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超声检查联合 MMP-2、MMP-9 水平检测对甲状腺癌的诊断价值

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摘要 目的:探讨超声检查联合基质金属蛋白酶-2(MMP-2)、基质金属蛋白酶-9(MMP-9)水平检测对甲状腺癌的诊断价值。**方法:**选取2014年6月-2016年6月我院收治的480例甲状腺结节患者作为研究对象,根据患者病情分为良性结节患者412例(良性结节组)和甲状腺癌患者68例(甲状腺癌组)。对所有患者进行超声检查与MMP-2、MMP-9水平检测,比较两组MMP-2、MMP-9水平,并比较超声检查与超声联合MMP-2、MMP-9水平检测对甲状腺癌的诊断价值。**结果:**甲状腺癌组MMP-2、MMP-9水平均显著高于良性结节组($P<0.05$),且甲状腺癌组超声弹性图像评分多为3~4分,良性结节组则多为0~2分,两组超声弹性成像评分所占比例比较差异有统计学意义($P<0.05$);超声联合MMP-2、MMP-9诊断良性甲状腺结节的阴性率和甲状腺癌的阳性率均高于超声诊断,差异有统计学意义($P<0.05$);超声联合MMP-2、MMP-9的灵敏性、特异性、准确性分别为89.7%、85.2%、85.8%,均显著高于超声诊断的76.5%、68.7%、69.8%,差异有统计学意义($P<0.05$)。**结论:**超声检查联合MMP-2、MMP-9水平检测能够有效鉴别甲状腺癌,其灵敏性、特异性、准确性均较高,值得在临床上推广。

关键词:超声检查;MMP-2;MMP-9;甲状腺癌

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Diagnostic Value of Ultrasonography Combined with MMP-2 and MMP-9 in Thyroid Carcinoma

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ABSTRACT Objective: To investigate the diagnostic value of ultrasonography combined with matrix metalloproteinase-2(MMP-2) and matrix metalloproteinase-9 (MMP-9) in thyroid carcinoma. **Methods:** 480 patients with thyroid nodules who were treated in our hospital from June 2014 to June 2016 were selected as the subjects. They were divided into 412 cases of patients with benign nodules (benign nodules group) and 68 cases of patients with thyroid cancer (thyroid cancer group) according to the condition of patients. All patients were examined by ultrasonography and MMP-2, MMP-9 level detection, compared the levels of MMP-2, MMP-9 in two groups, and compared the diagnostic value between ultrasound and ultrasound combined with MMP-2, MMP-9 level detection in the thyroid carcinoma. **Results:** The levels of MMP-2 and MMP-9 in thyroid cancer group were significantly higher than those in benign nodules group ($P<0.05$). The ultrasound elastography score of thyroid cancer group was 3~4, and the benign nodules group was 0~2, the difference between the two groups was statistically significant ($P<0.05$); The negative rate of ultrasound combined with MMP-2 and MMP-9 in the diagnosis of benign thyroid nodules and the positive rate of thyroid cancer were higher than those of ultrasound, the differences were statistically significant ($P<0.05$); The sensitivity, specificity and accuracy of ultrasound combined with MMP-2 and MMP-9 were 89.7%, 85.2%, and 85.8% respectively, which were significantly higher than those of ultrasonic diagnosis of 76.5%, 68.7%, 69.8%, the differences were statistically significant ($P<0.05$). **Conclusion:** Ultrasonography combine with MMP-2 and MMP-9 level detection can effectively identify thyroid cancer, the sensitivity, specificity and accuracy are higher, which is worthy of clinical promotion.

