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实时虚拟导航系统辅助超声引导下消融治疗肝癌患者疗效与安全性的系统评价 *

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摘要 目的：系统评价实时虚拟导航系统辅助超声引导下射频消融治疗肝癌患者疗效与安全性，为临床治疗提供参考。**方法：**计算机检索 Pubmed、EMbase、The Cochrane Library、Web of Science、WanFang Data、CNKI、CBM、VIP 数据库，同时辅以其他检索，收集所有相关的临床对照试验，检索时限从各数据库建库起至 2019 年 12 月。由两位评价员分别独立根据纳入与排除标准对文献进行筛选、提取资料及质量评价，后采用 RevMan 5.3 软件进行分析。**结果：**共纳入 6 个队列研究，包括 1845 例患者。试验组为实时虚拟导航系统(Real-time Virtual Navigation System, RVS)辅助超声引导下(Ultrosound, US)/(Contrast Enhanced Ultrosound, CEUS)消融治疗肝癌组，即 RVS+US/CEUS 组，对照组为超声引导下消融治疗肝癌组，即 US/CEUS 组。分析结果显示：在提高肿瘤消融率方面，试验组显著优于对照组（P<0.05），在并发症发生率方面，试验组与对照组结局指标无统计学差异。**结论：**RVS 辅助超声引导下射频消融治疗肝癌患者在提高肿瘤消融率方面优于传统超声引导下射频消融治疗。

关键词：肝癌；实时虚拟导航系统；超声引导下消融治疗

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Efficacy and Safety of Real-time Virtual Navigation System Assisted Ultrasound-guided Ablation for Hepatocellular Carcinoma : a Systematic Review*

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ABSTRACT Objective: To evaluate the clinical efficacy and safety of real-time virtual navigation system (RVS) assisted ultrasound (US)-guided ablation for hepatocellular carcinoma, so as to provide references for clinical treatment. **Methods:** We electronically searched databases including Pubmed, Embase, The Cochrane Library, Web of Science, WanFang Data, CNKI, CBM, VIP from inception to December 31st, 2019, for the all relevant clinical controlled trails. Other sources were also retrieved. Two reviewers independently screened literatures according to the inclusion and exclusion criteria, extracted data, and assessed the quality of included studies. Then, review was performed using RevMan 5.3 software. **Results:** A Total of 6 clinical controlled trails involving 1845 patients were included. The trial group was given real-time virtual navigation system (RVS) assisted ultrasound-guided ablation, including ultrosound (US) and contrast enhanced ultrosound (CEUS), for hepatocellular carcinoma, that was RVS+US/CEUS group, while the controlled group was given ultrasound-guided ablation for hepatocellular carcinoma alone, that was US/CEUS group. The results of the review showed that, the trail group was significantly superior to the controlled group in improving the rates of tumor ablation (P<0.05). There were also no statistical differences between the two groups in the rate of complacations. **Conclusions:** The efficacy of RVS assisted US-guided ablation for hepatocellular carcinoma is higher than traditional US-guided ablation.

Key words: Hepatocellular carcinoma; Real-time virtual navigation system; Ultrasound-guided ablation

Chinese Library Classification(CLC): R454 Document code: A

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前言

热消融治疗越来越多地被作为肝癌的首选治疗方案[1-3]，而对于不能切除的肝细胞癌和小肝癌部分指南亦建议采用热消融治疗[4-7]。我国《原发性肝癌诊疗规范(2017 版)》对于单个肿瘤直径≤ 5 cm，或肿瘤结节不超过 3 个、最大肿瘤直径≤ 3 cm，无血管、胆管和邻近器官侵犯以及远处转移的患者，推荐选择局部消融治疗[8]。超声因具有实时、无放射性等优点成为国内引导局部消融治疗主要的影像技术手段，但部分病灶因气体、位置及回声等原因显示困难[9]，难以实施消融治疗；同时术中超声由于受气化等影响使得部分残留肿瘤的检测往往不够准确[10]。虽然 CT/MRI 扫描视野宽广，但因其具有放射性、且图像为静态，

