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鼻息肉与鼻咽癌标本 VEGF 水平及微血管密度对比及其临床意义*

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摘要 目的: 对比研究鼻咽癌和鼻息肉标本中 VEGF 表达强度及 MVD 差异, 同时分析 VEGF、MVD 和鼻咽癌临床特征的相关性。**方法:** 纳入我科就诊的鼻咽癌患者 57 例, 鼻息肉患者 50 例。采用免疫组化 SABC 法检测癌组织、癌旁组织、及息肉组织中 VEGF 蛋白的表达, 及 MVD 强度。分析 VEGF、MVD 和鼻咽癌患者性别、临床分期、颈部淋巴结转移、远处转移、血清 EBV-IgA 阳性、WHO 病理分型相关性。统计分析随访结果, 对可能影响鼻咽癌预后的因素进行 Cox 回归模型分析。**结果:** 鼻咽癌组织、鼻咽癌旁组织、鼻息肉组织中 VEGF 表达、MVD 强度具有明显差异($p < 0.05$)。不同鼻咽癌临床分期、是否发生远处转移、不同 WHO 病理分型和 VEGF 表达、MVD 强度具有明显差异($p < 0.05$)。Cox 回归方程显示, 远处转移、病理分型、VEGF 表达强度是影响鼻咽癌生存的独立危险因素($p < 0.05$)。**结论:** 鼻咽癌高表达 VEGF, 促进新生血管, 形成高密度微小血管, 和鼻咽癌远处转移密切相关, 降低其生存率。

关键词: 鼻咽癌; 鼻息肉; 血管内皮生长因子

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Comparison of VEGF and Microvascular Density in Nasal Polyps and Nasopharyngeal Carcinoma and its Correlation with Clinical Features of Nasopharyngeal Carcinoma*

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ABSTRACT Objective: To investigate the VEGF expression and microvessel density (MVD) in nasopharyngeal carcinoma and nasal polyps specimens and compare their differences between the two kinds of specimens, as well as to analyze the correlation of VEGF and MVD with the clinical features of nasopharyngeal carcinoma (NPC). **Methods:** In this study included were 57 cases of nasopharyngeal carcinoma patients and 50 patients with nasal polyps. By immunohistochemical SABC method, the expression of VEGF protein and the intensity of MVD were detected in cancerous tissues, the tissues adjacent to carcinoma, and nasal polyps tissues. The correlation of VEGF and MVD were analyzed with the sex, clinical stage, cervical lymph node metastasis, distant metastasis, positive serum EBV-IgA, and WHO pathology classification of NPC patients. And follow up NPC patients to June 2016. The possible factors affecting the prognosis of NPC were analyzed with the Cox regression model. **Results:** There was significant difference in expression of VEGF and MVD intensity between nasopharyngeal carcinoma tissues, nasopharyngeal carcinoma adjacent tissues and nasal polyps tissues ($p < 0.05$). Different NPC clinical stage, distant metastasis or not, and different WHO pathological classification had correlation with the VEGF expression and MVD intensity ($p < 0.05$). Cox regression equation showed that distant metastases, the pathologic classification, the intensity of VEGF expression were independent risk factors of the survival of NPC patients ($p < 0.05$). **Conclusion:** The high expression of VEGF in nasopharyngeal carcinoma could promote new blood vessels and form high density of tiny blood vessels. It had close relation with the NPC distant metastasis and reduced the survival rate.

Key words: Nasopharyngeal carcinoma; Nasal polyps; Vascular endothelial growth factor

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前言

鼻咽癌是耳鼻喉科最常见的恶性肿瘤之一, 尤其在我国的南

方^[1]。虽然鼻咽癌对放射治疗较为敏感, 被公认为首选的治疗方案, 但其总 5 年生存率仍不高, 在 50%-60% 左右, 影响其生存的主要是因素是局部区域复发和远处转移^[2]。肿瘤的生长和转