Key words: Ultrasonography; Metalloproteinase-2; Matrix metalloproteinase -9; Thyroid carcinoma

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前言

甲状腺癌是临床上较为常见的一种恶性肿瘤,占全身恶性肿瘤的1%。除髓样癌外,绝大部分甲状腺癌起源于滤泡上皮细胞^[1,2]。甲状腺癌的发病率与地区、种族、性别有一定联系,欧美国家的甲状腺癌发病率较高,据统计,从1973年至2002年,美

国甲状腺癌的年发生率由3.6/10万上升到8.7/10万,大约增加了2.4倍,且这种趋势仍然在逐年增长。国内的甲状腺癌发病率较低,据统计,其中男性发病率约0.8-0.9/10万,女性发病率约2.0-2.2/10万。随着近些年人们的饮食行为和生活环境发生了重大改变,甲状腺癌的发病率不断升高,严重威胁我国居民的生命健康^[3]。由于甲状腺癌起病极为隐匿,且生物学特性多变,在早期并无特异性症状,而单纯依靠影像学诊断手段较难确诊,此外,某些比较小的癌病灶不容易被发现,这些病灶在初期有清晰的边界,而钙化等一些恶性特征则尚未出现,因此临

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床采用超声等影像学检查误诊率、漏诊率极高^[46]。基质金属蛋白酶(MMPs)是一类具有降解细胞外基质作用的蛋白酶,基质金属蛋白酶-2(matrix metalloproteinase-2, MMP-2)和基质金属蛋白酶-9(matrix metalloproteinase-9, MMP-9)是 MMPs 常见的类型,二者可以特异性降解细胞外基质与基底膜的主要成分,从而促使肿瘤转移与侵袭^[7-9]。为了寻求提高甲状腺癌诊断率的检测手段,本研究分析了超声检查联合 MMP-2、MMP-9 水平检测对甲状腺癌的诊断价值,且取得了较好成效,现报告如下。

1 资料与方法

1.1 一般资料

选取 2014 年 6 月-2016 年 6 月我院收治的 480 例甲状腺结节患者作为本次研究的对象,纳入标准:① 所有患者均未合并肝、肾等脏器严重疾病;② 均接受病理组织活检确诊;③ 患者及家属均对本次研究知情,并签署知情通知书。排除标准:① 合并有其他系统肿瘤者;② 存在精神疾病者;③ 拒绝参与研究或依从性较差者。其中良性甲状腺结节者 412 例纳入良性结节组,男 186 例,女 226 例,年龄 29~75 岁,平均年龄(51.6±5.4)岁,包括甲状腺腺瘤 231 例,结节性甲状腺肿 161 例,其他 20 例。甲状腺癌 68 例纳入甲状腺癌组,男 29 例,女 39 例,年龄 30~75 岁,平均年龄(51.2±5.3)岁,包括乳头状甲状腺癌 48 例,滤泡性甲状腺癌 11 例,其他 9 例。两组患者的一般资料相比,差异无统计学意义($P>0.05$),可行组间对比。

1.2 超声检查方法

所有患者均接受超声检查,仪器采用 philips iu22 彩色多普勒超声诊断仪,选择线阵相控探头,将探头的频率设置为 6.3-11.8MHz。检查开始前,指导患者呈仰卧位,并将头充分往后仰,从而充分将颈部显露出来,使用二维超声模式检查甲状腺结节,掌握其大小、形态、包膜等情况,之后使用超声弹性成像对甲状腺进行横、纵切面的探查,探查范围是病灶的 2 倍左右。检查过程中,应手持探头于病灶处轻微振动,探头应和患者皮肤保持紧贴,受力方向与皮肤垂直,保存稳定且可重复性好的图像。

1.3 MMPs 水平检测方法

所有患者均接受 MMPs 水平的检测。在禁食 12 h 后,取患者清晨空腹情况下的外周静脉血 10 mL,并在常温下放置 30 min 后,以 3000 r/min 转速离心 15 min,并取上层血清贮存在 -80℃ 冰箱中。MMP-2、MMP-9 均采用双夹心酶联免疫法(ELISA)测定,MMP-2、MMP-9 ELISA 试剂盒均购自上海和序生物科技有限公司,检测操作均严格按照相应的试剂盒说明书进行。

