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实时影像融合的超声虚拟导航技术联合射频消融术治疗原发性肝癌合并门静脉癌栓患者的疗效及对血清 Bax、Cyfra21-1 的影响*

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摘要 目的: 探讨实时影像融合的超声虚拟导航技术联合射频消融术治疗原发性肝癌合并门静脉癌栓患者的疗效及对血清 BCL-2 同源的水溶性相关蛋白(Bax)、细胞角蛋白 19 片段(Cyfra21-1)的影响。**方法:** 选择本院 2017 年 1 月到 2021 年 4 月收治的原发性肝癌合并门静脉癌栓患者 82 例作为研究对象,根据 1:1 随机数字表法将患者分为虚拟导航组与对照组各 41 例,虚拟导航组给予实时影像融合的超声虚拟导航技术联合射频消融术治疗,对照组给予单纯超声引导联合射频消融术治疗。**结果:** 虚拟导航组的进针次数、融合时间、布针时间少于对照组($P<0.05$);虚拟导航组治疗后 3 个月的胆汁瘤、肝脓肿、膈肌损伤、肺部感染等并发症发生率为 4.9%,低于对照组的 29.3%($P<0.05$)。虚拟导航组治疗后 3 个月的总有效率为 82.9%,高于对照组的 51.2%($P<0.05$)。两组治疗后 3 个月的血清谷丙转氨酶(ALT)、谷草转氨酶(AST)水平低于治疗前,虚拟导航组低于对照组($P<0.05$)。两组治疗后的血清 Bax、Cyfra21-1 含量低于治疗前,虚拟导航组低于对照组($P<0.05$)。**结论:** 实时影像融合的超声虚拟导航技术联合射频消融术治疗原发性肝癌合并门静脉癌栓能降低血清 Bax、Cyfra21-1 含量,改善患者的肝功能,提高消融效率,还可减少并发症的发生,最终提高患者的总体治疗效果。

关键词: 实时影像融合;超声虚拟导航技术;射频消融;原发性肝癌;门静脉癌栓

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Real-time Image Fusion Ultrasound Virtual Navigation Technology Combined with Radiofrequency Ablation in the Treatment of Patients with Primary Liver Cancer and Portal Vein Tumor Thrombus and Its Effect on Serum Bax and Cyfra21-1*

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ABSTRACT Objective: To investigate the efficacy of real-time image fusion ultrasound virtual navigation technology combined with radiofrequency ablation in the treatment of patients with hepatocellular carcinoma and portal vein tumor thrombosis and the treatment of serum BCL-2 homologous water-soluble related protein (Bax) and cytokeratin 19 Fragment (Cyfra21-1) influence. **Methods:** From January 2017 to April 2021, 82 cases of patients with hepatocellular carcinoma combined with portal vein tumor thrombus admitted to our hospital were selected as the research objects. All the patients were divided into virtual navigation group and control group with 41 cases in each groups accorded to the 1:1 random number table method. The virtual navigation group were treated with real-time image fusion ultrasound virtual navigation technology combined with radiofrequency ablation, and the control group were treated with pure ultrasound guidance combined with radiofrequency ablation. **Results:** The number of needle insertions, fusion time, and needle placement time in the virtual navigation group were less than those in the control group ($P<0.05$). The incidence of complications such as bileoma, liver abscess, diaphragm injury, and lung infection in the virtual navigation group at 3 months after treatment were 4.9 %, which were lower than 29.3 % in the control group ($P<0.05$). The total effective rate of the virtual navigation group at 3 months after treatment were 82.9 %, which were higher than 51.2 % in the control group ($P<0.05$). The levels of serum ALT and AST in the two groups at 3 months after treatment were lower than before treatment, and the virtual navigation group were lower than the control group ($P<0.05$). The serum Bax and Cyfra21-1 levels after treatment in the two groups at 3 months after treatment were lower than before treatment, and the virtual navigation group were lower than the control group ($P<0.05$). **Conclusion:** Real-time image fusion ultrasound virtual navigation technology combined with radiofrequency ablation in the treatment of hepatocellular carcinoma with portal vein tumor thrombus can reduce serum

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Bax and Cyfra21-1 levels, improve patients' liver function, increase ablation efficiency, and reduce complications, and ultimately improve the patient's overall treatment effect.

