Advances in Clinical Medicine 临床医学进展, 2024, 14(9), 942-951
Published Online September 2024 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2024.1492550

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转移性透明细胞肾细胞癌一线联合治疗方法研究进展

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收稿日期：2024年8月14日；录用日期：2024年9月7日；发布日期：2024年9月14日

摘　要

随着医疗技术的不断进步和对转移性肾透明细胞癌(mRCC)认识的日渐深入，mRCC的治疗模式发生了显著转变。目前除手术外，mRCC的治疗主要采用靶向治疗和免疫治疗，在取得显著疗效同时也面临着耐药和无反应性等问题。为了解决这些问题，新技术和药物的研发正在不断进行。本文将对mRCC的靶向及免疫治疗方式、探索性治疗方案及治疗趋势进行综述，并通过总结发现各项技术原理和适用人群的差异，认为联合治疗和精准治疗将成为未来发展的主要方向。在未来的研究中，重点将放在如何更好地综合利用不同治疗技术以及更精确地定位适用人群，以实现更有效的mRCC治疗。

关键词

转移性肾透明细胞癌，靶向治疗，免疫治疗，精准治疗，联合治疗

Research Progress on First-Line Combination Therapy for Metastatic Clear Cell Renal Cell Carcinoma

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Received: Aug. 14th, 2024; accepted: Sep. 7th, 2024; published: Sep. 14th, 2024

Abstract

With the continuous advancement of medical technology and the deepening of the understanding

文章引用: 赵家伟, 郝亮亮, 靳永胜. 转移性透明细胞肾细胞癌一线联合治疗方法研究进展[J]. 临床医学进展, 2024, 14(9): 942-951. DOI: 10.12677/acm.2024.1492550

of metastatic clear cell renal cell carcinoma (mRCC), the treatment mode of mRCC has undergone a significant transformation. At present, in addition to surgery, the treatment of mRCC mainly uses targeted therapy and immunotherapy, which has achieved remarkable efficacy but also faces problems such as drug resistance and non-responsiveness. In order to solve these problems, the research and development of new technologies and drugs is constantly underway. This article reviews the targeted and immunotherapy methods, exploratory treatment options and treatment trends of mRCC, and finds the differences in various technical principles and applicable populations, and believes that combination therapy and precision therapy will become the main direction of future development. In future research, the focus will be on how to better integrate different treatment technologies and more precisely target the appropriate population to achieve more effective mRCC treatment.

Keywords

Metastatic Clear Cell Renal Cell Carcinoma, Targeted Therapy, Immunotherapy, Precision Therapy, Combination Therapy

1. 引言

肾癌是十大最常见的癌症之一，占所有新发病例的 3.7%，发病率一直在上升[1] [2]。据美国癌症协会估计，2020 年将有 73,750 例肾癌新发病例和 14,830 例肾癌相关死亡病例[3]。死亡率很大程度上取决于疾病分期；局限性 I/II 期疾病的 5 年生存率超过 90%，而局部晚期和/或远处转移患者的预后较差[2] [4] [5]。

透明细胞肾细胞癌(ccRCC)起源于近端肾小管，占所有肾癌病例的 85%。RCC 的另一大类是非透明细胞癌，包括状癌、嗜色细胞癌、集合管癌和肾髓样癌[6] [7]。

绝大多数 ccRCC 与 3 号染色体上的 VHL 基因突变有关，该基因通过缺氧诱导因子-1 (hypoxia-inducible factor-1, HIF-1)在细胞对缺氧的反应中发挥作用[8] [9]。这些突变往往发生在此类癌症发展的早期[10]。VHL 突变通常导致基因失活，并影响对血管生成抑制剂药物的反应性、对化疗的耐药性和对放疗的耐药性[11]。与 ccRCC 相关的其他突变包括 TCEB1、SETD2、BAP1 和 PBRM1。值得注意的是，影响 mTORC1 通路调节的突变约占 ccRCCs 的 20% [11]，而 HIF-1 在对 mTOR 抑制剂的敏感性中也起着重要作用[12]。

此外，许多 RCC 肿瘤可能包括肉瘤样或横纹肌样特征；这些不是特异性的组织学亚型，而是 RCC 的去分化，可存在于任何亚型[13]。然而，这些特征的发生率受 RCC 亚型的影响，肉瘤样或横纹肌样特征的患病率从 1%到 32%不等，具体取决于 RCC 分类[13]。具有这些特征的 RCC 预后极差，生存率很少超过 2 年[13] [14]。然而，肉瘤样或横纹肌样特征的存在可能具有治疗意义，如下所述。

主动监测、减瘤性肾切除术(CN)和全身治疗都在转移性 ccRCC 的管理中发挥作用。正确的治疗方案取决于许多因素，包括疾病程度、既往治疗、患者合并症和其他患者因素[2]。正在进行的临床试验继续改变治疗格局。大多数数据来自在 ccRCC 中进行的临床研究，但在过去几年中，非透明细胞 RCC 的临床数据量有所增加。

本临床综述的目的是描述转移性 RCC (mRCC)管理的更新。我们深入研究了晚期 RCC 的管理，包括主动监测的作用、解决原发性肿瘤和远处病变的局部疗法，以及 mRCC 的当前和新兴全身疗法。

2. 转移性 ccRCC 的治疗

1) 主动监测

在 mRCC 的情况下，主动监测方案涉及对疾病的频繁重新评估和监测，目的是了解肿瘤生长和进展的速度。虽然以前仅用于小肾肿瘤，但对于较大的肿块和转移性疾病患者，主动监测已逐渐被接受[15]。肿瘤生物学和风险预测模型的进步促进了这一转变，这种策略在回顾性和前瞻性研究中都得到了探索。

一项针对 48 名初治、无症状 mRCC 患者的前瞻性研究表明，平均近 15 个月，监测可有效避免全身治疗。这些患者中的绝大多数患有 ccRCC (96%)。在本文评估的所有因素中，IMDC 不良危险因素较少的患者(从诊断到全身治疗<1 年内，Karnofsky < 80%，血红蛋白低于正常下限，钙、血小板和/或中性粒细胞高于正常上限)和转移性疾病部位数量较少的患者能够进行更长时间的主动监测[16]。这些发现已被最近的 IMPACT-RCC 研究所验证[17]。

