



· 论 著 ·

# 青年女性乳腺癌的影像学特征与免疫组织化学分子亚型相关性分析

黄峻琳<sup>1</sup>, 林青<sup>1</sup>, 崔春晓<sup>1</sup>, 苏晓慧<sup>1</sup>, 王成勤<sup>2</sup>, 王海波<sup>3</sup>, 李丽丽<sup>1</sup>, 马锦竹<sup>1</sup>, 张敏<sup>1</sup>

1. 青岛大学附属医院乳腺影像科, 山东 青岛 266100;
2. 青岛大学附属医院病理科, 山东 青岛 266100;
3. 青岛大学附属医院乳腺外科, 山东 青岛 266100

**[摘要]** 背景与目的: 乳腺癌在30岁以下的青年女性中很罕见, 但近几年乳腺癌趋向年轻化并且发病率逐年增高, 而早期乳腺癌免疫组织化学分子亚型的识别可以完善治疗方案。该研究旨在探讨青年女性(≤30岁)乳腺癌的超声、数字乳腺X线摄影(digital mammography, DM)及数字乳腺断层合成摄影(digital breast tomosynthesis, DBT)特征与免疫组织化学分子亚型的相关性。方法: 回顾并分析2013年12月—2019年7月于青岛大学附属医院进行过乳腺超声、DM和DBT检查, 且经手术后病理学检查证实为乳腺癌, 年龄≤30岁的139例青年女性患者。影像学特征参照第5版乳腺影像报告及数据系统(Breast Imaging Reporting and Data System, BI-RADS)进行评估及分类。对肿块样病变, 3种检查方法均评估了病变的形状、边缘, DM和DBT对肿块密度另加以评估, 超声对病变内部回声、后方回声、血流信号另加以评估; 对异常钙化评估其形态及分布; 依据BI-RADS评估了乳腺纤维腺体构成; 分子亚型根据2015年修订的St. Gallen国际专家共识建议确定。结果: 病变多表现为可触及肿块(89.9%)、临床T<sub>2</sub>期(50.4%)、组织学Ⅱ级(58.3%)、腋窝淋巴结转移(59.7%)、luminal B型乳腺癌(44.6%), BI-RADS多为4类或5类。在所有成像中, 肿块病变均多表现为不规则形( $P<0.001$ ), luminal A型乳腺癌及三阴性乳腺癌(triple-negative breast cancer, TNBC)多为肿块样病变, luminal B型乳腺癌中肿块伴钙化病变多见, HER2过表达型多见单纯钙化样病变( $P<0.001$ )。在DM和DBT上, 诊断为阴性情况更常见于luminal A型乳腺癌( $P<0.001$ )。对于肿块样病变, DM中最常见表现为边缘模糊(71.9%), 而DBT多见毛刺影(51.8%), 毛刺边缘多与luminal A和luminal B型乳腺癌相关( $P<0.01$ )。良性影像学特征多与TNBC相关, 表现为卵圆形或圆形( $P<0.001$ ), 边缘清楚( $P<0.01$ )。HER2过表达型和TNBC型两组中肿块病变的范围均大于luminal A和luminal B型乳腺癌( $P=0.003$ )。结论: 30岁以下青年女性乳腺癌的部分影像学特征可用于预测某些肿瘤免疫组织化学分子亚型。DBT的乳腺癌检出率高于DM, 对乳腺致密的青年女性具有广泛的应用价值。

**[关键词]** 乳腺癌; 乳腺X线摄影; 数字乳腺断层摄影; 超声; 分子亚型; 病理学

DOI: 10.19401/j.cnki.1007-3639.2020.10.013

中图分类号: R737.9 文献标志码: A 文章编号: 1007-3639(2020)10-0812-09

**Correlation between imaging features and molecular subtypes in very young women with breast cancer** HUANG Junlin<sup>1</sup>, LIN Qing<sup>1</sup>, CUI Chunxiao<sup>1</sup>, SU Xiaohui<sup>1</sup>, WANG Chengqin<sup>2</sup>, WANG Haibo<sup>3</sup>, LI Lili<sup>1</sup>, MA Jinzhu<sup>1</sup>, ZHANG Min<sup>1</sup> (1. Department of Breast Imaging, Affiliated Hospital of Qingdao University, Qingdao 266100, Shandong Province, China; 2. Department of Pathology, Affiliated Hospital of Qingdao University, Qingdao 266100, Shandong Province, China; 3. Department of Breast Surgery, Affiliated Hospital of Qingdao University, Qingdao 266100, Shandong Province, China)

Correspondence to: LIN Qing E-mail: linqing9180@126.com

**[Abstract]** **Background and purpose:** Breast cancer is rare in young women under 30 years old, but in recent years breast cancer patients have become younger and its incidence has increased year by year. The identification of early breast cancer

