标准残肝体积联合肝纤维化测定在原发性肝癌切除术安全性评估中的价值

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摘　要:[目的] 探讨标准残肝体积(SRLV)大小及肝纤维化程度与原发性肝癌切除术后发生肝功能代偿不全间的关系。[方法] 对因肝癌行肝切除术的 104 例病例进行研究。残肝体积=全肝体积-切除肝脏体积;SRLV=残肝体积/体表面积;根据声脉冲辐射力成像(acoustic radiation force impulse,ARFI)评分将所有病例分为 A 组(中、重度肝纤维化组)和 B 组(正常或轻度肝纤维化组)。通过受试者工作特征曲线(ROC)分析预防发生肝功能代偿不全的 SRLV 安全临界值。并将术后发生肝功能中度代偿不全患者的术前 ARFI 评分与术后 SRLV 进行直线回归分析。[结果] A 组病例术后发生肝功能轻度代偿不全、中度代偿不全及重度代偿不全分别为 53 例、22 例、4 例。在 A 组病例中,肝功能中、重度代偿不全发生率为 32.9%,(26/79),肝功能轻度代偿不全患者和中、重度代偿不全患者的 SRLV[(605.69±118.98)ml/m^2 *vs* (470.81±62.59)ml/m^2]比较具有显著差异(P<0.05)。ROC 曲线分析提示发生肝功能中、重度代偿不全的 SRLV 的临界值为 503ml/m^2。B 组病例数少,不作统计学分析。将术后发生肝功能中度代偿不全患者的术前 ARFI 评分及术后 SRLV 进行直线回归分析,显示呈正相关(R=0.719,P<0.01),其回归方程为:SRLV(ml/m^2)=149.6×ARFI 评分(m/s)+194.1。[结论]联合 SRLV 及肝纤维化程度测定对原发性肝癌术前安全切肝量评估有重要指导价值,对伴中、重度肝纤维化患者安全 SRLV 临界值为 503ml/m^2。

关键词:肝癌;标准残肝体积;肝纤维化;肝功能代偿不全;肝切除术
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Standard Residual Liver Volume Combined Liver Fibrosis Determination in Safety Assessment for Resection of Primary Liver Cancer

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Abstract:[Purpose] To evaluate of standard residual liver volume (SRLV) combined with liver fibrosis determination in safety assessment for resection of primary liver cancer (PLC). [Methods] One hundred and four consecutive patients with PLC who underwent hepatectomy were included in the study. Contrast-enhanced CT was used to measure the total liver volume and the acoustic radiation force impulse (ARFI) imaging was applied to estimate the degree of liver fibrosis pre-operatively. The volume of resected liver during the operation was estimated with drainage. SRLV was defined as the difference between the total liver volume and the resected liver volume divided by the body surface area of patients. All patients were classified into 2 groups according to the ARFI imaging. Group A was moderate or severe liver fibrosis,and group B was mild fibrosis or normal. The receiver operating characteristic(ROC) curves were used to establish the safety threshold value of SRLV to prevent decompensation of liver function. The relationship between SRLV and ARFI was analyzed by linear regression. [Results] The number of mild,moderate and severe liver function decompensation in groups A and B were 53,22,4 and 24,1,0,respectively. In group A, the incidence of moderate and severe liver function decompensation was 32.9%(26/79). Statistical analysis showed that the difference of SRLV [(605.69±118.98)ml/m^2 *vs* (470.81±62.59)ml/m^2] in patients with mild liver function decompensation and those with moderate and severe liver function decompensation was significant (P<0.05).The ROC curve showed that the safety threshold value of SRLV was 503ml/m^2. In group B,the incidence of moderate and sever hepatic insufficiency was