回顾性数据与这些结果一致。一项针对 58 名无症状至症状轻微且有透明细胞组织学和非透明细胞组织的 mRCC 患者的研究表明，积极监测是一种可接受的治疗选择。中位随访时间为 31.4 个月，其中 83% 的患者病情稳定，中位进展时间为 12.4 个月。监测时间较短的预测因素包括肝转移、Karnofsky 体能状态低于 100%，以及诊断与开始主动监测之间的时间较短(<1 年) [18]。

在 Kushnir 等[19]的另一项研究中，863 例符合主动监测标准的患者与 848 例立即接受治疗的患者进行了比较。主动监测患者被分为两组：370 名在诊断后 6 个月以上开始治疗(中位监测 14.2 个月)，493 名未接受全身治疗且寿命超过 1 年的患者。作者发现，与立即治疗患者相比，积极监测患者的 5 年总生存率(OS)显着更高(70.2% vs. 32.1%；<0.0001 页)。此外，在控制了国际转移性 RCC 数据库联盟(IMDC)风险标准和年龄后，监测 > 6 个月的 370 名患者的 OS 与立即接受治疗的 848 名患者相比有所改善(风险比[HR] 0.46，置信区间[CI] 95%，0.38~0.56，p < 0.0001)。与立即接受治疗 > 6 个月的组相比，监测 6 个月的组一线治疗失败率也更高(HR0.79, CI 95%, 0.69~0.92; p = 0.0021)。作者得出的结论是，一些患者可能会得到安全观察，而不是立即接受治疗，但前瞻性验证势在必行[19] [20]。

总体而言，这些数据表明，一些症状轻微或没有症状的 mRCC 患者无需治疗即可安全地观察较长时间，避免了全身治疗的潜在副作用[18]。

2) 手术

减瘤性肾切除术

减瘤性肾切除术(CN)或在转移性疾病背景下对原发肿瘤进行手术干预在治疗 mRCC 方面有着悠久的历史。CN 通常用于姑息治疗，包括减少由大肾肿块引起的出血或腰痛[21]。切除该肿块还可以去除免疫抑制或肿瘤促进生长因子的潜在来源，这可能带来生存优势[21]。

在 RCC 靶向治疗出现之前，CN 与细胞因子免疫疗法联合使用时，已被证明可有效改善结果。西南肿瘤学组(Southwest Oncology Group, SWOG)进行了一项试验，评估了单独使用干扰素 α-2b 与 CN 联合使用干扰素 α-2b 的比较[22]。这项研究检查了 120 名患有任何大小或淋巴结状态的初治 mRCC 患者。结果显示，在 IFN-α 中添加 CN 可使 OS 从 8.1 个月(95% CI, 5.4~9.5)增加到 11.1 个月(95% CI, 9.2~16.5; p = 0.05)，这种差异与体能状态、转移部位或转移性病灶的存在无关[22]。

同样，欧洲癌症研究与治疗组织(EORTC)进行的一项研究发现，在 IFN-α 治疗的背景下，接受 CN 有益。83 名患者如果患有进行性 mRCC，且无法通过当时的标准肾切除术切除术，则选择这些患者；既往接受过放射治疗或全身治疗、特定合并症或骨转移的患者被排除在外。CN 的增加使中位 OS 增加了一倍以上，达到 17 个月，而单独使用 IFN-α 为 7 个月(HR0.54, 95% CI, 0.31~0.94)。研究患者的疾病进展时间(TTP)也更好：对照组为 5 个月 vs 3 个月(HR0.60, 95% CI, 0.36~0.97) [23]。其他研究表明，这种方法具有类似的生存优势[24]。

随着血管生成疗法的出现，CN 的作用成为争议的话题[25] [26]。虽然几项回顾性研究的数据表明，肾切除术对接受靶向治疗的患者有益[27]-[29]，但 CARMENA 的 III 期研究结果使我们重新审视了此类患者前期手术的必要性[30]。这项非劣效性试验招募了 450 名 ccRCC 和纪念斯隆凯特琳癌症中心(Memorial Sloan Kettering Cancer Center, MSKCC)中度至低风险状态患者，并以 1:1 的比例将他们分配到单独使用舒尼替尼治疗组，或接受 CN 组然后使用舒尼替尼组。该研究有力地检测了两组间 OS 的差异，结果显示，与肾切除术联合舒尼替尼组相比，舒尼替尼单独使用组具有非劣效性(HR0.89, 95% CI, 0.71~1.10)，仅接受舒尼替尼治疗的患者的中位 OS 为 18.4 个月(95% CI, 14.7~23.0)，而联合 CN 的患者为 13.9 个月(95% CI, 11.8~18.3) [30]。

虽然总体而言，CARMENA 研究显示 CN 在此类患者中的作用有限，但更详细的分析表明患者选择和 IMDC 风险分层的重要性[21] [31]-[34]。一项对 CARMENA 的专题分析(包括使用 IMDC 进行分层)的随访时间更长，结果显示，在 IMDC 危险因素少于 2 个(即高钙血症、贫血、血小板增多症、中性粒细胞增多症、Karnofsky 评分低于 80%，或从诊断到治疗不到 1 年)的患者中，CN 具有潜在益处[32] [35]。

3) 转移部位的局部治疗

了解肿瘤负荷的不同生物学基础以及寡转移性和播散性 RCC 之间的差异，局部疗法对远处病灶的作用一直在积极研究中。转移灶切除术对部分孤立转移患者尤其有效，即使有多发性转移的证据，也能延长持久的缓解时间[36]-[40]。

