

影像组学在胰腺疾病中的应用进展

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【摘要】 影像组学是指从横断面影像学资料中获取定量特征并分析这些数据以支持临床决策。近 10 年来, 影像学在疾病诊断与治疗过程中的地位极大提高, 与此相关的研究数据也呈指数增长, 可供临床医师进行更有意义的探索。胰腺疾病, 包括胰腺癌、胰腺囊性肿瘤和胰腺神经内分泌肿瘤等, 需要复杂的临床决策, 这一直是影像组学研究的热点和难点。随着胰腺疾病影像组学的迅速发展, 患者和临床医师有望在短期内受益。影像组学已在判断肿瘤表型、疾病生物学和患者预后方面崭露头角, 即将成为胰腺疾病患者诊断与治疗的有力工具。

【关键词】 胰腺疾病; 影像学; 影像组学; 肿瘤生物学

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The current state of radiomics in pancreatic disease

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【Abstract】 Radiomics is the extraction of quantitative features from cross-sectional imaging and analysis of these data for decision support. As the role of medical imaging in patient care has increased exponentially over the past decade, so too have the data associated with these studies, allowing for more robust and meaningful exploration. Diseases of the pancreas requiring complex decision making including pancreatic cancer, pancreatic cystic neoplasms, and pancreatic neuroendocrine neoplasms, are the active subjects of radiomics research, and patients and clinicians stand to benefit from development of this technology in the near term. Radiomics has already revealed novel insights into tumor phenotype, disease biology, and patient outcomes, and will continue to become a more powerful tool in the care of patients with pancreatic disease.

【Key words】 Pancreatic diseases; Radiology; Radiomics; Tumor biology

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近几十年来, 随着影像学检查手段在人类疾病诊断与治疗中的作用愈加突出, 研究人员和临床医师开始探索从视觉以外的角度解读影像学资料, 其起源可追溯至 20 世纪 60 年代早期的计算分析^[1]。

影像学的现代定量分析则在 20 世纪 80 年代开始扎根^[2]。研究人员和临床医师开始意识到标准的横断面医学影像学资料(CT、MRI、PET 检查)中包含大量可挖掘的高维数据, 这些数据可用于深入了解成像组织的病理生理学, 这一过程被称为影像组学^[1,3]。

早期的定量图像分析催生了计算机辅助诊断(computer aided diagnosis, CAD)系统, 该系统最先在乳腺肿瘤学领域中取得成功^[3-4]。开发这些系统旨在回答一些基本问题, 例如在某影像学检查图像中是否存在病变或癌症。与 CAD 系统比较, 影像组学可从影像学检查图像中获取无数定量特征, 并利用复杂的算法或机器学习生成和验证假设^[5]。影像组学可综合分析影像学特征(例如亮度、形状、纹理等)以及临床和基因组数据, 这已远远超出早期 CAD 系统所解决的范围, 并且能够非侵入性地探究癌症表型和患者预后^[6-7]。笔者回顾几种胰腺疾病诊断与治疗中影像组学的应用现状, 并介绍该领域的未来发展前景。

1 胰腺导管腺癌

由于胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)预后极差且治疗反应个体差异大, 一直是胰腺影像组学研究的焦点。临床医师和研究人员分析了目前标准治疗下影像学检查中包含的大量数据, 以期更好地了解患者的疾病生物学并预测其对治疗的反应。Chakraborty 等^[8]进行生存预测的早期尝试, 通过 PDAC 患者的术前 CT 扫描预测其 2 年生存率。该研究纳入的 35 例患者接受基于吉西他滨方案的新辅助化疗后进行手术切除和吉西他滨辅助化疗。研究者分析了治疗前 CT 扫描中肿瘤区域的 255 个一阶参数、二阶参数和基于边缘的纹理特征, 并根据这些特征创建了多种算法, 将患者分为短期组和长期生存组(分别定义为生存时间 < 2 年或 ≥ 2 年)。在所有特征中, 基于方向边缘的角度共生矩阵模型区分能力最强, 受试者工作特征曲线下

面积高达 0.90, 准确度为 82.9%。导致生存差异的具体原因尚不清楚。有研究者假设驱动基因和肿瘤-基质相互作用可能造成 CT 检查上发现的纹理差异以及患者中观察到的生物学行为^[9-10]。