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4.0%. The amount of the patients who suffered from moderate and severe post-operative liver function decompensation was not enough for statistical analysis. The liner relation (R=0.719, P<0.01) was found by compared SRLV and ARFI of the patients with moderate post-operative liver function decompensation, and the regression equation was: SRLV(ml/m^2)=149.6×ARFI(m/s)+194.1. [Conclusion] SRLV and liver fibrosis determination are effective parameters to estimate the safety line of resected liver volume in patient undergoing hepatectomy. For patients with moderate or severe liver fibrosis, the safety threshold value of SRLV is 503ml/m^2.
Key words: liver cancer; standard remnant liver volume; liver fibrosis; hepatic insufficiency; hepatectomy

肝切除术是国内外治疗肝细胞癌(hepatocellular carcinoma, HCC)的普遍首选方法,总体上肝癌术后5年生存率为30%~40%,微小肝癌可高达90%[1]。肝脏外科借助现代科学技术已进入精准肝切除(precise liver resection)时代。精准肝切除旨在追求彻底清除目标病灶的同时,确保剩余肝脏解剖结构完整和功能性体积最大化[2]。术前精确的残肝体积(remnant liver volume, RLV)计算及肝纤维化程度测定将为手术安全性的把握提供有力保证。标准残肝体积(standard remnant liver volume, SRLV)综合考虑患者身高及体重差异对术后RLV需求的影响,较RLV更能反映个体化需求。关于RLV或SRLV与术后肝功能代偿不全间关系的研究在国内外已有较多文献报道[3,4]。但鲜有研究同时考虑肝纤维化程度差异对最小RLV需求的影响。经过学术委员会批准,结合SRLV及肝纤维化程度测定探讨预防肝癌术后发生肝功能中、重度代偿不全的安全切肝量界限,拟为临床应用提供依据,结果报道如下。

1 资料与方法

1.1 资 料

纳入标准:①具备肝癌手术适应证并接受肝切除术者;②术前Child-Pugh分级为A级者;③术后病理诊断原发性肝癌明确者。手术适应证参照"原发性肝癌诊疗规范(2011年版)"。排除标准:①伴梗阻性黄疸者;②术前丙氨酸转氨酶(ALT)水平升高者;③术前未完善声脉冲辐射力成像(acoustic radiation force impulse, ARFI)、64排螺旋CT等相关检查者。

根据纳入、排除标准,选取广西壮族自治区人民医院肝胆外科因肝癌行肝切除术的104例病例。根据ARFI技术进行肝纤维化程度测定,将所有病例分为2组,A组为中、重度肝纤维化组,B组为正常或轻度肝纤维化组。其中A组男性62例,女性17例,年龄16~79(平均48.0)岁,术后病理示肝细胞肝癌77例,胆管细胞癌2例。B组男性13例,女性12例,年龄21~74(平均49.2)岁,术后病理示肝细胞肝癌5例,胆管细胞癌20例。所有病例手术方式取决于患者肿瘤位置及侵犯范围。术后经病理证实A组病例均伴有中重度肝纤维化,B组病例均为正常肝脏或伴轻度肝纤维化;肝纤维化合并率为74.0%,肝炎合并率为67.3%。

1.2 方 法

术前实验室检查:所有病例术前均行肝功能、肾功能、凝血功能、乙肝两对半及AFP检查;并根据检查结果进行Child-Pugh分级。

肝纤维化程度测定及分级:术前采用ARFI技术对所有病例进行肝脏弹性测定,肝纤维化程度分级根据对应METAVIR评分标准:F0~F4期的ARFI值临界阈值分别为1.45m/s、1.52m/s、1.69m/s、1.79m/s。其中把F0~F1期合并为正常或轻度肝纤维化组,F2~F4期合并为中、重度肝纤维化组。

术前测量体重、身高,计算体表面积:依据计算公式[5]:体表面积(m^2) =0.0071×身高(cm)+0.0133×体重(kg)−0.1971,计算体表面积。

影像学检查及肝脏体积测定:术前常规64排螺旋CT检查,并通过计算机辅助测定全肝体积。

手术切除肝脏体积测定:术中切除的肝脏组织包括肿瘤和肿瘤周围的肝脏组织,采用排水法测量其体积,精确度达到10ml。

计算 RLV 及 SRLV：RLV=全肝体积-切除肝脏体积；SRLV=RLV/体表面积。

术后肝功能恢复判断：术后监测患者的肝功能指标［测定第 1、3、7、10、14d 的 ALT、总胆红素(TBIL)、凝血酶原时间(PT)、血氨］，观察术后腹水及临床转归(好转或死亡)。肝功能恢复情况及分级标准见表 1(Table 1)[6]。