然而，由于缺乏来自现代随机研究的高水平证据，转移灶切除术仍然是一个有争议的话题，并在特定病例中考虑。

了解到转移灶切除术后可能(影像学上)无疾病的患者发生复发/进展性疾病的风险非常高，因此已经进行了几项研究来调查辅助治疗的有效性。总体而言，这些研究显示疗效有限[41] [42]。例如，Appleman 等[41]对 129 例此类患者进行的一项研究显示，对于转移灶切除术后无疾病证据的 mRCC 患者，帕唑帕尼与安慰剂相比没有益处(HR2.65, 95% CI, 1.02~6.9; p = 0.05)。另一项研究(RESORT)也未能证明，与单独观察相比，76 例接受转移灶切除术的患者有 PFS 获益[42]。

虽然 RCC 历来被认为是一种放射耐药性疾病[43]，但已采用更高剂量的放射治疗(stereoorientation radiosurgery, SRS)治疗远处转移瘤[44] [45]。在免疫检查点抑制出现之前，对脑和脊柱进行立体定向放疗(stereoorientation body radiotherapy, SBRT)已获得阳性结果[46] [47]。特别是脊柱放疗在高达 90%的患者中实现了良好的局部控制和显著的疼痛改善[46] [47]。

其他则研究了 SBRT 治疗肺、骨、淋巴结和肝脏转移瘤的作用[58]。在一项研究中，患者作为他们自己的对照，与同一个体中未经治疗的病变相比，SBRT 反应更好。与对照组相比，SBRT 治疗的病灶平均面积减少有统计学意义($p < 0.01$)，包括使用较高辐射剂量(10 Gy 或更高)治疗的病灶完全缓解[48]。

此外，SBRT 也被建议用于寡进展性 mRCC 至脑和/或脊柱的一种选择(85%) [49]。最近的研究继续显示，SBRT 对颅外和颅内疾病的局部控制率都非常高[47]。

随着 ICIs 用于治疗 mRCC 的出现，最近一些小型前瞻性试验的证据表明，RT 可能会增加接受 ICI 治疗的患者的抗肿瘤反应，并可能诱导 PD-L1 表达[50]-[52]。RADVAXRCC 试验纳入了 25 例患者，研究了 SBRT 联合伊匹木单抗和纳武利尤单抗[50]。入组患者有 2 个或更多转移灶，并且要么未接受过治疗，要么既往接受过 TKI 或细胞因子治疗。观察到的 ORR 为 56%，中位 PFS 为 8.2 个月(95% CI, 4.6~18.0) [53]。虽然安全性不是问题，但疗效结果并不比不加放疗的伊匹木单抗和纳武利尤单抗联合治疗好。

虽然这些结果并未表明在 ICI 中加入 SBRT 具有明显的治疗优势，但正在计划进一步研究以优化 RT 对 mRCC 的使用。

4) 全身治疗

(1) 免疫前检查点抑制

从历史上看，mRCC 的细胞因子时代始于干扰素 α (interferon alfa, INF-α)和高剂量白细胞介素-2 (HD IL-2)，这是该疾病中首个显示出显著临床活性的方案[54]。尽管 ORR 低(10~20%)，但这些治疗与持久、完全的反应有关，尤其是 HDIL-2。然而，治疗主要受到严重毒性的限制，尤其是心血管毒性[55]-[57]。

随着对 mRCC 生物学的不断发展和更深入的理解，发现了多种靶向疗法。哺乳动物雷帕霉素靶点(mTOR)抑制剂、酪氨酸激酶抑制剂(TKI)和靶向 VEGF 受体(例如 VEGFRs、舒尼替尼)和 PDGF 受体(PDGFRs)的疗法，以及靶向 VEGF 的抗体(例如贝伐珠单抗)，都属于这些在 mRCC 中具有活性的新型药物。

2007 年，第一种 mTOR 抑制剂替西罗莫司在全球 ARCC 试验中进行了研究。该研究比较了替西罗莫司与 INF-α；在研究的患者中，80%患有透明细胞组织学疾病，94%具有三个或更多不良的预后因素。结果显示，中位生存期分别为 10.9 个月和 7.3 个月($p = 0.008$)，mPFS 为 3.8 个月和 1.9 个月($p < 0.001$)。与联合组相比，OS 无显著差异(HR0.96, 95% CI, 0.76~1.20; $p = 0.70$)。该试验的结果支持使用替西罗莫司作为 mRCC 的一线治疗[58]。

VEGFR-TKIs 于 2007 年开始被广泛使用，当时索拉非尼根据 III 期 TARGET 试验获得批准，该试验显示，在既往治疗进展的 mRCC 患者中，与对照组(安慰剂)相比，索拉非尼具有显著的 PFS 优势(HR0.44, 95% CI, 0.35~0.55; $p < 0.01$) [59]。这是基于 III 期试验成功测试和批准的几种抗 VEGF 疗法中的第一种，最终包括舒尼替尼、帕唑帕尼和贝伐珠单抗联合 INF-α [60]-[63]。根据 COMPARZ 和 PISCES 的研究，舒尼替尼和帕唑帕尼已被证明同样有效，但安全性不同[64] [65]。这些靶向治疗成为 mccRCC 患者的标准治疗，与其危险因素状态无关。

最近，在 CABOSUN 的 II 期研究中，将靶向 c-MET、VEGFR2 和 AXL 的第二代 TKI 卡博替尼与舒尼替尼在中度和低危疾病患者中的疗效进行了比较[66]。该研究表明，在中度至低危 mRCC 患者中，与当时的标准护理舒尼替尼相比，卡博替尼在 PFS (8.2 个月 vs 5.6 个月)和 ORR (33% vs 12%)方面具有显著的临床益处;卡博替尼使进展率或死亡率降低了 34% (校正 HR0.66，95% CI，0.46~0.95；单侧 $p = 0.012$)。

(2) 免疫检查点抑制剂和一线联合治疗方案

免疫调节疗法，尤其是免疫检查点抑制剂(ICI)，重塑了 RCC 的治疗，并显着改善了临床结果。这些药物包括针对 CTLA-4 (ipilimumab)、程序性细胞死亡蛋白 1 (PD-1)的药物——帕博利珠单抗和纳武利尤单抗——或其配体、程序性细胞死亡蛋白配体(PD-L1)——avelumab 和阿替利珠单抗。抑制这一过程会导致免疫系统增加对癌细胞的细胞毒性反应[67]。

