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Australia and New Zealand Horizon Scanning Network

ANZHSN

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AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

Microwave ablation for hepatic tumours

August 2008



**Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical**



**Royal Australasian
College of Surgeons**

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PRIORITISING SUMMARY

REGISTER ID S000084

NAME OF TECHNOLOGY MICROWAVE ABLATION FOR THE TREATMENT OF HEPATIC TUMOURS.

PURPOSE AND TARGET GROUP PATIENTS WITH UNRESECTABLE HEPATIC TUMOURS.

STAGE OF DEVELOPMENT (IN AUSTRALIA)

- | | |
|--|---|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input checked="" type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | | |
|---|-------------|---------------|
| <input checked="" type="checkbox"/> Yes | ARTG number | 129880 |
| <input type="checkbox"/> No | | |
| <input type="checkbox"/> Not applicable | | |

INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia	✓		
China	✓		
Japan			✓
UK	✓		
USA	✓		

IMPACT SUMMARY

Microwave ablation is a potential alternative to radiofrequency ablation in patients with hepatic tumours who are not candidates for surgical resection. This technology is currently in the experimental stage in Australia.

BACKGROUND

Hepatocellular carcinoma (HCC) describes the abnormal and uncontrolled proliferation of cells in the liver, more commonly known as liver cancer. Although the gold standard for the treatment of liver cancer is surgical resection, there are a significant proportion of hepatic tumours where this is not possible (Bertram et al. 2006). Up to 33% of patients with HCC are ineligible for surgery due to the already advanced stage of their tumour or underlying liver cirrhosis (Xu et al. 2004; Iannitti et al. 2007). Liver transplantation, which is appropriate in patients with concurrent liver failure, results in significantly lower rates of HCC recurrence compared with resection. However, the increased mortality and long wait time associated with liver transplantation means very few patients benefit from this treatment (Xu et al. 2004).

For patients with HCC that cannot be treated with surgery or chemotherapy due to advanced liver dysfunction, or those who have undergone these treatments to no avail, there are minimally invasive options, which can be classified into two treatment groups (Dodd et al. 2000; Xu et al. 2004):

1. Chemical ablation

- Ethanol injection: This is the most common chemical method for treating primary malignant liver tumours. Percutaneous injection of ethanol into tumour cells, under local anaesthetic, causes dehydration of the cytoplasm, coagulation necrosis and fibrous reaction. Injection into tumour vessels causes necrosis of endothelial cells and platelet aggregation, resulting in clotting (thrombosis) and tissue ischaemia (Dodd et al. 2000).
- Acetic acid injection: Performed percutaneously, under local anaesthetic, the capacity of 50% acetic acid to cause coagulative necrosis is approximately three times greater than that of 100% ethanol. Acetic acid has a strong ability to penetrate cells, dissolve lipids and extract collagen (Liang et al. 2000).

2. Temperature-based catheter ablation

- Radiofrequency ablation (RFA): Alternating electric currents in the radiofrequency range are applied via an electrode to living tissue. This causes ionic agitation within the tissue and the resulting friction produces temperatures in excess of 50°C, which cause coagulative necrosis of the tumour. This procedure can be carried out percutaneously or intraoperatively, under local or general anaesthetic, respectively (Dodd et al. 2000; Head et al. 2004).
- Cryoablation: This method uses extremely low temperatures (-20 to -30°C) to irreversibly destroy abnormal cells. Delivered through a cryoprobe, the freezing of cells denatures cellular proteins and causes cell membrane rupture, cell dehydration and ischaemic hypoxia. Cryotherapy is traditionally performed in open or laparoscopic surgery under general anaesthetic, a thinner cryoprobe allows for percutaneous delivery under local sedation (Adam 2002).

Of the minimally invasive treatments for HCC, RFA is the most widely used technique (Iannitti et al. 2007). However, the disadvantages of RFA include its lengthy treatment time and variability in recurrence rates, particularly for larger lesions where recurrence rates can range from 2% to 39% (Iannitti et al. 2007; Martin et al. 2007).

An alternative ablative technique is microwave ablation (MWA), which has a similar mechanism to RFA, but uses energy from a different part of the electromagnetic spectrum (Iannitti et al. 2007). MWA uses electromagnetic energy to agitate adjacent water molecules, creating thermal friction and coagulative necrosis in the target tissue (Iannitti et al. 2007). Like RFA, MWA can be performed percutaneously, under local sedation, with ultrasound guidance (Dodd et al. 2000). Proponents of MWA claim that it offers the ability to perform multiple ablations simultaneously, as well as consistently higher intra-tumoural temperatures, larger tumour ablation volumes, faster ablation times, improved convection profile, and less procedural pain compared with RFA (Martin et al. 2007).

