

RESEARCH COMMUNICATION

Microwave Ablation Treatment of Liver Cancer with a 2,450-MHz Cooled-shaft Antenna: Pilot Study on Safety and Efficacy

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Abstract

To evaluate efficacy of microwave ablation in a primary clinical study, sixty patients (44 men, 16 women; mean age 53 years) with 96, 1-8 cm (mean 3.20 ± 0.17 cm) liver cancers were treated with 2,450-MHz internally cooled-shaft antenna. Complete ablation (CA) and local tumor progression (LTP) rates as well as complications were determined. CA rates in small (< 3.0 cm), intermediate (3.1–5.0 cm) and large (5.1–8.0 cm) liver cancers were 96.4% (54/56), 92.3% (24/26) and 78.6% (11/14), respectively. During a mean follow-up period of 17.17 ± 6.52 months, LTP occurred in five (5.21%) treated cases. There was no significant difference in the CA and LTP rates between the HCC and liver metastasis patient subgroups ($P < 0.05$). Microwave ablation provides a reliable, efficient, and safe technique to perform hepatic tumor ablation.

Keywords: Liver cancer - microwave ablation - clinical study - China

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Introduction

Imaging-guided thermal ablation using different energy sources (such as RF, microwave, or laser) continues to gain favor as a minimally invasive technique for the treatment of primary and metastatic hepatic malignant tumors (Ng et al., 2005; Pacella et al., 2005; Cabassa et al., 2006; Clasen et al., 2006; Shibata et al., 2006).

Regardless of the primary energy source, all of these modalities induce cellular destruction by means of the direct effects of heat, with irreversible cellular damage occurring at temperatures above 50°C when applied for 4~6 minutes and almost instantaneously at temperatures above 60°C (Goldberg et al., 2006). Thus, the main difference between modalities lies in the ability to translate energy efficiently into heat throughout the entire tumor ablation target volume. During the past decades, most studies have focused on the potential of radiofrequency (RF) ablation, fueled in part by the substantial morbidity and mortality associated with hepatic resection (Lencioni et al., 2005; Tateishi et al., 2005).

Results of studies on RF ablation suggest that characteristics of the tissue, such as electrical conductivity, can substantially affect and occasionally retard energy deposition and heating throughout a tumor (Goldberg et al., 2001). Additionally, exponential rises in electrical impedances of tumor tissue may result from the application of high RF current, thus limiting the total amount of energy that can be delivered into tissue (Goldberg et al., 2000). This limits the amount of coagulation that can be

achieved. On the other hand, microwave energy deposition is dominated by the absorption caused by rapid rotation of the polar water molecule and is far less dependent on the electrical conductivities of tissue (English et al., 2003). However, compared with RF, few data are available on the extent of tumor destruction possible with microwave ablation, especially at frequencies near 2450 MHz, which are now used in conventional microwave ovens given optimal heating profiles (Shock et al., 2004; Hines-Peralta et al., 2006).

Traditional antennas have been plagued by excessive amounts of reflected power from the antenna. This increases the amount of undesired heating along the needle shaft and feed cable which may reduce the amount of energy deposited into the tissue and cause collateral damages, such as skin burn (Dong et al., 1998). Internal cooling of the antenna may be a solution to minimize heating of the shaft and feed cable which may decrease tissue charring, facilitate microwave energy deposition, and avoid collateral damages at the same time. Thus, the aim of our study was to characterize the ablative effects on the extent of tissue coagulation achieved with an internally cooled 2450 MHz microwave applicator in a clinical study.

Materials and Methods

Microwave coagulation system

A microwave delivery system (ECO-100A; Nanjing Yigao Microwave Electric Institute, Nanjing, China) was used in the experiment. This system consisted of a

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microwave generator with a frequency of 2,450-MHz, a power output of 10-120 W, a flexible low-loss cable and a 14-gauge cooled-shaft antenna. The cooled-shaft antenna, which consisted of a 10 cm-long cable connection portion, a 16.5 cm-long shaft coated with Teflon, and a 1.5 cm-long active tip coated with polytetrafluoroethylene, was used to deliver energy to the liver tissue. The antenna shaft contained two lumina that enabled the delivery of 4°C saline deliver energy to the liver tissue. The antenna shaft contained two lumina that enabled the delivery of 4°C saline solution to the tip of the shaft and the return of the warmed solution to a 500-mL plastic bag outside the body. A steady-flow pump was used to push the chilled saline solution circulating within the lumina of the antenna shaft at 50-60 ml/min. The amount of circulating chilled solution could be adjusted to maintain a mean shaft temperature of $10 \pm 2^\circ\text{C}$ (standard deviation).