2015 年，根据 III 期试验 Checkmate-025 的研究结果，纳武利尤单抗被批准为二线治疗药物，ICI 被纳入 mRCC 的治疗中。在这项研究中，难治性 mRCC 患者，其中共有 821 名在索拉非尼或舒尼替尼后进展的患者被随机分配到纳武利尤单抗组和依维莫司组。结果显示 OS 更好(25 个月 vs 19.6 个月)，死亡 HR 为 0.73 (98.5% CI, 0.57~0.93; $p = 0.002$)与依维莫司相比，纳武利尤单抗组[68]以及纳武利尤单抗组的安全性要好得多。随后，对纳武利尤单抗与舒尼替尼、帕唑帕尼和伊匹木单抗的不同组合进行了评估。虽然由于安全性问题，两种 TKI 的联合疗法被暂停，但纳武利尤单抗联合伊匹木单抗联合疗法的初步结果支持了一项大型 III 期 Checkmate-214 试验。该研究比较了纳武利尤单抗联合伊匹木单抗与舒尼替尼在既往未经治疗的 mRCC 患者中的疗效，并首次显示出基于 ORR、PFS 和 OS 复合终点的 ICI 方案在中度和低危 RCC 患者中的优越性。该联合疗法在中度和低危 mRCC 患者中达到主要终点，但在有利风险 mRCC 患者中的获益不太明显，与舒尼替尼相比，联合方案的缓解率更低(39% vs. 50%) [69]-[71]。值得注意的是，在中位随访 42 个月后，所有风险组的完全缓解率均保持在 10%以上[53]。

临床前数据表明血管抑制和检查点抑制之间存在协同作用，因此在一线领域已经研究了几种联合治

疗方案[72] [73]。目前，已经报告了三项将 ICIs 与 VEFG 靶向治疗相结合的 III 期试验的数据，比较了与舒尼替尼的不同联合方案。其中第一项研究在 Keynote-426 试验中检查了阿昔替尼与帕博利珠单抗与舒尼替尼的联合疗法。在这项研究中，帕博利珠单抗–阿昔替尼组的 PFS 明显更长(HR0.71, 95% CI, 0.60~0.84; p < 0.001)；24 个月 PFS 率，38% vs 27%和 OS (HR0.68, 95% CI, 0.55~0.85; p < 0.001)与舒尼替尼相比，中位随访 27 个月后的更新分析显示[74]。帕博利珠单抗联合阿昔替尼在 IMDC 风险组(即有利、中等和低风险)中均观察到获益，无论程序性死亡配体 1 表达如何[75]。

在 Javelin Renal 101 试验中，在 886 例既往未经治疗的转移性 ccRCC 患者群体中，阿昔替尼联合 avelumab 与舒尼替尼进行了对比试验[76]。在这项研究中，avelumab 联合阿昔替尼组在总人群中的 PFS 明显更长(HR0.61，95% CI，0.47 至 0.79；p < 0.001)以及 PD-L1 阳性肿瘤(HR0.69，95% CI，0.56 至 0.84，p < 0.001)，均为该研究的共同主要终点。然而，在中位随访 11 个月的读数时，未检测到 OS 差异，需要更长的随访才能确定总生存获益[77]。

3. 结论

总之，mRCC 的管理已经发生了重大变化，目前医生治疗肾癌有不同的策略。虽然一些患有更惰性疾病的患者可能受益于局部治疗，例如转移灶切除术或细胞减灭性肾切除术，但其他患者可能会安全地开始积极的监测计划或接受靶向治疗。然而，在大多数 mRCC 病例中，包括 ICI 在内的联合方案是最有效的方案，应强烈考虑。未来的研究将有助于确定哪些因素可以进一步用于优化治疗选择和个性化疾病管理。

参考文献

[1] Turajlic, S., Swanton, C. and Boshoff, C. (2018) Kidney Cancer: The Next Decade. *Journal of Experimental Medicine*, **215**, 2477-2479. https://doi.org/10.1084/jem.20181617

[2] Barata, P.C. and Rini, B.I. (2017) Treatment of Renal Cell Carcinoma: Current Status and Future Directions. *CA*: *A Cancer Journal for Clinicians*, **67**, 507-524. https://doi.org/10.3322/caac.21411

[3] Siegel, R.L., Miller, K.D. and Jemal, A. (2020) Cancer Statistics, 2020. *CA: A Cancer Journal for Clinicians*, **70**, 7-30. https://doi.org/10.3322/caac.21590

[4] American Cancer Society. Survival Rates for Kidney Cancer. https://www.cancer.org/cancer/types/kidney-cancer/detection-diagnosis-staging/survival-rates.html#references

[5] National Cancer Institute. Cancer Stat Facts: Kidney and Renal Pelvis Cancer. https://seer.cancer.gov/statfacts/html/kidrp.html

[6] Störkel, S. and van den Berg, E. (1995) Morphological Classification of Renal Cancer. *World Journal of Urology*, **13**, 153-158. https://doi.org/10.1007/bf00184870

[7] Srigley, J.R., Delahunt, B., Eble, J.N., Egevad, L., Epstein, J.I., Grignon, D., *et al*. (2013) The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. *American Journal of Surgical Pathology*, **37**, 1469-1489. https://doi.org/10.1097/pas.0b013e318299f2d1

[8] Maxwell, P.H., Wiesener, M.S., Chang, G., Clifford, S.C., Vaux, E.C., Cockman, M.E., *et al*. (1999) The Tumour Suppressor Protein VHL Targets Hypoxia-Inducible Factors for Oxygen-Dependent Proteolysis. *Nature*, **399**, 271-275. https://doi.org/10.1038/20459

[9] Clark, P.E. (2009) The Role of VHL in Clear-Cell Renal Cell Carcinoma and Its Relation to Targeted Therapy. *Kidney International*, **76**, 939-945. https://doi.org/10.1038/ki.2009.296

