81125_Auto_Edited.docx

WORD COUNT 3476
TIME SUBMITTED 16-FEB-2023 11:57AM
PAPER ID 96662884

Name of Journal: *World Journal of Hepatology*
Manuscript NO: 81125
Manuscript Type: MINIREVIEWS

Ablative Strategies for Recurrent Hepatocellular Carcinoma

Ablative Strategies for Recurrent HCC

Lin Wang, Bao-xian Liu, Hai-yi Long

Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, and is the fifth leading cause of cancer death worldwide and the third leading cause of all diseases worldwide. Liver transplantation, surgical resection and ablation are the three main curative treatments for HCC. Liver transplantation is the optimal treatment option for HCC, but its usage is limited by the shortage of liver sources. Surgical resection is considered the first choice for early-stage HCC, but it does not apply to patients with poor liver function. Therefore, more and more doctors choose ablation for HCC. However, intrahepatic recurrence occurs in up to 70% patients within 5 years after initial treatment. For patients with oligo recurrence after primary treatment, repeated resection and local ablation are both alternative. Only 20% patients with recurrent HCC (rHCC) indicate repeated surgical resection because of limitations in liver function, tumor location and intraperitoneal adhesions. Local ablation has become an option for the waiting period when liver transplantation is unavailable. For patients with intrahepatic recurrence after liver transplantation, local ablation can reduce the tumor burden and prepare them for liver transplantation. This review systematically describes the various ablation treatments for rHCC, including radiofrequency ablation (RFA), microwave ablation (MWA), laser ablation (LA), high-intensity focused ultrasound ablation (HIFU), cryablation (CRA), irreversible electroporation (IRE), percutaneous ethanol injection (PEI), and the combination of ablation and other treatment modalities.

Key Words: Hepatocellular carcinoma; recurrence; ablative therapy; thermal ablation

Wang L, Liu BX, Long HY. Ablative Strategies for Recurrent Hepatocellular Carcinoma. *World J Hepatol* 2023; In press

Core Tip: Despite the tremendous efforts in the fight against hepatocellular carcinoma, there is still no way to prevent its recurrence. Intrahepatic recurrence can be treated by repeated resection and ablation, and there is only one randomized controlled clinical trial showing the advantages and disadvantages of each treatment method. For tumors≤3 cm in diameter, there is no significant difference between repeated resection and radiofrequency ablation treatment. High-intensity focused ultrasound ablation results in a better outcome compared to radiofrequency ablation. Non-thermal ablation treatment has clearer borders but a higher postoperative recurrence rate. Percutaneous ethanol injection has comparable efficacy to radiofrequency ablation for small tumors but is being phased out due to the high recurrence rate. Multiple recurrences require combined systemic therapy.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third leading cause of cancer death worldwide [1]. Up to 20% of HCC patients relapse within 2 years after liver transplantation and 1/3 of post liver transplantation patients with recurrent HCC (rHCC) experienced late recurrence (>5 years after liver transplantation) [2]. Nearly half of patients with early-stage HCC experienced recurrence after Hepatic resection [3]. The local recurrence rate in patients with HCC treated RFA varied between 18.2% and 46.6% [4]. The incidence of intrahepatic recurrence has been reported to be approximately 50–70% within 5-years [5].Thus, the treatment and management of HCC recurrence is very important.

Recurrent HCC (rHCC) can be divided into two types: oligo recurrence and disseminated recurrence [6]. Patients with oligo recurrrnce were consider for radical treatmet, including surgery and RFA [7]. Whereas patients with disseminated recurrrence received palliative treatment or supportive care only [7]. The curative approaches for intrahepatic rHCC include salvage liver transplantation, repeat resection and radiofrequency ablation (RFA). SLT has been proposed to be the optimal option but have precluded its extensive application because of the shortage of organ donors and the strict selection criteria for patients [8-10]. In addition, because of progressive liver dysfunction, the presence of multiple tumors, various tumor sites, and intraperitoneal adhesions, only 20% patients with recurrence are eligible for repeated resection[11, 12].

Ablation has the advantages of minimal invasiveness, fewer complications and good repeatability[13]. Ablative therapy is a locoregional treatment that can be used alone or in combination with other treatment modalities[14]. Monotherapy includes RFA, microwave ablation (MWA), laser ablation (LA), high-intensity focused ultrasound (HIFU) ablation, cryoablation (CRA), irreversible electroporation (IRE), and percutaneous ethanol injection (PEI). Combination therapy includes RFA/MWA-transcatheter arterial chemoembolization (TACE) and RFA-PEI.

