食管癌放疗联合免疫治疗的进展与挑战

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摘　要：放疗作为标准的局部治疗，近年来相关研究发现其通过产生免疫刺激和免疫抑制作用，发挥不同的免疫调节效应。因此，放疗联合免疫治疗已被视为一种有效的癌症治疗新策略；然而，联合治疗的适用性仍存在一定争议，包括联合治疗的毒性和安全性、排序与时机、最佳剂量和分次等问题。全文总结当前放疗联合免疫治疗在食管癌治疗中的新进展，为全面了解、设计优化食管癌放疗联合免疫治疗方案提供必要的理论支撑。

主题词：食管癌；放射疗法；免疫疗法；免疫检查点抑制剂
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Advances and Challenges of Radiotherapy Combined with Immunotherapy for Esophageal Cancer

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Abstract: Radiotherapy, as a standard local treatment, can produce various immune modulation effects by generating immune stimulation and suppression. The combination of radiotherapy and immunotherapy has been considered as an effective new strategy for cancer treatment. However, the applicability of combination therapy remains controversial in terms of toxicity and safety, sequencing and timing, optimal dosage and fractionation. This paper reviews the latest advances in radiotherapy combined with immunotherapy for esophageal cancer treatment, to provide a reference for novel strategies of esophageal cancer treatment.

Suject words: esophageal cancer; radiotherapy; immunotherapy; immune checkpoint inhibitors

根据2020年度世界卫生组织统计数据，全球范围内食管癌在所有恶性肿瘤中的发病率位列第8位[1]。迄今，手术治疗依然是食管癌最常见的治疗方法，然而手术治疗的适应证仅限于早期寡转移且一般状况良好可以耐受手术治疗的患者；对于出现了远处转移的晚期食管癌患者以及存在严重心肺功能不足的患者来说，手术治疗不仅无法达到根治的目的，甚至会带来生命危险。相对于手术治疗，食管癌放疗有着更广泛的适应证，尤其对于无法进行手术的晚期食管癌，姑息性放疗可显著性延缓肿瘤进展[2]。对于一些难以进行手术治疗的食管癌患者，可以通过术前放疗缩小肿瘤体积，进而创造手术机会[3]。已有研究比较了接受新辅助放疗同时手术治疗的食管癌患者与单纯手术治疗患者的临床治疗效果，结果显示，接受新辅助放疗治疗的患者疗效提高，心肺毒性降低，表明新辅助放疗在食管癌多模式治疗中发挥着重要作用[4]。一项Ⅲ期临床试验中，在不可单纯切除治疗的食管癌患者中，将同期放化疗与单纯放疗进行比较，与单纯放疗的患者相比，接受同期放化疗患者的5年生存率明显提高，但同时放化疗也导致了较为严重的急性毒副作用[5]。这两项临床研究都是在二维放疗时代进行的，均存在放疗辐射面积较大、对人体和正常器官的毒性较大等缺陷。

目前，高精度放疗使治疗靶区更加精确、中心剂量高，而附近正常组织的剂量低[6]。新的放疗技术，如三维适形放疗(three-dimensional conformal radio-

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therapy,3D CRT)、调强适形放疗(intensity modulated radiation therapy,IMRT) 和容积旋转调强放疗(volume modulated arc therapy,VMAT) 已被广泛应用于食管癌的治疗。Sun 等[7]研究表明,与接受 3D CRT 的患者相比,IMRT 食管癌患者的局部控制率显著性提高、总生存期延长,与放疗相关的不良反应更少,提示 IMRT 可能是食管癌的优选方案之一。近年来,质子治疗作为精准放疗的重要方式,因其可以向靶区提供高剂量的辐射但周围正常组织的照射剂量很小,进而显著性降低不良反应,这一优势源于质子的特殊深度剂量分布,即布拉格峰现象[8]。特别当靶区位于肺部时,正常肺组织、心脏和脊髓几乎完全不会受到辐射影响。因而可以预见质子治疗在食管癌的放疗中将发挥重要作用。2019 年发布于美国放射肿瘤学会会议上的一项质子束治疗与 IMRT 治疗食管癌的单中心研究, 比较不同疗法患者的总毒性反应和无进展生存期,结果显示,两组 3 年无进展生存率和总生存期相当, 但 IMRT 组的平均总毒性反应是质子治疗组的 2.3 倍,显著性高于质子治疗组,表明质子治疗除剂量学优势外, 严重不良事件明显减少[9]。尽管如此,质子治疗作为一种新型的放疗手段, 还需要采用更大的样本量和更长的随访时间来进一步明确其有效性和安全性。

