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HER2 基因突变对非小细胞肺癌临床特征及其与 CT 征象的相关性研究 *

张 辉¹ 刘怀军² 杨直堂^{3Δ} 高 洁¹ 梁腾飞¹ 袁丁玲¹ 李保卫¹ 王晓敏¹

(1 河北工程大学附属医院医学影像科 河北 邯郸 056002; 2 河北医科大学第二医院医学影像科 河北 石家庄 050005;

3 河北工程大学附属医院神经内科 河北 邯郸 056002)

摘要 目的:探讨表皮生长因子受体 2(human epidermal growth factor receptor2, HER2)基因突变对非小细胞肺癌临床特征及其与 CT 征象的相关性。方法:回顾性选择我院 2010 年 1 月至 2019 年 12 月收治的 351 例非小细胞肺癌患者,收集 351 例非小细胞肺癌患者的 HER2 突变位点、CT 影像学征象、一般资料等资料。分析 351 例患者中的 HER2 基因突变发生情况;单因素、多因素分析 HER2 突变情况与非小细胞肺癌患者的临床病理特征、CT 表现特征相关性。结果:351 例患者中,基因突变者 20 例,占比为 5.70%(20/351)。单因素结果表明,非小细胞肺癌患者中,HER2 基因突变与有家族史有关($P<0.05$)。病灶边界分叶/毛刺、有坏死征、胸膜凹陷征与 HER2 基因突变存在相关性($P<0.05$)。多因素结果表明,有家族史、病灶边界分叶/毛刺、有坏死征、胸膜凹陷征是 HER2 基因突变的危险因素($P<0.05$)。结论:有家族史、病灶边界分叶/毛刺、有坏死征、胸膜凹陷征与 HER2 基因突变有关,对指导临床治疗有重要意义。

关键词:HER2 基因突变;非小细胞肺癌;临床特征;CT 征象;相关性

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Study on HER2 Gene Mutation in Non-small Cell Lung Cancer Clinical Characteristics and Its Correlation with CT Findings*

ZHANG Hui¹, LIU Huai-jun², YANG Zhi-tang^{3Δ}, GAO Jie¹, LIANG Teng-fei¹, YUAN Ding-ling¹, LI Bao-wei¹, WANG Xiao-min¹

(1 Department of Medical Imaging, Affiliated Hospital of Hebei University of Engineering, Handan, Hebei, 056002, China;

2 Department of Medical Imaging, Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, 050005, China;

3 Department of Neurology, Affiliated Hospital of Hebei University of Engineering, Handan, Hebei, 056002, China)

ABSTRACT Objective: To investigate the clinical features of HER2 gene mutation in non-small cell lung cancer and its correlation with CT findings. **Methods:** A total of 351 patients with non-small cell lung cancer, who were admitted to Affiliated Hospital of Hebei University of Engineering from January 2010 to December 2019, were retrospectively selected. HER2 mutation sites, CT imaging signs and general data of 351 cases of non-small cell lung cancer were collected. The mutation of HER2 gene in 351 patients was analyzed. The correlation of HER2 mutation with clinicopathological characteristics and CT features of patients with non-small cell lung cancer was analysed by single-factor and multi-factor analysis. **Results:** In 351 patients, 20 patients had gene mutation, accounting for 5.70% (20/351). Univariate results showed that HER2 gene mutation was associated with family history in NSCLC patients ($P<0.05$). There was correlation between the boundary lobules/burrs, signs of necrosis, and pleural pitting signs with HER2 gene mutation ($P<0.05$). The multivariate results showed that family history, focal boundary lobules/burrs, necrotic sign, and pleural pitting sign were risk factors for HER2 gene mutation ($P<0.05$). **Conclusion:** HER2 gene mutation is associated with family history, lesion boundary lobules/burr, necrotic sign and pleural pitting sign, which is of great significance for guiding clinical treatment.

