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乳腺癌超声征象与 ER、PR、连环蛋白 p120、癌基因 CerbB-2、原癌基因 Her-2/neu 表达的关系研究*

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摘要 目的:探讨乳腺癌超声征象与雌激素受体(ER)、孕激素受体(PR)、连环蛋白 p120、癌基因 CerbB-2、原癌基因 Her-2/neu 表达的关系。**方法:**将 2014 年 10 月至 2017 年 10 月我院收治的 50 例乳腺癌患者纳入本研究,术前获得患者完整乳腺超声图像资料,术后通过免疫组织化学法检测 ER、PR、CerbB-2、Her-2/neu 和 p120 的表达情况。记录超声检查与组织标本检测结果,比较不同乳腺癌超声征象中 ER、PR、CerbB-2、Her-2/neu 和 p120 的表达情况。**结果:**p120 阴性表达率为 62.00%,ER 阳性表达率为 50.00%,PR 阳性表达率为 36.00%,CerbB-2 阳性表达率为 74.00%,Her-2/neu 阳性表达率为 30.00%。病灶边缘有毛刺征、周边有高回声晕征、无淋巴结转移患者的 ER 阳性表达率高于病灶边缘无毛刺征、周边无高回声晕征、淋巴结转移者($P<0.05$);病灶边缘有毛刺征、周边有高回声晕征患者的 PR 阳性表达率高于病灶边缘无毛刺征、周边无高回声晕征者($P<0.05$);内部有微小钙化、血流显像分级 2-3 级、淋巴结转移患者的 p120 阴性表达率高于内部无微小钙化、血流显像分级 0-1 级、无淋巴结转移者($P<0.05$);内部有微小钙化、血流显像分级 2-3 级、淋巴结转移患者的 CerbB-2 阳性表达率高于内部无微小钙化、血流显像分级 0-1 级、无淋巴结转移者($P<0.05$);内部有微小钙化、淋巴结转移患者的 Her-2/neu 阳性表达率高于内部无微小钙化、无淋巴结转移者($P<0.05$)。**结论:**乳腺癌超声征象与 ER、PR、CerbB-2、Her-2/neu 和 p120 的表达有紧密联系,可为治疗方案拟定提供参考。

关键词:乳腺癌;超声征象;雌激素受体;孕激素受体;p120;CerbB-2;Her-2/neu

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The Correlation between the Ultrasonic Signs of Breast Cancer and the Expression of ER, PR, Catenin p120, oncogene CerbB-2 and Proto Oncogene Her-2/neu*

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ABSTRACT Objective: To explore the correlation between the ultrasonic signs of breast cancer and the expression of estrogen receptor (ER), progesterone receptor (PR), catenin p120, oncogene CerbB-2 and proto oncogene Her-2/neu. **Methods:** 50 patients with breast cancer who were treated in our hospital from October 2014 to October 2017 were included in this study. Complete breast ultrasound image data of patients were obtained before operation, and the expression of ER, PR, CerbB-2, Her-2/neu and p120 was detected by immunohistochemistry after operation. The results of ultrasonic examination and tissue specimen examination were recorded. The expression situation of ER, PR, CerbB-2, Her-2/neu, p120 were compared. **Results:** The negative expression rate of p120 was 62.00%, the positive expression rate of ER was 50.00%, the positive expression rate of PR was 36.00%, the positive expression rate of CerbB-2 was 74.00%, and the positive expression rate of Her-2/neu was 30.00%. The positive expression rate of ER in patients with marginal burrs sign around the edge of lesions, peripheral hyperechoic signs and without lymph node metastases was higher than that without marginal burrs sign around the edge of lesions, without peripheral hyperechoic signs and having lymph node metastases ($P<0.05$). The positive expression rate of PR in patients with marginal burrs sign around the lesion and high echo halo sign around the lesion was higher than that without marginal burrs sign around the lesion and without high echo halo sign around the lesion ($P<0.05$). The negative expression rate of p120 in patients with internal micro calcification, blood flow imaging grade 2-3 and lymph node metastasis was higher than that without internal micro calcification, without blood flow imaging grade 0-1 and without lymph node metastasis ($P<0.05$). The expression rate of CerbB-2 in patients with internal micro calcification, blood flow imaging grade 2-3 and lymph node metastasis was higher than that without internal micro calcification, without blood flow imaging grade 0-1 and without lymph node metastasis ($P<0.05$). The positive expression rate of Her-2/neu in patients with internal micro calcification and lymph node metastasis was higher than that without internal micro calcification and without lymph node metastases ($P<0.05$). **Conclusion:** The ultrasonic signs of breast cancer are closely related to the expression of ER, PR, CerbB-2, Her-2/neu and p120, which can provide a reference for the formulation of the