基金项目: 国家重点研发计划课题(2016YFC1303004)。

通信作者: 林青 E-mail: linqing9180@126.com

immunohistochemical molecular subtypes can improve the treatment plan. The primary purpose of the present study was to analyze the ultrasonography (US), digital mammography (DM) and digital breast tomosynthesis (DBT) features of breast cancer in very young women ( $\leq 30$  years old) and the correlation with molecular subtypes. **Methods:** We performed a retrospective review of imaging and pathological features of consecutive young women under 30 years old who were treated in the Affiliated Hospital of Qingdao University and were diagnosed and histopathologically confirmed with breast cancer from Dec. 2013 to Jul. 2019. Three imaging techniques were used to assess the features of the lesions. DM, DBT and US were available for 139 patients. The imaging findings were evaluated according to the Breast Imaging Reporting and Data System (BI-RADS) lexicon. For mass lesions, the three examination methods all evaluated the shape and margin. DM and DBT were used to evaluate the density of the mass, and US was used to evaluate the echogenicity, posterior feature and vascularity. The morphology and distribution were evaluated for isolated microcalcifications. The composition of mammary fibrous glands was evaluated according to BI-RADS lexicon. The molecular subtypes were defined according to the 2015 revised St. Gallen International Expert Consensus Recommendation. There were four molecular subtypes: luminal A, luminal B, HER2 enriched and triple-negative breast cancer (TNBC). **Results:** The lesions mostly showed as a palpable mass (89.9%), clinical T<sub>2</sub> (50.4%), histological grade II (58.3%), axillary lymph node metastasis (59.7%), luminal B type (44.6%), and BI-RADS were mostly 4 or 5 categories. Irregular shapes were the most common imaging features ( $P < 0.001$ ). In all examination, the luminal A type and TNBC type were mostly shown as mass alone lesions, luminal B was more common mass with microcalcification, and HER2 enriched type was mostly shown with microcalcifications alone lesions ( $P < 0.001$ ). Using both DM and DBT, negative diagnosis was more common in luminal A type tumors ( $P < 0.001$ ). For mass lesion, the most common findings on DM were indistinct margins (71.9%), whereas DBT detected spiculated margins (51.8%) which were related to luminal A type and luminal B type tumors ( $P < 0.01$ ). Benign morphological features on imaging may be correlated with TNBC type tumors, such as an oval or round shape ( $P < 0.001$ ) and circumscribed margin ( $P < 0.01$ ). The HER2 enriched type and TNBC type were larger than the luminal A type and luminal B type in the mass lesions ( $P = 0.003$ ). **Conclusion:** Some imaging features of breast cancer in young women  $\leq 30$  years old can be used to predict certain tumor molecular subtypes. The cancer detection rate of DBT was higher than that of DM, which has a wide application value for young women with dense breasts.

[Key words] Breast cancer; Mammography; Tomosynthesis; Ultrasonography; Molecular subtype; Pathology

乳腺癌在30岁以下的青年女性中很罕见,其发病率在西方国家是0.43%<sup>[1]</sup>,而在亚洲国家超过3.1%<sup>[2]</sup>。由于该年龄段的青年女性被标准筛查方案指南排除在外,且乳腺纤维腺体实质组织密度较高,可遮挡病变,降低敏感性,导致数字乳腺X线摄影(digital mammography, DM)的检出率和诊断准确率下降,可能使诊断延迟;此外,当DM发现不对称致密区域时,需要进一步的影像检查评估是否存在病变,而数字乳腺断层合成摄影(digital breast tomosynthesis, DBT)可以降低重叠乳腺实质的遮蔽效应,减少假阴性,提高检出率<sup>[3-4]</sup>。目前对30岁以下青年女性乳腺癌的影像学报道很少,其与免疫组织化学分子亚型的相关性分析极少,因此本研究旨在研究30岁以下的青年女性乳腺癌的影像学(DM、DBT、超声)特征与免疫组织化学分子亚型的关联。据我们所知,尚无DBT用于30岁以下年龄段乳腺癌的研究报道,也没有将其与免疫组织化学分子亚型联系

分析的报道。

## 1 资料和方法

### 1.1 研究对象

医院伦理审查委员会批准了该项研究。回顾并分析2013年12月—2019年7月青岛大学附属医院符合以下标准的患者资料。纳入标准:①年龄 $\leq 30$ 岁的女性;②经手术后病理学检查证实为乳腺癌;③手术前均进行双侧乳腺超声检查和患侧乳腺DM、DBT检查。排除标准:①影像学资料不全;②无免疫组织化学法检查结果。由于国际上尚未建议对40岁以下的年轻女性每年行乳腺筛查,因此在青岛大学附属医院,对于30岁以下的女性最先进行的是超声检查,当超声检查发现可疑结果(BI-RADS判定为4A及以上)而拟行手术之前,建议仅进行患侧的DBT检查。所有患者均签署了知情同意书。患者中只有18例术前进行了磁共振成像(magnetic resonance imaging, MRI)

检查, 病例数较少, 统计效能较弱, 因此本研究并未将MRI检查纳入本研究。

最终纳入139例患者, 年龄20~30岁, 中位年龄29岁。患者均无乳腺癌家族史。未婚患者35例, 结婚非哺乳期患者87例, 哺乳期患者17例。采用新辅助化疗31例(25例好转, 6例进展)。

临床表现: 可触及肿块125例(89.9%), 乳头溢液5例(3.6%), 局部疼痛2例(1.4%), 无异常(体检)7例(5.1%)。以每个手术标本的病理报告作为金标准。病理组织学报告记录了病变的病理学分型、临床T分期、组织学分级、腋窝淋巴结是否转移。

## 1.2 仪器与方法

超声检查采用德国Siemens公司生产的ACUSON-S2000或日本HITACHI公司生产的EBU-7500彩色多普勒超声诊断仪, 探头频率10~14 MHz, 对双侧乳腺实质、腋窝、颈部、胸壁及胸骨旁区域行常规超声检查。

手术前采用美国Hologic公司生产的Selenia Dimensions数字乳腺摄影机对超声诊断分类为4A及以上有可疑病变的患侧乳房进行DBT检查, 根据乳腺腺体量进行自动曝光。DBT使患者暴露的剂量水平略高于DM<sup>[5]</sup>, 为了减小辐射剂量, 我们对有可疑病变的患侧和健侧的乳腺采用了不同的投照模式。在Combo模式下一次投照同步获得患侧乳腺DM和DBT的头尾(craniocaudal, CC)位及内外侧斜(mediolateral oblique, MLO)位片, 对于健侧乳腺是在Convention模式下获得MLO位及CC位片。对于DBT, 曝光后经机器自带的计算机后处理软件重建出一系列层厚约1 mm的薄层图像。

