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多模态影像技术评估乳腺癌术后复发的研究进展

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摘　要

乳腺癌是全世界女性最常见的恶性肿瘤，目前的治疗主要是以手术为主的综合性治疗。但是，手术后的复发或转移，是造成患者治疗失败以及死亡的主要原因。所以，提前预测乳腺癌术后复发的高危因素，并制定相应的干预措施，对进一步改善患者的预后有着重要意义。随着影像诊断技术的进步，X线、超声、MRI、CT及PET等影像学检查用于乳腺疾病的鉴别及诊断。现就影像检查技术方面评估乳腺癌术后复发的研究进展进行综述。

关键词

乳腺癌，多模态影像学，术后复发

Research Progress of Multimodal Imaging in Evaluating Postoperative Recurrence of Breast Cancer

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Abstract

Breast cancer is the most common malignant tumor in women all over the world, and the current treatment is mainly surgical-based comprehensive treatment. However, recurrence or metastasis

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after surgery is the main cause of treatment failure and death of patients. Therefore, predicting the risk factors of postoperative recurrence of breast cancer in advance and formulating corresponding intervention measures are of great significance to further improve the prognosis of patients. With the progress of imaging diagnosis technology, X-ray, ultrasound, MRI, CT and PET imaging examinations are used to identify and diagnose breast diseases. Here is to make a review on the research progress of imaging technology in evaluating postoperative recurrence of breast cancer.

Keywords

Breast Cancer, Multi-Modality Imaging, Postoperative Recurrence

1. 前言

乳腺癌因其高死亡率和发病率而成为女性关注的主要健康问题。即使进行辅助化疗，转移性乳腺癌的五年生存率也低于 30% [1]。最近由 IARC (国际癌症研究机构)从 185 个国家/地区生成的 GLOBOCAN 2018 数据报告了 230 万例乳腺癌新病例(11.7%)，死亡率为 6.9% [2]。乳腺癌发病率在高收入国家(571/100,000)比在低收入国家(95/10,000)更常见，这反映了与全球化的关联。乳腺癌是一种高度异质性的肿瘤，它的预后和治疗方案除了与肿瘤的大小、分级、区域淋巴结转移相关，还与生物学预后因子雌激素受体(ER)、孕激素受体(PR)、人表皮生长因子受体-2 (HER-2)、Ki-67 的表达和分子分型有关。其存在反映不同分子谱和临床病理学特征的各种生物学亚型[2] [3]。此外，除了组织学亚型基因表达谱将乳腺癌分为不同的分子亚型，即受体阳性(Luminal A、Luminal B、正常样和 HER-2 (人类表皮生长因子受体) 2 阳性)和受体阴性(TNBC (三阴性乳腺癌))或基底样) [4] [5] [6]。这些乳腺癌亚型具有不同的组织病理学和临床行为，并且与不同的年龄组和种族相关[4]，例如 TNBC 和 HER-2 阳性亚型，这些亚型在年轻人和绝经前尤为常见女性，在非裔美国人和亚洲女性中更为普遍，表现出更多的转移潜力和高复发率[7] [8] [9]。大多数乳腺癌的局部复发是可以治疗的，早期发现局部复发将改善患者的整体预后。目前乳腺 X 线钼靶摄影(mammography, MAM)、超声(Ultrasound, US)、磁共振(Magnetic resonance imaging, MRI)、18F-脱氧葡萄糖(18F-FDG)正电子发射断层扫描/计算机断层扫描(PET/CT)摄影(18F-fluorodeoxyglucose positron emission tomography/computed tomography, 18FDGPET/CT)等影像成像技术具有多种临床应用，能为疾病的诊断及复发转移提供相关依据，针对高危因素制定相应的干预措施，对改善患者预后具有重要的意义。

2. 乳腺癌影像学技术

2.1. 乳腺 X 线钼靶摄影

在全球范围内，大多数国家都认为乳腺癌最佳的筛查方式和手段是乳腺 X 线钼靶摄影(mammography, MAM)，欧美国家研究表明在欧美多个大型随机对照试验中，用乳腺 X 线钼靶摄影用来筛查乳腺癌，可以降低乳腺癌死亡率[10]。随着乳腺摄影技术也在不断发展，全数字化乳腺 X 线摄影(full field digital mammography, FFDM)，数字化断层乳腺摄影(digital breast tomography, DBT)和乳腺 X 线摄影对比增强能谱技术(contrast enhanced spectral mammography, CESM)等新技术相应出现。如今，数字乳腺摄影术(MG)

