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Original article

Renal tumors

Outcomes of treatment, laboratory results, adverse effects, and tolerability of cancer treatment in patients with metastatic renal cell carcinoma treated with ipilimumab and nivolumab after cytoreductive nephrectomy

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Abstract

Introduction. This publication aims to present the results of a retrospective analysis of the treatment outcomes of patients with metastatic renal cell carcinoma (mRCC) treated with ipilimumab and nivolumab (IPI-NIVO) who underwent cytoreductive nephrectomy (CN), radical nephrectomy (RN) or nephron-sparing surgery (NSS) and in whom surgery was omitted.

Material and methods. The retrospective analysis includes the results of 34 patients treated and followed at the Institute of Oncology, Poznań University of Medical Sciences, from May 2022 to February 2024.

Results. Progression-free survival (PFS) was compared in two groups of patients — those who underwent CN (n = 8) and those who had no prior surgical treatment before IPI-NIVO (n = 12). There was a statistically significant difference in the length of PFS between the two groups compared in favour of patients who underwent CN before starting systemic treatment (p = 0.004). The majority of patients (n = 27) reported adverse events during IPI-NIVO treatment. There was no effect of CN performed before initiation of systemic treatment on the occurrence of adverse events during therapy (p = 0.677). The most common reasons for discontinuation of systemic treatment were the drugs adverse effects (n = 8) and disease progression (n = 7).

Conclusions. The results presented in the study suggest the important role of CN in the treatment of mRCC. Appropriate selection of patients suitable for CN is critical to achieving optimal treatment outcomes. Due to limited literature data, further studies are needed to

evaluate the role and validity of performing CN in patients with mRCC treated with IPI-NIVO regimens.

Keywords: metastatic renal cell carcinoma, immune checkpoint inhibitors, ipilimumab, nivolumab, cytoreductive nephrectomy

Introduction

Renal cell carcinoma (RCC) is a heterogeneous disease with several histological subtypes identified. The most common subtype is clear cell carcinoma, accounting for over 80% of all renal cancer cases [1]. Despite significant advances in the diagnosis and treatment of cancer, advanced-stage RCC, i.e., with distant metastases (metastatic renal cell carcinoma, mRCC), remains a common clinical problem. Despite increasing access to diagnostic tools, such as ultrasound and computed tomography, it is estimated that approximately 25% of patients with RCC have metastases at the time of diagnosis. Statistically, only 8% of patients survive 5 years after diagnosis [2, 3].

Due to the lack of satisfactory response of mRCC to conventional chemotherapy and radiotherapy, effective systemic treatment of this cancer has been sought for many years [4]. Immunotherapies based on cytokines, such as interleukin-2 and interferon-alpha (IFN-α), were used for many years in the systemic therapy of mRCC until the introduction of molecularly targeted drugs [5, 6]. Immune checkpoint inhibitors (ICIs), such as ipilimumab and nivolumab (IPI-NIVO), have been used for several years and show high efficacy in the treatment of patients with mRCC. Ipilimumab and nivolumab are monoclonal antibodies that bind to the immune checkpoints CTLA-4 and PD-1, respectively. Studies have shown that the effect of IPI-NIVO at different stages of the immune response (CTLA-4 and PD-1 checkpoints) increases the efficacy of oncological treatment [7, 8].

For many years, the validity of cytoreductive nephrectomy (CN) has remained a controversial issue among urologists and oncologists treating metastatic renal cell carcinoma (mRCC). Cytoreductive nephrectomy is a surgical intervention that involves the non-radical removal of a cancer-affected kidney with the goal of reducing tumor mass and ultimately improving systemic treatment outcomes. The aim of CN is to remove as much cancerous tissue as possible, though not necessarily the entire tumor. Often, part of the tumor is left behind, especially if other organs are involved. Cytoreductive nephrectomy is often performed in patients with mRCC when a complete cure for the cancer is not possible [9]. Radical nephrectomy (RN), on the other hand, is a procedure in which the entire kidney is removed along with the surrounding adipose tissue, part of the ureter, and — in some cases — the