## 1.3 图像分析

影像学图像上所有病变均采用2013年美国放射学会第5版乳腺影像报告和数据系统(Breast Imaging Reporting and Data System, BI-RADS)标准进行评估及分类<sup>[6]</sup>。根据DM摄影片判断BI-RADS乳腺构成分类, a为乳腺内几乎全是脂肪组织, b为乳腺内散在纤维腺体组织, c为乳腺组织密度不均匀, d为乳腺组织极其致密; 将a、b归为非致密型乳腺, c、d归为致密型乳腺。可

疑结果判定标准为BI-RADS判定为4A及以上。

DM、DBT所显示的病变分为肿块(伴或不伴钙化)、单纯钙化。US检出的病变分为肿块(伴或不伴钙化)、导管内钙化。评估肿块病变的形状、边缘、大小, 并对DM、DBT显示的肿块病变评估病变致密度; 还评估了超声显示肿块病变的内部回声, 后方回声以及血流信号。评估异常钙化的形态和分布。

由2名具有3~8年以上乳腺影像诊断经验的放射科医师以及3名从事5年以上乳腺超声诊断工作经验的超声科医师分析图像。使用回顾性双盲方法, 在其他信息以及其他检查结果未知的情况下, 在达成共识后分别评估DM及DBT的影像学特征。每位医师首先评估DM图像, 然后评估DBT图像, 最后评估超声图像。当医师之间对同一图像评估不一致时, 通过讨论达成共识。

## 1.4 免疫组织化学分子亚型分析

乳腺癌的免疫组织化学分子亚型根据2015年修订的St. Gallen国际专家共识建议确定<sup>[7]</sup>。免疫组织化学检测雌激素受体(estrogen receptor, ER)、孕激素受体(progesterone receptor, PR)、人表皮生长因子受体2(human epidermal growth factor receptor 2, HER2)表达水平及Ki-67增殖指数。在HER2评估中, 3+评分的肿瘤被归为HER2阳性, 0或1+评分的肿瘤被归为阴性, 在2+评分的肿瘤中, 采用FISH分析基因扩增来确认HER2的状态。病变分为4种分子亚型: luminal A型(ER<sup>+</sup>, PR $\geq$ 20%, Ki-67<20%和HER2<sup>-</sup>)、luminal B型(ER<sup>+</sup>, HER2<sup>-</sup>, Ki-67 $\geq$ 20%, PR<sup>-</sup>或<20%; ER<sup>+</sup>, HER2<sup>+</sup>, 任何Ki-67, 任何PR)、HER-2过表达型(ER<sup>-</sup>, PR<sup>-</sup>, HER2<sup>+</sup>)和三阴性乳腺癌(triple-negative breast cancer, TNBC)(ER<sup>-</sup>, PR<sup>-</sup>和HER2<sup>-</sup>)。

## 1.5 统计学处理

采用SPSS 20.0统计学软件, 计量资料以 $\bar{x}\pm s$ 表示; 定量资料采用单因素方差分析, 定性资料采用 $\chi^2$ 检验或Fisher精确检验, 用post hoc test检验判断阳性组的差异; 假设检验水准 $\alpha=0.05$ ,  $P<0.05$ 为差异有统计学意义。

## 2 结 果

### 2.1 临床病理学特征

临床病理学特征见表1。肿块型病变大小范围为1.0~13.0 cm(平均3.1 cm,中位数2.5 cm),钙化型病变范围为0.4~11.0 cm(平均4.6 cm,中位数3.0 cm)。浸润性导管癌(invasive ductal carcinoma, IDC)是最常见的病理学类型,占78.4%(109/139),其次是导

管原位癌(ductal carcinoma *in situ*, DCIS),占13.7%(19/139),还包括黏液癌3例,微乳头状癌4例,化生性癌2例,小细胞神经内分泌癌和恶性叶状肿瘤各1例。最多见的是临床T<sub>2</sub>期(50.4%),组织学Ⅱ级(58.3%),59.7%患者有淋巴结转移。该研究中包括luminal B型乳腺癌62例(44.6%),luminal A型乳腺癌31例(22.3%),TNBC 26例(18.7%),HER2过表达型乳腺癌20例(14.4%)。

表1 139例青年女性(≤30岁)乳腺癌患者的临床病理学资料

Tab. 1 Clinicopathological features of breast cancer in young women (≤30 years) according to molecular subtypes

Item	TNBC (N=26)	HER2 enriched (N=20)	Luminal A (N=31)	Luminal B (N=62)	[n (%)]	P value
Mean tumor size d/cm $\bar{x} \pm s$	4.04 ± 2.80	3.99 ± 2.88	2.15 ± 1.34	2.93 ± 1.52		0.003***
Mean microcalcification size d/cm $\bar{x} \pm s$	6.15 ± 5.44	3.48 ± 3.42	5.23 ± 4.69	4.72 ± 3.60		0.829***
Histologic type						0.199*
IDC	21 (80.8)	15 (75.0)	22 (70.9)	51 (82.2)		
DCIS	2 (7.7)	5 (25.0)	7 (22.6)	5 (8.1)		
Other	3 (11.5)	0 (0.0)	2 (6.5)	6 (9.7)		
T stage						0.001*
T <sub>1</sub>	5 (19.2)	8 (40.0)	19 (61.3)	20 (32.3)		
T <sub>2</sub>	15 (57.7)	8 (40.0)	8 (25.8)	39 (62.9)		
T <sub>3</sub>	6 (23.1)	4 (20.0)	4 (12.9)	3 (4.8)		
Tumor grade						<0.001*
I	0 (0.0)	0 (0.0)	9 (29.0)	1 (1.6)		
II	9 (34.6)	10 (50.0)	21 (67.7)	41 (66.1)		
III	17 (65.4)	10 (50.0)	1 (3.3)	20 (32.3)		
Axillary lymph node metastasis <sup>#</sup>						0.146**
Negative	10 (38.5)	7 (35.0)	8 (25.8)	31 (50.0)		
Positive	16 (61.5)	13 (65.0)	23 (74.2)	31 (50.0)		

