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术前血清 TSH 水平联合多普勒超声对分化型甲状腺癌的诊断价值*

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摘要 目的:研究术前血清促甲状腺激素(TSH)水平联合多普勒超声对分化型甲状腺癌(DTC)的诊断价值。**方法:**选择从2015年1月到2017年6月在北京市第一中西医结合医院诊治的甲状腺结节患者528例作为研究对象。经病理学诊断显示DTC患者268例,记为观察组;良性甲状腺结节患者260例,记为对照组,检测并对比两组超声指标,两组TSH水平分布情况,分析观察组患者血清TSH水平与其颈淋巴结转移及肿瘤直径的关系,以及术前血清TSH联合多普勒超声对DTC的诊断价值。**结果:**观察组病灶数目为单个、病灶大小为小结节以及有沙粒样钙化者占比均分别明显高于对照组,差异均有统计学意义(均 $P<0.05$)。观察组TSH水平为 $2.20\sim 4.20\ \mu\text{IU/mL}$ 及 $>4.20\ \mu\text{IU/mL}$ 者占比均分别明显高于对照组,且 $<0.27\ \mu\text{IU/mL}$ 、 $0.27\sim 1.44\ \mu\text{IU/mL}$ 及 $1.45\sim 2.19\ \mu\text{IU/mL}$ 者占比均分别明显低于对照组,差异均有统计学意义(均 $P<0.05$)。观察组患者中,有颈淋巴结转移者的TSH水平明显高于无转移者,肿瘤直径为 $2\sim 4\text{ cm}$ 和 $>4\text{ cm}$ 者的TSH水平均分别明显高于 $<2\text{ cm}$ 者,且肿瘤直径 $>4\text{ cm}$ 者也明显高于 $2\sim 4\text{ cm}$ 者,差异均有统计学意义(均 $P<0.05$)。术前血清TSH联合多普勒超声对DTC的诊断结果中,灵敏度为73.88%(198/268),特异度为82.31%(214/260),准确率为78.03%(412/528),均分别高于单纯超声诊断的57.46%(154/268),75.77%(197/260),66.48%(351/528),差异有统计学意义($P<0.05$)。联合诊断的ROC曲线下面积是0.847,其中TSH诊断临界值是3.153 mIU/L。**结论:**应用术前血清TSH水平与多普勒超声的联合诊断方式能够有效诊断DTC患者,临床上可考虑将此种联合诊断方式进行推广,从而为DTC患者的诊治及病情评价发挥指导作用,值得给予重视。

关键词:术前;血清TSH水平;多普勒超声;分化型甲状腺癌;诊断价值

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Diagnostic Value of Preoperative Serum TSH Level Combined with Doppler Ultrasonography for Differentiated Thyroid Carcinoma*

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ABSTRACT Objective: To investigate the diagnostic value of preoperative serum thyroid stimulating hormone (TSH) level combined with Doppler ultrasonography for differentiated thyroid carcinoma (DTC). **Methods:** 528 patients with thyroid nodules who were treated in Beijing First Hospital of Integrated Chinese and Western Medicine from January 2015 to June 2017 were selected as the subjects, 268 patients with DTC who were diagnosed by pathologically were recorded as the observation group, another 260 patients with benign thyroid nodules were recorded as the control group. The ultrasonic indexes, level of TSH in the two groups were detected and compared. The relationship between serum TSH level, lymph node metastasis and tumor diameter in the observation group was analyzed, and the diagnostic value of preoperative serum TSH combined with Doppler ultrasound in DTC was observed. **Results:** The number of lesions was single, the size of the lesion was small nodules, and the rate of sand like calcification in the observation group were significantly higher than those of the control group, the differences were statistically significant ($P<0.05$). The proportion of patients with TSH level ranged from 2.20 to $4.20\ \mu\text{IU/mL}$ and $>4.20\ \mu\text{IU/mL}$ in the observation group were significantly higher than those in the control group, and the proportion of patients with TSH level ranged from $<0.27\ \mu\text{IU/mL}$, 0.27 to $1.44\ \mu\text{IU/mL}$ and 1.45 to $2.19\ \mu\text{IU/mL}$ were significantly lower than those of the control group, the differences were statistically significant ($P<0.05$). The TSH level of the patients with cervical lymph node metastasis in the observation group were significantly higher than those in the non metastasis group,

