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人工智能在肺癌领域的应用与思考

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[摘要] 医疗大数据的可获得性和计算机软硬件的飞速发展, 极大地促进了智慧医疗的发展。人工智能(artificial intelligence, AI)已成功应用于医学多个领域, 在肺癌方面的应用尤为突出, 在某些特定任务上的准确度已经超越了人类; 部分AI软件已经深入临床决策, 正在深刻影响着临床医师的临床决策。目前AI在肺癌领域的应用主要包括检出、分割、分类、预后预测、疗效评估等; AI在数据获取、标注以及可解释性方面面临着一定的挑战和大数据时代的机遇。在肺癌领域AI已得到较为深入、广泛的研究, 有望成为肺癌防治的得力助手。AI正给放射科医师带来一场前所未有的革新, 但放射科医师的角色在AI发展过程中至关重要。

[关键词] 人工智能; 深度学习; 卷积神经网络; 肺癌

Artificial intelligence in lung cancer: Application and future thinking

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ABSTRACT

The availability of medical big data and the rapid development of computer software and hardware have greatly promoted the advancement of intelligent medical healthcare. Artificial intelligence (AI) has been successfully applied in many fields of medicine, especially in lung cancer. The performance of AI in some specific tasks has surpassed that of humans. Several AI software has been deeply used in clinical practice to help decision-making, which is producing a profound influence on clinicians. At present, the application of AI in the field of lung cancer mainly includes detection, segmentation, classification, prognosis prediction, efficacy evaluation, and so on. AI faces certain challenges and

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opportunities in the era of big data in terms of data acquisition, annotation and interpretability. Researchers have conducted deep and extensive studies using AI in the field of lung cancer, and AI is expected to become a powerful assistant in the prevention and treatment of lung cancer. AI is bringing an unprecedented revolution to radiologists, but the role of radiologists is crucial in the development of AI.

KEY WORDS artificial intelligence; deep learning; convolutional neural network; lung cancer

肺癌一直是严重威胁人类健康的一类疾病。最新发布的2021年全球癌症统计报告^[1]显示:肺癌位列肿瘤致死率的第1位,发病率在男性和女性中分别位列第1和第2位。尽管低剂量计算机体层成像(low dose computed tomography, LDCT)筛查的普及化和治疗方式的多样化一定程度上改善了肺癌预后,但患者的整体5年生存率仍仅为19.4%^[2],防治形势十分严峻。医疗大数据的可获得性和计算机软硬件的发展,极大地促进了人工智能(artificial intelligence, AI)在医学领域的应用。基于影像、病理等医疗大数据,学者对AI在不同病种(如肺癌、乳腺癌、脑胶质瘤等)、不同临床应用场景(如筛查、诊断、治疗、疗效评估、随访等)方面进行了较为深入的研究和探索,并取得不错的成绩^[3]。AI在此次2019冠状病毒病(corona virus disease 2019, COVID-19)疫情中也发挥了巨大作用^[4-5]。AI在医学领域应用的飞速发展,为肺癌的防治提供了新的解决方案;其在肺癌领域已有较为深入、广泛的研究,在部分任务上的表现已经超越人类,且有部分AI软件已经进入临床使用。本综述旨在总结AI在肺癌领域的应用情况以及最新进展,并浅析AI在该领域面临的挑战与机遇,为该领域的同行提供重要参考和潜在研究方向。

1 AI在肺癌领域作用的研究进展

医学影像为临床各个环节必不可少的检查手段,影像数据多而易得,因此针对AI在肺癌领域的研究绝大部分是基于影像数据进行的。目前AI在肺癌领域的应用主要包括检出、分割、分类、预后预测、疗效评估等。

1.1 检出

肺癌筛查的影像学手段主要包括X线和CT。X线图像为重叠图像,密度分辨率较低,且容易漏诊小病灶。即使任务相对困难,经过大数据的训练,AI也能取得不错的效果^[6]。Li等^[6]构建的多分辨率卷积神经网络能够检出胸部X线片上99%的结节,并

在检出小于2 cm的结节中也有很好的表现。Chen等^[7]采用平衡卷积神经网络和经典的候选检测方法在日本放射技术学会(Japanese Society of Radiological Technology, JSRT)公开的数据集上检测胸部X线片肺结节的敏感度达到91.4%和97.1%。