CLINICAL NEED AND BURDEN OF DISEASE

Liver cancer is one of the most common cancers worldwide, with approximately 1.2 million people diagnosed with the disease each year (Cancer Council 2008). In Australia alone, more than 800 new cases of liver cancer are reported annually (Cancer Council 2008).

In Australia, less than 10% of all cases of liver cancer occur in otherwise healthy individuals. The majority of liver cancers are catalysed by cirrhosis, which equates to 80% of liver cancer patients having concurrent liver cirrhosis (The Liver Centre 2008). Causes of cirrhosis include hepatitis B, hepatitis C, alcoholic liver disease, aflatoxin (a metabolic product of a mould contaminant of nuts, grains and beans) and haemochromatosis (a genetic condition leading to excessive iron accumulation in the body) (Fattovich et al. 2004). Hepatitis B and C are the first and second leading causes of liver cancer worldwide, respectively (Fattovich et al. 2004).

The number of deaths caused by cirrhosis and other diseases of the liver was 1,320 in 1997, 1,196 in 2001 and 1,400 in 2006 (Australian Bureau of Statistics 2008a). A high proportion of these deaths were in men (69%) (Australian Bureau of Statistics 2008a). The standardised death rate for malignant tumours of the liver and intra-hepatic bile ducts increased from 3 deaths per 100,000 in 1994 to 4 deaths per 100,000 in 2004 (Australian Bureau of Statistics 2008b). In men, this increase was from 5 to 6 deaths per 100,000 over the same time period and in women from 2 to 3 deaths per 100,000 (Australian Bureau of Statistics 2008b).

DIFFUSION

In 1986 a Japanese team developed a small-diameter coaxial microwave system that could be used to percutaneously ablate deep liver tissue (Dodd et al. 2000). In the early 1990s, MWA was applied to the treatment of liver tumours; however it was not widely adopted because it was only capable of small ablation diameters due to its single 2.4 GHz needle antenna (Iannitti et al. 2007). This issue was resolved with the introduction of

multiple, clustered antennae, which allowed the ablation of larger tumours (Iannitti et al. 2007).

There is one listing for a microwave surgical ablation device on the Australian Register of Therapeutic Goods (ARTG 2008). The registered product name is Guidant Flex 10® Microwave Surgical Ablation Device (ARTG number 129880; product ID number 214632), sponsored by Guidant Australia Pty Ltd (ARTG 2008).

Trials of MWA are currently being conducted in the United States, United Kingdom and China. Australia appears to be in the experimental stage with this technology. Australian trials for MWA of other tissues, such as myocardial and endometrial tissue, are currently being conducted; however, little literature was available regarding its status in the treatment of hepatic tumours.

COMPARATORS

The main comparator of MWA is radiofrequency ablation, as it is the most commonly used ablative technique (Iannitti et al. 2007).

SAFETY AND EFFECTIVENESS ISSUES

Three publications were retrieved for inclusion in this summary. One randomised controlled trial (RCT) (Shibata et al. 2002) and one nonrandomised comparative study (Lu et al. 2005) comparing the safety and effectiveness of MWA and RFA, and one case series study reporting the outcomes of MWA alone (Iannitti et al. 2007).

Shibata et al. (2002) recruited 72 consecutive patients with either a solitary HCC nodule < 4 cm in diameter or 2 to 3 HCC nodules < 3 cm in diameter to be randomly allocated to receive MWA or RFA. Patients were randomly assigned using sealed envelopes (the method of random number sequence generation was not specified) so that a total of 36 patients (46 nodules) were treated with MWA and a total of 36 patients (48 nodules) were treated with RFA. Of the MWA recipients, 78% (28 patients) had a solitary HCC compared with 69% (25 patients) in the RFA group; 17% (6/36) of MWA patients had two HCCs compared with 28% (10/36) of RFA patients; and 6% (2/36) of MWA patients had three HCCs compared with 3% (1/36) of RFA patients. There was no significant difference between the groups regarding the number or size of nodules per patient. The mean age of the 24 men and 12 women in the MWA group was 62.5 years (range 52 to 74 years) and 63.6 years (44 to 83 years) for the 26 men and 10 women in the RFA group ($P>0.05$). There were also no statistically significant differences between the groups with respect to the proportion of patients with elevated serum α -fetoprotein levels (a biomarker used to detect HCC), Child-Pugh cirrhosis class (a measure of prognosis of chronic liver diseases) or the proportion of patients with positive antibodies against hepatitis B and C surface antigens.

The clinical background of the participating patients was confirmed using ultrasound-guided needle biopsy of the solitary HCC in patients with a single nodule and in the largest of the HCC's in patients with multiple nodules (Shibata et al. 2002). All treatment sessions were completed within one month of the initial treatment. At one-week follow

up, dynamic computed tomography (CT) scans were conducted to determine if tumour necrosis was complete; patients with nodule enhancement were considered incomplete and underwent further MWA or RFA. Patients with complete tumour necrosis had a non-enhancing area \geq the diameter of the original lesion. Therapeutic effect was measured with dynamic CT at one month follow up; at this time no nodule enhancement indicated complete therapeutic effect. The mean duration of follow up was 18 months (range 6 to 27) (Shibata et al. 2002).

