论 著

MR灌注成像联合血清SKA3、ProGRP对肺癌脑转移瘤患者预后的预测价值*

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【摘要】**目的** 探讨MR灌注成像联合血清纺锤体与着丝粒相关蛋白(SKA)3、胃泌素释放肽前体(ProGRP)对肺癌脑转移瘤患者预后的预测价值。**方法** 选取本院2021年3月至2023年2月期间收治的102例肺癌脑转移瘤为研究对象，根据预后分为生存亚组(n=43)和死亡亚组(n=59)。ELISA检测血清SKA3和ProGRP水平。肺癌脑转移瘤患者预后的影响因素采用多因素Cox回归分析；MR灌注成像参数联合血清SKA3、ProGRP水平对肺癌脑转移瘤患者预后的预测价值采用ROC分析。**结果** 死亡亚组最大相对脑血容量(rCBVmax)、脑血流量(rCBF)、血清SKA3、ProGRP水平均显著高于生存亚组(*P*＜0.05)。死亡亚组低分化和多发脑转移灶的占比明显高于生存亚组(*P*＜0.05)。Cox回归显示，低分化(OR=1.154)、多发脑转移灶(OR=1.449)、rCBVmax(OR=1.439)、rCBF(OR=1.445)、SKA3(OR=2.121)、ProGRP(OR=2.257)均为肺癌脑转移患者预后的独立危险因素(*P*＜0.05)。ROC结果显示，rCBVmax、rCBF、SKA3、ProGRP联合预测肺癌脑转移瘤患者预后的敏感度为77.97%，特异度为93.02%，AUC为0.913，显著高于rCBVmax(Z/*P*=2.590/0.010)、rCBF(Z/*P*=2.247/0.025)、SKA3(Z/*P*=2.627/0.009)、ProGRP(Z/*P*=1.965/0.049)单独预测的AUC。**结论** 血清SKA3和ProGRP与肺癌脑转移瘤患者预后密切相关，MR灌注成像参数联合血清SKA3和ProGRP对肺癌脑转移瘤患者预后具有较高预测价值。

【关键词】肺癌脑转移瘤；MR灌注成像；纺锤体与着丝粒相关蛋白3；胃泌素释放肽前体；预后；预测价值
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Predictive Value of MR Perfusion Imaging Combined with Serum SKA3 and ProGRP for the Prognosis of Patients with Lung Cancer Brain Metastases*

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ABSTRACT
Objective To explore the predictive value of MR perfusion imaging combined with serum spindle and kinetochore-associated protein (SKA) 3 and pro-gastrin releasing peptide (ProGRP) for the prognosis of patients with lung cancer brain metastases. ***Methods*** A total of 102 patients with lung cancer brain metastases admitted to our hospital from March 2021 to February 2023 were selected as the study subjects, and were divided into survival subgroup (n=43) and death subgroup (n=59) according to prognosis. ELISA was applied to detect serum SKA3 and ProGRP levels. The prognostic factors of patients with lung cancer brain metastases were analyzed using multivariate Cox regression. The predictive value of MR perfusion imaging parameters combined with serum SKA3 and ProGRP levels for the prognosis of patients with lung cancer brain metastases was analyzed using ROC. ***Results*** The maximum relative cerebral blood volume (rCBVmax), regional cerebral blood flow (rCBF), serum SKA3, and ProGRP levels in the death subgroup were greatly higher than those in the survival subgroup (*P*<0.05). The proportions of low differentiation and multiple brain metastases in the death subgroup was greatly higher than that in the survival subgroup (*P*<0.05). Cox regression showed that low differentiation (OR=1.154), multiple brain metastases (OR=1.449), rCBVmax (OR=1.439), rCBF (OR=1.445), SKA3 (OR=2.121), and ProGRP (OR=2.257) were all independent risk factors for the prognosis of patients with lung cancer brain metastases (*P*<0.05). ROC found that the sensitivity of the combination of rCBVmax, rCBF, SKA3, and ProGRP in predicting the prognosis of patients with lung cancer brain metastases was 77.97%, the specificity was 93.02%, and the AUC was 0.913, which was greatly higher than the AUC predicted separately by rCBVmax (Z/*P*=2.590/0.010), rCBF (Z/*P*=2.247/0.025), SKA3 (Z/*P*=2.627/0.009), and ProGRP (Z/P=1.965/0.049). ***Conclusion*** Serum SKA3 and ProGRP are closely related to the prognosis of patients with brain metastases of lung cancer. MR Perfusion imaging parameters combined with serum SKA3 and ProGRP have high predictive value in the prognosis of patients with brain metastases of lung cancer.
Keywords: Lung Cancer Brain Metastases; MR Perfusion Imaging; Spindle and Kinetochore-associated Protein 3; Pro-gastrin Releasing Peptide; Prognosis; Predictive Value

