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热消融与手术切除治疗异时性结直肠癌肝转移的临床疗效比较

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【摘要】 目的 比较热消融与手术切除治疗异时性结直肠癌肝转移（colorectal liver metastasis, CRLM）的疗效，探讨热消融的潜在合适人群。**方法** 回顾性收集2007年11月–2021年1月在中国医学科学院肿瘤医院接受根治性治疗的319例CRLM患者资料，根据治疗方法的不同，分为热消融组和手术切除组。运用倾向性评分匹配（propensity scoring match, PSM）平衡患者基线资料。运用Cox回归分析确定影响患者复发及生存的危险因素。两组间进行生存分析。**结果** 按照1∶1比例，PSM后热消融组和手术切除组各匹配92例患者。热消融组中位总生存时间为49（95%置信区间37～76）个月，短于手术切除组（P<0.01）。多因素Cox回归分析提示原发肿瘤T分期、转移瘤数目、转移瘤最大直径、术前血清癌胚抗原水平及治疗方式是影响总生存时间的独立危险因素。与手术切除组相比，热消融组肝脏复发率较高（59.8% vs. 23.9%，P<0.01），无病生存期较短（10个月 vs. 33个月，P<0.01），但住院时间更短（7.0 d vs. 14.0 d，P<0.01）。亚组分析使用匹配前的319例样本进行，显示早期复发的患者接受热消融和手术切除的中位总生存期相当（29个月 vs. 42个月，P=0.35）；非早期复发的患者接受热消融治疗的中位总生存期短于手术切除组（P<0.01）。**结论** 手术切除CRLM的疗效优于热消融治疗，但在早期复发患者中两者疗效相当。

【关键词】 结直肠癌肝转移 热消融 手术切除

Comparison of Clinical Efficacy of Thermal Ablation vs. Surgical Resection of Metachronous Colorectal Liver Metastasis

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【Abstract】 Objective To compare the treatment efficacy of thermal ablation versus surgical resection of metachronous colorectal liver metastasis (CRLM) and to explore the potential candidates suited for thermal ablation. **Methods** The data of 319 patients with CRLM who underwent radical treatment at the Cancer Hospital, Chinese Academy of Medical Sciences between November 2007 and January 2021 were retrospectively collected. The patients were divided into two groups, the thermal ablation group and the surgical resection group, according to the actual treatments they received. Propensity score matching (PSM) was applied to balance the baseline characteristics between the two groups. Cox regression analysis was conducted to identify the risk factors for recurrence and survival. Survival analysis was performed for intergroup comparison. **Results** Using PSM at 1∶1 ratio, 92 patients were included in the thermal ablation group and 92 patients were included in the surgical resection group.The median overall survival (OS) in the thermal ablation group was 49 (95% confidence interval, 37-76) months, which was shorter than that of the surgical resection group (P<0.01). Multivariate Cox regression analysis indicated that the T staging of primary tumor, number of metastatic tumor, maximum diameter of metastatic tumor, preoperative serum carcinoembryonic antigen (CEA) level, and treatment method were independent risk factors affecting OS. Compared with the surgical resection group, the thermal ablation group demonstrated higher hepatic recurrence rate (59.8% vs. 23.9%, P<0.01), shorter disease-free survival (DFS) (10 months vs. 33 months, P<0.01), and shorter length of hospital stay (7 days vs. 14 days, P<0.01). Subgroup analysis, conducted with the data of the 319 patients before PSM, showed that early recurrence patients who underwent thermal ablation or surgical resection had comparable median OS (29 months vs. 42 months, P=0.35). For the non-early recurrence patients, the median OS of the thermal ablation group was shorter than that of the surgical resection group (P<0.01). **Conclusion** For the treatment of CRLM, the efficacy of surgical resection was better than that of thermal ablation. However, the efficacy was comparable between the two treatments for early recurrence patients of

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CRLM.