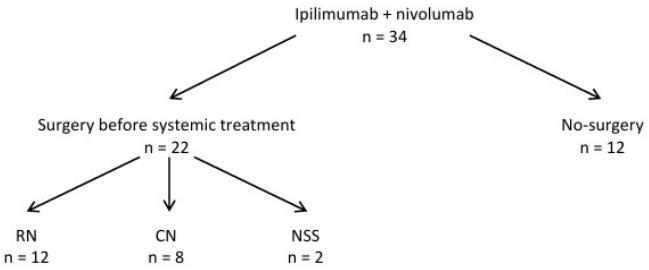
lymph nodes. The main goal of RN is to completely remove the tumor when it is confined to the kidney, and there is no evidence of metastasis to other organs. It is a treatment with radical intent, i.e., to cure the patient completely [10]. In some patients, it is possible to perform nephron-sparing surgery (NSS), which is the surgical removal of a kidney tumor while preserving as much healthy kidney tissue as possible. Nephron-sparing surgery is the preferred treatment for patients with small-diameter RCC, typically less than 4 cm, but it may also be performed in selected cases of larger tumors [11, 12].

There is still limited data in the literature regarding the efficacy of treatment in patients with mRCC treated with IPI-NIVO who have undergone CN, and in whom CN was omitted. Therefore, it was decided to conduct a scientific study to evaluate the role of CN in mRCC patients treated with IPI-NIVO.

Material and methods

This article presents the results of a retrospective analysis of the treatment of patients with mRCC (stage IV according to the TNM classification). The study included patients treated systemically with IPI-NIVO therapy who underwent surgery (CN, RN, or NSS) prior to systemic treatment, and patients who did not undergo surgery prior to systemic therapy. A detailed analysis was conducted on the outcomes of patients treated with IPI-NIVO who underwent CN, comparing them to the outcomes of patients who did not undergo surgical treatment. The retrospective analysis includes the results of 34 patients treated and followed at the Institute of Oncology, Poznań University of Medical Sciences, from May 2022 to February 2024. Prior to the start of the study, the Bioethics Committee of the Poznań University of Medical Sciences issued an opinion that the study did not have the characteristics of a medical experiment.

Statistical analysis was performed using software by Dell Inc. (2016), Dell Statistica (data analysis software system) version 13, and Cytel Studio version 11.1.0. The normality of the distribution of the variables studied was tested using the Shapiro-Wilk test. Student’s t-test, Mann-Whitney, and Wilcoxon tests for dependent samples were used to compare individual statistical data. Categorical parameters were described as n (%). The statistical significance of the relationships examined was tested at the level of $\alpha = 0.05$.



Ipilimumab + nivolumab n = 34

Surgery before systemic treatment n = 22

RN n = 12

CN n = 8

NSS n = 22

No-surgery n = 12

Figure 1. Distribution of patients included in the study; CN — cytoreductive nephrectomy; NSS — nephron-sparing surgery; RN — radical nephrectomy

Results

Among the 34 patients included in the study, 64.71% (n = 22) were men and 35.29% (n = 12) were women. The mean age of patients at the start of IPI-NIVO treatment was 64.85 years (range: 44 to 80 years). The mean age of the women enrolled in the study was 67.33 years, while the mean age of the men was 63.50 years. The tumor was more frequently located in the right kidney (n = 19, 55.88%) and less frequently in the left kidney (n = 15, 44.12%). 64.71% of patients underwent surgery prior to systemic treatment (n = 22), of which RN was the most common (n = 12, 54.55%), CN less common (n = 8, 36.36%), and NSS the least common (n = 2, 9.09%). Some patients (n = 8, 23.53%) underwent tumor embolization before the start of treatment, of which 2 patients underwent surgical treatment after embolization (CN in 1 patient, RN in 1 patient), and 6 patients were not eligible for surgical treatment after embolization due to advanced neoplastic process. Histopathologically, the most frequently diagnosed tumor was clear cell carcinoma (n = 30, 88.24%), while clear cell carcinoma with a sarcomatoid component was diagnosed in 4 patients (11.76%). In most histopathological diagnoses, the grade of malignancy on the Fuhrman scale was G2 (n = 21, 61.76%), Fuhrman

