

CT 在肾错构瘤与肾细胞癌鉴别诊断中的应用及进展

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摘要:肾错构瘤(renal angiomyolipoma)与肾细胞癌(renal cell carcinoma)均为常见的肾脏肿瘤,但其治疗方案及预后却差异较大。电子计算机断层扫描技术(computed tomography, CT)作为肾脏肿瘤常用的术前诊断手段,在鉴别诊断这两种肿瘤时常存在影像特征重叠而导致误诊。本文综述了两种肾脏肿瘤的一般 CT 检查表现,并介绍一种新的肾错构瘤影像学分型,并探讨根据该新分型鉴别两种肿瘤的相关影像特征,最后总结了目前基于 CT 影像的高通量定量技术在鉴别两种肿瘤中的应用及进展,以期鉴别肾错构瘤与肾细胞癌提供新的思路。

关键词:肾错构瘤;肾细胞癌;电子计算机断层扫描技术;鉴别诊断;影像组学;机器学习
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Progress in Differential Diagnosis Between Renal Angiomyolipoma and Renal Cell Carcinoma Based on CT Scan

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Abstract: Renal angiomyolipoma and renal cell carcinoma are common kidney tumors, but have different treatment strategy and prognosis. Computed tomography (CT), as a common preoperative diagnostic method for kidney tumors, often shows overlapping of imaging features between these two tumors; which may lead to misdiagnosis. In this article, we demonstrate the common CT imaging features between renal angiomyolipoma and renal cell carcinoma; introduce a new radiologic classification for renal angiomyolipoma and discuss the imaging features to distinguish the two tumors with the new classification. The article also reviews the progress of a novel high-throughput quantitative technique based on CT imaging, which can improve the differential diagnosis between renal angiomyolipoma and renal cell carcinoma.

Key words: renal angiomyolipoma; renal cell carcinoma; computed tomography; differential diagnosis; radiomics; machine learning

肾血管平滑肌脂肪瘤(renal angiomyolipoma)常称为肾错构瘤,是肾脏最常见的良性肿瘤。大多数肾错构瘤含有大量的脂肪组织,临床可通过影像学检查确定肿物中脂肪组织的成像特征进行诊断^[1]。目前主动监视(active surveillance)仍是大多数肾错构瘤的一线选择^[2]。肾细胞癌(renal cell carcinoma),简称肾癌,在成人恶性肿瘤中发病比例为2%~3%,占肾恶性肿瘤的85%^[3]。肾癌的组织病理学分型很多,主要有三种:肾透明细胞癌、乳头状肾细胞癌和肾嫌

色细胞癌,而当中又以肾透明细胞癌最常见^[4]。且肾透明细胞癌中常缺乏脂肪组织的局灶性沉积^[5]。到目前为止,外科手术一直是局限性肾癌的首选治疗方案^[6]。肾错构瘤与肾细胞癌相比,大部分患者可采取主动监视的保守方案,而无需立即行手术治疗。可见两种肿瘤在治疗与预后中均有较大差异,因此有效鉴别肾错构瘤与肾细胞癌,对临床制定治疗方案具有重要的指导意义。

电子计算机断层扫描技术(computed tomography, CT)是肾错构瘤与肾癌的常规诊断方法之一,具有无创、直观、准确性较高等优势^[7-8]。但肾错构瘤与

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肾癌的 CT 影像特征仍会出现重叠^[9]。因此,充分了解有利于辨别肾错构瘤与肾癌的 CT 影像学特征及该领域的进展对临床工作者很有必要。

1 肾错构瘤与肾癌的 CT 影像学表现

1.1 肾错构瘤的 CT 影像学表现

典型的肾错构瘤影像检查可显示肿瘤内脂肪,CT 值因含有较多脂肪可呈现负值,多可由此与其他肾脏肿瘤相鉴别^[10-12]。当瘤体突出于肾外生长时,CT 影像还可出现“杯口征”与“劈裂征”^[13]。而大约 5% 的肾错构瘤由于脂肪含量太少,很难在手术治疗或有创检查前通过影像学检查初步诊断,这类肾错构瘤常被称为乏脂肪肾错构瘤^[1,12,14-15]。乏脂肪肾错构瘤的 CT 平扫常表现出均一的高密度^[12,16]。而在增强扫描时,典型的乏脂肪肾错构瘤通常在肾皮质期出现早期的快速明显强化,肾实质期及排泄期表现为强化减退^[17-19]。由于这类肾错构瘤血管较丰富,所以会表现为“快进快出”这种一过性强化,与肾透明细胞癌的 CT 影像学表现相近^[20]。Hakim 等^[17]发现约 33% 的乏脂肪错构瘤会出现渐进性强化的模式,与乳头状肾细胞癌相似。