在 Memorial Sloan Kettering 癌症中心进行的一项后续研究将这一方法扩展到 161 例未经化疗的患者, 并将影像组学分析手术前后 CA19-9、术后 Brennan 评分的临床数据相结合^[11]。虽然 CA19-9 单独产生的一致性指数较弱, 仅为 0.51 (仅略优于偶然结果, 综合 Brier 评分为 0.165), 但在生存模型中加入影像学纹理特征后可将一致性指数增加至 0.68 (综合 Brier 评分为 0.141)。当加入术后病理学特征时, 一致性指数进一步增加至 0.74 (综合 Brier 评分为 0.20)。这项研究证明影像组学在生存评估方面的潜力, 但其临床应用仍受到限制, 因为基于术前可用数据的模型尚不足以手术和新辅助化疗的决策提供指导。然而, 该研究确实为进一步前瞻性研究提供了方向, 并整合了基因测序和组织学数据。在接受立体定向放射治疗的患者中, 也有类似结果报道: 病灶局部控制 (一致性指数 0.75, $P=0.004$) 以及总体生存 (一致性指数 0.75, $P=0.05$) 的影像组学预测模型预测能力均较强^[12]。不止一项研究探讨了 CT 纹理特征预测新辅助化疗治疗反应的能力, 早期研究结果显示: 首次 CT 检查的定量参数可以预测新辅助化疗的组织学反应, 且在 PDAC 手术患者中优于 CA19-9^[13]。但这一结论还需更多研究证实。

影像组学分析也被用于预测接受化疗的局部进展期和转移性胰腺癌患者的生存情况^[14-15]。Sandrasegaran 等^[14]的研究结果显示: 对于局部进展期和转移性胰腺癌患者, 原发肿瘤异质性的 CT 纹理分析, 包括阳性像素平均值 (mean value of positive pixels, MPP) 和峰度, 是影响总体生存情况的独立因素。具体而言, $MPP > 31.625$ 或峰度 > 0.565 患者的中位生存时间 $<$ 整个队列。其作者提出: 原发肿瘤异质性的增加可能是由于基因表达差异、血管生成、缺氧和微坏死的变异, 这些均可能影响肿瘤对全身和局部治疗的反应能力^[16-17]。以上结果与前期肿瘤异质性在食管癌、结肠直肠癌和非小细胞肺癌中作用的研究结果一致, 证明了肿瘤异质性与患者总体生存情况之间的负相关性^[18-22]。

2 胰腺囊性肿瘤

PDAC 对临床医师的挑战主要在治疗方面, 而胰腺囊性肿瘤 (pancreatic cystic neoplasm, PCN) 的

难点主要在于诊断。 $>2\%$ 的正常人群存在胰腺囊肿, 但其中仅有很少一部分会发展为恶性肿瘤^[23]。目前, 用于识别高风险病变的临床指南较为繁杂, 通常需要借助侵入性的影像学检查或活组织检查, 且在多个学术组织之间存在争议^[24-25]。所幸的是, 随访监测和术前影像学检查提供了大量的数据, 可用于该领域的影像组学研究。最终通过影像组学数据鉴别高风险和低风险 PCN, 只对具有显著恶性潜能的患者行手术切除, 对低风险病变患者仅观察随访。

MD 安德森癌症中心进行的一项早期研究纳入 53 例导管内乳头状黏液性肿瘤行手术切除患者, 通过分析术前 CT 检查结果, 以区分重度与轻度不典型增生的患者^[26]。该团队在术前 CT 扫描的病灶中提取了 360 个影像特征 (包括熵、对比度、1D 和 2D 灰度强度分布的峰度等) 进行分析。预测能力最强的“影像学标志”在区分重度与轻度不典型增生时, 受试者工作特征曲线下面积可达 0.86 (灵敏度为 85%、特异度为 68%)。且当组合多个指标建立“影像学生物标记组”时, 受试者工作特征曲线下面积高达 0.96 (灵敏度和特异度分别为 97% 和 88%)。研究者认为: 福冈指南有约 36% 的假阳性率, 该方法与之比较更具优势^[25]。

分支胰管型导管内乳头状黏液性肿瘤的恶性潜能低于主导管型导管内乳头状黏液性肿瘤。一项研究纳入 103 例手术切除的分支胰管型导管内乳头状黏液性肿瘤患者, 其中 74% 的切除标本是低风险病变, 26% 是高风险病变^[27]。研究者通过临床和影像学特征建立风险预测模型, 试图在术前识别高风险病变, 其研究结果显示: 单纯基于影像学定量数据模型的预测能力已超过临床参数模型 (受试者工作特征曲线下面积为 0.76 比 0.67)。当联合术前影像组学和临床数据建立风险预测模型时, 结合两种模型的优势, 总体受试者工作特征曲线下面积增加至 0.79。笔者认为: 未来预测高风险导管内乳头状黏液性肿瘤的模式将会纳入临床信息、基因和细胞学标志物以及影像学数据, 以更全面地评估患者病灶。