【Key words】 Colorectal liver metastasis Thermal ablation Resection

2021年GLOBOCAN公布数据显示全球范围内结直肠癌(colorectal cancer, CRC)在恶性肿瘤中的发病率和死亡率分别居第三位、第二位[1]。约50% CRC患者会出现转移,肝脏为最常见的转移部位[2]。15%~25% CRC患者在确诊时即发现肝转移,称为同时性结直肠癌肝转移(colorectal liver metastasis, CRLM)[3],约50%的CRLM患者原发灶切除术后出现肝转移,称为异时性CRLM。距原发肿瘤诊断时间间隔小于12个月的异时性肝转移称为近期异时性CRLM,反之称为远期异时性CRLM[4]。目前,手术切除是CRLM的一线治疗方案[5]。自20世纪90年代将消融应用于CRLM以来[6],热消融,尤其是射频消融和微波消融在临床诊疗中的地位逐渐得到了认可[7]。在早期小肝癌中,热消融与手术切除均可作为一线治疗的选择[8],但在CRLM的治疗中,消融通常作为不适合手术切除患者的替代治疗[9-10]。目前,关于既可手术切除又可热消融治疗的异时性CRLM的研究报道较少[11],因此针对这部分异时性CRLM患者,本研究拟通过比较热消融与手术切除的疗效,探讨热消融的潜在合适人群。

1 对象和方法

1.1 研究对象

本研究符合2013年版《世界医学会赫尔辛基宣言》,所有研究对象在接受根治性治疗前均签署知情同意书。本研究经中国医学科学院肿瘤医院伦理委员会批准(审批号:22/118-3319)。

回顾性收集2007年11月–2021年1月在中国医学科学院肿瘤医院接受根治性治疗的634例CRLM患者资料。入组标准:①原发肿瘤接受根治性R0切除,且术后病理为腺癌;②转移瘤经过术后病理或术前影像学检查明确诊断;③转移瘤数目<5且最大直径≤5 cm;④转移瘤首次接受手术切除或者热消融治疗,且符合既可行手术切除又可行热消融治疗的标准。排除标准:①转移瘤同时接受手术切除和消融治疗;②同时性肝转移;③双原发癌;④患者信息不齐全。

1.2 治疗方法

1.2.1 热消融 采用局部麻醉,根据病灶位置选择超声引导下经皮微波消融或射频消融。射频消融采用 Cool-tip消融系统(Covidien, Boulder, CO, USA),微波消融使用KY-2000 微波消融治疗仪(康友,南京,江苏)。对于部分病灶位置不佳或者不易观察,术中可采用人工胸/腹水,必要时联合超声增强检查。完全消融定义为靶病灶完全被高回声区覆盖或超声造影发现靶病灶无增强。消融完成后,常规消融针道、退针。治疗1个月后复查影像学检查。

1.2.2 手术切除 采用全身麻醉,根据病灶的数目、大小、位置及毗邻结构,经过多学科团队讨论后制定肝脏切除方案。当决定行肝大部切除时,术前需行吲哚氰绿实验以明确肝储备充足。术中对肝脏及腹腔进行探查以判断有无肝外转移灶。切除标本行冰冻切片病理诊断证实切除边缘无肿瘤浸润。

1.3 随访

采用电话及门诊复查方式随访,末次随访时间为2021年12月1日。前2年每季度行影像学检查和癌胚抗原的检测,之后每半年复查一次持续至第5年。本研究中肝脏复发(hepatic recurrence, HR)定义为:治疗区域出现新病灶或肝内治疗区域外出现复发。

总生存时间(overall survival, OS)为本研究的主要研究终点,无病生存期(disease-free survival, DFS)、肝脏复发率以及术后并发症为本研究次要研究终点。术后并发症按Clavien-Dindo分类[12],严重并发症定义为≥3级。

