pleural effusions in 20% (2/10) of lesions and adenopathies with maximum dimensions < 1 centimeter at the level of the treated lesion in 10% (1/10) of lesions. Cavitory changes were identified in 43% of tumors in the study by Wolf et al (2008) and were statistically related to a reduction in cancer-specific mortality ($P=0.02$). Also in the study by Wolf et al, ablated tumors abutting the visceral pleura resulted in pleural thickening in 44% (22/50) of patients or pleural retractions in 8% (4/50) of patients. Minor pleural effusions were detected in 30% (15/50) of

⁵ Ground-glass attenuation describes the appearance of hazy lung opacity which often indicates the presence of an active and potentially treatable process; active disease is present in more than 80% of patients who show this finding. Because of its association with active lung disease, the presence of ground-glass attenuation often leads to further diagnostic evaluation, including lung biopsy.

patients and lymphadenopathy developed in the region of 10 treated tumors in 20% (10/50) of patients but was not significantly related to first recurrences or death.

Disease recurrence

Two studies reported the incidence of disease recurrence (Carrafiello et al 2010; Wolf et al 2008). Carrafiello et al (2010) reported disease recurrence at 3 months in one patient; this patient underwent reablation leading to complete necrosis of the recurrent lesion as seen at CT examination several days following the secondary procedure. In the study by Wolf et al (2008) the rate of recurrent disease at the ablation site was considerably higher; 26% (13/50) of patients showed evidence of recurrence at 6-month follow-up imaging. The occurrence of recurrent disease appeared to be more prominent in patients with tumors that were > 3 centimeter in diameter; thus, index tumor size > 3 centimeter was found to be significantly predictive of recurrent disease, as shown by using logistic regression analysis ($P=0.01$). During follow-up, Wolf et al (2008) reported recurrent disease distant from the ablation site in 22% (11/50) of patients including progressive disease within the treated lung but not at the ablation site in 82% (9/11) and new metastatic disease in the untreated lung or other organs in the remaining 2 patients. As a result 1-year local control rate was 67% (standard deviation [SD] 10%), with a mean of 16.2 months (SD 1.3 months) to first recurrence distant from the ablation site.

Patient survival

Two of the included studies reported patient survival outcomes (Carrafiello et al 2010; He et al 2006). Carrafiello et al (2010) reported Kaplan-Meier median time to death from any cause, including pulmonary malignancy, for all patients to be 19 months (SD 1 month). The 1, 2 and 3 year actuarial survival rates were 65%, 55% and 45%, respectively. Cancer-specific mortality yielded a median time to death of 22 months (SD 1 month) and a 1, 2 and 3 year survival rates of 83%, 73% and 61%, respectively. Tumor size did not significantly affect cancer-specific mortality rate or actuarial survival. In the study by He et al (2006), seven patients remained alive and five patients died from metastases at 10, 11, 12, 18 and 38 month follow-up.

Other

He et al (2006) reported additional outcomes including the improvement of clinical symptoms and blood flow status (measuring by CDFI). Symptoms disappeared in five patients and were alleviated in seven patients at 1 to 4 week follow-up. Blood flow within the 16 treated tumors was significantly reduced following ablation ($P<0.01$).

Liver cancer

Treatment success

Fourteen studies included in the review by Ong et al (2009) reported on rate of complete ablation, ranging from 80% to 100%, with an average of approximately 93% of tumors completely ablated. Hompes et al (2010) assessed treatment success by measuring tumor diameter pre- and post ablation (Table 7).

Table 7 Tumor diameter, microwave ablation versus radiofrequency ablation (historical controls)

Dimension (median)	Pre-MWA	Pre-RFA	P value	Post-MWA	Post-RFA	P value
Transverse	12 mm	12 mm	>0.792	18.5 mm	34 mm	0.003
Antero-posterior	12 mm	12 mm		26 mm	35 mm	0.046
Cranio-caudal	10.5 mm	11 mm		20 mm	32 mm	0.025

MWA: microwave ablation; RFA: radiofrequency ablation.

The increase in all three dimensions was larger following radiofrequency ablation compared with microwave ablation, and most apparent for the transverse diameter. Cumulative diameter increase, for all three dimensions, was 2.1 times (95% confidence interval 1.8-2.5) after microwave ablation compared with 2.6 times (95% confidence interval 2.3-3.1) after radiofrequency ablation ($P=0.058$). Similarly, Ohmoto et al (2009) reported a significantly larger area of necrosis achieved with radiofrequency ablation (maximum 2.7 centimeter/minimum 2.4 centimeter) compared with microwave ablation (2.2 centimeter/1.9 centimeter) ($P<0.001$).