Adjusted residuals appeared in parentheses below observed frequencies; \*: Fisher's exact test; \*\*:  $\chi^2$  test; \*\*\*: One-way ANOVA; #: Axillary lymph node metastasis was the pathological result

### 2.2 影像学特征

#### 2.2.1 超声

超声影像学特征见表2,超声检出了所有病变(100.0%),单纯肿块型病变(56.8%,79/139)最常见。对于肿块病变,最常见的是不规则形(70.4%),低回声(60.0%),边缘模糊(32.0%),后方回声无改变(36.8%),内部血流信号(89.9%),BI-RADS分类为5类(42.4%)。

#### 2.2.2 DM和DBT

DM和DBT影像学特征见表3。DBT检出7例结构扭曲病变,均呈放射样改变,我们将其归

类为边缘呈毛刺样的肿块病变。肿块伴钙化型病变均最常见(DM:36.0%,50/139;DBT:41.7%,58/139)。在DM中,12.2%(17/139)病变呈阴性,而在DBT中,5.0%(7/139)呈阴性,其中4例,由于乳腺实质极其致密遮蔽了病变(图1)。在DM、DBT,肿块病变中最常见的均是不规则形(77.1%,75.0%)和高密度肿块(52.1%,50.9%)。在DM中,模糊边缘(71.9%)最常见,而在DBT中毛刺边缘(51.8%)最常见,毛刺多短于肿块长径(76.5%)。对于单纯钙化病变(图2),最常见

的均是细线样或细小分支状 (50.0%, 55.0%), (45.0%)。在DBT分类为BI-RADS 4C或5的病  
DM中多成簇分布 (42.4%), DBT中多呈线样 例多于DM (70.5%, 38.1%)。91.4%患者的乳  
或段样分布 (45.0%)。腋窝淋巴结状态多增大 腺构成是致密型乳腺 (c或d型)。

表 2 139例青年女性(≤30岁)乳腺癌患者的超声检查结果

Tab. 2 Ultrasonography features of breast cancer in young women (≤30 years) according to molecular subtypes

Feature	TNBC (N=26)	HER2 enriched (N=20)	Luminal A (N=31)	Luminal B (N=62)	P value
Abnormality <sup>△</sup>					<0.001*
Mass only	19 (73.1)	10 (50.0)	28 (90.3)	22 (35.5)	
Mass with microcalcifications	6 (23.1)	5 (25.0)	2 (6.5)	33 (53.2)	
Intraductal calcifications	1 (3.8)	5 (25.0)	1 (3.2)	7 (11.3)	
Shape <sup>△</sup>					<0.001*
Oval/round	18 (72.0)	4 (26.7)	9 (30.0)	6 (10.9)	
Irregular	7 (28.0)	11 (73.3)	21 (70.0)	49 (89.1)	
Margin <sup>△</sup>					0.002*
Circumscribed	9 (36.0)	0 (0.0)	2 (6.7)	2 (3.6)	
Indistinct	7 (28.0)	5 (33.4)	9 (30.0)	19 (34.5)	
Microlobulated	4 (16.0)	2 (13.3)	3 (10.0)	3 (5.5)	
Spiculated	1 (4.0)	2 (13.3)	10 (33.3)	9 (16.4)	
Angular	4 (16.0)	6 (40.0)	6 (20.0)	22 (40.0)	
Echogenicity <sup>△</sup>					0.05*
Hypoechoic	12 (48.0)	9 (60.0)	24 (80.0)	30 (54.5)	
Heterogenous	10 (40.0)	6 (30.0)	5 (16.7)	24 (43.6)	
Complex cystic and solid	3 (12.0)	0 (0.0)	1 (3.3)	1 (1.9)	
Posterior feature <sup>△</sup>					0.078*
No	8 (32.0)	6 (40.0)	12 (40.0)	20 (36.4)	
Enhancement	13 (52.0)	6 (40.0)	6 (20.0)	11 (20.0)	
Shadowing	3 (12.0)	2 (13.3)	8 (26.7)	21 (38.2)	
Combined	1 (4.0)	1 (6.7)	4 (13.3)	3 (5.4)	
Vascularity					0.299*
Absent	2 (7.7)	0 (0.0)	2 (6.5)	0 (0.0)	
Internal	22 (84.6)	18 (90.0)	27 (87.0)	58 (93.5)	
Rim	2 (7.7)	2 (10.0)	2 (6.5)	4 (6.5)	
Axillary lymph node					0.086**
Negative	9 (34.6)	10 (50.0)	21 (67.7)	29 (46.8)	
Positive	17 (65.4)	10 (50.0)	10 (32.3)	33 (53.2)	
BI-RADS category					0.008*
C4a	1 (3.8)	1 (5.0)	3 (9.7)	1 (1.6)	
C4b	14 (53.8)	7 (35.0)	7 (22.6)	11 (17.7)	
C4c	4 (15.4)	8 (40.0)	7 (22.6)	16 (25.8)	
C5	7 (26.9)	4 (20.0)	14 (45.2)	34 (54.8)	

