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Needle track seeding after percutaneous microwave ablation of malignant liver tumors under ultrasound guidance: Analysis of 14-year experience with 1462 patients at a single center

Jie Yu, Ping Liang*, Xiao-ling Yu, Zhi-gang Cheng, Zhi-yu Han, Bao-wei Dong

Department of Interventional Ultrasound, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China

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ABSTRACT

Objective: To determine the incidence and risk factors associated with needle tract seeding after percutaneous microwave ablation (MWA) of liver cancer under ultrasound guidance.
Materials and methods: Over a 14-year period, a total of 1462 patients with 2530 malignant nodules were treated by MWA. The influence of age, sex, Child-pugh classification, tumor size, tumor position, previous biopsy, insertion number and antenna type on the risk of neoplastic seeding was assessed. The survival of seeding patients after the MWA was analyzed.
Results: Eleven patients with 12 nodules (0.47% per tumor, 0.75% per patient) were identified with needle tract seeding with an interval time of 6–37 (median 10) months after MWA. The mean size of the seeding nodule was 2.3 ± 0.7 cm (from 1.3 to 3.9 cm). Only previous biopsy was significantly associated with neoplastic seeding ($P = 0.02$). All the seeding lesions were successfully treated by resection, MWA, radiation or high intensity focus ultrasound. The median survival period of the 11 patients after the MWA was 36.0 months. The cumulative survival rates of the 11 patients after the MWA at 1-, 2-, 3-, 4- and 5-year were 90.9%, 72.7%, 62.3%, 31.2% and 15.6%, respectively.
Conclusion: The results showed that the neoplastic seeding was a low risk complication of percutaneous MWA of liver cancer and was considered acceptable in general.

Liver cancer is the fifth most common malignant disorder and the third most common cause of cancer death worldwide [1]. Majority of patients suffering from liver tumors are not candidates for surgery because of severe underlying cirrhosis, multiple tumors and recurrent tumors. Currently, minimal invasive techniques have become available for local destruction of hepatic tumors. Microwave ablation (MWA) is based on biological response to tissue hyperthermia for liver tumor treatment with relatively low-risk and favorable therapeutic efficacy [2,3]. Various complications associated with MWA for liver have been reported infrequently [4–6], however, as one of the most unfavorable complications, neoplastic seeding was only reported by Liang et al. [5] with an incidence of 0.44% among 1136 liver cancer patients treated by percutaneous MWA. While for the other two major ablation techniques such as percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA), the risks of seeding after liver cancer treatment varied from 0.3% to 1.9% [7,8] and from 0.5% to 12.5% [9–12], respectively.

As a major complication, several studies showed relatively low seeding rate after ablation treatment [7–10], which suggested that the percutaneous modality of tumor puncture for treatment is not intrinsically problematic when applied to the appropriate patient with careful attention to the technique. However, even if the ablation modalities have been proven to be a generally safe procedure, the risk of needle track seeding should be paid great attention to because the seeding lesions may render subsequent treatment difficult or impossible. Multiple researches have reported that tumor seeding after liver puncture procedure could be related to several factors: calibre and type of electrode used, number of punctures, subcapsular location of the tumor, and poor differentiation of the tumor [9–12]. However, their conclusions were not in complete consistency and there were not seeding risk factors achieved from the MWA treatment analysis. Viable tumor cells may adhere to a biopsy needle or to the thermal applicator during its retraction, and tumor cells may be forced into the track by sudden intra-tumoral hyper-pressure during thermal ablation [13]. Because MWA shows higher thermal efficiency compared with RFA [14], whether the incidence and risk factors of needle track seeding after MWA of liver

* Corresponding author. Tel.: +86 10 66939530; fax: +86 10 88210006.
E-mail addresses: yu-jie301@hotmail.com (J. Yu), liangping301@hotmail.com (P. Liang), dyuxl301@yahoo.com.cn (X.-l. Yu), qlczg@hotmail.com (Z.-g. Cheng), hanzhiyu301@hotmail.com (Z.-y. Han), dongbw301@yahoo.com (B.-w. Dong).

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malignant tumor will show different results from RFA is expected to investigate.