放疗被认为是标准的局部治疗, 主要是通过直接诱导靶细胞 DNA 损伤来发挥抗肿瘤作用[10]。近年来相关研究发现, 放疗还能通过产生免疫刺激和免疫抑制作用而发挥不同的免疫调节效应; 而这种效应与放疗剂量、分割方式、肿瘤类型和照射野等密切相关。机制学研究现已明确,局部放疗可以明显增加 MHC 抗原的表达,释放的肿瘤抗原诱导原位接种和放大的免疫刺激信号 (钙蛋白、热休克蛋白和 HMGB1 等)有助于放疗的免疫刺激作用[11]。此外,放疗还可以诱导免疫抑制细胞 (包括调节性 T 细胞、骨髓源性的抑制细胞和肿瘤相关的巨噬细胞等)在肿瘤组织中的积累,发挥免疫抑制作用[12]。

1 食管癌免疫治疗进展

肿瘤的免疫治疗是指通过激活体内的免疫细胞、增强机体抗肿瘤的免疫应答,克服肿瘤的免疫逃逸,通过自身免疫来清除肿瘤细胞的一种治疗方式。近年来,免疫治疗在肿瘤治疗中突飞猛进,为晚期肿瘤患者带来了新的希望。例如:免疫检查点 PD-1 抑制剂已经证实可以增强包括食管癌在内的多种肿瘤的 T 细胞抗肿瘤活性[13-14]。近期一项随机、开放的Ⅲ期研究 CheckMate 648 显示, 在肿瘤细胞 PD-L1 表达≥1%患者和整体人群中,PD-1 抑制剂纳武单抗联合化疗的总生存期均显著性优于单纯化疗; 纳武单抗加伊匹单抗(CTLA-4 抑制剂)也显著延长了总生存期。在肿瘤细胞 PD-L1 表达≥1%患者中,纳武单抗联合化疗组的无进展生存期也显著延长[15]。另一项多中心、双盲的Ⅲ期试验 ASTRUM-007 共招募了 551 例 PD-L1 合并阳性得分≥1 的未接受过治疗的局部晚期或转移性食管鳞状细胞癌患者, 将其随机分为斯鲁利单抗(PD-1 抑制剂)联合化疗组和安慰剂加化疗组。研究结果显示, 相对于安慰剂加化疗组, 斯鲁利单抗联合化疗显著改善了患者的无进展生存期和总生存期, 治疗相关不良事件的发生率在两组之间有统计学差异[16]。值得注意的是,食管腺癌 PD-L1 阳性率仅为 18%, 而食管鳞状细胞癌 PD-L1 阳性率约 44%,提示食管鳞状细胞癌可能对免疫治疗的有效性更佳[17]。

对近年来食管癌临床免疫治疗研究领域 5 项重要研究的异同点进行了对比 (Table 1), 包括 ASTRUM-007、RATIONALE-306、KEYNOTE 590、ATTRACTION-3 以及 CheckMate 648 研究。这些临床试验结果均表明,在食管癌治疗中,免疫治疗发挥着至关重要的作用,具有重要的前景和应用价值。

2 放疗的远隔效应

1953 年 Mole 首次提出“远隔效应”(abscopal effect),认为放疗不仅能缩小目标肿瘤, 还能对未照射的远端肿瘤产生治疗效果[18],这种现象在结直肠癌、肺癌等肿瘤中已有报道[19-20]。“远隔效应”受到放疗的剂量、分割方式、介入时机以及肿瘤类型等多种因素的影响,但其具体机制仍未被完全阐明。目前研究已经证实肿瘤抗原、免疫抑制细胞如髓系抑制性细胞(myeloid-derived suppressor cells,MDSCs) 和调节性 T 细胞(regulatory T cells,Tregs)、免疫抑制细胞因子(IL-10 和 TGF-β)会阻碍低免疫原性放射部位的“远隔效应”的发生[21]。2018 年,Bruton 等[22]报道了 1 例

Table 1 Comparison and summary of different immunotherapy clinical trials for esophageal cancer