RADIOFREQUENCY ABLATION

RFA generates 400-500kHz radiofrequency current through the distal end of the uninsulated part of the puncture needle, which causes high-frequency friction of water molecules in the tumor tissue and local high temperature, leading to co-degeneration necrosis and protein degeneration in the tumor tissue [4, 15, 16]. RFA is one of the curative treatment modalities for early-stage HCC with advantages of safety, tolerability, ease of operation, and cost-effectiveness[4]. Previous study has demonstrated that RFA provided similar long-term survival rates for isolated HCC of 5 cm or less, regardless of whether the treatment was initial or salvage therapy [17]. Indications of RFA for rHCC are the same as those for initial HCC, including single nodule<5cm in diameter or less than 3 nodules with the largest diameter<3cm, and without vascular invasion nor extrahepatic metastasis [13].

There were no significant differences in overall survival (OS), re-recurrence rate, distant progression-free survival rate, local progression-free survival rate, nor complications between RFA and repeated resection in early-staged rHCC[14, 18]. Another recent randomized controlled trial showed no statistically significant difference in OS and repeat RFS between repeated resection and RFA in early-staged rHCC [19]. Additionally, in patients with rHCC diameter greater than 3 cm or AFP level greater than 200 ng/mL, local disease control and long-term survival may be better with repeated resection [19].Moreover, thermal ablation is superior to repeated resection in safety, such as significantly shorter average hospital stay, less risk of intraoperative blood transfusion, and less invasive[14, 20, 21].

The main contraindications of RFA are severe bleeding diathesis (platelet count less than 50000/μL), hemostatic compromise, decompensated ascites, jaundice and the presence of metallic devices such as pacemakers[22]. Relative contraindications are lesions near the gastrointestinal tract, biliary system and heart. RFA should also be avoided for tumors within 1 cm proximal to the hepatic portal tract[22].

MICROWAVE ABLATION

MWA causes cell death by increasing the temperature of tumor tissue caused by electromagnetic energy deposition in the tumor[23]. The advantages of MWA over RFA are as follows: (1) MWA uses electromagnetic wave energy without grounding poles, so it does not cause skin burns and has no taboos to metals[24]; (2) the electromagnetic field of the MWA causes rapid and uniform heating of the tissue, creating a more uniform and predictable ablation zone with less time; (3) MWA provides faster heating and higher temperature, so MWA is suitable for perivascular, subcapsular lesions and those adjacent to bile duct[25-27]. The indication for MWA is larger diameter HCC masses, and numerous studies have shown that MWA can treat tumors with a diameter of 5-8cm[28].

Previous study has demonstrated no significant difference in OS nor disease-free survival (DFS) between MWA and surgical resection[29]. Meanwhile, the meta-analysis demonstrated that MWA was associated with shorter operation time, less amount of blood loss in operation, and less complications when compared to surgical resection[29].

The complications of MWA and RFA are similar, such as bleeding, liver abscess, hemothorax, colon perforation and bile duct stenosis[30].

LASER ABLATION

Laser ablation (LA) is a procedure based on laser devices that convert heat energy into light energy and generate heat with tissues to cause cell death [31] and was firstly described in 1983 for the treatment of liver tumors [32].

A randomized controlled trial confirmed LA should be considered a viable treatment option for HCC ≤20 mm, given lower incidence of complications than the RFA group and comparable primary technique efficacy rate and RFS rate [33]. Traditional thermal ablation techniques (RFA and MWA) are considered less effective than TACE in obtaining a complete response for solitary large HCC ≥40 mm [34-36]. A recently published retrospective case-control study indicated that multifiber LA approach was more effective than TACE by achieving a complete tumor ablation and reducing the recurrence rates [37]. However, LA is rarely used and has been superseded by MWA or RFA in many centers partly because LA requires a high level of equipment and its results need to be confirmed by randomized controlled trials [38].

HIFU ABLATION

HIFU ablation is a non-invasive ablation mode using an ultrasound frequency of 0.8-3.5MHz focused through intact skin on a distant therapeutic transducer[39, 40]. Compared with RFA, HIFU has the following advantages: (1) HIFU is an *ex vivo* conformal therapy without invasiveness; (2) tumor seeding is unlikely to occur in HIFU; (3) no direct puncture of target tumor[41].