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移离不开血管再生及其供血,近年来随着肿瘤血管生成机制的研究,肿瘤的血管生成、血管的密度和转移及预后关系的研究取得了很大的进展,发现肿瘤血管密度与肿瘤的侵袭转移和预后密切相关^[3,4]。VEGF是目前已知的一族最强的促血管形成物质,诱导宿主毛细血管新生并长入肿瘤组织,是肿瘤新生血管形成的决定因素之一^[5]。鼻咽癌的发病和 VEGF 的分泌及血管形成一样密不可分,本研究主要探讨鼻咽癌组织和鼻息肉 VEGF 表达水平、微血管密度和其临床特征的相关性。

1 材料与方法

1.1 研究对象

2012 年 3 月到 2014 年 5 月,我科住院的获得病理标本确诊的鼻咽癌患者 57 例,其中男 33 例,女 24 例,年龄 43~66 (53.3±12.5)岁。鼻息肉患者 50 例,其中男 31 例,女 19 例,年龄 37~62(52.8±11.3)岁。所有患者均经过病理诊断,未进行放疗治疗前所采集的标本,排除了其他鼻咽部疾病可能,有完整的临床病例资料,包括病理切片、影像学、血常规、生化、随访等资料。

1.2 鼻咽癌患者临床特征

包括患者的性别、临床分期、颈部淋巴结转移、远处转移、血清 EBV-IgA 阳性、WHO 病理分型。其中 WHO 病理分型包括 WHO- I (高分化鳞状细胞癌、中分化鳞癌细胞癌、角化性鳞状细胞癌)、WHO- II (低分化鳞状细胞癌、分化型非角化癌)、WHO-III(泡状核细胞癌、未分化型非角化癌、大圆形细胞癌、未分化癌)。

1.3 瘤体组织及旁组织中 VEGF 表达水平、微血管密度(MVD)检测

采用免疫组化 SABC 法检测癌组织、癌旁组织、及息肉组织中 VEGF 蛋白的表达。根据细胞浆的着色程度及着色细胞的百分率进行评分计算阳性系数:基本不着色者为 0 分,着色淡者为 1 分,着色适中者为 2 分,着色深者为 3 分。着色细胞占计数细胞百分率≤5%为 0 分,6%-25%为 1 分,26%-50%为 2 分,≥51%为 3 分。将每张切片着色程度得分与着色细胞百分率得分各自相乘,即为阳性系数。阳性系数为 0,1 分为阴性(-);2,3 分为弱阳性(+);4-6 分为阳性(++);9 分为强阳性(+++)。

微血管密度(Microvessle density,MVD)计算方法:在低倍镜下(×100)下找出标本中血管密度最高的 5 个视野,再在每个低倍镜的视野下换取高倍镜(×400)视野,并计算 5 个视野的 MVD,以平均值作为 MVD 值。凡在镜下呈棕色染色的内皮细胞或细胞簇,且与肿瘤细胞的背景区别明显的均视为一个血管计数。

1.4 统计学方法

计量资料采用均值±标准差($\bar{x} \pm s$),应用 t 检验;计数资料采用 检验;采用 Cox 回归模型分析影响鼻咽癌患者预后的因素;P<0.05 为差异有统计学意义。

2 结果

2.1 鼻咽癌组和鼻息肉组标本 VEGF、MVD 差异

表 1 看出,鼻咽癌组织、鼻咽癌旁组织、鼻息肉组织中 VEGF 表达具有明显差异(p<0.05),鼻咽癌组织中 VEGF 高表达,阳性率达到 100%,其中阳性和强阳性占比 73.68%。癌旁组织中 VEGF 表达水平仍高于鼻息肉组,鼻息肉组多数表达为弱阳性。三组组织标本中鼻咽癌组织微血管密度最大,鼻息肉组织 MVD 最低,三组间差异有统计学意义(p<0.05)。

表 1 鼻咽癌组和鼻息肉组标本 VEGF、MVD 差异

Table 1 VEGF and MVD differences in nasopharyngeal carcinoma and nasal polyp specimens

Groups	N	VEGF				MVD
		Negative	Weakly positive	Positive	Strong Positive	
Nasopharyngeal carcinoma tissues	57	0	15	29	13	33.09± 8.33
Nasopharyngeal carcinoma adjacent tissues	57	5	32	17	3	19.09± 5.38
Nnasal polyp tissues	50	12	31	6	0	12.36± 3.82
E/ χ^2			43.86			16.32
P			0.00			0.00