1.4 统计学方法

为减少组间基线资料的不均衡性,本研究使用倾向性评分匹配(propensity scoring matching, PSM),并按照1∶1比例最邻近匹配法进行匹配,卡钳值设置为0.05。热消融组与手术切除组进行匹配时纳入以下变量:年龄、原发肿瘤位置、原发肿瘤大体类型、原发肿瘤分化程度、原发肿瘤T分期、原发肿瘤N分期、异时性CRLM转移类型(近期、远期)、转移瘤数目、转移瘤分布情况、转移瘤最大直径、CRS(clinical risk score)、转移瘤治疗后是否化疗及转移瘤治疗前血清癌胚抗原(carcinoembryonic水平。

计数资料采用数值(百分比)形式,组间比较应用Fisher精确概率法。计量资料采用中位数(四分位数间距)形式,组间比较应用秩和检验。单因素分析检验水准设定为0.1,多因素分析检验水准为0.05。运用Kaplan-Meier法和log-rank分别进行生存分析和检验,并用Cox比例风险模型进行多因素分析。运用最小P值法得到DFS期的最佳阈值并将患者分为早期复发和非早期复发[13]。

2 结果

2.1 基线资料

见表1。根据纳入排除标准,共计入组319例患者,其

表 1　匹配前后患者的基线资料

Table 1　Patient baseline data before and after propensity scoring matching (PSM)

Characteristic	Before matching			After matching		
	Thermal ablation (*n*=148)	Resection (*n*=171)	*P*	Thermal ablation (*n*=92)	Resection (*n*=92)	*P*
Gender/case (%)			0.653			0.652
Male	92 (62.2)	101 (59.1)		57 (62.0)	53 (57.6)	
Female	56 (37.8)	70 (40.9)		35 (38.0)	39 (42.4)	
Age/yr., median (P_{25}-P_{75})	59.8 (57.9-61.6)	56.1 (54.7-57.5)	0.002	59.0 (50.0-64.0)	57.5 (52.8-64.0)	0.994
Age at the time of the procedure/case (%)			0.030			1.000
⩽60 yr.	106 (71.6)	141 (82.5)		74 (80.4)	74 (80.4)	
>60 yr.	42 (28.4)	30 (17.5)		18 (19.6)	18 (19.6)	
Primary tumor side/case (%)			0.688			1.000
Left-sided	123 (83.1)	146 (85.4)		82 (89.1)	81 (88.0)	
Right-sided	25 (16.9)	25 (14.6)		10(10.9)	11(12.0)	
Gross type/case (%)			0.019			1.000
Ulcerative	109 (73.6)	103 (60.2)		63 (68.5)	64 (69.6)	
Protuberant	38 (25.7)	67 (39.2)		28 (30.4)	27 (29.3)	
Infiltrative	1 (0.7)	1 (0.6)		1 (1.1)	1 (1.1)	
Differentiation (primary)/case (%)			0.666			0.834
Well	11 (7.4)	10 (5.9)		5 (5.6)	6 (6.5)	
Moderate	107 (72.3)	131 (76.6)		67 (72.8)	69 (75.0)	
Poor	30 (20.3)	30 (17.5)		20 (21.6)	17 (18.5)	
T stage/case (%)			0.033			0.720
1-2	6 (4.1)	19 (11.1)		5 (5.4)	3 (3.3)	
3-4	142 (95.9)	152 (88.9)		87 (94.6)	89 (96.7)	
N stage/case (%)			0.569			0.871
N^-	44 (29.7)	57 (33.3)		28 (30.4)	26 (28.3)	
N^+	104 (70.3)	114 (66.7)		64 (69.6)	66 (71.7)	
Metachronous type/case (%)			0.010			1.000
Early (⩽12 months)	89 (60.1)	77 (45.0)		50 (54.3)	49 (53.3)	
Late (>12 months)	59 (39.9)	94 (55.0)		42 (45.7)	43 (46.7)	
Metastases distribution/case (%)			0.333			1.000
Unilobar	128 (86.5)	140 (81.9)		74 (80.4)	73 (79.3)	
Bilobar	20 (13.5)	31 (18.1)		18 (19.6)	19 (20.7)	
Metastases diameter/case (%)			0.021			1.000
⩽3 cm	119 (80.4)	117 (68.4)		69 (75.0)	70 (76.1)	
>3 cm, ⩽5 cm	29 (19.6)	54 (31.6)		23 (25.0)	22 (23.9)	
Metastases number/case (%)			1.000			0.766
Single	94 (63.5)	109 (63.7)		51 (55.4)	54 (58.7)	
Multiple	54 (36.5)	62 (36.3)		41 (44.6)	38 (41.3)	
CRS/case (%)			0.278			0.820
⩽2	134 (90.5)	147 (86.0)		80 (87.0)	82 (89.1)	
>2, ⩽5	14 (9.5)	24 (14.0)		12 (13.0)	10 (10.9)	
Postoperative chemotherapy/case (%)			0.003			1.000
No	36 (24.3)	19 (11.1)		13 (14.1)	12 (13.0)	
Yes	112 (75.7)	152 (88.9)		79 (85.9)	80 (87.0)	
CEA level before procedure/case (%)			0.512			1.000
⩽200 ng/mL	145 (98.0)	165 (96.5)		90 (97.8)	90 (97.8)	
>200 ng/mL	3 (2.0)	6 (3.5)		2 (2.2)	2 (2.2)	