There is no special paper to report the seeding incidence after MWA of liver cancer and the related risk factors by now. Thus, we conducted this study to elucidate the incidence of neoplastic seeding after percutaneous MWA, to assess its characteristics, and to evaluate the risk factors that experienced in a single high-volume center with a long follow-up.

1. Materials and methods

1.1. Patients

Written informed consent was obtained from each enrolled patient, and the protocol was approved by the Institutional Ethics Committee. Inclusion criteria for MWA was as follows: (1) absence of ascites or the depth of ascites on ultrasound (US) less than 4 cm; (2) a normal serum total bilirubin level or less than 60 μmol/L; (3) a normal albumin level or not less than 30 g/L; (4) platelet count no less than $50 \times 10^3/\text{mm}^3$ and prothrombin activity no less than 50%; (5) for radical treatment, single lesion of 8 cm or smaller; three or fewer lesions with a maximum diameter of 4 cm or less; absence of portal vein thrombosis or extrahepatic metastases; (6) for palliative treatment, the aiming was to reduce the tumor load and prolong the survival for later period patients; (7) those with large or multiple lesions, suffering multiple metastases and unsuitable for other modalities could be considered to undergo the MWA on the condition of good hepatic function and systematic status to tolerate the procedure.

Between May 1994 and September 2008, 1492 patients with malignant hepatic tumors underwent percutaneous MWA at our center; 30 of these patients were lost to follow-up and were excluded. Thus, 1462 patients (2530 nodules) were enrolled to analyze the needle seeding data. Among them, 1131 patients had primary liver cancers (1102 hepatocellular carcinomas and 29 intrahepatic cholangiocarcinomas) and 331 patients had liver metastases. There were 1158 men and 304 women. The mean age among all patients was 54.5 ± 11.4 years (range, 25–90 years). The maximum diameter of the tumor in each patient ranged from 0.7 to 10.5 cm (mean, 3.4 ± 1.7 cm). According to the Child-pugh classification, the present study included 447 Child A patients, 942 Child B patients and 73 Child C patients. The diagnosis of malignancy was obtained in 877 patients by histopathological evaluation with core needle biopsy (needle diameter 18-gauge) and 585 patients were diagnosed by a combination of contrast-enhanced US and contrast-enhanced computed tomography (CT)/magnetic resonance imaging (MRI) associated with a high serum tumor marker level. For patients underwent biopsy, if with more than one tumor to ablate, the biopsy was only performed for one tumor to get histological diagnosis.

To assess the depth of tumor location as a possible risk factor for neoplastic seeding, we categorized the locations into the following two groups: direct subcapsular insertion when the tumor was located just under the surface of the liver and the ablation needle was directly inserted to the tumor without passing through the liver parenchyma, and deep when otherwise. When a tumor was located just under the liver surface but the needle was approached from the opposite direction through non-tumorous tissue, the location was defined as deep.

1.2. Microwave equipment and technology

Until the end of 2004, a non-cooled shaft system (PLA General Hospital and Institute 207 of the Aerospace Industry Company, Beijing, China) with a frequency of 2450 MHz delivering a maximum power of 80 W through a 16-gauge needle antenna was used for MWA in our institution. Since 2005, it was replaced by a cooled-shaft system (KY-2000, Kangyou Medical, Nanjing, China). The cooled-shaft microwave unit consists of a microwave generator, a flexible coaxial cable, a water-pumping machine and a needle antenna. The generator is capable of producing 100 W of power at 2450 MHz or 915 MHz. The needle antenna has a diameter of 1.9 mm, one 18 cm shaft which could be easily visualized under US. The shaft has a coating to prevent tissue adhesion. A narrow radiating segment of 3 mm is embedded on the shaft, 5, 11 or 22 mm away from the tip. Inside the shaft, there are dual channels through which distilled water under room temperature is pumped by a peristaltic pump, continuously cooling the shaft proximal to the radiating segment. The flow rate of the distilled water remains constant (40 ml/min) throughout all ablations, which can effectively prevent overheating of the shaft. Both of the two MW machines are equipped with a thermal monitoring system which can measure temperature in real time during ablation.