In the RCT by Shibata et al (2002), complete therapeutic effect was shown in 89% (41/46) of nodules in the microwave ablation group and in 96% (46/48) of nodules in the radiofrequency ablation group ($P=0.26$), meaning that residual lesions or incomplete therapeutic effect were observed in 11% and 4% of cases, respectively. In both groups, the majority of lesions with a diameter < 2 centimeter showed complete therapeutic effect whereas lesions > 2 centimeter or close to blood vessels were more likely to experience incomplete ablation. Residual foci of untreated disease were seen in 10% of nodules in the microwave ablation group and in 4% of nodules in the radiofrequency ablation group at 1 year follow-up; this increased to 24% and 12% of nodules by 2 year follow-up in each group, respectively.

Disease recurrence

Nineteen studies included in the Ong et al (2009) review reported local recurrence rates that ranged from 0% to 50% (mean 15%). One study concluded that microwave ablation is as effective as radiofrequency ablation for the treatment of HCC when comparing the completeness of tumor ablation and local recurrence rates. A wider treatment margin was shown to reduce tumor recurrence.

Three of the four comparative studies reported disease recurrence outcomes.

- Hompes et al (2010) reported one biopsy-proven local recurrence in the microwave ablation group (in a patient treated for a solitary colorectal liver metastasis) compared with no cases of local recurrence in the radiofrequency group.
- Ohmoto et al (2009) reported local recurrence rates at 1, 2, 3 and 4 years following microwave ablation and radiofrequency ablation; these were 13% versus 9%, 16% versus 9%, 19% versus 9% and 19% versus 9%, respectively ($P=0.031$).
- Wang et al (2008) reported recurrence or new tumors in 70% (80/114) of patients following microwave ablation and in 76% (61/80) of patients following hepatic resection. In the microwave ablation group, 13% (15/114) of patients had local regrowth of a microwave-treated lesion, 23% (26/114) had new tumors in the same Couinaud segment of the liver but apart from the original tumor site and 24% (27/114) had new tumors in a different Couinaud segment. Extrahepatic tumors were found in 11% (12/114) of microwave ablation patients. In the resection group, new tumors in the ipsilateral and contralateral lobe, but apart from the resection line, occurred in 21% (17/80) and 33% (26/80) of patients, respectively and new

tumors near the resection line occurred in 10% (8/80) of patients. Extrahepatic new tumors were found in 12.5% (10/80) of cases.

Patient survival

The review by Ong et al (2009) reported patient survival outcomes (Table 8).

Table 8: Patient survival rates in the Ong et al (2009) review of 25 studies

Reporting period (year)	# studies reporting	Survival rate range (%)
1	12	71-100
2	10	57-86
3	14	14-92
4	7	17-78
5	8	29-78

In addition, two of the included studies reported median survival time at 35 months and 24 months, respectively (Ong et al 2009).

Two of the included comparative studies described survival outcomes (Ohmoto et al 2002; Wang et al 2008):

- Ohmoto et al (2009): Cumulative survival rate was significantly lower in the microwave ablation group compared with the radiofrequency group at 1- (89% versus 100%), 2- (70% versus 83%), 3- (49% versus 70%) and 4-year follow-up (39% versus 70%) ($P=0.018$).
- Wang et al (2008): Disease-free survival rates at 1-, 3- and 5-year follow-up for patients undergoing microwave ablation or hepatic resection were not significantly different: 73% versus 69%, 54% versus 60% and 33% versus 26%, respectively (P values not reported).

Other

Ohmoto et al (2009) reported the average number of treatment sessions required which was significantly greater for microwave ablation (2.6 sessions, SD 1.2) compared with radiofrequency ablation (1.7 sessions, SD 0.6) ($P<0.001$). Similarly, the average number of microwave ablation treatment sessions (2.4 sessions) required in the study by Shibata et al (2002) was significantly higher compared with radiofrequency ablation (1.1 sessions) ($P<0.001$). The mean session times were 33 and 53 minutes, respectively ($P<0.001$) (Shibata et al 2002).

Cost impact

No economic studies were identified on the use of microwave ablation in cancer. It has been noted, however, that an advantage of image-guided ablative therapies compared with traditional cancer treatments is the lower procedural cost, due in part to the use of outpatient therapy (Simon et al 2005). The costs of various ablative devices were only available in an older article (Dodd et al 2000):

- Microwave generator, \$45,000; single use needle electrode \$500
- Radiofrequency generator, \$12,000 to \$30,000; single use needle electrode \$500-\$1000.

Clinical practice guidelines and consensus statements

No directly relevant clinical practice guidelines or consensus statements were located. Evidence-based clinical practice guidelines for the treatment of non-small cell lung cancer (stage I and II) exist but do not as yet include microwave ablation as a treatment option (Scott et al 2007). As the popularity, experience and evidence base for microwave ablation for lung cancer increases guidelines are likely to be produced.

Interventional procedure guidance documents for the use of microwave ablation for the treatment of HCC and for the treatment of liver metastases were published in 2007 by the National Institute for Health and Clinical Excellence in the United Kingdom (NICE 2007a, NICE 2007b).

Training and education impact

No literature was located regarding training and education in the use of microwave ablation for the treatment of lung cancer.