HIFU is currently used mainly for palliative treatment of advanced HCC [42].There was only one retrospective study showed that the OS of HIFU was slightly higher than that of RFA, but the DFS was lower than that of RFA, and the procedure-related morbidity was lower after a median follow-up time of 27.9 mo of patients with rHCC[43]. Notably, this study was retrospective in nature and had a small sample size.

The main limitation to the clinical application of HIFU is the long ablation time required. Other challenges are the difficulty in precise localization and monitoring, and the difficulty in transmitting ultrasonic energy through the covering bone structure to the lesions behind the ribs[44]. The main complication of HIFU is self-limited skin burns and pain. Other serious complications include ablation of the small bowel in the surrounding area requiring laparotomy, transient hyperbilirubinemia, and the liver abscess [45].

CRYOABLATION

CRA uses extremely low temperatures to directly cause intracellular and extracellular ice crystal formation and lytic agent deformation, leading to cell dehydration and rupture. Vascular injury leads to ischemic hypoxia indirectly destroying tumor tissue. CRA has several potential advantages over RFA: (1) multiple probes can be used simultaneously to produce a large puck; (2) the size and shape of the puck produced by cryotherapy can be easily seen by intraoperative computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound; (3) relatively painless procedure compared to thermal-based ablation, which can be performed under local anesthesia rather than the general anesthesia required for radiofrequency ablation[46].

The efficacy of CRA for HCC has been demonstrated by a large study cohort including 1595 patients with 2313 tumors[46]. The complete response (CR) rates were 81.2% (1893/2313), 99.4% (780/784), 94.4% (1622/1719), and 45.6% (271/594) in all tumors, tumors<3cm, tumors<5cm, and tumors>5cm, respectively. The CR rate was high than that for RFA that ranged from 50% to 80% in HCCs of 3 to 5cm[47]. A CR rate of CRA in tumors>5cm was as low as 25%[48]. At present, the application of CRA in the treatment of rHCC has not been reported.

The most common complications of CRA are postoperative pain, postoperative fever, transient elevations of alanine aminotransferase, hepatic hemorrhage, liver and pleural abscesses and cryoreaction (chills, fever, tachycardia, tachypnea and temporary renal damage, *etc.*) [49, 50]. CRA is recommended as first-line therapy for tumors<5cm. For tumors>5cm, CRA can reduce tumor burden[46].

IRREVERSIBLE ELECTROPORATION

IRE works by generating high voltage (>640 V/cm) and high intensity (>20 A) electrical pulses of short duration (70–100μsec) which render the cellular bilipid membrane of the cells permanently irreversible porous[51, 52]. IRE is a good option for patients who cannot undergo surgery, thermal ablation surgery, or whose tumors are close to important structures[51].

A recent meta-analysis reported an OS of 81.3 % at 12 mo, 61.5 % at 2 years, and 40.9 % at 3 years; PFS was reported as 64.2 % at 12 mo and 49.1 % at 2 years [53].Since RFA and MWA are preferred in tumors located at “non-risk” locations and IRE is used in “high location”, the efficacy of IRE cannot be directly compared with RFA and MWA in a clinical setting [53].

The major complications are liver abscess, hemorrhage, fever, mild pleural effusion, mild hemoperitoneum, subcapsular hematomas, atrial fibrillation and partial portal vein thrombosis.[54-57]

PERCUTANEOUS ETHANOL INJECTION

Injection of ethanol caused dehydration and necrosis of tumor cells accompanied by thrombosis in small vessels to kill tumor tissue[58]. A matched case-control comparative analysis showed that the OS of PEI is comparable to RFA in patients with HCC smaller than 1.5 cm [59]. The major limitation of PEI is significantly higher local recurrence than RFA [60, 61]. Interestingly, recent studies have shown that the combination of PEI with RFA in the treatment of HCCs provides comparable OS rates and RFS.

The mechanisms of RFA-PEI are as follows: (1) RFA enhances the ablative effect of ethanol due to its low boiling point (78.3°C), (2) ethanol embolizes small vessels to reduce the heat-sink effect, (3) ethanol distributes to RFA enabled areas (or difficult-to-treat areas), (4) ethanol diffuses beyond the RFA ablation zone to establish a safety margin, and (5) an ethanol makes the tissue around the electrode less prone to carbonization and further thermal conduction[62-64].