Trial	Investigational drug	Study participants	Sample size	Results evaluation
ASTRUM-007	Serplulimab	Patients with previously untreated, locally advanced or metastatic ESCC and PD-L1 combined positive score ⩾1	551	Serplulimab plus chemotherapy improved PFS (5.8 *vs* 5.3 months) and OS (15.3 *vs* 11.8 months) compared to placebo plus chemotherapy. Grade 3 or higher adverse events were observed in 53% and 48% of patients in respective groups
RATIONALE-306	Tislelizumab	Patients with advanced or metastatic ESCC	649	Tislelizumab with chemotherapy improved median OS (17.2 *vs* 10.6 months), PFS (7.3 *vs* 5.6 months), and ORR. Safety was similar between groups, with comparable treatment-emergent adverse events
KEYNOTE 590	Pembrolizumab	Patients aged 18 years old or older with previously untreated, advanced oesophageal cancer and siewert type 1 gastro-oesophageal junction cancer	749	Pembrolizumab plus chemotherapy improved OS and PFS in oesophageal cancer patients compared to chemotherapy alone, with similar treatment-related adverse events
ATTRACTION-3	Nivolumab	Previously treated patients with advanced ESCC	419	Nivolumab significantly improved OS compared to chemotherapy (median OS: 10.9 months *vs* 8.4 months), fewer grade 3 or 4 treatment-related adverse events were reported in the nivolumab group compared to the chemotherapy group
CheckMate 648	Nivolumab, ipilimumab	Adults with previously untreated, unresectable advanced, recurrent, or metastatic ESCC	970	Nivolumab plus chemotherapy and nivolumab plus ipilimumab significantly improved OS compared to chemotherapy alone in patients with advanced ESCC. Treatment-related adverse events were observed in each group

Notes: ESCC: esophageal squamous cell carcinoma; PFS: progression-free survival; OS: overall survival; ORR: objective response rate

食管腺癌多处转移而接受姑息性放疗的 74 岁男性患者，在其受照射和未受照射的转移淋巴结中都显示出完全缓解反应。同年，Zhao 等[23]报道了 1 例 65 岁的左侧腹膜后淋巴结转移的男性食管癌患者，经过射波刀（全身立体定位放疗设备）靶向左腹膜治疗后，PET/CT 扫描显示在放疗治疗后 2 个月内未发现任何淋巴结转移。上述研究表明，放疗诱导食管癌“远隔效应”的产生，具有重要的临床价值。但鉴于“远隔效应”的罕见性和不可预测性，如何有效地利用其对食管癌临床治疗的有益作用，仍需要更多的前瞻性临床研究和机制学研究去进一步证实。

3 放疗联合免疫治疗是食管癌临床治疗的新方向

2012 年 Postow 等[24]首次报道了 1 例恶性黑色素瘤患者用伊匹单抗联合放疗治疗，不仅原发病变完全消退，甚至在照射区之外的肿瘤（右肝淋巴结和脾脏）也完全消退。近年来，随着对 T 细胞调控机制相关研究的不断深入，越来越多的免疫检查点抑制剂（immune checkpoint inhibitors, ICIs）被开发出来，并在针对多种恶性肿瘤（包括一些以前被认为对免疫治疗不敏感的肿瘤）的临床研究中显示出喜人的疗效，这些针对放疗联合免疫治疗的开创性研究激发了更多食管癌相关临床研究的开展。近期，一项单臂、Ⅱ期临床试验 EC-CRT-001 针对无法手术切除的局部晚期食管鳞状细胞癌患者，提供了特瑞普利单抗（PD-1 抑制剂）与放化疗的综合治疗方案。在参与试验的患者中，62%达到完全缓解，1 年总生存率为 78.4%，1 年无进展生存率为 54.5%。相比较于传统治疗方法，这一方案为局部晚期食管鳞癌患者带来了显著的疗效和可接受的副作用[25]。另一项临床试验 PALACE-1 通过预先应用帕姆单抗（PD-1 抑制剂）与同步放化疗（preoperative pembrolizumab with concurrent chemoradiotherapy, PPCT）方法，对 20 例可切除食管鳞状细胞癌患者进行治疗。结果表明，65%患者出现了Ⅲ级及以上不良事件，其中淋巴细胞减少症占比最高（92%）。在接受手术治疗的 18 例患者中，病理完全缓解（pathologic complete response, pCR）率达到了 55.6%。研究显示，PPCT 治疗在安全性及诱导切除病例实现 pCR 方面具有潜在优势[26]。研究结果表明，对于局部晚期食管癌患者来说，无论是特瑞普利单