Patients were placed in the supine or oblique position in the interventional US suite. Color Doppler and gray-scale US were performed to choose a safest intercostal or subcostal needle access. Biopsy was a separate procedure just before MWA procedure. After local anesthesia with 1% lidocaine, US-guided biopsy was performed first by an automatic biopsy gun with an 18-gauge core cutting needle, two-three specimens were obtained. Then, antenna was percutaneously inserted into the tumor and placed at designated place under US guidance. For tumors less than 1.5 cm, one antenna was inserted, and for tumors measuring 1.5 cm or greater, two antennae were inserted in parallel with an inter-antenna distance of 1.0–2.5 cm, which were used simultaneously during MWA to obtain larger ablation zone. A 20-gauge thermocouple was inserted about 0.5–1 cm away from the tumor for real-time temperature monitoring during MWA. A power output of 50–60 W for 600 s was routinely used during MW ablation. If the heat-generated hyperechoic water vapor did not completely encompass the entire tumor and if the measured temperature did not reach 60 °C or remain above 54 °C for at least 3 min, prolonged MW emission was applied until the desired temperature was reached. After all insertions, intravenous anesthesia was administered by a combination of propofol and ketamine via the peripheral vein during standard hemodynamic monitoring. When withdrawing the antenna, the needle track was coagulated with the circulated distilled water in the shaft channel stopped to prevent bleeding and tumor cell seeding.

1.3. Follow up

After 1–2 sessions of MWA, 1–3 days after the last course of a defined ablation protocol contrast-enhanced imaging (contrast-enhanced US, CT or MRI) was performed to evaluate the treatment efficacy. If irregular peripheral enhancement in scattered, nodular, or eccentric pattern occurred, it represented residual unablated tumor existing. This sign indicated incomplete local treatment and further ablation should be considered as soon as possible if the patient still met the criteria for MWA. On the contrary, if complete ablation was achieved, then routine contrast-enhanced imaging and serum tumor markers were repeated at 1 month and 3 months after MWA and then at 6-month intervals. For seeding patients after treatment, contrast-enhanced imaging and serum tumor markers were also repeated at 1 month and 3 months after seeding treatment and then at 6-month intervals.

1.4. Neoplastic seeding

For the purposes of the study, we defined needle track seeding of liver tumor as the development of new neoplastic disease outside the liver capsule, either in the subcutaneous soft tissue, intercostal muscle or attached to the peritoneum or the pleura. The neoplastic seeding was detected by imaging modalities, which was usually performed as surveillance for intrahepatic recurrence. The diagnosis of the seeding was confirmed by histopathological evaluation from biopsy or resection tissues. The incidence of neoplastic seeding was assessed on the basis of the number of tumors.

1.5. Statistical analysis

To elucidate the risk factors of tumor seeding, the following variables were evaluated: age, sex, tumor size, Child-pugh classification, tumor position, percutaneous biopsy prior to MWA, insertion number of the MWA antenna, type of antenna. Continuous variables were compared between those with and without tumor seeding by Student's *t*-test. χ^2 test or Fisher's exact test was applied to compare categorical variables between the groups. All statistical analyses were performed using the SPSS 16.0 for windows statistical package. The difference with a *P* value of less than 0.05 was considered statistically significant.

2. Results

Over a 14-year period, 1462 patients (2530 nodules) with malignant hepatic tumors underwent percutaneous MWA. The median follow-up period for all he patients after MWA was 35.7 months (range 4–126 months). Neoplastic seeding was diagnosed in 11 patients with 12 lesions (0.47% per tumor, 0.75% per patient) all with the pathological diagnosis of hepatocellular carcinoma, with an interval time of 6–37 (median 10) months after MWA. Seven seeding cases were detected by contrast-enhanced MRI, two by contrast-enhanced CT and another two by contrast-enhanced ultrasound. The mean size of the seeding nodule was 2.3 ± 0.7 cm (from 1.3 to 3.9 cm). The number of seeding nodule was one in ten cases, two in one case. Seeding deposits were located on the peritoneum (two) (Fig. 1), the pleura (four), intercostal muscle (two), the subcutaneous soft tissue of the abdomen (two) (Fig. 2) and the external capsule of liver (one) (Fig. 3). All the seeding patients were successfully treated by resection (three), MWA (three), radiation (three) and high intensity focus US (two), according to the size of seeding lesions and patients' choice. In no patient did the presence of tumor seeding have a negative impact on survival. The median survival period of the 11 patients after the MWA treatment was 36.0 months. The cumulative survival rates of the 11 patients after the MWA treatment at 1, 2, 3, 4 and 5 year were 90.9%, 72.7%, 62.3%, 31.2% and 15.6%, respectively.