Key words: Real-time image fusion; Ultrasound virtual navigation technology; Radiofrequency ablation; Primary liver cancer; Portal vein tumor thrombus

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前言

肝癌是全世界最常见的恶性肿瘤之一,其中绝大多数为原发性肝癌(Hepatocellular carcinoma, HCC),也是严重威胁人类健康的一种恶性疾病^[1]。肝癌生长至一定程度易侵犯门静脉形成门静脉癌栓(Portal Vein Tumor Thrombus, PVTT),后者是肝癌的生物学特征之一,在肝癌患者的发生率在 70.0 %左右,可加重门静脉高压,加快病情的进展,并造成肝内肿瘤播散,易发展为肝功能衰竭和肝昏迷^[2,3]。根治性手术为原发性肝癌合并门静脉癌栓的主要治疗方法,但大量患者已处于中晚期,通常伴有肝脏储备功能不足,并失去了手术指征^[4,5]。随着医学技术的发展,射频消融术得到了广泛应用,其优势为:安全性好、创伤小、等,是最有前景的肝癌介入性治疗方法^[6]。传统影像学引导方法的应用可造成肝癌消融率较低,且引导定位精度不高,导致治疗效果一直无法持续提高^[7]。实时影像融合的超声虚拟导航技术联合射频消融术依靠超声探头上的电磁感应器和构架于治疗床上的导航系统电磁转换器,具有多种优点,可实现实时任意切换两者同步同屏、融合显示,从而获得更加精确的解剖定位效果,确保周边脏器的安全性,双重保证病灶的定性价值^[8,9]。随着分子医学的不断发展,目前发现多种与原发肝癌合并门静脉癌栓相关的肿瘤抗原与细胞因子,BCL-2 同源的水溶性相关蛋白(Bcl-2-Associated X, Bax)、细胞角蛋白 19 片段

(Cytokeratin 19 Fragment Antigen, Cyfra21-1)是近年来原发性肝癌合并门静脉癌栓具有特异性的指标,可通过参与肿瘤细胞的凋亡进而实现对肿瘤生长的调控作用^[10,11]。本文具体探讨了实时影像融合的超声虚拟导航技术联合射频消融术治疗原发性肝癌合并门静脉癌栓患者的疗效及对血清 Bax、Cyfra21-1 的影响,现报道如下。

1 资料与方法

1.1 研究对象

选择本院 2017 年 1 月到 2021 年 4 月收治的原发性肝癌合并门静脉癌栓患者 82 例作为研究对象。

纳入标准:符合原发性肝癌合并门静脉癌栓的诊断标准;具有射频消融的指征;预计生存期 ≥ 3 个月;病灶数目 ≤ 3 个;单个病灶直径 ≤ 5 cm;Child-Pugh 肝功能评估 A 级或 B 级;自愿受试患者;本院伦理委员会批准了此次研究。

排除标准:无法配合治疗者;严重肝硬化伴大量腹水患者;妊娠与哺乳期妇女;肝外转移患者;已安装心脏起搏器的患者;不能耐受射频消融术的病例。

根据 1:1 随机数字表法将患者分为虚拟导航组与对照组各 41 例,两组患者的甲胎蛋白(Alpha-fetoprotein, AFP)含量等资料对比无差异($P>0.05$)。

表 1 一般资料对比

Table 1 Comparison of general data

Groups	n	AFP(ng/mL)	Gender (Male/female)	Body mass index (kg/m ²)	Age (years)	Maximum diameter of lesion (cm)	Number of lesions (PCS)	Liver function grading (Grade A /B)
Virtual navigation group	41	342.53 $\pm$ 24.19	31/10	20.82 $\pm$ 1.11	56.44 $\pm$ 2.13	4.56 $\pm$ 0.23	1.87 $\pm$ 0.24	32/9
Control group	41	343.09 $\pm$ 17.49	30/11	20.59 $\pm$ 1.58	56.43 $\pm$ 2.56	4.61 $\pm$ 0.36	1.85 $\pm$ 0.11	31/10