Key words: HER2 gene mutation; Non-small cell lung cancer; Clinical features; CT signs; The correlation

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前言

近年来,随着二代测序技术的成熟,推动了非小细胞肺癌

驱动基因的检测及靶向治疗^[1,2]。以往国内外关于非小细胞肺癌驱动基因研究以 ALK、EGFR 基因居多,有研究证实^[3,4], HER2 基因突变也具有致癌性,若其功能失调,会在癌症发生中产生

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作者简介:张辉(1977-),男,硕士研究生,副主任医师,研究方向:神经放射学,电话:18031023605, E-mail: zhanghuiyx1977@163.com

Δ 通讯作者:杨直堂(1975-),男,硕士研究生,副主任医师,研究方向:神经病学,电话:15133023261, E-mail: yangzhitong@126.com

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相应的信号转导作用。HER2 基因靶向药物研究已陆续进入临床试验中,其中国家综合癌症网已将曲妥珠单抗及阿法替尼列为 HER2 基因突变非小细胞肺癌患者的潜在药物选择^[5,6]。而临床中,虽肿瘤基因可显示与其相关的潜在生物学重要信息,而侵入性活检组织检测只能获取不均质瘤体的一部分,其不能完全代表病变的功能、解剖结构与生理特性^[7,8]。而与分子技术相比,影像学检查可提供全面、无创伤的视角评估肿瘤,帮助活检定位提供最可行的数据^[9,10]。若可确定 HER2 基因突变与 CT 影响表现特点的相关性,可重新定义现有肿瘤分级^[11],因此本文分析了 HER2 基因突变对非小细胞肺癌临床特征及其与 CT 征象的相关性,以评估 CT 检查在 HER2 基因突变中的价值。

1 资料与方法

1.1 一般资料

回顾性选择我院 2010 年 1 月至 2019 年 12 月收治的 351 例非小细胞肺癌患者,所有患者均行 HER2 基因检测,所有患者中男 181 例,女 170 例,年龄范围为 34~85 岁,平均 65.12±4.15 岁。60 例患者根据 HER2 检测结果分为两组,将 HER2 基因突变作为观察组,将无 HER2 基因突变作为对照组。纳入标准,351 例患者均经病理检查确诊,同时行 CT 检查确诊,具有年龄、性别、吸烟史等完整的临床资料;排除 CT 检查前已行化疗、放疗、射频消融等抗肿瘤治疗者;胸部 CT 图像病灶主题不清、图像不符合标准、影响病灶大小判断者;存在其他部位肿瘤转移者;在其他医疗机构行胸部 CT 检查,无法获得完整影像检查资料者。

1.2 方法

收集 351 例非小细胞肺癌患者的 HER2 突变位点、CT 影像学征象、性别、年龄、家族史、性别、饮酒史、吸烟史、临床症状等。其中无临床症状者多为体检时发现,有临床症状者包括咳嗽、干咳、咯血、咳痰、呼吸困难、胸痛等。影像学资料包括病灶部位、形态、最大直径、数量、有无胸腔积液等情况,所有患者均采用二代测序方法检测为 HER2 基因突变,本研究使用标本的患者知情同意。所有患者在确诊为 HER2 基因突变后给予相应治疗,包括靶向治疗、手术治疗、放疗、免疫治疗等。

所有患者均采用美国 GE 公司生产的 Light-Speed 64 排螺旋 CT,患者取仰卧位,从胸锁关节扫描至横膈。参数设置:层厚为 0.625 mm,层间距为 0.625 mm,重建层厚为 5.000 mm。若结节 <3 cm,行薄层重建,层厚为 1.250 mm,自动管电流,管电压为 120 kV。采用增强用高压注射器经患者的肘正中静脉,以 2.5 mL/s 注射速度一次性团注 300 mgI/mL 的碘佛醇 100 mL,剂量为 1.3~1.5 mL/kg,在注射 90 s 后开始扫描。

所有 CT 影像学诊断均由两位副主任医师以上的放射科诊断医师以双盲法按统一标准分别进行评价,以结果一致为准,意见不一致时通过讨论达成一致。读片所用肺窗位为 -550 HU,窗宽为 1400 HU,纵膈窗窗宽为 350 HU,窗位为 35 HU。CT 征象包括病灶位置、直径、性状、边缘、密度、空洞、坏死征。病灶直径:横断面肺窗上测量最大直径;病灶密度包括部分实性结节、磨玻璃密度结节、实性结节;病灶性状为规则与不规则;空洞为病灶中出现低密度区域含气区域;坏死征为实性成分中是否有明显低密度区域(CT 值 <31 HU),边界情况包括毛

