



# Management of Patients with Renal Cell Carcinoma during Coronavirus Pandemic: Proposed Algorithm in Russia

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## Abstract

The World Health Organization has announced the pandemic of coronavirus infection (COVID-19) that cause acute respiratory syndrome. Cancer patients are more susceptible to infections due to systemic immunosuppression caused by malignant neoplasms and by anticancer therapy. Patients with Renal Cell Carcinoma (RCC) could be more sensitive to infections due to disorders in the immune system. The proposed algorithm is based on the recommendations of professional communities or on information published on the official websites of professional societies, adapted for planning care for RCC patients during the spread of COVID-19.

## Background

The World Health Organization has announced the pandemic of coronavirus infection (COVID-19) that cause acute respiratory syndrome. As of April 1, more than 2,700 cases of COVID-19-positive patients have been reported in Russia. Cancer patients are more susceptible to infections due to systemic immunosuppression caused by malignant neoplasms and by anticancer therapy [1]. Patients with Renal Cell Carcinoma (RCC) could be more sensitive to infections due to disorders in the immune system [2].

The proposed algorithm is based on the recommendations of professional communities or on information published on the official websites of professional societies, adapted for planning care for RCC patients during the spread of COVID-19. Despite the fact that no specific treatment of RCC based on valid evidence in the pandemic of COVID-19, the aim of the proposed algorithm is optimized surgical and medical treatment of patients to decrease the rate of adverse events, the number of patient visits to the hospital, and potential risks associated with COVID-19 infection. Each medical facility should be guided by federal and local decrees and orders. Oncologists should consider management of RCC by the existing standards of patient care, practical guidelines for the diagnosis and treatment of kidney cancer, and should discuss with the patient available treatment and follow-up options in time of coronavirus pandemic.

## Surgical Treatment and Follow-Up

Patients who have had radical or partial nephrectomy have a risk of surgical complications (14% to 34%), including the risk of developing infections (10% to 43%) [3-6]. Some patients will require mechanical ventilation and/or admission to an intensive care unit. Therefore, planned surgical treatment for patients with localized RCC may be postponed. Small primary tumors have a low growth rate, which is within the range from 1 mm to 5 mm per year according to various studies [7,8]. The risk of systemic disease progression in these patients is also low (an average of about 5%) [9].

Surgical treatment of locally advanced RCC can also be postponed for the coming weeks until the situation with the spread of coronavirus is clarified.

Cytoreductive nephrectomy before the start of systemic therapy in patients with metastatic RCC may be canceled. The results of CARMENA study demonstrate that there are no differences in efficacy between a group of patients with an intermediate/poor MSKCC prognosis who underwent cytoreductive nephrectomy followed by sunitinib and a group receiving sunitinib without nephrectomy (median overall survival, 13.9 vs. 18.4 months, respectively), while the authors noted a risk of complications of Clavien–Dindo grade III or higher associated with cytoreductive nephrectomy in 15.9% of patients [10,11].

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Received Date: 02 May 2020

Accepted Date: 29 May 2020

Published Date: 03 Jun 2020

### Citation:

Tsimafeyeu I, Volkova M. Management of Patients with Renal Cell Carcinoma during Coronavirus Pandemic: Proposed Algorithm in Russia. *Clin Oncol.* 2020; 5: 1707.

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Palliative nephrectomy and/or thrombectomy, that are being performed to eliminate the symptoms of the disease and potentially dangerous complications (hematuria, sever pain, thromboembolic event due to tumor thrombus fragmentation, anemia, etc.), retain their significance.

Follow-up after surgical treatment of RCC could be recommended 6 months after surgery.

## Systemic Therapy of Patients with Metastatic RCC

Patients with symptoms of the virus infection (fever, cough, and dyspnea) or with COVID-19 positive test should discontinue any anticancer therapy until recovery, defined as the first negative Polymerase Chain Reaction (PCR) test for coronavirus.

In patients with metastatic RCC without the symptoms of COVID-19 and with a negative PCR test, systemic therapy can be initiated or continued. It is worth noting that metastatic RCC has an aggressive course, especially in patients with intermediate and poor prognosis according to the criteria of MSKCC/IMDC [10,12]. The median overall survival in the poor prognosis group is 4 to 7 months [10,13]. Consequently, the risk of death from cancer in the case of delayed therapy in these patients exceeds the risk of death from a potential infection with coronavirus.

In these patients treatment with mTOR inhibitors (temsirolimus, everolimus) is not recommended, both in the first and subsequent lines of therapy, because their use is associated with an increased risk of infectious complications due to their immunosuppressive mechanism of action, as well as with pneumonitis [14,15]. The overall incidence of fatal adverse events was 3.2% in the mTOR inhibitors arm from everolimus and temsirolimus trials [16].

When selecting first-line therapy options for the patients with a favorable prognosis the preferences should be given to oral forms, sunitinib or pazopanib, with subsequent follow-up every 3 cycles/months. Sunitinib and pazopanib are also preferred treatment options in this group according to the recommendations of NCCN [17].

Patients with single IMDC risk factor (favorable-intermediate prognosis) may receive treatment with tyrosine kinase inhibitors in outpatient settings [18]. Patients with subcompensated or decompensated types of chronic respiratory disease have a potentially high risk of autoimmune pulmonitis developing during treatment with checkpoint inhibitors. They may be administered with tyrosine kinase inhibitors.

In patients with an intermediate (2 risk factors) and poor (3 or more risk factors) prognosis according to IMDC, the main treatment option is a combination of nivolumab and ipilimumab. This combination showed promising efficacy in Check Mate 214 study with median overall survival of 47 months in patients with intermediate and poor prognosis [19]. Intravenous agents in the induction period are administered once in 3 weeks, and this regimen does not require frequent visits of patients to the clinic. There were no large trials evaluating delayed toxicity of checkpoint inhibitors in metastatic RCC patients with virus infections, however, some studies showed an acceptable safety profile of immunotherapy in patients infected with chronic hepatitis C [20].

The best options for the second- and subsequent treatment lines could be nivolumab in cases of disease progression following previous targeted therapy or axitinib in cases of disease progression after

previous checkpoint inhibitors treatment. Nivolumab is preferably used in a dose of 480 mg administered once a month. Axitinib should be taken orally in outpatient settings.

Taken into account the frequency of grade 3-4 adverse events, which were observed in more than half of patients treated with a combination of pembrolizumab and axitinib (75.8%), a combination of lenvatinib with everolimus (71%), as well as monotherapy with cabozantinib (68%), the use of these regimens during coronavirus pandemic should be considered only in selected patients [21-23].

Monitoring of the patient's condition and adverse events during systemic therapy can be carried out remotely *via* telephone contacts, telemedicine, and other distant methods.

The algorithm of the management of patients with renal cell carcinoma in Russia during coronavirus pandemic was published on the website of the Russian Society of Clinical Oncology (RUSSCO) on March 24, 2020 [24].

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