Adjusted residuals appear in parentheses below observed frequencies; \*: Fisher's exact test; \*\*:  $\chi^2$  test; <sup>△</sup>: Including mass only and mass with microcalcifications

表3 139例青年女性(≤30岁)乳腺癌患者的DM及DBT检查结果

Tab. 3 DM and DBT features of breast cancer in young women (≤30 years) according to molecular subtypes

Feature	TNBC <i>n</i> (%)		HER2 enriched <i>n</i> (%)		Luminal A <i>n</i> (%)		Luminal B <i>n</i> (%)		<i>P</i> value		
	DM	DBT	DM	DBT	DM	DBT	DM	DBT	DM	DBT	
Breast density										0.618*	
a, b	4 (15.4)		1 (5.0)		2 (6.5)		5 (8.1)				
c, d	22 (84.6)		19 (95.0)		29 (93.5)		57 (91.9)				
Abnormality										<0.001*	<0.001*
No abnormality	1 (3.8)	0 (0.0)	1 (5.0)	1 (5.0)	11 (35.5)	6 (19.4)	4 (6.5)	0 (0.0)			
Mass only	15 (57.7)	16 (61.5)	5 (25.0)	5 (25.0)	13 (41.9)	18 (58.1)	13 (21.0)	15 (29.0)			
Mass with microcalcifications	7 (26.9)	8 (14.5)	8 (40.0)	9 (45.0)	4 (12.9)	4 (12.9)	31 (50.0)	37 (54.8)			
Microcalcifications only	3 (11.5)	2 (7.7)	6 (30.0)	5 (25.0)	3 (9.7)	3 (9.7)	14 (22.6)	10 (16.1)			
Shape (for mass)										<0.001*	<0.001*
Oval/round	14 (63.6)	17 (70.8)	0 (0.0)	0 (0.0)	3 (17.6)	5 (22.7)	5 (11.4)	6 (11.5)			
Irregular	8 (36.4)	7 (29.2)	13 (100.0)	14 (100.0)	14 (82.4)	17 (77.3)	39 (88.6)	46 (88.5)			
Margin (for mass)										0.009*	0.003*
Circumscribed	5 (22.7)	5 (20.8)	0 (0.0)	0 (0.0)	1 (5.9)	2 (9.1)	1 (2.3)	2 (3.8)			
Indistinct	16 (72.7)	4 (16.7)	12 (92.3)	7 (50.0)	9 (52.9)	4 (18.2)	32 (72.7)	9 (17.3)			
Microlobulated	1 (4.5)	8 (33.3)	0 (0.0)	4 (28.6)	1 (5.9)	2 (9.1)	2 (4.5)	7 (13.5)			
Spiculated	0 (0.0)	7 (29.2)	1 (7.7)	3 (21.4)	6 (35.3)	14 (63.6)	9 (20.5)	34 (65.4)			
Density (for mass)										0.112**	0.059**
Iso	6 (27.2)	7 (29.2)	6 (46.2)	6 (42.9)	11 (64.7)	15 (68.2)	23 (52.3)	27 (51.9)			
Hyper	16 (72.7)	17 (70.8)	7 (53.8)	8 (57.1)	6 (35.3)	7 (31.8)	21 (47.7)	25 (48.1)			
Shape (for microcalcifications)										0.857*	0.910*
Amorphous	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)			
Fine pleomorphic or coarse heterogeneous	2 (66.7)	1 (50.0)	2 (33.3)	2 (40.0)	2 (66.7)	2 (66.7)	5 (35.7)	4 (40.0)			
Fine linear or linear branching	1 (33.3)	1 (50.0)	3 (50.0)	3 (60.0)	1 (33.3)	1 (33.3)	8 (57.1)	6 (60.0)			
Distribution (for microcalcifications)										0.992*	0.709*
Diffuse	1 (33.3)	1 (50.0)	1 (16.7)	1 (20.0)	0 (0.0)	0 (0.0)	1 (7.1)	1 (10.0)			
Regional	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	2 (20.0)			
Grouped	1 (33.3)	1 (50.0)	2 (33.3)	1 (20.0)	2 (66.7)	2 (66.7)	6 (42.9)	2 (20.0)			
Linear/segmental	1 (33.3)	0 (0.0)	2 (33.3)	3 (60.0)	1 (33.3)	1 (33.3)	5 (35.7)	5 (50.0)			
Axillary lymph node										0.092**	
Positive	8 (30.8)		4 (20.0)		14 (45.2)		30 (48.4)				
Negative	18 (69.2)		16 (60.0)		17 (54.8)		32 (51.6)				
BI-RADS category										<0.001*	0.001*
C2	1 (3.8)	0 (0.0)	1 (5.0)	1 (5.0)	11 (35.5)	6 (19.4)	4 (6.5)	0 (0.0)			
C4a	6 (23.1)	3 (11.5)	1 (5.0)	0 (0.0)	3 (9.7)	3 (9.7)	6 (9.7)	2 (3.2)			
C4b	13 (50.0)	8 (30.8)	10 (50.0)	5 (25.0)	11 (35.5)	6 (19.4)	19 (30.6)	7 (11.3)			
C4c	5 (19.2)	9 (34.6)	5 (25.0)	6 (30.0)	1 (3.2)	5 (16.1)	14 (22.6)	16 (25.8)			
C5	1 (3.8)	6 (23.1)	3 (15.0)	8 (40.0)	5 (16.1)	11 (35.5)	19 (30.6)	37 (59.7)			