几乎完全取代了模拟乳腺摄影术，实现了高分辨率、高动态性以及快速数据和图像处理的高质量乳腺成像。然而，其检测乳腺癌的总体敏感性和特异性仍保持在62%~75% [10] [11] [12] [13] [14]。多数学者通过分析肿块的形态、边缘及肿块内部的微钙化等影像特征来判断疾病性质及预后，Haka 等人[15]利用拉曼光谱检测羟基磷灰石晶体结构中的碳酸盐取代度，得出钙化可以鉴别良性和恶性病变。除了在判断性质外，乳腺 X 线上钙化也可能提示患者的预后，在一项研究中，Tabar 等人[16]提出铸型钙化(微钙化中的一种形态)患者的死亡率远远高于此类肿瘤的预期死亡率(20 年生存率为 55%)。Ling 等人[17]发现，出现钙化的女性复发风险增加 2 倍，与无钙化的女性相比，死于乳腺癌的风险增加 2.4 倍。最新研究发现，乳腺 X 线钙化患者在保乳术后局部复发的风险比为 2.46，转移风险比为 2.24，死亡率为 2.5，钙化呈线性或节段性分布的患者尤其容易复发[18]。大多数的研究也强调了微钙化与复发风险增加之间的联系。相关文献提出钙化也可预测对新辅助治疗的反应，尽管目前证据相对较弱[19] [20] [21]。这些研究[19] [20] [21]中一致发现伴有钙化的乳腺肿瘤显示 HER-2 过度表达率增加，生存率降低，复发风险增加，肿瘤分级高，扩散或转移到淋巴结的可能性增加。可能是钙化的存在与 HER2 过度表达之间存在强烈的相关性。尽管有些研究对此存在一定分歧，但就目前大多数研究表明微钙化，尤其是铸型钙化，在预测恶性肿瘤风险、复发可能性起着至关重要的作用。

2.2. 超声(US)

超声成像是基于高频机械声波在组织中的传导和反射，将超声脉冲及其作为回波的反射信息转换并处理成实时图像。乳房超声是临床检查和乳房 X 线摄影的理想补充技术，它能够评估乳房切除术后的胸壁或重建的乳房。乳房超声也是评估区域淋巴结的绝佳工具。与乳房 X 线摄影相比，US 的检测性能不受致密乳腺组织的影响。US 的主要限制是大量非特异性或假阳性结果。弹性超声和对比增强超声(Contrast enhanced ultrasound, CEUS)也越来越多的应用在乳腺癌的性质及预后判断中。弹性超声可以通过测量组织的硬度来判断乳腺病变良恶性。一项对 127 名乳腺癌患者的前瞻性研究[22]表明，浸润性小叶癌和浸润性导管癌患者在超声毛刺、钙化、形态和后方回声衰减方面存在显著差异。Xu 等人[23]提出肿瘤最长/最短尺寸比(>1)、毛刺边缘和晕征与 ER 和 PR 的阳性表达有关。内坏死与 PR 的阴性表达有关。肿瘤大小、形态、后部回声类型及血流与 ER、PR、C-erbB-2 表达无显着相关性。据相关文献[24]提出超声后声增强与高组织学分级相关，超声图像中的后方特征代表了肿瘤的衰减特征。Choi 等人[25]提出在 ER 阳性、HER2 阴性、淋巴结阳性的浸润性乳腺癌患者中，超声图像中的后部特征可以预测复发的高风险。超声图像中的后方强化和后方阴影消失与复发风险高独立相关。

2.3. 磁共振成像(MRI)

磁共振成像具有多参数、多序列成像、高组织分辨力且无辐射损伤等特点，在这种背景下，磁共振成像(MRI)已成为一种功能强大、用途广泛且精确的成像技术。乳腺 MRI 是乳腺成像的重要工具，有多种适应证，例如术前分期、治疗监测、复发检测、评估乳房植入术后改变、高危女性筛查等。动态对比增强 MRI (CE-MRI)是检测乳腺癌最敏感的检测方法，具有良好的特异性[26] [27]。CE-MRI 可以综合性评价乳腺癌的整体肿瘤的细节，主要检测出肿瘤灌注和血管的形态学信息，在一定程度上还提供功能信息来判断肿瘤的异质性。而且，MRI 中的几种功能成像技术，如扩散加权成像和波谱成像等，可以在多个层面上可视化和量化癌症发展和进展的功能过程，并提供有关癌症特征的具体信息，如：新生血管、肿瘤微环境、受体状态、组织 PH 值等。这种利用多模态 MRI 技术能够突出区分恶性、良性和恶性病变，在提高诊断准确性的同时避免不必要的乳腺活检，并可对术后复发或转移进行评估和预测。此外，更高场强的应用(3T)已证明提高了乳腺癌检测的敏感性和特异性。