随着LDCT的发展和人们健康意识的提高,CT已逐步取代X线成为肺癌筛查的有效手段。因肺结节与背景肺实质密度差别较大,肺结节被自动检出相对简单,技术也相对成熟。目前,AI从CT图像检出肺结节的准确度为82.2%~99.5%,敏感度为83.1%~100%,特异度为71.4%~99.0%^[8-9]。不同大小和不同类型的结节,检出效能存在一定差别;结节的位置(如胸膜下)和周边的结构(如与血管相邻)也影响结节检出的效能^[10-11]。非实性结节、直径较小的结节以及胸膜下结节AI检出的效能相对较差。Nithila和Kumar^[12]的研究表明:AI检出实性结节、亚实性结节和非结节结构的准确度分别为98%、99.5%和97.2%。这可能与亚实性结节和磨玻璃结节边界欠清,与背景肺实质对比差异小于实性结节相关。Zheng等^[13]构建了一个专门检出小结节(<6 mm)的深度卷积神经网络,敏感度达到93.4%。通过学习大量人工标注数据以及改进算法,AI有望准确识别血管影、胸膜增厚等非结节结构,以减少假阳性。

AI自动检出肺结节的另一个优势是十分高效。AI处理一套CT数据的平均时间少于放射科医师^[14]。部分AI辅助自动检出肺结节软件已经投入临床使用,并取得了放射科医师的初步信任。AI与放射科医师无缝结合的阅片方式将成为今后的主流阅片方式,既高效又准确。随着多任务深度学习的发展,肺结节检出不再是单一任务,多与定性^[15]、分割^[16]等任务同时进行,相互辅助^[17],这是深度学习未来的发展方向。

1.2 分割

肺结节的准确分割可辅助定性及其他医学任务^[18],也是提取定量特征(如影像组学特征)的关键步骤。相对手动分割,自动分割能解放大量人工劳动

力并提高效率。AI自动分割肺结节时间可缩短至3.15 s,远短于人工分割需要的时间^[19]。评估AI分割精度最常用的指标为Dice相似系数(Dice similarity coefficient, DSC),取值范围为0~1,分割的最好结果为1。大部分研究^[20]的分割精度为0.7~0.9,涉及的深度学习网络包括U网络、全卷积网络(fully convolutional network, FCN)、生成对抗神经网络(generative adversarial network, GAN)等^[21]。部分研究的分割精度特别突出,Liu等^[22]基于随机森林构建的全自动肺结节分割模型的DSC达0.986;Singadkar等^[23]构建的深度去卷积残差网络(deep deconvolutional residual network, DDRN)在LIDC/IDRI公共数据集验证的平均DSC达0.9497。类似于肺结节的检出,孤立实性结节的精准分割相对于非实性结节、胸膜下结节、与血管关系密切的结节更容易实现。Savic等^[24]研究显示:针对实性结节,模型分割类圆形结节和不规则结节的DSC可达到0.933和0.901;但在非实性结节和空洞结节中,DSC下降到0.799和0.614。实际上,不同放射科医师标注非实性、胸膜下等结节本身就存在一定差异^[25],这对AI学习的金标准提出了挑战。不断纳入高质量标注数据,将专家先验知识嵌入网络,有望进一步提高AI自动分割的精度。

1.3 分类

分类指良恶性鉴别、浸润程度风险分级、肺结节类型自动分类、肺癌病理类型分类等。放射科医师一般依靠少量可见的特征来进行分类,比如分叶、毛刺、胸膜牵拉、实性成分、CT值、最大径等。实际上,肉眼可见的特征仅为医学图像蕴含特征的冰山一角,大量不可见且高维的特征可被挖掘^[26]。利用AI挖掘图像内部隐藏的特征来辅助分类成为近年来研究的热点。数据挖掘的方法主要包括深度学习和影像组学方法^[27],前者在大多数分类任务上超越后者^[28],且不需要耗时的像素级标注。

AI辅助鉴别良恶性肺结节的应用最早也最成熟,准确度为75.01%~97.58%^[21,29],诊断效能超过胸部专业放射科医师^[30]。Zhao等^[18]借助深度学习预测亚厘米级肺腺癌的浸润程度,准确度超过低年资医师;Wang等^[31]利用深度学习对肺腺癌浸润程度、不同镜下成分以及预后进行多分类分析,也取得不错的效果;Zhao等^[32]利用深度学习预测T1期肺癌患者纵隔淋巴结转移情况,在内部和外部测试集上的曲线下面积(area under the curve, AUC)分别达到0.945和0.948。除了分析CT图像,AI利用其他资料进行研究也有良好的表现。Chabon等^[33]借助AI方法分析二代测序的游离DNA(cell-free circulating DNA,

cfDNA)和循环肿瘤DNA(circulating tumor DNA, ctDNA),无创辅助肺癌的早期诊断;Dehkharghanian等^[34]利用深度学习分析病理切片来鉴别肺腺癌和鳞癌,AUC达到0.92;也有研究^[35]基于PET/CT图像进行肺癌相关的分类任务,取得不错的成绩。最近,Iuga等^[36]验证了AI自动评估肺癌N分期的可行性;Kirienko等^[37]也证实AI在肺癌T分期自动评估中的潜力。也有研究者^[28]利用AI分析CT图像预测肺癌EGFR、ALK等基因的表达,辅助临床方案的制订。随着研究的不断深入,AI有望成为精准医疗的得力助手。