1.3 统计学处理

研究数据中的计量资料均以($\bar{x}\pm s$)表示，两组间均数比较采用 t 检验，如数据不呈正态分布或方差不齐，则采用秩和检验；计数资料率的比较采用 χ^2 检验；采用相关检验处理相关分析；采用受试者工作特征曲线（ROC）分析预防发生肝功能代偿不全的 SRLV 的安全临界值。检验水准 $P<0.05$。所有统计分析均用 SPSS19.0 统计软件完成。

2 结 果

2.1 术后肝功能代偿不全相关因素分析

A 组病例(n=79)行肝脏切除术后发生肝功能轻度代偿不全、中度代偿不全及重度代偿不全分别为 53 例、22 例和 4 例。因肝功能重度代偿不全组例数过少，并入中度代偿不全组进行统计比较。即肝功能轻度代偿不全组(n=53)与肝功能中、重度代偿不全组(n=26)。肝功能中、重度代偿不全发生率为 32.9%。两组病例在年龄、病灶大小、手术时间、肝门阻断时间等方面无明显差异（$P>0.05$）；而在手术出血量、ARFI 评分、RLV、SRLV 间具有显著差异（$P<0.05$）(Table 2)。B 组病例(n=25)行肝脏切除术后仅 1 例发生肝功能中度代偿不全，中、重度肝功能代偿不全发生率为 4.0%，SRLV 为(596±103)ml/m^2。B 组病例数少，术后发生肝功能中、重度代偿不全病例数不足，无统计学意义。

2.2 ROC 曲线分析

ROC 曲线分析 A 组病例术后发生肝功能中、重度代偿不全的 SRLV 的临界值为 503ml/m^2，曲线下面积(AUC)为 0.888，敏感性 88.7%，特异性 69.2% (Figure 1)。以 503ml/m^2 为界将 A 组病例分为两组，其中 SRLV≤503ml/m^2 组共有 25 例，7 例术后表现为肝功能轻度代偿不全，18 例术后发生中、重度代偿不全，中、重度代偿不全发生率为 72.0%。SRLV>503ml/m^2 组共有 54 例，其中 46 例术后表现为肝功能轻度代偿不全，8 例术后发生中、重度代偿不全，中、重度代偿不全发生率为 14.8%，两组间中、重度代偿不全发生率比较具有显著统计学差异(P<0.001) (Table 3；Figure 2)。所以，当 SRLV≤503ml/m^2 时，术后肝功能中、重度代偿不全发生率明显升高。

Table 1 Criterion for the diagnosis of different degree of liver function damage

Liver function damage	ALT(U/L)	TBIL(mmol/L)	Extension of prothrombin time(s)	Ascites	Blood ammonia
Mild decompensation	<300	<34	<3	No or little	Normal
Moderate decompensation	Once>300	34~51	3~5	Moderate	Once higher than normal
Severe decompensation	Twice consecutive>300	Twice consecutive>51	>5	Mass	Twice higher than normal

Note：Patients according with 3 of 5 items can be diagnosed.