2.3.1. 动态对比磁共振(DCE-MRI)

动态对比增强主要通过形态学、动力学和灌注参数判断良、恶性，乳腺癌通常以不规则状、毛刺边缘和 III 型动力学曲线为特征。癌症发展和转移潜力的一个标志是肿瘤血管生成，即形成具有异常血管通透性的专用脉管系统的发展，支持对氧气和营养物质的高代谢需求，尤其是在侵袭性肿瘤中。DCE-MRI 能够在静脉注射钆螯合物后，通过评估乳腺动力学增强特征，把它作为肿瘤特异性特征来描述这种异常的血管和通透性。术前 DCE-MRI 上肿瘤周围实质增强可能反映微环境的状态，这与保乳治疗后癌症复发有关，Choi 等人[28]发现同侧全乳腺血管显著增加与早期乳腺癌复发相关，而中度或显著的肿瘤背景实质增强与晚期复发相关。Cheon. H 等人[29]的研究结果显示瘤周水肿的存在是与疾病复发相关的依赖因素。在与生物侵袭性肿瘤的特点(较高的 T 期、较高的 N 期、较高的肿瘤分级和较高的 Ki-67 指数)可能是导致肿瘤复发的原因。此外，在已知的临床－病理特征之外，瘤周水肿的存在显著改善了疾病复发的相关性。大多数文献报道，肿瘤周围水肿在三阴性乳腺癌中更常见[30]。在 DCE-MRI 上，大多数研究试图将形态学和动力学特征与病理标志物相关联。关于形态特征，乳腺癌的 Luminal A 和 B 亚型均为肿块样病变，边缘不规则，组织学分级为低级别或中低级别[31]。大多研究证明最显著的 DCE-MRI 参数是增强(肿瘤和背景实质乳房增强成像)。Kawashima 等人[32]进行的一项综合研究证明了 DCE-MRI 上的信号增强率是评估高 Ki-67 指数的独立预测因子，发现具有早期达峰时间(TTP)和较大峰值增强率(PER)的病变与较高的 Ki-67 指数相关。

2.3.2. 扩散加权成像(Diffusion Weighted Imaging, DWI)

DWI 可通过测量 ADC (apparent diffusion coefficient 表观扩散系数)值从分子水平检测组织水分子受限制的情况，间接反映组织细胞质和量的改变。水分子所处的微环境的差异导致了 ADC 值的不同，进而反映组织良恶性的差异。由于恶性肿瘤细胞密度高，比正常组织或良性肿瘤扩散更加受限对应更低的 ADC 值。ADC 值不仅有助于区分良、恶性，而且还可预测侵袭性生物标志物，可用于识别不同的肿瘤亚型、侵入性与非侵入性疾病、肿瘤受体状态和肿瘤分级。Shin 等人[33]提出 liminal B 型 ADC 值较低，并且 Ki-67 增值指数较高的乳腺癌的平均 ADC 值也较低。Kim [34]等人的研究也验证具有较低 ADC 值主要与 Luminal B 亚型预后较差的乳腺癌患者和较高 Ki-67 指数有关。

2.3.3. 扩散张量成像(Diffusion Tensor Imaging, DTI)

扩散张量磁共振成像可以绘制生物组织中水分子的扩散图，已由相关研究证明对病变检测、区分良恶性病变以及评估乳腺肿瘤的预后生物标志物非常有用。磁共振扩散成像的独特之处在于它能够在细胞水平上观察肿瘤细胞密度和微结构或微血管，而无需使用对比剂。它可以通过编码六个或更多方向的扩散来计算组织中水扩散的各向异性和方向性[35]。DTI 参数包括分数各向异性(FA)、平均扩散率(MD)和三个正交扩散系数(λ1、λ2、λ3)，可以提供有关乳腺微观结构和病理生理学的细微信息，有助于区分不同的病变。多项研究表明，与良性病变相比，DWI 衍生的表观扩散系数(ADC)值(DTI 协议中也称为 MD)在乳腺癌中显著降低，并提高了 DCE-MRI 区分癌症和良性病变的能力[36] [37]。然而，在一大群患者中，DTI 衍生参数是否具有与 DWI 相当的诊断准确性仍不清楚。此外，在已发表的研究中，DTI 对乳腺病变的鉴别仍存在一些争议。例如，大多数研究[35] [38] [39]表明，乳腺癌的 FA 值高于良性病变，MD、λ1、λ2 和 λ3 值低于良性病变，而 Partridge 等人[40] [41] [42]，恶性病变和良性病变之间的 FA 值没有统计学差异。在 Wang 等人的研究中，MD 而非 FA、体积比和相对各向异性值可以进一步区分浸润性乳腺癌(IBC)和导管原位癌(DCIS)，这在一定程度上降低了 DTI 的诊断可信度。在个别研究中，MD 或 FA 与 ER 状态、Ki-67 标记指数和组织学分级显著相关，并可检测乳腺癌患者的淋巴结血管浸润和腋窝淋巴结转移[35] [43] [44]。