CRS: Clinical risk score; CEA: Carcinoembryonic antigen.

中热消融组148例,手术切除组171例。匹配前,两组之间的年龄、手术年龄、原发肿瘤大体类型、原发肿瘤T分期、异时性CRLM转移类型、转移瘤最大直径、转移瘤术后是否化疗差异有统计学意义($P<0.05$)。匹配后,两组各纳入92例,两组之间的所有变量差异均无统计学意义。

2.2 影响OS、DFS的单因素和多因素分析

单因素Cox回归模型分析显示:年龄、原发肿瘤大体类型、原发肿瘤T分期、原发肿瘤淋巴结状态、异时性CRLM转移类型、转移瘤数目、转移瘤术前血清CEA水平及治疗方式是影响患者OS的危险因素。将以上因素及可能影响预后的因素,如原发肿瘤位置、原发肿瘤分化程度、转移瘤最大直径、CRS及转移瘤术后是否化疗纳入多因素Cox分析,最后结果显示:原发肿瘤T3~4期($HR=5.03$, $P=0.024$)、多发转移瘤($HR=1.47$, $P=0.048$)、转移瘤最大直径>3 cm且<5 cm($HR=1.74$, $P=0.013$)、转移瘤术前血清CEA水平>200 ng/mL($HR=2.91$, $P=0.044$)及热消融($HR=3.22$, $P<0.001$)是OS更差的独立危险因素。见表2。

单因素Cox分析显示:原发肿瘤大体类型、原发肿瘤T分期、原发肿瘤淋巴结状态、异时性CRLM转移类型、转移瘤数目及治疗方式是影响患者DFS的危险因素。将以上因素纳入多因素Cox分析,最后结果显示:原发肿瘤淋巴结转移($HR=1.50$, $P=0.010$)、多发转移瘤($HR=1.78$, $P<0.001$)及热消融($HR=2.78$, $P<0.001$)是DFS更差的独立危险因素。见表3。

2.3 生存分析

热消融组和手术切除组的中位随访时间分别为61(56~76)个月和44(37~57)个月。匹配后,热消融组中位OS期为49〔95%置信区间(confidenceinterval, *CI*):37~76〕个月,短于手术切除组($P<0.01$),1、3、5年OS率分别为91%、61%、42%和96%、83%、66%。匹配后,热消融组和手术切除组的中位DFS期分别为10(95%*CI*:8~12)个月及33(95%*CI*:19~未达到)个月($P<0.01$),1、3、5年DFS率分别为38%、18%、14%和72%、49%、47%。匹配后生存分析见图1。