In the nonrandomised comparative study by Lu et al. (2005), 102 patients who had previously undergone thermal ablation were retrospectively analysed. The inclusion criteria for these patients were < 5 nodules, < 8 cm diameter of any given nodule, no vascular invasion, no lymph node spread and/or distant metastasis and Child-Pugh class $< C$. Ultrasound-guided needle biopsy was performed on all patients to confirm the histology of their HCC. Forty-nine patients (98 nodules) underwent MWA between August 1997 and March 2000, and 53 patients (72 nodules) underwent RFA between March 2000 and July 2002. The mean age of the 44 men and 5 women in the MWA group was 50.1 ± 13.7 (standard deviation [SD]) years (range 24 to 74 years), and the mean age of the 43 men and 10 women in the RFA group was 54.4 ± 11.7 years (20 to 74 years). The mean diameter of the tumours was 2.5 ± 1.2 cm (0.9 to 7.2 cm) in the MWA group and 2.6 ± 1.2 cm (1.0 to 6.1 cm) in the RFA group. Groups were comparable at baseline regarding sex, age, maximum nodule size, hepatitis B and C background, serum α -fetoprotein levels and mean tumour diameter ($P > 0.05$). There was a significant difference seen between the groups in the number of single to multiple nodules, which was 21/28 in the MWA group and 36/17 in the RFA group ($P < 0.05$). Child-Pugh class ratio (A/B) was also significantly different between the groups, with 22/27 in the MWA group and 47/6 in the RFA group ($P < 0.001$). The follow up period in the MWA group was 25.1 ± 12.7 months (2.0 to 50.6 months) compared with 24.8 ± 14.6 months (2.0 to 51.0 months) ($P > 0.05$).

Therapeutic efficacy was assessed with contrast-enhanced CT scans one month after treatment. Complete ablation was considered to have occurred in patients with uniform hypo-attenuation without contrast enhancement in the ablated area. If this was not the case, further ablative treatment was administered. For the first six months of follow up, colour Doppler ultrasounds were carried out and serum α -fetoprotein levels and liver function were measured monthly (3 to 6 monthly thereafter). CT scans of the liver were conducted when these measurements were abnormal. Local recurrence was considered to have occurred when there was regrowth of the tumour inside or neighbouring the previously treated nodule. Distant recurrence occurred when there was an intra- or extra-hepatic growth non-adjacent to the original tumour. Both types of recurrence were treated with additional ablation, where possible (Lu et al. 2005).

Iannitti et al. (2007) conducted a multi-centre study where 87 patients received MWA to treat unresectable primary or metastatic liver cancer. Primary HCC was apparent in 26.4% (23 patients) of cases, with colorectal, breast and carcinoid metastasis being the most common indications for treatment. A total of 94 ablations on 224 tumours took place either percutaneously (48%), laparoscopically (7%) or through open incision

(45%). Of the 87 patients included, 41 were men and 46 were women, with an average age of 67 years (range 37 to 92 years). Average tumour diameter was 3.6 cm (0.5 to 9.0 cm), with 22 tumours > 4 cm in diameter.

All tumours were localised and measured using intraoperative ultrasound or CT fluoroscopy. Patients were also scanned one month after treatment and every four months thereafter for two years. The mean length of follow up was 19 months (Iannitti et al. 2007).

Safety

In the RCT conducted by Shibata et al. (2002), there were no life threatening adverse events observed as a result of either ablation method. Major complications occurred in 4 patients (11% per patients) in the MWA group in 4 sessions (4% per sessions). In this group major complications included liver abscess in one patient, which was resolved using a percutaneous drainage catheter; cholangitis with intra-hepatic bile duct dilation in another patient, which was resolved using antibiotics; subcutaneous abscess with skin burn in one patient, which was resolved by drainage through a skin incision; and subcapsular haematoma in one patient, which resolved with conservative therapy. Major complications occurred less frequently in the RFA group, in one patient (3% per patient) and one session (2% per session). In this case, the patient developed a segmental hepatic infarction, which caused prolonged abdominal pain for two weeks after treatment and elevated serum aspartate transaminase and alanine transaminase (> 1000 U/L) for three days. The patient eventually recovered with conservative therapy. The difference between the two groups in regards to the occurrence of major complications was not significant by patient or session ($P=0.36$; $P=0.67$, respectively). The majority of patients (number not reported) without major complication had elevated serum liver enzymes one day after treatment, but levels returned to normal by seven days follow up (Shibata et al. 2002).

