Oligo-Recurrent and Oligo-Progressive Renal Cell Carcinoma

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One-third of renal cell carcinomas (RCCs) without metastases develop metastatic disease after extirpative surgery for the primary tumors. The majority of metastatic RCC cases, along with treated primary lesions, involve limited lesions termed “oligo-recurrent” disease. The role of metastasis-directed therapy (MDT), including stereotactic body radiation therapy (SBRT) and metastasectomy, in the treatment of oligo-recurrent RCC has evolved. Although the surgical resection of all lesions alone can have a curative intent, SBRT is a valuable treatment option, especially for patients concurrently receiving systemic therapy. Contemporary immune checkpoint inhibitor (ICI) combination therapies remain central to the management of metastatic RCC. However, one objective of MDT is to delay the initiation of systemic therapies, thereby sparing patients from potentially unnecessary burdens. Undertaking MDT for cases showing progression under systemic therapies, known as “oligo-progression”, can be complex in considering the treatment approach. Its efficacy may be diminished compared to patients with stable disease. SBRT combined with ICI can be a promising treatment for these cases because radiation therapy has been shown to affect the tumor microenvironment and areas beyond the irradiated sites. This may enhance the efficacy of ICIs, although their efficacy has only been demonstrated in clinical trials.

renal cell carcinoma | oligo-metastasis | oligo-recurrence | oligo-progression | metastasectomy | stereotactic body radiation therapy

1. Classifications and Definition of Oligo-Metastatic Diseases

Oligo-metastatic diseases are typically defined by the number of metastatic sites, specifically the presence of five or fewer lesions. However, the number of organs involved and the size of the metastatic lesions have not been clearly specified. Treatment strategies and prognoses vary based on the organs involved and the size, number, and growth rate of the metastatic lesions.

Niibe et al. introduced a classification system based on the condition of the primary tumors: oligo-metastasis with uncontrolled primary sites and oligo-recurrence with previously treated primary sites, where all evident recurrence or metastatic sites can be addressed using local therapy [1]. The biological behavior and clinical outcomes of synchronous oligometastatic disease (occurring within a 6-month interval of the primary cancer diagnosis) and metachronous oligometastatic disease (occurring >6 months after the primary cancer diagnosis) differ [1].

Synchronous diseases are typically viewed as more aggressive compared to metachronous ones [2][3]. Previous studies have proposed another definition of “oligo-progression”, which refers to patients who show progression in a few lesions while primary and other metastases are controlled by systemic therapies [2][4][5].

According to the European Society for Radiotherapy and Oncology and the European Organization for Research and Treatment of Cancer, the OligoCare project developed a classification system representing the state of oligo-metastases [2]. First, the imaging-based diagnosis of oligo-metastatic disease was divided into two classifications according to the history of poly-metastatic or oligo-metastatic disease. Patients without a history of poly-metastatic or oligo-metastatic disease were identified as having de novo oligo-metastatic disease. Second, they were divided based on the presence of the primary site and the timing of the occurrence of metastatic disease. Metachronous oligo-metastatic disease, “metachronous oligo-recurrence”, and “metachronous oligo-progression” have been recognized based on the presence of ongoing systemic therapy [2]. Other classifications depend on the history of poly-metastasis, local therapy, or systemic therapy, and these have different treatment goals.

2. Novel Imaging to Detect Oligo-Recurrence

Typically, most RCC diagnoses and metastatic sites are based on non-invasive radiological techniques, including ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). These imaging techniques are the most relevant diagnostic methods for defining oligo-metastatic disease, owing to the scarcity of biomarkers [2]. In terms of nuclear medicine imaging, fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F] FDG-PET/CT) has been thoroughly examined for diagnosing metastatic RCC [6]. Previous studies have suggested that the expression of glucose transporter 1, which correlates with FDG’s biological activity, varies widely according to the histological subtype of RCC [6]. In contrast, Park et al. found that the accuracy of [^{18}F] FDG-PET/CT for diagnosing per-lesion recurrence after radical nephrectomy surpassed that of conventional imaging, including chest and pelvic CT [7]. Several studies have confirmed its effectiveness in detecting the recurrent foci of RCC, although [^{18}F] FDG-PET/CT is not deemed a standard imaging test, especially for clear-cell subtypes.

Recently, many studies have highlighted the effectiveness of prostate-specific membrane antigen (PSMA)-based positron emission tomography (PSMA-PET) for detecting oligo-metastatic prostate cancers. PSMA is also found in the tumor-associated neovasculature of primary and metastatic RCC. Several studies have revealed its superiority in identifying metastatic sites compared to conventional imaging and [^{18}F] FDG-PET/CT [6]. Moreover, the uptake of PSMA radioligands may serve as an indicator of the efficacy of targeted and immune checkpoint agents [8]. On the other hand, various radiotracers are currently available, each with distinct pharmacokinetic properties. Differences in the diagnostic capacities of RCC are yet to be established. Additionally, to date, no studies have compared their cost-effectiveness with conventional imaging [6]. Further research is required to delineate the role of PSMA-PET/CT in RCC management.