1.4 预后预测

相比传统的基于临床特征预测预后,AI辅助预测预后更加准确、高效^[38]。Amini等^[39]基于影像组学方法构建多层次、多模态PET/CT融合模型,其预测非小细胞肺癌的总生存时间(overall survival, OS)的性能超过了单模态模型和临床模型;Le等^[40]基于影像组学特征挖掘影像组学标签,其预测非小细胞肺癌1、3和5年OS的准确度超过基于年龄、性别、分期构建的临床模型。Choi等^[41]利用3D神经网络构建的模型能够自动区分微乳头和实体型成分(AUC达0.8),并预测患者的预后;Guo等^[42]利用深度学习分析免疫组织化学病理图像构建一个预后预测模型,其预测OS和无复发生存期(relapse-free survival, RFS)的AUC分别达到0.9和0.85;Doppalapudi等^[43]构建的深度学习模型能够准确预测肺癌患者的生存期(≤ 6 个月,0.5~2年和 > 2 年),准确度达71.18%,性能超过传统的机器学习方法;She等^[44]构建的深度学习模型预测肺癌生存期的准确度超过TNM分期,有望通过该模型预测预后为临床决策提供帮助。也有研究者^[45]通过分析多次随访CT的数据对CT检出肺结节的患者预测1年后和2年后患癌风险,AUC分别为94.4%和87.3%,该方法有助于指导临床决策,及时干预。

1.5 疗效评估

疗效评估对于临床治疗方案的及时调整至关重要。人工评估实体肿瘤疗效多采用实体肿瘤疗效评价标准(Response Evaluation Criteria in Solid Tumours, RECIST)^[46]。但此标准仅能评估病变的大小,无法确定是肿瘤组织还是炎性改变,可能出现假阳性的情况。此外,人工主观评估难以保证测量的准确性,并需要考虑时间成本。因此,如何快速精准地评估疗效,临床意义重大。

AI辅助评估疗效具有独特的优势。首先,AI可

对不同时间点的图像进行自动校准,为后续精准对比提供基础;其次,AI能够挖掘肉眼不可见的内在特征及其随治疗发生的变化,以达到更精准的评估。目前,已有研究采用AI预测肺癌的免疫、放射、靶向等治疗的效果。Mu等^[47]设计一个小残差卷积网络(small-residual-convolutional-network, SResCNN)分析PET/CT数据来预测PD-L1的表达(AUC \geq 0.82),同时可准确预测免疫抑制剂治疗的持续临床获益(durable clinical benefit, DCB)、无进展生存期(progression-free survival, PFS)和OS,从而辅助个性化治疗方案的制订;Cui等^[48]提出一种新型精算深度学习神经网络(actuarial deep learning neural network, ADNN)架构,用于联合预测III期非小细胞肺癌患者的放射治疗效果,该模型考虑了多组学信息之间的复杂相互作用,包括PET放射组学、细胞因子和miRNA,其预测效能超过传统的计算模型,同时预测放疗后发生放射性肺炎和局部控制的AUC达0.729;Hou等^[49]利用深度学习预测酪氨酸激酶抑制剂(tyrosine kinase inhibitor, TKI)治疗患者的PFS,结合临床信息预测的AUC为0.771,预测效能超过基于临床特征建立的模型。纳入多时序的数据进行分析,能够更好地辅助疗效评估。Xu等^[50]研究发现:相对纳入单次CT数据,纳入多次随访CT数据预测常规化学药物治疗肺癌患者的预后准确度得到提升。尽管AI在疗效评估中体现出巨大的优势,但预测长期治疗的效果仍然有很大进步空间。Trebeschi等^[51]研究发现:AI预测免疫治疗1年OS的准确度要低于3~5个月的OS。进一步加大数据量,纳入非影像的医学资料可能会进一步提升AI评估疗效的效能。

1.6 其他方面的应用

除上述应用外,AI在肺癌其他领域的应用也存在巨大的潜力。比如辅助病理科医师进行自动阅片^[52],辅助临床医师进行RECIST自动评估^[53],通过自然语言处理方法自动识别影像报告中的肺结节信息^[54],自动生成影像报告^[55]等。因此,AI正在肺癌临床路径的每个关键点上发挥巨大作用,有望成为精准医疗的得力助手。

2 AI所面临的挑战和机遇

2.1 挑战

尽管AI在医学领域初放异彩,但要无缝应用到临床可能还需要一定的时间。AI最先攻克的可能是那些数据量大、人类需求大以及逻辑要求不高的问题,比如肺癌筛查、良恶性鉴别等。如果需要攻克