In the nonrandomised comparative study by Lu et al. (2005), the total rate of major complications was 6.9% (7/102 patients). In the MWA group, two patients had slight discharge from their puncture wound, which cleared up with local treatment, while another two patients had subcapsular haematoma, which spontaneously absorbed within two weeks. In the RFA group, two patients had skin burns and one had a puncture wound infection. Thus, the rate of major complications within each group was 8.2% (4/49 MWA patients) and 5.7% (3/53 RFA patients), respectively ($P=0.71$). There were no deaths related to either ablation technique. However, throughout follow up 49% (24/49 patients) of the MWA group and 69.8% (37/53 patients) of the RFA group died. Causes included tumour progression (MWA n=13; RFA n=23), liver function failure (13; 10), upper gastrointestinal bleeding (4; 3) and unknown causes (1; 1) (Lu et al. 2005).

In the case series study by Iannitti et al. (2007), no treatment-related deaths occurred. Two deaths unrelated to either ablation method occurred several months later, resulting in an overall mortality rate of 2.3%. One of the deaths was due to myocardial infarction and the other a cerebrovascular ischaemic event. Non-life threatening procedure-related complications included, skin burns in three patients; wound breakdown, re-admission for nausea or over-sedation, fluid collections and persistent postoperative ileus in two

patients each; and pain requiring termination of the procedure, subcapsular haematoma and fever/staphylococcal infection in one patient each (Iannitti et al. 2007).

Effectiveness

In the RCT by Shibata et al. (2002), 1 to 5 ablation session/nodule were required by patients in the MWA group, with 110 sessions in total (mean 2.4 sessions, SD 1.0). This was significantly more total treatment sessions compared with the RFA group, which required 55 sessions (mean 1.1, SD 0.46) ($P<0.001$). In the MWA group, 24% (11/46 nodules) underwent a single session, 26% (12/46 nodules) underwent two, 39% (18/46 nodules) underwent three, 9% (4/46 nodules) underwent four and 2% (1/46 nodules) of patients underwent five. In the RFA group, 90% (43/48 nodules) underwent a single session, 6% (3/48 nodules) underwent two and 4% (2/48 nodules) underwent three sessions. Mean operative time was significantly lower in the MWA group (33 minutes/session, SD 11) compared with RFA patients (53 minutes/session, SD 16) ($P<0.001$). Intravenous analgesics were required by 15 patients immediately following 15 treatment sessions in the MWA group and 10 patients immediately following 10 treatment sessions in the RFA group. Three of the 15 MWA patients who required analgesics were unable to complete their treatment because of severe pain and underwent subsequent treatment under general anaesthetic.

Complete therapeutic effect was observed in 89% (41/46 nodules) in the MWA group, compared with 96% (46/48 nodules) in the RFA group ($P=0.26$). Residual lesions or incomplete therapeutic effect was seen in 11% (5/46 nodules) in the MWA group. The residual nodules were between 2.5 and 3.4 cm in diameter, four of which (three > 3 cm in diameter and one with a 2.5 cm diameter) were situated near the right portal vein. In addition, all of the nodules ≤ 2 cm ($n=19$) in the MWA group experienced complete therapeutic effect. In the RFA group, 4% (2/48 nodules) had incomplete therapeutic effect. Of the residual nodules < 2 cm in diameter ($n=23$), all had complete therapeutic effect; the two nodules with incomplete effect were 2.4 to 3.0 cm in diameter and situated near the hepatic vein (Shibata et al. 2002).

Residual foci of untreated disease were seen in 17% (8 nodules) of the MWA group (four of which showed incomplete therapeutic effect) and 8% (four nodules) of the RFA group. Rates of residual foci of untreated disease at one year follow up were 10% in the MWA group and 4% in the RFA group, and 24% and 12%, respectively, at two years' follow up. There was no significant difference between the groups for these rates ($P=0.20$) (Shibata et al. 2002).

In the study by Lu et al. (2005), complete ablation was achieved in 94.9% (93/98 nodules) of the MWA group and 93.1% (67/72 nodules) of the RFA group ($P=0.75$). Although the overall difference was not significant, when broken down by tumour size a significant difference was seen. In the MWA group, tumours ≤ 3 cm in diameter were ablated more readily (98.6%; 73/74 nodules) than tumours > 3 cm (83.3%; 20/24 nodules) ($P=0.01$). The same applies in the RFA group, where tumours ≤ 3 cm in diameter were successfully ablated significantly more (98%; 50/51 nodules) than tumours > 3 cm (81%; 17/21 nodules) ($P=0.02$).

There was no significant difference in the overall rate of local recurrences between the groups ($P=0.12$); however, when broken down by tumour size there was. In the MWA group, local recurrence was significantly more frequent in tumours > 3 cm in diameter (30%; 6/20 nodules) compared with tumours ≤ 3 cm (6.8%; 5/73 nodules) ($P=0.04$). The same was apparent in the RFA group, where 33.3% (7/21 nodules) > 3 cm had local recurrence, compared with 11.8% (6/51 nodules) ≤ 3 cm ($P=0.01$). Overall, distant recurrence occurred at a comparable rate between the groups ($P=0.49$), and the time until distant recurrence from initial treatment was also similar ($P=0.53$) (Lu et al. 2005).