3. Current Options in Treating Oligo-Metastatic RCC

The National Comprehensive Cancer Network guidelines suggest MDT, including metastasectomy, SBRT, and ablative therapy, in treating oligometastatic diseases in both stage IV and relapse RCC, regardless of histologic subtypes [9].

3.1. Active Surveillance

According to the American Society of Clinical Oncology guidelines, selected patients may be offered initial active surveillance (AS) in addition to MDT [10]. Prospective data on the natural history of metastatic RCC and the safety of AS as an initial strategy are limited. This is because contemporary metastatic RCC trials often excluded patients who did not undergo treatment [11][12]. Nonetheless, AS may be a viable treatment for patients with slow-growing tumors. Current guidelines suggest that AS should be offered to selected patients, specifically those with a limited tumor burden, no symptoms, a favorable histological profile, and a long interval between radical surgery and the development of metastases [13]. Additionally, a previous study hypothesized that some patients with metastatic RCC could safely opt for initial surveillance without compromising their response to later systemic therapies [11]. Although modern medications, including VEGFR-TKIs and ICI drugs, demonstrate high efficacy, they can be toxic and prohibitively expensive for some patients and health systems. Harrison et al. conducted an interesting study in which patient-reported QOL was assessed using completed patient-reported outcomes [12]. The results of these questionnaires indicated that the QOL at baseline was significantly better in patients who underwent AS than in those who underwent systemic therapy. However, it is crucial that clinicians discuss the observation period until disease progression is confirmed.

3.2. Surgery

Surgical interventions for metastatic RCC encompass cytoreductive nephrectomy (CN) and metastasectomy. Tumor resection has the potential to be curative if all tumor deposits are removed. In the era of targeted therapy, the advantages of CN are unclear [14]. With the introduction of novel ICI combination therapies, the immediate use of CN in patients with advanced RCC has declined [15]. Furthermore, the role and timing of deferred CN remain controversial. The efficacy of metastasectomies in the treatment of metastatic RCC has also been disputed, given the absence of randomized controlled trials. Existing studies exhibit considerable heterogeneity, primarily because ideal candidates are typically those with a good performance status, prolonged periods without evidence of disease, and relatively minor metastatic burdens [16]. Surgeries for advanced primary and metastatic sites can be invasive, potentially leading to severe complications and delaying or postponing subsequent systemic therapies [17]. Cytoreductive surgery is currently considered an option for patients with fully resectable primary and metastatic lesions. Performing upfront CN for oligo-metastatic RCC is deemed acceptable when complete local treatment can be achieved or when a significant portion of the tumor burden can be excised.

3.3. Ablation Therapy

Thermal ablation, such as cryoablation or radiofrequency ablation (RFA), is another option. Ablation is considered a less-invasive treatment option than surgery and has the advantage of repeated treatment. A previous small series showed high local control rates in visceral metastases of RCC [18]. In addition, a previous study suggested that

RFA could trigger inflammatory cell activation, similar to radiation therapy [18]. However, the use of thermal ablation for specific metastases may be limited to patients with small single or localized lesions.

3.4. Radiation Therapy

Although RCC was previously considered radioresistant, SBRT has emerged as an effective option for oligometastatic RCC [19][20]. A preclinical study examining radiosensitivity in vitro in multiple human cancer cell lines revealed that RCC is relatively resistant to conventional fractionated radiation therapy. Another clinical trial indicated that conventional adjuvant radiation therapy for RCC did not improve local recurrence rates and was associated with severe toxicity [19]. However, radiation therapy, when administered at a higher dose per fraction, has been proven to be effective for RCC. SBRT is characterized as a treatment approach that delivers a high radiation dose to the target using either a single dose or a limited number of fractions, maintaining a high level of precision within the body. Radiation therapy offers a wide range of potential applications across various tumor types and locations, and is both effective and safe. It can also serve as a palliative treatment for lesions that cause local symptoms. Furthermore, the efficacy of SBRT has been demonstrated in unresectable lesions, with high local control rates. The treatment duration is generally brief and reduces patient discomfort owing to its minimally invasive nature. Moreover, in most cases, systemic therapies do not need to be interrupted during the treatment, thus eliminating the risk of tumor progression that could arise from interrupting systemic therapies.