Patients

The study was approved by our hospital ethics committee, and written informed consent was obtained from each patient. From January 2007 to January 2009, 60 patients (44 men, 16 women; mean age 53 years; age range 23-79 years) with liver cancer underwent CT-guided percutaneous microwave ablation with internally cooled-shaft antennas at our hospital. None of the patients was considered to be surgical candidates because of the following: had previously undergone hepatectomy and/or transcatheter arterial embolization (n = 34), had bilobar tumors (n = 8), had insufficient liver reserve (n = 4), was advanced in age and had chronic heart or renal disease (n = 2) or had refused to undergo surgery (n = 12). Eligibility criteria included no evidence of extrahepatic metastases, no tumoral invasion of adjacent organs, five or fewer tumor nodules, and no severe coagulopathy (e.g. platelet count $<50 \times 10^{10}/\text{L}$ or prolonged prothrombin time >7 seconds). Of the 60 patients, 40 had hepatocellular carcinoma (HCC); and hepatic metastases of colorectal (n = 11), lung (n=2), nasopharyngeal (n=2), breast (n=2), gastric (n =1) origin. The numbers of the patients with one, two, three, four, or five nodules were 39, 14, 2, 2, 3, respectively. A total of 96 tumors 1-8 cm in diameter were treated: 56 (58.3%) were small (≤ 3.0 cm); 26 (27.1%), intermediate in size (3.1-5.0 cm); and 14 (14.6%), large (≥ 5.1 cm). The mean maximum diameters of the small, intermediate, and large tumors were 2.11 ± 0.48 cm (standard deviation), 3.79 ± 0.55 cm, and 6.45 ± 0.91 cm, respectively. Liver function status was classified as Child-Pugh class A in 56 (93.33%) patients and class B in four (6.67%). Sixty-eight (76.67%) patients had liver cirrhosis.

CT-guided percutaneous microwave coagulation therapy

Thirty patients were initially treated with transcatheter arterial chemoembolization (TACE) using the Seldinger technique, with the aim of reducing the local blood supply of the tumor foci. Percutaneous microwave coagulation therapy (PMCT) was initiated 2-4 weeks after TACE. To relieve pain in the patients, morphine (10 mg) and diazepam (10 mg) were injected intramuscularly 10 min before the PMCT. The puncture site and pathway were

determined under the guidance of CT (Scanner of Picker CT-Twin Flash with hepatic scanning condition of 120 kV, 275 mA and slice width of 5 mm). After anesthetizing the puncture site with 2% lidocaine, a 14-gauge cooled-shaft antenna was placed into the tumor focus accurately. The electrode needle of the microwave device was connected to the output machine of the microwave instrument via a flexible coaxial cable, and the cooling water tube was connected. The constant flow pump was switched onto test the functioning of the cold water cycling system. The microwave power was set at 70-85 W. The coagulation time for each focus was 10-45 min, and the coagulation area covering the tumor focus and its surrounding area measured 5 mm or more. For tumors smaller than 3.0 cm, a single ablation was performed. For tumors larger than 3.0 cm, multiple over-lapping ablations as described by Chen et al. were performed (Chen et al., 2004). The first ablation started at the location farthest away from the skin puncture site. After the ablation was completed, the needle was withdrawn to the second predetermined location. A 22-gauge needle was first inserted into the tumor when combining PEI. Absolute alcohol was slowly injected into the portion of the tumor farthest away from the skin puncture site and then into the rest of the tumor. Particular attention was paid to inject the parts of the tumor where the PMCT was likely to be incomplete, such as near large vessels or the gallbladder, and in the subcapsular region. The amount of mixture (iodized oil and ethanol, proportion was 1:9) injected into the tumors was determined according to the size of the tumors and was always kept below the estimated volume of the tumor: $V = 4/3\pi (r+0.5)^3$ (r: radius of tumor, cm, regular dosage 10-60 ml). Injection of ethanol was stopped if resistance to the injection was felt. After PMCT treatment, liver protection, anti-inflammatory and sedation therapies were prescribed.