Of the 11 patients with neoplastic seeding, 5 patients had a subcapsular hepatic tumor, and all had undergone previous percutaneous biopsy and 4 were treated by non cooled-shaft microwave ablation system. There were no significant difference between seeding and no seeding group in the following variables including age, sex, Child-pugh classification, tumor size, tumor position, number of the insertion and antenna type ($P > 0.05$). Only previous biopsy was significantly associated with tumor seeding ($P = 0.02$) (Table 1).

3. Discussion

Although MWA is considered a relatively safe and minimally invasive technique, some major complications including bile duct stenosis, uncontrollable bleeding, liver abscess, colon perforation, skin burn and tumor seeding have been reported with the rate of 1.9–9.2% [5,6,12,15]. The trade-off between the risks and benefits must be considered and a better understanding of the pertinent complications which may occur post-treatment is the key to

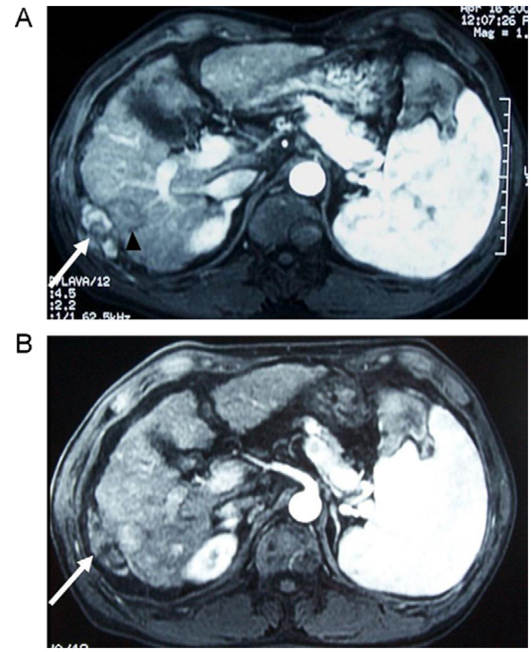

Fig. 1. A 54-year-old man with elongated configuration of needle tract seeding after percutaneous microwave ablation of subcapsular hepatocellular carcinoma, who was previously performed biopsy for two insertions. (A) Transverse contrast-enhanced MRI image shows hypointensity subcapsular ablation zone for 17-mm diameter HCC lesion (arrowhead) in early venous phase. A heterogeneous hyperintensity 23-mm diameter seeding nodule (arrow) is showed attached to the peritoneum 11 months after MWA. (B) Contrast-enhanced MRI shows hypointensity MWA zone (arrow) for seeding lesion in arterial phase.

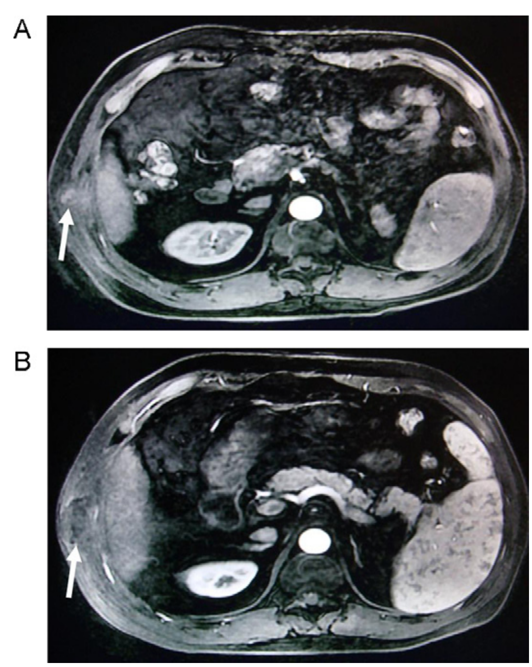

Fig. 2. A 53-year-old man with needle tract seeding after percutaneous microwave ablation of deep hepatocellular carcinoma, who was previously performed biopsy for three insertions. (A) Transverse contrast-enhanced MRI shows hyperintensity 19-mm diameter seeding nodule (arrow) in the subcutaneous soft tissue 6 months after MWA in arterial phase. (B) Contrast-enhanced MRI shows hypointensity HIFU treatment zone (arrow) for seeding lesion in arterial phase.