4. Treatment Strategy for Metachronous Oligo-Recurrent RCC

In cases of metachronous oligo-recurrence, a particularly favorable subgroup includes patients who manifest metachronous metastases for more than a year after undergoing radical surgery for primary lesions. These patients typically have an indolent disease course. For such patients, any of the approaches, AS, metastasectomy, and SBRT, are viable options. Rini et al. conducted a phase II trial to determine the time to initiation of systemic therapy in patients with metastatic RCC and AS [11]. Of the 48 patients, 47 were systemically treatment-naïve and presented with metachronous, asymptomatic, oligo-recurrent disease. The median duration until the initiation of treatment or withdrawal of consent was 14.9 months. In the multivariate analyses, a greater number of International Metastatic RCC Database Consortium (IMDC) risk factors and an increased number of metastatic disease sites were correlated with a shorter surveillance period. The authors identified a favorable group consisting of patients with either no or one IMDC risk factor and metastases in two or fewer organs, and an unfavorable group comprising all other patients. The former had an estimated median surveillance time of 22.2 months, while the latter's median was 8.4 months (p = 0.0056). Hannan et al. performed a phase II analysis to examine the effect of metastasis-targeted SBRT on outcomes in patients with systemic therapy-naïve oligo-recurrent RCC [21]. They included 23 patients with RCC with up to three extracranial metastases, with a total of 57 sites receiving upfront SBRT. All but one patient had previously undergone radical nephrectomy. Impressively, 91.3% of the patients remained free from systemic therapy for one year. Moreover, the local control rate for sites treated with SBRT stood at 100%. Similarly, Tang et al. published a phase II trial involving patients with oligo-metastatic RCC who had previously undergone nephrectomies [22]. Their findings indicated that SBRT for all metastatic lesions prolonged

the disease duration without the need for systemic treatment. Retrospective studies have also supported the efficacy of each approach for oligo-recurrent lesions, identifying several risk factors, such as favorable intermediate-risk IMDC scores and fewer (≤3) metastatic lesions associated with progression [23]. Based on the results of these studies, it is evident that a longer interval since nephrectomy and fewer metastatic sites are associated with improved outcomes.

5. Treatment Strategy for Metachronous Oligo-Progressive RCC

The aim of MDT for the treatment of metachronous oligo-progression is to delay the escalation or withdrawal of systemic therapies if alternative lines are limited [24]. When considering disease progression, altering systemic agents should be considered alongside MDT [20]. Nonetheless, previous studies have indicated that combining systemic therapies enhances outcomes and that MDT extending the period before systemic therapy needs to be intensified [25][26]. Among MDTs, radiation therapy may be a more favorable choice than surgical resection when concurrent systemic therapy is used. This preference arises for two main reasons: firstly, radiation can amplify the immune-related effect on the tumor microenvironment, and secondly, there is no need to interrupt systemic therapy during radiation therapy. However, it is crucial to note that exposure to the toxicities of systemic therapies can influence patient OS. Meyer et al. studied a large cohort of 188 patients who underwent SBRT for oligo-metastatic RCC [26]. Their findings revealed that patients with oligo-progression during systemic treatment had a shorter OS compared to those with systemic treatment-naïve oligo-metastatic RCC (23.2 months vs. 33.9 months). De et al. demonstrated that SBRT effectively delayed the intensification of systemic therapy for patients with oligo-progressive RCC, irrespective of the systemic treatment agents used [25]. Notably, half of the patients had not started systemic therapy at the time of progression, and patients receiving TKI at the onset of oligo-progression were at a heightened risk of mortality.

The NIVES study was a single-arm phase II trial designed to evaluate the efficacy of SBRT combined with nivolumab in treating metastatic RCC [27]. Eligible patients had one or more lesions suitable for SBRT and had undergone one or more lines of targeted therapy but were ICI-naïve. The primary endpoint, namely, the objective response rate (ORR), was 17% in this study, which was lower than that observed in the Check Mate 025 trial [28]. This result failed to provide compelling evidence that the combination of nivolumab and SBRT offers additional benefits to previously treated patients with metastatic RCC. Notably, not all metastatic sites in this study were irradiated, leading the authors to suggest that the abscopal effect may be infrequent. In contrast, the SABR-COMET study demonstrated that SBRT at all sites of oligo-metastatic disease led to improved OS compared to palliative radiation therapy across various types of cancer [29]. Because standard systemic therapies for various cancers were permitted in this study, it was challenging to assess the efficacy of SBRT in isolation. Nevertheless, this study implies that it may be essential to treat all metastatic lesions with SBRT, although the effect of radiation beyond the targeted lesion remains uncertain [30].

Several studies have highlighted the efficacy of SBRT in delaying the need for subsequent systemic therapy. Cheung et al. published a phase II study illustrating that SBRT for oligo-metastatic lesions could help delay

changing to VEGFR-TKIs [24]. Patients who demonstrated stable responses to systemic therapy for >3 months were enrolled. The study revealed that the cumulative incidence of transition to different systemic therapies was 47% at one year, with a median transition time of 12.6 months. Moreover, the median progression-free survival (PFS) was >9 months, although most cases of disease progression were observed outside the irradiated area. Hannan et al. demonstrated that SBRT prolonged the duration of current systemic therapy in patients experiencing oligo-progression, provided that all lesions were suitable for SBRT [31]. Their findings also indicated that the median time from SBRT to the initiation of new systemic therapy or death was approximately one year. Ma et al. conducted a retrospective study with a small cohort to assess the efficacy of SBRT in the treatment of oligo-progressive RCC using targeted therapies [23]. In this study, favorable and intermediate risk scores in the IMDC risk classification and fewer than three metastases were associated with longer OS and PFS. Thus, SBRT appears beneficial for patients either with stable disease or those with oligo-metastatic lesions that are amenable to SBRT. Consequently, the full irradiation of all metastatic lesions, which are managed by systemic treatments, may offer superior local control for patients with oligo-progressive disease [23].

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