中国激光

口腔癌筛查与诊断的影像学技术及发展趋势

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摘要 目前，口腔黏膜病的筛查和诊断主要依靠临床医生的目视观察和触诊，组织病理学仍然是口腔癌诊断的金标准。目视观察、触诊和组织病理学方法都存在不同的局限性。近年来，随着影像学技术的不断发展，X射线计算层析、核磁共振、超声、荧光、光声、光学相干层析等技术逐渐被应用于口腔黏膜病的成像研究。不同影像学技术的成像原理、成像能力及性能各不相同，在口腔癌的筛查与诊断中可以发挥不同的优势，具有极大的临床应用潜力。本文主要总结了现有影像学技术在辅助口腔癌筛查和诊断中的研究进展，分析了它们的临床适用性，并预测了口腔癌筛查与诊断影像学技术未来的发展趋势。

关键词 医用光学；医学和生物成像；口腔癌；影像学技术；筛查；诊断

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1 引 言

口腔连接着呼吸道和消化道，周围重要器官密集，血供和淋巴结丰富[1-2]。口腔癌是一种常见恶性肿瘤。据统计，按全身恶性肿瘤患者数量排序，口咽癌患者数量居第8位[3]，其中，超过90%的口腔癌是源于上皮层的口腔鳞状细胞癌（OSCC）。由于OSCC易转移、手术全切困难，某些国家口腔癌患者的平均五年生存率不足50%[4]。

临床上，口腔癌主要靠目视观察和触诊进行初诊，然后结合可疑部位的组织病理学检查进行诊断。仅仅从外观上很难准确区分良性和恶性病变，尤其是一些癌前病变，因此，目视观察和触诊存在漏诊和误诊的可能。组织病理学检查方法是口腔癌诊断的金标准，但需要切取部分组织，进行固定、包埋、切片、染色等处理，耗时、费力，并且病人会遭受不同程度的创伤。

为了解决口腔癌临床诊断中面临的上述问题，国内外开展了各种辅助诊断方法的研究，并提出了活体染色[5]、细胞刷[6]等生化方法以及各类影像学技术[7]。这些辅助诊断方法旨在提供接近无损、客观和定量的评估。本文重点对现有的影像学技术进行简要总结，分析它们在口腔癌临床筛查和诊断中应用的潜力及发展趋势。

目前，包括X射线计算层析术（X-CT）、核磁共振成像（MRI）、超声成像（UI）、荧光成像（FI）、光声成像（PAI）、光学相干层析术（OCT）等在内的多种成像技术已经实现了临床应用或正被尝试用于口腔黏膜病的辅助检测。不同技术的成像原理、检测能力和应用范围不尽相同，且临床可行性值得深入探讨。本文从成像技术原理出发，重点介绍了这些技术在口腔癌检测方面的研究成果，并总结了其作为辅助筛查和诊断方法的优势与不足，最后讨论了这些技术在口腔临床上应用面临的挑战以及未来的发展方向。

2 成像技术

2.1 X-CT技术

X-CT技术通过测量X射线束在样品中的衰减特性实现对样品不同深度部位的成像。在X-CT成像过程中，探测器采集不同角度的X射线信号，并使用计算机重建身体内部骨骼、血管和软组织的三维图像[8]。多项研究表明，X-CT可以用于评估头颈部肿瘤[9-10]，并可以表征原发肿瘤的大小，评估骨侵袭和淋巴结转移，其典型结果[11-12]如图1所示。

口腔癌骨侵袭的检测对于治疗和预后至关重要。Nae等[11]评价了X-CT对OSCC下颌骨侵袭的诊断性能。除了常规X-CT技术以外，锥形束CT（CBCT）也

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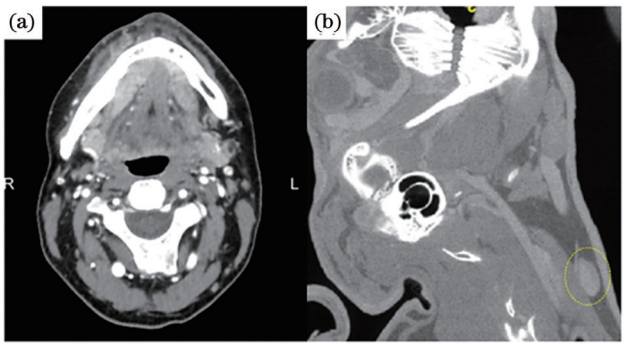

图 1 口腔癌的 X-CT 成像结果。(a) OSCC 下颌骨侵袭[11]；(b) OSCC 兔子模型的淋巴结转移[12]

Fig. 1 X-CT imaging of oral cancer. (a) Mandibular involvement of oral squamous cell carcinoma (OSCC)[11]; (b) metastatic lymph node in a rabbit model of OSCC[12]

可以用于口腔癌骨侵袭的检测[13]。Chin 等[14]研究了口腔舌鳞癌浸润深度(DOI)的术前增强 CT(CECT)检测结果与组织病理学检测结果的相关性，验证了 CECT 检测的准确性。Qureshi 等[15]进一步评价了 CECT 对口腔鳞癌伴颈部淋巴结转移的诊断准确性。在这项研究中，CECT 扫描的灵敏性、特异性、阳性预测值和阴性预测值分别为 83%、61.7%、70.9% 和 76.3%，总体诊断准确率为 73%[15]。

目前，作为一种通用型设备，X-CT 机已在口腔临床中得到了应用。通过描述原发肿瘤的大小和范围，可以评估骨侵袭和淋巴结转移，而且 X-CT 在骨侵袭深度测量方面有很大优势。随着 X-CT 技术的发展，CBCT 和 CECT 因具有较好的诊断性能而逐渐凸显出来。然而，为了获得高质量图像，X 射线辐射剂量导致的辐射暴露以及需要注射碘对比剂等仍是目前 X-CT 技术应用的短板。

2.2 MRI 技术

MRI 是在 X-CT 之后发展起来的，该技术一问世便很快成为评估头颈部肿瘤的一种方法。MRI 利用射频电磁波在静磁场中激发自旋非零的质子产生核磁共振。不同生物组织磁共振信号的频率不同，MRI 采用感应线圈收集不同的磁共振信号，实现图像重建[16]。

虽然 X-CT 和 MRI 在临床上都已被应用于口腔癌的辅助诊断，但 MRI 在测量软组织上的技术优势使其通常能更好地反映原发病灶[17]。MRI 在判断下颌组织侵袭方面比 X-CT 具有更高的灵敏性(94% VS 64%)，但其测量结果的特异性较低(73% VS 89%)[18]。