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the TSH level of patients with tumor diameter ranged from 2 to 4 cm and > 4 cm were significantly higher than those patients with < 2 cm, and the diameter of tumor >4 cm of patients was significantly higher than those patients with 2 to 4 cm, the differences were statistically significant ($P<0.05$). The sensitivity of preoperative TSH combined with Doppler ultrasonography for DTC diagnosis was 73.88% (198/268), specificity was 82.31% (214/260), and accuracy was 78.03% (412/528), which were significantly higher than those of pure ultrasound diagnosis of 57.46% (154/268), 75.77% (197/260), 66.48% (351/528), the differences were statistically significant ($P<0.05$). The area under the ROC curve of combined diagnosis was 0.847, in which the critical diagnostic value of TSH was 3.153 mIU/L. **Conclusion:** The DTC patients can be diagnosed by preoperative serum TSH level combined with Doppler ultrasonography effectively, this combined diagnosis can be popularized in clinical practice, so as to play a guiding role in the diagnosis, treatment and disease evaluation of patients with DTC, which is worth to be pay attention.

Key words: Preoperative; Serum TSH level; Doppler ultrasonography; Differentiated thyroid carcinoma; Diagnostic value

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前言

甲状腺癌为临床十分常见的恶性肿瘤类型,按照组织学标准进行分类可分成分化型甲状腺癌(differentiated thyroid carcinoma, DTC)与未分化型甲状腺癌。据统计发现,甲状腺癌通常为 DTC,其所占比例甚至高达 90%^[1,2]。甲状腺癌的发病机制非常复杂,性别、年龄以及环境等多类因素均可能导致甲状腺发生恶性病变,最终发展成 DTC,对患者的健康和生命安全造成严重威胁^[3,4]。随着医疗水平的不断提高,多普勒超声在 DTC 的临床诊断工作上得到了广泛的应用,其具有较高的诊断准确率,能够对甲状腺结节作出准确判断,并且不会在检查过程中对患者造成伤害^[5,6]。事实上,超声发现甲状腺结节并确认结节的良恶性是制定针对性治疗方案的关键。但由于单纯的超声诊断仅能通过影像学方式进行观察判断,缺乏实验室指标对机体内环境的反映,因此也较易产生误诊和漏诊的情况,因此在超声诊断的基础上增加其他指标的检测显得十分必要^[7-9]。有报道指出,若甲状腺结节患者血清促甲状腺激素(thyroid stimulating hormone, TSH)水平呈异常高表达,则提示发生甲状腺癌的风险较大^[10,11]。因此,将血清 TSH 水平检测与多普勒超声二者相联合应用于 DTC 临床诊断,可能有助于后续手术方案的制定。鉴于此,本研究对术前血清 TSH 水平联合多普勒超声对 DTC 的诊断价值进行探讨,旨在为临床诊治提供参考依据,现报道如下。

1 资料和方法

1.1 一般资料

选择 2015 年 1 月到 2017 年 6 月在北京市第一中西医结合医院诊治的甲状腺结节患者 528 例作为研究对象。入选标准为:(1)患者均首次入院接受手术治疗;(2)术后接受病理学检查者;(3)病历资料数据齐全者;(4)对此次研究知情同意,且签署了同意书。排除标准:(1)存在甲状腺疾病史;(2)半年内接受过冠脉造影等含碘药物检查或治疗者;(3)存在甲状腺癌家族史者。TSH 水平分布:528 例患者中,TSH 水平<0.27 μ IU/mL 者 43 例,0.27~1.44 μ IU/mL 者 134 例,1.45~2.19 μ IU/mL 者 110 例,2.20~4.20 μ IU/mL 者 159 例,>4.20 μ IU/mL 者 82 例。观察组:经病理学诊断显示 DTC 患者 268 例,记为观察组,男 106 例,女 162 例。年龄 43~69 岁,平均(53.61 $\pm$ 2.34)