只有极少数 PCN 需行手术切除, 因为它们几乎没有进展或恶变的风险, 尤其是浆液性囊性肿瘤 (serous cystic neoplasm, SCN)。虽然大多数外科医师认为 SCN 通常应该非手术治疗, 但临床上 SCN 诊断的准确率很低, $>50\%$ 的患者接受了不必要的手术切除^[28-31]。Wei 等^[32]分析 260 例 PCN 行手术切除患者的影像学资料, 包括 102 例 SCN, 74 例导管内乳头状黏液性肿瘤, 35 例黏液性囊性肿瘤, 49 例实

性假乳头状瘤,并以此建立 CAD 预测模型以协助临床诊断。其研究结果显示:在 102 例行手术切除的 SCN 中,临床医师术前仅正确诊断出 31 例(30.4%),这表明大量患者接受了不必要的手术。研究者在 409 个提取的影像学特征中,选择 22 个用于 CAD 建模,最终受试者工作特征曲线下面积为 0.837。在进行了额外的数据收集和验证后,作者设想将这一 CAD 模型整合到临床路径中,为基于影像学的临床诊断提供参照,以减少对这些良性病变的过度治疗。

3 胰腺神经内分泌肿瘤

胰腺神经内分泌肿瘤(pancreatic neuroendocrine neoplasm, PNEN)在诊断和治疗方面均具挑战性。对于 PNEN 患者,临床医师根据其增殖能力(Ki-67 指数或核分裂象)判断级别,再综合考虑肿瘤直径大小,决定相应的诊断与治疗策略^[33]。大多数病灶较小的低级别肿瘤仅需随访观察^[34]。术前可通过超声内镜引导下细针穿刺(endoscopic ultrasound-guided fine-needle aspiration biopsy, EUS-FNA)检查对肿瘤分级进行评估,但术前活组织检查有 10%~20%的误诊率^[35]。影像组学是一种非侵入性分期方法,可预测 PNEN 的侵袭性并最终指导手术治疗。

在麻省理工大学总医院的一项早期研究中,研究者结合定性和定量影像学检查结果(CT 扫描)进行 PNEN 术前分期^[36]。该研究结果显示:除了典型的影像学表现(例如肿瘤直径>2 cm、血管受累、胰管扩张和淋巴结肿大等)之外,肿瘤纹理熵亦可预测分级和无进展生存时间。在结合熵和标准 CT 特征建立模型后,G1、G2、G3 级肿瘤区分的准确度为 79.3%。熵值>4.65 的肿瘤最终为高级别(G2 级和 G3 级)的概率是熵值较低肿瘤的 3.7 倍。高肿瘤熵也是无进展生存时间的独立预测指标($\chi^2 [df, 1] = 4.4, P = 0.037$)。该研究者认为:采样误差或标本处理可能导致 EUS-FNA 检查对肿瘤侵袭性的误判,而该影像组学模型的准确性与 EUS-FNA 检查相当;这些影像学标志在患者的手术决策中将扮演重要角色。

D'Onofrio 等^[37]的一项后续研究建立了仅使用 CT 纹理特征的肿瘤级别预测模型。研究者分析 100 例行手术切除的 PNEN 患者的 CT 扫描结果,从中获取定量影像学特征(如增强比、标准化增强率和肿瘤渗透率)以及肿瘤纹理特征(平均值、方差、偏度、峰度和熵等)。增强比和通透性指数均可区

分 G1、G2、G3 级肿瘤。而采用 CT 纹理分析进行区分的准确性更高,尤以峰度为甚,可区分 PNEN 的所有级别。对于 G3 级肿瘤的诊断,峰度受试者工作特征曲线下面积高达 0.924,灵敏度和特异度分别为 82%和 85%。虽然以上研究结果还需要进一步的前瞻性验证,该研究者设想:在影像学诊断 PNEN 的同时,临床医师就可通过影像组学方法预测肿瘤级别,协助手术决策。