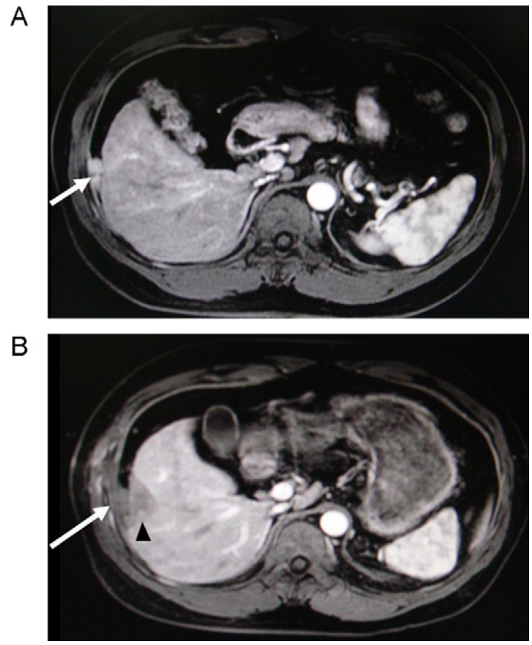

Fig. 3. A 36-year-old man with needle tract seeding after percutaneous microwave ablation of subcapsular hepatocellular carcinoma, who was previously performed biopsy for three insertions. (A) Transverse contrast-enhanced MRI shows hyperintensity 20-mm diameter seeding nodule (arrow) at the external capsule of liver 11 months after MWA in arterial phase. (B) Contrast-enhanced MRI shows hypointensity MWA zone (arrow) for seeding lesion and part of liver tissue (arrowhead) in arterial phase.

successful MWA treatment. As a severe complication, the only report on neoplastic seeding after MWA was made by Liang et al. with an incidence of 0.44%, whereas the complication has been made specialized analyses by several studies on RFA, PEI and biopsy procedure. Except for a small sample RFA study with a report of 12.5% needle track seeding rate [11], most of the researches showed that the low incidence of seeding with successful control would not worsen the patients' overall survival condition [7–10,16]. Even some researchers suggested that a solitary local or subcutaneous focus that can be treated with a repeat ablation procedure be considered to be classified as a minor complication, as which can be likened to a situation of local tumor progression successfully managed by means of repeat ablation [17]. According to the literatures report, tumor seeding after invasive procedures was bound to several risk factors: larger diameter needles, more passes, probably the type of needle, superficial location of the tumor in the liver, tumor histology, intrinsic metastatic property of the tumor, tumor size or patients' immunodepression [9–12].

Table 1
Variables associated with neoplastic seeding among 1462 patients with 2530 hepatic tumors treated by MW ablation.

Variable	Seeding ($n = 11$)	No seeding ($n = 1451$)	P value
Age (y)	52.4 ± 7.8	55.5 ± 11.7	0.9141
Sex			
Male	10	1148	0.5571
Female	1	303	
Child-pugh classification			
A	6	441	0.1963
B	5	937	
C	0	73	
Mean tumor size (mm)	30.8 ± 8.4	33.6 ± 15.7	0.2780
Tumor position			
Deep	6	1487	0.9957
Subcapsular	5	1032	
Previous percutaneous biopsy			
Yes	11	866	0.0159
No	0	585	
No. of insertions	3.5 ± 1.2	2.8 ± 1.9	0.6731
Type of antenna			
Non cooled-shaft	4	579	0.9440
cooled-shaft	7	872	