肿瘤厚度是另一个重要的预后因素。MRI 可以测量肿瘤厚度，从而帮助医生制定治疗计划[19-20]。目前，MRI 已被证明在评估 OSCC 尺寸和厚度、神经周围侵犯、骨髓侵犯和淋巴结浸润及囊外扩散方面是可行的[11,21-23]。图 2 给出了口腔癌的典型 MRI 成像结果。但是，采用 MRI 对口腔成像时，可能会由于出血和炎症改变而高估肿瘤的侵袭程度，导致假阳性结果[24-25]。另外，MRI 检查时间长，人体不自主的吞咽等相关运动会在 MRI 图像中产生伪影。

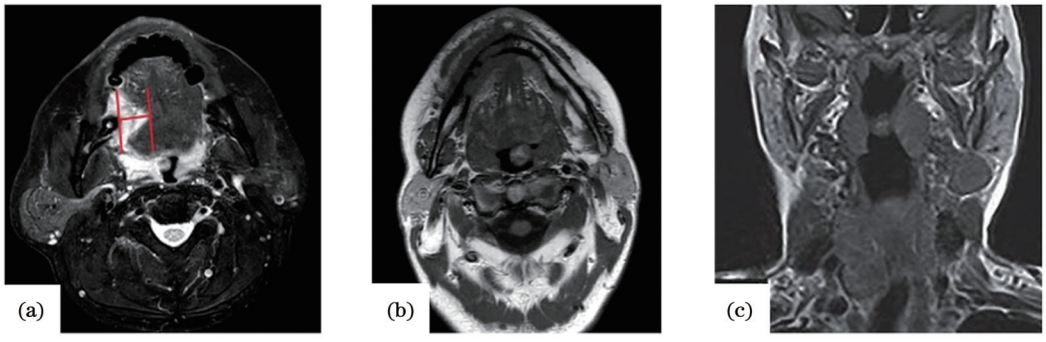

图 2 口腔癌的 MRI 成像结果。(a)右舌部 OSCC，显示浸润深度[21]；(b)OSCC 下颌骨髓质侵犯[11]；(c)淋巴结转移[23]

Fig. 2 MRI imaging of oral cancer. (a) Right tongue OSCC, indicating depth-of-invasion (DOI)[21]; (b) medullary invasion of mandibular bone of OSCC[11]; (c) metastatic cervical lymph node[23]

由于分辨率受限，基于 MRI 和 X-CT 的术前检查可能不能很好地发现口腔早期肿瘤，尤其是直径小于 5 mm 的肿瘤。

2.3 UI 技术

UI 技术通过采集和处理样品返回的超声波来获得样品的内部图像，其分辨率取决于超声波的频率。UI 技术以其实时性和安全性被广泛应用于人体各器官的常规检查和疾病筛查中[26]。

已有多项研究表明，术前进行 UI 可以得到深部肿瘤与正常组织界面的可视化信息，并且可以确定肿瘤浸润深度[27-31]。Angelelli 等[32]利用口腔内超声对肿瘤分布于舌、颊、腭及牙槽嵴部位的共计 32 例口腔癌患者的肿瘤浸润程度进行了评估。Bulbul 等[33]探讨了口腔内超声在测量口腔舌癌浸润深度以及指导口腔舌癌深度边缘清除方面的潜在应用。如图 3(a)所示，术中超声成像显示了肿瘤厚度(白色虚线)，白色横线代表正常黏膜与肿瘤的边界，白色竖实线表示浸润深度。图 3(b)显示了在肿瘤切除过程中超声指导的边缘切除，如蓝色箭头所示。蓝色细线表示深度切缘，与肿瘤边界的距离为 10 mm。图中星号代表肿瘤位置。

超高频超声(UHFUS)是近年来引入临床的一种超声技术。与传统超声(3～15 MHz)相比，UHFUS 使

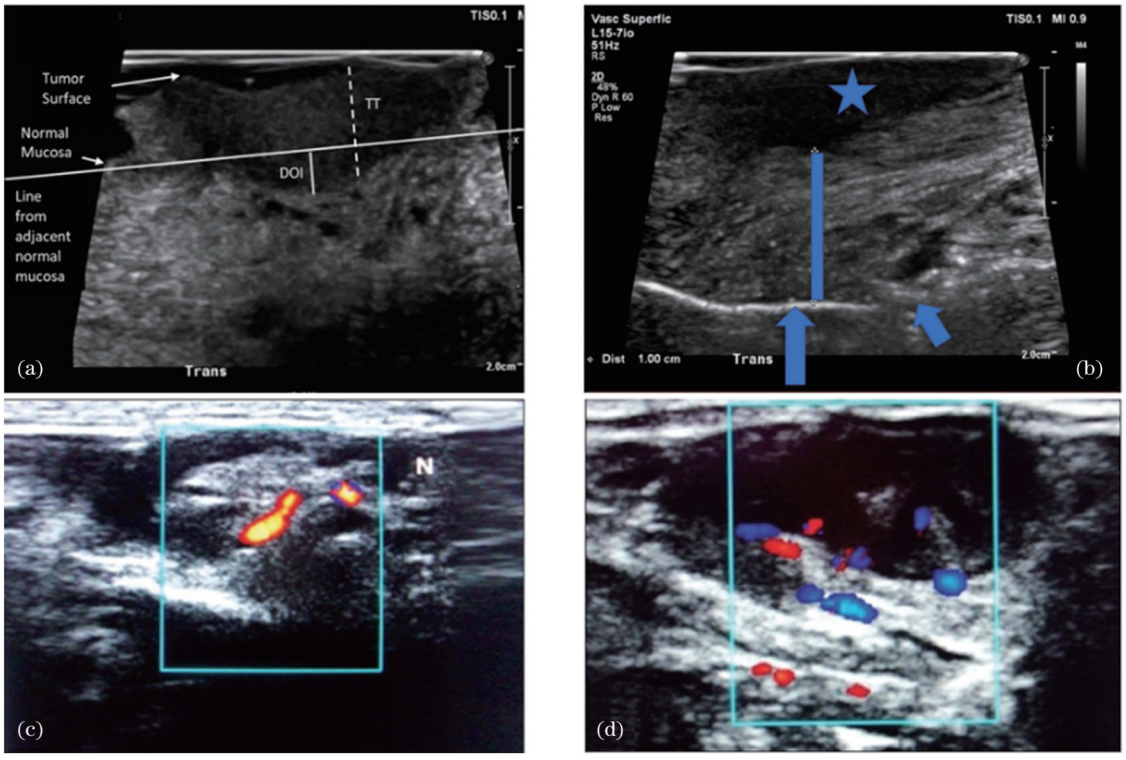

图 3　口腔癌的超声成像结果。(a)(b)常规超声图像[33]；(c)(d)彩色多普勒超声图像[40]

Fig. 3　UI results of oral cancer. (a)(b) Conventional UI results[33]; (c)(d) color DUI results[40]

用更高的频率(30～100 MHz)，对于浅表组织层可以获得约 30 μm 的分辨率，提升了超声成像的效果[34-36]。Izzetti 等[37]利用 UHFUS 对 160 例口腔软组织病变患者的病变组织进行了成像，该技术的诊断灵敏性、特异性及阴性预测值均超过了 90%。