2.2 鼻咽癌 VEGF、MVD 和临床特征相关性

表 2 看出,鼻咽癌临床分期越晚,其 VEGF 表达越强,微血管密度越大,不同临床分期差异有统计学意义(p<0.05)。发生远处转移鼻咽癌患者 VEGF 及 MVD 明显高于未发生转移的患者,差异有统计学意义(p<0.05)。根据 WHO 鼻咽癌分级,分级越高,VEGF 表达越强,微血管密度越大,差异有统计学意义(p<0.05)。VEGF 表达水平及 MVD 和鼻咽癌是否发生颈部淋巴结转移、血清 EBV-IgA 无明显相关性(p>0.05)。

2.3 Cox 回归分析对鼻咽癌患者预后的因素

对本研究纳入的 57 例具有完整资料的病例进行 Cox 模型回归多因素分析,生存时间从 2012 年 3 月纳入,以月为单位,随访至 2016 年 6 月份,随访结束时仍然存活按截尾值 0 对待,死亡为 1。对可能对预后产生影响的因素进行量化赋值后引入 Cox 回归方程,包括性别、年龄、颈部淋巴结转移、远处转移、临床分期、病理分型、血清 EBV-IgA、VEGF、MVD。赋值方案(表 3)。结果显示,远处转移、病理分型、VEGF 表达强度是影响鼻咽癌生存的独立危险因素(p<0.05)(表 4)。

表 2 鼻咽癌组织 VEGF、MVD 和其临床特征相关性

Table 2 Correlation of VEGF and MVD in nasopharyngeal carcinoma tissues and its clinical characteristics

Clinical Features		N	VEGF				Mvd
			Negative	Weakly positive	Positive	Strong Positive	
Clinical stages	I	12	0	5	6	1	23.14± 5.83
	II	23	0	7	13	3	25.24± 5.37
	III	17	0	3	8	6	30.92± 6.92
	IV		0		2	3	35.95± 8.39
			$\chi^2 = 8.34; p = 0.00 < 0.05$				E = 6.09; p = 0.00 < 0.05
Neck lymph node metastasis	Yes	42	0	9	19	8	34.19± 9.34
	No	15	0	6	10	5	32.46± 8.37
			$\chi^2 = 2.34; p = 0.13 > 0.05$				t = 1.09; p = 0.21 > 0.05
Distant metastases	Yes	16	0	5	18	11	35.83± 9.35
	No	41	0	10	11	2	27.86± 7.03
			$\chi^2 = 5.47; p = 0.00 < 0.05$				t = 6.73; p = 0.00 < 0.05
Serum EBV-IgA	Positive	34	0	7	17	5	32.58± 7.82
	Negative	23	0	8	12	8	33.72± 7.37
			$\chi^2 = 2.68; p = 0.11 > 0.05$				t = 0.73; p = 0.37 > 0.05
WHO Pathological classification	I	19	0	5	13	1	24.63± 4.86
	II	25	0	6	13	6	29.76± 6.31
	III	13	0	2	7	4	34.76± 9.24
			$\chi^2 = 6.03; p = 0.00 < 0.05$				E = 9.43; p = 0.00 < 0.05

表 3 影响鼻咽癌预后可能存在因素变量及赋值

Table 3 The variable and assignment of possible risk factors for prognosis of NPC patients

Attribute Indexes	Symbol	Valuation
Age	X1	"<50"0;"≥50"1
Gender	X2	"women"0;"men"1
Neck lymph node metastasis	X3	"no"0;"yes"1
Distant metastasis	X4	"no"0;"yes"1
Clinical staging	X5	"I, II"0;"III, IV"1
Pathological classification	X6	"I"0;"II, III"1
Serum EBV-IgA	X7	"negative"0;"positive"1
VEGF	X8	"negative, Weakly positive"0;"positive, Strong Positive"1
MVD	X9	"<30"0;"≥30"1