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限制了其在局部消融治疗的应用。实时虚拟导航系统(Real-time Virtual Navigation System, RVS)成功地结合了超声实时成像和 CT/MRI 静态容积成像两种技术优势,使术者在此系统引导下能够更加准确的评估肿瘤空间位置、边界、监控整个消融过程，可能会有利于以上问题的解决 [11,12]。本研究采用 Cochrane 协作网推荐的 RevMan5.3 软件进行系统评价实时虚拟导航系统辅助超声引导下消融治疗肝癌患者疗效与安全性，以期为临床治疗策略提供更可靠的依据。

1 资料与方法

1.1 纳入标准

1.1.1 研究类型 临床对照试验。

1.1.2 研究对象 肝癌患者,包含原发性肝癌、转移性肝癌,包含新发或复发肝癌病灶;种族、国籍、病程不限。

1.1.3 干预措施 试验组 RVS+US/CEUS 组(RVS 辅助超声引导下消融治疗肝癌：将平扫 / 增强 CT/MRI 数据信息输入超声设备中，在超声引导下对肝癌病灶进行消融治疗)，对照组 US/CEUS 组(超声引导下消融治疗肝癌)。

1.1.4 结局指标 ① 有效性指标:肿瘤完全消融率、局部肿瘤复发率;② 安全性指标:并发症发生率。

1.2 排除标准

排除① 非中、英文文献,② 重复发表文献,③ 无相关结局指标文献。

1.3 检索策略

计算机检索 Pubmed、EMbase、The Cochrane Library、Web of Science、WanFang Data、CNKI、CBM、VIP 数据库，收集所有相关的临床对照试验,同时追溯纳入文献的参考文献,以补充获取相关文献，检索时限从各数据库建库起至 2019 年 12 月。所有文献均采取主题词检索和自由词检索相结合的方式,并根据具体数据库调整检索策略,所有检索策略通过多次预检索后确定。在自由词检索前,首先搜集检索词的同义词,提高查全率以提高目标文献的检出率。同时从相关文献的参考文献中进行追溯查找以提高查全率。中文检索词:肝癌,影像融合,实时虚拟,实时影像,实时虚拟导航系统,多影像融合介入导航,实时影像虚拟导航系统,实时影像融合虚拟导航系统;英文检索词:liver cancer, hepatocellular carcinoma, hepatocarcinoma, liver neoplasms, real-time virtual navigation system, real-time virtual sonography, image fusion, real-time imaging, real-time image。以 Pubmed 为例,具体检索策略见图 1。

1.4 文献筛选、资料提取与质量评价

根据预先制定的纳入与排除标准筛选文献,阅读检索获得文献的题目及摘要,排除明显不符合纳入标准的文献,对可能符合标准的文献进行全文阅读，进一步确定是否符合纳入标准。对符合标准的文献提取资料,填写资料提取表。使用澳大利亚 JBI 循证卫生保健中心对队列研究的真实性评价工具评估纳入的队列研究的偏倚风险。文献筛选、资料提取与质量评价分别由两名研究者(贾凡、张羽)独立完成,并进行交叉核对,如遇分歧,通过讨论及第三位研究员(杨秀华)进行裁定。

1.5 统计分析

采用 Cochrane 协作网推荐的 RevMan5.3 软件进行分析。二分类变量采用 OR 值及其 95%CI 为效应分析统计量。采用 x^2 检验对纳入研究间结果的异质性进行分析(检验水准设为 α=0.1),并结合 I^2 值判断异质性大小。若各研究间结果不存在统计学异质性(P>0.1, I^2<50%)则采用固定效应模型。若各研究间结果存在统计学异质性,分析其来源,若存在明显临床异质性,则应用亚组分析或敏感性分析等方法进行处理；若无明显临床异质性,则应用随机效应模型进行 Meta 分析。当 P 值与 I^2 值出现矛盾时,以 I^2 值为准。异质性过大,则行描述性分析。Meta 分析检验水准设为 α=0.05。

#1	real-time virtual navigation system[MeSH]
#2	real-time virtual navigation system[Title/Abstract]
#3	real-time virtual sonography[Title/Abstract]
#4	image fusion[Title/Abstract]
#5	real-time imaging[Title/Abstract]
#6	real-time image[Title/Abstract]
#7	#2 OR #3 OR #4 OR #5 OR #6
#8	#1 OR #7
#9	liver cancer[MeSH]
#10	hepatocellular carcinoma[MeSH]
#11	liver cancer[Title/Abstract]
#12	hepatocellular carcinoma[Title/Abstract]
#13	hepatocarcinoma[Title/Abstract]
#14	liver neoplasms[Title/Abstract]
#15	#11 OR #12 OR #13 OR #14
#16	#9 OR #10 OR #15
#17	#8 AND #16