Effectiveness and follow-up

Local effectiveness of the microwave ablation was assessed by comparing the baseline contrast-enhanced CT or MR images with those obtained 1 month after treatment. Dual-phase contrast-enhanced spiral CT or MR were done 4 weeks after treatment and thereafter every 2 months in the first 2 years. All examinations were performed with spiral CT scanner (Brilliance 16, Philips, the Netherlands) by using a sequential acquisition of 5-mm-thick sections, 120kV, and 250mA. MRI was performed with 1.5T scanners (CVi, GE medical systems, USA), using a sequential acquisition of 5-mm-thick section thickness. Pulse sequences included a nonenhanced breath-hold T1-weighted gradient-echo sequence (120/1.5 [repetition time ms/echo time ms], 80. flip angle, 320×224 matrix, and 1 2-mm intersection gap) and a respiratory-triggered fat-saturated T2-weighted fast spin-echo sequence (4000-6000/102-108, four signals acquired, 384×224 matrix, and 1 2-mm intersection gap). Contrast enhanced T1-weighted breath-hold gradient-echo images were acquired in the transverse plane with and without fat saturation by using the same technical parameters described for the nonenhanced sequence. For MR imaging, an intravenous contrast agent (gadodiamide, Omniscan; Nycomed

Amersham, Princeton, NJ, USA) was used during dynamic postcontrast imaging. CT scanning and MRI scanning were performed by a group in our radiology department which composed of six radiologists (including Qing-Sheng Zhen, Lin Chen, Yan Zhang, Yan Wang, Yue Zhong, and Hao-Qiang He), who had 25, 13, 11, 10, 10, 5 years of experience in operating CT scanner and MRI scanner, respectively. All images were interpreted by a group in our radiology department which composed of four radiologists (including Chao-Mei Ruan, Chuan-Miao Xie, Lie Zheng, and Yun-Xian Mo), who had 15, 11, 11, 10 years of experience in image diagnosis, respectively. Complete ablation (CA) was defined as uniform hypoattenuation (at CT) or hypointensity (at MR) without enhancement in the ablation zone; for the incompletely ablated nodules, an additional session of PMCT was given with the aim of CA. Tumor with CA were followed up, while those with incomplete ablation after two microwave ablation sessions were considered to be unsuccessfully treated and were excluded from the current study. Local tumor progression (LTP) was defined as relapse of tumor inside or adjacent to the nodule that initially was completely ablated. Distant recurrence was defined as the presence of new intra- or extrahepatic tumors. For local recurrence and intrahepatic metastasis, if the patients still met the inclusion criteria, TACE or/and PMCT was repeated. Major complications were defined as complications which resulted in an admission to the hospital for therapy, an unplanned increase in the level of medical care, prolonged hospitalization, permanent adverse sequelae, or death.

Statistical analysis

Continuous data were expressed as means \pm standard deviations. The test was used to compare the differences in CA and LTP rates between the HCC and liver metastasis patient subgroups. All statistical analysis was performed by using SPSS 10.0 statistical software (SPSS Company, Chicago, IL, USA). A P value of less than 0.05 was considered to indicate a statistically significant difference.

Results

CA was achieved in 89 (92.71%) of the treated 96 tumors. CA rate were 96.43% (54 of 56), 92.31% (24 of 26), and 78.57% (11 of 14) for the small, intermediate, and large tumors, respectively (Table 1, Figure 1). Seven tumors closed to the major intrahepatic branches of the portal vein or inferior vena cava (n = 4), liver capsule (n = 2), gastrointestinal tract (n = 1) were not completely ablated after the first microwave ablation session, and incomplete ablation was considered. Two (3.57%) of these tumors were small (2.5 cm and 2.6 cm); two (7.69%), intermediate in size (4.2 cm and 4.9 cm); and three (21.43%), large (6 cm, 6.4 cm, and 7.8 cm). There was no significant difference in CA rate between the HCC and the metastasis patient subgroups (p = 0.76 > 0.05). All seven tumors were completely eradicated after one additional session of microwave ablation.