岁。有颈淋巴结转移者 62 例,无转移者 206 例。肿瘤直径<2 cm 者 89 例,2~4 cm 者 104 例,>4 cm 者 75 例。对照组:良性甲状腺结节者 260 例,记为对照组,男 121 例,女 139 例。年龄 45~68 岁,平均(53.63 $\pm$ 2.19)岁。结节型甲状腺肿 194 例,甲状腺腺瘤 66 例。两组的性别与年龄数据相比,差异均无统计学意义(均 $P>0.05$)。关于本次研究,医院的伦理委员会已审批通过。

1.2 研究方法

对两组患者均在术前采集其晨间的空腹静脉血 4 mL,给予 10 min 1000 r/min 的离心后提取其上清液,应用购自美国 BECKMAN COULTER 公司的 DX1800 型化学发光仪、配套试剂及化学发光法对血清 TSH 水平进行检测,相关步骤严格按照说明书的要求进行。再对两组患者实施超声检查,仪器为 GE 公司生产的 Vivid E7 彩色多普勒超声诊断仪,探头频率设置 12MHz,取患者的仰卧位,将其颈部充分给予暴露,再对其双侧甲状腺实施多层面扫描,主要观察以下影像项目:(1)甲状腺结节的病灶数目;(2)病灶形态;(3)病灶边缘;(4)病灶大小;(5)沙粒样钙化。

1.3 观察指标

对比两组超声指标,两组 TSH 水平分布情况,分析观察组患者血清 TSH 水平与其颈淋巴结转移及肿瘤直径的关系,以及术前血清 TSH 联合多普勒超声对 DTC 的诊断价值。

1.4 统计学方法

运用 SPSS21.0 统计软件实施分析。其中计数资料用(n,%)表示,比较采用 χ^2 检验。计量资料用($\bar{x}\pm s$)表示,比较采用 t 检验。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组超声指标的对比

观察组病灶数目为单个、病灶大小为小结节以及有沙粒样钙化者占比均分别明显高于对照组,差异均有统计学意义(均 $P<0.05$)。两组病灶形态和病灶边缘的超声诊断结果相比,差异无统计学意义($P>0.05$),见表 1。

2.2 两组 TSH 水平分布情况的对比

观察组 TSH 水平为 2.20~4.20 μ IU/mL 及>4.20 μ IU/mL 者占比均分别明显高于对照组,且<0.27 μ IU/mL、0.27~1.44 μ IU/mL 及 1.45~2.19 μ IU/mL 者占比均分别明显低于对照组。整体来看,经等级资料秩和检验,两组的差异均有统计学意义

($P<0.05$), 经计数资料 Cochran Armitage 趋势检验, 随 TSH 水平显著性意义($P<0.05$), 见表 2。
平的逐渐上升, 观察组分布比例(占比)逐渐上升, 上升趋势有

表 1 两组超声指标的对比[n(%)]
Table 1 Comparison of ultrasonic indexes between two groups[n(%)]

Items		Observation group(n=268)	Control group(n=260)	χ^2	P
Lesions number	Single	177(66.04)	104(40.00)	35.957	0.000
	Multiple	91(33.96)	156(60.00)		
Lesion morphology	Rule	213(79.48)	223(85.77)	3.631	0.057
	Irregular	55(20.52)	37(14.23)		
Lesion margin	Clear	165(61.57)	144(55.38)	2.078	0.149
	Unclear	103(38.43)	116(44.62)		
Lesion size	Big nodules	123(45.90)	162(62.31)	14.309	0.000
	Small nodules	145(54.10)	98(37.69)		
Sand like calcificationin	Yes	166(61.94)	105(40.38)	24.545	0.000
	No	102(38.06)	155(59.62)		

表 2 两组 TSH 水平分布情况的对比[n(%)]
Table 2 Comparison of TSH level distribution between the two groups[n(%)]

