

乳腺癌MRI表现与Ki-67、E-cad表达的关系

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【摘要】目的:探讨乳腺癌MRI表现与Ki-67、E-cad表达的关系。**方法:**对经病理证实的60例乳腺癌患者的病理切片行Ki-67、E-cad免疫组化检测, 观察MRI表现[大小、形状、边缘、强化形式、有无淋巴结转移、时间-信号强度曲线(TIC)类型、最大增强斜率], 并将二者进行相关性分析。**结果:**病变大小与Ki-67阳性表达呈正相关($r=0.298, P<0.05$); 病变边缘为不规则或毛刺时, 其Ki-67阳性表达率较高($r=0.319, P<0.05$); 不伴有淋巴结转移的患者E-cad阳性表达率越高($r=-0.349, P<0.05$); 病变倾向于TIC III型时, Ki-67阳性表达率高($r=0.574, P<0.01$)。**结论:**乳腺癌MRI表现可以部分反映肿瘤的生物行为, 为预测肿瘤预后及临床治疗提供一定帮助。

【关键词】乳腺癌; 磁共振成像; Ki-67; E-cad

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Correlation between magnetic resonance imaging manifestations and expression of Ki-67 and E-cad in patients with breast cancer

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Abstract: Objective To explore the correlation between magnetic resonance imaging (MRI) manifestations of breast cancer and expression of Ki-67 and E-cad. **Methods** The pathological sections of 60 patients with pathologically confirmed breast cancer were examined with Ki-67 and E-cad immunohistochemical testing. We observed their breast MRI manifestations, including the size, shape and edge of lesions, enhancement type, with or without lymph node metastases, time-signal intensity curve (TIC) type and maximum strengthening slope, and analyzed the relationship between MRI manifestations and the expression of Ki-67 and E-cad. **Results** The size of lesion was positively related with the positive expression of Ki-67 ($r=0.298, P<0.05$). When the edge of lesion was irregular or had burrs, the positive rate of Ki-67 was higher ($r=0.319, P<0.05$). Patients with lesions tending to TIC III had a higher positive rate of Ki-67 ($r=0.574, P<0.01$), and those without lymph node metastasis had a higher positive rate of E-cad ($r=-0.349, P<0.05$). **Conclusion** Breast MRI findings may partly reflect the biological behavior of tumor and provide some help for the prediction of prognosis and treatment.

Keywords: breast cancer; magnetic resonance imaging; Ki-67; E-cad

前言

Ki-67是直接影响乳腺癌预后的最相关指标之一, E-cad水平下降可引起肿瘤细胞间的黏附力下降,

从而引起肿瘤细胞的侵袭和转移^[1]。一些学者对乳腺癌影像学表现与癌基因表达进行了探讨^[2-3]。本研究分析乳腺癌MRI增强特征与Ki-67、E-cad表达的关系, 为临床治疗方案的选择提供参考。

1 材料与方法

1.1 一般资料

收集2012年12月~2015年12月在广州中医药大学第一附属医院乳腺科住院经手术或穿刺病理证实的60例乳腺癌患者, 术前均行磁共振动态增强检查(DCE-

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MRI),患者均为女性,年龄29~84岁,平均年龄49.6岁。所有被纳入患者均在行DCE-MRI前签署知情同意书,这些患者在检查前及术前均未行放、化疗治疗。

1.2 MRI检查方法

使用美国GE HDxt 3.0T MRI超导型磁共振扫描仪,8通道乳腺专用相控阵表面线圈。患者检查位置取俯卧位,双乳自然下垂置于线圈双孔内,扫描范围包括双乳腺及腋窝区。常规三平面定位扫描后,采用轴位水脂分离(IDEAL)序列扫描,TR 6 000 ms,TE 100 ms,视野(FOV)32 cm×32 cm,带宽62.5 kHz,层厚5 mm,层距1 mm,矩阵320×192,激励次数(NEX)3次;并行矢状位抑脂快速自旋回波(FSE)序列T₂WI扫描,TR 3 200 ms,TE 88.9 ms,FOV 20 cm×20 cm,带宽31.2 kHz,层厚5 mm,层距1 mm,矩阵256×224,NEX 2次。DWI采用单次激发自旋回波EPI序列(SE-EPI)横断位扫描,TR 6 000 ms,TE 85.3 ms,FOV 32 cm×32 cm,带宽250 kHz,层厚5 mm,层距1 mm,矩阵128×128,NEX 3次,采用频率选择脂肪抑制技术,扩散敏感因子(b值)为1 000s/mm²。动态增强采用快速乳腺容积成像序列(VIBRANT)扫描,参数设置:TR 4.4 ms,TE 2.1 ms,TI 14 ms,FOV 35 cm×35 cm,带宽83.3 kHz,层厚1.0 mm,无间隔,矩阵384×256,NEX 0.7次。增强前先扫描蒙片,然后按0.2 mmol/kg采用高压注射器经肘静脉以2.5 mL/s流率快速团注对比剂钆喷酸葡胺(Gd-DTPA),注药后30 s开始扫描,包括蒙片在内共扫描11个时相,单期扫描时间为75 s。对比剂注射完毕后,以相同速度注入20 mL生理盐水冲洗导管内的对比剂。