肺癌是起源于支气管黏膜的发病率和病死率都极高的恶性肿瘤，其发生与长期吸烟、接触电离辐射、肺部基础疾病、基因、饮食等多方面因素有关[1-2]。晚期肺癌容易发生远处转移，例如脑转移、骨转移等，其中，脑转移具有极高的发生率[3]。肺癌脑转移患者会出现颅内高压，发生偏瘫、失语、视力下降、癫痫等，预后极差[4]。MR灌注成像是近几年发展起来的能够观察脑部血管分布及血流灌注情况的无创检查技术，有利于对脑部肿瘤进行诊断和监测[5]。既往研究报道，纺锤体与着丝粒相关蛋白(SKA)3和胃泌素释放肽前体(ProGRP)与肺癌细胞的生长、增殖密切相关，且二者表达情况对肺癌患者预后具有一定预测价值，但SKA3及ProGRP对肺癌脑转移瘤患者预后的预测效能尚不明确[6-7]。因此，本研究主要探讨血清SKA3及ProGRP在肺癌脑转移瘤患者中的表达及与患者预后的关系，分析MR灌注成像联合血清SKA3及ProGRP对肺癌脑转移瘤患者预后的预测价值，报道如下。

1 资料与方法

1.1 研究对象 前瞻性选取本院2021年3月至2023年2月期间收治的102例肺癌脑转移瘤患者为研究对象。

纳入标准：(1)均符合肺癌诊断标准且经病理学证实[8]；(2)脑转移组经影像学确诊；(3)年龄≥18岁且签署知情同意书；(4)入院前未接受相关治疗。排除标准：(1)既往肿瘤史；(2)脑部手术史；(3)精神状态异常/认知障碍；(4)不接受随访；(5)治疗依从性差；(6)伴脑血管疾病(7)近半年内严重外伤史。本研究经医学伦理委员会批准。

1.2 方法

1.2.1 MR灌注成像检查 西门子skyra3T对所有脑转移患者进行MR灌注成像，仰卧位，8通道头部线圈，常规扫描T1WI、T2WI，以3mL/s向患者肘静脉注射钆喷酸葡胺(0.2 mmol/kg)，5 s后开始扫描，MR灌注成像采用多层采集方式，18层，TR 1 400 ms，TE 25 ms，FOV 240 mm×240 mm，矩阵256 mm×256 mm，层厚3 mm，层距2 mm。

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GE处理站获取相对脑血容量(CBV)和脑血流量(CBF)伪彩图，病灶强化区域勾画5个感兴趣区，CBV取最大值(VBVmax)，CBF取平均值(CBF)，另在病灶对侧正常组织(镜像区)放置5个感兴趣区，获取平均CBV和CBF。rCBVmax=病变区CBVmax/镜像区CBV，rCBF=病变区CBF/镜像区CBF。