Table 2 Indicators in different degree of liver function decompensation patients in moderate and severe liver fibrosis group ($\bar{x}\pm s$)

Items	Postoperative decompensation of liver function		t	P
	Mild(N=53)	Moderate and severe(N=26)		
Age (years old)	46.17±12.00	51.62±13.13	−1.837	0.070
Focal length (cm)	5.81±3.23	6.36±2.67	−0.745	0.458
Surgical blood loss (ml)	525.70±512.81	734.00±474.28	−2.131	0.036
Operation time (min)	168.70±57.38	175.15±41.83	−0.510	0.611
Blocking of hepatic portal (min)	12.25±14.43	11.27±8.93	0.369	0.713
ARFI(m/s)	1.77±0.29	2.05±0.54	−2.422	0.021
RLF (ml)	1070.98±198.83	821.73±102.74	7.403	0.000
SRLF(ml/m^2)	605.69±118.98	470.81±62.59	6.598	0.000

Table 3 Comparison of incidence of moderate and severe decompensation of liver function in groups divided according to SRLV threshold

Groups	Decompensation of liver function		Incidence of moderate and severe decompensation of liver function(%)	χ^2	P
	Mild	Moderate and severe			
SRLV≤503ml/m²	7	18	72.0	25.309	0.000
SRLV>503ml/m²	46	8	14.8		
Total	53	26	43.4		

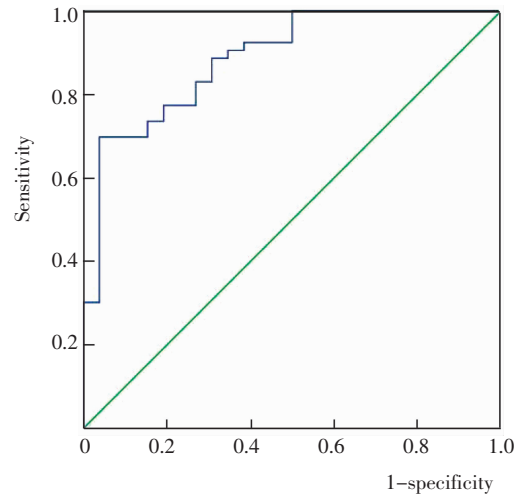

Figure 1 ROC curve of SRLV and postoperative decompensation of liver function

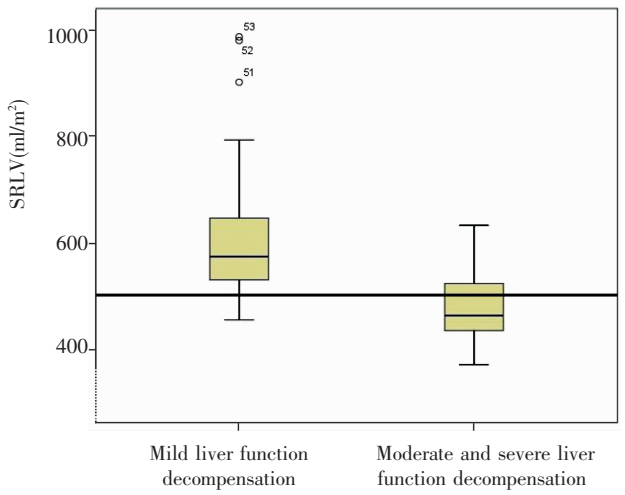

Figure 2 SRLV box diagram for different degree of liver function decompensation patients

2.3 散点图及直线回归分析

将所有病例术前测得 ARFI 评分及术后 SRLV 绘制成散点图(Figure 3),同时对术后发生肝功能中度代偿不全患者的术前 ARFI 评分及术后标准残肝体积进行直线回归分析,结果显示,二者呈正相关(R=0.719,P<0.01),其回归方程为:SRLV (ml/m²)=149.6×ARFI 评分 (m/s)+194.1。图中可见,发生肝功能轻度代偿不全组病例主要分布于直线的左上方,而 4 例肝功能重度代偿不全组病例均分布于直线的右下方。