Disease free survival rates at one, two, three and four years in the MWA group were 45.9%, 26.9%, 26.9% and 13.4%, and for the RFA group were 37.2%, 20.7% and 15.5%. Therefore, the mean disease free period in each group was not significantly different at 15.5 months (95% confidence interval [CI], 11.3 to 20.0) for MWA treatment and 16.5 months for RFA (95% CI, 10.1 to 19.2) ($P=0.53$). The cumulative survival rates at one, two, three and four years in the MWA versus RFA groups were as follows, 81.6% versus 71.7%, 61.2% versus 47.2%, 50.5% versus 37.6% and 36.8% versus 24.2%. The mean survival time for patients in the MWA and RFA groups were also not significantly different, at 32.5 months (95% CI, 27.4 to 37.7) and 27.1 months (95% CI, 22.5 to 31.8), respectively ($P=0.12$). Cumulative survival rates in patients with ≤ 3 nodules that were ≤ 3 cm in diameter were also not significantly different between the groups ($P=0.12$) (Lu et al. 2005).

In the study by Iannitti et al. (2007), unexpected residual disease was observed in five patients and expected residual disease occurred in three patients. Local recurrence at the ablation site occurred in 2.7% (6/224) of tumours and regional recurrence at the ablation site occurred in 43% (37/87) of patients. By the end of follow up, at 19 months, 47% (41/87 patients) were alive with no sign of disease, 23% (20/87 patients) were alive with cancer and 30% (26/87 patients) had died from the disease. For HCC ($n=23$) specifically, 61% (14 patients) were alive without disease, 13% (3 patients) were alive with the disease and 26% (6 patients) had died. No statistical analyses were reported (Iannitti et al. 2007).

COST IMPACT

The cost of a procedure is generally influenced by its operative duration, the number of treatments required and its risk of complications. Procedures with a greater risk of complication potentially incur more costs as a result of increased recovery time, resulting in either increased medical costs, loss of income, or both. RFA has longer operative duration but requires fewer treatment sessions than MWA, which makes the overall operative time of RFA and MWA comparable. MWA and RFA also have similar safety profiles, therefore the basis of their expense variation will most likely lay in the cost of the equipment required for each.

Economic analysis data from one publication described the costs of various HCC treatment options in US dollars (Dodd et al. 2000). In 2000, RFA generators ranged from US\$12,000 to US\$30,000 and required needle electrodes valued at US\$50 to US\$1,000

(non-reusable) (Dodd et al. 2000). MWA generators cost approximately US\$45,000, with reusable needles valued at US\$500 (Dodd et al. 2000).

Table 1 lists the current treatment options for HCC which are covered by the Medicare Benefits Schedule (MBS), as well as the number of claims made annually for these procedures over the previous four years.

Table 1 Current HCC treatments listed on Medicare Benefits Schedule (MBS 2008).

Item	Description	Fee	Number of Claims/Calendar Year ¹
50950	NONRESECTABLE HEPATOCELLULAR CARCINOMA, destruction of, by percutaneous radiofrequency ablation, including any associated imaging services, not being a service associated with a service to which item 30419 or 50952 applies (Anaes.)	Fee: \$737.95	2007: 32 2006: 42 2005: 21 2004: 18
50952	NONRESECTABLE HEPATOCELLULAR CARCINOMA, destruction of, by open or laparoscopic radiofrequency ablation, where a multi-disciplinary team has assessed that percutaneous radiofrequency ablation cannot be performed or is not practical because of one or more of the following clinical circumstances: - percutaneous access cannot be achieved; - vital organs/tissues are at risk of damage from the percutaneous RFA procedure; or - resection of one part of the liver is possible however there is at least one primary liver tumour in a non-resectable region of the liver which is suitable for radiofrequency ablation, including any associated imaging services, not being a service associated with a service to which item 30419 or 50950 applies (Anaes.)	Fee: \$737.95	2007: 7 2006: 9 2005: 2 2004: 0
30419	LIVER TUMOURS, destruction of, by hepatic cryotherapy, not being a service associated with a service to which item 50950 or 50952 applies (Anaes.) (Assist.)	Fee: \$737.95	2007: 38 2006: 44 2005: 30 2004: 42

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified from the retrieved material.

OTHER ISSUES

No issues were identified from the retrieved material.