The present study reported the results obtained in 1462 liver cancer patients with 2530 lesions treated by percutaneous MWA over a 14-year period. The rate of neoplastic seeding was 0.47% for per tumor, whereas for biopsy combined with RFA the median risk of seeding was 0.95% for per patient (range, 0–12.5%) in 2218 patients of eight studies [12]. Two thermal ablation techniques, though share completely different heat-producing theories: in RFA, a high frequency alternating electrical current (375–500 kHz) is used to create ionic agitation, which produces frictional heat and heat conduction to achieve subsequent tissue necrosis [18]; in MW ablation, electromagnetic energy is used to rapidly rotate adjacent polar water molecules which is less dependency on the electrical conductivities of tissue and can produce consistently higher intratumoral temperature, and larger ablation volumes [14], MW and RF substantially showed comparable seeding risk for liver tumor treatment. This study showed 7 (63.6%) of 11 seeding patients were treated by cool-tip antennae and 5 (45.5%) patients had a subcapsular tumor. Both of two factors were not associated with the risk of neoplastic seeding, which was similar to other variables including age, sex, Child-pugh classification, tumor size and number of insertions. The only risk factor related to the seeding was previous percutaneous biopsy, though MWA as a thermal therapy could destroy the tumor surrounding the biopsy needle track to decrease the possibility of tumor cell dissemination. Several possible explanations of neoplastic seeding in our study are analyzed as followings: (1) according to Snoeren et al. [13] reporting, no morphologically intact or viable tumor cells could be demonstrated when track ablation was applied during RFA procedure, while the incidence of viable cells was 17.9% and the incidence of morphologically intact tumor cells was 28.6% when track ablation was not performed. When the repositioning of unsatisfactory initial antenna insertion without intervening microwave heating, viable tumor cells adherent to the needle applicators could also occurrence during MWA procedure; (2) in our study, we usually performed 2–3 biopsy punctures to get enough tissues for pathological test. The biopsy needle prior to MWA did not do in a coaxial fashion to allow parallel placements of the microwave probes. Though MWA was hardly started when the biopsy finished and the antenna was placed through the track perforated by the biopsy needle as far as possible, the track ablation zone of microwave antenna insertion may not completely cover the multiple biopsy needle tracks; (3) by using cool-tip antenna, the microwave applicator can achieve higher thermal efficacy and larger ablation zone [19], thus, tumor cells may be forced into the track by sudden intra-tumoral hyper-pressure during thermal ablation; (4) another possible reason for neoplastic seeding may be insufficient track ablation when the emitting antenna was withdrawn to the surface of the liver for the sake of preventing skin burning.

However, all the seeding lesions in the present study were successfully treated by resection, MWA, high intensity US. The median survival period of the neoplastic seeding patients was 36.0 months. Therefore, the seeding nodules themselves did not affect directly the patients' survival. To minimize the seeding complication, some procedures are advised to be noted according to our experience: (1) performing the needle punctures of solid masses by trained teams; (2) puncturing through normal parenchyma whenever possible; (3) ensuring optimal positioning on the first pass to keep the number of insertions to the very minimum; (4) getting the diagnosis by combination of multiple imaging criteria as far as possible and decreasing the biopsy before ablation to the minimum if imaging scan can get definite diagnosis; (5) maintaining sufficient MW energy by stopping the cooling-shaft water dump to heat the applicator track; (6) lasting MW energy emitting more than 5 s when the antenna was withdrawn to the hepatic capsule.

Our study has three main limitations. Firstly, the majority of the data is retrospectively collected once their importance became known. Secondly, we are unable to assess the significance of tumor grade on the incidence of tract seeding because not all patients have a biopsy. Thirdly, it is possible that the frequency of tract seeding is underestimated for a metastatic tumor may grow from a few months to several years after biopsy or ablation. In an effort to weaken the disadvantage, we have not evaluated the last 12 months of patients treated at our center. Finally, further randomized controlled trials between the two major ablative therapies of MWA and RFA on the incidence of seeding are warranted to be tested.

4. Conclusion

Results of this study confirm that MWA for the treatment of malignant liver tumors achieves a relatively low-risk neoplastic seeding, although the risk of seeding significantly increases if prior needle biopsy was performed. Taking into consideration the relatively low incidence with affordable treatment, even if negligible, the risk of neoplastic seeding after MWA will be considered acceptable in general.

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Conflicts of interest

All have no direct or indirect commercial financial incentive associated with publishing the article.

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