刺征与叶征,空气支气管征为实变扩张至肺门附近,较大含气支气管与实变肺组织对比,在实变区中可见含气支气管分支影。

1.3 观察指标

(1)分析 351 例患者中的 HER2 基因突变发生情况;(2)分析非小细胞肺癌患者的临床病理特征及 HER2 突变情况相关性;(3)分析 HER2 基因突变与 CT 表现特征相关性;(4)多因素分析非小细胞肺癌患者的 HER2 基因突变 CT 征象及临床特征的相关性。

1.4 统计学方法

采用 SPSS 23.0 软件,计数资料或计量资料分别用%或 $\bar{x} \pm s$ 表示,用卡方检验或 t 检验,多因素分析采用多元 Logistic 回顾分析。

2 结果

2.1 分析 351 例非小细胞肺癌患者中的 HER2 基因突变发生情况

351 例患者中,基因突变者 20 例,占比为 5.70%(20/351)。其中 16 例为 20 外显子插入突变,占比 80.00%(16/20),其中 1 例同时发生 20 外显子突变合并 HER2 基因扩增;1 例为 16 外显子错义突变,占比 5.00%(1/20),1 例为 22 外显子错义突变,占比 5.00%(1/20),2 例为 19 外显子确实突变,占比为 10.00%(2/20)。

2.2 分析非小细胞肺癌患者的临床病理特征及 HER2 突变情况相关性

非小细胞肺癌患者中,HER2 基因突变与有家族史有关($P<0.05$),见表 1。

2.3 分析 HER2 基因突变与 CT 表现特征相关性

表 2 结果表明,病灶边界分叶/毛刺、有坏死征、胸膜凹陷征与 HER2 基因突变存在相关性($P<0.05$)。

2.4 Logistic 多因素分析非小细胞肺癌患者的 HER2 基因突变 CT 征象及临床特征的相关性

有家族史、病灶边界分叶/毛刺、有坏死征、胸膜凹陷征是 HER2 基因突变的危险因素($P<0.05$)。

3 讨论

肺癌在全球恶性肿瘤中居于首位,且多数为非小细胞肺癌,因此类肺癌的恶性程度较高,缺乏有效治疗方式,死亡率居全球首位^[12-14]。目前肺癌的发病机制不清晰,大多数患者确诊时已为晚期,从而失去了早期手术的机会,无有效的治疗方式,需行全身治疗,而传统化疗无特异性,治疗时会给患者带来较大不良反应^[15,16];同时此类肿瘤患者若尚有手术机会行肿瘤根治性切除术后,患者的转移率与肿瘤复发率仍高达 1/3^[17,18]。目前随着肺癌驱动基因的深入研究及探索,临床上已更好的了解非小细胞肺癌的分子生物学,在驱动基因靶向治疗方面取得了有效成果,与传统化疗相比,靶向治疗在肺癌治疗方面有低毒性、高效性、精准性、最低不良反应的特点,开辟了非小细胞肺癌的治疗新途径,提高了此类患者的治疗有效性及安全性^[19,20]。

HER2 基因位于 17q21,包括 27 个外显子与 26 个内显子,是由原癌基因 HER2 表达生成的蛋白质受体,在细胞表面实现二聚体后会发挥信号传导作用,将生长信号从细胞外传递至细

胞内,对细胞增殖、凋亡、生长、分化产生调控作用,编码产物为跨膜糖蛋白 P185,其分子量约为 185ku,分子长度为 1255 个氨基酸。包括胞内域、胞外域、跨膜亲脂片段,其中胞外域可释放 sp185her2,其是一种 HER2 癌基因可溶性产物,在血液中产生积聚作用,是一种公认的肿瘤标志物^[21-23]。目前,多数研究表明,一些靶向药物 HER2 基因突变者有明显获益,表明在肿瘤靶向治疗前有必要行基因突变检测,而判断 HER2 基因突变多通过

组织学穿刺活检,其会出现气胸、病灶破损出血等不良事件,同时穿刺取样无代表性,不能反应全部信息,给治疗方案提供准确的指导^[24-26]。非小细胞肺癌有典型 CT 表现,对预测晚期非小细胞肺癌有指导意义^[27-29],因此分析了解 HER2 基因突变与 HER2 基因突变与 CT 影像学的相关性,有助于给肿瘤靶向治疗提供理论依据。