图 1 PubMed 检索策略

Fig.1 Retrieval strategy of PubMed

2 结果

2.1 文献检索结果

初检得到 2403 篇文献，逐层筛选，最终获得 6 篇文献,3 篇英文 [15-17],3 篇中文 [19-21]，共 1845 例患者，文献 Su Joa Ahn 2017[18]最后因纳入研究的实验组与对照组的研究对象差异具有统计学意义,两组间结果不具有可比性,最终予以排除。文献筛选流程及结果见图 2。

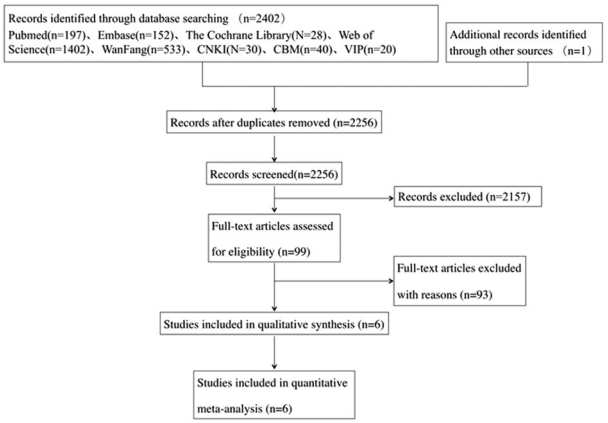

图 2 文献筛选流程及结果

Fig.2 Flow chart of literature search strategies

2.2 纳入研究的基本特征

提取纳入文献的基本信息,即文献类型、患者数量、肿瘤数量、年龄、性别、随访时间及结局指标,并填写资料提取表,详见表 1。

表 1 纳入研究的基本特征表

Table 1 Characteristics of included studies

Study	Type of study(T/C)	No.of patients(T/C)	No.of tumers(T/C)	Age (yrs)	Gender (M/F)	Groups		Follow-up period(month)	Outcome
						T	C		
Jin-Xiu Ju 2019[15]	P	98/92	126/120	(53.6± 10.4)/(53.8± 9.9)	(91/7)/83/9)	CEUS-CT/MRI	CEUS	75	① ② ③
Qiu-Ping Ma 2019[16]	R	97/83	110/90	(52.0± 10.6)/(52.6± 12.2)	(90/7)/(70/13)	CEUS-CT/MRI	US	72	① ② ③
Nobuyuki Toshikuni 2017[17]	R	25/20	23/22	(73± 8)/(74± 9)	(14/11)/(8/12)	CEUS-CT/MRI	CEUS/US	27/63	① ②
Peng Ning 2019[19]	P	42/38	50/45	(50.32± 8.22)/(43.5± 9.51)	(34/8)/(31/7)	US-CT	US	3	① ② ③
Xu Qian 2018[20]	P	78/33	86/38	58.0± 9.0	76/35	CEUS-CECT/CEMRI	CEUS	84	① ②
Zhong Li-yun 2015[21]	P	213	265	53.40± 11.2	169/44	CEUS-CT/MRI/PET	CEUS	60	① ②

Note: P: Prospectively collected data; R: Retrospectively collected data

T: Trail group: RVS+CEUS/US, C: Control group: CEUS/US

① Complete ablation rate ② Local tumer progression rate③ Complication rate

2.3 纳入研究的方法学质量评价

使用澳大利亚 JBI 循证卫生保健中心对队列研究的真实性评价工具对纳入文献进行偏倚风险评估，详见表 2。

表 2 纳入研究的方法学质量评价

Table 2 Quality assessment of included studies

Study	Entry										
	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩	⑪
Jin-Xiu Ju 2019[15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Qiu-Ping Ma 2019[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Nobuyuki Toshikuni 2017[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Peng Ning 2019[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Xu Qian 2018[20]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes
Zhong Li-yun 2015[21]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes

Note: ① Whether the subjects in each group had similar characteristics; ② Using the same method to evaluate the exposure factors; ③ The method of evaluating the exposure factors was effective; ④ If considering the confounding factors; ⑤ Taking measures to control the confounding factors; ⑥ The beginning of the study to describe the subjects did not appear the observation outcome; ⑦ The method of evaluating the outcome indicators was effective; ⑧ The follow-up time was reported and the time was long enough; ⑨The follow-up was complete; ⑩Take measures to deal with losting visits; ⑪The data analysis method was appropriate.