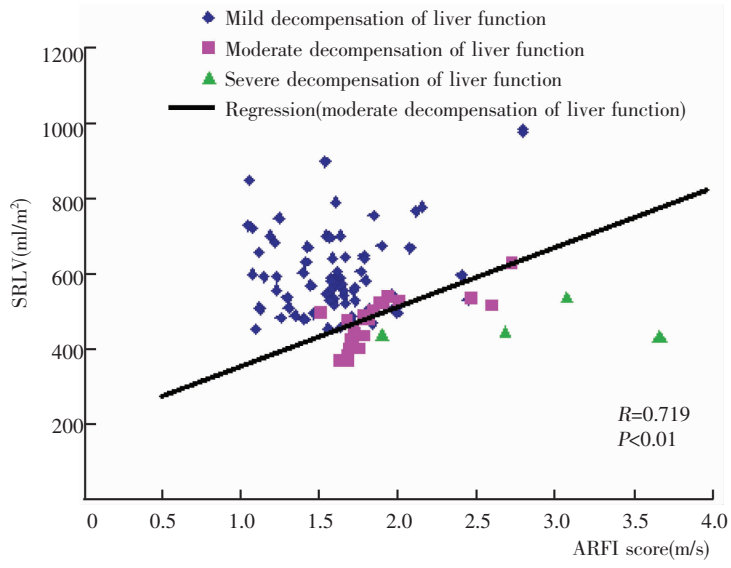

Figure 3 Scatter diagram for SRLV and ARFI score and linear regression analysis for moderate liver function decompensation

3 讨 论

目前国内外对于肝癌的治疗方式仍以肝切除术为主,因此,术前对肝癌切除手术的安全性的评估至关重要。建立 RLV 安全临界值,于肝切除术前预计术后 RLV 对患者手术的安全性和切除范围的估计有着重要意义。国外已将其视为与 Child-Pugh 分级同等重要的肝脏储备功能评价的指标[7]。

本组研究使用 ARFI 技术测定患者术前肝纤维

化程度,经术后病理证实 A 组病例均伴有中重度肝硬化，而 B 组病例为正常肝脏或肝纤维化程度较低。正确地进行肝纤维化分期对慢性肝病患者个体化治疗至关重要。非侵入性检测手段的发展为持续进行病情监测及观察治疗反应提供了可能性。考虑非侵入性技术的诊断率较肝活检相比仍有一定的差距，肝癌术前肝纤维化程度评估必要时联合不同检测方法方可提高诊断的准确率[8]。考虑国外纳入研究的肝癌患者较少伴有肝硬化，我们并不能直接借鉴外国的标准来指导我们的肝手术切除量。本组研究中,A 组病例肝癌术后发生肝功能中、重度代偿不全的临界 SRLV 为 503ml/m^2。以此临界值，肝功能中、重度代偿不全发生率分别为 72.0%和 14.8%($P<0.01$)。这与文献同类研究结果相类似[9,10]。

本组研究中两组病例在年龄、病灶大小、手术时间、肝门阻断时间等因素无明显差异。而肝功能中、重度代偿不全组的 RLV、SRLV 明显小于轻度代偿不全组,这与其他学者的相关研究结果一致[11]。研究通过线性回归分析发现，术后发生肝功能中度代偿不全的患者术前 ARFI 评分与术后 SRLV 大小呈正相关。对 SRLV 及肝纤维化程度评估的最大意义在于指导包括手术切除在内不同治疗方案的选择。对于伴中、重度肝纤维化的患者，当预计的 SRLV>503ml/m^2 时手术是安全的;而 SRLV≤503ml/m^2 时，术后发生肝功能中、重度代偿不全的机会较大,应避免直接手术切除。运用此种方法,可以较精确地计算出患者所能耐受的最大肝切除体积，减少肝脏切除术后发生肝功能中、重度代偿不全可能性,降低肝切除术的风险。对于术后肝功能中、重度代偿不全发生机会大的病例,可通过行门静脉栓塞术(PVE)或行联合肝脏分割和门静脉结扎的分阶段肝切除术(ALPPS)后,待对侧肝脏代偿增生后重新评估 SRLV 大小，对于符合条件者仍可行手术切除治疗。Vennarecci 等[12]通过 ALPPS 术成功地为 1143 例伴门脉侵犯的巨大肝癌患者行根治性切除术。可见 SRLV 在术前治疗策略选择中有着重要临床意义。

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