Adjusted residuals appeared in parentheses below observed frequencies; \*: Fisher's exact test; \*\*:  $\chi^2$  test; DBT: Digital breast tomosynthesis; DM: Digital mammography

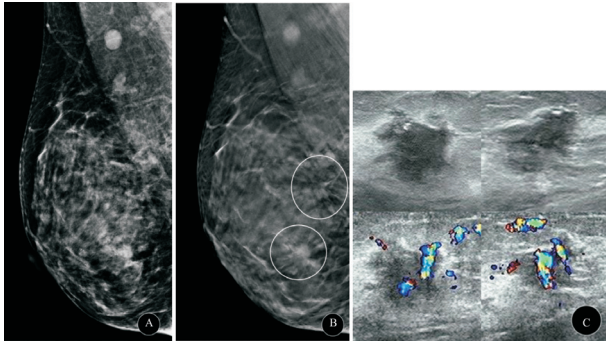


图1 患者女性, 30岁, luminal B型乳腺癌

Fig. 1 A 30-year-old young female patient with luminal B type breast cancer

A: Digital mammography (DM) did not show the lesions; B: Digital breast tomosynthesis (DBT) showed two lesions both were irregular, iso-density with spiculated margins, and microcalcifications within one of the lesions; C: Ultrasound showed that both lesions were irregular, hypoechoic with spiculated and angled margins, no change in posterior feature, and rich internal vascularity

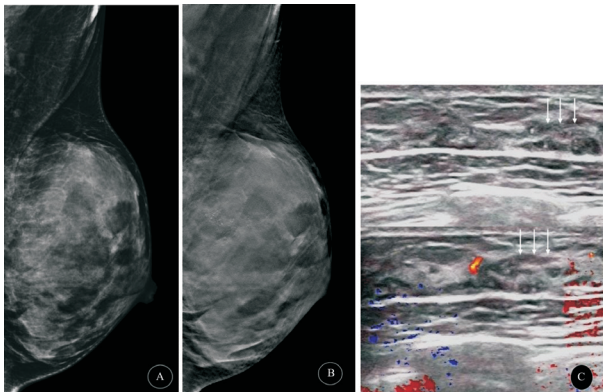


图2 患者女性, 26岁, HER2过表达型乳腺癌

Fig. 2 A 26-year-old young female patient with HER2 enriched breast cancer

A, B: Digital mammography (DM) and digital breast tomosynthesis (DBT) showed fine linear or fine pleomorphic calcifications with segmental distribution; C: Ultrasound showed intraductal calcifications

### 2.3 分子亚型与临床病理、影像学特征的关系

Luminal B型乳腺癌多为临床T<sub>2</sub>期 ( $P=0.001$ ); 在3种成像中, luminal B型乳腺癌更常表现为肿块伴钙化样病变 ( $P<0.001$ ), 不规则形 ( $P<0.001$ ); 在超声图像中, 肿块病变边缘多成角 ( $P=0.002$ ); 在DBT中, 多见毛刺边缘 ( $P=0.003$ )。Luminal A型乳腺癌患者更多为临床T<sub>1</sub>期 ( $P=0.001$ ), 以及组织学I级 ( $P<0.001$ ); 在3种成像中均多呈单纯肿块形态 ( $P<0.001$ ); 在DM和DBT, 诊断为阴性结果更常见于luminal A型乳腺癌 ( $P<0.001$ ); 在

超声和DM, 肿块多见毛刺 (超声:  $P=0.002$ ; DM:  $P=0.009$ ; 图3)。HER2过表达型在超声中多呈单纯钙化病变 ( $P<0.001$ ); 在DM和DBT中, 肿块多呈不规则形 ( $P<0.001$ ); 在DBT病变边缘多模糊 ( $P=0.003$ )。TNBC更多显示为组织学III级 ( $P<0.001$ ), 多表现为单纯肿块型 ( $P<0.001$ ), 在3种影像检查中更多表现出良性病变形态 (图4), 呈椭圆形或圆形 ( $P<0.001$ ), 边缘清楚 (超声:  $P=0.002$ ; DM、DBT:  $P<0.001$ )。TNBC和HER2过表达型乳腺癌的肿块样病变大小大于luminal A型和luminal B型乳腺癌 ( $P=0.003$ )。

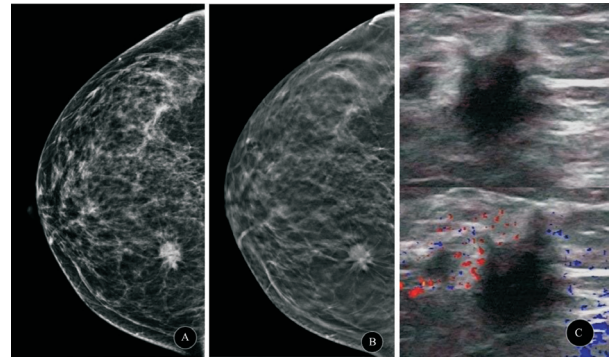


图3 患者女性, 28岁, luminal A型乳腺癌

Fig. 3 A 28-year-old young female patient with luminal A breast cancer

A, B: Digital mammography (DM) and digital breast tomosynthesis (DBT) showed the lesion was irregular, iso-density with spiculated margins (that was more obvious in DBT); C: Ultrasound showed the lesion was irregular, hypoechoic with spiculated margins, no change in posterior feature, and vascularity in rim