随着超声造影剂的出现，科研人员研究了超声造影(CEUS)在预测口腔癌患者早期淋巴结转移上的临床价值[38]。Wei 等[39]评估了 CEUS 引导下经口腔针刺活检与传统超声引导下经口腔针刺活检、标准切口活检在口腔肿瘤患者中的耐受性、安全性和诊断价值。

结合多普勒技术的多普勒超声技术(DUI)可以利用多普勒效应检测血流信息[40]，如图 3(c)和图 3(d)所示。Aggarwal 等[40]通过多普勒超声评估了口腔癌患者淋巴结的血管状态，并确定了在检测口腔癌转移淋巴结时其临床表现与多普勒超声特征之间的相关性。Rebol 等[41]使用三维多普勒超声测量了口腔肿瘤的体积和血管情况。Dangore-Khasbage 等[42]研究了彩色多普勒超声在口腔癌患者颈部淋巴结病变诊断中的应用。Kagawa 等[43]基于口腔癌患者的多普勒超声图像定量评估了淋巴结血管状态与淋巴结大小之间的关系。

UI 是一种不断发展的口腔癌检测方法，可以检测沿深度方向的肿瘤边界，并具有与多普勒技术相结合对血管进行分析的能力。然而，UI 技术的成像分辨率与其成像深度相互制约，在获得足够成像深度的前提下无法获得精细的病变结构与准确的侵袭深度。

2.4　FI 技术

FI 是通过采集组织中被激发到高能级的电子跃迁回低能级时发出的荧光而成像的一种技术[44]。FI 技术包括采用本征荧光团的自发荧光成像(AFI)技术和注入荧光剂的外源性荧光成像(EFI)技术。

在一定波长范围(如 400～460 nm)光的照射下，口腔上皮和黏膜下层的自发荧光团可以被激发，产生组织自发荧光。内在荧光团的增加或减少可以作为一种指示，用于识别由荧光团浓度和性质改变而造成的口腔病变[45]。一些研究人员评估了自发荧光成像技术对口腔癌前病变和口腔癌筛查的可行性[46-48]。与正常的口腔黏膜相比，恶性病变与自发荧光丧失相关，在显像时呈现暗沉[49]。然而，许多良性病变也显示为自发荧光的丧失，降低了其特异性[50]。Morikawa 等[51]研究了不同口腔黏膜病变的荧光可视化成像。OSCC 的荧光图像显示为整体不均匀、边界不清晰的自发荧光丧失，如图 4(a)所示；口腔白斑的荧光特征为边缘清晰的自发荧光增强，如图 4(b)所示；口腔扁平苔藓部分区域表现为自发荧光增强，并在红斑区域表现为均匀的荧光丧失，如图 4(c)所示；口腔炎的自发荧光特征同样表现为边界清晰、均匀的荧光丧失，如图 4(d)所示。

吲哚菁绿(ICG)是一种荧光染料，已被证明在术中组织灌注成像和血管造影术中具有较高价值。在口腔黏膜疾病的诊断方面，Stubbs 等[52]评估了 ICG 显示原发肿瘤和区域转移的可行性，结果显示，在 86% 的

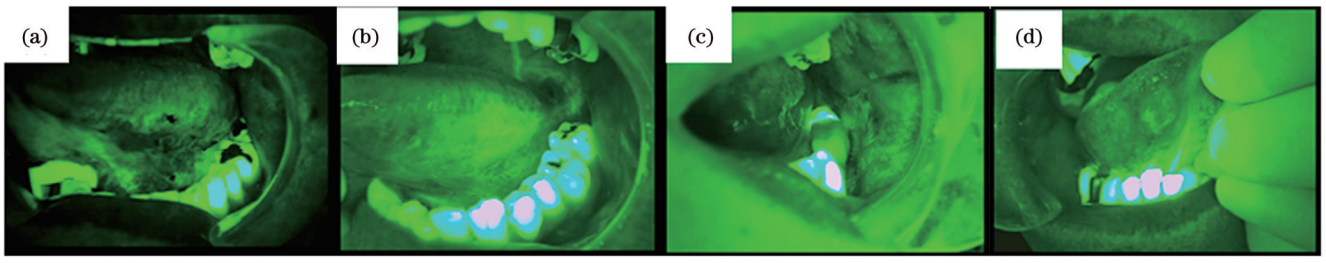

图 4 口腔黏膜病变的荧光图像[51]。(a)OSCC;(b)口腔白斑;(c)口腔扁平苔藓;(d)口腔炎

Fig. 4 Fluorescent images of oral mucosal diseases[51]. (a) OSCC; (b) leukoplakia; (c) lichen planus; (d) stomatitis

肿瘤中检测到ICG信号,但由于缺乏特异性,ICG在OSCC术中切缘评估中的适用性受到限制。5-氨基乙酰丙酸(5-ALA)是另一种已被提出用于口腔癌辅助诊断的外源性染料[53]。5-ALA本身不发光,但它是血红素合成途径中具有光敏性的PPIX(protoporphyrin IX)的生物前体。当5-ALA应用于口腔肿瘤检测时,可使PPIX在肿瘤细胞中选择性积累[54]。另外,为了提高ICG的特异性,研究人员开展了靶向肿瘤特异性生物标志物的研究,包括肿瘤细胞或肿瘤微环境中受体和蛋白的过度表达以及代谢活动的改变。有研究团队利用小麦胚芽凝集素结合异硫氰酸荧光素(WGA-FITC)研究了口腔肿瘤和异常增生病变,55名受试者的荧光成像表明,WGA-FITC可以检测口腔癌症和异常增生病变,灵敏度分别达到了100%和81%,但由于良性炎症病变的信号干扰,特异性只达到了82%[55]。

随着荧光技术的发展,其检测灵敏度和特异性逐步提高,但其安全性、分辨率以及定量测量等还有待进一步验证和改善,这些特性共同决定了荧光技术未来能否在口腔疾病检测中得到临床应用。

2.5 PAI技术

PAI技术是近几年发展起来的一种基于光声效应的无创生物医学成像技术[56],它可以很好地结合光学和UI技术的优势,获得内源性或外源性发色团的信息[56]。在PAI过程中,暴露于激光脉冲下的生物组织吸收光子后产生热弹性膨胀和弛豫,导致宽带(MHz)超声发射,用超声波换能器对信号进行采集[57-58]。目前,PAI已被用于各种肿瘤的临床前研究和临床诊断[59-60]。光吸收与血红蛋白浓度、氧饱和度等生理特性密切相关,因此,光声信号与局部能量沉积成正比,可以揭示光吸收的生理特异性[61]。

Fatakdawala等[62]将PAI用于仓鼠颊部癌变组织的在体成像,评估了PAI信号强度与肿瘤新生血管的相关性,如图5所示。Guo等[63]研究了PAI检测人类舌部肿瘤的可行性。