[10] Nickerson, M.L., Jaeger, E., Shi, Y., Durocher, J.A., Mahurkar, S., Zaridze, D., *et al*. (2008) Improved Identification of Von Hippel-Lindau Gene Alterations in Clear Cell Renal Tumors. *Clinical Cancer Research*, **14**, 4726-4734. https://doi.org/10.1158/1078-0432.ccr-07-4921

[11] Brugarolas, J. (2014) Molecular Genetics of Clear-Cell Renal Cell Carcinoma. *Journal of Clinical Oncology*, **32**, 1968-1976. https://doi.org/10.1200/jco.2012.45.2003

[12] Thomas, G.V., Tran, C., Mellinghoff, I.K., Welsbie, D.S., Chan, E., Fueger, B., *et al*. (2005) Hypoxia-Inducible Factor Determines Sensitivity to Inhibitors of mTOR in Kidney Cancer. *Nature Medicine*, **12**, 122-127.

https://doi.org/10.1038/nm1337

[13] Lebacle, C., Pooli, A., Bessede, T., Irani, J., Pantuck, A.J. and Drakaki, A. (2018) Epidemiology, Biology and Treatment of Sarcomatoid RCC: Current State of the Art. *World Journal of Urology*, **37**, 115-123. https://doi.org/10.1007/s00345-018-2355-y

[14] Samiei, A., Tayshetye, P., Sanguino, A., Miller, R., Lyne, J., Cohen, J., *et al*. (2019) The Clinical Outcome of Renal Cell Carcinoma with Rhabdoid and Sarcomatoid Differentiation. *Journal of Clinical Oncology*, **37**, e16083. https://doi.org/10.1200/jco.2019.37.15_suppl.e16083

[15] Herrera-Caceres, J.O. and Jewett, M.A.S. (2018) Roles for Active Surveillance in Renal Cancer. *Current Opinion in Urology*, **28**, 375-382. https://doi.org/10.1097/mou.0000000000000506

[16] Rini, B.I., Dorff, T.B., Elson, P., Rodriguez, C.S., Shepard, D., Wood, L., *et al*. (2016) Active Surveillance in Metastatic Renal-Cell Carcinoma: A Prospective, Phase 2 Trial. *The Lancet Oncology*, **17**, 1317-1324. https://doi.org/10.1016/s1470-2045(16)30196-6

[17] Verhoeff, S., van Es, S.C., Elias, S.G., Gerritse, S., Angus, L., Oosting, S., *et al*. (2020) Prediction of Watchful Waiting in Newly Diagnosed Metastatic Clear Cell Renal Cell Carcinoma Patients with a Good or Intermediate Prognosis. *Journal of Clinical Oncology*, **38**, 5079-5079. https://doi.org/10.1200/jco.2020.38.15_suppl.5079

[18] Park, I., Lee, J., Ahn, J., Lee, D., Lee, K., Jeong, I.G., *et al*. (2014) Active Surveillance for Metastatic or Recurrent Renal Cell Carcinoma. *Journal of Cancer Research and Clinical Oncology*, **140**, 1421-1428. https://doi.org/10.1007/s00432-014-1680-9

[19] Kushnir, I., Basappa, N.S., Ghosh, S., Lalani, A.A., Soulieres, D., Bjarnason, G.A., *et al*. (2019) Active Surveillance in Metastatic Renal Cell Carcinoma (mRCC): Results from the Canadian Kidney Cancer Information System (CKCis). *Journal of Clinical Oncology*, **37**, 4516-4516. https://doi.org/10.1200/jco.2019.37.15_suppl.4516

[20] ASCO 2019: Active Surveillance in Metastatic Renal Cell Carcinoma: Results from the Canadian Kidney Cancer Information System. https://www.urotoday.com/conference-highlights/asco-2019-annual-meeting/asco-2019-kidney-cancer/113043-asco-2019-active-surveillance-in-metastatic-renal-cell-carcinoma-results-from-the-canadian-kidney-cancer-information-system.html

[21] Motzer, R.J. and Russo, P. (2018) Cytoreductive Nephrectomy—Patient Selection Is Key. *New England Journal of Medicine*, **379**, 481-482. https://doi.org/10.1056/nejme1806331

[22] Flanigan, R.C., Salmon, S.E., Blumenstein, B.A., Bearman, S.I., Roy, V., McGrath, P.C., *et al*. (2001) Nephrectomy Followed by Interferon Alfa-2b Compared with Interferon Alfa-2b Alone for Metastatic Renal-Cell Cancer. *New England Journal of Medicine*, **345**, 1655-1659. https://doi.org/10.1056/nejmoa003013

[23] Mickisch, G., Garin, A., van Poppel, H., de Prijck, L. and Sylvester, R. (2001) Radical Nephrectomy Plus Interferon-Alfa-Based Immunotherapy Compared with Interferon Alfa Alone in Metastatic Renal-Cell Carcinoma: A Randomised Trial. *The Lancet*, **358**, 966-970. https://doi.org/10.1016/s0140-6736(01)06103-7

[24] Franklin, J.R., Figlin, R., Rauch, J., Gitlitz, B. and Belldegrun, A. (1996) Cytoreductive Surgery in the Management of Metastatic Renal Cell Carcinoma: The UCLA Experience. *Seminars in Urologic Oncology*, **14**, 230-236.