1.2 治疗方法

所有患者都给予射频消融治疗,超声机设备为美国 GE LOGIQ E9,实时虚拟导航系统为 Aurora 6DOF Probe 工作站(意大利 Esaote 公司),射频机为美国 GE 公司的 Ablation system 射频电极针,肿瘤消融治疗三维可视化软件系统来自东芝 Aquilion 公司。

虚拟导航组:给予实时影像融合的超声虚拟导航技术联合射频消融术治疗,患者空腹 8 h 左右,将实时影像图像载入超声导航系统,图像融合成功后形成立体定位图像(任意切面的超声图像与定位精确图像同步关联同屏显示,并且可进行任意程度的融合显示)。根据超声导航系统虚拟融合三维图像,在实时超声引导融合虚拟导航下进针,对病灶进行消融治疗。

对照组:给予单纯超声引导联合射频消融术治疗。将超声引导按照以设计好的路径穿入患者体内肿瘤,利用电流使患者的肿瘤组织离子能随着电流的变化而发生争端。此外,还需使得消融电极周围形成 50℃ 以上的高温区,以此确保肿瘤细胞可凝固性坏死。手术后,将电极拔出。在此过程中,需经超声密切关注患者体内的肿瘤及周围肝组织的变化情况。

1.3 观察指标

(1)记录两组患者的进针次数、融合时间、布针时间。

(2)记录两组治疗 3 个月期间出现的胆汁瘤、肝脓肿、膈肌损伤、肺部感染等并发症情况。

(3)在治疗后 3 个月进行总体疗效评定,完全缓解(Complete remission, CR):所有目标病灶消失,癌栓完全消失;部分

缓解(Partial remission, PR):目标病灶直径总和缩小 $\geq 30.0\%$,癌栓缩小 $\geq 50\%$;稳定(Stable disease, SD):目标病灶缩小未达PR或增加未达PD,癌栓缩小 $<50\%$ 或增大 $<25\%$;进展(Progressive disease, PD):目标病灶直径总和 $\geq 20\%$ 或出现新病灶,癌栓增大 $\geq 25\%$ 或门静脉其他分支出现新的癌栓。(CR+PR)/组内例数 $\times 100.0\%$ =总有效率。

(4) 所有患者治疗前后抽取清晨空腹静脉血 5 mL, 1500 rpm/min 离心 10 min, 将上层血清分为两份。其中一份血清采用酶联免疫法检测血清 Bax, Cyfra21-1 含量, 另外一份采用全自动生化分析仪检测谷丙转氨酶 (Alanine transaminase, ALT)

以及谷草转氨酶(Aspartate aminotransferase, AST)含量。

1.4 统计方法

统计软件为 SPSS27.00, 计量数据选择均数 $\pm$ 标准差表示, 对比采用 t 检验; 而计数数据采用频数或者百分比表示, 对比采用卡方 χ^2 检验分析, 检验水准为 $\alpha=0.05$ 。

2 结果

2.1 消融情况对比

虚拟导航组的进针次数、融合时间、布针时间少于对照组 ($P<0.05$)。见表 2。

表 2 两组消融情况对比(均数 $\pm$ 标准差)

Table 2 Comparison of ablation conditions between the two groups (mean $\pm$ standard deviation)

Groups	n	Times of needle insertion (times)	Fusion time (s)	Stitch time (s)
Virtual navigation group	41	1.39 $\pm$ 0.13*	254.92 $\pm$ 16.93*	367.98 $\pm$ 43.19*
Control group	41	2.33 $\pm$ 0.19	341.84 $\pm$ 21.84	474.92 $\pm$ 45.18

Note: Compared with control group, * $P<0.05$.