2.4 Meta 分析结果

2.4.1 肿瘤完全消融率 共纳入 6 篇临床对照实验，包括1845例患者。固定效应模型 Meta 分析结果显示：RVS+US/CEUS 组引导下消融治疗的肝癌患者其肿瘤完全消融率优于 US/CEUS 组[OR=4.47, 95%CI(2.57,7.79), *P*<0.00001](图 3)。

2.4.2 局部肿瘤复发率 共纳入 4 篇临床对照实验，包括 730 例患者。随机效应模型 Meta 分析结果显示：RVS+US/CEUS 组引导下消融治疗的肝癌患者其局部肿瘤复发率低于 US/CEUS 组[OR=0.27, 95%CI(0.11,0.67), *P*=0.005](图 4) 。

2.4.3 并发症发生率 共纳入 3 篇临床对照实验，包括 461 例患者。固定效应模型 Meta 分析结果显示：RVS+US/CEUS 组与 US/CEUS 组引导下消融治疗的肝癌患者其并发症发生率无统计学差异[OR=0.75, 95%CI(0.22,2.50), *P*=0.64](图 5)

3 讨论

EASL 指南指出对于肝脏肿瘤直径小于 5 cm 的患者，消融治疗应该是主要的治疗方式，具有较高循证证据支持[13]，因此提高消融治疗的有效性、降低并发症发生率刻不容缓，以期为更多的肝癌患者谋求福利。

RVS 辅助超声引导下的消融治疗可以帮助超声医师实时监测热消融过程、指导穿刺，并提供治疗效果的即时评估[14,24-26]，其同时显示超声图像和 CT/MR 图像的能力，更利于超声医师发现病灶。此外，即使病灶位置具有挑战性，超声医师也可根据术前计划更精准地排布消融针，不受术中气化影响[25,26]。精准的计划不仅可以提高病灶的完全消融率，而且可以减少靶位置外正常组织的损伤。另 RVS-CEUS 可对消融效果进行及时评估，发现残余病灶并进行补充治疗。遗憾的是，虽然文献报道消融

边界(Ablative margin, AM)是局部肿瘤复发(Local tumor progression, LTP)的独立危险因素[27-29],但由于纳入分析的文献中研究结果评测标准不一并数量少,未能进行有效合成。

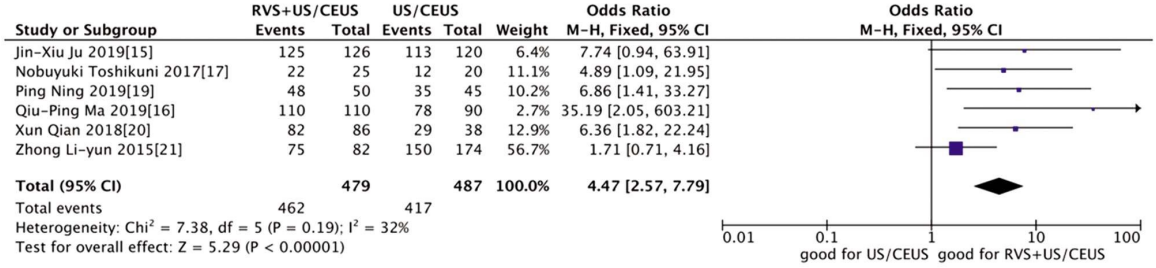

图 3 RVS+US/CEUS 组与 US/CEUS 组引导下消融治疗肝癌患者肿瘤完全消融率的 Meta 分析结果

Fig. 3 Meta analysis of complete ablation rate in patients with liver cancer undergoing RVS+US/CEUS and US/CEUS guided ablation