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treatment scheme.

Key words: Breast cancer; Ultrasonic sign; Estrogen receptor; Progesterone receptor; P120; CerbB-2; Her-2/neu

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前言

乳腺癌是女性常见的恶性肿瘤,随着现代社会女性工作压力增加以及环境的改变,乳腺癌的发病率逐年升高且呈年轻化趋势^[1,2]。乳腺癌的早期诊断与治疗一直是临床研究的热点。超声检查是诊断乳腺癌的常用影像手段,但在显示微小钙化病灶方面效果欠佳,而彩色多普勒血流显像又容易受到血流速度、声束和血流的夹角以及检查位置等多种因素影响,因此在鉴别良恶性肿瘤方面有一定局限性^[3-5]。目前基因和细胞因子检测在乳腺癌早期诊断中效果逐渐凸显^[6,7]。已有文献报道^[8-10],对雌激素受体(estrogen receptor α , ER)、孕激素受体(progesterone receptor, PR)、癌基因CerbB-2、原癌基因Her-2/neu、连环蛋白p120等与乳腺癌发病的相关性进行了证实,指出其可作为诊断乳腺癌和评估预后的可靠指标。研究ER、PR、CerbB-2、Her-2/neu和p120蛋白与超声征象的联系能够指导临床医师从超声图像中预判其表达情况,从而为乳腺癌的临床诊治以及乳腺癌发病的生物学机制研究提供参考。现报道如下。

1 资料与方法

1.1 一般资料

将2014年10月至2017年10月我院收治的50例乳腺癌患者纳入本研究。纳入标准:(1)均为初诊病例;(2)符合《中国抗癌协会乳腺癌诊治指南与规范(2015版)》^[11]中乳腺癌相关诊断标准;(3)经超声及病理组织学检查确诊;(4)无肝、肺或其他部位转移者;(5)意识状态良好,均签署知情同意书者。排除标准:(1)合并其他恶性肿瘤者;(2)入院前接受过放化疗或手术治疗者;(3)入选前4周内抗凝药物用药史或有凝血功能障碍者。术前获得50例完整乳腺超声图像资料,术后获得50个符合要求的乳腺癌组织标本。患者年龄为32-65岁,平均 (47.11 ± 6.53) 岁,病灶直径:0.71-9.52cm,平均 (2.16 ± 0.47) cm,肿瘤类型:浸润性导管癌34例,浸润性小叶癌11例,粘液腺癌5例。标本采集经医院伦理委员会批准。

1.2 方法

1.2.1 超声检查 使用Philips IU22型彩色多普勒超声诊断仪(荷兰飞利浦公司生产)与其配套的高频线阵探头进行检查,探头频率为7.5-10MHz。检查时患者仰卧,双臂自然上举使双侧乳房和腋窝均充分暴露。先对病灶位置、大小、形态、边缘、微小钙化以及腋窝淋巴结肿大等情况进行扫描,之后使用彩色多普勒血流显像对病灶内部及周边血流情况进行检查。由两位资深阅片师独立阅片,记录所有患者病灶大小、边缘有无毛刺征、周边高回声晕征、内部无回声区、血流显像分级以及是否存在微小钙化和淋巴结转移。