SUMMARY OF FINDINGS

From the retrieved literature MWA appears to have a similar safety profile and therapeutic effectiveness as RFA. MWA is less intense than RFA, therefore required greater treatment sessions to remove a tumour than RFA; however, because the individual operative duration of MWA was shorter the overall operative times of both procedures are still comparable, resulting in neither procedure having a cost advantage in this regard. Both procedures are also less efficient in removing tumours greater than 3 cm in diameter. MWA technology is still being refined and future modifications may increase its efficacy in removing HCC.

The quality of the existing studies is insufficiently high to reach reliable conclusions, for example the nonrandomised comparative study by Lu et al. (2005) compared the outcomes of patients with a better Child-Pugh class and fewer multiple nodules (RFA group) with patients with a worse Child-Pugh class and greater multiple nodules (MWA group), confounding its results greatly. Therefore, further evidence (specifically RCTs) is required to fully evaluate the efficacy of MWA, as well as to identify particular patient or tumour subgroups which may respond better to the treatment than others.

HEALTHPACT ACTION

The evidence currently available does not reveal that MWA is in any way more effective compared to RFA for hepatic tumours. Further studies are required before any conclusions can be made. Due to the lack of evidence to support its purported advantages, MWA for hepatic tumours will be archived.

NUMBER OF STUDIES INCLUDED

Total number of studies	3
Level II evidence	1
Level III-3 evidence	1
Level IV evidence	1

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SOURCES OF FURTHER INFORMATION

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SEARCH CRITERIA TO BE USED

Hepatic tumour/tumor OR Liver tumour/tumor

Hepatic cancer OR Liver cancer

Hepatocellular carcinoma

Microwave ablation

Thermal ablation

PRIORITISING SUMMARY (UPDATE 2010)

NAME OF TECHNOLOGY

MICROWAVE ABLATION FOR THE TREATMENT OF HEPATIC TUMOURS

PURPOSE AND TARGET GROUP

PATIENTS WITH UNRESECTABLE HEPATIC TUMOURS

2010 SAFETY AND EFFECTIVENESS ISSUES

Study descriptions

One randomised controlled trial (RCT) and two comparative studies were selected for inclusion in this update (Liu et al 2010; Ohmoto et al 2009; Wang et al 2008).

The RCT by Liu et al (2010) compared the effectiveness of ultrasound-guided percutaneous 915 MHz MWA (a newer generation of MWA) with the original 2450 MHz MWA for large (>4cm diameter) HCC. A total of 39 patients (28 men; 11 women) with 40 large unresectable HCC were randomly assigned (using sealed envelopes) to the 915 MHz MWA group (n=20) or the 2450 MHz MWA group (n=19). There were no significant differences between the groups in regards to patient characteristics at baseline; including age, gender and tumour features. Therapeutic efficacy was assessed using contrast-enhanced imaging and serum tumour marker levels following treatment. Technique effectiveness was measured by 'complete ablation' of the macroscopic tumour as seen by postoperative imaging. Local tumour progression (LTP) was defined as incompletely treated viable tumour continuing to grow or a new tumour ('daughter' or 'satellite' tumours) growing at the original site during follow-up. The total number of antenna placements required for each tumour to be completely ablated was also recorded. Overall, for both groups, median follow-up duration was 9 months (range: 6-24 months).

Ohmoto et al (2009) compared 49 patients with 56 small (≤ 2 cm diameter) HCC who were treated with a single MWA probe between June 1998 to June 2006 with 34 patients (37 nodules) who were treated with a single cooled-tip RFA electrode between August 2002 and August 2006. Baseline characteristics were not significantly different between these groups in regards to mean age, gender, viral markers, Child-Pugh classification, or tumour stage. Local recurrence was defined as recurrence of the tumour at a site adjacent to the treated site as seen on contrast CT scans. Ectopic recurrence was defined as recurrence at any location away from the treated site. When recurrence was detected additional MWA or RFA was undertaken where possible. Mean follow-up duration was 1019 ± 722 (standard deviation [SD]) days in the MWA group and 787 ± 345 days in the RFA group.

The final comparative study by Wang et al (2008) analysed the long-term therapeutic results of small (<5cm diameter) HCC after MWA or hepatic resection (HR). A total of 114 (99 men; 15 women) patients underwent MWA and 80 (72 men; 8 women) patients underwent HR. Patient characteristics at baseline were not significantly different between

the groups in regards to age, gender, Child-Pugh classification, disease aetiology, and tumour characteristics.

Safety

Liu et al (2010) reported no deaths or thrombosis of major vessels in patients undergoing 915 MHz or 2450 MHz MWA. One patient from each treatment group had a large sub-diaphragmatic tumour and both required aspiration due to a large amount of pleural fluid. Similarly, one patient in each group who had an ablated lesion adjacent to the surface of the liver had moderate right upper quadrant pain (grade 2 – scale not specified). Both patients' required oral analgesics and their symptoms subsided after one week. Seven patients receiving 915 MHz MWA and six patients receiving 2450 MHz MWA had non-infective high fevers, which reduced to normal within 2-7 days without intervention. One patient in the 2450 MHz group experienced subcutaneous tumour seeding of needle track 6 months after the procedure. The rate at which minor complications occurred in both groups was not significantly different ($P>0.05$).