4 结语

随着影像学检查的图像质量日益提高、临床应用渐趋广泛,笔者认为:对这些图像中包含的数据进行严格和系统的分析,不仅可以为胰腺疾病的病理学诊断及疾病生物学开拓更多思路,且其分析结果可为判断预后提供更多线索。众多研究已经证实影像组学在判断 PDAC 生物学特性、预测治疗反应方面的应用前景。此外,对于诊断和预后判断均相对复杂的 PCN 和 PNEN,影像组学也可以提供更多信息以协助临床决策。随着大样本影像组学研究的深入开展,其在胰腺疾病诊断与治疗中的作用必将愈发重要。

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参 考 文 献

- [1] Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data[J]. *Radiology*, 2016, 278(2):563-577. DOI:10.1148/radiol.2015151169.
- [2] Avanzo M, Stancanello J, El Naqa I. Beyond imaging: The promise of radiomics[J]. *Phys Med*, 2017, 38:122-139. DOI:10.1016/j.ejmp.2017.05.071.
- [3] Doi K. Computer-aided diagnosis in medical imaging: historical review, current status and future potential[J]. *Comput Med Imaging Graph*, 2007, 31(4-5):198-211. DOI:10.1016/j.compmedimag.2007.02.002.
- [4] Giger ML. Update on the potential role of CAD in radiologic interpretations: are we making progress? [J]. *Acad Radiol*, 2005, 12(6):669-670. DOI:10.1016/j.acra.2005.05.004.
- [5] Lambin P, Leijenaar RTH, Deist TM, et al. Radiomics: the bridge between medical imaging and personalized medicine [J]. *Nat Rev Clin Oncol*, 2017, 14(12):749-762. DOI:10.1038/nrclinonc.2017.141.
- [6] Gatenby RA, Grove O, Gillies RJ. Quantitative imaging in cancer evolution and ecology[J]. *Radiology*, 2013, 269(1):8-15. DOI:10.1148/radiol.13122697.
- [7] Aerts HJ. The potential of radiomic-based phenotyping in precision medicine: A review[J]. *JAMA Oncol*, 2016, 2(12):1636-1642. DOI:10.1001/jamaoncol.2016.2631.
- [8] Chakraborty J, Langdon-Embry L, Cunanan KM, et al. Preliminary study of tumor heterogeneity in imaging predicts two year survival in pancreatic cancer patients [J]. *PLoS One*, 2017, 12(12):e0188022. DOI:10.1371/journal.pone.0188022.