1.2 肾癌的 CT 影像学表现

根据 2016 年世界卫生组织(WHO)肾脏肿瘤分型^[4],共有 14 种分型,其中肾透明细胞癌、乳头状肾细胞癌和肾嫌色细胞癌这 3 种亚型占据了肾癌的 90% 以上,因此研究者会更加关注于这三种肾癌的影像学特征^[21-23]。①肾透明细胞癌:由于典型的肾透明细胞癌的胞质疏松透明,且瘤内常因为出血、坏死和囊变而显示出异质性^[24],故在平扫时 CT 值较低^[25]。而肾透明细胞癌血流丰富,所以皮质期出现明显强化,高于乳头状肾细胞癌和肾嫌色细胞癌,最后在实质期和排泄期强化效应明显降低,总体呈“快进快出”的特征^[16]。②乳头状肾细胞癌:典型的乳头状肾细胞癌常表现为血供较少且具有同质性,因此皮质期呈轻度或轻中度强化^[26-27],且强化效应减退慢,呈“渐进式强化”,并且双侧或多中心性的病灶较其他亚型的肾癌更多见^[25]。③肾嫌色细胞癌:这类肾癌起源于润细胞,在增强 CT 中显示出均一的、轻至中度强化,且由于肾嫌色细胞癌的血供一般介于肾透明细胞癌及乳头状肾细胞癌之间,因此其强化程度亦介

于两者之间^[24-25];若肿瘤体积较大时,还可见中央星状瘢痕与节段强化反转^[28]。而该肿瘤内少见出血、坏死及囊变^[24]。

2 肾错构瘤与肾癌的鉴别

Jinzaki 等^[12]根据临床特征、影像特征、组织学特征以及基因特征对肾错构瘤进行了分型,但这种分型过于复杂,需要的特征类型繁多,难以在实际临床工作中应用。后来,Song 等^[29]根据肾错构瘤的影像学特征提出了一种更简化、易用的新分型,该分型将肾错构瘤分为三种亚型:脂肪富含型错构瘤(fat-rich angiomyolipoma)、脂肪缺乏型错构瘤(fat-poor angiomyolipoma)和脂肪不可见型错构瘤(fat-invisible angiomyolipoma)。现针对这三种亚型的肾错构瘤以及易与其相混淆的肾癌的鉴别进行探讨。

2.1 脂肪富含型肾错构瘤与含脂肪肾癌

脂肪富含型错构瘤被定义为在 CT 平扫下,病灶的 CT 值小于等于 -10HU^[29]。这一亚型涵盖了约 95% 的肾错构瘤^[14]。虽然这种典型的肾错构瘤因含有丰富的脂肪而很容易在 CT 平扫中被诊断,但有极少数肾癌也会含有脂肪成分^[30-32],因此临床工作者也需要了解如何鉴别这两种肿瘤。首先,含脂肪肾癌的体积一般较大,根据文献报道,其中最大直径可达 13cm^[30-36],而肿瘤内脂肪的含量却相对较少且较分散,平均脂肪体积小于 1cm^[30-36]。因此,肿瘤体积大而瘤内脂肪含量较少可能是含脂肪肾癌的一个特征。另外,影像学检查常可探测到含脂肪肾癌内有钙化^[33-34,36]或坏死^[31,36]。所以如果含脂肪的肾肿瘤内有钙化或坏死灶,则推荐行经皮穿刺活检以排除肾癌的可能性^[37]。

2.2 脂肪缺乏型肾错构瘤与肾透明细胞癌

约有 5% 的肾错构瘤内仅含有很少量的脂肪成分^[14],这类肾错构瘤按照 Song 等^[29]的分型被称为脂肪缺乏型或脂肪不可见型错构瘤。其中脂肪缺乏型错构瘤被定义为在 CT 平扫中,病灶的 CT 值大于 -10HU,但肿瘤/脾脏比值小于 0.71 或在磁共振化学位移成像(chemical-shift MR)中信号强度指数(signal intensity index)高于 16.5%。可以看出,Song 等新分型中的脂肪缺乏型肾错构瘤与许多文献中提到的乏脂肪肾错构瘤有很大不同^[38-39]。但是部分肾透明细