All of the patients reported in the study by Ohmoto et al (2009) reported pain at varying severities during treatment; however, the incidence of pain was not significantly different between the MWA and RFA groups. Post-procedural pain ($P=0.035$) and fever ($P=0.016$) occurred at a significantly higher rate in the MWA group compared with the RFA group. Bile duct injuries, including bile duct dilation and biloma ($P=0.025$), as well as pleural effusion ($P=0.043$) and ascites ($P=0.026$), were all significantly more common in the MWA group. Serious complications (such as liver abscess, intraperitoneal bleeding, hepatic infarction, portal thrombus, and biliary peritonitis) only occurred in the MWA group. However, these complications were only observed in a small proportion of patients (2% at most) and the difference between the treatment groups was not statistically significant.

In the study by Wang et al (2008) there were no severe complications observed in either MWA or HR patients. Most patients in the MWA group experienced mild to severe intraprocedural pain at the insertion site, or diaphragm irritation with right shoulder tip pain, lasting 1-7 days postprocedure and relieved in 70 patients. Seventy-three percent of patients in the HR group experienced mild pain at the cutting edge. Fever occurred in 68.4% (78/114) of MWA patients and 20% (16/80) of HR patients, beginning on the day of treatment and persisting for 3 to 5 days. In 6/12 MWA patients with lesions located in the dome of the liver, pleural effusion was observed on sonography after 1 to 2 days and cleared up after 1 to 8 weeks. The majority of patients in both groups experienced elevated transaminase levels 2 to 8 times that of baseline during the first 3 postoperative days. A slight and severe increase in total bilirubin and unconjugated bilirubin was observed in 68 MWA and 72 HR patients, respectively. All of these tests, in both groups, decreased to preoperative levels by 7-10 days follow-up.

Effectiveness

Liu et al (2010) reported that all patients were treated successfully with either 915 or 2450 MHz MWA. At 6-24 months follow-up, 85.7% (18/21) of tumours in the 915 MHz MWA group were completely ablated, compared with 73.7% (14/19) of tumours in the

2450 MHz MWA group. Technique effectiveness rate was not significantly different between the groups (P=0.44), as was emission energy (P=0.53), total emission time (P=0.83) or LTP rate (P=0.44). However, the total number of antenna insertions was significantly less in the 915 MHz MWA group (3.69 ± 0.6 (SD) insertions) compared with the 2450 MHz MWA group (4.71 ± 1.61) (P=0.01). The rate of LTP was not significantly different between the 915 and 2450 MHz groups on follow-up contrast-enhanced imaging (14.3% [3/21] of tumours versus 26.3% [5/19] of tumours) (P=0.44). In the 915 MHz group, 2/3 cases of LTP involved tumours located in the vicinity of the diaphragm and one in contact with the hepatic capsule. In the 2450 MHz group, 3/5 cases involved tumours located in the vicinity of the diaphragm and one was adjacent to the para-umbilical veins and another in contact with the hepatic capsule. All of these tumours were completed ablated with further MWA. There were five and six cases of α -fetoprotein levels exceeding 200ng/L postoperatively in the 915 and 2450 MHz MWA groups, respectively. In the 915 MHz group by one month follow-up, four of these cases decreased to normal α -fetoprotein levels and another fell below 200ng/L but remained abnormal and had LTP. In the 2450 MHz group by one month follow-up four cases decreased to normal α -fetoprotein levels and two cases fell below 200ng/L but remained abnormal and had LTP at three months follow-up.

The average number of treatment sessions reported by Ohmoto et al (2009) was significantly greater in the MWA group (2.6 ± 1.2 sessions) compared with the RFA group (1.7 ± 0.6 sessions) (P<0.001). The maximum/minimum diameter of necrotic area caused by MWA (2.2 ± 0.5 cm/ 1.9 ± 0.4 cm) was significantly smaller than that of RFA (2.7 ± 0.6 cm/ 2.4 ± 0.5 cm) (P<0.001). Local and ectopic recurrence rates throughout follow-up are depicted in Table 2. The local recurrence rate for MWA was significantly higher than for RFA (P=0.031); however, there were no significant differences in local recurrence between the different tumour locations or procedures. Ectopic recurrence was not significantly differently between the MWA and RFA groups.

Table 2: Local and ectopic recurrence rate

	Local recurrence rate		Ectopic recurrence rate	
	MWA group	RFA group	MWA group	RFA group
1-year	13%	9%	35%	28%
2-year	16%	9%	65%	52%
3-year	19%	9%	72%	65%
4-year	19%	9%	78%	65%

The cumulative survival rate of MWA was significantly lower than that of RFA (P=0.018). See Table 3 below.