1.3 图像观察、后处理及数据处理

60例病人的图像资料由2位高年资MRI诊断医师对MRI平扫、增强图像及时间-信号强度曲线(TIC)进行评定,观察并记录乳腺癌患者的MRI平扫、增强及TIC特点。

1.4 感兴趣区(ROI)的选择及观测指标

选取病灶实质部分、强化最明显的区域作为ROI。ROI大小通常取决于病灶大小并且稍小于病变,尽可能避开肉眼能辨别的血管及液化、坏死、囊变、出血区,ROI大小一般为10 mm×10 mm~20 mm×20 mm。由2位放射科诊断医师采用双盲法对所有病例的图像进行分析和诊断。根据美国放射学会规定的BI-RADS中的MRI部分对病灶增强后形态学表现及TIC进行分析记录^[4]。有争议的结果由2位诊断医师协商决定。病变ROI的强化形态学表现:病灶大小分为≤2 cm和>2 cm组;形状分为类圆形、分叶形和不规则形;边缘情况分为光滑、不规则和毛刺;淋巴

结分为无转移和转移组;磁共振动态增强强化情况分为均匀、不均匀及环形强化;TIC类型分为I型、II型及III型。病灶兴趣区最大增强斜率的计算: $\Delta SI = [(SIC-SI)]/\Delta t$,其中SIC、SI分别为最大斜率段后、前点信号强度, Δt 为该段对应持续时间。

1.5 统计学分析

利用SPSS 17.0软件包进行统计学分析,采用非参数统计中的Spearman等级相关分析评价乳腺癌MRI增强特点各参数间(形态学表现、有无淋巴结转移、TIC类型、最大增强斜率)与Ki-67、E-cad表达的相关性。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 MRI表现

60例乳腺癌中形状为类圆形12例(20.0%),分叶形28例(46.7%),不规则形20例(33.3%)。病灶边缘光滑2例(3.3%),边缘不规则30例(50.0%),边缘毛刺28例(46.7%)。肿瘤内部均匀强化8例(13.3%),不均匀强化42例(70.0%),环形强化10例(16.7%)。磁共振动态增强扫描TIC为I型曲线者3例(5.0%),II型曲线者20例(33.3%),III型曲线者37例(61.7%)。典型病例见图1和图2。

2.2 病理诊断及免疫组化结果

60例乳腺癌患者经手术病理证实,浸润性导管癌I级8例(13.3%),浸润性导管癌II级30例(50.0%),浸润性导管癌III级10例(16.6%),浸润性小叶癌3例(5.0%),粘液腺癌3例(5.0%),导管内乳头状癌1例(1.7%),浸润性乳头状癌1例(1.7%),小管癌1例(1.7%),混合型的乳腺癌3例(5.0%),其中包括中级别导管内癌并导管内乳头状癌1例、浸润性小叶癌并导管内癌2例。肿瘤最大径≤2 cm者29例(48.3%),肿瘤最大径>2 cm者31例(51.7%)。伴有淋巴结转移者26例(43.3%),不伴有淋巴结转移者34例(56.7%)。免疫组化结果中,Ki-67阳性者41例(68.3%),E-cad阳性者49例(81.7%)。

