·论　著·

乳腺X线摄影影像学特征与21基因检测复发风险评分的相关性影像基因组学研究

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［摘要］ **背景与目的：**21基因检测虽然已被许多临床指南推荐用于指导早期乳腺癌患者化疗决策选择，但由于有创性、价格昂贵、无法全面反映肿瘤异质性及整体情况等原因尚不能广泛应用于临床。乳腺X线摄影常规用于检测乳腺病灶、评估病灶良恶性和评估疗效等方面，有关乳腺X线摄影是否可以预测化疗受益情况的研究十分有限。探究乳腺X线摄影影像学特征与Oncotype DX 21基因检测复发风险评分（recurrence score，RS）的相关性。**方法：**回顾性分析2017年4月—2019年3月在复旦大学附属肿瘤医院进行乳腺X线摄影及21基因检测的529例乳腺癌患者的乳腺X线摄影图像和临床资料。根据2013版乳腺影像报告和数据系统（Breast Imaging Reporting and Data System，BI-RADS）标准对入组患者乳腺X线摄影图像进行分析和收集。采用单因素方差分析和Spearman相关检验分析乳腺X线摄影影像学特征与RS的相关性。运用多元线性回归评估有意义的乳腺X线摄影影像学特征附加作用。**结果：**乳腺X线摄影钙化分布和肿块边缘与RS显著相关（P<0.001和P=0.005）。区域钙化分布的平均RS为39.9，明显高于段样分布和集群分布（分别为24.4和31.8）。边缘清楚肿块的患者平均RS为17.4，明显低于其他肿块边缘的患者（27.6）。将钙化分布和肿块边缘加入包括病理学因素在内的多元线性回归模型中时，肿块边缘差异仍有统计学意义，模型R^2从0.170增加到0.193。**结论：**乳腺X线摄影影像学特征对预测乳腺癌患者长期复发风险和指导化疗决策有潜在价值。

［关键词］乳腺癌；乳腺X线摄影；21基因检测；复发风险评分；影像基因组学
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Radiogenomics: association between BI-RADS mammographic imaging features and the 21-gene recurrence score

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［**Abstract**］ **Background and purpose:** The 21-gene assay has been recommended by guidelines for helping clinicians decide whether adjuvant chemotherapy is needed in estrogen receptor-positive, lymph node-negative breast cancer patients. However, as an invasive and expensive test, the Oncotype DX 21-gene test can't fully reflect the gene expression of the overall heterogeneous tumors. The 21-gene test has not been routinely used clinically. Mammography has been widely used to detect, diagnose and evaluate the treatment effect of breast diseases, but it has been unclear whether mammography has prognostic value. This study aimed to explore the association between mammographic imaging features and recurrence risk quantified with 21-gene recurrence score (RS) in breast cancer patients. **Methods:** A total of 529 patients who underwent a 21-gene expression assay from Apr. 2017 to Mar. 2019 were identified. Mammographic imaging features were reviewed and recorded according to the 2013 version of the Breast Imaging Reporting and Data System (BI-RADS) lexicon. One-way analysis of variance and Spearman's correlation test were used to evaluate the correlation between mammographic imaging features and the RS. Multivariate linear regression was used to assess the added effect of significant mammographic features. **Results:** Mammographic calcification distribution and mass margin were significantly associated with the RS (P<0.001 and P=0.005). The average RS for regional calcification distribution was 39.9, which

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was obviously higher than that for segmental and grouped calcification distributions, corresponding to 24.4 and 31.8, respectively. Mass with circumscribed margins had a lower average RS of 17.4, whereas the RS for all other mass margins was 27.6. When these two significant features were added to a multivariable regression model including pathological factors, the mass margin remained statistically significant, and the R-squared value increased from 0.170 to 0.193. **Conclusion:** Calcification distribution and mass margin upon mammography have the potential to predict a breast cancer patient's recurrence risk. Further prospective studies are needed to verify this preliminary finding.