更高层次的医学任务,需解决以下挑战。

2.1.1 大数据的获取和高质量的标注

众所周知,数据是AI的命脉与核心。输入模型的数据越精准、越全、越多、越符合日常场景,建立的模型也就越准确、越泛化、越稳定。尽管影像数据储存系统能够满足大数据储存的要求,也有相关的公共数据集,比如TCIA(The Cancer Imaging Archive)和NLST(National Lung Screening Trials),但这些数据很少为某个特定的医学任务专门设定,且数据质量参差不齐,无法做到很好的整合。此外,不同机构数据采集方式没有统一的标准,也可能影响模型的结果。获取的数据另一个阻力来自于数据共享,目前机构对数据共享持保守观念,这可能需要政府层面的政策支持和监管才能改变。

高质量的数据标注是另一个挑战。数据的标注(包括病灶的分割以及病理标注)对于大多数AI研究是必需的,但需要耗费大量的人力。尽管目前自动分割以及半自动分割方法能够给标注医师减轻负担,但仍需要医师审核。此外,某些少见疾病数据量缺乏^[56],且只有少数专家能够对这部分疾病进行标注,为AI实现自动分割增加了难度。非监督学习、自监督学习可能是解决这类问题的方案^[57-58]。数据标注的另一方面是病理标注。自然图像可以让非专家来进行标注,但医学影像的标注要求标注者具有相关领域的专业知识,既增高了标注者的专业门槛,也增加了标注难度。

2.1.2 AI的可解释性

AI虽被称为人工智能,但目前并不完美,原因之一是缺乏可解释性,被称为“黑匣子”。换言之,人们只看到AI的输出结果,但AI如何给出输出结果、依靠什么作出判断、哪些征象鉴别权重最大都无法清楚地展示给专家,这有悖于循证医学的观点。这也许就是目前很多医师不信任AI的一个原因。庆幸的是,AI可解释研究,包括特征可解释、逻辑可解释、神经网络可视化,已经成为工程学领域的研究重点及热点^[59],相信不久的将来,AI的神秘面纱会被慢慢解开。

2.1.3 AI的数据安全和法律效应

AI面临的另一个问题是数据安全的挑战。如何保护患者隐私信息是临床关注的重点。解决安全问题的一种方法是共享不同机构模型算法而不是共享患者的数据,也能够到达提高模型泛化的目的。另一种方法便是数据加密。“Cryptonets”是一种在加密数据上训练出的网络,它输出的预测结果也是加密的,只有数据对应的本人才能够解密,这保证了数据在整个过程的使用都是非常安全的^[60]。

AI进入临床使用必须通过药监局等权威部门审批。目前大部分获批的AI软件为三类医疗器械,不能独立用于临床诊断。因此,AI输出结果该由谁来承担法律责任,是我们不得不思考的一个问题。假设AI漏诊了一个肺结节,该由谁来承担责任?毫无疑问,肯定是放射科医师。这样一来,放射科医师要完全信任AI还需要很长的一段路。

2.2 机遇

随着数据量的增加,数据质量的提高,越来越多的医学任务可能被AI攻克,那时AI将成为临床医师的得力帮手,助力肺癌的防治。其实,AI在肺癌领域的应用还有很大的潜力。比如影像图像的“分诊”,自动推送危急值;自动检出转移灶;辅助影像归档和通信系统自动搜索目标文档或图像;CT图像的模拟生成等。所以,实际上可以将AI整合到整个肺癌临床路径中,从患者就诊、治疗到监测、随访;也可以进行多方平台综合管理和监测,助力智慧医疗。

3 浅谈AI对医师的影响

AI对放射科医师的影响最为深刻,正在给放射科领域带来的一场前所未有的革新,放射科医师是否会被AI取代,是大家思考的一个问题。笔者认为取代是不可能的。不管AI如何发展,都不可能拥有人类的智力;在某些任务上很有可能超过人类,但在需要逻辑推理的工作上AI是无法超越人类的。因此,AI不能被高估。AI擅长发现感官感知的信息,其在医学领域的发展尚处于婴儿阶段,需要理性对待。但肯定的是,AI将会成为医师很好的助手,解决一些繁琐而重复的工作,辅助临床诊断。从这个层面讲,也许今后对于低年资医师的需求会降低。但放射科医师的角色在AI发展过程中至关重要。因为,没有专家给予AI正确的指导,AI很难成为一款适用于临床的产品。因此,放射科医师对AI既应该表示欢迎,还要有一定的担忧,在努力掌握自己专业知识的同时,应了解工程学领域的相关知识,努力做医工结合的主导者,而不是淘汰者。除了放射科,AI对临床科室也会产生一定的影响,包括尚处于研究阶段的治疗方案的自动决策^[56]。

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