The mean follow-up periods were 17.2 months \pm 6.52 (range, 6-30 months) for all patients, 17.7 months \pm 6.70 for the patients with HCC, and 16.1 months \pm 6.16 for

Table 1. Local Effectiveness of Microwave Ablation with Internally Cooled-shaft Antennas for Treatment of Liver Cancers

Patient Group	No. of Tumors	Tumor Diameter (cm)	CA Rate (%)	LTP Rate (%)
HCC				
≤ 3	34	2.18 \pm 0.07	97.06 (33/34)	5.88 (2/34)
3.1-5	15	3.80 \pm 0.14	93.34 (14/15)	6.67 (1/15)
5.1-8.0	11	6.51 \pm 0.30	81.82 (9/11)	9.09 (1/11)
Metastasis				
≤ 3	22	2.01 \pm 0.12	95.45 (21/22)	4.55 (1/22)
3.1-5	11	3.78 \pm 0.18	90.91 (10/11)	0 (0/11)
5.1-8.0	3	6.23 \pm 0.38	66.67 (2/3)	0 (0/3)

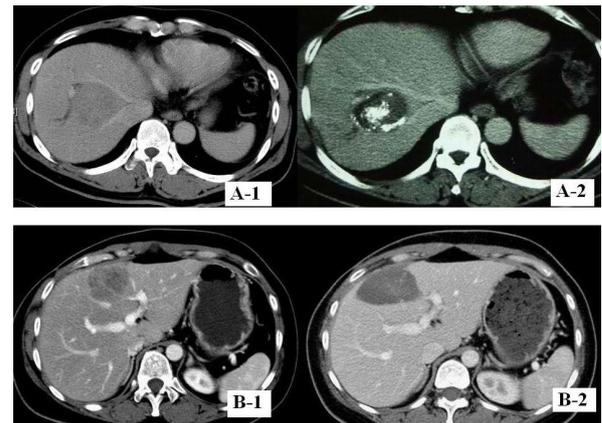


Figure 1. Transverse Contrast-enhanced CT Scans in a Patient who Underwent Combined Therapy with TACE and CT-guided PMCT of HCC (A-1 pretreatment scan showed a 6.5 cm \times 5.7 cm tumor in the right lobe; A-2 scan obtained 25 months after combined therapy). Contrast-enhanced CT scans in a patient who underwent CT-guided PMCT of hepatic metastases (B-1 pretreatment scan showed a 4.6 cm \times 4.8 cm tumor; B-2 scan obtained 19 months after PMCT)

the patients with hepatic metastasis. 12 (20.0%) patients were followed up for more than 24 months, 16 (26.67%) for 18-24 months, 19 (31.67%) for 12-18 months, 13 (21.66%) for less than 12 months. LTP was observed in five (5.21%) tumors 3, 3.5, 4.5 (6.4) and 11.5 months after microwave ablation sessions. Tumors with LTP were close to the liver capsule (n = 2), gastrointestinal tract (n = 2), the major intrahepatic branches of the portal vein or inferior vena cava (n = 1). LTP rates were 5.36% (three of 56), 3.85% (one of 26), and 7.14% (one of 14) for the small, intermediate, and large tumors, respectively. The difference in LTP rate was not significant between the HCC and metastasis groups (p = 0.72 > 0.05). One patient with LTP without new intra- or extrahepatic tumors, received another PMCT session, and the tumor were completely destroyed. These patients with LTP received TACE and PMCT combined therapy, because of multiple new intrahepatic tumors. One patient refused to further treatments. New intra- or extrahepatic tumors were found in 28 (46.67%) patients during follow-up period. 3 patients died in 15, 26, 27 months after PMCT, because of acute variceal bleeding (HCC origin), abdominal dropsy and Hepatic failure (HCC origin.), and multiple metastasis and multiple organ failure (colorectal origin), respectively.