［**Key words**］ Breast neoplasms; Mammography; 21-gene expression assay; Recurrence score; Radiogenomics

2018年最新数据显示，乳腺癌仍是全球女性发病率最高的癌症[1]。随着基因表达谱研究的进展，乳腺癌已经被证实是一类异质性疾病，不同分子分型的乳腺癌患者往往伴有不同的临床表现，治疗方法和预后也不尽相同[2]。Oncotype DX 21基因检测（美国Genomic Health公司）通过分析16个癌症相关基因和5个参考基因得到一个复发风险评分（recurrence score，RS），RS可以预测雌激素受体（estrogen receptor，ER）阳性、淋巴结阴性的乳腺癌患者经过他莫昔芬治疗后的远期复发风险，并评估化疗受益情况[3-5]。因此，21基因检测被许多指南推荐用于指导临床辅助化疗决策[6-7]。然而，作为一种有创检查，21基因检测价格昂贵，只能反映一小块病理学组织的基因表达情况，而无法全面反映肿瘤异质性及整体情况[8]。

临床上，乳腺X线摄影是一项常规检查项目，具有无创、操作简便、对钙化灶敏感等优势。目前，乳腺X线摄影主要通过运用乳腺影像报告和数据系统（Breast Imaging Reporting and Data System，BI-RADS）标准对乳腺及病灶进行分析描述，从而达到检测病灶、评估病灶良恶性、评估疗效的目的[9]。然而，有关乳腺X线摄影是否可以评估患者预后及化疗受益情况的研究十分有限。

近年来，影像基因组学发展迅速，其主要目的是研究影像学表现与分子谱之间的关系[10-12]。先前有关乳腺癌影像学特征与21基因关系的研究主要集中在磁共振成像（magnetic resonance imaging，MRI）影像学方面[8, 11, 13-17]。有关乳腺X线摄影影像学表现与21基因关系的研究报道甚少，其研究结果也不一致[13, 18-19]。因此，本研究旨在探究乳腺X线摄影BI-RADS影像学特征与21基因RS之间的关系。

1 资料和方法

1.1 研究对象

回顾性分析2017年4月—2019年3月在复旦大学附属肿瘤医院行术前乳腺X线摄影检查及21基因检测的600例乳腺癌患者的资料。按排除标准被排除的病例如下：男性患者1例；乳腺X线摄影图像质量欠佳或病灶显示不完全24例；病理学检查结果为新辅助治疗后13例；病理学检查报告缺失2例；有乳腺癌病史或双侧乳腺癌31例。

从电子病例系统收集患者人口学资料，包括年龄、身体质量指数（body mass index，BMI）、绝经与否及一代亲属乳腺癌家族史。病理学资料包括病理学类型、组织学分级、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）、是否伴有导管原位癌（ductal carcinoma *in situ*，DCIS)）、DCIS等级及淋巴结转移情况。如果病理学类型或DCIS等级为一个范围，取最大值。如果为多中心病灶，选取主要病灶入组。

1.2 RS

首先，取研究对象的乳腺癌组织石蜡包埋标本，使用两个10 μm未染色的切片进行RNA水平的提取和测量，并证实不存在DNA污染。然后，使用Omniscript RT试剂盒（德国Qiagen公司）进行反转录。使用先前报道的Primer Express和Primer 3设计反转录聚合酶链反应（reverse transcription polymerase chain reaction，RT-PCR）引物和探针[20]。通过使用Applied Biosystems 7500 PCR仪（美国Applied Biosystems公司），测定21个基因的*Ct*值。21个基因包括16个乳腺癌相关基因［增殖组（*Ki*-67、*CCNB*1、

MYBL2、*STK15*、Survivin）、雌激素组（*ER*、*PR*、*SCUBE2*、*Bcl-2*）、侵袭组（*MMP11*、*CTSL2*）、*HER2*组（*GRB7*、*HER2*）、*GSTM1*、*BAG1*、*CD68*］和5个参考基因（*ACTB*、*GUS*、*GAPDH*、*TFRC*、*RPLPO*）。通过特定运算[3]获得RS，RS范围为0~100，并可分为3组：低危组（RS<18）、中危组（18≤RS < 31）和高危组(RS≥31)，10年复发风险分别为6.8%、14.3%和30.5%。