Summary

Although the supporting literature is very scant, microwave ablation may prove to be a safe and effective treatment for primary and secondary lung cancers; in particular, it may offer inoperable patients a less invasive and less resource intensive alternative to chemo/radiotherapy. Treatment success following microwave ablation was moderate or high, and disease recurrence and the need for re-ablation low (although less favorable in the largest study). Common complications include pneumothorax and pain, although the majority of cases were mild or self-limiting.

From the literature included for liver cancer, microwave ablation had a safety and effectiveness profile similar to that of radiofrequency ablation and hepatic resection although one study found disease recurrence to be significantly higher and patient survival to be significantly lower following microwave ablation compared with radiofrequency ablation. Common complications were pain and fever. One study comparing microwave ablation with radiofrequency ablation suggested these complications occur more often after microwave ablation.

Microwave ablation is less intense than radiofrequency ablation therefore a greater number of treatment sessions are needed; however, because operating time for microwave ablation is generally shorter, the overall durations of both procedures are comparable. Both procedures are also safer and more efficient in removing tumors < 3 centimeter in diameter. Microwave technology is still being refined and future modifications may increase its efficacy in removing both lung and liver cancers.

Recommendation

The evidence base for microwave ablation for the treatment of lung cancer is extremely scanty, i.e., there are very few studies and these are small and generally of low quality. High-quality comparative studies of microwave ablation versus other treatment modalities are required to determine if microwave ablation has a place in the care of patients with lung cancer and which types of patients would benefit the most.

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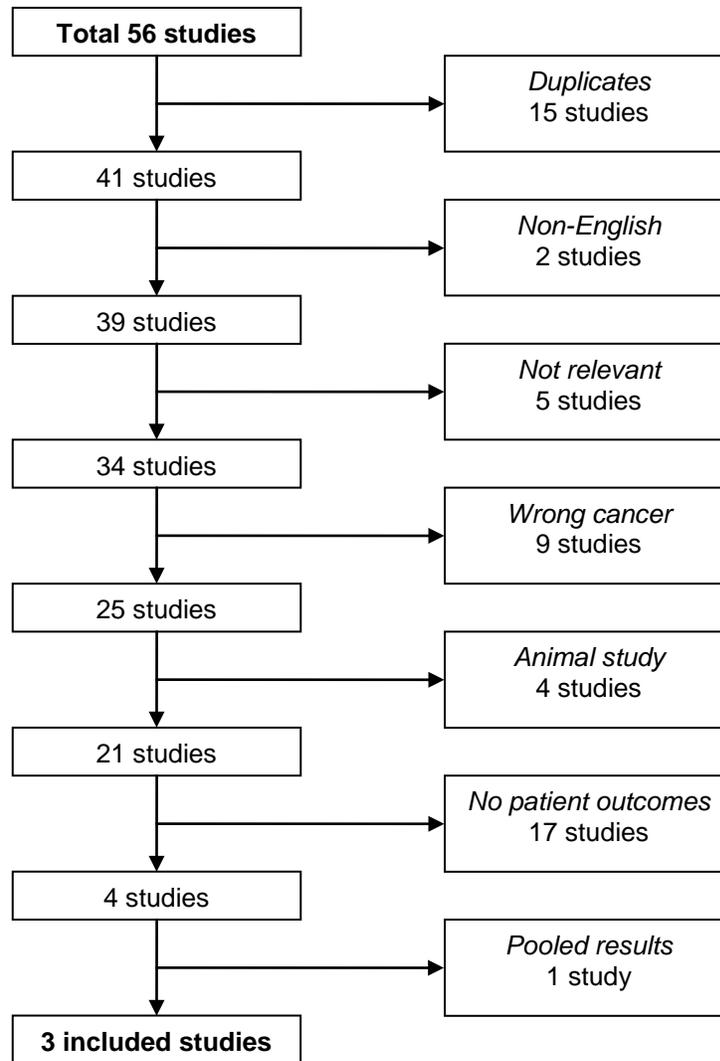
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Appendix A

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Pooled results

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Appendix B

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question

Level	Intervention ¹	Diagnostic accuracy ²	Prognosis	Aetiology ³	Screening Intervention
I ⁴	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ⁵ among consecutive persons with a defined clinical presentation ⁶	A prospective cohort study ⁷	A prospective cohort study	A randomized controlled trial
III-1	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, ⁵ among non-consecutive persons with a defined clinical presentation ⁶	All or none ⁸	All or none ⁸	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomized, experimental trial⁹ ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group 	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomized, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study¹⁰ ▪ Interrupted time series without a parallel control group 	Diagnostic case-control study ⁶	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard) ¹¹	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Explanatory notes

1. Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).
2. The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).
3. If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilized.
4. A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.
5. The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).
6. Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).
7. At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomized controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.
8. All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.
9. This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C with statistical adjustment for B).
10. Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C but where there is no statistical adjustment for B).
11. Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomized controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.