- [9] Bailey P, Chang DK, Nones K, et al. Genomic analyses identify molecular subtypes of pancreatic cancer [J]. *Nature*, 2016, 531 (7592):47-52. DOI:10.1038/nature16965.
- [10] Waddell N, Pajic M, Patch AM, et al. Whole genomes redefine the mutational landscape of pancreatic cancer [J]. *Nature*, 2015, 518(7540):495-501. DOI:10.1038/nature14169.
- [11] Brennan MF, Kattan MW, Klimstra D, et al. Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas [J]. *Ann Surg*, 2004, 240(2):293-298. DOI:10.1097/01.sla.0000133125.85489.07.
- [12] Cozzi L, Comito T, Fogliata A, et al. Computed tomography based radiomic signature as predictive of survival and local control after stereotactic body radiation therapy in pancreatic carcinoma [J]. *PLoS One*, 2019, 14(1):e0210758. DOI:10.1371/journal.pone.0210758.
- [13] Seiser N, Jennifer M, Dewan R, et al. A Novel Imaging Biomarker for Assessment and Prediction of Response to Neoadjuvant Chemotherapy in Patients with Resectable Pancreatic Cancer: CT-Derived Texture Analysis [J]. *Society of Surg*, 2018, 25(1):29. DOI:10.1245/s10434-018-6349-1.
- [14] Sandrasegaran K, Lin YN, Asare-Sawiri M, et al. CT texture analysis of pancreatic cancer [J]. *Eur Radiol*, 2019, 29(3):1067-1073. DOI:10.1007/s00330-018-5662-1.
- [15] Cheng SH, Cheng YJ, Jin ZY, et al. Unresectable pancreatic ductal adenocarcinoma: Role of CT quantitative imaging biomarkers for predicting outcomes of patients treated with chemotherapy [J]. *Eur J Radiol*, 2019, 113:188-197. DOI:10.1016/j.ejrad.2019.02.009.
- [16] Logothetis CJ. Re: intratumor heterogeneity and branched evolution revealed by multiregion sequencing [J]. *Eur Urol*, 2013, 64(1):170. DOI:10.1016/j.eururo.2013.04.025.
- [17] Nelson DA. Hypoxia and defective apoptosis drive genomic instability and tumorigenesis [J]. *Genes & Development*, 2004, 18(17):2095-2107. DOI:10.1101/gad.1204904.
- [18] Yip C, Landau D, Kozarski R, et al. Primary esophageal cancer: heterogeneity as potential prognostic biomarker in patients treated with definitive chemotherapy and radiation therapy [J]. *Radiology*, 2014, 270(1):141-148. DOI:10.1148/radiol.13122869.
- [19] Ganeshan B, Skogen K, Pressney I, et al. Tumour heterogeneity in oesophageal cancer assessed by CT texture analysis: preliminary evidence of an association with tumour metabolism, stage, and survival [J]. *Clin Radiol*, 2012, 67(2):157-164. DOI:10.1016/j.crad.2011.08.012.
- [20] Ng F, Ganeshan B, Kozarski R, et al. Assessment of primary colorectal cancer heterogeneity by using whole-tumor texture analysis: contrast-enhanced CT texture as a biomarker of 5-year survival [J]. *Radiology*, 2013, 266(1):177-184. DOI:10.1148/radiol.12120254.
- [21] Lubner MG, Stabo N, Lubner SJ, et al. CT textural analysis of hepatic metastatic colorectal cancer: pre-treatment tumor heterogeneity correlates with pathology and clinical outcomes [J]. *Abdom Imaging*, 2015, 40(7):2331-2337. DOI:10.1007/s00261-015-0438-4.
- [22] Ahn SY, Park CM, Park SJ, et al. Prognostic value of computed tomography texture features in non-small cell lung cancers treated with definitive concomitant chemoradiotherapy [J]. *Invest Radiol*, 2015, 50(10):719-725. DOI:10.1097/RLI.0000000000000174.
- [23] Laffan TA, Horton KM, Klein AP, et al. Prevalence of unsuspected pancreatic cysts on MDCT [J]. *AJR Am J Roentgenol*, 2008, 191(3):802-807. DOI:10.2214/AJR.07.3340.
- [24] Park WG, Mascarenhas R, Palaez-Luna M, et al. Diagnostic performance of cyst fluid carcinoembryonic antigen and amylase in histologically confirmed pancreatic cysts [J]. *Pancreas*, 2011, 40(1):42-45. DOI:10.1097/MPA.0b013e3181f69f36.
- [25] Tanaka M, Fernández-Del Castillo C, Kamisawa T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas [J]. *Pancreatol*, 2017, 17(5):738-753. DOI:10.1016/j.pan.2017.07.007.
- [26] Hanania AN, Bantis LE, Feng ZD, et al. Quantitative imaging to evaluate malignant potential of IPMNs [J]. *Oncotarget*, 2016, 7(52):85776-85784. DOI:10.18632/oncotarget.11769.
- [27] Attiyeh MA, Chakraborty J, Gazit L, et al. Preoperative risk prediction for intraductal papillary mucinous neoplasms by quantitative CT image analysis [J]. *HPB (Oxford)*, 2019, 21(2):212-218. DOI:10.1016/j.hpb.2018.07.016.
- [28] Del Chiaro M, Segersvard R, Pozzi Mucelli R, et al. Comparison of preoperative conference-based diagnosis with histology of cystic tumors of the pancreas [J]. *Ann Surg Oncol*, 2014, 21(5):1539-1544. DOI:10.1245/s10434-013-3465-9.
- [29] Sawhney MS, Al-Bashir S, Cury MS, et al. International consensus guidelines for surgical resection of mucinous neoplasms cannot be applied to all cystic lesions of the pancreas [J]. *Clin Gastroenterol Hepatol*, 2009, 7(12):1373-1376. DOI:10.1016/j.cgh.2009.06.026.
- [30] Salvia R, Malleo G, Marchegiani G, et al. Pancreatic resections for cystic neoplasms: from the surgeon's presumption to the pathologist's reality [J]. *Surgery*, 2012, 152(3 Suppl 1):S135-S142. DOI:10.1016/j.surg.2012.05.019.
- [31] Cho CS, Russ AJ, Loeffler AG, et al. Preoperative classification of pancreatic cystic neoplasms: the clinical significance of diagnostic inaccuracy [J]. *Ann Surg Oncol*, 2013, 20(9):3112-3119. DOI:10.1245/s10434-013-2986-6.
- [32] Wei R, Lin KR, Yan WJ, et al. Computer-aided diagnosis of pancreas serous cystic neoplasms: A radiomics method on preoperative MDCT images [J]. *Technol Cancer Res Treat*, 2019, 18:1533033818824339. DOI:10.1177/1533033818824339.
- [33] Bosman FT, Carneiro F, Hruban RH, et al. WHO Classification of Tumors of the Digestive System [M]. Lyon: International Agency for Research on Cancer. 417.
- [34] Falconi M, Eriksson B, Kaltsas G, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors [J]. *Neuroendocrinology*, 2016, 103(2):153-171. DOI:10.1159/000443171.
- [35] Piani C, Franchi GM, Cappelletti C, et al. Cytological Ki-67 in pancreatic endocrine tumours: An opportunity for pre-operative grading [J]. *Endocr Relat Cancer*, 2008, 15(1):175-181. DOI:10.1677/ERC-07-0126.
- [36] Canellas R, Burk KS, Parakh A, et al. Prediction of pancreatic neuroendocrine tumor grade based on CT features and texture analysis [J]. *AJR Am J Roentgenol*, 2018, 210(2):341-346. DOI:10.2214/AJR.17.18417.
- [37] D'Onofrio M, Ciaravino V, Cardobi N, et al. CT enhancement and 3D texture analysis of pancreatic neuroendocrine neoplasms [J]. *Sci Rep*, 2019, 9(1):2176. DOI:10.1038/s41598-018-38459-6.