1.2.2 免疫组织化学法检测 将50个乳腺癌组织标本常规进行甲醛溶液固定、石蜡包埋和4 μ m组织切片,用于检测ER、

PR、CerbB-2、Her-2/neu和p120的表达情况。检测方法为免疫组织化学法,试剂盒均购自上海江莱生物科技有限公司。操作步骤:准备试剂、样品和标准品;加入准备好的样品和标准品,37℃反应30 min;洗板5次,加入酶标试剂,37℃反应30 min;洗板5次,加入显色液A、B,37℃显色10 min;加入终止液;15 min内读取光密度(optical density, OD)值,根据标准曲线计算结果。

1.3 观察指标

记录超声检查与组织标本检测结果,比较不同乳腺癌超声征象ER、PR、CerbB-2、Her-2/neu和p120的表达情况。ER、PR判断标准:细胞核无着色为阴性(-),细胞核呈浅棕色、棕色、棕黄色为阳性(+). CerbB-2、Her-2/neu判断标准:未着色或<10%的肿瘤细胞膜着色,亦或仅有胞质非特异性着色为阴性(-),超过10%的肿瘤细胞阳性表达,连续膜显色为阳性(+). p120蛋白判断标准:在400倍镜下选择任意10个视野进行染色细胞(细胞中出现棕黄色细胞颗粒即可判断为阳性染色)计数,阳性染色细胞比例计分:<10%为1分,10%-50%为2分,51%-75%为3分,>75%为4分;阳性染色强度计分:淡黄色颗粒为1分,棕黄色颗粒为2分,棕褐色颗粒为3分。阳性染色细胞比例计分 $\times$ 阳性染色强度计分的总分 ≥ 3 分判断为p120蛋白表达阳性,反之为阴性。

1.4 统计学方法

使用SPSS 19.0进行统计学处理,计数资料以百分率表示,组间比较用 χ^2 检验, $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 超声检查与组织标本检测结果

超声检查结果显示:病灶直径<2 cm者21例, ≥ 2 cm者29例,病灶边缘有毛刺征34例,有微小钙化31例,有淋巴结转移23例,周边有高回声晕征15例,内部无回声9例,血流显像分级:0-1级14例、2-3级36例;免疫组织化学法检测结果显示:p120蛋白阴性31例,占62.00%,ER蛋白阳性25例,占50.00%,PR蛋白阳性18例,占36.00%,CerbB-2蛋白阳性37例,占74.00%,Her-2/neu蛋白阳性15例,占30.00%。

2.2 不同乳腺癌超声征象ER、PR、CerbB-2、Her-2/neu和p120的表达情况

病灶边缘有毛刺征、周边有高回声晕征、无淋巴结转移患者的ER阳性表达率高于病灶边缘无毛刺征、周边无高回声晕征、淋巴结转移者($P<0.05$);病灶边缘有毛刺征、周边有高回声晕征患者的PR阳性表达率高于病灶边缘无毛刺征、周边无高回声晕征者($P<0.05$);内部有微小钙化、血流显像分级2-3级、淋巴结转移患者的p120阴性表达率高于内部无微小钙化、血流显像分级0-1级、无淋巴结转移者($P<0.05$);内部有微小钙化、血流显像分级2-3级、淋巴结转移患者的CerbB-2阳性表达率高于内部无微小钙化、血流显像分级0-1级、无淋巴结转移

移者($P<0.05$);内部有微小钙化、淋巴结转移患者的 Her-2/neu 见表 1、表 2。
阳性表达率高于内部无微小钙化、无淋巴结转移者($P<0.05$),

表 1 不同乳腺癌超声征象 ER、PR、p120 的表达情况[n(%)]
Table 1 The expression of ER, PR, p120 in different ultrasonic signs of breast cancer [n (%)]