1.3 乳腺X线摄影影像学特征

2名有经验的放射科医师根据2013版BI-RADS标准对入组患者乳腺X线摄影图像进行回顾性分析[9]。当意见出现分歧时，经2名医师协商达成一致。乳腺纤维腺体类型分为脂肪型（A型）、散在纤维腺体型（B型）、不均匀致密型（C型）和极度致密型（D型）。乳腺X线摄影影像学表现分为正常、肿块、单纯钙化、结构扭曲和不对称。分析并记录肿块大小（长径和短径）、形状（圆形、卵圆形和不规则形）、边缘（清楚、遮蔽、小分叶、模糊和毛刺）和密度（高密度、低密度、等密度和含脂肪）。钙化形态分为点状、无定形、细线状或细线分枝状、细小多形性及粗大不均质。钙化分布分为散在分布、区域分布、集群分布、线样分布和段样分布。不对称包括不对称、局灶性不对称、大团样不对称和进展性不对称。

1.4 统计学处理

采用SPSS 25.0软件进行统计学分析，$P < 0.05$为差异有统计学意义。采用单因素方差分析法分析分类型影像学特征的差异性。采用Spearman相关性检验检测连续型影像学特征及等级特征与RS的相关性。运用LSD和Dunnett's T3检验进行多重比较。运用多元线性回归分析有意义影像特征的附加价值。

2 结　果

共纳入529例研究对象，年龄26~76岁，平均年龄（51.9±9.5）岁。平均BMI为（23.0±2.9）kg/m^2。其中，将近一半（48.7%）的患者已绝经，仅2.9%的患者有一代亲属乳腺癌家族史。患浸润性导管癌的患者占绝大多数（89.4%），患浸润性小叶癌和其他类型浸润性乳腺癌的患者分别占4.7%和5.9%。82.5%的患者乳腺癌组织学分级为Ⅱ级，远超Ⅰ级（3.6%）和Ⅲ级（13.9%）患者数，其中93例患者同时伴有DCIS。多数患者表现为ER阳性（100.0%）、PR阳性（92.1%）、HER2阴性（98.3%）和淋巴结阴性（87.5%）。所有入组患者平均RS为27.8±8.1（0~52.2）。详见表1。

表 1　患者及乳腺癌病灶特征

Tab. 1　Characteristics of patients and tumors

Characteristic	*N*	%
Age/year	529	51.9 ± 9.5*
Body mass index/(kg·m^{-2})	500	23.0 ± 2.9*
Postmenopausal	256	48.7
First degree relative with breast cancer	15	2.9
Pathology	529	
Invasive ductal carcinoma	473	89.4
Invasive lobular carcinoma	25	4.7
Other types of invasive breast carcinoma	31	5.9
Invasive malignancy grade	502	
Grade Ⅰ	18	3.6
Grade Ⅱ	414	82.5
Grade Ⅲ	70	13.9
Receptor status	529	
ER positive	529	100.0
PR positive	487	92.1
HER2 negative	520	98.3
DCIS present	93	17.6
DCIS grade	34	
Low	5	14.7
Intermediate	20	58.8
High	9	26.5
Negative lymph node	463	87.5
Recurrence score	529	27.8 ± 8.1*

*: Data are $\bar{x}\pm s$

乳腺X线摄影影像学特征统计学描述见表2。正如在日常工作中所见，最常见的乳腺类型为C型，占所有患者74.1%；19.7%的患者乳腺为B型，剩余少量患者乳腺为A型（2.1%）和D型（4.2%）。肿块是最常见的影像学表现（71.5%）。接着是不对称（12.7%）和结构扭曲（6.6%）。多数肿块表现为高密度（81.2%）、

表 2 乳腺X线摄影影像学特征

Tab. 2 Descriptive statistics of mammography features

Mammography features	*N*	%	*P* value
Finding	529		0.222
Normal findings	24	4.5	
Mass	378	71.5	
Calcification only	25	4.7	
Asymmetry	67	12.7	
Architectural distortion	35	6.6	
Breast density	529		0.085
Fatty (category A)	11	2.1	
Scattered (category B)	104	19.7	
Heterogeneous (category C)	392	74.1	
Extremely dense (category D)	22	4.2	
Mass shape	365		0.906
Round	2	0.5	
Oval	69	18.9	
Irregular	294	80.5	
Margin	369		0.005
Spiculated	202	54.7	
Circumscribed	6	1.6	
Microlobulated	0	0.0	
Obscured	24	6.5	
Indistinct	137	37.1	
Mass density	377		0.644
High density	306	81.2	
Equal density	69	18.3	
Low density	1	0.3	
Fat containing	1	0.3	
Mass long diameter *D*/mm	365	17.7 ± 6.4*	0.957
Mass short diameter *D*/mm	365	13.6 ± 5.4*	0.495
Calcification morphology	177		0.219
Amorphous	89	50.3	
Coarse heterogeneous	8	4.5	
Fine pleomorphic	52	29.4	
Fine linear or fine-linear branching	6	3.4	
Punctate	22	12.4	
Calcification distribution	25		<0.000 1
Diffuse	0	0.0	
Regional	2	8.0	
Grouped	16	64.0	
Linear	0	0.0	
Segmental	7	28.0	
Asymmetry	66		0.961
Asymmetry	0	0.0	
Global asymmetry	0	0.0	
Focal asymmetry	65	98.5	
Developing asymmetry	1	1.5	