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附英文原文:

The Current State of Radiomics in Pancreatic Disease

What is “Radiomics”?

As the role of medical imaging in the diagnosis and management of human disease has expanded exponentially in recent decades, researchers and clinicians have explored methods to utilize these images beyond standard visual interpretation^[1]. While its origins trace back to the early days of computational analysis in the 1960's, the modern quantitative examination of medical imaging began to take root in the 1980's^[2]. Clinicians and researchers began to appreciate the sheer volume of mineable, high-dimensional data contained within standard cross-sectional medical images [computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)]^[3] with the hope that this data might be exploited to gain insight into the pathophysiology of imaged tissues; a process we now refer to as *radiomics*^[1].

Early quantitative image analysis generated computer-aided diagnostic (CAD) systems which found early success in the field of breast oncology^[3-4]. These systems were developed to answer basic questions such as whether or not a lesion or cancer was present on a particular imaging study. In contrast, radiomics extracts (potentially) innumerable quantitative features from digital standard-of-care medical images and utilizes complex algorithms or machine learning to test and generate hypotheses^[5]. Complex analysis of radiomic features (e.g. intensity, shape, texture, etc.) along with clinical and genomic data allow inquiry far beyond those addressed with early CAD systems, and enable non-invasive inquest into the powerful questions of cancer phenotype and patient outcomes^[6-7]. This report aims to review the current state of radiomics in the diagnosis and management of several pancreatic pathologies, and provide a context for the field's future development.

Pancreatic Ductal Adenocarcinoma

Given its overall dismal prognosis and highly

variable response to treatment, pancreatic ductal adenocarcinoma (PDAC) has been a major focus of pancreatic radiomics research. Clinicians and researchers, eager to find additional tools to combat this deadly disease, have looked to the abundance of data contained within standard-of-care cross-sectional imaging in hopes to understand patients' disease biology better and expected response to treatment.

An early attempt at survival prediction was performed by Chakraborty and colleagues who attempted to estimate 2-year survival based on preoperative CT scans of patients with PDAC^[8]. Their study included 35 patients who underwent gemcitabine-based neoadjuvant chemotherapy followed by surgical resection and subsequent adjuvant gemcitabine. The authors analyzed 255 first-order, second-order, and edge-based textural features of tumor regions on pre-treatment CT scans. From these features, multiple algorithms were created in an attempt to stratify patients into short- and long-term survivor groups (defined as < 2 years or \geq 2 years). Across all features, a directional edge-based angle co-occurrence matrix (ACM) model was best able to discriminate between groups with a receiver operator characteristic (ROC) curve area under the curve (AUC) of 0.90 and accuracy of 82.9%. While the causal features of differential survival are not known, the authors postulate that several genetic drivers and tumor-stromal interactions may result in both textural differences found on CT as well biologic behaviors observed in patients^[9-10].