1.2.2 血清SKA3和ProGRP水平检测 采用ELISA检测患者治疗前血清(空腹静脉血离心获取)SKA3(货号: ZX18158；重庆智选生生物科技有限公司)和ProGRP(货号: TL15182；上海肽链生物科技有限公司)水平。

1.2.3 随访 对102例肺癌脑转移瘤患者进行一年随访(电话/门诊)，随访率100%，随访过程中癌因死亡的患者归为死亡亚组(n=59)，剩余患者归为生存亚组(n=43)。

1.3 统计学分析 SPSS 25.0处理数据。计数资料用n(%)表示，采用检验。计量资料用($\bar{x}\pm s$)表示，采用t检验。 肺癌脑转移瘤患者预后的影响因素采用多因素Cox回归分析；MR灌注成像参数联合血清SKA3、ProGRP水平对肺癌脑转移瘤患者预后的预测价值采用ROC分析。P＜0.05为差异有统计学意义。

2 结 果

2.1 生存亚组、死亡亚组rCBVmax、rCBF、血清SKA3、ProGRP水平比较 死亡亚组rCBVmax、rCBF、血清SKA3、ProGRP水平均显著高于生存亚组(t=10.837、8.434、7.755、8.314，P＜0.05)。见表1。

2.2 生存亚组、死亡亚组临床资料比较 死亡亚组低分化和多发脑转移灶的占比明显高于生存亚组(χ^2=5.928、6.151，P＜0.05)。两组原发肿瘤类型及直径等均无显著差异(P＞0.05)。见表2。

2.3 肺癌脑转移瘤患者预后的多因素Cox回归分析 以肺癌脑转移瘤患者预后(生存=0，死亡=1)为因变量，以分化程度、脑转移灶数目、rCBVmax、rCBF、SKA3、ProGRP为自变量进行Cox回归，结果显示，低分化(OR=1.154)、多发脑转移灶(OR=1.449)、rCBVmax(OR=1.439)、rCBF(OR=1.445)、SKA3(OR=2.121)、ProGRP(OR=2.257)均为肺癌脑转移患者预后的独立危险因素(P＜0.05)。见表3。

2.4 MR灌注成像参数联合血清SKA3、ProGRP水平对肺癌脑转移瘤患者预后的预测价值 以肺癌脑转移瘤患者预后为因变量，以rCBVmax、rCBF、SKA3、ProGRP为检验变量绘制ROC曲线，结果显示，rCBVmax、rCBF、SKA3、ProGRP预测肺癌脑转移瘤患者预后的AUC分别为0.780、0.784、0.773、0.826，敏感度分别为83.05%、81.36%、81.36%、79.66%，特异度分别为72.09%、67.44%、72.09%、74.42%，rCBVmax、rCBF、SKA3、ProGRP联合预测肺癌脑转移瘤患者预后的敏感度为77.97%，特异度为93.02%，AUC为0.913，显著高于rCBVmax(Z/P=2.590/0.010)、rCBF(Z/P=2.247/0.025)、SKA3(Z/P=2.627/0.009)、ProGRP(Z/P=1.965/0.049)单独预测的AUC。见图1、表4。

表1 生存亚组、死亡亚组rCBVmax、rCBF、血清SKA3、ProGRP水平比较

组别	例数	rCBVmax	rCBF	SKA3(pg/mL)	ProGRP(pg/mL)
生存亚组	43	2.41±0.43	1.32±0.23	54.71±8.14	78.25±10.42
死亡亚组	59	3.63±0.64	1.76±0.28	68.49±9.35	99.57±14.26
t	-	10.837	8.434	7.755	8.314
P	-	＜0.001	＜0.001	＜0.001	＜0.001

表2 生存亚组、死亡亚组临床资料比较[n(%)]