2.4 复发、并发症和住院时间

匹配后,接受热消融和手术切除治疗后复发的患者分别为73例(79.3%)、43例(46.7%)($P<0.001$)。其中,肝脏复发的患者分别为55例(59.8%)、22例(23.9%)($P<0.001$)。热消融组和手术切除组之间并发症发生率、严重并发症发生率差异均无统计学意义。热消融组的中位住院时间短于手术切除组($P<0.001$)。匹配后患者复发情况见表4。

表2 匹配前患者基线数据影响OS的单因素和多因素分析结果

Table 2 Results of univariate and multivariate analyses of patients' baseline data affecting OS before PSM

Variable	Univariate analysis		Multivariate analysis	
	HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
Age (≤60 yr. vs. >60 yr.)	1.68 (1.16-2.43)	0.006	–	–
Primary tumor side (left vs. right)	1.02 (0.60-1.73)	0.948	–	–
Gross type		0.005		
Ulcerative	1 (ref)		–	–
Protuberant	0.48 (0.30-0.76)	0.002	–	–
Infiltrative	1.18 (0.16-8.48)	0.870	–	–
Differentiation (primary)		0.281		
Poor	1 (ref)		–	–
Moderate	0.79 (0.49-1.27)	0.332	–	–
Well	1.24 (0.60-2.55)	0.566	–	–
T stage (1-2 vs. 3-4)	6.73 (1.66-27.31)	0.008	5.03 (1.23-20.57)	0.024
N stage (negative vs. positive)	1.64 (1.08-2.48)	0.021	–	–
Metachronous type (early vs. late)	0.64 (0.44-0.93)	0.018	–	–
Metastases number (single vs. multiple)	1.76 (1.21-2.55)	0.003	1.47 (1.00-2.15)	0.048
Metastases diameter (≤3 cm vs. >3 cm, ≤5 cm)	1.50 (0.99-2.27)	0.054	1.74 (1.12-2.70)	0.013
CRS score (≤2 vs. >2, ≤5)	1.48 (0.86-2.55)	0.162	–	–
CEA level before procedure (≤200 ng/mL vs. >200 ng/mL)	3.45 (1.26-9.50)	0.016	2.91 (1.03-8.24)	0.044
Post-procedure chemotherapy (no vs. yes)	0.92 (0.58-1.47)	0.725	–	–
Treatment (thermalablation vs. resection)	3.13 (2.08-4.76)	<0.001	3.22 (2.13-4.76)	<0.001

HR: Hazard ratio; *CI*: Confidence interval; CRS: Clinical risk score; CEA: Carcinoembryonic antigen.

表 3　匹配前患者基线数据影响DFS的单因素和多因素分析结果

Table 3　Results of univariate and multivariate analyses of patients' baseline data affecting DFS before PSM

Variable	Univariate analysis		Multivariate analysis	
	HR (95% *CI*)	*P*	*HR* (95% *CI*)	*P*
Gross type		0.016		
Ulcerative	1 (ref)		–	–
Protuberant	0.64 (0.46-0.87)	0.005	–	–
Infiltrative	1.18 (0.29-4.76)	0.818	–	–
T stage (1-2 vs. 3-4)	3.41 (1.60-7.27)	0.001	–	–
N stage (negative vs. positive)	1.48 (1.09-2.02)	0.013	1.50 (1.10-2.05)	0.010
Metachronous type (early vs. late)	0.60 (0.46-0.80)	<0.001	–	–
Metastases number (single vs. multiple)	1.71 (1.29-2.27)	<0.001	1.78 (1.33-2.37)	<0.001
Treatment (thermal ablation vs. resection)	2.86 (2.13-3.85)	<0.001	2.78 (2.08-3.85)	<0.001

HR: Hazard ratio; *CI*: Confidence interval.