A follow-up study performed at Memorial Sloan Kettering Cancer Center expanded this technique to 161 chemo-naive patients and combined radiomic analysis with both preoperatively (CA19-9) and postoperatively (CA19-9, Brennan score^[11]) available clinical data. While CA19-9 alone yielded a weak concordance index (c-index) of 0.51 (only slightly better than chance) with an integrated Brier score (IBS) of 0.165, the addition of radiomic textural

features to survival modeling increased the model's c-index to 0.68 (IBS 0.141). When postoperative pathologic features are added, the c-index further increased to 0.74 (IBS 0.20). While this study demonstrates the potential of radiomics-based survival estimation, direct clinical applicability is limited as modeling based on preoperatively available data provided insufficient guidance for decision-making regarding surgery and neoadjuvant chemotherapy. The report does, however, provide justification for further prospective validation, with integration of gene sequencing and histologic data. Similar results have been reported in patients undergoing stereotactic body radiotherapy (SBRT) for their disease, with reasonable model concordance with local control (c-index 0.75, $P=0.004$) and overall survival (c-index 0.75, $P=0.05$)^[12]. At least one study has investigated the ability of CT textural features to predict response to neoadjuvant chemotherapy^[13]. Early-stage data suggest that quantitative parameters on baseline CT can predict histologic response to neoadjuvant chemotherapy and outperform CA 19-9 in patients undergoing surgery for PDAC. However, additional work is ongoing in this area.

Radiomic analysis has also been used to predict survival in patients with locally advanced (LA) and metastatic disease undergoing chemotherapy^[14-15]. Sandrasegaran and colleagues demonstrated that in these patients, CT textural analysis of primary tumor heterogeneity [as measured by mean value of positive pixels (MPP) and kurtosis] were independently associated with differences in overall survival. Specifically, patients with MPP >31.625 or kurtosis >0.565 had a lower median survival than the overall cohort. The authors suggest that increased heterogeneity within primary tumors might result from variable genomic expression, angiogenesis, hypoxia, and micronecrosis, all of which may affect a tumor's ability to respond to systemic and local therapies^[16-17]. These findings are consistent with previous studies in esophageal^[18-19], colorectal^[20-21] and non-small cell lung cancer^[22] demonstrating the inverse association between tumor heterogeneity and overall survival.

Pancreatic Cystic Neoplasms

While PDAC presents the principal therapeutic

challenge for clinicians treating pancreatic disease, pancreatic cystic neoplasms (PCN) represent their primary diagnostic dilemma. While it is estimated that greater than 2% of the general population harbors a pancreatic cyst^[23], a significant minority of these will progress to malignancy. Identifying high-risk lesions has become a cottage industry with complex clinical guidelines, often requiring invasive imaging or biopsies, disputed between multiple groups^[24-25]. Fortunately, an abundance of surveillance and preoperative cross-sectional imaging provides a significant amount of data on which to base radiomics research in this area, with the holy grail of radiographic discrimination of high- and low-risk PCNs, enabling surgical removal of only those with significant malignant potential, sparing patients with low-risk lesions a potentially morbid operation.

An early study performed at MD Anderson Cancer Center took 53 consecutive patients with intraductal papillary mucinous neoplasms (IPMN) who underwent surgical resection and analyzed their preoperative CT scans in an attempt to differentiate between those with high-grade dysplasia (HGD) vs. low-grade dysplasia (LGD) on final pathology^[26]. Three-hundred sixty imaging features (including entropy, contrast, kurtosis of the 1D and 2D gray-level intensity distribution, etc.) were extracted from lesions on pre-surgery CT scans for analysis. Their most predictive "imaging biomarker" differentiated HGD from LGD with a respectable AUC of 0.86 (sensitivity 85%, specificity 68%). However, when multiple markers were combined to create an "imaging biomarker panel", the best logistic regression yielded an impressive AUC of 0.96 with sensitivity and specificity of 97% and 88%, respectively. The authors state this compares favorably to available clinical guidelines such as the Fukuoka criteria^[25], which have a false positive rate of around 36%.

A later study by Attiyeh and colleagues evaluated a series of 103 resected branch-duct IPMNs (BD-IPMN)^[27], which have a lower overall malignant potential than their main duct IPMN (MD-IPMN) counterparts. Here 74% of resected specimens were found to be low-risk, while 26% represented high-risk disease. Clinical and imaging characteristics were used to create risk-predicting models in an attempt to

preoperatively identify high-risk lesions. Quantitative imaging-only modeling out-performed clinically-based models (AUC 0.76 *vs* 0.67). When the preoperative imaging and clinical data were merged to create a comprehensive risk-prediction model, the overall AUC increased to 0.79, highlighting the utility of incorporating both factors. In the future, tools to differentiate high- and low-risk IPMNs will likely involve a combination of clinical suspicion, genetic and cytologic markers, and imaging characteristics in order to safely manage patients with this disease.