2.3 MR表现与Ki-67、E-cad表达及的相关性

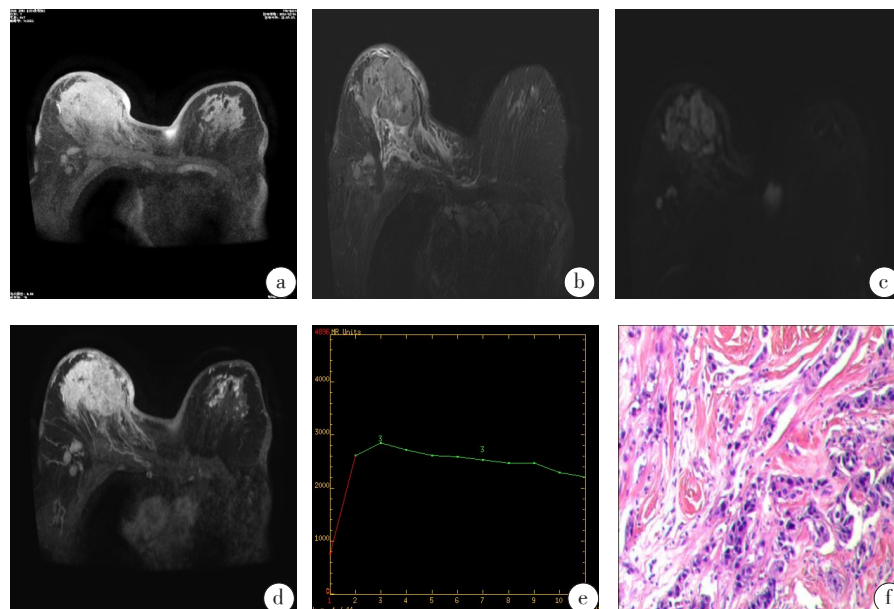
60例乳腺癌患者病变MRI表现与Ki-67、E-cad表达及相关性见表1、2。

3 讨论

本文着重对乳腺癌病变大小、形态、边缘、强化特点及淋巴结有无转移与分子生物学指标Ki-67、E-cad的关系进行初步探讨。

3.1 病变大小

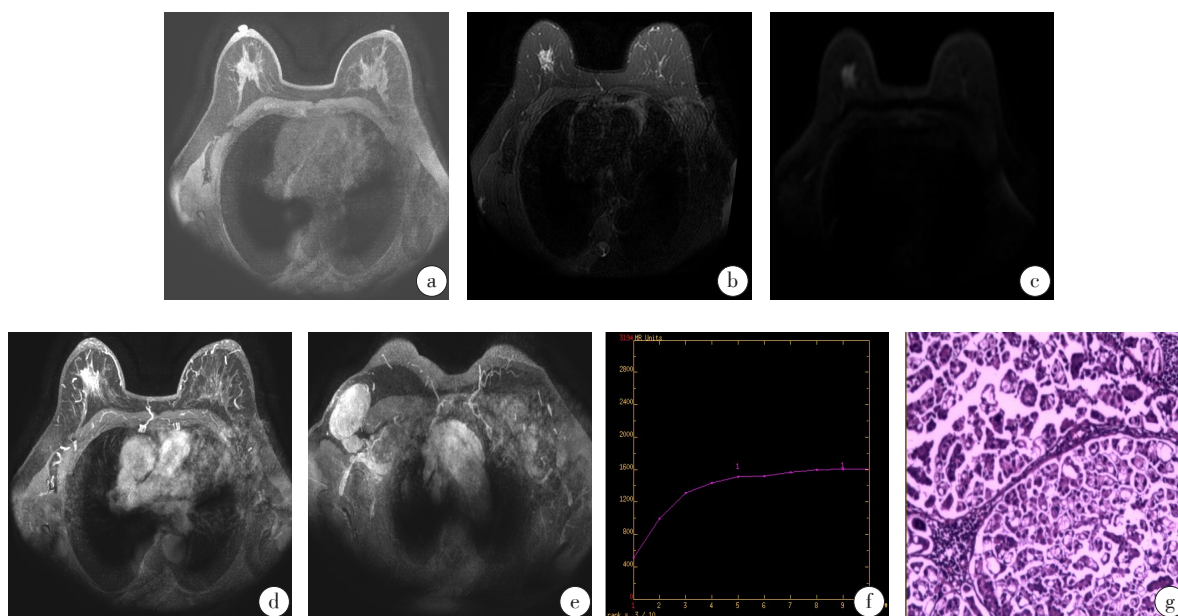
国内外关于肿块大小与分子生物学指标Ki-67、



a: A lobule mass was found in the center of the right breast, with a slightly higher signal in MASK image; b: T₂ weighted image (T₂WI) showed lesion with high signal, irregular and rough edge; c: Diffusion weighted imaging (DWI) image showed restricted diffusion and lesion with high signal; d: Dynamic enhanced scan showed obviously uneven enhancement in mass with irregular and rough edge, an enlargement artery beside mass, and multiple large lymph nodes in the right axillary; e: Time-signal intensity curve (TIC) presented for type III (clear), and the maximum enhanced slope was 24.1; f: The lesion was confirmed as infiltrating ductal carcinoma by pathology, and immunohistochemical testing showed ki-67 (++) , E-cad (+++) , ×200.

图1 女,84岁,右乳浸润性导管癌,III级,肿物最大径为8.8 cm

Fig.1 Case presentation of an 84-year-old female diagnosed with right breast invasive ductal carcinoma (class III), with a maximum diameter at 8.8 cm



a: Irregular nodules were seen in the upper quadrant of the right breast, with a slightly higher signal in MASK image; b: T₂WI showed an iso-high signal, irregular and rough edges; c: DWI showed local restricted diffusion and high signal; d: Dynamic enhancement scanning showed obviously uneven enhancement in the irregular nodule; e: Dynamic enhanced scanning showed enlarged lymph nodes in the right axillary; f: TIC of lesion presented for type II (platform type), and the maximum enhanced slope was 6.4; g: The lesion was confirmed as micropapillary carcinoma at the right breast duct and focal infiltration by pathology, and immunohistochemical testing showed Ki-67 (++) , E-cad (+++) , ×200.