胞癌由于胞浆内含有丰富的脂质,可导致肿瘤/脾脏比值亦小于 0.71 或信号强度指数也高于 16.5%^[18,40-42]。鉴于肾透明细胞癌是常见的肾恶性肿瘤,因此准确鉴别脂肪缺乏型肾错构瘤与肾透明细胞癌是有必要的。在 CT 平扫中,脂肪缺乏型错构瘤由于含有丰富的肌肉成分而显示出高密度^[1,18,43],而肾透明细胞癌却因为含有丰富的胞浆内脂质而显示出低密度^[43-44]。而增强 CT 不适用于鉴别这两种肿瘤,因为两者均会显示不均匀强化^[1,45-46]。脂肪缺乏型错构瘤可以根据血管数量表现出不同程度的增强。当血管数量较少时,强化程度比肾透明细胞癌弱^[47]。当血管数量较多时,强化程度与肾透明细胞癌相似^[48]。虽然这两种肿瘤似乎在 CT 平扫等影像学检查中可以相鉴别,但是否需要进行穿刺活检仍存在争议^[9]。

2.3 脂肪不可见型肾错构瘤与非透明细胞肾癌

脂肪不可见型肾错构瘤被定义为在 CT 平扫中,病灶的 CT 值大于-10HU,但肿瘤/脾脏比值大于等于 0.71 或在磁共振化学位移成像中信号强度指数小于等于 16.5%。许多非透明细胞肾癌也会在 CT 或 MRI 上显示这样的特征^[18,37,49],而肾透明细胞癌却很少出现这样的影像特征^[18]。因此,在临床工作中对脂肪不可见型肾错构瘤与非透明细胞肾癌进行有效鉴别是很有必要的。但是,CT 并不能有效地鉴别这两种肿瘤,CT 平扫显示两者均为均匀的高密度,增强 CT 上两者均显示均匀且持续的强化^[1,14,18,50]。而磁共振成像等影像学检查也不能直观地提供有效鉴别两种肿瘤的信息,因此这种情况下需要经皮穿刺活检以明确诊断^[18,37,49,51-52]。

3 CT 鉴别肾癌与肾错构瘤的进展

目前为止,对乏脂肪肾错构瘤与肾癌的鉴别仍缺乏一种有效、无创、个体化的工具。并且传统的影像学由于受成像特点及主观因素影响,对乏脂肪肾错构瘤与肾癌的鉴别诊断具有局限性。因此,目前越来越多的研究者将目光聚集到基于大数据的高通量定量分析上,以更好地解决这些难题。

3.1 纹理分析

纹理分析是通过影像学检查图像的灰度级和(或)像素强度直方图研究病变组织的异质性的图像后处理技术,可使肉眼难以探查的细微差异得以量

化^[53]。Yang 等^[54]对 56 例患者的 CT 图像进行了纹理分析,其中包括 32 例乏脂肪肾错构瘤及 24 例肾嫌色细胞癌,共提取了 177 个二维特征及 183 个三维特征;之后利用最小绝对收缩和选择算子(least absolute shrinkage and selection operator,LASSO)回归模型进行特征筛选;最终得到由 5 个二维特征和 8 个三维特征分别构建的二维及三维的 CT 纹理分析模型,其曲线下面积(area under the curve,AUC)值分别为 0.811 和 0.915,证明这两种基于增强 CT 的模型可有效地鉴别乏脂肪肾错构瘤与肾嫌色细胞癌。李清等^[55]回顾性分析了 16 例乏脂肪肾错构瘤与 79 例肾透明细胞癌的 CT 增强图像,通过纹理分析认定标准差、熵、不均匀度三个参数是鉴别两种肿瘤的有效指标。同时 3 个指标联合的灵敏度可达 87.5%,标准差联合熵的特异性和准确度均较高(81.0%和 80.0%)。该实验表明部分纹理参数(标准差、熵、不均匀度)可以用于鉴别乏脂肪肾错构瘤与肾透明细胞癌,进而为临床治疗方案的制订提供重要指导参考。