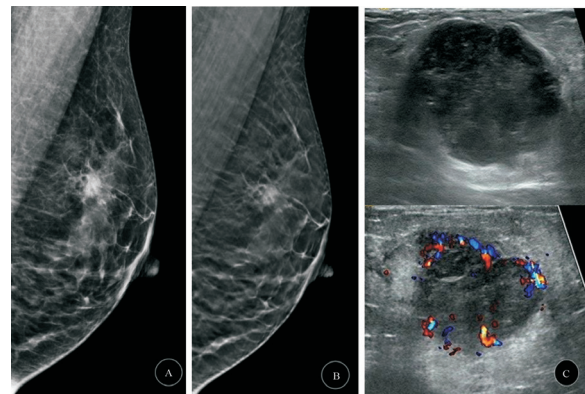


图4 患者女性, 29岁, TNBC

Fig. 4 A 29-year-old young female patient with TNBC

A, B: DM and DBT showed the lesion was irregular, hyper-density with part of indistinct margin (DBT showed circumscribed margin of the lesion); C: Ultrasound showed the lesion was oval, hypoechoic with lobulated and circumscribed margins, and had enhanced posterior feature and rich internal vascularity

### 3 讨 论

亚洲国家年轻女性乳腺癌发病率明显高于欧美国家,越来越受到关注。对于年龄 $\leq 30$ 岁年轻女性的乳腺癌影像学表现与免疫组织化学分子亚型的相关性研究鲜见报道。我们将青年女性( $\leq 30$ 岁)乳腺癌的影像学特征与分子亚型进行关联分析,发现某些影像学特征与特定的分子亚型有关。由于乳腺癌不同分子亚型的临床表现、治疗反应及预后存在显著差异<sup>[3, 8]</sup>,所以早期的乳腺癌分子亚型的识别可以完善治疗方案,延长患者存活时间。有研究<sup>[2, 4, 8-9]</sup>显示,与中老年女性乳腺癌相比,青年女性的生物学特征更具侵袭性,预后相对较差,趋向于更晚期的肿瘤分期,更高的组织学分级,更多的淋巴侵犯,在本研究中,大多数为IDC,临床T<sub>2</sub>期,组织学II级肿瘤,有症状的临床表现(94.9%)是患者检查的主要原因,而临床触诊病变大于手术切除和影像学检查显示的病变大小,这可能与更具侵袭性的生物学特征相关。因此,在该症状组中考虑其为恶性肿瘤。此外,HER2过表达型和TNBC型两组中肿块病变的范围均大于luminal A和luminal B型,这可能也与它们的高侵袭性有关,这与Cai等<sup>[3]</sup>的研究结果相同。

本研究中最常见的分子亚型为luminal B型乳腺癌,其次为luminal A型乳腺癌,再次为TNBC型乳腺癌,而HER2过表达型乳腺癌最少。这一分子亚型的比例与以往研究报道相似<sup>[3, 10]</sup>,但与Lin等<sup>[11]</sup>的研究略有不同: luminal A型乳腺癌在年轻患者中患病率最高, TNBC最低;可能的原因是他们的分类是基于2011年St. Gallen国际专家共识。此外,我们的结果与欧美国家的一些研究不同<sup>[7, 12-13]</sup>,其显示青年女性的TNBC和HER2过表达型乳腺癌更多,造成这种差异的原因可能是种族差异。而中国中老年女性乳腺癌患者的免疫组织化学亚型与欧美国家相比无明显差异, luminal A型和luminal B型均较HER2过表达型乳腺癌和TNBC多见<sup>[3, 12, 13]</sup>。

超声因其简便易行、灵敏度高、无辐射,是有症状或接受体检的青年女性的主要影像学检

查方法<sup>[14]</sup>,国际上尚不建议青年女性常规行乳腺X线检查。在本研究中,超声检出了全部病变(100.0%),并归类为可疑病变(BI-RADS 4A及以上),建议进行活检,病理学检查结果均显示为恶性。超声显示肿块多表现为不规则形,边缘模糊,低回声,后方回声无改变,病变内探及血流信号,与以往研究相似<sup>[2, 4]</sup>,但Bullier等<sup>[9]</sup>的研究显示更多的病变后方伴声影,原因可能与肿块中钙化数量和纤维组织的含量有关。本研究发现luminal A型乳腺癌肿块边缘多见毛刺,与以往研究相似<sup>[4, 9]</sup>,可能原因是癌组织向周围浸润性生长,导致较高的基质反应和纤维结缔组织增生。由于卵圆形或圆形肿块可能被误认为良性病变,在这种情况下,有必要仔细评估病变边缘和内部血流信号,以避免遗漏癌症病变。另外,在An等<sup>[2]</sup>的研究中, TNBC大多被分为BI-RADS 3或4A,而本研究中主要是BI-RADS 4B,这可能与观察者在图像分析上的差异有关。

Osako等<sup>[15]</sup>的研究表明,虽然超声对可触及的肿块病变检出灵敏度高,但对不可触及的微小钙化病变不敏感。DM对于钙化病变的诊断敏感性和特异性明显优于超声。部分可疑钙化,尤其是成簇的微钙化(如无定形钙化),可能表明存在早期乳腺癌,如DCIS。因此对超声所示可疑患者有必要进行DM以明确诊断、检测钙化病变以及确定病变范围。DBT对于致密型乳腺所掩盖病变的检出敏感性和诊断特异性均优于DM, $\leq 30$ 岁年轻女性绝大多数是致密型乳腺。在本研究中,DM、DBT诊断的假阴性均多是luminal A型乳腺癌,可能是由于luminal A型乳腺癌多表现为单纯肿块型,而致密乳腺会掩盖病变,但部分病变可以通过DBT检测到,因此DM的假阴性诊断较DBT更多(12.2%, 5.0%);另外,在我们的结果中,有2例是由于导管内乳头状瘤、1例纤维腺瘤、1例导管上皮增生发生部分导管内原位癌癌变导致了假阴性诊断。在肿块性病变特征方面,如其他研究报道<sup>[2, 4]</sup>表明,多呈不规则形,在DM上显示模糊的边缘;而本研究中, DBT更常见毛刺边缘,毛刺影多与luminal型乳腺癌相