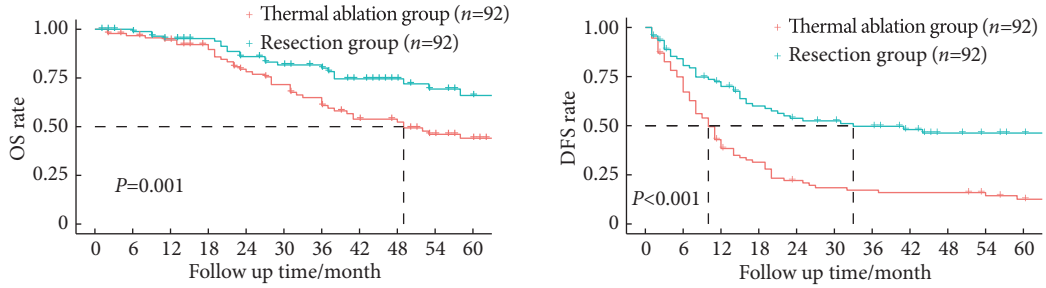

图 1 匹配后接受热消融或手术切除的CRLM患者的OS和DFS

Fig 1 Survival curves of overall survival and disease-free survival of CRLM patients undergoing thermal ablation or resection after PSM

OS: Overall survival; DFS: Disease-free survival.

表 4　倾向性评分匹配后热消融组和手术切除组的复发和并发症评估

Table 4　Recurrence evaluation of thermal ablation and resection after PSM

Recurrence/Complication	Thermal ablation (*n*=92)	Resection (*n*=92)	*P*
Recurrence/case (%)	73 (79.3)	43 (46.7)	<0.001
Hepatic recurrence/case (%)	55 (59.8)	22 (23.9)	<0.001
Complication/case (%)	13 (14.1)	24 (26.1)	0.057
Serious complication/case (%)	0 (0)	2 (2.2)	0.497
Hospital day (median [P_{25}, P_{75}])	7.0 (6.7-7.3)	14.0 (10.0-16.0)	<0.001

2.5　亚组分析

亚组分析使用匹配前的319例样本进行。运用最小*P*值法，结果显示复发的最佳阈值位于第10个月，因此我们定义早期复发为治疗后10个月内出现复发的患者(107例)，非早期复发为治疗后10个月后出现复发和未出现复发的患者(212例)。通过分别比较早期复发、非早期复发患者接受热消融、手术切除的中位OS期发现早期复发患者两组差异无统计学意义〔29(95%*CI*: 23 ~ 41)个月 vs. 42(95%*CI*: 23 ~ 未达到)个月，*P*= 0.35〕，非早期复发患者接受热消融治疗的中位OS期为77(95%*CI*: 65 ~ 未达到)个月，短于接受手术切除治疗的中位OS期(*P*< 0.05)。见图2。

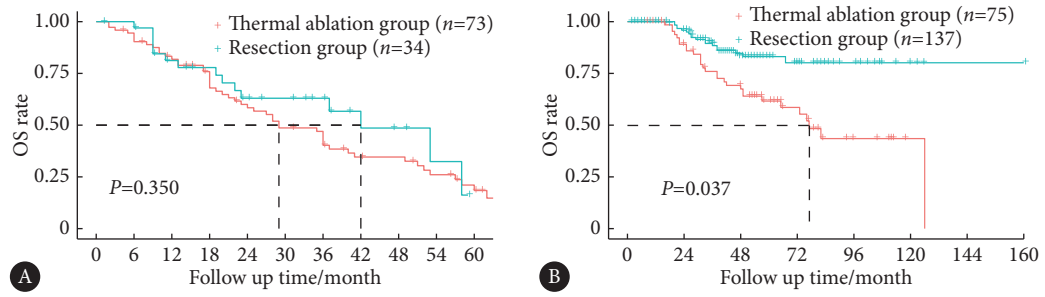

图 2 匹配前早期复发（A）和非早期复发（B）患者的OS

Fig 2 Survival curves of overall survival (OS) for early recurrence (A) and non-early recurrence (B) patients before PSM