指标	生存亚组(n=43)	死亡亚组(n=59)	t/χ^2	P
年龄(岁)	64.58±8.49	67.14±8.92	1.460	0.147
体质量指数(kg/m^2)	22.15±2.23	21.87±2.18	0.634	0.527
男性	26(60.47)	38(64.41)	0.165	0.684
吸烟史	21(48.84)	35(59.32)	1.104	0.293
原发肿瘤类型			0.167	0.920
腺癌	18(41.86)	27(45.76)		
鳞癌	9(20.93)	12(20.34)		
小细胞癌	16(37.21)	20(33.90)		
原发肿瘤直径			0.289	0.591
≥3 cm	30(69.77)	44(74.58)		
＜3 cm	13(30.23)	15(25.42)		
分化程度			5.928	0.015
高中分化	25(58.14)	20(33.90)		
低分化	18(41.86)	39(66.10)		
脑转移灶数目			6.151	0.013
单发	22(51.16)	16(27.12)		
多发	21(48.84)	43(72.88)		
脑外转移灶			2.937	0.087
有	26(60.47)	45(76.27)		
无	17(39.53)	14(23.73)		
脑转移治疗方式			1.897	0.594
手术治疗	14(32.56)	14(23.73)		
单纯化疗	2(4.65)	4(6.78)		
单纯放疗	6(13.95)	15(25.42)		
放化疗	19(44.19)	21(35.59)		
对症治疗	2(4.65)	5(8.47)		

表3 肺癌脑转移瘤患者预后的多因素Cox回归分析

变量	变量赋值	B	SE	Wald χ^2	P	HR	95% CI
rCBVmax	连续变量	0.372	0.128	8.458	0.004	1.154	1.129~1.865
rCBF	连续变量	0.371	0.131	8.015	0.005	1.449	1.121~1.873
SKA3	连续变量	0.364	0.142	6.569	0.010	1.439	1.089~1.901
ProGRP	连续变量	0.368	0.137	7.220	0.007	1.445	1.105~1.890
分化程度	高中分化=0，低分化=1	0.752	0.186	16.341	＜0.001	2.121	1.473~3.054
脑转移灶数目	单发=0，多发=1	0.814	0.193	17.790	＜0.001	2.257	1.546~3.295

表4 MR灌注成像参数联合血清SKA3、ProGRP水平对肺癌脑转移瘤患者预后的预测价值

变量	AUC	截断值	95%CI	敏感度(%)	特异度(%)	约登指数
rCBVmax	0.780	3.12	0.687~0.856	83.05	72.09	0.551
rCBF	0.784	1.39	0.692~0.859	81.36	67.44	0.488
SKA3	0.773	59.24 pg/mL	0.679~0.850	81.36	72.09	0.535
ProGRP	0.826	88.82 pg/mL	0.739~0.894	79.66	74.42	0.541
联合预测	0.913	-	0.841~0.960	77.97	93.02	0.710

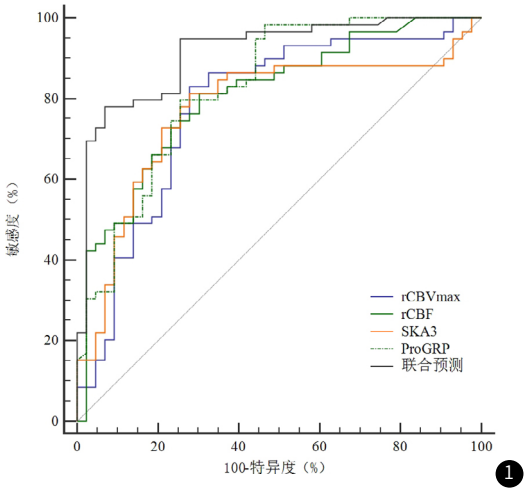

图1 MR灌注成像参数联合血清SKA3、ProGRP水平预测肺癌脑转移瘤患者预后的ROC曲线。

3 讨 论

由于肺癌早期症状易被忽视，多数患者确诊时已是中晚期，远处转移率高[9]。据统计，在所有脑转移瘤中，以肺癌脑转移瘤最为常见，这与肺部血管和淋巴系统丰富、肺部供给脑部的血液量多、肺部血管与椎动静脉吻合支多等因素有关[10-11]。在所有肺癌类型中，小细胞肺癌恶性程度高，最容易发生脑转移，其次为腺癌。肺癌脑转移瘤常为多发转移病灶，预后极差，不治疗的情况下1~3个月内死亡[12]。探讨MR灌注成像联合血清SKA3和ProGRP对肺癌脑转移瘤患者预后的预测价值对患者预后提高具有一定帮助。