3 讨论

鼻咽癌是耳鼻喉科常见的恶性肿瘤之一，尤其在在我国南方。根据我国不完全统计，中国南方鼻咽癌的发病率约 15-50/10 万，病理上多数属于 WHO-II 型^[6]。肿瘤的血管生成、血管的密度和转移及预后关系的研究取得了很大的进展，发现肿瘤血管密度与肿瘤的侵袭转移和预后密切相关^[7]。VEGF 是目前发现的，具有强大功能，具有多种生物学效应的细胞因子，于机体血管再生密切相关^[8]。

研究表明血管的生长和成熟过程中需要用多种细胞因子及受体和配体序贯活化一系列受体而完成，阻止其中任何一个环节均可能导致 VEGF 分泌及血管再生障碍，是目前抗肿瘤药物研究的一个主要方向之一^[9]。在缺氧、缺血等刺激下，机体的 VEGF 表达上调，通过促进内皮细胞有丝分裂作用，使得已有的血管形成尾足，形成新生血管形成，改善组织供血^[10]。在肿瘤组织中，肿瘤细胞通过刺激周围的巨嗜细胞、肥大细胞等，促进其分泌高水平的 VEGF，从而刺激肿瘤血管形成，使得肿瘤持续生长^[11]。研究认为，鼻咽癌的生长和发展取决于血管生成，刺

表 4 影响鼻咽癌患者生存因素 Cox 回归模型

Table 4 Cox regression model of factors affecting survival of NPC patients

Factors	Regression coefficient	Standard error of regression coefficient	Wald	p
Age	0.65	0.52	2.03	0.153
Gender	-0.87	0.47	3.98	0.093
Neck lymph node metastasis	-0.64	0.66	1.45	0.275
Distant metastasis	2.35	1.08	4.34	0.022
Clinical staging	0.78	0.62	0.89	0.457
Pathological classification	1.93	1.21	5.98	0.000
Serum EBV-IgA	0.84	0.69	1.67	0.162
VEGF	3.82	1.57	7.82	0.00
MVD	1.72	1.46	2.29	0.12

激鼻咽癌肿瘤内内皮细胞增殖的主要因子是 VEGF^[12]。鼻咽癌中 VEGF 表达强度和微血管密度(MVD)表达存在密切相关,等报道鼻咽癌组织中 VEGF 和 MVD 呈正相关^[13]。

鼻咽癌患者血清 VEGF 及鼻咽癌病理组织 VEGF 高表达,与肿瘤快速生长及肿瘤的侵袭、转移有密切关系^[14]。Chen J 等报道鼻咽癌组织中 VEGF 表达强度可作为鼻咽癌淋巴结转移、复发、肿瘤临床分期的重要依据,可以作为评估鼻咽癌预后的指标^[15]。研究发现,高表达 VEGF 和鼻咽癌的病理分型密切相关,尤其是 WHO-III型的患者,其 VEGF 水平较高,伴有高密度的微小血管形成,血管的通透性增加,可能早期出现血行转移^[16,17]。本研究发现,鼻咽癌组织、鼻咽癌旁组织、鼻息肉组织中 VEGF 表达具有明显差异($p<0.05$),鼻咽癌组织中 VEGF 高表达,阳性率达到 100%,其中阳性和强阳性占比 73.68%。癌旁组织中 VEGF 表达水平仍高于鼻息肉组,鼻息肉组多数表达为弱阳性。三组组织标本中鼻咽癌组织微血管密度最大,鼻息肉组织 MVD 最低,三组间差异有统计学意义($p<0.05$)。研究结果表明,鼻咽癌组织以及癌旁组织中 VEGF 表达水平仍明显高于鼻息肉组,说明肿瘤对周围组织同样具有一定的刺激和影响,导致周围组织中供血加强^[18-20]。

恶性程度较高、发生远处转移的鼻咽癌具有高表达 VEGF 特性,促进新生血管,形成高密度微小血管,和鼻咽癌远处转移密切相关。本研究 Cox 回归模型分析结果显示,远处转移、病理分型、VEGF 表达强度是影响鼻咽癌生存的独立危险因素,说明 VEGF 的表达强度具有重要的影响,影响了鼻咽癌的预后。

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