2.2 并发症情况对比

虚拟导航组治疗后 3 个月的胆汁瘤、肝脓肿、膈肌损伤、肺

部感染等并发症发生率为 4.9%, 低于对照组的 29.3% ($P<0.05$)。见表 3。

表 3 两组治疗后 3 个月的并发症情况对比(n)

Table 3 Comparison of complications between the two groups 3 months after treatment (n)

Groups	n	Biloma	Hepatopostema	Diaphragm Injury	Pulmonary infection	Summation
Virtual navigation group	41	1	1	0	0	2(4.9%)*
Control group	41	2	3	4	3	12(29.3%)

Note: Compared with control group, * $P<0.05$.

2.3 总体疗效对比

虚拟导航组治疗后 3 个月的总有效率为 82.9%, 高于对照

组的 51.2% ($P<0.05$)。见表 4。

表 4 两组治疗后 3 个月的总有效率对比(n)

Table 4 Comparison of total effective rates between the two groups 3 months after treatment (n)

Groups	n	CR	PR	SD	PD	The total effective rate
Virtual navigation group	41	21	13	4	3	34(82.9%)
Control group	41	7	14	11	9	21(51.2%)

Note: Compared with control group, * $P<0.05$.

2.4 血清肝功能指标变化对比

两组治疗后 3 个月的血清 ALT 与 AST 水平低于治疗前,

虚拟导航组较对照组低 ($P<0.05$)。见表 5。

表 5 血清肝功能指标变化对比(U/L, 均数 $\pm$ 标准差)

Table 5 Comparison of changes in serum liver function indexes (U/L, mean $\pm$ standard deviation)

Groups	n	ALT		AST	
		Before the treatment	3 months after treatment	Before the treatment	3 months after treatment
Virtual navigation group	41	65.09 $\pm$ 7.45	32.55 $\pm$ 3.67**	52.98 $\pm$ 5.24	30.22 $\pm$ 2.98**
Control group	41	65.12 $\pm$ 7.33	41.43 $\pm$ 4.75 [#]	53.11 $\pm$ 4.89	49.20 $\pm$ 3.11 [#]

Note: Compared with control group, * $P<0.05$; Compared with before the treatment, [#] $P<0.05$.

2.5 血清 Bax、Cyfra21-1 含量变化对比

导航组低于对照组($P<0.05$)。见表 6。

两组治疗后的血清 Bax、Cyfra21-1 含量低于治疗前, 虚拟

表 6 两组治疗前后血清 Bax、Cyfra21-1 含量变化对比(ng/L, 均数± 标准差)

Table 6 Comparison of serum Bax and Cyfra21-1 contents between the two groups before and after treatment (ng/L, mean ± standard deviation)

Groups	n	Bax		Cyfra21-1	
		Before the treatment	3 months after treatment	Before the treatment	3 months after treatment
Virtual navigation group	41	122.48± 17.29	34.77± 5.68	12.86± 1.48	5.82± 0.57
Control group	41	122.09± 18.00	56.99± 9.11	12.76± 2.93	8.27± 0.18

Note: Compared with control group, * $P<0.05$; Compared with before the treatment, # $P<0.05$.

3 讨论

肝癌起病隐匿, 早期多无典型的临床症状和体征, 大量患者确诊时伴随有门静脉癌栓, 具有浸润和转移强等特征, 使死亡率居高不下^[12]。一旦形成癌栓, 不但造成肝内肿瘤播散, 还可加重门静脉高压, 导致患者预后不良^[13]。目前原发性肝癌合并门静脉癌栓的病因尚不明, 主要病因包括肝炎感染与酒精滥用, 在临床上也有多种治疗手段。射频消融是一种物理热消融技术, 其通过热效应引发肿瘤死亡进而治疗疾病^[14,15]。本研究显示虚拟导航组的进针次数、融合时间、布针时间少于对照组; 虚拟导航组治疗后 3 个月的胆汁瘤、肝脓肿、膈肌损伤、肺部感染等并发症发生率为 4.9%, 低于对照组的 29.3%, 表明实时影像融合的超声虚拟导航技术联合射频消融术治疗原发性肝癌合并门静脉癌栓能提高消融效率, 还可减少并发症。这一结果与 Miyata A 等人^[16]以及 Huang HC 等人^[17]的研究具有一致性。从机制上分析, 实时影像融合的超声虚拟导航技术的引导对肝癌具有靶向定位的作用, 可于术中实时观察进针途径, 可准确定位病灶, 使得进针过程避免损伤血管等重要结构^[18]。实时影像融合的超声虚拟导航技术的引导对于病灶以及周围器官、组织的解剖层次易于辨认, 准确定位引导进针, 保证消融安全范围, 从而有效提高效果, 减少对患者的创伤, 进而降低因手术所引起的并发症^[19]。