1.4 观察指标

① 超声弹性成像评分:观察超声检查得到的图像。若结节呈现为红、绿、蓝三色相间,则得分为 0 分;若所有组织均为绿色,则得分为 1 分;若结节大部分为绿色,且均匀分布,则得分为 2 分;若结节为绿色、蓝色相间,较为杂乱,则得分为 3 分;若结节绝大部分均呈现为蓝色,则得分为 4 分。② 记录单纯超声检查与超声监测联合 MMP-2、MMP-9 水平诊断甲状腺良恶性结节阳性率与阴性率。超声诊断甲状腺癌阳性标准:(1)有沙砾样钙化;(2)结节回声低;(3)结节内部血流丰富、紊乱;(4)结节边界不规则并向周边浸润;(5)横截面前后径大于左右径。③ 记录两种诊断方式诊断甲状腺癌的准确性、灵敏性与特异性。准确性=(真阳性例数+真阴性例数)÷总例数×100%。灵敏度=真阳性例数÷(真阳性例数+假阴性例数)×100%。特异性=真阴性例数÷(真阴性例数+假阳性例数)×100%。

1.5 统计学方法

通过 SPSS18.0 统计学软件进行分析,MMP-2、MMP-9 水平等计量资料用($\bar{x} \pm s$)表示,采用 t 检验,准确性、灵敏度等计数资料用百分率(%)表示,采用 χ^2 检验,以 $\alpha=0.05$ 为检验标准。

2 结果

2.1 两组血清 MMP-2、MMP-9 水平与超声弹性成像评分比较

甲状腺癌组 MMP-2、MMP-9 水平均显著高于良性结节组($P<0.05$),且甲状腺癌组超声弹性图像评分多为 3~4 分,良性结节组则多为 0~2 分,两组超声弹性成像评分所占比例比较,差异有统计学意义($P<0.05$)。见表 1。

表 1 甲状腺良性结节患者与甲状腺癌超声弹性成像评分比较

Table 1 Comparison of ultrasound elastography score in patients with benign thyroid nodules and thyroid carcinoma

Groups	Cases	MMP-2(ng/mL)	MMP-9(ng/mL)	Ultrasound elastography score[n(%)]	
				0~2 score	3~4 score
Benign nodules group	412	512.65±60.57	140.98±44.96	386(93.7)	26(6.3)
Thyroid cancer group	68	865.41±96.24	269.18±46.28	18(26.5)	50(73.5)
t/X ² value	-	38.641	12.398	169.451	
P value	-	0.000	0.000	0.000	

2.2 两种方法诊断甲状腺良恶性结节上的阳性率、阴性率比较

超声联合 MMP-2、MMP-9 诊断良性甲状腺结节的阴性率和甲状腺癌的阳性率分别为 85.2%、89.7%,均高于超声诊断的 68.74%、76.5%,差异具有统计学意义($P<0.05$)。见表 2。

2.3 两种方法对甲状腺癌的诊断价值比较

超声联合 MMP-2、MMP-9 的灵敏度 89.7%、特异性

85.2%、准确性 85.8%,均显著高于超声诊断的 76.5%、68.7%、69.8%,差异具有统计学意义($P<0.05$)。见表 3。

3 讨论

超声检查是当前应用于甲状腺癌检查与诊断的主要方法,但由于甲状腺癌早期无特异性症状,超声检查仍可能造成误

表 2 两种方法诊断甲状腺良性恶性结节上的阳性率、阴性率比较[n(%)]

Table 2 Comparison of the positive and negative rates in the diagnosis of benign and malignant thyroid nodules between the two methods[n(%)]

Methods	Benign nodule(n=412)		Thyroid cancer(n=68)	
	+	-	+	-
Ultrasound	129(31.3)	283(68.7)	52(76.5)	16(23.5)
Ultrasound+MMP-2 and MMP-9	61(14.8)	351(85.2)	61(89.7)	7(10.3)
X ² value	6.584		18.615	
P value	0.029		0.000	

表 3 两种方法诊断甲状腺癌的效能比较[n(%)]

Table 3 Comparison the efficiency in the diagnosis of thyroid carcinoma between the two methods[n(%)]

Methods	Cases	Sensitivity	Specificity	Accuracy
Ultrasound	480	76.5(52/68)	68.7(283/412)	69.8(335/480)
Ultrasound+MMP-2 and MMP-9	480	89.7(61/68)	85.2(351/412)	85.8(412/480)
x ² value	-	6.584	18.615	20.871
P value	-	0.029	0.000	0.000