抗还是帕姆单抗治疗都是安全、可行的辅助性疗法。

总结近期的放疗联合免疫治疗的几项临床试验研究(Table 2)。目前仍有几项关于放疗联合免疫检查点抑制剂治疗食管癌的前瞻性、多中心、随机临床试验正在进行中。预期在不远的将来,放化疗联合免疫检查点抑制剂和新辅助治疗的安全性及有效性将更加清晰,这将有助于临床放化疗联合免疫治疗方案的进一步完善与规范化。

4 放疗联合免疫治疗在食管癌临床治疗中面临的问题与挑战

尽管放疗与免疫治疗联合治疗已被视为一种有效的癌症治疗新策略,但其适用性仍存在一定争议。相关研究表明多种因素可能影响放疗联合免疫治疗的疗效。

4.1 联合治疗的毒性与安全性尚待明确

大量临床研究已发现,单独使用免疫调节剂即引起严重的不良反应,包括暴发性心肌炎伴横纹肌溶解、免疫相关的肺炎和间质性肺炎等[27]。近期的免疫调节剂联合放疗相关临床试验普遍报道了治疗相关的毒性反应。在一项开放性的Ⅱ期临床试验中,研究人员评估了联合应用纳武单抗和伊匹单抗治疗未接受过 ICIs 以及曾接受过 ICIs 治疗的晚期 Merkel 细胞癌患者的安全性和疗效。在50 例参与试验的患者中,有 45 例(占 90%)出现了不良反应,其中 8 例患者因毒性而中止了治疗方案[28]。在这项研究中,不良反应主要归因于纳武单抗和伊匹单抗的联合使用。在另一项开放标签、随机、对照的Ⅱ期研究中,研究人员旨在评估立体定向放射治疗(stereotactic body radiotherapy,SBRT)联合派姆单抗和曲美替尼(MEK1/2 抑制剂)在术后局部复发的胰腺癌患者中的疗效。结果显示,丙氨酸氨基转移酶(alanine aminotransferase,ALT)或门冬氨酸氨基转移酶(aspartate aminotransferase,AST)升高为最常见的不良反应。在接受 SBRT 联合派姆单抗和曲美替尼治疗的 85 例患者中,有 19 例(22%)出现严重不良事件[29]。而在食管癌中,虽然放疗联合免疫治疗显示出了良好的临床效果,但研究已显示该治疗策略比单独进行放疗或免疫治疗更易发生严重不良事件[30]。因此,明确不同免疫治疗策略与放化疗联合应用的毒性和副反应对于建立合适的联合治疗方案具有重要的现实意义。

4.2 放疗联合免疫治疗的序贯方案尚不确定

尽管放疗引起免疫微环境的激活可显著提高疗效,但放疗本身也会造成细胞免疫的抑制作用[31]。Herrera 等[32]在有关小鼠卵巢癌的研究中发现,与单纯放疗或单纯使用免疫检查点抑制剂相比,放疗后给予 PD-1 和 CTLA-4 抑制剂治疗可以显著性减小肿瘤体积,提高生存率。Young 等[33]发现,在荷瘤小鼠中,在使用 20 Gy 放疗的前 7 d 给予 CTLA-4 抑制剂取得了最佳疗效,表明在放疗前给予 CTLA-4 抑制剂可以诱导免疫调节效应。Wu 等[34]在膀胱癌中的研究发现,PD-L1 表达与膀胱癌的疾病进展呈正

Table 2 Comparison and summary of different radiotherapy combined with immunotherapy clinical trials for esophageal cancer

Trial	Treatment methods	Study participants	Sample size	Results evaluation
EC-CRT-001	Concurrent thoracic radiotherapy,chemotherapy,and toripalimab	Patients with unresectable,stage Ⅰ~ⅣA ESCC	42	62%(26/42) had a complete response,1-year OS was 78.4%,1-year PFS was 54.5%. The most common grade 3 or worse adverse event was lymphopenia(86%). One patient died from treatment-related pneumonitis(2%)
PALACE-1	PPCT	Patients with resectable ESCC	20	65%(13/20) experienced grade 3 or higher adverse events,with 92%(12/13) having lymphopenia as the most frequent grade 3 adverse event. pCR rate was 55.6%(10/18) among patients who underwent surgery
PERFECT	nCRT combined with atezolizumab	Patients with rEAC	40	85% of patients received all cycles of atezolizumab,83% proceeded to surgery,and the pCR rate was 25%(10/40)

Notes:PPCT:preoperative pembrolizumab with concurrent chemoradiotherapy; pCR:pathologic complete response; nCRT:neoadjuvant chemoradiotherapy; rEAC:resectable esophageal adenocarcinoma;ESCC:esophageal squamous cell carcinoma; OS:overall survival; PFS:progression-free survival

相关;在膀胱癌小鼠模型中,辐射明显上调了 PD-L1 的表达,提示放疗可能增加患者对 PD-L1 治疗的敏感性。KEYNOTE-001 研究针对局部晚期或转移性非小细胞肺癌患者，探讨了派姆单抗单药治疗的效果，次级分析结果表明，在接受派姆单抗治疗过程中，曾经接受过放疗患者的无进展生存期和总生存期显著优于未接受过放疗的患者,表明在接受派姆单抗治疗前进行放疗对于提高患者的生存期具有重要意义[35]。在食管癌中,CRISEC 研究关注新辅助放化疗联合替雷利珠单抗(PD-1 抑制剂)的应用。该研究成果有助于阐明在局部晚期可切除食管癌中替雷利珠单抗序贯添加的安全性和有效性[36]。然而,免疫治疗与新辅助放化疗的最佳组合时机尚未明确。而且，由于射线引起的机体免疫激活效应持续时间短且不可预测,因此还有待进行更详尽的基础研究和临床试验来进一步确定放疗联合免疫治疗的最佳序贯方案。

4.3 联合治疗中放疗最佳剂量与分割方式尚无标准化方案

在传统分割与大分割的照射条件下，肿瘤患者的预后有很大差别[37-38]。随着放疗技术的发展,靶区顺应性增强,周围正常组织的辐射剂量降低,使得采用单次高剂量的照射方案得以实现，并表现出更优的生物等效剂量和更好的临床疗效[39]。Twyman-Saint等[40]在小鼠 B16 恶性黑色素瘤移植模型中发现,ICIs 与单次 20 Gy 剂量照射之间有着充分的协同作用。然而,Dewan 等[41]的研究中发现,相比单次大剂量放疗联合 CTLA-4 抑制剂,分次局部放疗与 CTLA-4 抑制剂联合使用时表现出更佳的协同效应,在乳腺癌、结肠癌模型中诱导远隔效应和抗肿瘤 T 细胞的浸润。该研究认为长时间的分次局部放疗在临床治疗中可能更为有利。根据现有研究结果可见,放疗联合免疫治疗实践中最佳照射剂量和剂量分割方式要视具体临床情况而定,目前尚无确定的标准化方案。

另一个尚未明确的问题是关于放疗的总剂量,在抑制肿瘤的同时需要考虑炎症反应的诱导和免疫反应的激活。鉴于机体淋巴细胞对电离辐射的高度敏感性，过高的总剂量可能会破坏宿主的抗肿瘤免疫力，而过低的放射总剂量则有可能无法引发有效的抗肿瘤免疫反应[42]。Bradley 等[43]研究发现,标准剂量放疗组(60 Gy) NSCLC 患者 1 年总生存率为81%,而高剂量组(74 Gy)为 70.4%,说明更高的总剂量可能并不意味着更好的预后,但其机制仍未阐明,可能是与不同剂量导致的抗肿瘤免疫反应不同有关,仍需进一步的研究来证实。

5 展　望

放疗联合免疫治疗食管癌的治疗策略临床潜在价值较高。已有临床前研究显示抗肿瘤免疫反应激活,证实了放疗联合免疫治疗对于食管癌临床干预的有效性[44-48]。目前正在进行的关于食管癌联合同期放化疗的前瞻性研究也显示了这种组合的多种优势,然而,放疗和免疫治疗最佳的联合策略仍有待确定,包括分割模式、放疗剂量、联合治疗的时间窗等。

综上所述，放疗联合免疫治疗在食管癌临床治疗方面具有广阔的前景，相信经过不断完善和优化治疗方案后,必将发挥越来越重要的作用。

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