A retrospective study enrolled 271 patients to compare combined RFA-PEI with hepatic resection in the treatment of resectable solitary HCC with 2.1-5.0 cm diameter [65]. RFA-PEI had higher OS rates at 1, 3 and 5 years and RFS rates at 1, 3 and 5 years over hepatic resection in the treatment of solitary HCCs, especially for those with 2.1-3.0 cm in diameter. Additionally, RFA-PEI was superior to hepatic resection in major complication rates, length of hospital stay and cost . A meta-analysis showed that for tumors with 3-5cm in diameter, the 2-year OS was slightly higher in the RFA-PEI than in the RFA group[66, 67]. There were another two studies showed significant clinical improvements in the combination group in terms of the 1-/1.5-/2-/3-/ 5-year OS[68, 69]. Furthermore, post-procedural major complications and pain did not significantly differ between the RFA-PEI groups and RFA groups[70]. A retrospective study found that the combined RFA-PEI group had comparable OS and RFS to repeat hepatectomy for elderly patients with small rHCC after hepatectomy, but with shorter hospital stays and lower rates of major complications and non-tumour-related deaths [71].In summary, combined therapy with RFA-PEI is suitable for 2 to 3cm lesions with liver function compensation.

ABLATION COMBINED WITH TACE

Iodized oil and gelatin sponge particles used in TACE can increase RFA- or MWA-induced coagulation necrosis by going through multiple arterio-portal communications.

TACE enhances heat transfer in RFA or MWA treatment by blocking hepatic arterial blood flow and reducing perfusion-mediated hepatic blood flow cooling (heat-sink effect)[4, 22]. It has been improved in (1) minimizing heat loss due to the heat-sink effect, (2) increasing the area of coagulative necrosis, (3) producing more thorough necrosis within the mass, and (4) enlarging the ablation margin, destroying the satellite lesion[4, 22, 72]. In addition, the digital subtraction angiography technique during TACE helps to detect multiple small tumors and subsequent eradication these tumors[73].

A recent study by Li *et al* that included 3000 cases of HCC showed the OS rate and CR rate of the TACE-RFA group was significantly higher than the TACE alone group[74]. Another review presented that TACE-RFA combined therapy and surgical resection had a similar 1-year OS rate, 3-year OS rate , 1-year RFS rate), and 3-year RFS rate for early HCC [75]. However, the 5-year OS rate and 5-year RFS rate were lower in patients with TACE-RFA than in those with surgical resection. Furthermore, there were two studies found that TACE-RFA treatment is superior to RFA used alone in OS and RFS [76, 77]. A recent study demonstrated that for HCC patients with microvascular invasion (MVI) and rHCC up to three nodules smaller than 3 cm within 2 years, TACE-RFA could achieve better secondary RFS than repeated resection or RFA alone, while RFA alone had survival benefits comparable to repeated resection in other rHCC patients with small recurrence[78]. There was a study that selected 186 patients who underwent TACE-RFA (n = 107) or repeated resection (n = 79) for rHCC with a diameter<5cm[73]. It showed fewer complications and shorter hospital stays in the TACE-RFA group than in the repeated resection group, and there were no significant differences in OS nor RFS.

A recent study conducted by Zaitoun *et al* screened 278 patients with HCC >3-<5 cm. patients were randomized into three groups: 90 underwent TACE (Group 1); 95 underwent MWA (Group 2); and 93 underwent combined therapy (Group 3) [79]. Their study found that group 3 had the significantly lower recurrence rate after 12 mo, and the significantly higher OS and mean progression-free survival than Groups 1 and 2. Therefore, the combination of thermal ablation with TACE theraphy is an optimal choice for patients with HCC tumors ＞3 cm [79, 80].

RFA or MWA can be performed the same day or less than 2 wk after TACE[76, 79]. The most common complications of TACE-RFA are gastrointestinal bleeding, abscess, liver failure, liver infarction[72].