*: Data are $\bar{x}\pm s$

不规则形（80.5%），54.7%肿块边缘表现为毛刺状。表现为无定形（50.3%）、集群分布钙化（64%）的患者人数分别占总人数的一半以上。有1例患者表现为进展性不对称，其余不对称患者均归为局灶性不对称。

在所有影像学特征中，肿块边缘和钙化分布的差异有统计学意义（*P*<0.001和*P*=0.005）。区域性钙化分布（图1）平均RS为39.9，明显高于段样钙化（24.4）和集群样钙化（31.8）（*P*<0.001，图2）。边缘清楚肿块（图3）的患者平均RS为17.4，明显低于肿块边缘表现为毛刺（27.4）、遮蔽（25.3）和模糊（28.5）的患者（图4）。

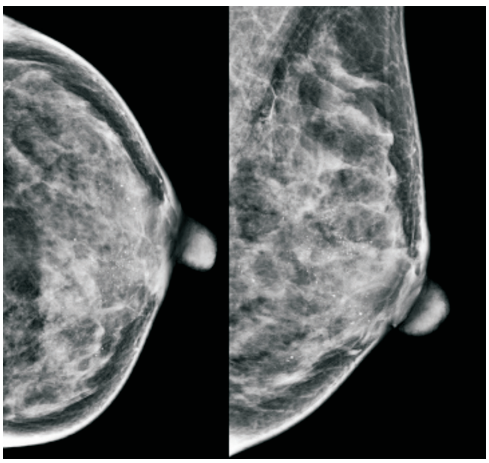

图 1 乳腺X线摄影区域分布钙化

Fig. 1 Regional calcifications on mammogram

Images in a 40-year-old woman whose breast tissue was heterogeneously dense. Mammogram showed regional fine pleomorphic calcifications in left breast. Postoperative pathology confirmed invasive ductal carcinoma and DCIS (RS=40.7)

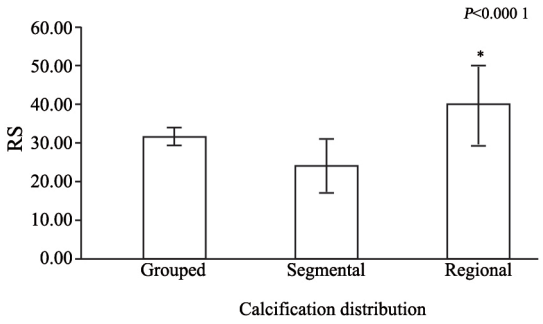

图 2 不同钙化分布组别RS比较

Fig. 2 Bar chart shows the average RS by using the calcification distribution

*: Regional calcification versus all other distributions

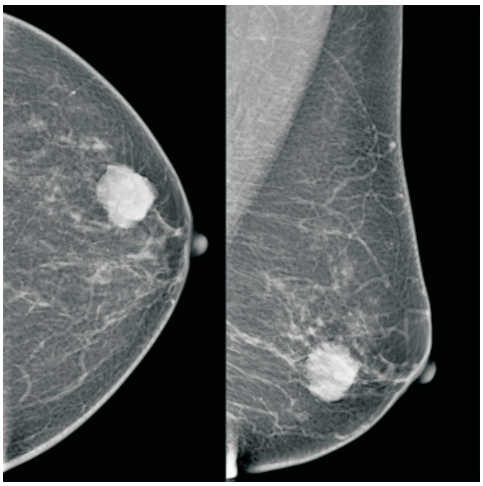

图 3　乳腺X线摄影边缘清楚肿块

Fig. 3　A mass with circumscribed margin on mammogram

Images in a 53-year-old woman whose breast tissue was almost entirely fatty. Mammogram showed a 27 mm×25 mm mass with circumscribed margins in lower outer left breast. Postoperative pathology confirmed pure mucinous breast cancer (RS=35.7)