图2 女,58岁,右乳导管内微乳头状癌并灶性浸润,肿物最大径为1.2 cm

Fig.2 Case presentation of a 58-year-old female confirmed with micropapillary carcinoma at the right breast duct and focal infiltration, with a maximum diameter at 1.2 cm

表1 60例乳腺癌患者病变MRI表现与Ki-67、E-cad表达
Tab.1 MRI manifestations and expression of Ki-67, E-cad in 60 patients with breast cancer

MRI manifestation	Case	Ki-67		E-cad	
		-	+	-	+
Size of lesions					
≤2 cm	29	13	16	3	26
> 2 cm	31	6	25	8	23
Shape of lesions					
Round like	12	3	9	1	11
Lobule	28	10	18	6	22
Irregular shape	20	6	14	4	16
Edge of lesions					
Smooth	2	0	2	0	2
Irregular	30	13	17	7	23
Burr	28	6	22	4	24
Enhancement type					
Uniform	8	3	5	1	7
Heterogeneous	42	13	29	8	34
Rings	10	3	7	2	8
Lymph node metastasis					
Yes	34	13	21	2	32
No	26	6	20	9	17
TIC type					
Type I	3	1	2	0	3
Type II	20	10	10	2	18
Type III	37	8	29	9	28

MRI: Magnetic resonance imaging

表2 乳腺癌患者病变MRI表现与Ki-67、E-cad的相关性
Tab.2 The correlation between MRI manifestations of breast cancer and Ki-67 and E-cad

DCE-MRI	Ki-67		E-cad	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
Size of lesions	0.298	0.021*	-0.222	0.088
Shape of lesions	0.041	0.754	0.028	0.830
Edge of lesions	0.319	0.013*	0.209	0.109
Enhancement type	0.063	0.630	-0.034	0.794
Lymph node metastasis	0.145	0.268	-0.349	0.006**
TIC type	0.339	0.008**	0.040	0.763
Maximum enhanced slope	0.122	0.352	0.077	0.559

DCE: Dynamic contrast-enhanced; * $P < 0.05$; ** $P < 0.01$

E-cad的关系的报道较少。夏红强等^[5]研究认为肿块大小与Ki-67的表达呈显著正相关。杨莉等^[6]研究认为Ki-67表达与肿瘤直径无相关性。本研究结果与前者相符,研究显示病变大小与Ki-67阳性表达呈正相关,即肿块直径越大,其Ki-67的阳性表达越高,反映其增殖活性、恶性程度及侵袭性越强,转移的几率高,预后差。本研究中Ki-67的总阳性表达率为68.3%,在直径>2 cm的病变中其阳性率高达80.6%(25/31)。谭米多等^[7]研究表明E-cad阳性表达率与乳腺癌肿瘤直径无相关性。李伟等^[8]研究表明E-cad阳性表达与肿瘤大小无关。本研究结果也显示肿瘤大小与E-cad表达无相关性。