Table 3: Cumulative survival rate

	MWA group	RFA group
1-year	89%	100%
2-year	70%	83%
3-year	49%	70%
4-year	39%	70%

Liver function tests found no significant changes in total bilirubin, albumin, or the prothrombin time after treatment. Both groups experienced a significant increase in alanine aminotransferase level from before treatment to 3 days after treatment ($P < 0.001$ and $P = 0.025$) and a restoration of these levels to baseline equivalent by 7 days postoperative.

Wang et al (2008) reported disease-free survival rate at 1-, 3- and 5-years postoperative. Patients who underwent MWA had a disease-free survival rate of 72.8%, 54.0%, and 33.0% at these timepoints; meanwhile, patients who underwent HR had a disease-free survival rates of 68.5%, 60.0%, and 25.6%, respectively ($P > 0.05$). In the MWA and HR groups, recurrence or new tumours were found in a total of 70.2% (80/114) and 76.3% (61/80) of patients, respectively. In patients receiving MWA, 13.2% (15/114) of patients had local regrowth of a treated lesion, 22.8% (26/114) had new tumours in the same Couinaud segment (apart from the original sites), 23.7% (27/114) had new tumours in a different Couinaud segment, and 10.5% (12/114) had extrahepatic tumours. In patients receiving HR, 21.3% (17/80) had new tumours in the ipsilateral lobe (apart from the resection line), 32.5% (26/80) had new tumours in the contralateral lobe (apart from the resection line), 10% (8/80) had new tumours near the resection line and 12.5% (10/80) had extrahepatic new tumours.

Thirty patients in the MWA group died of HCC and its complications and five patients died of non-hepatic diseases. Causes of death in this group included variceal bleeding or liver disease ($n=20$), progression of HCC ($n=10$), cardiopulmonary distress ($n=1$), renal failure ($n=1$), lung infection ($n=2$), and cerebral haemorrhage ($n=1$). Twenty-four patients in the HR group died of HCC and its complications and four patients died of non-hepatic diseases. Causes of death included variceal bleeding or liver disease ($n=18$), progression of HCC ($n=6$), cardiopulmonary distress ($n=2$), heart attack ($n=1$), and renal failure ($n=1$) (Wang et al 2008).

OTHER ISSUES

Three systematic reviews have been published since the original summary was conducted in 2008 (Bhardwaj et al 2010; Boutros et al 2010; Ong et al 2009); however, none of these reviews included studies published after 2008. Consequently these articles were excluded from this update and data from more recent comparative evidence (published after 2008) were included in their place in order to capture the most recent impressions of microwave ablation for hepatic tumours.

2010 SUMMARY OF FINDINGS

Recent high-quality literature was retrieved for MWA of hepatic tumours including systematic reviews. The data reported in this update suggests MWA is less effective than RFA and as effective as HR for treatment of small HCC, and 915 MHz MWA appears to be safe and effective for the treatment of large HCC, compared with higher frequency MWA. These results do not provide adequate additional information to support or negate the purported benefits of MWA for the treatment of hepatic tumours.

2010 HEALTHPACT ACTION

Based on the inconclusiveness of these findings and the abundance of high-quality literature that has become available since the original summary was conducted it is recommended that a horizon scanning report be carried out on microwave ablation for the treatment of various cancer types.

2010 INCLUDED STUDIES

Total number of studies	3
Level II intervention evidence	1
Level III-3 intervention evidence	2

2010 REFERENCES

Bhardwaj N, Strickland AD, Ahmad F, Dennison AR, Lloyd DM. Liver ablation techniques: a review. *Surg Endosc* 2010; **24**(2): 254-265.

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Liu FY, Yu XL, Liang P, Wang Y, Zhou P, Yu J. Comparison of percutaneous 915 MHz microwave ablation and 2450 MHz microwave ablation in large hepatocellular carcinoma. *Int J Hyperthermia* 2010 [Epub ahead of print].

Ohmoto K, Yoshioka N, Tomiyama Y, Shibata N, Kawase T, Yoshida K, Kuboki M, Yamamoto S. Comparison of therapeutic effects between radiofrequency ablation and percutaneous microwave coagulation therapy for small hepatocellular carcinomas. *J Gastroenterol Hepatol* 2009; **24**(2): 223-227.

Ong SL, Gravante G, Metcalfe MS, Strickland AD, Dennison AR, Lloyd DM. Efficacy and safety of microwave ablation for primary and secondary liver malignancies: a systematic review. *Eur J Gastroenterol Hepatol* 2009; **21**(6): 599-605.

Wang ZL, Liang P, Dong BW, Yu XL, Yu dJ. Prognostic factors and recurrence of small hepatocellular carcinoma after hepatic resection or microwave ablation: a retrospective study. *J Gastrointest Surg* 2008; **12**(2): 327-337.