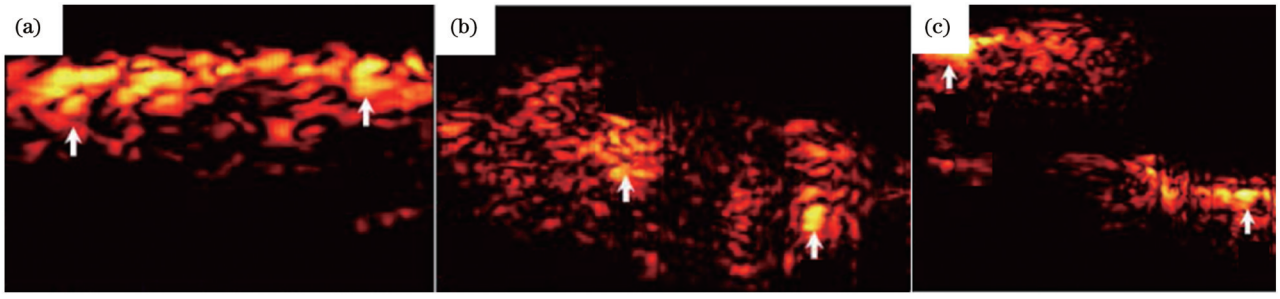

图 5 仓鼠颊袋模型的PAI成像结果,其中白色箭头所指高强度信号为血管[62]。(a)正常颊部组织;(b)癌前病变组织;(c)OSCC组织

Fig. 5 PAI results of hamster buccal pouch model, where high-intensity PAI signal pointed by white arrows is vascularization[62]. (a) Normal cheek tissue; (b) precancerous tissue; (c) OSCC tissue

国内奚磊教授课题组在光声成像系统小型化方面进行了探索:他们研制了旋转扫描式口腔探头,并采用该探头对口腔舌部和唇部进行了光声成像[64];之后通过结构优化设计,开发了质量仅为20 g、成像范围为2 mm×2 mm的便携式口腔探头[65],并利用该便携式超声探头对人体唇部血管网络进行了三维成像,观察了口腔溃疡毛细血管循环的恢复过程[66]。杨思华教授课题组[67]开发了手持式光声成像笔,利用该光声成像笔可以对口腔微血管进行前向和侧向实时高速成像。

2.6 OCT技术

OCT技术利用宽带光源的低相干性,通过探测和解调样品背向反射光或散射光与参考臂反射光的干涉信号,可以实时、无创、无标记地获得样品内部的二维、三维高分辨率断层图像[68-69]。OCT发展至今已有30余年的历史,已在临床上成功应用于眼科、心内科和消化内科[70-72]。

OCT技术在口腔领域的应用研究也得到了高度重视。Matheny等[73]使用OCT对仓鼠颊囊诱导的发育不良和恶性肿瘤进行了在体和离体成像。Wilder-Smith等[74-75]利用OCT对仓鼠颊袋进行了成像,观察

了口腔黏膜癌变过程中上皮和皮下组织的变化。Jung等[76]展示了正常仓鼠和癌前病变仓鼠颊囊标本的二维和三维OCT图像，以评估OCT诊断不同时期口腔病变的可行性。台湾大学的Yang教授课题组[77-79]利用OCT扫描口腔颊部黏膜癌前病变及癌变组织，分析了处于口腔癌不同发展阶段的黏膜特征。

笔者课题组对69例患者的19大类口腔病变组织（包含颌、颊、腭、舌、牙龈等部位的病变组织）进行了OCT术中离体成像[80]，图6显示了其中6种口腔肿瘤组织的OCT图像以及相应的组织病理学图像，这6种口腔肿瘤分别是腺样囊性癌、OSCC、基底细胞癌、脂肪瘤、成釉细胞瘤和多形性腺瘤组织，其中前3种属于恶性肿瘤，后3种属于良性肿瘤。图6所示结果表明OCT技术可以获得与组织病理学几乎一致的形态学图像，验证了OCT分辨不同口腔病变组织的可行性。

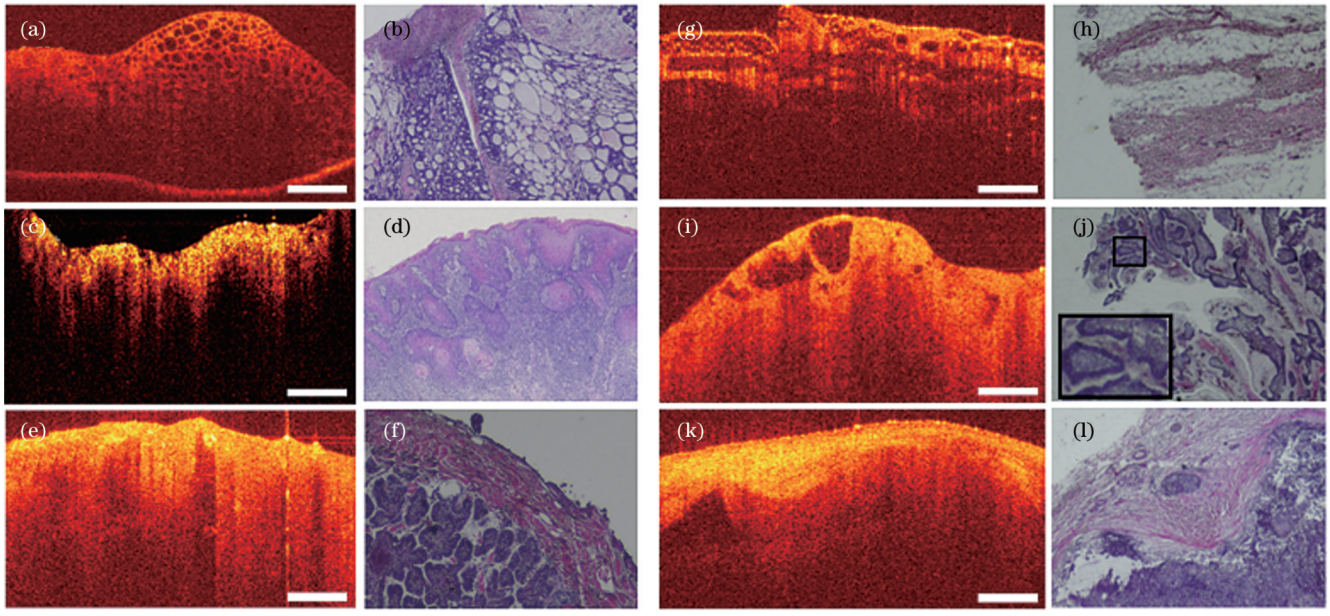

图6 6种口腔肿瘤的OCT图像与相应的组织病理学图像[80]。(a)(b)腺样囊性癌；(c)(d)OSCC；(e)(f)基底细胞癌；(g)(h)脂肪瘤；(i)(j)成釉细胞瘤；(k)(l)多形性腺瘤