[25] Pindoria, N., Raison, N., Blecher, G., Catterwell, R. and Dasgupta, P. (2017) Cytoreductive Nephrectomy in the Era of Targeted Therapies: A Review. *BJU International*, **120**, 320-328. https://doi.org/10.1111/bju.13860

[26] Grant, M., Szabados, B., Kuusk, T., Powles, T. and Bex, A. (2020) Cytoreductive Nephrectomy: Does CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques) Change Everything? *Current Opinion in Urology*, **30**, 36-40. https://doi.org/10.1097/mou.0000000000000696

[27] Kokorovic, A. and Rendon, R.A. (2019) Cytoreductive Nephrectomy in Metastatic Kidney Cancer: What Do We Do Now? *Current Opinion in Supportive and Palliative Care*, **13**, 255-261. https://doi.org/10.1097/SPC.0000000000000433

[28] Alhalabi, O., Karam, J.A. and Tannir, N.M. (2019) Evolving Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma of Variant Histology. *Current Opinion in Urology*, **29**, 521-525. https://doi.org/10.1097/mou.0000000000000661

[29] Graham, J., Bhindi, B. and Heng, D.Y.C. (2019) The Evolving Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma. *Current Opinion in Urology*, **29**, 507-512. https://doi.org/10.1097/mou.0000000000000657

[30] Méjean, A., Ravaud, A., Thezenas, S., Colas, S., Beauval, J., Bensalah, K., *et al*. (2018) Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. *New England Journal of Medicine*, **379**, 417-427. https://doi.org/10.1056/nejmoa1803675

[31] Hsiang, W.R., Kenney, P.A. and Leapman, M.S. (2020) Redefining the Role of Surgical Management of Metastatic Renal Cell Carcinoma. *Current Oncology Reports*, **22**, Article No. 35. https://doi.org/10.1007/s11912-020-0895-y

[32] Mejean, A., Thezenas, S., Chevreau, C., Bensalah, K., Geoffrois, L., Thiery-Vuillemin, A., *et al*. (2019) Cytoreductive

Nephrectomy (CN) in Metastatic Renal Cancer (mRCC): Update on Carmena Trial with Focus on Intermediate Imdc-Risk Population. *Journal of Clinical Oncology*, **37**, 4508. https://doi.org/10.1200/jco.2019.37.15_suppl.4508

[33] Lázaro, M., Valderrama, B.P., Suárez, C., de-Velasco, G., Beato, C., Chirivella, I., *et al*. (2020) SEOM Clinical Guideline for Treatment of Kidney Cancer (2019). *Clinical and Translational Oncology*, **22**, 256-269. https://doi.org/10.1007/s12094-019-02285-7

[34] Massari, F., Di Nunno, V., Gatto, L., Santoni, M., Schiavina, R., Cosmai, L., *et al*. (2018) Should CARMENA Really Change Our Attitude Towards Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma? A Systematic Review and Meta-Analysis Evaluating Cytoreductive Nephrectomy in the Era of Targeted Therapy. *Targeted Oncology*, **13**, 705-714. https://doi.org/10.1007/s11523-018-0601-2

[35] AS-CO2019: Update on the CARMENA Trial with Focus on Intermediate IMDC-Risk Population: Cytoreductive Nephrectomy in Metastatic Renal Cancer. https://www.urotoday.com/conference-highlights/asco-2019-annual-meeting/asco-2019-kidney-cancer/113069-asco-2019-cytoreductive-nephrectomy-in-metastatic-renal-cancer-update-on-carmena-trial-with-focus-on-intermediate-imdc-risk-population.html

[36] Kavolius, J.P., Mastorakos, D.P., Pavlovich, C., Russo, P., Burt, M.E. and Brady, M.S. (1998) Resection of Metastatic Renal Cell Carcinoma.. *Journal of Clinical Oncology*, **16**, 2261-2266. https://doi.org/10.1200/jco.1998.16.6.2261

[37] Alt, A.L., Boorjian, S.A., Lohse, C.M., Costello, B.A., Leibovich, B.C. and Blute, M.L. (2011) Survival after Complete Surgical Resection of Multiple Metastases from Renal Cell Carcinoma. *Cancer*, **117**, 2873-2882. https://doi.org/10.1002/cncr.25836

[38] You, D., Lee, C., Jeong, I.G., Song, C., Lee, J., Hong, B., *et al*. (2016) Impact of Metastasectomy on Prognosis in Patients Treated with Targeted Therapy for Metastatic Renal Cell Carcinoma. *Journal of Cancer Research and Clinical Oncology*, **142**, 2331-2338. https://doi.org/10.1007/s00432-016-2217-1

[39] Palumbo, C., Pecoraro, A., Knipper, S., Rosiello, G., Tian, Z., Shariat, S.F., *et al*. (2019) Survival and Complication Rates of Metastasectomy in Patients with Metastatic Renal Cell Carcinoma Treated Exclusively with Targeted Therapy: A Combined Population-Based Analysis. *Anticancer Research*, **39**, 4357-4361. https://doi.org/10.21873/anticanres.13604

[40] Ouzaid, I., Capitanio, U., Staehler, M., Wood, C.G., Leibovich, B.C., Ljungberg, B., *et al*. (2019) Surgical Metastasectomy in Renal Cell Carcinoma: A Systematic Review. *European Urology Oncology*, **2**, 141-149. https://doi.org/10.1016/j.euo.2018.08.028

[41] Appleman, L.J., Puligandla, M., Pal, S.K., Harris, W., Agarwal, N., Costello, B.A., *et al*. (2019) Randomized, Double-Blind Phase III Study of Pazopanib versus Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastasectomy: A Trial of the ECOG-ACRIN Cancer Research Group (E2810). *Journal of Clinical Oncology*, **37**, 4502-4502. https://doi.org/10.1200/jco.2019.37.15_suppl.4502

[42] Procopio, G., Apollonio, G., Cognetti, F., Miceli, R., Milella, M., Mosca, A., *et al*. (2019) Sorafenib versus Observation Following Radical Metastasectomy for Clear-Cell Renal Cell Carcinoma: Results from the Phase 2 Randomized Open-Label RESORT Study. *European Urology Oncology*, **2**, 699-707. https://doi.org/10.1016/j.euo.2019.08.011

[43] Lee, C.C., Tey, J.C.S., Cheo, T., Lee, C.H., Wong, A., Kumar, N., *et al*. (2020) Outcomes of Patients with Spinal Metastases from Renal Cell Carcinoma Treated with Conventionally-Fractionated External Beam Radiation Therapy. *Medicine*, **99**, e19838. https://doi.org/10.1097/md.0000000000019838

[44] DiBiase, S.J., Valicenti, R.K., Schultz, D., Xie, Y., Gomella, L.G. and Corn, B.W. (1997) Palliative Irradiation for Focally Symptomatic Metastatic Renal Cell Carcinoma. *The Journal of Urology*, **158**, 746-749.