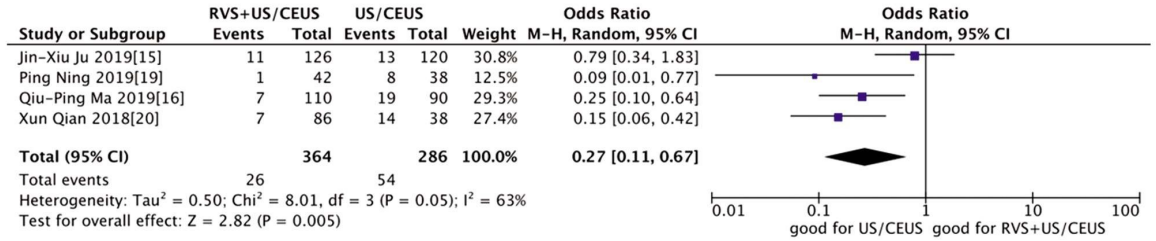

图 4 RVS+US/CEUS 组与 US/CEUS 组引导下消融治疗肝癌患者局部肿瘤复发率的 Meta 分析结果

Fig. 4 Meta analysis of local tumor recurrence rate in patients with liver cancer undergoing RVS+US/CEUS and US/CEUS guided ablation

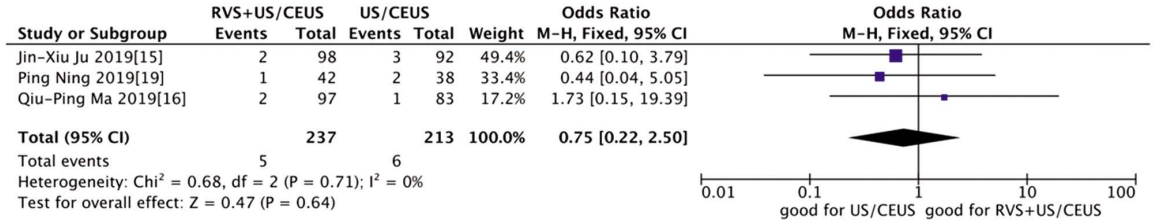

图 5 RVS+US/CEUS 组与 US/CEUS 组引导下消融治疗肝癌患者并发症发生率的 Meta 分析结果

Fig. 5 Meta analysis of complication rate in patients with liver cancer undergoing RVS+US/CEUS and US/CEUS guided ablation

本次分析发现,RVS 辅助超声引导下的消融治疗其在提高肝癌完全消融率方面显著优于传统超声组,差异具有统计学意义。两组在并发症发生率方面无显著差异,但由于纳入研究过少,并不能排除偏倚可能。而在降低局部肿瘤复发率方面,虽然 RVS+US/CEUS 组低于 US/CEUS 组,但研究间存在一定的异质性,逐一剔除单个研究进行敏感性分析,发现剔除 Jin-Xiu Ju 2019[17]后差异性消失,由于研究数量少,并不能进行亚组分析,降低了该方面结果可信度,未来仍需更多研究以得出确切结论。有 2 篇文献[17,21]虽对局部肿瘤进展率进行描述,但并未明确最终具体研究对象数目,致未能纳入本次研究。

本次系统评价的局限性:① 本文仅纳入中文及英文文献,未纳入其他语种文献,可能增加选择性偏倚;② 纳入研究的文献数量少且样本量小,加之各指标报道标准不一,进一步减少了可用于合成的指标数量,导致检验效能不足,降低结果可信性;③ 纳入研究因伦理问题,均未能进行随机对照试验,4 篇文献[15,19,20,21]为前瞻性研究,2 篇文献[16,17]为回顾行研究,有 2 篇文献[20,21]未能明确是否考虑混杂因素、并采取措施对其进行控制;④ 纳入研究的 2 篇文献[20,21]未能对纳入研究的两组研究对象的进行基础水平的评估,可能具有一定的临床异质性。

综上:应用实时虚拟导航系统辅助超声引导下消融治疗肝癌患者在肿瘤完全消融率方面显著优于传统超声引导下消融治疗,在并发症发生率方面无统计学差异,受纳入研究的文献的数量及质量限制,上述结论尚需更多大样本、高质量、结局指标规范全面的临床对照试验予以验证。

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（上接第 501 页）

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