PERCUTANEOUS *VS* LAPAROSCOPIC TECHNIQUES

Thermal ablation can be performed safely using percutaneous or laparoscopic techniques. RFA was generally applied to HCC patients who could not endure repeated resection of the tumor or were not eligible for liver transplantation. RFA is commonly used to eliminate percutaneous tumors and is the most appropriate method for HCC masses far from the intestine, bile duct, ureter, or diaphragm[81]. In contrast, the laparoscopic RFA (LRFA) procedure requires general anesthesia, so the patient is more cooperative, the ablation boundaries are clearer, and the ablation can reach deeper. Therefore, laparoscopic RFA performed better than PRFA in the deep-seated liver cancers, such as subphrenic lesions[82].

According to Min's study on subphrenic HCC, the local tumor progression (LTP) rate of the LRFA group was significantly lower than that of the PRFA group, the cumulative OS rate of the LRFA group was significantly higher than that of the PRFA group, and there was no statistical difference in DFS rate between the two groups[83]. Another study showed that laparoscopic MWA (LMWA) seemed to have a tendency to be more effective than percutaneous MWA (PMWA) in the treatment of subcapsular HCC[84]. However, the laparoscopic approach has a higher rate of postoperative complications than the percutaneous approach[81, 83, 84]. Consequently, LRFA can be a valuable treatment option for subphrenic and subcapsular HCC if accessible using the laparoscopic approach.

ABLATION *VS* OTHER LAGICAL TREATMENT

Apart from ablation, non-operative local treatment of HCC includes TACE, stereotactic body radiation therapy (SBRT) and Proton beam radiotherapy (PBT). Many articles have shown that RFA has long-term benefits comparable to repeat hepatectomy

(RH) for tumours less than 3 cm[14, 18, 19, 85]. The study showed that RFA has better OS and RFS advantages than TACE for rHCCS in both ≤3cm and > 3cm lesions[85]. RFA and SBRT showed considerable therapeutic benefit for rHCC ≤3cm, better OS but lower RFS rate for rHCC > 3cm[85]. A prospective randomized study showed that the LPFS rate of PBT was comparable to that of RFA observed in rHCC patients with≤2 tumor(s) of <3 cm[86].

The 2-year OS was slightly higher in the RFA-PEI than in the RFA group, and current evidence was difficult to draw a definite conclusion regarding the therapeutic management in terms of local recurrence free proportion and complete tumor necrosis. However, TACE-RFA is comparable to RH in both OS and RFS, and has a lower complication rate and hospital stay than RH. Therefore, in patients with liver function compensation, TACE-RFA local therapy may be considered as a preferred option.

The use of percutaneous fusion imaging-guided RFA is effective and safe for the treatment of subcentimeter rHCC[87]. However, PRFA was not feasible in 34.3% (72/210) of sub-centimeter rHCCs primarily due to poor lesion conspicuity[88]. And fusion imaging with or without CEUS does not always satisfactorily locate sub-centimeter rHCC. Cone-beam CT-guided TACE can also be used as an alternative local therapy for subcentimeter recurrent hcc due to its high technical feasibility and detectability [89].

HIGHLIGHTS

This review methodically describes the treatment of rHCC by various ablation procedures in recent years. Moreover, this study compares the indications, advantages and survival analysis of various ablative treatments. Therefore, we summarize how to choose the appropriate ablation therapy for different rHCC patients (Table 1).

CONCLUSION

RFA, MWA and CRA can be considered recommended as first-line treatment for rHCC<3cm in diameter. RFA is currently the most widely used, PRFA can be used in percutaneous tumors and LRFA can be used in subphrenic and subcapsular tumors, while MWA is more recommended for patients with perivascular lesions and TACE-RFA could be consider for patients with MVI(+). CRA is an option for patients who are not candidates for thermal ablation. For patients with 2 to 3cm lesions with liver function compensation, PEI-RFA can be selected. TACE combined with RFA/MWA provided better overall and disease-free survival than TACE alone. For tumors with diameter ranging from 3cm to 5cm, MWA, CRA, and TACE-RFA are recommended. Remarkably, TACE-RFA is a better choice for patients with 3-5cm rHCC with liver function compensation. For tumors>5cm in diameter, local ablation can reduce the tumor burden as a bridging therapy during the waiting period for liver transplantation, or as palliative treatment for recurrence after liver transplantation. In conclusion, the treatment decisions were individualized requires a professional liver surgeon to consider the patient performance status, liver fuctiom, and recurrent tumor status.