Fig. 6 OCT images and corresponding histopathological images of 6 types of oral tumors[80]. (a)(b) Adenoid cystic carcinoma; (c)(d) OSCC; (e)(f) basal cell carcinoma; (g)(h) lipoma; (i)(j) ameloblastoma; (k)(l) pleomorphic adenoma

口腔黏膜的典型癌前病变是口腔白斑病。OSCC呈浸润性生长，当口腔白斑发生癌变时，癌变部分会突破基底膜。基底膜被破坏是判断口腔白斑区域癌变的一个重要标志。笔者课题组利用自主研发的OCT系统扫描了多种口腔黏膜白斑组织，扫描结果如图7所示[80]。从疣状白斑和均质白斑的OCT图像中可以清晰地看到基底膜，而对于发生癌变的白斑，其基底膜已被破坏。这些结果与组织病理学结果一致，验证了OCT技术在早期浸润性癌筛查方面的潜在价值。

除了OCT结构成像外，基于OCT的功能成像也被用于口腔癌检测，主要包括多普勒OCT、OCT血管造影和偏振敏感OCT成像。结合显微结构形态和微血管，OCT为正常和异常口腔组织的鉴别提供了更有力的工具[81-84]。Chen等[85]结合口腔OCT的结构和血管信息对小鼠舌部早期恶性病变和良性病变进行了区分，弥补了仅通过OCT结构成像识别良性增生性病变和早期恶性病变的不足。

结合偏振信息的偏振敏感OCT（PS-OCT）可以通过探测组织的双折射和退偏振信息来检测组织的病变。Chen等[86]使用PS-OCT对小鼠舌部组织进行了在体和离体成像，分析了口腔基质从正常、增生、异常增生到早期癌症的变化，该技术对异常增生和早期癌的灵敏性、特异性、阳性预测值和阴性预测值分别为100%、95%、93.75%和100%，初步验证了PS-OCT检测口腔早期微小恶性肿瘤的准确性[86]。该技术对口腔正常组织与癌症组织的检测结果如图8(a)、(b)所示。笔者课题组利用自行研发的高分辨率PS-OCT系统分析了离体口腔舌部OSCC和正常组织的双折射特性[87]，结果如图8(c)、(d)。这些结果表明，通过增加偏振等功能性信息，可以进一步提升OCT技术对口腔肿瘤筛查的准确性。

作为一种无创、高分辨率的成像技术，OCT技术在系统小型化方面也得到了快速发展，许多学者在设备小型化和便携性方面开展了大量研究，设计出了用于口腔黏膜成像的各种小型化探头，如图9所示。图9(a)是一种利用二维扫描振镜实现三维扫描的手持式探头[88]。图9(b)是一种光纤旋转回拉式侧成像导管探头，可覆盖2.5 mm宽的扫描视场，回拉速度最大为15 mm/s[89]。图9(c)是一种部署在远端的微机电（MEMS）侧向扫描探头，可实现近1.5 mm×1.5 mm

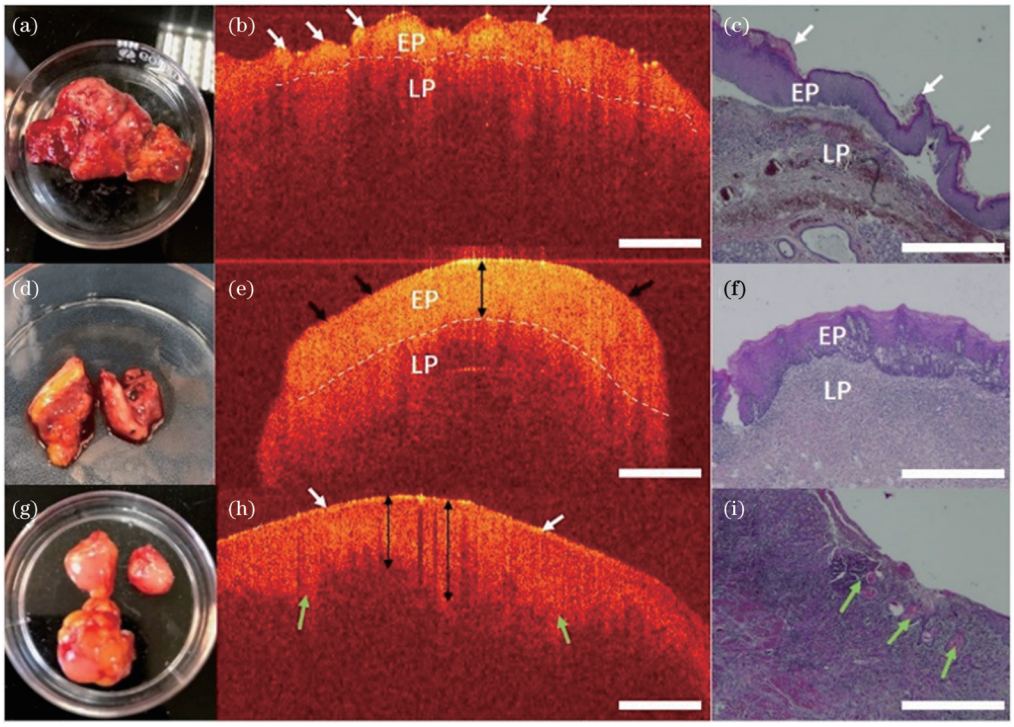

图 7 口腔白斑的离体组织照片、OCT 图像和相应的组织病理学图像[80]。(a)～(c)疣状白斑;(d)～(f)均质白斑;(g)～(i)癌变的白斑

Fig. 7 Photos, OCT images and corresponding histopathological images of *ex vivo* oral leukoplakia[80]. (a)–(c) Verrucous leukoplakia; (d)–(f) homogeneous leukoplakia; (g)–(i) leukoplakia canceration