2.3.4. 磁共振波谱成像(Magnetic Resonance Spectroscopy, MRS)

现代医学已经进入基因组精确治疗方法，需要了解肿瘤生物学及潜在过程。脂肪酸和脂质代谢失调是许多癌症包括乳腺癌恶性转化的典型组成部分。正常组织和恶性组织的脂质代谢差异使这些途径成为乳腺癌诊断和治疗的靶点。近年来的多项研究表明，质子磁共振波谱(1H-MRS)可以作为动态对比增强(DCE)MRI 的补充，在体内评估肿瘤代谢，从而提高乳腺肿瘤的诊断和定性。迄今为止，在乳腺成像中，MRS 的价值主要基于胆碱(Cho)代谢物的检测用于乳腺癌诊断[45] [46]以及新辅助化疗期间 Cho 代谢物变化的空间纵向监测[47] [48] [49]。Shin 等人[50]研究 184 例乳腺癌病人发现，浸润性癌中的胆碱峰较原位癌中高，并且胆碱的浓度与核分级、组织学分级及 ER 相关。然而，除了 Cho 代谢物外，其他相关代谢物(包括脂质)也可以通过 1H-MRS 进行检测和监测。因此，通过 1H-MRS 对脂质代谢的无创定量评估，可能有助于乳腺癌的诊断、表征和预后。

2.4. 18F-脱氧葡萄糖(18F-FDG)正电子发射断层扫描/计算机断层扫描(PET/CT)摄影

18F-FDG 正电子发射断层摄影是一种通过检测癌细胞中葡萄糖代谢水平对乳腺癌进行诊断、分期、评估治疗反应、再分期、预测预后的检查技术。18F-FDG PET/CT 具有解剖和代谢双重功能。全身评估可以通过一次成像完成，这对乳腺癌的诊断，尤其是判断乳腺癌的远处转移有很大的优势[51]。研究表明，PET/CT 成像中的参数包括患者病灶最大标准化摄取值(SUVmax)、代谢肿瘤体积(MTV)和总病灶糖酵解(TLG)与肿瘤的生物学行为密切相关。18F-FDG 高摄取提示肿瘤增殖旺盛，侵袭能力强，预后差。Kajary 等人[52]回顾性分析了 83 例乳腺癌患者 18F-FDG PET/CT 代谢参数与临床分期的相关性，表明肿瘤大小对 18F-FDG 代谢的影响，尤其是 TLG 的差异，TLG 可以反映肿瘤的生物学行为。Kaida 等[53]回顾性分析了 93 例乳腺癌患者的临床资料，发现原发肿瘤的 SUVmax、MTV 和 TLG 可随着组织学分级的增加而增加。Tchou J 等人研究指出 Ki-67 与 18F-FDG 摄取呈显著正相关[54] [55]。大多研究发现[55] [56] 18F-FDG PET/CT 对预测乳腺癌患者的预后有重要价值。多因素 logistic 回归分析显示，乳腺癌术前主要病灶的代谢参数 SUVmax、MTV 和 TLG 是术后 5 年内发生事件的独立危险因素。治疗前病变的代谢参数与复发率有关。原发病灶的代谢参数越高，复发和远处转移的可能性越大。

3. 总结及展望

综上所述，动态对比增强 MRI (DCE-MRI)是乳腺成像领域不可缺少的影像技术，可以提供形态学和一定程度的功能信息，具有多种临床适应症。同时结合功能性 MRI 参数，如扩散加权成像、扩散张量成像及磁共振光谱成像，以及正电子发射断层扫(PET)/MRI 和不同放射性示踪剂的多模态成像技术可以提供有关癌症发展和进展的潜在致癌过程的详细信息，并可以为早期预测乳腺癌术后复发提供依据。相信未来多模态成像技术将在癌症诊断及预后中发挥关键作用，为乳腺癌通过改进风险分层实现定制性治疗。

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