[45] Klausner, G., Troussier, I., Biau, J., Jacob, J., Schernberg, A., Canova, C., *et al*. (2019) Stereotactic Radiation Therapy for Renal Cell Carcinoma Brain Metastases in the Tyrosine Kinase Inhibitors Era: Outcomes of 120 Patients. *Clinical Genitourinary Cancer*, **17**, 191-200. https://doi.org/10.1016/j.clgc.2019.02.007

[46] Taunk, N.K., Spratt, D.E., Bilsky, M. and Yamada, Y. (2015) Spine Radiosurgery in the Management of Renal Cell Carcinoma Metastases. *Journal of the National Comprehensive Cancer Network*, **13**, 801-809. https://doi.org/10.6004/jnccn.2015.0093

[47] Zaorsky, N.G., Lehrer, E.J., Kothari, G., Louie, A.V. and Siva, S. (2019) Stereotactic Ablative Radiation Therapy for Oligometastatic Renal Cell Carcinoma (SABR ORCA): A Meta-Analysis of 28 Studies. *European Urology Oncology*, **2**, 515-523. https://doi.org/10.1016/j.euo.2019.05.007

[48] Dengina, N., Mitin, T., Gamayunov, S., Safina, S., Kreinina, Y. and Tsimafeyeu, I. (2019) Stereotactic Body Radiation Therapy in Combination with Systemic Therapy for Metastatic Renal Cell Carcinoma: A Prospective Multicentre Study. *ESMO Open*, **4**, e000535. https://doi.org/10.1136/esmoopen-2019-000535

[49] Barata, P.C., Mendiratta, P., Kotecha, R., Gopalakrishnan, D., Juloori, A., Chao, S.T., *et al*. (2018) Effect of Switching Systemic Treatment after Stereotactic Radiosurgery for Oligoprogressive, Metastatic Renal Cell Carcinoma. *Clinical*

Genitourinary Cancer, **16**, 413-419.e1. https://doi.org/10.1016/j.clgc.2018.07.018

[50] ASCO GU 2020: Combined Dual Checkpoint Inhibition and Stereotactic Body Radiotherapy in the Metastatic Renal Cell Carcinoma Setting (RADVAX RCC). https://www.urotoday.com/conference-highlights/asco-gu-2020/asco-gu-2020-kidney-cancer/119323-asco-gu-2020-combined-dual-checkpoint-inhibition-and-stereotactic-body-radiotherapy-in-the-metastatic-renal-cell-carcinoma-setting-radvax-rcc.html

[51] Twyman-Saint Victor, C., Rech, A.J., Maity, A., Rengan, R., Pauken, K.E., Stelekati, E., *et al*. (2015) Radiation and Dual Checkpoint Blockade Activate Non-Redundant Immune Mechanisms in Cancer. *Nature*, **520**, 373-377. https://doi.org/10.1038/nature14292

[52] ASCO GU 2020: Nivolumab in Combination with Stereotactic Body Radiotherapy in Pre-Treated Patients with Metastatic Renal Cell Carcinoma (NIVES). https://www.urotoday.com/conference-highlights/asco-gu-2020/asco-gu-2020-kidney-cancer/119278-asco-gu-2020-nivolumab-in-combination-with-stereotactic-body-radiotherapy-in-pre-treated-patients-with-metastatic-renal-cell-carcinoma-nives.html

[53] Motzer, R.J., Rini, B.I., McDermott, D.F., Arén Frontera, O., Hammers, H.J., Carducci, M.A., *et al*. (2019) Nivolumab Plus Ipilimumab versus Sunitinib in First-Line Treatment for Advanced Renal Cell Carcinoma: Extended Follow-up of Efficacy and Safety Results from a Randomised, Controlled, Phase 3 Trial. *The Lancet Oncology*, **20**, 1370-1385. https://doi.org/10.1016/s1470-2045(19)30413-9

[54] Garcia, J.A. and Rini, B.I. (2007) Recent Progress in the Management of Advanced Renal Cell Carcinoma. *CA*: *A Cancer Journal for Clinicians*, **57**, 112-125. https://doi.org/10.3322/canjclin.57.2.112

[55] Choueiri, T.K. and Motzer, R.J. (2017) Systemic Therapy for Metastatic Renal-Cell Carcinoma. *New England Journal of Medicine*, **376**, 354-366. https://doi.org/10.1056/nejmra1601333

[56] Allard, C.B., Gelpi-Hammerschmidt, F., Harshman, L.C., Choueiri, T.K., Faiena, I., Modi, P., *et al*. (2015) Contemporary Trends in High-Dose Interleukin-2 Use for Metastatic Renal Cell Carcinoma in the United States. *Urologic Oncology*: *Seminars and Original Investigations*, **33**, 496.e11-496.e16. https://doi.org/10.1016/j.urolonc.2015.06.014

[57] Negrier, S., Escudier, B., Lasset, C., Douillard, J., Savary, J., Chevreau, C., *et al*. (1998) Recombinant Human Interleukin-2, Recombinant Human Interferon Alfa-2a, or Both in Metastatic Renal-Cell Carcinoma. *New England Journal of Medicine*, **338**, 1272-1278. https://doi.org/10.1056/nejm199804303381805

[58] Hudes, G., Carducci, M., Tomczak, P., Dutcher, J., Figlin, R., Kapoor, A., *et al*. (2007) Temsirolimus, Interferon Alfa, or Both for Advanced Renal-Cell Carcinoma. *New England Journal of Medicine*, **356**, 2271-2281. https://doi.org/10.1056/nejmoa066838

[59] Escudier, B., Eisen, T., Stadler, W.M., Szczylik, C., Oudard, S., Siebels, M., *et al*. (2007) Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma. *New England Journal of Medicine*, **356**, 125-134. https://doi.org/10.1056/nejmoa060655