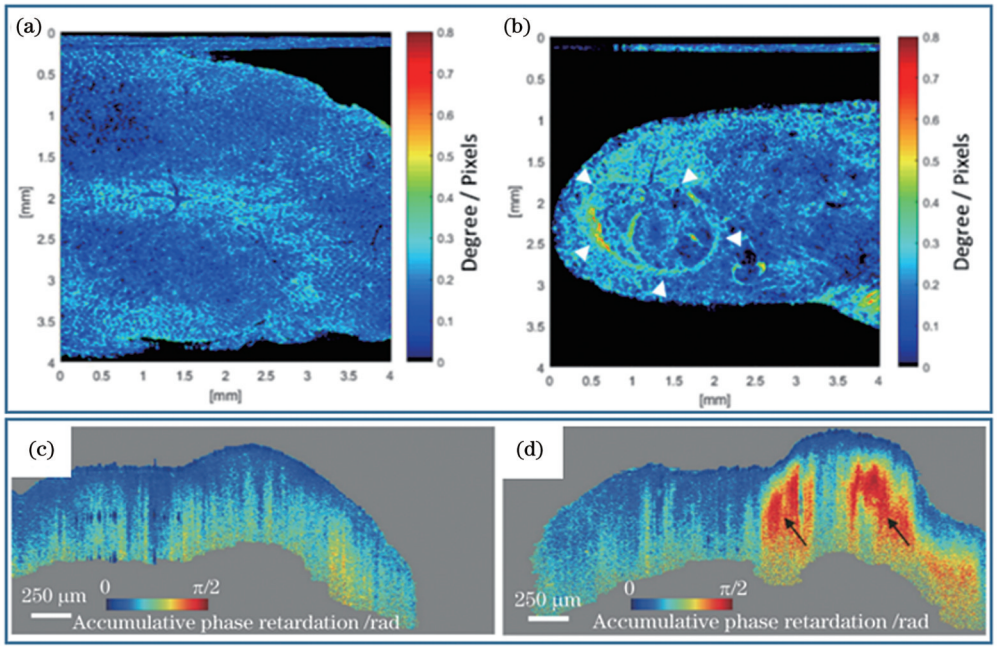

图 8 口腔正常组织与癌症组织的 PS-OCT 图像。(a)正常舌部组织的 *en face* 双折射图像[86];(b)癌症组织的 *en face* 双折射图像[86];(c)正常舌部组织的累积相位延迟图像[87];(d)正常组织与癌症组织边界处的累积相位延迟图像[87]

Fig. 8 PS-OCT images of normal and cancerous oral tongue tissues. (a) *En face* birefringence image of normal tongue tissue[86]; (b) *en face* birefringence image of cancerous tongue tissue[86]; (c) cumulative phase retardation images of normal tongue tissue[87]; (d) cumulative phase retardation images of the boundary between normal and cancerous tongue tissues[87]

的扫描视场[90]。为了实现口腔不同部位的成像,华盛顿大学的 Wang 教授课题组[91]开发了一种基于二维振镜的兼顾侧向和前向扫描的口腔探头,如图 9(d)和图 9(e)所示。图 9(f)是笔者课题组设计的一种部署在近端的 MEMS 二维扫描前向手持式探头,其质量仅为 25 g,可实现 2 mm×2 mm 的成像视场[92]。

2.7 不同成像学技术的对比

迄今为止,除了以上几种常见的成像技术之外,拉

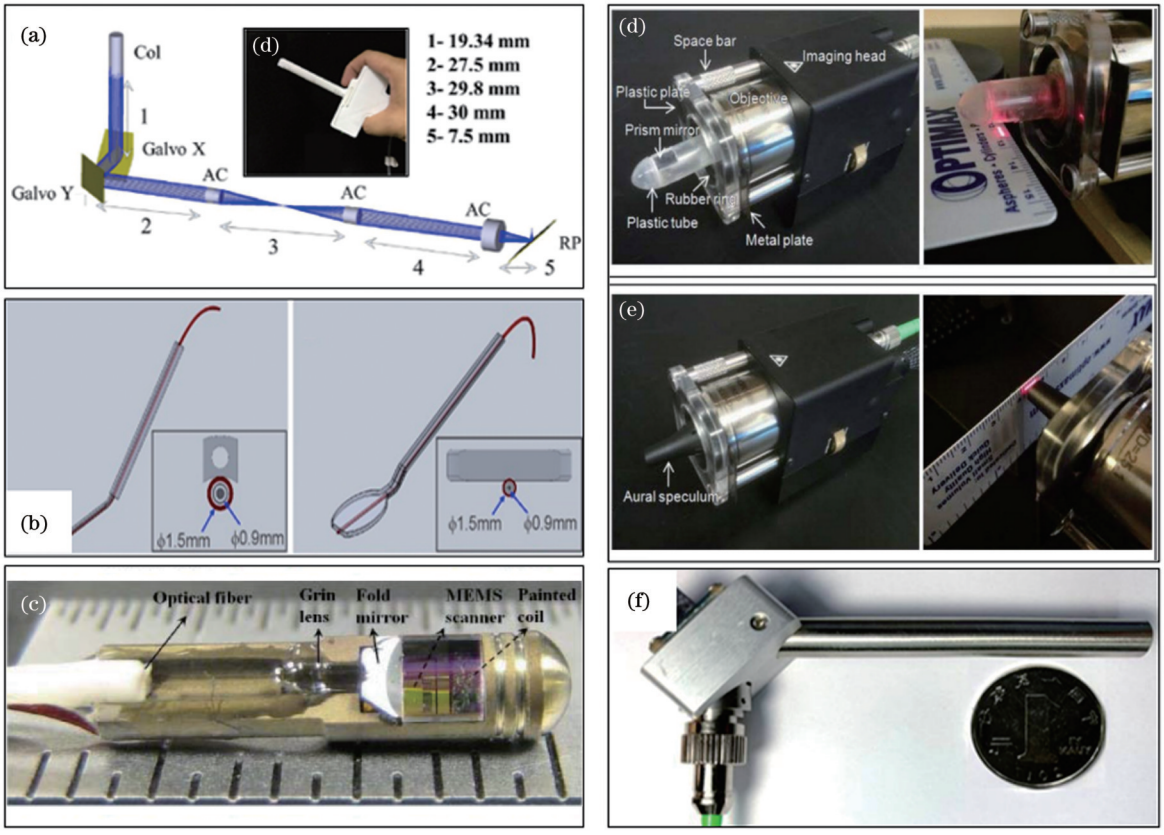

图 9 应用于口腔成像的 OCT 小型化探头。(a)基于二维扫描振镜的手持式探头[88];(b)基于光纤回拉式的导管探头[89];(c)MEMS 扫描镜部署于末端的探头[90];(d)(e)兼顾侧向和前向成像的探头[91];(f)MEMS 扫描镜部署于前端的探头[92]

Fig. 9 Different miniaturized OCT probes for oral imaging. (a) A handheld probe based on two-dimensional galvanometer[88]; (b) a fiber-optic rotary pullback scanning catheter probe[89]; (c) a scanning probe deployed a MEMS mirror at the distal end[90]; (d)(e) a scanning probe with side-view and forward view imaging[91]; (f) a scanning probe deployed a MEMS mirror at the proximal end[92]

曼光谱和窄带光谱等成像技术也被应用于口腔组织的成像研究中[93-94]。之所以分析这些成像技术的特点及成像结果,一方面是因为它们在口腔黏膜病临床上均具有潜在的应用价值,另一方面是因为探测深度和分辨率等关键性能参数限制了这些影像学技术在口腔黏膜病临床上的适用范围。另外,成像系统的小型化程度和造价同样影响着其在口腔黏膜病临床上的应用范围。表 1 给出了部分影像学成像技术性能参数的对比。由于 FI 涉及很多不同方案,研究人员更多地强调它的特异性和灵敏性,而且目前对其探测深度和分辨率还没有明确的定量,所以表中没有给出 FI 的探测深度和分辨率。