As for side effects, almost all patients reported a

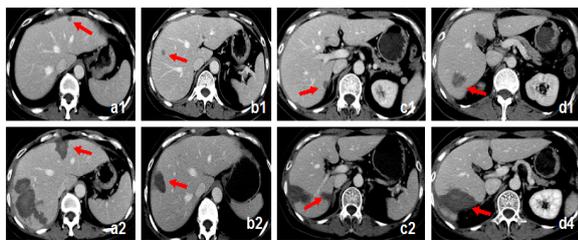


Figure 2. Contrast-enhanced CT Scans in a Patient who Underwent CT-guided PMCT of 4 Hepatic Metastases (a1, a2, a3 and a4 pretreatment scan showed that the tumor sizes were 0.8 cm × 1.1 cm, 0.6 cm × 0.9 cm, 1.2 cm × 1.3 cm, and 2.4 cm × 2.6cm; B-2 scan obtained 16 months after PMCT)

sensation of heat in the upper abdominal region during PMCT 44 (73.34%) patients experienced some pain during treatment, but the pain was not severe enough to warrant cessation of the PMCT.

Generally speaking, PMCT only coagulates hepatic tumors, it caused limited damage to normal hepatic tissue, so it had no significant influence on hepatic function. In our clinical study, only one patient with tumor size 8 cm, the serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) levels rose transiently after treatment but returned to pretreatment levels after about 1 week. In addition, 46 (76.7%) patients developed a fever 8-72 hr after treatment, with a temperature ranging from 37.5°C to 38.8°C, which resolved without therapy within 1 week. No other clinically relevant complications, such as bleeding, subcapsular hematoma, bile duct injury, or burn injury of the skin, were noted during the follow-up period. None of the patients in this study developed local dissemination of cancer cells along the electrode puncture line.

Discussion

Although surgical resection is the only potentially curative approach for patients with primary and metastatic liver tumors, most patients with hepatic malignancy are precluded from resection due to multifocal disease, anatomic limitations, inadequate functional liver reserve, extrahepatic metastasis or medical comorbidities. Consequently, several methods of tumor ablation have been developed as alternate treatment strategies for patients with unresectable hepatic tumors or as adjuncts in total cancer therapy (Dong et al., 1998; Chen et al., 2004). The liver-directed strategies can be broadly divided into 2 groups: regional transarterial therapies and local (chemical and thermal) ablative therapies. Transarterial therapies deliver “bland” or chemotherapeutic agents to tumors via their blood supply to induce cytotoxic ischemia. Chemical and thermal ablative therapies, by contrast, cause tumor necrosis by injection of cytotoxic or ischemia-inducing chemicals or transmission of thermal energy into the tumor tissue itself. Ozaki T et al. (2003) reported that these hepatocytes were positive for the Na⁺-K⁺-ATPase antigenicity but negative for enzyme activity, indicating that they were undergoing cell death necrosis and peripheral haemorrhage. Hepatocytes in ablation area showed nuclear hyperchromatism and chromatin ‘smearing’ and the caspase-3 activity (an

early marker of apoptosis) increased four-fold from the baseline and peaked after 2h, indicating that they were undergoing cell death necrosis (Ohno et al., 2001). Of all the thermal ablation modalities, RF is most commonly adopted. Besides treating liver cancers, clinical application has been expanded to the treatment of neoplasms in other sites (Hadjicostas et al., 2006; Dib et al., 2009; Imoto et al., 2009; Pua et al., 2009; Rasekhi et al., 2009) Microwave, though less adopted at present, is a promising new modality for tumor ablation. In the past, microwave ablation was only performed in the Far East (Dong et al., 2003; Liang et al., 2003; Liang et al., 2005; Yang et al., 2009). Encouraging therapeutic results have been obtained both for primary and metastatic liver cancers (Dong et al., 2003; Liang et al., 2003; Liang et al., 2005; Yang et al., 2009). As the potential benefits of microwave became more apparent, western investigators also began to do experimental and clinical researches recent years (Wright et al., 2003; Wright et al., 2005; Hines-Peralta et al., 2006; Hines-Peralta et al., 2009).