3.2 病变形状

乳腺癌的恶性侵袭性造成了肿块形状的差异。有研究表明大部分恶性肿瘤的形态多不规则^[9]。本研究中肿瘤形状各占比例为类圆形20%、分叶形46.7%、不规则形33.3%,其中分叶形及不规则形病变比例较大。王黎明^[10]研究显示肿块的形态与Ki-67存在相关性。彭泽华等^[11]研究报道肿瘤分叶与Ki-67密切相关,表明分叶状肿瘤有更强的侵袭性。而关于病变形状与E-cad表达的研究较少。本研究显示病变形状与Ki-67、E-cad表达无相关性。这一点与前者研究不一致,可能与样本量不足有关,需要扩大样本量进一步验证。

3.3 病变边缘

乳腺癌肿块边缘的特征性表现是毛刺征,病理上由乳腺小导管及周围纤维结缔组织增生所形成,表现为肿块四周放射状的细线条影。边缘毛刺的肿块反应了病变对周围的浸润^[12]。Lee等^[13]研究认为肿块毛刺边缘与Ki-67低表达相关,而且可以单独预示肿瘤的低分化。李玮等^[14]研究发现毛刺征与Ki-67无相关性。国内外学者对病变边缘与E-cad的关系研究较少。本组边缘不规则肿块所占比例为50%,其Ki-67、E-cad阳性表达率分别为56.7%(17/30)和76.7%(23/30),边缘毛刺肿块占46.7%,其Ki-67、E-cad阳性表达率分别为78.6%(22/28)、85.7%(24/28)。本研究显示病变边缘与Ki-67阳性表达呈正相关,与E-cad表达无相关性,即病变边缘为不规则或毛刺时其Ki-67的阳性表达率较高,乳腺癌侵袭性强。这与部分文献研究不符,可能与不同病理类型的Ki-67阳性表达不同、容易造成假阳性有关。本研究还显示病变大小与边缘呈正相关,即肿块越大,病变边缘多表现为不规则或毛刺。

3.4 强化形式

当肿瘤内部由于供血不足导致液化坏死或出血时,可表现为不均匀强化。微血管在肿瘤边缘聚集是环形强化的主要原因。本研究将病变的强化形式分为均匀强化、不均匀强化和环形强化。有研究发现乳腺癌环

形强化的病理基础是由于肿瘤中心的坏死,而边缘的肿瘤细胞增殖旺盛^[15]。有学者认为环形强化对乳腺癌的阳性预测值较高,为79%~92%^[16]。罗建东等^[17]研究认为环形强化的出现提示肿瘤生物学侵袭行为较高。Szabo等^[18]研究发现环形强化与Ki-67阳性呈正相关。本研究结果中均匀强化、不均匀强化及环形强化所占比例分别为13.3%、70%、16.7%,显示病变强化形式与Ki-67、E-cad表达无相关性,可能与样本量较小及样本构成不同有关,需要进一步验证。本研究结果还显示病变大小、边缘与强化形式呈正相关,即当病变越大,边缘表现为不规则和毛刺时,强化形式多倾向于不均匀和环形强化,提示预后较差。

3.5 淋巴结有无转移

当乳腺癌浸润性增强时则发生淋巴结的转移。Frixen等^[19]研究表明乳腺癌中E-cad蛋白表达与淋巴结转移呈负相关。刘桂桃^[20]研究显示Ki-67阳性表达与其是否发生淋巴结转移无关,E-cad在乳腺浸润性导管癌中的表达与淋巴结转移相关,随着乳腺癌组织发生腋淋巴结转移,E-cad阳性表达率明显下调。本研究中伴有淋巴结转移的乳腺癌所占比例为43.3%,不伴有淋巴结转移者所占比例为56.7%。有无淋巴结转移在Ki-67中的阳性表达率分别为76.9%(20/26)、61.8%(21/34),有无淋巴结转移在E-cad中的阳性表达率分别为65.4%(17/26)、94.1%(32/34)。本研究结果显示病变是否伴有淋巴结转移与E-cad阳性表达呈负相关,与Ki-67表达无相关性,即不伴有淋巴结转移的患者E-cad阳性表达率越高。

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