Certain PCNs should be resected rarely, if ever, as they pose little-to-no risk of progression or malignant transformation. Chief among these are serous cystic neoplasms (SCN). While most surgeons agree that SCNs generally should be managed nonoperatively, our ability to accurately diagnose them clinically is poor, with more than 50% of patients undergoing unnecessary surgical resection^[28-31]. Wei, et al. generated a radiomics-based CAD protocol from 260 patients who underwent PCN resection [102 SCN, 74 IPMN, 35 mucinous cystic neoplasm (MCN), 49 solid pseudopapillary neoplasm (SPN)] in an attempt to aid in their clinical diagnosis^[32]. Astonishingly, of the 102 resected SCNs, clinicians correctly diagnosed only 31 (30.4%) preoperatively, meaning a large number of these patients underwent unnecessary surgery. Of 409 extracted imaging features, 22 were selected for CAD generation with a validation AUC of 0.837. After additional data collection and validation, the authors envision integration of their CAD scheme into the clinical workflow, providing a powerful reference tool for imaging-based clinical diagnosis, with the overall goal of reducing overtreatment of these benign lesions.

Pancreatic Neuroendocrine Neoplasms

Pancreatic neuroendocrine neoplasms (PNE) present yet another diagnostic and management challenge to the clinician. For patients with these tumors, appropriate management is based on size and tumor grade, as determined by their proliferative capacity (Ki-67% or mitotic rate)^[33], with most small and low-grade tumors requiring only observation^[34]. Preoperatively, tumor-grade can be assessed via invasive endoscopic-ultrasound-guided fine needle aspiration (EUS-FNA), however preoperative biopsy

can misstage tumors in 10% - 20% of cases^[35]. Radiomics offers a non-invasive staging modality to potentially predict the aggressiveness of PNEs and ultimately guide surgical management.

An early study from the Massachusetts General Hospital used a combination of qualitative and quantitative imaging findings to differentiate between PNE grades on preoperative CT scans^[36]. In addition to more classic imaging findings suggestive of high grade tumors (e.g. size >2 cm, vascular involvement, pancreatic ductal dilation, lymphadenopathy), the tumoral textural entropy was also found to predict grade and progression-free survival. Models combining both entropy and standard CT features demonstrated an accuracy of 79.3% in differentiating G1 from G2/G3 tumors. Tumors with entropy values of >4.65 were 3.7 times more likely to be high grade (G2/G3) when compared to those with lower values. High tumoral entropy also independently predicted progression-free survival [$\chi^2(df, 1) = 4.4, P = 0.037$]. The authors point out that the accuracy of their radiomics model is comparable to EUS-FNA, which may overestimate or underestimate a tumor's aggressiveness due to sampling error or specimen processing, and contend that one day such imaging biomarkers may play a central role in determining which patients may benefit from surgery rather than a watch-and-wait management approach.

A follow-up study by D'Onofrio and colleagues developed a tumoral grade-predicting model using only CT textural features^[37]. The CT scans of 100 surgically resected PNEs were analyzed to obtain both quantitative imaging characteristics (relative enhancement ratio, standardized enhancement ratio, and tumor permeability ratio) as well as tumoral textural features (mean value, variance, skewness, kurtosis, and entropy). Both enhancement ratio and permeability index allowed distinction between G1 and G2/G3 tumors. However, CT textural analysis, specifically kurtosis, was even more accurate, allowing differentiation between all three grades of PNEs with statistical significance. The AUC of the ROC curve for kurtosis was an impressive 0.924 for the diagnosis of G3 tumors, with a sensitivity and specificity of 82% and 85%, respectively. While further prospective validation is required, the authors imagine an exciting potential future of PNE diagnosis and staging,

envisioning that “in the same moment that a neuroendocrine neoplasm is detected, characterized and staged, texture analysis could provide tumor grade prediction, allowing better patient management.”

Conclusions

As cross-sectional imaging becomes higher-quality and more integral to clinical practice, the rigorous and systematic analysis of data contained within these images provides the opportunity to gain novel insights into the pathologic diagnosis, disease biology, and expected outcomes of patients with pancreatic disease.

Multiple studies have demonstrated the promise of radiomics in determining disease biology in PDAC and even predicting response to systemic therapy. Pathologies such as PCN and PNEN, which present diagnostic and prognostic complexities for clinicians, are ideal diagnoses to benefit from the additional information afforded by radiomic analysis. Large-scale quantitative imaging analysis will only continue to improve and expand in the coming years. The question is not if, but when, the technology plays a routine role in clinical care.

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