关<sup>[4, 9]</sup>, 因此DBT提高了BI-RADS分类以及成像的灵敏度和特异度, 使乳腺癌的检出率更高, 假阴性更少, 影像诊断更符合最终病理学诊断结果, 这与Bullier等<sup>[9]</sup>的研究结果一致。在单纯钙化病变方面, 多与HER2过表达型乳腺癌相关, 与其他研究结果一致<sup>[2, 3, 9]</sup>, 而DBT中检查到的肿块伴钙化的病变更多, 是因为DBT更容易检出钙化所在区域的被纤维腺体组织重叠掩盖的肿块。在本研究还发现大多数具有良性特征的病变是TNBC, 呈圆形或卵圆形, 边缘清楚, 与既往的报道<sup>[4, 9]</sup>一致。

本研究显示, luminal A型乳腺癌多呈单纯肿块, 边缘见毛刺, 在超声和DBT影像上均可看到毛刺, 但极其致密的乳腺可能会导致DBT漏诊, 因此通过超声观察更容易。Luminal B型乳腺癌多呈肿块伴钙化, DBT更容易看到钙化下的肿块, 因此通过DBT观察更容易。HER2过表达型多呈单纯钙化, 而超声观察钙化灵敏度较差, DM、DBT均易观察钙化, 但DBT观察模糊钙化更容易。TNBC则多呈良性形态, 建议三者结合观察。

综上所述, 对于30岁以下的青年女性, 某些影像学特征与特定的免疫组织化学分子表型有关。DBT的乳腺癌检出率和诊断准确率高于DM, 对于乳腺致密的青年女性恶性病变的评估具有广泛的应用价值。

#### [参 考 文 献]

- [1] HAMILTON L J, CORNFORD E J, MAXWELL A J. A survey of current UK practice regarding the biopsy of clinical and radiologically benign breast masses in young women [J]. *Clin Radiol*, 2011, 66(8): 738-741.
- [2] AN Y Y, KIM S H, KANG B J, et al. Breast cancer in very young women (< 30 years) imaging features with clinicopathological features and immunohistochemical subtypes [J]. *Eur J Radiol*, 2015, 84: 1894-1902.
- [3] CAI S, YAO M, CAI D, et al. Association between digital breast tomosynthesis and molecular subtypes of breast cancer [J]. *Oncol Lett*, 2019, 17(3): 2669-2676.
- [4] DURHAN G, AZIZOVA A, ÖNDER Ö, et al. Imaging findings and clinicopathological correlation of breast cancer in women under 40 years old [J]. *Eur J Breast Health*, 2019, 15(3): 147-152.
- [5] BOUWMAN R W, VAN ENGEN R E, YOUNG K C, et al. Average glandular dose in digital mammography and digital breast tomosynthesis: comparison of phantom and patient data [J]. *Phys Med Biol*, 2015, 60(20): 7893-7907.
- [6] American College of Radiology. Breast Imaging and Reporting and Data System (ACR BI-RADS® Atlas), 5th ed [M]. Reston, VA: American College of Radiology, 2013.
- [7] COATES A S, WINER E P, GOLDBIRSCHE A, et al. Tailoring therapies--improving the management of early breast cancer: St. Gallen International Expert Consensus on the primary therapy of early breast cancer 2015 [J]. *Ann Oncol*, 2015, 26(8): 1533-1546.
- [8] MURPHY B L, DAY C N, HOSKIN T L, et al. Adolescents and young adults with breast cancer have more aggressive disease and treatment than patients in their forties [J]. *Ann Surg Oncol*, 2019, 26(12): 3920-3930.
- [9] BULLIER B, MACGROGAN G, BONNEFOI H, et al. Imaging features of sporadic breast cancer in women under 40 years old: 97 cases [J]. *Eur Radiol*, 2013, 23(12): 3237-3245.
- [10] COLLINS L C, MAROTTI J D, GELBER S, et al. Pathologic features and molecular phenotype by patient age in a large cohort of young women with breast cancer [J]. *Breast Cancer Res Treat*, 2012, 131(3): 1061-1066.
- [11] LIN C H, SHEN C Y, LEE J H, et al. High prevalence of the BIM deletion polymorphism in young female breast cancer in an East Asian country [J]. *PLoS One*, 2015, 10(4): e0124908.
- [12] SOLÁR A, ÚJHELYI M, POLGÁR C, et al. A long-term retrospective comparative study of the oncological outcomes of 598 very young ( $\leq 35$  years) and young (36-45 years) breast cancer patients [J]. *Eur J Surg Oncol*, 2019, 45(11): 2009-2015.
- [13] JOHANSSON A L V, TREWIN C B, HJERKIND K V, et al. Breast cancer-specific survival by clinical subtype after 7 years follow-up of young and elderly women in a nationwide cohort [J]. *Int J Cancer*, 2019, 144(6): 1251-1261.
- [14] DESTOUNIS S, SANTACROCE A. Age to begin and intervals for breast cancer screening: balancing benefits and harms [J]. *AJR Am J Roentgenol*, 2018, 210(2): 279-284.
- [15] OSAKO T, IWASE T, TAKAHASHI K, et al. Diagnostic mammography and ultrasonography for palpable and nonpalpable breast cancer in women aged 30 to 39 years [J]. *Breast Cancer*, 2007, 14(3): 255-259.

(收稿日期: 2020-02-15 修回日期: 2020-05-09)