A major limitation of current microwave ablation system is that its efficiency is subjected to power feedback due to impedance mismatches between the antenna and the surrounding tissue, which may cause elongation of coagulation zone along the shaft due to thermal conduction, resulting in collateral damages to normal liver parenchyma and skin burn (Dong et al., 1998; Dong et al., 2003). The new cooled-shaft antenna is specially designed to limit impedance mismatches and subsequent power feedback. Furthermore, the antenna adopted a design similar to that of internally cooled RF electrode which can prevent over heating of the shaft during ablation. Thus, it is our hypothesis that the undesired elongation of coagulation along the needle shaft can be prevented, avoiding possible collateral damages. Moreover, as charring along the needle shaft may be decreased or postponed by the circulating water, more energy maybe deposited in direction perpendicular to the shaft, expanding the short-axis diameter of coagulation. Of course, internal cooling may not be always beneficial. The risk of tumor cell seeding along the needle tract may be increased, thus, for clinical trials, coagulating the needle track when withdrawing the antenna may be necessary.

While not as prevalent as RFA in the United States, MCT has been adopted in the East of Asia using MCT devices with microwave frequency in the 2 GHz range. To our knowledge, MWA has been used clinically in more than 100 hospitals in China. Several clinical series demonstrate favorable responses and long-term survival following MCT for patients with HCC and metastatic tumors. An extensive experience with MCT comes from the work of Dong et al. in China. These authors published several large clinical series demonstrating the safety and therapeutic efficacy of MCT. In 2003, Dong et al. reported treating 234 patients with unresectable large HCC (4.1 cm±1.9) using MCT. Color flow Doppler showed complete disappearance of arterial flow signal in 263 of the 286 nodules (92.0%) that originally had signals. Additionally, 89.2% and 89.1% of nodules that were originally detected on Cd MRI, respectively, showed no contrast enhancement on post-MCT treatment imaging. Of 194 biopsied nodules,

180 (92.78%) demonstrated complete tumor necrosis. 5 of 6 patients who underwent subsequent resection also demonstrated complete tumor necrosis in the resected specimen. Martin et al. (2007) reported treating 67 hepatic tumors in 20 patients in the U.S.A. Total median ablation time was 10 min (range 5-40 min) and the overall ablation success at the discharge CT of the abdomen was 100%. After median follow-up of 19 months there was only one recurrence.

Lu et al. (2001) used ultrasound guided PMCT to treat 50 patients with HCC of unreported etiology. Tumor size ranged from 0.8 to 6.4 cm, with a mean diameter of 2.7cm. Using a multiple insertion technique, the authors observed an overall response rate of 94.4% on 1-month follow-up CT scan, and a 3-year survival rate of 73%. Abe et al. (Abe et al., 2000) performed laparoscopic MWA in 43 HCC patients. The complete ablation rate was 93% for tumors measuring 4 cm or less and 38.5% for tumors larger than 4 cm, and the authors concluded that laparoscopic MWA is preferable for tumors of 4 cm or smaller. Yin XY et al. (2009) reported using MWA or PRFA to treat 109 HCC patients with at least 1 tumor measuring between 3.0 cm and 7.0 cm. CA rate was 92.6%. Local recurrence (LR) occurred in 22% patients, with a median time to LR of 4.6 months. Distant recurrences developed in 53.2% patients, and the major complication rate was 9.2%. In our clinical study, CA was achieved in 89 (92.71%) of the treated 96 tumors. CA rate were 96.43% (54 of 56), 92.31% (24 of 26), and 78.57% (11 of 14) for the small, intermediate, and large tumors, respectively. During a mean follow-up period of 17.17 months \pm 6.52 (range, 6–30 months), LTP occurred in five (5.21%) treated cancers. There was no significant difference in CA and LTP rate between the HCC and liver metastasis patient subgroups ($p>0.05$). No patients had major complications. Consistent with our expectation, tumor size did significantly influence response to therapy, as evidenced by comparable response rates in tumors less 5 cm and those larger than 5 cm (95.12% [78/52] vs 78.57% [11/14]). The CA rate response to treatment in tumors measuring 5-8 cm was as high as 78.57%, which we considered acceptable.

Of course, the present study has some limitations. In the clinical study, we only included 60 patients and followed them up for a maximum of 30 months. More cases and longer follow-up are desired for future survival analysis.

In conclusion, our internally cooled microwave antenna can produce clinically usable coagulation diameters without undesired extension of coagulation along the shaft. The design of internal cooling may prevent collateral damages like skin burn during ablation. CT guided PMCT represents a reliable, efficient, and safe technique to perform hepatic tumor ablation, clinically.

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