TSH(μ IU/mL)	n	Observation group	Control group
<0.27	43	12(27.91)	31(72.09)
0.27~1.44	134	46(34.33)	88(65.67)
1.45~2.19	110	45(40.91)	65(59.09)
2.20~4.20	159	101(63.52)	58(36.48)
>4.20	82	64(78.05)	18(21.95)
Difference test	Hc,P	62.404, 0.000	
Trend test	χ^2 , P	131.140, 0.000	

2.3 观察组患者血清 TSH 水平与其颈淋巴结转移及肿瘤直径的关系分析

观察组患者中, 有颈淋巴结转移者的 TSH 水平明显高于

无转移者, 肿瘤直径为 2~4 cm 和 >4 cm 者的 TSH 水平均分别明显高于 <2 cm 者, 且肿瘤直径 >4 cm 者也明显高于 2~4 cm 者, 差异均有统计学意义(均 $P<0.05$), 见表 3。

表 3 观察组患者血清 TSH 水平与其颈淋巴结转移及肿瘤直径的关系分析

Table 3 Relationship analysis between serum TSH level and cervical lymph node metastasis, tumor diameter of the observation group

Items		n	TSH(μ IU/mL)	t(F)	P
Cervical lymph node metastasis	No	206	2.72 $\pm$ 1.03	10.989	0.000
	Yes	62	4.97 $\pm$ 1.51		
	<2	89	1.73 $\pm$ 1.02		
Tumor diameter(cm)	2~4	104	2.26 $\pm$ 1.37 ^a	30.018	0.000
	>4	75	3.17 $\pm$ 1.50 ^{ab}		

Note: Compared with tumor diameter <2 cm, ^a $P<0.05$; Compared with tumor diameter 2~4 cm, ^b $P<0.05$.

2.4 术前血清 TSH 联合多普勒超声对 DTC 的诊断价值分析

术前血清 TSH 联合多普勒超声对 DTC 的诊断结果中, 灵敏度为 73.88%(198/268), 特异度为 82.31%(214/260), 准确度为 78.03%(412/528), 均分别高于单纯超声诊断的 57.46%(154/268), 75.77%(197/260), 66.48%(351/528), 差异有统计学意义($P<0.05$)。见表 4。联合诊断的 ROC 曲线下面积是 0.847, 其中 TSH 诊断临界值是 3.153mIU/L。而单纯超声诊断的 ROC 曲线下面积为 0.792。两种方法诊断价值的 ROC 曲线见图 1。

3 讨论

甲状腺结节是临床多发病, 可分为良性结节以及恶性结节, 其中恶性结节以 DTC 最为常见, 其主要包含乳头状癌以及滤泡状癌等类型。据调查结果显示, 甲状腺癌在甲状腺结节患者群体中所占的比例高达 10%, 并且近年来其发病率不断上升, 且甲状腺癌类型以 DTC 为主^[12,13]。同时研究还证实, 及早对发现的甲状腺结节进行良恶性诊断, 并对确诊的 DTC 患者制

表 4 术前血清 TSH 联合多普勒超声对 DTC 的诊断价值分析

Table 4 Diagnostic value of preoperative serum TSH combined with Doppler ultrasound in DTC

Items		Pathological results		Total
		Positive	Negative	
Combined diagnosis	Positive	198	46	244
	Negative	70	214	284
	Total	268	260	528
Simple ultrasound diagnosis	Positive	154	63	217
	Negative	114	197	311
	Total	268	260	528

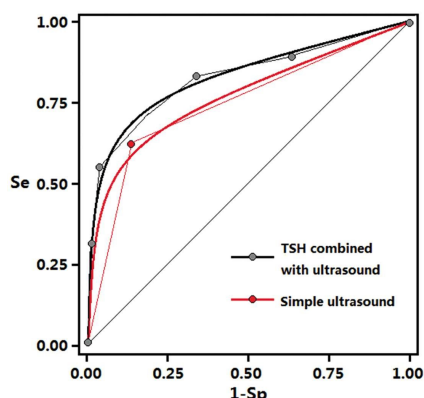


图 1 两种方法的诊断价值的 ROC 曲线

Fig. 1 Diagnostic value ROC curve of the two methods

Note: The curve is theoretical ROC curve of Smoothing simulation in the graph.