表 1 各类影像学技术的性能参数对比

Table 1 Performance parameter comparison of various imaging techniques

Imaging technique		Penetration depth	Resolution	Detection site	Miniaturization	Cost
Non-optical	CT	No limit	~1 mm	Bone involvement, metastatic lymph node	Low	Medium
	MRI	No limit	~1 mm	Bone involvement, metastatic lymph node	Low	High
	UI	<5 cm	>30 μm	Bone involvement, metastatic lymph node	High	Low
Optical	FI			Oral mucosa	High	Medium
	PAI	<10 mm	x: 1–20 μm z: 50–500 μm	Oral mucosa	High	Medium
	OCT	1–3 mm	1–20 μm	Oral mucosa	High	Low

非光学方法,如 X-CT 和 MRI,已经在常规的口腔临床上得到了应用,但是仍存在各种局限性,如:X-CT 具有足够的成像深度,可以评估是否存在骨侵袭,但其分辨率和特异性较差;MRI 同样具有大的探测深度,

且特异性比 X-CT 高，但其分辨率较差，成像时间长；随着超高频超声和超声造影的发展，UI能够满足大深度的口腔癌临床检查，但其分辨率依然无法满足微米级形态学病变结构早期变化的检测。

在光学方法中，FI可以提供分子信息，具有大视场和高灵敏性，但无法提供可解析的深度信息；PAI综合利用光学和声学优势，具有高的横向分辨率和大的成像深度，但纵向分辨率无法满足微小病变的检测；OCT具有微米级分辨率和毫米级成像深度，无法探测深层的癌变组织。光学方法将在口腔癌的早期筛查与诊断以及术中判断肿瘤边界等方面发挥重要作用，并由此改善病人的生存率和生活质量。

3 发展方向

口腔领域成像技术应用研究的最终目的是实现对口腔黏膜病变（尤其是口腔癌）的无损、实时、高分辨活体临床筛查和诊断。为了实现这一目标，需要进一步优化各类成像技术的性能，同时，以下技术也是未来影像学技术在口腔医学临床应用中重点发展的方向。

3.1 多模态技术

从上述分析可以看出，单一成像技术难以实现全面的辅助筛查和诊断。为了弥补单一成像技术的不足，近年来多模态系统得到了国内外的广泛关注[95-97]。Higgins 等[98]设计了一款高分辨率荧光成像和 OCT 技术相结合的便携探头。Yoon 等[99]报道了可同时进行宽视场反射/荧光成像和 OCT 成像的前视探头，该探头能够获得口腔组织表面形态和血管分布以及口腔组织内部的层状结构和双折射等多模态信息。Quang 等[100]开发了一种多模态成像辅助诊断系统，其中的 AFI 用于识别口腔内的高危区域，高分辨率微内镜用于确认肿瘤是否存在。Fatakdawala 等[62]报道了一种结合 FI、US 和 PAI 的无标记组织诊断多模态系统，该系统能够提供生化、结构和功能特征，增强了口腔癌的探测能力。

3.2 图像的定量化分析

在临床实践中，直观的图像观察或定性分析会不可避免地引入观察者自身或观察者之间的差异，并且需要相当大的时间成本。为了提高识别精度，降低读取图像的时间成本，基于口腔图像的定量分析技术被广泛研究，这种技术可以从图像中提取丰富的客观信息，制定定量化标准，帮助医生进行临床决策。

Huang 等[101]通过评估感兴趣区域的平均强度和异质性，开发了用于口腔癌筛查的自发荧光图像定量分析技术。Jeng 等[102]利用线性判别分析和二次判别分析对口腔颊部、舌部及牙龈处的正常黏膜组织以及癌前病变组织和恶性病变组织的自发荧光图像进行了定量分类。Kaneoya 等[103]定量评估了口腔舌部超声图像中 OSCC 的浸润程度与病理恶性分级之间的相关性。笔者课题组[104]提出了基于光学衰减模型来定量区分口腔舌部及牙龈黏膜 OCT 图像中癌组织和非癌组织的方法，并在此基础上应用光学衰减系数结合统计学参数（标准差）实现了 4 种唾液腺肿瘤的定量区分[105]。图 10 是基于光学衰减模型重建的口腔癌组织和正常组织的 OCT 伪彩色图像。基于光学衰减模型，通过设定合适阈值重建的伪彩色图像可以帮助医生清楚地分辨癌和非癌组织。

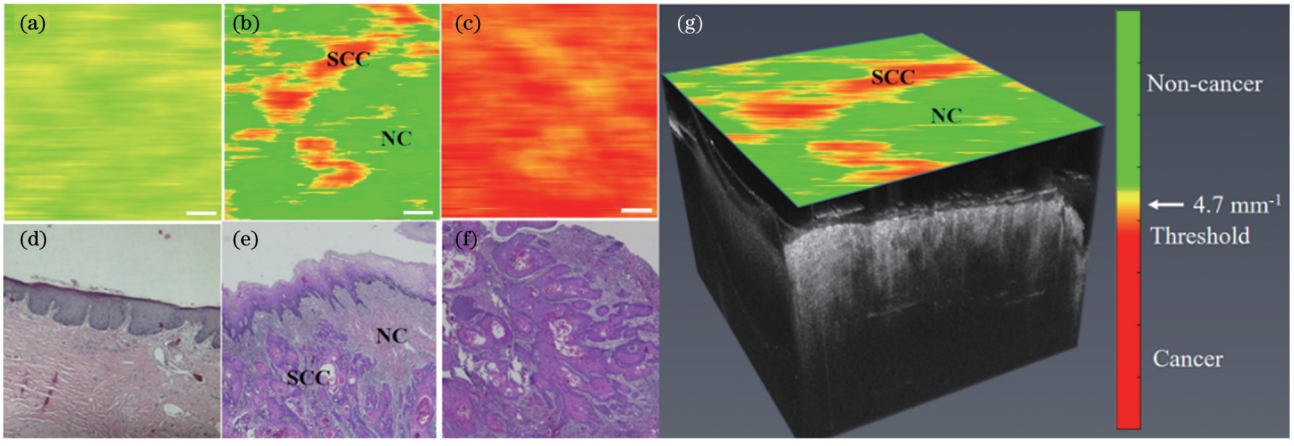

图 10 基于光学衰减模型的不同口腔组织的 *en face* 图像及相应的组织病理学图像[104]。(a)(d)非癌组织；(b)(e)非癌与癌症边界区域；(c)(f)癌组织；(g)三维重建结果

Fig. 10 *En face* images based on optical attenuation model of different oral tissues and their histopathological images[104]. (a)(d) Non-cancerous tissue; (b)(e) boundary between non-cancerous and cancerous tissues; (c)(f) cancerous tissue; (g) three-dimensional reconstruction