3.2 影像组学

2012 年 Lambin 等^[56]首次提出影像组学的概念。影像组学通过对病灶的分割、特征数据提取、数据库的建立和个体化数据的分析逐步实现,是一种从标准医疗影像中提取量化图像特征并应用于临床决策支持系统中,以提高诊断及预测预后准确性的技术^[57]。Nie 等^[58]纳入了 99 例病例,其中包含 36 例乏脂肪错构瘤和 63 例均质肾透明细胞癌(homogeneous clear cell renal cell carcinoma),并对入组病例增强 CT 的皮质期与实质期图像进行影像组学特征提取,随后由 LASSO 回归从 2818 个影像组学特征中最终筛选出 14 个特征以构成影像组学分类器并计算影像组学风险评分(radiomics score),该分类器在训练组及验证组中的 AUC 值分别为 0.879 和 0.846;同时根据多因素 Logistic 回归筛选出临床独立危险因素,并最终与影像组学风险评分组合构成影像组学-临床复合预测模型,复合模型在训练组及验证组中的 AUC 分别为 0.896 及 0.949。说明该研究所构建的模型能有效鉴别乏脂肪错构瘤和均质肾透明细胞癌。Ma 等^[59]除了构建了基于增强 CT 的影像组学模型来鉴别乏脂肪肾错构瘤与肾透明细胞癌,还进行了传统 CT 的定量及定性特征分析,并最

后筛选出成角交界(angular interface)、囊性改变和假包膜三个影像学特征以构成传统 CT 分析模型,其 AUC 值为 0.935。最后,利用影像组学风险评分与传统 CT 影像特征构建 Logistic 预测模型,其 AUC 为 0.988,高于传统 CT 分析模型。说明加入影像组学的相关因素可使模型的准确性得到一定提高。

3.3 机器学习

人工智能(artificial intelligence, AI)影像分析技术的发展为解决个体化、精准化诊疗提供了一个全新的方案。而机器学习(machine learning)是达成 AI 的一种途径,可发掘许多肉眼不易观察到的肿瘤信息,并且能在短时间内对大量的医疗数据进行数据分析、建模和训练,探究数据信息中的通用模式,最后通过训练后的模型来预测并辅助诊断疾病,预测治疗反应及预测预后等^[60-61]。Yang 等^[62]提取了 118 例肾癌及 45 例乏脂肪错构瘤患者多相 CT 的 4 个 CT 期(非增强期、皮质期、实质期和排泄期)的影像纹理特征,并经过观察者间一致性评价后,最终在每个 CT 期均筛选出 103 个候选特征,并经过一定的排列组合后进一步得出了 15 种特征集。同时,本研究选择了 28 种特征选择方法(feature selection strategy)和 8 种分类器(classifier),共组合出 224 种鉴别模型。最终根据 AUC 值、准确度、灵敏度以及特异性 4 种指标,进行了 3360(15×224)种特征选择方法与分类器之间的相互选择,筛选得出 CT 非增强期中所得出的特征对鉴别肾癌及乏脂肪肾错构瘤的效果最好;并同时得出“支持向量机(support vector machine, SVM) 分类器+ t_score 特征选择方法”或“SVM 分类器+relief 特征选择方法”两种鉴别模型均拥有最高的 AUC 值(0.90),是鉴别两种肿瘤最佳的模型。随后用 CT 非增强期的 103 个特征作为特征输入,对 224 种鉴别模型的表现进行评估并得出相应 AUC 值;在 AUC 值大于 0.85 的所有鉴别模型中,根据 CT 非增强期中每个特征在五折交叉验证(five fold cross-validation)中被选为前 20 个特征的次数,从中筛选出 10 个特征用于鉴别肾癌与乏脂肪肾错构瘤,其中包括 1 个 Shape-based 特征、5 个 First-order-based 特征和 4 个 Texture-based 特征。由此可见,机器学习的应用可进一步提高大数据的分析与建模的效率,并进一步量化人类无法检测到的影像信息,从而补充临床决策。

4 总结与展望

由于肾癌与肾错构瘤的治疗方案与预后不同,两者的术前鉴别诊断具有重大意义。传统 CT 检查作为术前鉴别两种肾脏肿瘤的主要手段之一,却存在一定局限,为临床诊疗带来困扰。而与此同时,影像组学与 AI 等相关高通量定量技术的出现与发展,可为解决这类困扰提供帮助。但目前大部分相关初始工作受限于单一中心、样本量小、算法单一、开发成本较高和患者隐私保护等一系列问题,导致这类技术的临床应用受阻^[63]。但随着肾脏肿瘤诊疗服务需求以及诊疗服务产生数据的不断增加,高通量定量技术正好为临床诊疗流程的优化和简化提供了一种方案,因此影像组学与 AI 等技术会成为未来临床诊疗的一种重要辅助工具。

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