定合适的治疗方案,可有效提高患者的生存率^[14]。因此,对甲状腺结节进行临床良恶性诊断是提高 DTC 患者治疗以及预后效果的关键。随着医疗水平的提高及影像学技术的不断发展,超声技术以及细针穿刺等检查手段在甲状腺相关疾病诊断中得到推广使用,特别是无创性的多普勒超声的广泛应用,使甲状腺结节的临床检出率显著提高^[15,16]。目前,超声检查虽然是甲状腺结节患者诊断及术前评估等工作的首选检查方式,但因影像学结果的判断较为主观,在结节良恶性的判断上仍存在一定的缺陷。有学者指出,TSH 作为人体腺垂体所分泌的一种促甲状腺生长类因子,其水平的高低与 DTC 的发生及发展直接相关,可用于辅助诊断 DTC^[17-19]。

本研究中有个体会:应用血清 TSH 与多普勒超声的联合诊断方式在病灶数目、大小以及沙粒样钙化方面的检出率要高一些,与张润晓等人^[20]的报道结果基本类似。原因可能与多普勒超声的工作机制有关,其所应用的彩超成像诊断技术更有利于分辨甲状腺结节的具体情况。而小结节和有钙化往往预示着恶性结节,有研究表明,沙粒样微钙化的产生与癌细胞的快速分裂联系紧密,癌细胞的快速增长致使组织增生、变性,并形成钙盐沉积,并在超声诊断过程中更易较为清晰地显示^[21-23]。再者,本研究中观察组 TSH 水平为 2.20~4.20 $\mu\text{IU/mL}$ 及 $>4.20 \mu\text{IU/mL}$ 者占比均分别明显高于对照组,这提示了 DTC 患者的 TSH 水平明显更高,原因可能与血清 TSH 在 DTC 发病过程中的作用机制有关^[24]。高水平的 TSH 可刺激机体甲状腺有关滤泡上皮不断增生,进而引起甲状腺结节。Ha J 等人^[25]报道指出,

TSH 属于 DTC 的一种风险预测性因子,随着 TSH 水平的不断升高,患 DTC 的风险也进一步加剧。

本研究还发现,DTC 患者中,有颈淋巴结转移及肿瘤直径为 2~4 cm 和 $>4 \text{ cm}$ 者的 TSH 水平明显高于无转移和 $<2 \text{ cm}$ 者,且肿瘤直径 $>4 \text{ cm}$ 者也明显高于 2~4 cm 者(均 $P<0.05$)。这提示了 TSH 水平还可能与 DTC 患者的预后及肿瘤直径的大小有关,这也再次说明了 TSH 与 DTC 的关系密切,同时也表明了 TSH 对 DTC 的诊断具有一定的应用价值。原因主要在于 TSH 可能参与到了 DTC 的发病与进展过程中^[26,27]。此外,术前血清 TSH 联合多普勒超声对 DTC 的诊断结果中,灵敏度、特异度、准确度均分别明显高于单纯超声诊断,且联合诊断的 ROC 曲线下面积是 0.847,其中 TSH 诊断临界值是 3.153 mIU/L。这些数据提示了术前血清 TSH 与多普勒超声的联合诊断方式能够获得更加精准的诊断结果,在诊断 DTC 时的灵敏度和特异度以及准确度均达到 73% 以上^[28]。原因考虑与联合诊断弥补了单一诊断方式的主观性较强、对不同质量的影像图片判断欠准确等不足,从不同诊断机制上更加立体化地呈现出患者的实际病情有关^[29,30]。

综上所述,应用术前血清 TSH 水平与多普勒超声的联合诊断方式能够有效诊断 DTC 患者,临床上可考虑将此种联合诊断方式进行推广,从而为 DTC 患者的诊治及病情评价发挥指导作用,值得给予重视。

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