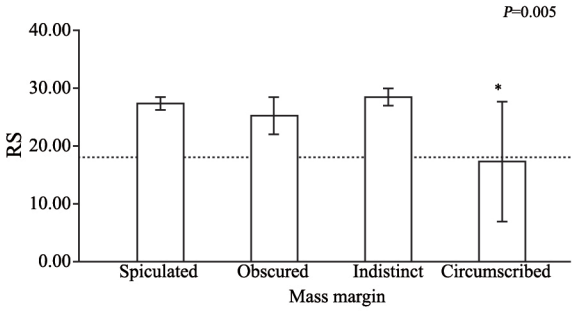

图 4　不同肿块边缘组别RS比较

Fig. 4　Bar chart shows the average RS by using the mass margin

*: Circumscribed mass margin versus all other margins

包含病理学类型、组织学分级、PR状态和DCIS分级的多元线性回归模型R^2为0.170，新加入钙化分布和肿块边缘后，肿块边缘在模型中仍有意义，且模型R^2从0.170上升到0.193。

3　讨　　论

影像基因组学是新兴的研究领域，在传统影像学和精准治疗之间架起了桥梁。目前，有关乳腺21基因影像组学的研究主要集中在MRI影像学方面[11, 14-15, 21-23]。乳腺X线摄影是一项重要的常规检查方法，具有价格低廉、快速和操作简便等优势。目前，乳腺X线摄影主要用于检测疾病、评估病灶良恶性和评估疗效，其对预后及化疗获益是否具有提示价值尚不清楚。因此，本研究旨在探究乳腺X线摄影影像学特征是否具有预测预后及化疗受益情况的价值。

本研究结果显示，钙化分布与RS之间具有相关性，区域分布钙化患者RS在所有钙化分布类型中分值最高，提示相较于线样分布和段样分布，区域钙化分布患者预后可能更差。先前多数研究主要涉及钙化形态而非钙化分布与预后的关系，这些研究提示伴有铸状（即细线状或细线分枝状）钙化乳腺癌或乳腺DCIS的患者预后可能更差[24-27]。一项纳入409例患者的研究[28]显示，钙化分布形式而非钙化形态与保乳术后患者的复发情况相关，这与本研究结果一致；然而，该研究进一步统计学分析显示，线样分布或段样分布患者保乳术后复发风险更大，与本研究结果不一致。此外，Woodard等[13]研究显示，钙化分布与RS之间没有明显相关性。因此，钙化分布是否与预后相关目前尚没有达成共识，还需要进一步研究。

本研究结果显示，边缘清楚肿块的患者RS最低，提示该分类患者相较于表现为其他肿块边缘的患者预后可能更好，这与常识一致，即边缘清楚肿块的恶性程度更低。本研究中不规则、遮蔽、模糊肿块边缘的患者之间RS未见明显差异，这与一些先前研究[18-19]的结果相一致。然而，Woodard等[13]研究显示，乳腺X线摄影图像上表现为边缘模糊肿块的患者RS最高，乳腺MRI图像上表现为边缘不规则肿块的患者RS明显高于边缘毛刺肿块的患者。

多元线性回归结果显示，肿块边缘对RS有独立预测价值，提示乳腺X线检查影像学特征具有提示患者预后及辅助治疗决策的潜在价值。本研究结果显示，尽管乳腺X线检查影像学特征尚不足以替代RS，但可能是RS替代指标的重要组成部分。

本研究有一些不足之处。首先，本研究仅包含乳腺X线摄影这一检查方法，信息量有限。未来需要包含乳腺X线摄影、乳腺MRI、乳腺超声等更为丰富的影像学信息的研究进一步探究影像学表现是否对乳腺癌患者预后具有提示价值。第

二，本研究为单中心、回顾性研究，仍需要大样本量、多中心及前瞻性研究进一步验证。最后，21基因RS作为患者预后的一种替代指标，仍有一定程度的不足，未来需要通过有关乳腺影像学特征与患者真实预后方面的研究进一步验证。

综上所述，乳腺X线摄影诸多特征中的钙化分布和肿块边缘对乳腺癌患者预后具有潜在预测价值。

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