[60] Motzer, R.J., Hutson, T.E., Tomczak, P., Michaelson, M.D., Bukowski, R.M., Rixe, O., *et al*. (2007) Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma. *New England Journal of Medicine*, **356**, 115-124. https://doi.org/10.1056/nejmoa065044

[61] Roskoski, R. (2017) Vascular Endothelial Growth Factor (VEGF) and VEGF Receptor Inhibitors in the Treatment of Renal Cell Carcinomas. *Pharmacological Research*, **120**, 116-132. https://doi.org/10.1016/j.phrs.2017.03.010

[62] Sternberg, C.N., Davis, I.D., Mardiak, J., Szczylik, C., Lee, E., Wagstaff, J., *et al*. (2010) Pazopanib in Locally Advanced or Metastatic Renal Cell Carcinoma: Results of a Randomized Phase III Trial. *Journal of Clinical Oncology*, **28**, 1061-1068. https://doi.org/10.1200/jco.2009.23.9764

[63] Frampton, J.E. and Keating, G.M. (2008) Bevacizumab: In First-Line Treatment of Advanced and/or Metastatic Renal Cell Carcinoma. *BioDrugs*, **22**, 113-120. https://doi.org/10.2165/00063030-200822020-00004

[64] Motzer, R.J., Hutson, T.E., Cella, D., Reeves, J., Hawkins, R., Guo, J., *et al*. (2013) Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma. *New England Journal of Medicine*, **369**, 722-731. https://doi.org/10.1056/nejmoa1303989

[65] Escudier, B., Porta, C., Bono, P., Powles, T., Eisen, T., Sternberg, C.N., *et al*. (2014) Randomized, Controlled, Double-Blind, Cross-Over Trial Assessing Treatment Preference for Pazopanib versus Sunitinib in Patients with Metastatic Renal Cell Carcinoma: PISCES Study. *Journal of Clinical Oncology*, **32**, 1412-1418. https://doi.org/10.1200/jco.2013.50.8267

[66] Choueiri, T.K., Halabi, S., Sanford, B.L., Hahn, O., Michaelson, M.D., Walsh, M.K., *et al*. (2017) Cabozantinib versus Sunitinib as Initial Targeted Therapy for Patients with Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. *Journal of Clinical Oncology*, **35**, 591-597. https://doi.org/10.1200/jco.2016.70.7398

[67] Wiechno, P., Kucharz, J., Sadowska, M., Michalski, W., Sikora-Kupis, B., Jonska-Gmyrek, J., *et al*. (2018) Contemporary Treatment of Metastatic Renal Cell Carcinoma. *Medical Oncology*, **35**, Article No. 156. https://doi.org/10.1007/s12032-018-1217-1

[68] Motzer, R.J., Escudier, B., McDermott, D.F., George, S., Hammers, H.J., Srinivas, S., *et al*. (2015) Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *New England Journal of Medicine*, **373**, 1803-1813. https://doi.org/10.1056/nejmoa1510665

[69] Atkins, M.B. and Tannir, N.M. (2018) Current and Emerging Therapies for First-Line Treatment of Metastatic Clear Cell Renal Cell Carcinoma. *Cancer Treatment Reviews*, **70**, 127-137. https://doi.org/10.1016/j.ctrv.2018.07.009

[70] Ornstein, M.C. and Rini, B.I. (2018) Radical Shifts in the First-Line Management of Metastatic Renal Cell Carcinoma. *Nature Reviews Clinical Oncology*, **16**, 71-72. https://doi.org/10.1038/s41571-018-0146-4

[71] Hahn, A.W., Klaassen, Z., Agarwal, N., Haaland, B., Esther, J., Ye, X.Y., *et al*. (2019) First-Line Treatment of Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-Analysis. *European Urology Oncology*, **2**, 708-715. https://doi.org/10.1016/j.euo.2019.09.002

[72] Yasuda, S., Sho, M., Yamato, I., Yoshiji, H., Wakatsuki, K., Nishiwada, S., *et al*. (2013) Simultaneous Blockade of Programmed Death 1 and Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) Induces Synergistic Anti-Tumour Effect *in Vivo*. *Clinical and Experimental Immunology*, **172**, 500-506. https://doi.org/10.1111/cei.12069

[73] Dirkx, A.E.M., Egbrink, M.G.A.o., Castermans, K., Schaft, D.W.J., Thijssen, V.L.J.L., Dings, R.P.M., *et al*. (2006) Anti-Angiogenesis Therapy Can Overcome Endothelial Cell Anergy and Promote Leukocyte-Endothelium Interactions and Infiltration in Tumors. *The FASEB Journal*, **20**, 621-630. https://doi.org/10.1096/fj.05-4493com

[74] Plimack, E.R., Rini, B.I., Stus, V., Gafanov, R., Waddell, T., Nosov, D., *et al*. (2020) Pembrolizumab plus Axitinib versus Sunitinib as First-Line Therapy for Advanced Renal Cell Carcinoma (RCC): Updated Analysis of Keynote-426. *Journal of Clinical Oncology*, **38**, 5001. https://doi.org/10.1200/jco.2020.38.15_suppl.5001

[75] Rini, B.I., Plimack, E.R., Stus, V., Gafanov, R., Hawkins, R., Nosov, D., *et al*. (2019) Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *New England Journal of Medicine*, **380**, 1116-1127. https://doi.org/10.1056/nejmoa1816714

[76] Motzer, R.J., Penkov, K., Haanen, J., Rini, B., Albiges, L., Campbell, M.T., *et al*. (2019) Avelumab Plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *New England Journal of Medicine*, **380**, 1103-1115. https://doi.org/10.1056/nejmoa1816047

[77] Rini, B.I., Powles, T., Atkins, M.B., Escudier, B., McDermott, D.F., Suarez, C., *et al*. (2019) Atezolizumab Plus Bevacizumab versus Sunitinib in Patients with Previously Untreated Metastatic Renal Cell Carcinoma (IMmotion151): A Multicentre, Open-Label, Phase 3, Randomised Controlled Trial. *The Lancet*, **393**, 2404-2415. https://doi.org/10.1016/s0140-6736(19)30723-8