Ultrasonic signs		n	ER(+)	χ^2	P	PR(+)	χ^2	P	p120(-)	χ^2	P
Lesion diameter	<2 cm	21	10(47.62)	0.082	0.774	6(28.57)	0.867	0.352	13(61.90)	0.069	0.793
	≥ 2 cm	29	15(51.72)			12(41.38)			18(62.07)		
Marginal burrs sign	Yes	34	21(61.76)	5.882	0.015	16(47.06)	5.640	0.018	25(73.53)	0.965	0.326
	No	16	4(25.00)			2(12.50)			6(37.5)		
Microcalcification	Yes	31	18(58.06)	2.122	0.145	9(29.03)	1.719	0.190	29(93.55)	7.371	0.007
	No	19	7(36.84)			9(47.37)			2(10.53)		
Peripheral hyperechoic halo sign	Yes	15	11(73.33)	4.667	0.031	9(60.00)	5.357	0.021	6(40.00)	3.024	0.082
	No	35	14(40.00)			9(25.71)			25(71.43)		
Internal echo	No	9	4(44.44)	0.136	0.713	2(22.22)	0.904	0.342	4(44.44)	0.582	0.445
	Yes	41	21(51.22)			16(39.02)			27(65.85)		
Blood flow imaging grade	0-1 grade	14	5(35.71)	1.587	0.208	4(28.57)	0.466	0.495	5(35.71)	4.131	0.042
	2-3 grade	36	20(55.56)			14(38.89)			26(72.22)		
Lymph node metastases	Yes	23	8(34.78)	3.945	0.047	7(30.43)	0.573	0.449	18(78.26)	4.780	0.029
	No	27	17(62.96)			11(40.74)			13(48.15)		

表 2 不同乳腺癌超声征象 CerbB-2、Her-2/neu 的表达情况[n(%)]
Table 2 The expression of CerbB-2, Her-2/neu in different ultrasonic signs of breast cancer [n (%)]

Ultrasonic signs		n	CerbB-2(+)	χ^2	P	Her-2/neu(+)	χ^2	P
Lesion diameter	<2 cm	21	15(71.43)	0.124	0.724	5(23.81)	0.661	0.416
	≥ 2 cm	29	22(75.86)			10(34.48)		
Marginal burrs sign	Yes	34	23(67.65)	2.229	0.135	8(23.53)	2.118	0.146
	No	16	14(87.50)			7(43.75)		
Microcalcification	Yes	31	26(83.87)	4.131	0.042	13(41.94)	5.534	0.019
	No	19	11(57.89)			2(10.53)		
Peripheral hyperechoic halo sign	Yes	15	11(73.33)	0.005	0.944	3(20.00)	1.020	0.312
	No	35	26(74.29)			12(34.29)		
Internal echo	No	9	6(66.67)	0.307	0.580	2(22.22)	0.316	0.574
	Yes	41	31(75.61)			13(31.71)		
Blood flow imaging grade	0-1 grade	14	7(50.00)	5.821	0.016	2(14.29)	2.286	0.131
	2-3 grade	36	30(83.33)			13(36.11)		
Lymph node metastases	Yes	23	21(91.30)	6.629	0.010	11(47.83)	6.445	0.011
	No	27	16(59.26)			4(14.81)		

3 讨论

乳腺癌是威胁女性健康的全球性疾病,由于乳腺不属于机体维持生命活动的主要器官,因此出现原位乳腺癌时并不致命,但若不及时治疗将导致癌细胞脱落,甚至癌细胞可经血液或淋巴系统向全身转移,危及患者生命安全^[12-14]。且有研究报道指出,乳腺癌的早期诊治是改善患者预后的关键^[15]。影像学检

查是早期诊断乳腺癌的常用手段,其中超声检查具有操作简单、耗时短、可重复性好等优点,应用范围较广,彩色多普勒血流显像也容易受到多种因素影响导致准确率下降,临床效果难以令人满意^[16-18]。随着分子生物学技术的不断发展,基因和细胞因子检测在乳腺癌早期诊断中显示出了良好的应用前景^[19]。专家指出,基因和细胞因子的表达能够造成组织的病理改变,最终通过影像学特征显现出来,通过检查乳腺癌的超声征象能够

在一定程度上显示乳腺癌的生物学行为^[20]。

ER 与 PR 是国内研究较多的两种载体类激素受体, 多项研究报道证实 ER 与 PR 的表达情况与乳腺癌病变程度及预后情况密切相关^[21,22]。病灶边缘有毛刺征及高回声晕征表示肿瘤分化程度较好, 具有较低的侵袭性, 此时肿瘤细胞生长仍受到激素调控, 采取内分泌治疗一般预后较好^[23]。本研究中 ER 阳性表达率为 50.00%, PR 阳性表达率为 36.00%, 且病灶边缘有毛刺征和周边有高回声晕征患者的 ER、PR 阳性表达率更高, 分析原因可能与病灶周围间质纤维结缔组织的反应性增生限制了癌细胞的扩展有关, 但具体保护性机制尚需进一步研究证实。有研究指出, 激素受体阳性的乳腺癌病灶分化较好, 不易发生内脏转移, 对内分泌治疗更为敏感^[24,25]。此外, 存在淋巴结转移者 ER 阳性表达率更低, 证实淋巴结转移情况与 ER 的阳性表达相关, 主要是因为乳腺癌患者内源性雌激素水平更高, 将病灶组织内的受体占据, 导致 ER 阴性率升高, 病灶分化程度降低, 侵袭力增强, 从而更易发生淋巴结转移。

p120 是连环蛋白的一种, 能够通过结合转录抑制因子快速参与 Wnt 信号通路的信号转导过程, 对细胞的正常增殖、生长及分化过程均有一定影响^[26]。近几年, 有研究指出, p120 表达的缺失与乳腺癌的发生紧密相关, 在乳腺病灶的生长、浸润及转移中均有不同程度的表达^[27,28]。本研究中 p120 的阴性表达率为 62.00%, 且内部有微小钙化、血流显像分级 2-3 级、淋巴结转移者 p120 阴性表达率更高, 分析原因主要为血流显像分级 2-3 级使病灶周围血流丰富, 发生淋巴结转移和周围侵袭的风险更高, 病灶中的坏死组织也更容易进一步钙化, 病灶的恶性病变程度也更高。

CerbB-2、Her-2/neu 是两种肿瘤相关基因, 其中 CerbB-2 属于原癌基因, 参与了细胞的生长、分化与存活过程^[29,30]。本研究中 CerbB-2 阳性表达率为 74.00%, Her-2/neu 阳性表达率为 30.00%, 且内部有微小钙化、淋巴结转移患者者的 CerbB-2、Her-2/neu 阳性表达率更高, 血流显像分级 2-3 级的 CerbB-2 阳性表达率更高, 主要是因为血流丰富的病灶肿瘤细胞代谢更为旺盛, 生长、侵袭和转移情况更明显, 病灶也更容易出现微小钙化。CerbB-2 的阳性表达能够促进细胞有丝分裂增强, 导致肿瘤细胞获得机体无法有效控制的独立生长能力, 从而增加了肿瘤细胞的转移风险, 预后一般较差。Her-2/neu 可促进机体蛋白水解酶分泌, 促使恶性细胞运动能力增强, 增强肿瘤细胞的侵袭和转移能力, 肿瘤恶性程度更高, 容易出现微钙化现象。

综上所述, 乳腺癌超声征象与 ER、PR、CerbB-2、Her-2/neu 和 p120 的表达有紧密联系, 可通过超声检查一定程度反映乳腺癌患者的 ER、PR、CerbB-2、Her-2/neu、p120 的表达情况, 从而有助于判断患者的病情。

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