诊、漏诊。浸润性转移与生长是甲状腺癌的重要特征,而肿瘤细胞的侵袭与转移必须穿透细胞外基质与血管壁基底膜才可实现^[10,11]。MMPs 是一类锌离子依赖性内肽酶,能够充分降解细胞外基质中的蛋白,同时可以破坏肿瘤细胞的组织屏障,进而促进肿瘤更快地在机体中发生侵袭与转移^[12,13]。目前,MMPs 家族已发现 MMP1~26 这 26 种类型,根据作用底物的不同和片断的同源性差异又可将 MMPs 分为胶原酶、基质降解素、furin 活化的 MMP、基质溶解素、明胶酶和其他分泌型 MMP^[14,15]。明胶酶作为 MMPs 的主要组成,包括 MMP-2 和 MMP-9,二者能够分解Ⅳ型胶原蛋白以降解基底膜,并促进甲状腺癌发展^[16,18]。

在本次研究中,我们发现甲状腺癌组 MMP-2、MMP-9 水平均显著高于良性结节组,且甲状腺癌组超声弹性图像评分多为 3~4 分,良性结节组则多为 0~2 分,两组所占比例差异有统计学意义(P<0.05)。分析超声检查图像可知,甲状腺癌组织硬度明显高于良性病变,再结合检查过程中收集的有无包膜、高低回声、是否钙化和是否囊性变能够大致对甲状腺癌进行诊断。此外,结果还提示 MMP-2、MMP-9 的水平检测也能够对良性甲状腺结节和甲状腺癌进行初步诊断。新生血管的形成是导致肿瘤组织进展的重要因素,MMP-2、MMP-9 均具有调节微循环与血管生成的作用,在受到甲状腺癌的影响后肿瘤组织中的血管内皮因子会大量增加,并诱导尿激酶型和组织纤溶酶型激活物的产生,最终使 MMP-2、MMP-9 的释放量增加、MMPs 组织抑制剂的释放被抑制,促进新生血管的形成^[19-21]。有研究^[22]还发现,MMPs 在降解细胞外基质时会释放出某些生物活性片段,这些片段对肿瘤细胞的增殖与迁移也存在促进作用。此外,我们还发现在鉴别甲状腺良性恶性结节上,超声联合 MMP-2、MMP-9 诊断良性甲状腺结节的阴性率和甲状腺癌的阳性率均高于超声诊断。同时,超声联合 MMP-2、MMP-9 的灵敏性 89.7%、特异性 85.2%、准确性 85.8%均显著高于超声诊断的 76.5%、68.7%、69.8%,差异具有统计学意义(P<0.05)。上述结果均表明,超声联合 MMP-2、MMP-9 检测对甲状腺癌的鉴别诊

断效果更好,且相对单纯超声检查具有更高的效能。MPPs 对甲状腺癌进展的推动主要通过促血管生成和降解细胞外基质实现,一方面在肿瘤组织中 MMP-2、MMP-9 能够以酶原形式释放并对肿瘤组织表明的细胞外基质与基底膜进行破坏,从而导致肿瘤细胞向外侵袭;另一方面 MMP-2、MMP-9 能够促进血管内皮细胞的释放,并为新生血管的生长提供足够的空间,加速肿瘤的侵袭^[23-25]。在对甲状腺癌进行诊断时,应该对患者进行超声检查,据此充分掌握甲状腺的形态、边界、包膜、内部回声、后方回声等情况乃至病灶状态;同时,再通过测定患者血清 MMP-2、MMP-9 的水平,了解患者患者血清 MMP-2、MMP-9 的水平,二者相结合对甲状腺癌情况进行深入的诊断,其临床诊断价值更高^[26-28]。有研究认为,术前对患者进行 MMPs 检测操作较为简单,且检测结果可立即获得,具有较好的临床应用的价值^[29-30]。

综上所述,超声检查联合 MMP-2、MMP-9 水平检测能够有效鉴别诊断甲状腺癌,且具有较高的诊断价值,值得在临床上推广。

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