准确的射频定位对原发性肝癌合并门静脉癌栓的治疗具有重要价值, 常规超声定位难以清晰分辨病灶形态与形态, 病灶与周围器官、组织的关系难以明确, 射频时消融范围可能不足, 且易造成误损伤, 肿瘤残留或复发率较高, 不利于患者预后改善^[20]。实时影像融合的超声虚拟导航技术可明确清晰的显示相应部位解剖全景, 也可准确引导穿刺进针, 保障消融过程中周边脏器的安全性。并且其在定位追踪病灶的同时, 还可进行实时病灶分析, 从而有利于提高疗效^[21,22]。本研究显示虚拟导航组治疗后 3 个月的总有效率高于对照组; 两组治疗后 3 个月的血清 ALT 与 AST 水平低于治疗前, 虚拟导航组低于对照组, 表明实时影像融合的超声虚拟导航技术联合射频消融术治疗原发性肝癌合并门静脉癌栓能提高治疗总体效果, 改善患者的肝功能。这一结果与 Chang Q 等人^[23]以及 Cheng Y M 等人^[24]的研究具有一致性。进一步分析可知: ALT 和 AST 均为肝功能系列中重要的指标。ALT 是一种经肝脏向胆外排出的酶, 其表达水平与肝细胞受损程度大致平行。AST 主要存在于心肌细胞中, 同时也存在于肝细胞中, 该物质的失衡也与肝细胞受损息

息相关。实时影像融合的超声虚拟导航技术提高了定位的精准度和一次消融率, 可实时进行超声图像引导进针, 有利于降低肿瘤复发率, 对病灶的安全范围进行有效消融, 从而改善患者的长期预后生存效果^[25,26]。

本研究显示两组治疗后的血清 Bax、Cyfra21-1 含量低于治疗前, 虚拟导航组低于对照组, 表明实时影像融合的超声虚拟导航技术联合射频消融术治疗原发性肝癌合并门静脉癌栓能降低血清 Bax、Cyfra21-1 含量。这一结果与刘占钰等人^[27]以及 Lebeaupin C 等人^[28]的研究具有一致性。进一步分析可知: Bax、Cyfra21-1 均为一种血清肿瘤标志物, Cyfra21-1 属于构成细胞框架的间丝状物, 也是一种细胞角蛋白 19 可溶性片段之一。机体发生癌变时, 可促进细胞角蛋白能够促进 Cyfra21-1 的表达及释放, 导致患者病情恶化。Bax 为一种代表性凋亡蛋白, 主要分布在线粒体外膜上, Bax 过表达可促进肿瘤细胞的转移, 还可抑制肿瘤细胞凋亡。实时影像融合的超声虚拟导航技术联合射频消融术治疗可降低以上物质的表达, 进而提高疗效^[29,30]。但在实时影像融合的超声虚拟导航技术联合射频消融术在实际应用中应掌握下列适应证: 肿瘤最大直径≤5 cm; 肝功能分级为 Child A 级或 B 级; 未形成脉管癌栓及侵犯邻近器官。由于本次研究所能入选的病例数有限, 未进行长期随访分析, 将在下一步的研究中进一步扩大样本量, 希望得到更精确的效果。

总之, 实时影像融合的超声虚拟导航技术联合射频消融术治疗原发性肝癌合并门静脉癌栓能降低血清 Bax、Cyfra21-1 含量, 改善患者的肝功能, 提高消融效率, 还可减少并发症, 最终提高总体疗效。

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