81125_Auto_Edited.docx

ORIGINALITY REPORT

21%

SIMILARITY INDEX

PRIMARY SOURCES

1	De-En Lu, Sheng-Wei Cheng, Yang-Sheng Lin, Mei-Wen Tu, Chia-Hsiang Lee, Chiehfeng Chen, Kee-Hsin Chen. "Combination of radiofrequency ablation and percutaneous ethanol injection versus radiofrequency ablation alone for hepatocellular carcinoma: a systematic review and meta-analysis", Annals of Hepatology, 2022 Crossref	140 words — 4%
2	www.wjgnet.com Internet	53 words — 1%
3	www.ncbi.nlm.nih.gov Internet	50 words — 1%
4	www.thieme-connect.com Internet	47 words — 1%
5	coek.info Internet	43 words — 1%
6	www.tandfonline.com Internet	43 words — 1%
7	Yan Fang, Hong-Yan Li, Hao-Hao Yin, Shi-Hao Xu et al. "Radiofrequency-Sensitive Longitudinal Relaxation Tuning Strategy Enabling the Visualization of Radiofrequency Ablation Intensified by Magnetic Composite", ACS Applied Materials & Interfaces, 2019	41 words — 1%

Crossref

8 Min Woo Lee, Hyo Keun Lim. "Management of sub-centimeter recurrent hepatocellular carcinoma after curative treatment: Current status and future", World Journal of Gastroenterology, 2018
Crossref
34 words — 1%

9 zenodo.org
Internet
34 words — 1%

10 Xiaoyun Zhang, Chuan Li, Tianfu Wen, Wei Peng, Lunan Yan, Jiayin Yang. "Treatment for intrahepatic recurrence after curative resection of hepatocellular carcinoma: Salvage liver transplantation or re-resection/radiofrequency ablation?", International Journal of Surgery, 2017
Crossref
32 words — 1%

11 academic.hep.com.cn
Internet
31 words — 1%

12 Zhenwei Peng, Mengchao Wei, Shuling Chen, Manxia Lin et al. "Combined transcatheter arterial chemoembolization and radiofrequency ablation versus hepatectomy for recurrent hepatocellular carcinoma after initial surgery: a propensity score matching study", European Radiology, 2018
Crossref
27 words — 1%

13 academic.oup.com
Internet
24 words — 1%

14 www.intechopen.com
Internet
19 words — 1%

15 www.dovepress.com
Internet
18 words — < 1%

16 Min Hwan Kwak, Min Woo Lee, Seong Eun Ko, Hyunchul Rhim, Tae Wook Kang, Kyoung Doo Song, Jong Man Kim, Gyu-Seong Choi. "Laparoscopic radiofrequency ablation versus percutaneous radiofrequency ablation for subphrenic hepatocellular carcinoma", Ultrasonography, 2022 — 16 words — < 1%
Crossref

17 Shuling Chen, Zhenwei Peng, Han Xiao, Manxia Lin et al. "Combined radiofrequency ablation and ethanol injection versus repeat hepatectomy for elderly patients with recurrent hepatocellular carcinoma after initial hepatic surgery", International Journal of Hyperthermia, 2017 — 16 words — < 1%
Crossref

18 www.thefreelibrary.com — 16 words — < 1%
Internet

19 Yang, T., J.-H. Lu, J. Zhai, C. Lin, G.-S. Yang, R.-H. Zhao, F. Shen, and M.-C. Wu. "High viral load is associated with poor overall and recurrence-free survival of hepatitis B virus-related hepatocellular carcinoma after curative resection: A prospective cohort study", European Journal of Surgical Oncology (EJSO), 2012. — 15 words — < 1%
Crossref

20 bsdwebstorage.blob.core.windows.net — 14 words — < 1%
Internet

21 medworm.com — 14 words — < 1%
Internet

22 onlinelibrary.wiley.com — 14 words — < 1%
Internet

23 Xuqi Sun, Ziliang Yang, Jie Mei, Ning Lyu, Jinfa Lai, Minshan Chen, Ming Zhao. "The guiding value of — 13 words — < 1%

microvascular invasion for treating early recurrent small hepatocellular carcinoma", International Journal of Hyperthermia, 2021
Crossref

24 www.futuremedicine.com
Internet
13 words — < 1%

25 www.pubfacts.com
Internet
13 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS