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·专题报道·

^{177}Lu-PSMA-617治疗转移性去势抵抗性前列腺癌新进展

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［摘要］ 姑息性手术、试验性局部治疗、外放射治疗、内分泌治疗、化学治疗等常规治疗手段对转移性去势抵抗性前列腺癌（mCRPC）患者的预后和生活质量改善效果有限。以前列腺特异性膜抗原（PSMA）为靶点的放射性配体治疗（RLT）有望改变mCRPC患者生存期短、生活质量差的现状。^{177}镥（^{177}Lu）标记的PSMA-617（^{177}Lu-PSMA-617）的理化性质和药代动力学特性优异，与其他放射性核素标记的治疗探针相比，已积累了较多临床研究数据和经验，有效性、安全性、易获得性高，显示出了较好的临床价值和应用前景，但尚存在一些局限。目前，^{177}Lu-PSMA-617 RLT仍以小样本单中心研究为主，但随着全球研究大数据的积累，其有望成为mCRPC临床常规治疗的延伸和补充。

［关键词］ 前列腺肿瘤；转移性去势抵抗性前列腺癌；前列腺特异性膜抗原；放射性配体治疗；^{177}镥
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^{177}Lu-PSMA-617 in treatment of metastatic castration-resistant prostate cancer: an update

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［Abstract］ Conventional therapy (such as palliative surgery, experimental local therapy, external radiotherapy, endocrine therapy and chemotherapy) has limited effect on the prognosis and quality of life in patients with metastatic castration-resistant prostate cancer (mCRPC). Radioligand therapy (RLT) with prostate-specific membrane antigen (PSMA) targeted probe is expected to change the situation (short survival and poor quality of life in mCRPC patients). ^{177}Lutetium labelled PSMA targeted ligand PSMA-617 (^{177}Lu-PSMA-617) has excellent physical and chemical properties and pharmacokinetic properties. Compared with other radionuclide labelled probes, we have accumulated more clinical research data and experience on ^{177}Lu-PSMA-617. High efficacy, safety and easy availability, endowed it with high clinical value and application prospects in spite of several limitations. Although research on RLT with ^{177}Lu-PSMA-617 is still based on small sample size and single center research at present, it is expected to become an extension and supplement to clinical conventional therapy for mCRPC patients with the accumulation of big data of global research.

［Key words］ prostatic neoplasms; metastatic castration-resistant prostate cancer; prostate-specific membrane antigen; radioligand therapy; ^{177}lutelium
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前列腺癌是全球男性最常见的恶性肿瘤之一，近20年我国前列腺癌发病率增长迅速。转移性前列腺癌患者经药物去势或手术去势后会经过1～2年的激素敏感期，之后绝大部分患者的去势治疗效果逐渐丧失[1-2]，患者的血清前列腺特异性抗原（prostate-specific antigen，PSA）会持续升高

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并出现新的转移病灶，疾病最终进展为转移性去势抵抗性前列腺癌[3]（metastatic castration-resistant prostate cancer，mCRPC）。mCRPC已属疾病晚期，是临床治疗的难点，姑息性手术、试验性局部治疗、外放射治疗、内分泌治疗、化学治疗等对mCRPC患者的预后及生活质量的提高效果有限[4]。近年来，以前列腺特异性膜抗原（prostate-specific membrane antigen，PSMA）作为靶点的研究越来越受到关注。以^{177}镥（^{177}Lu）标记的PSMA-617（^{177}Lu-PSMA-617）为代表的分子探针在前列腺癌的靶向治疗中取得成功，其理化性质、药代动力学特性优异，较其他放射性核素标记的治疗探针有更好的有效性、安全性和易获得性，显示出了较好的临床价值和应用前景，但尚存在一些局限。目前，^{177}Lu-PSMA-617靶向放射性配体治疗（radioligand therapy，RLT）仍以小样本单中心研究为主，但随着全球研究大数据的积累，其有望成为mCRPC临床常规治疗的延伸和补充。本文综述^{177}Lu-PSMA-617治疗mCRPC的应用现状。

1　理化特性和治疗机制

PSMA是^{68}Ga-PSMA-11用于显像和^{177}Lu-PSMA-617用于治疗的共同分子基础。^{177}Lu-PSMA-617是最常用的2种^{177}Lu-PSMA靶向探针之一，另外一种为^{177}Lu-PSMA-I&T（^{177}Lu-DOTAGA-PSMA-imaging & therapy），两者药代动力学和药效学特性相似。^{177}Lu-PSMA-617是一种含高亲和性脲基、性能优良的RLT探针。^{177}Lu-PSMA-617经静脉注射，与细胞膜PSMA膜外段特异性结合后经内吞作用在细胞内浓聚，达到细胞内照射治疗的作用[5]。小分子配体PSMA-617决定了该探针较好的药代动力学表现，在注射后24 h靶本比高，唾液腺、泪腺、近端小肠、脾脏、纵隔、肝脏及肾脏为其主要生理性摄取部位，排泄器官主要为肾脏[6]。

虽然前列腺癌的RLT始于β衰变核素^{131}碘（^{131}I），但趋甲状腺性使其应用受到一定限制。^{177}Lu没有趋甲状腺性，释放的β射线组织穿透力适中，穿透厚度为1～3 mm；释放的γ低能射线对血液系统内照射不良反应小；物理半衰期（$t_{1/2}$）为6.65 d，治疗时间窗适中，隔离和住院周期短，易于防护。上述物理性质使其逐渐成为前列腺癌治疗性核素的首选。

^{177}Lu-PSMA-617在转移瘤中对高表达的PSMA亲和力高，可静脉重复给药以实现全身病灶的RLT。不同于传统的外照射，进入肿瘤细胞内的^{177}Lu-PSMA-617会持续释放β射线，形成交叉火力效应持续杀伤肿瘤细胞，均衡了因PSMA表达不均匀造成的细胞水平的放射性差异；辐射诱导的旁观者效应进一步增强了治疗效果，改善了预后情况。

2　治疗优势

前列腺癌通常经1～2年的内分泌治疗不可避免地转归为mCRPC，这可能与惰性细胞株死亡、耐药细胞株生长的治疗选择效应相关。新一代抗雄激素药物（阿比特龙、恩杂鲁胺等）及化学治疗药物是mCRPC的主要治疗手段，但疗效仍不足。常规核素治疗主要集中在^{223}镭（^{223}Ra）、^{153}钐（^{153}Sm）、^{89}锶（^{89}Sr）、^{188}铼（^{188}Re）等放射性核素标记的钙-磷族趋骨性化合物对转移性骨痛的姑息治疗方面，尚缺乏PSMA靶向治疗与姑息治疗比较的数据[7-8]。

PSMA靶向的小分子结构稳定，制备工艺简单，具有亲和力高、内化快、血池清除快等优点；此外，诊断性和治疗性放射性核素可以螯合方式标记相同的PSMA配体而合成药代动力学相近的一组探针，因此诊断与治疗的靶向一致性高，且操作便捷，更易质控，实用性强，这样的探针组合称为诊疗一体化组合。^{68}镓（^{68}Ga）-PSMA PET-CT在前列腺癌诊断方面具有明显优势，尤其在低PSA值（＜0.5 ng/mL）时优势更显著[9]。一项包含63项研究的meta分析表明，^{68}Ga-PSMA PET-CT灵敏度高达77%～98%[10]。诊疗一体化组合优势互补，以^{68}Ga-PSMA-11/^{177}Lu-PSMA-617组合为例，诊断探针^{68}Ga-PSMA-11用于筛选适合RLT的患者，具有预警健康脏器因生理性摄取而发生不良反应等优势，再以治疗探针^{177}Lu-PSMA-617对适合患者进行靶向治疗；两者可以交替应用，能直观可视地动态评估疗效，进行再分期。诊疗一体化技术有加速发展的趋势，它体现了核医学精准化和个性化的诊治理念，可以实现所疗即所见。

3　安全性和有效性

继^{131}I-PSMA RLT后，海德堡大学医院德国癌症研究中心于2015年推出了mCRPC患者的^{177}Lu-PSMA RLT。目前^{177}Lu-PSMA RLT的临床试验主要在德国和澳大利亚开展，虽然临床需求迫切，但mCRPC的^{177}Lu-PSMA RLT尚未得到美国FDA及欧洲药品管理局（European Medicines Agency，EMA）的批准，因此还未形成正式的适用标准，尚以小规模的临床试验为主，且仅用于终末期mCRPC患者的同情治疗（尤其适用于常规治疗失

效后病情仍在进展或全身多发 PSMA 高表达转移病灶的 mCRPC 患者）。在目前的共识中，适宜入组 ^{177}Lu-PSMA RLT 临床试验的患者应同时满足以下条件：（1）常规治疗失效后 mCRPC 病情持续进展；（2）通过 PSMA PET-CT、PSMA 单光子发射计算机断层成像（single photon emission computed tomography，SPECT）-CT 或 PSMA PET-MRI 确诊和随访的 mCRPC，且以病灶的摄取程度作为 ^{177}Lu-PSMA-617 RLT 治疗前的基线；（3）有足够的骨髓储备和较好的肝、肾功能（白细胞计数≥ 3.0×10^9/L，血小板计数≥75.0×10^9/L，血清肌酐和主要肝酶水平分别不高于正常参考值上限的 2 倍和 5 倍）；（4）无尿路梗阻。^{177}Lu-PSMA-617 RLT 最佳治疗剂量、周期、间隔等治疗模式尚在探索[11]，现有研究的单个疗程的中位剂量范围为 2～10 GBq，治疗间隔为 6 周，最多 6 个周期[12-13]，治疗脱落往往是疾病进展或患者死亡所致[14]。尚缺乏大样本随机对照试验研究。

3.1 *安全性* 非病变脏器和组织的生理性摄取是影响 ^{177}Lu-PSMA RLT 治疗安全性的重要因素。2016 年 Kratochwil 等[15] 的研究表明，^{177}Lu-PSMA-617 生理性清除主要通过肾脏在 48 h 内完成，弥漫性骨髓摄取是红骨髓抑制的危险因素；红骨髓摄取安全剂量阈值约为 0.03 Gy/GBq、肾脏约为 0.75 Gy/GBq、唾液腺约为 1.4 Gy/GBq，第 1 个周期肿瘤平均吸收剂量为 6～22 Gy/GBq。2019 年 Sarnelli 等[16] 报道了 9 例患者 ^{177}Lu-PSMA-617 RLT 后 1 h、16～24 h、36～48 h 和 120 h 的剂量学数据，腮腺、肾脏、红骨髓、全身的有效半衰期和放射性活度中位数（范围）分别为 33.0（25.6～60.7）h 和 0.48（0.33～2.63）Gy/GBq、31.4（12.2～80.6）h 和 0.70（0.26～1.07）Gy/GBq、8.2（2.5～14.7）h 和 0.044（0.023～0.067）Gy/GBq、40.1（31.6～79.7）h 和 0.04（0.02～0.11）Gy/GBq。可见与唾液腺、腮腺、肾脏相比，^{177}Lu 在红骨髓内的有效半衰期较短，放射性活度接近于全身本底的较低水平。另外，口服谷氨酸片等酸制剂和冰敷可能减少唾液腺摄取；RLT 前应充分水化，尽可能排出血池中游离的 ^{177}Lu-PSMA-617 以减少本底和生理性摄取；必要时给予镇吐、利尿、促泄、抗炎等对症治疗，但尚需进一步研究如何减少肝肾等的生理性摄取。本文总结了近 6 年 ^{177}Lu-PSMA-617 治疗 mCRPC 主要研究的骨髓毒性数据[17-26]，见表 1。

表 1 近 6 年 ^{177}Lu-PSMA-617 治疗 mCRPC 的骨髓毒性资料

Tab 1 Bone marrow toxicity data of ^{177}Lu-PSMA-617 in treatment of mCRPC in recent 6 years

Study	Anemia		Leucopenia		Lymphocytopenia		Thrombopenia	
	Grade	% (*n*/*N*)	Grade	% (*n*/*N*)	Grade	% (*n*/*N*)	Grade	% (*n*/*N*)
Ahmadzadehfar, et al[17]	4	10.0 (1/10)	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Ahmadzadehfar, et al[18]	3	8.3 (2/24)	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Rahbar, et al[19]	3	1.4 (1/74)	Unknown	Unknown	Unknown	Unknown	3	1.4 (1/74)
Rahbar, et al[20]	3	4.5 (1/22)	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Ferdinandus, et al[21]	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	4	2.5 (1/40)
Rahbar, et al[22]	3-4	10.3 (15/145)	3-4	3.3 (4/121)	Unknown	Unknown	3-4	4.1 (5/121)
Hofman, et al[23]	Unknown	Unknown	Unknown	Unknown	3	36.7 (11/30)	3-4	13.3 (4/30)
Rathke, et al[24]	Unknown	Unknown	2	7.5 (3/40)	Unknown	Unknown	Unknown	Unknown
Yordanova, et al[25]	3	10.0 (3/30)	3	6.6 (2/30)	Unknown	Unknown	3	13.3 (4/30)
Rasul, et al[26]	3	1.9 (1/54)	3	3.7 (2/54)	Unknown	Unknown	Unknown	Unknown

^{177}Lu-PSMA-617: ^{177}Lutetium labelled prostate-specific membrane antigen (PSMA) targeted ligand PSMA-617; mCRPC: Metastatic castration-resistant prostate cancer.

3.2 *有效性* 肿瘤摄取程度是 ^{177}Lu-PSMA RLT 治疗有效性的重要因素，有效性的评价主要建立在 PSA 动态变化的基础上，此外还应参考影像学的改变和症状的改善情况。^{177}Lu-PSMA RLT 2 周后，PSA 下降超过基线的 50% 提示疗效显著，PSA 上升则提示病情进展[27]。2017 年发表的纳入 10 项研究共 334 例患者的 meta 分析结果显示，66% 的患者 PSA 下降，下降超过基线 50% 的为 37%[28]。2018 年发表的纳入 10 项研究共 455 例患者的 meta 分析结果显示，68% 的患者 PSA 下降，下降超过基线 50% 的为 34.45%[29]。2018 年发表的纳入 12 项研究共 669 例患者的 meta 分析也得到了相似的结果：^{177}Lu-PSMA RLT 与三线化疗药物治疗相比，效果好且不良反应少；两者治疗后 PSA 下降超过 50% 的患者分别为 44% 和 22%，客观缓解率分别为 28% 和 16%，中位生存期分别为 14 和 11 个月[30]。2018 年 Hofman 等[23] 报道 30 例 mCRPC 患者接受 ^{177}Lu-PSMA-617 RLT 后疼痛评分均有所降低，

11例患者在第2个疗程后疼痛评分改善超过10分。2019年Emmett等[31]报道14例接受^{177}Lu-PSMA-617治疗的前列腺癌患者中，10例PSA出现不同程度的下降，PSA下降超过30%的有9例，超过50%的有5例，治疗后病灶最大标准摄取值（maximum standard uptake value，SUV_{max}）、平均标准摄取值（mean standard uptake value，SUV_{mean}）均显著降低，而以[^{18}氟]-氟代脱氧葡萄糖(^{18}F-fluorodeoxyglucose，^{18}F-FDG）为探针的PET-CT摄取参数、体积、病变部位均不能预测PSA反应。2019年van Kalmthout等[32]报道的30例接受^{177}Lu-PSMA-617治疗的mCRPC患者显示了良好的安全性和有效性，中位总生存期为11.3个月，患者骨痛缓解、血清PSA下降，而其血液学毒性等不良反应较易缓解。本文回顾了近6年^{177}Lu-PSMA-617治疗mCRPC的主要研究[17-26,31,33-39]，其有效性数据见表2。

表2　近6年^{177}Lu-PSMA-617治疗mCRPC的有效性研究

Tab 2　Studies on the efficacy of ^{177}Lu-PSMA-617 in treatment of mCRPC in recent 6 years

Study	Year	*N*	Baseline PSA /(ng•mL^{-1})	First round treatment dose/GBq	Round of treatment
Ahmadzadehfar, et al[17]	2015	10	298.5 (5-853)[a]	5.6 (4.1-6.1)[a]	1.0
Ahmadzadehfar, et al[18]	2016	24	522 (17-2 360)[a]	6.0 (4.1-7.1)[a]	1.9 (1.0-2.0)[b]
Rahbar, et al[19]	2016	74	342 (5-5 910)[a]	5.9±0.5[c]	1.0
Rahbar, et al[20]	2016	22	381 (5-1 844)[a]	5.9±0.4[c]	1.8 (1.0-2.0)[b]
Kratochwil, et al[33]	2016	30	Unknown	5.2 (3.7-6.0)[a]	2.0 (1.0-3.0)[a]
Rahbar, et al[22]	2017	99	214 (0.4-5 436)[a]	5.9 (2.0-8.0)[a]	1.7 (1.0-4.0)[b]
Ahmadzadehfar, et al[34]	2017	52	510 (5-5 910)[a]	6.0 (4.0-7.2)[a]	3.6 (3.0-6.0)[b]
Bräuer, et al[35]	2017	59	346 (126, 881)[d]	6.1 (5.9, 6.3)[d]	2.7 (1.0-7.0)[b]
Ferdinandus, et al[21]	2017	40	325.5 (4.7-2 360)[a]	6.0 (4.1-7.1)[a]	1.0
Rahbar, et al[36]	2018	104	361 (80, 755)[d]	6.1 (5.9, 6.3)[d]	3.4 (1.0-8.0)[b]
Hofman, et al[23]	2018	30	189.8 (80.1, 372)[d]	7.5 (4.4-8.7)[b]	3.0 (2.0-4.0)[a]
Rathke, et al[24]	2018	40	Unknown	4.0, 6.0, 7.4, 9.3	3.0
Maffey-Steffan, et al[37]	2019	32	Unknown	6.0	2.0-6.0[e]
Yordanova, et al[25]	2019	30	208 (2.6-2 009)[a]	8.0 (6.0-9.0)[a]	3.0 (1.0-6.0)[a]
Emmett, et al[31]	2019	14	88 (7-2 950)[a]	7.0 (6.0-8.0)[a]	3.0 (2.0-4.0)[a]
Aghdam, et al[38]	2019	14	217.31 (0.4-1 533)[a]	5.7 (4.4-6.6)[a]	1.0 (1.0-6.0)[a]
Yadav, et al[39]	2020	90	333 (1.1-2 493)[a]	1.1-7.8[e]	4.0 (1.0-7.0)[a]
Rasul, et al[26]	2020	54	66 (1.0-4 890)[a]	7.3±0.6[c]	3.0

Study	Assesment time point	Patients with decreased PSA, *n* (%)	Patients with PSA decreased over 50%, *n* (%)
Ahmadzadehfar, et al[17]	8 weeks after first round of treatment	7 (70.0)	5 (50.0)
Ahmadzadehfar, et al[18]	8 weeks after first round of treatment	19 (79.2)	10 (41.7)
Rahbar, et al[19]	8 weeks after first round of treatment	47 (63.5)	23 (31.1)
Rahbar, et al[20]	8 weeks after first round of treatment	13 (59.1)	7 (31.8)
Kratochwil, et al[33]	8 weeks after first round of treatment	21 (70.0)	13 (43.3)
Rahbar, et al[22]	8 weeks after first round of treatment	65 (65.7)	40 (40.4)
Ahmadzadehfar, et al[34]	8 weeks after first round of treatment	42 (80.8)	23 (44.2)
Bräuer, et al[35]	8 weeks after first round of treatment	33 (55.9)	13 (22.0)
Ferdinandus, et al[21]	8 weeks after first round of treatment	27 (67.5)	13 (32.5)
Rahbar, et al[36]	8 weeks after first round of treatment	70 (67.3)	34 (32.7)
Hofman, et al[23]	12 weeks after first round of treatment	29 (96.7)	17 (56.7)
Rathke, et al[24]	8 weeks after first round of treatment	31 (77.5)	15 (37.5)
Maffey-Steffan, et al[37]	8 weeks after first round of treatment	23 (71.9)	12 (37.5)
Yordanova, et al[25]	8 weeks after first round of treatment	16 (53.3)	7 (23.3)
Emmett, et al[31]	Unknown	10 (71.4)	5 (35.7)
Aghdam, et al[38]	8 weeks after first round of treatment	11 (78.6)	5 (35.7)
Yadav, et al[39]	12 weeks after first round of treatment	56 (62.2)	29 (32.2)
Rasul, et al[26]	4 weeks after third round of treatment	43 (79.6)	31 (57.4)

[a]: Median (range); [b]: Mean (range); [c]: $\bar{x}\pm s$; [d]: Median (lower quartile, upper quartile); [e]: Range. ^{177}Lu-PSMA-617: ^{177}Lutetium labelled prostate-specific membrane antigen (PSMA) targeted ligand PSMA-617; mCRPC: Metastatic castration-resistant prostate cancer; PSA: Prostate-specific antigen.

国内关于 ^{177}Lu-PSMA-617 治疗 mCRPC 的研究数据有限。卜婷等[40]对 11 例接受 ^{177}Lu-PSMA-617 治疗的 mCRPC 患者进行了安全性和有效性评估，所有患者的红细胞、白细胞、血小板、血红蛋白、肾功能等指标在治疗前后的差异均无统计学意义，但有 9 例患者 PSA 水平和病灶 SUV_{max} 显著降低。衡量治疗性探针有效性和安全性的标准是多维度的，综合国内外研究，^{177}Lu-PSMA-617 疗效高、毒性低、可有效缓解癌痛，作为终末期 mCRPC 患者的同情治疗有较高的临床价值。

4 与其他探针的比较

4.1 其他β⁻衰变核素标记的 PSMA 靶向探针 目前尚无 ^{177}Lu-PSMA-617 与其他 PSMA 靶向探针比较的随机对照试验研究，对于其他探针的研究主要为单中心小样本量研究，其安全性和有效性尚需进一步探讨。Baum 等[41]对 56 例 mCRPC 患者共 125 个疗程的 ^{177}Lu-PSMA I&T 治疗发现，80.3% 的患者血清 PSA 降低；在治疗不少于 2 个疗程的 25 例患者中，14 例缓解、2 例稳定、9 例进展；中位无进展生存期为 13.7 个月。Weineisen 等[42]用 ^{177}Lu-PSMA I&T 治疗前列腺癌患者的临床研究结果也显示患者的 PSA 下降。Afshar-Oromieh 等[43]对 34 例 mCRPC 患者进行了 ^{131}I-PSMA 治疗，并随访 5 年（8 例患者治疗 1 次，23 例患者治疗 2 次，3 例患者治疗 3 次），第 1 次治疗后 70.6% 的患者血清 PSA 下降超过 50%，后 2 次治疗后 PSA 下降不明显；血液学毒性、口干症等不良反应随着治疗次数的增加而增加。在 ^{90} 钇（^{90}Y）、^{177}Lu 标记的第 2 代 PSMA 多克隆抗体 J591 的Ⅰ期临床试验中，患者 PSA 下降或稳定、PSA 基线稳定时间增加、影像学肿瘤负担减少[44-45]。对 47 例 mCRPC 患者的 ^{177}Lu-J591 安全性和有效性的双中心Ⅱ期研究中，绝大多数患者出现的血液毒性等不良反应可以纠正，2.59 GBq/m^2 的剂量内照射后，患者骨痛缓解、PSA 下降、PSA 倍增时间延长、病灶数量减少、病灶摄取降低、生存期延长[46]。Rathke 等[47]对 4 例接受 ^{90}Y-PSMA-617 治疗的 mCRPC 患者的临床研究发现，患者骨痛症状缓解、PSA 下降，而急性血液学毒性、恶心、口干等临床不良反应与 ^{177}Lu-PSMA-617 文献数据相当。

4.2 α衰变核素标记的 PSMA 靶向探针 ^{225} 锕（^{225}Ac）、^{213} 铋（^{213}Bi）等α粒子发射体标记的 PSMA 靶向治疗探针也有一些小样本报道。与 ^{177}Lu 相比，以 ^{225}Ac 为代表的α粒子的衰变射线能量高但射程较短，交叉火力效应较弱，适用于经 ^{177}Lu-PSMA-617 治疗后疾病仍进展但骨髓储备较弱的弥漫性骨转移患者[48]。Kratochwil 等[49]首次报道了 2 例接受 ^{225}Ac-PSMA-617 治疗的患者，治疗前后经 ^{68}Ga-PSMA-11 PET-CT 扫描评估，治疗剂量为每 2 个月 100 kBq/kg，2 例患者均表现为 PSA 下降和 PET-CT 影像缓解，除口干症外无明显的血液学毒性。Sathekge 等[50]对 73 例 mCRPC 患者进行了共 210 个周期（人均 2.88 个周期）的 ^{225}Ac-PSMA-617 治疗，约 70% 的患者 PSA 下降超过 50%；中位无进展生存期和总生存期分别为 15.2 个月和 18 个月。Khreish 等[51]研究发现，^{225}Ac-PSMA-617 与 ^{177}Lu-PSMA-617 联合使用可提高 RLT 对终末期 mCRPC 患者的疗效，减轻口干症的严重程度。Sathekge 等[52]报道了用 ^{213}Bi-PSMA-617 治疗 1 例 mCRPC 的首次人体试验，该患者接受了 2 个疗程的 ^{213}Bi-PSMA-617 治疗，累积放射活度为 592 MBq，11 个月后 PSA 下降，^{68}Ga-PSMA PET-CT 显示病灶摄取下降。

另外，中等能量核素如 ^{64} 铜（^{64}Cu）、^{43} 钪（^{43}Sc）、^{44} 钪（^{44}Sc）、^{152} 铽（^{152}Tb）、^{155} 铽（^{155}Tb）等用于诊断，其同位素 ^{67}Cu、^{47}Sc、^{161}Tb 等标记的多肽或抗体用于 RLT，也有成为新的诊疗一体化组合的潜在可能[53]。

综上所述，较其他探针，^{177}Lu-PSMA-617 有如下优势：（1）^{177}Lu 的内吞效果好，可形成肿瘤细胞内照射环境[42]；（2）^{177}Lu 半衰期适中，防护窗口窄，隔离时间短；（3）小分子抑制剂 PSMA-617 体内理化性质稳定，且已商品化，易于获得和制备；（4）衰变时释放的低能γ射线可进行 SPECT 和半定量评估，检查费用相对低廉；（5）同中心诊疗一体化，便于质控和科研；（6）治疗剂量范围安全，不良反应小且可耐受[54]；（7）^{177}Lu-PSMA-617 治疗 mCRPC 已积累了较多临床研究数据和经验；（8）易于多中心合作。

5 ^{177}Lu-PSMA-617 治疗的局限

一项临床研究显示，部分 PSMA 低表达的 mCRCP 患者不能从靶向的内照射中受益，因而并不适合进行 ^{177}Lu-PSMA-617 治疗[55]。免疫组织化学和病理学研究也表明，肿瘤细胞膜表达 PSMA 存在异质性[56]。这种异质性表现在：控制其他变量后，患者间 PSMA 表达程度差异有统计学意义；即使同一例患者，不同转移灶甚至相同转移灶的不同组织间的差异亦有统计学意义。这种异质性可能会

造成不同病灶间疗效乃至患者间疗效及生存时间的差异，尚需开展前瞻性大规模试验探讨如何规避这种异质性对疗效造成的影响。

6 小　结

目前，PSMA靶向诊疗一体化的临床应用是核医学发展的热点。PSMA靶点成像已发展为常规影像工具的重要补充，同时靶向PSMA的RLT对常规治疗后进展的mCRPC患者表现出了良好的应用前景，其中^{177}Lu-PSMA-617应用范围最广，治疗效果呈现出高应答率、低毒反应、可缓解癌痛症状等特点，越来越多的回顾性研究和早期前瞻性研究证明了^{177}Lu-PSMA-617 RLT的安全性和有效性。我国在PSMA靶点成像中积累了一定的数据和经验，但由于放射性药品管理较严格等政策性原因，靶向PSMA的RLT尚未大规模推广使用。

国内外对mCRPC患者的RLT研究仍以单中心小样本报道为主，缺乏^{177}Lu-PSMA-617与其他探针、常规方案联合治疗的临床研究和基础研究；亦缺乏健康组织脏器保护的相关研究，此类研究的意义在于探索如何减少生理性摄取的竞争效应，进一步增加肿瘤摄取以改善RLT的有效性和安全性。目前，以^{177}Lu-PSMA-617 RLT为代表的靶向PSMA的RLT仅用于终末期mCRPC患者的同情治疗，属三线方案，尚缺乏早期干预的研究数据，应当以患者获益最大化为着眼点，探索RLT的适用条件和范围。

总之，^{177}Lu-PSMA-617 RLT是很有前途的mCRPC治疗新方案，可作为现有前列腺癌诊治模式的补充，值得在更大样本规模的前瞻性多中心试验中总结经验，使更多mCRPC患者受益。

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