3 讨论

国内外许多指南将热消融推荐为CRLM患者局部治疗的重要选择[7, 14-15],但通常是作为不适宜或者拒绝外科手术患者的替代治疗,对于既可外科手术又可热消融治疗的CRLM患者,热消融能否作为一线治疗选择尚未达成一致。因此,针对这部分患者,我们运用PSM方法比较热消融和手术切除治疗异时性CRLM的疗效,以期为热消融治疗可手术切除CRLM提供循证医学证据。本研究结果显示,手术切除组OS、DFS优于热消融组,复发率较低,但热消融组住院时间明显缩短,另外亚组分析显示早期复发CRLM组内热消融预后非劣于手术切除。

近年来,随着外科、消融诊疗技术和系统治疗的发展,CRLM患者的中位OS期可延长至30个月以上[16]。关于热消融和手术切除治疗CRLM的疗效比较充满争议,TINGUELY等[17]对727例接受微波消融或手术切除的CRLM患者进行分析,结果显示手术切除组OS率高于消融组(76% vs. 69%, $P<0.01$)。HUANG等[18]研究结果认为微波消融与手术切除治疗CRLM的5年OS率差异无统计学意义。本研究结果显示手术切除组与热消融组OS差异有统计学意义($P<0.01$)。另外,手术切除组5年OS率高于热消融组($P<0.01$),与近年来其他类似研究结果一致[19-20]。

CRLM接受根治性治疗后出现复发在临床上较为常见,且常发生于术后2年内[4]。本研究经PSM匹配后,热消融组复发率高于手术切除组($P<0.001$),另外,热消融组肝脏复发率也高于手术切除组($P<0.001$)。相应地,手术切除组DFS较热消融组延长($P<0.01$)。CRLM手术切除后复发率与既往文献报道相一致[20-22],热消融组复发率高于既往相关研究[23],DFS较文献报道缩短[19]。导致上述结果的可能原因是:第一,"热沉效应"可能增加了局部复发的风险;第二,手术切除组患者都是经过术中病理检查证实为R0切除,而热消融组治疗后未行组织学检查,仅仅通过治疗后1个月的影像学检查确认为完全消融。对于CRLM根治性治疗后早期复发的定义尚未统一,有研究定义为术后6个月、1年、2年或3年[24-25],但我们分析发现治疗后在10个月前后复发的患者生存差异最大,因此本研究定义10个月为早期复发与非早期复发的界值。通过进一步研究发现早期复发患者热消融与手术切除OS无差异。

本研究存在一些局限性:首先,虽然在研究设计中运用了PSM尽可能减少混杂偏倚,但由于单中心、回顾性研究自身的特性,本研究中的早期复发亚组分析仅相当于单因素分析,这是单中心研究样本量不足导致的(若使用匹配后的样本量,亚组分析的样本量将进一步受限,故本研究使用匹配前的样本量),研究结果还需要前瞻性、多中心试验的验证;其次,本研究由于涉及的人群周期较长,近一半患者未行基因检测,因此未纳入患者分子学特征,如大鼠肉瘤(rat sarcoma, RAS)基因、v-raf鼠肉瘤病毒癌基因同源物B1(v-raf murine sarcoma viral oncogene homolog B1, BRAF)和微卫星不稳定(microsatellite instability, MSI)状态。

综上所述,手术切除对于CRLM的治疗效果优于热消融治疗,但是对于早期复发的患者,热消融治疗与手术切除疗效相当,可作为一线治疗选择。

* * *

利益冲突 所有作者均声明不存在利益冲突

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