肿瘤的诊断鉴别离不开影像技术，MR灌注成像有助于评估病灶区微血管灌注情况。杨厚义等[13]研究报道，MR灌注成像获取的rCBF参数有助于预测肺癌脑转移瘤病理分型。本研究结果中，死亡亚组rCBVmax、rCBF高于生存亚组，多因素Cox分析也提示rCBVmax、rCBF为肺癌脑转移瘤患者预后的独立危险因素，表明预后不良患者病灶区新生血管较多，rCBVmax、rCBF有助于评估肺癌脑转移瘤患者预后。严君等[14]的研究也显示，rCBV和rCBF在鉴别脑胶质瘤复发与假性进展中具有较高的应用价值。本研究ROC分析显示，rCBVmax和rCBF预测肺癌脑转移瘤患者预后的AUC分别为0.780和0.784，提示具有一定区分度，但特异度较低。

SKA3在维持着丝粒蛋白稳定性中发挥重要作用，通过影响有丝分裂过程影响细胞周期、增殖和凋亡，从而影响肿瘤发生发展过程，人SKA3编码基因位于染色体13q区域[15-16]。吴福林等[17]研究显示，非小细胞肺癌患者术后血清中SKA3水平较术前显著降低。本研究结果显示，死亡亚组血清SKA3水平显著高于生存亚组，且多因素Cox分析表明肺癌患者血清SKA3水平越高，1年内死亡的几率越高，提示SKA3与肺癌脑转移瘤患者预后密切相关。Lin等[18]认为，SAK3在肺腺癌中高表达，且可能成为其预后标记物。本研究ROC分析显示，血清SKA3预测肺癌脑转移瘤患者预后的敏感度为81.36%，特异度为72.09%，提示血清SKA3有助于预测肺癌脑转移患者预后，当患者血清SKA3水平高于59.24 pg/mL时，一年内死亡的几率较高。

ProGRP是一种胃肠激素，广泛分布于胃肠道、神经系统等，生理状态下ProGRP在血液中浓度较低[19]。研究认为，癌细胞能够分泌ProGRP，ProGRP又会刺激癌细胞生长，目前，ProGRP已成为肺癌特异性肿瘤标记物[20]。王英英等[21]研究认为，血清ProGRP是小细胞肺癌预后的影响因素，有助于化疗疗效评估及预后预测。本研究发现，死亡亚组血清ProGRP水平较生存亚组高，提示ProGRP与脑转移患者预后紧密相关。多因素Cox分析也提示血清ProGRP为肺癌脑转移瘤患者预后的独立危险因素。Ueki等[22]研究发现，治疗前ProGRP水平有助于预测局限性小细胞肺癌脑转移风险，指导进一步治疗。本研究ROC结果中，血清ProGRP预测肺癌脑转移瘤患者预后敏感度中等，特异度略低。由于单一指标对肺癌脑转移瘤患者预后的预测效能不佳，本研究进一步采用串联的方式分析MR灌注成像参数(rCBVmax、rCBF)联合血清SKA3和ProGRP的预测效能，结果显示，四者联合预测肺癌脑转移瘤患者预后的AUC达0.913，优于单独预测的AUC，特异度也得到明显提高。

综上所述，SKA3和ProGRP高表达的肺癌脑转移瘤患者预示着预后不良，MR灌注成像参数联合血清SKA3和ProGRP对肺癌脑转移瘤患者预后具有较高预测价值。

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