表 1 分析非小细胞肺癌患者的临床病理特征及 HER2 突变情况相关性

Table 1 Correlation of HER2 mutation with clinicopathological characteristics of patients with non-small cell lung cancer

Pathological characteristics	Project	n	HER2		χ^2/t	P
			+	-		
Gender	Male	181	7(3.87)	174(96.13)	2.331	0.127
	Female	170	13(7.64)	157(92.36)		
Age (years)	-	-	65.08± 4.09	65.23± 4.25	-0.154	0.878
History of smoking	Yes	129	5(3.88)	124(96.12)	1.260	0.262
	No	222	15(6.76)	207(93.24)		
Family history	Yes	62	8(12.90)	54(87.10)	7.275	0.007
	No	289	12(4.15)	277(95.85)		
Pathological type	Adenocarcinoma	291	18(6.19)	273(93.81)	0.753	0.385
	Squamous cell carcinoma	46	2(4.35)	44(95.65)		
	Squamous cell carcinoma	14	0	14(100.00)		

表 2 分析 HER2 基因突变与 CT 表现特征相关性

Table 2 Correlation between HER2 gene mutations and CT features

CT performance	Classification	n	HER2		χ^2	P
			+	-		
Lung lobe of lesion	Upper leaf	235	13	222	0.02	0.889
	Lower lobe	116	6	110		
Location of focus	Perimeter Type	302	16	286	-	0.501
	Central	49	4	45		
Diameter of lesion (mm)	-	-	51.23± 3.51	51.89± 3.85	-0.748	0.455
Focused traits	Rules	220	11	209	0.561	0.454
	Irregularity	131	9	121		
Focal boundary	Smooth	224	6	218	10.504	0.001
	Blots/burrs	127	14	113		
Focus density	Reality	330	19	311	-	1.000
	Non-real	21	1	20		
Air bronchogram	Yes	22	1	21	-	1.000
	No	329	19	310		
Void	Yes	64	4	60	-	0.770
	No	287	16	271		
Bad Death	Yes	101	14	87	17.587	<0.001
	No	250	6	244		
Pleural concave sign	Yes	224	18	106	14.329	<0.001
	No	127	2	125		

表 3 Logistic 多因素分析非小细胞肺癌患者的 HER2 基因突变 CT 征象及临床特征的相关性

Table 3 Logistic multivariate analysis of correlation of CT signs and clinical features with HER2 gene mutations in patients with non-small cell lung cancer

Factors	β	Wald χ^2	P	OR	95%CI
Family history	0.531	6.231	0.012	2.615	1.314~5.784
Blots and burrs at lesion boundary	1.034	10.649	0.001	2.839	1.415~5.509
Bad death	0.741	4.362	0.027	2.220	1.053~4.105
Pleural concave sign	0.589	7.315	0.012	2.478	1.105~5.128

多因素分析结果表明,性别、年龄、吸烟史、病理类型、病灶所在肺叶、病灶位置、病灶直径、病灶性状、病灶密度、空气支气管征、空洞征等与 HER2 基因突变无相关性;而有家族史、病灶边界分叶/毛刺、有坏死征、胸膜凹陷征是 HER2 基因突变的危险因素,表明出现病灶边界分叶/毛刺、有坏死征、胸膜凹陷征等 CT 征象的患者更易出现 HER2 基因突变,因此对于年龄较大、肺气肿、穿刺部位不佳、有严重出血倾向及冠心病等有较高穿刺风险者,肿块较小肺癌,不易穿刺道有诊断意义组织,或存在穿刺禁忌证者,以上 CT 征象有助于辅助 HER2 基因突变的预测^[30,31]。

综上所述,有家族史、病灶边界分叶/毛刺、有坏死征、胸膜凹陷征与 HER2 基因突变有关,对指导临床治疗有重要意义。本研究仍存在一定局限性,虽是回顾性研究,严格按照纳入、排除标准选择病例,但仍会出现偏倚;同时本研究选择了 351 例患者,但 HER2 发生率低,有待更大样本的研究,同时与肺癌相关基因较多,还有待进一步临床的深入研究。

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