3.3 结合人工智能的成像技术

人工智能方法提供了另一种进行图像评价的客观方法。近年来，越来越多的研究人员通过人工智能结合相应成像技术对提高诊断准确率以及病变可视化进行了探索，如：Jeyaraj 等[106]提出了一种用于口腔癌高光谱图像分类的深度卷积神经网络算法；Xu 等[107]建立了一种基于三维卷积神经网络的图像处理算法，该方法可基于 CT 图像实现口腔癌的早期诊断；Song

等[108]提出了一种基于深度学习的自发荧光和白光图像分类方法，验证了深度学习对口腔癌双模态图像分类的有效性；Bhandari等[109]专注于在MRI图像中检测口腔肿瘤，提出了一种基于卷积神经网络的算法来区分肿瘤的良、恶性；Marsden等[110]研究了在口腔扁桃体、舌等FI图像中区分健康组织和肿瘤的方法，证明了机器学习方法可以辅助医生分辨FI图像中的肿瘤边界，具有指导口腔癌切除手术的潜力；笔者课题组采用一种基于纹理特征的方法来识别口腔舌部及牙龈组织OCT图像中的口腔肿瘤[111-112]，并通过建立人工神经网络，实现了口腔癌前病变与癌组织的区分[113]。随着人工智能方法的推陈出新，它们将在口腔癌的筛查与诊断中发挥重要作用。

4 结束语

发展无损、实时、高分辨、高灵敏、高特异性的影像学技术对于口腔癌的筛查与诊断具有重要意义。笔者总结了目前在口腔癌筛查与诊断中应用的影像学技术的研究成果，分析了各技术的成像特点以及临床应用的可行性与适用场景。不同的影像学技术有着其独特的优势与适用场景限制，非光学方法已经在口腔临床上发挥了重要作用，但是受限于分辨率，无法发现早期口腔癌；光学方法具有高分辨、高灵敏度的优势，但其成像深度不足以覆盖完整的癌症区域，适合早期癌症的筛查。结合多种成像技术构建的多模态系统可实现优势互补。在改善影像学技术硬件性能指标的同时，开发定量化及基于人工智能的计算机辅助方法是各种影像学技术在口腔癌筛查与诊断应用中的重点发展方向。

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Imaging Technologies for Oral Cancer Screening and Diagnosis and Their Development Trends

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Abstract

Significance Oral cancer is among the most common cancers of the head and neck. Despite advancements in targeted cancer therapy, the survival rates of oral cancer patients have plateaued over the last 50 years. Common screening methods for oral lesions, such as visual inspection and palpation of tissue surfaces, are highly dependent on the experience of clinicians. Even if the biopsy or histopathological examination is performed for highly suspicious tissue regions, the limitations of time-consuming, invasive, and label-intensive are still inevitable. In clinical practice, intraoperative frozen section biopsies for surgical margins are routine procedures performed after en bloc resections of oral cancers. However, surgical margins are usually selected according to surgeon estimates of sites that may be suspicious of inadequate resection, resulting in the omission of positive margins. In addition, early detection of oral cancer plays a critical role in improving the prognosis and survival rate, but, accurate identification is difficult based on conventional screening methods.

To improve the clinical diagnosis of oral diseases, researchers have conducted numerous studies on auxiliary diagnostic techniques, including X-ray computed tomography (X-CT), magnetic resonance imaging (MRI), ultrasound imaging (UI), fluorescence imaging (FI), photoacoustic imaging (PAI), and optical coherence tomography (OCT). Based on the associated imaging theories, different imaging technologies have unique advantages in terms of detecting oral diseases, resulting in different application scenarios. In this paper, we review the research on the foregoing auxiliary imaging technologies, summarize their advantages and disadvantages, and discuss the challenges and future developments in oral clinical applications.

Progress Different technologies demonstrate different features in terms of improving diagnostic sensitivity, specificity, resolution, and so on. Notably, X-CT and MRI are the earliest techniques used in oral clinics. They are exceptional in terms of their imaging depth and can evaluate bone invasion and the thicknesses of oral cancers.

In recent years, with improvements in ultrasonic technology, the imaging resolution of UI using ultra-high-frequency ultrasound (30–100 MHz) has considerably improved. Such improved resolutions facilitate the observations of smaller microstructures

(approximately 30 μm in size) of oral tissues. One recent study demonstrated that diagnostic sensitivity, specificity, and negative predictivity with values of over 90% were achieved in 150 patients with oral soft tissue lesions using an ultra-high UI system. In addition, Doppler ultrasound plays a major role in evaluating the neovascularization of oral neoplasms and metastatic lymph nodes by obtaining blood flow information (Fig. 3).

Advancements in FI, including both auto- and extrinsic fluorescence, have enabled the exploitation of molecular information. Interestingly, autofluorescence of the oral epithelium and submucosa can be generated by laser excitation at 400–460 nm, which can then be used to identify oral lesions derived from changes in the concentration and properties of fluorophores. In contrast to benign oral mucosal lesions, malignant lesions are associated with autofluorescence loss. However, several benign lesions also exhibit fluorescence decay, resulting in low specificity. Through the continual exploration of fluorescent dyes and targeted tumor biomarkers, FI can achieve higher specificity in the detection of oral tumors.

PAI is an imaging technology that has undergone developments in recent years and is based on the photoacoustic effect. Combining the advantages of optics and ultrasound, this technique has technical advantages in detecting oral tumor neovascularization (Fig. 5).

OCT, which is a high-resolution, non-destruction, and label-free method, has been successfully used in ophthalmology, cardiology, and gastroenterology. Moreover, the feasibility of OCT in distinguishing different oral tumors has been verified (Fig. 6). In addition, for the early detection of oral cancer, OCT has been used to detect different types of oral mucosal leukoplakia (Fig. 7).

To facilitate oral clinical studies, PAI and OCT are also undergoing rapid developments in terms of system miniaturization. In recent years, researchers have developed various miniaturized probes for oral imaging (Fig. 9).

To compensate for the shortcomings of single-imaging techniques, multi-modal systems combining multiple diagnostic techniques have also been developed.

With visual observations or qualitative analysis, misdiagnosis is inevitable. To improve the accuracy of image recognition and reduce the time cost associated with image reading, quantitative analysis and artificial intelligence approaches based on oral tissue images have been widely studied with the aim of extracting rich information from images (Fig. 10).

Conclusions and Prospects Imaging technologies with non-destruction, high resolution, high sensitivity, high specificity, and real-time will play a critical role in assisting clinicians in screening and diagnosing oral cancers. Owing to the unique characteristics of different imaging techniques, their clinical application scenarios are different. Single-imaging techniques cannot completely satisfy all the requirements of oral disease diagnoses. Therefore, combining multiple imaging techniques to construct a multi-modal system can provide more abundant diagnostic information. In addition, quantitative and AI-based computer-aided methods that can provide objective screening and diagnostic results are expected to be developed.

Key words medical optics; medical and biological imaging; oral cancer; imaging technique; screening; diagnosis