G3 (n = 8, 23.53%), Fuhrman G4 (n = 3, 8.82%), and Fuhrman G1 (n = 2, 5.89%). All patients included in the study (n = 34, 100%) had distant metastases at the time of treatment initiation. Distant metastases were found in more than one organ in 70.59% of patients (n = 24) and in only one organ in 29.41% of patients (n = 10). Metastases were most commonly found in the lungs (n = 23, 67.65%), less commonly in the adrenal glands (n = 11, 32.35%), liver (n = 9, 26.47%), bones (n = 5, 14.71%), pancreas (n = 4, 11.76%), central nervous system (n = 2, 5.88%), and other organs (n = 7, 20.59%). Metastases in the surrounding lymph nodes were found in 58.82% of patients (n = 20). Some patients (n = 14, 41.18%) were eligible for additional metastatic treatment with surgery, radiotherapy, or a combination of both. Surgical treatment of metastases was used in 6 patients (42.86%), radiotherapy was performed in 4 patients (28.57%), and a combination of surgery and radiotherapy was used in 4 patients (28.57%). All patients included in the study were graded according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) scale and classified into individual prognostic groups. The study included patients with intermediate (1–2 risk factors) and poor prognosis (3 or more risk factors), according to the IMDC. 58.82% of patients (n = 20) were in the intermediate prognosis group, while 41.18% (n = 14) were in the poor prognosis group, according to IMDC. The performance status of the patients was assessed according to the Eastern Cooperative Oncology Group (ECOG) scale. The performance status of 44.12% of patients (n = 15) was ECOG 1, 38.24% (n = 13) was ECOG 0, and 17.64% (n = 6) was ECOG 2. The study did not include patients with ECOG 3 or higher. Patients in the study were also assessed using the Karnofsky Performance Status Scale. 38.24% of patients (n = 13) scored 100 points on the Karnofsky scale, 23.53% of patients (n = 8) scored 70 points on the Karnofsky scale, 20.59% of patients (n = 7) scored 80 points on the Karnofsky scale, and 17.64% of patients (n = 6) scored 90 points on the Karnofsky scale. The study did not include patients whose performance status was 60 or less on the Karnofsky scale.

The mean time from surgery (RN, CN, or NSS) to initiation of systemic treatment was 1703.55 days. The longest time from surgical treatment to systemic treatment occurred in patients who had previously undergone RN, averaging 2605.75 days. In patients who had previously undergone NSS, the mean time from procedure to initiation of systemic treatment was 2523.50 days, while in patients who had previously undergone CN, the mean time from procedure to initiation of systemic treatment was 145.25 days.

The mean duration of treatment with the IPI-NIVO regimen was 195.71 days. The mean number of cycles a patient received was 7.03 cycles. For patients who underwent RN

prior to systemic treatment, the mean duration of treatment with the IPI-NIVO regimen was 226.75 days (mean of 8.17 cycles). For patients who underwent NSS prior to systemic treatment, the mean duration of treatment with the IPI-NIVO regimen was 259 days (mean of 9 cycles). For patients who underwent CN prior to systemic treatment, the mean duration of treatment with the IPI-NIVO regimen was 236.13 days (mean of 8.50 cycles). There were no significant statistical differences in the duration of systemic treatment with the IPI-NIVO regimen and the number of treatment cycles among patients who underwent RN, NSS, or CN prior to systemic treatment.

Treatment was discontinued in the combination phase of the IPI-NIVO cycle in 52.94% of patients (n = 18), while 47.06% of patients (n = 16) continued nivolumab therapy in the monotherapy phase. 55.88% of patients included in the study (n = 19) completed systemic treatment with the IPI-NIVO regimen and 44.12% of patients (n = 15) continued treatment after completion of the study. The most common reasons for discontinuation of systemic treatment were drug adverse effects (n = 8, 42.11%), disease progression (n = 7, 36.84%), death due to unrelated causes (n = 2, 10.53%), and other causes (n = 2, 10.53%). Due to treatment discontinuation before the first control point (i.e., after completion of the IPI-NIVO combination phase), 32.35% of patients (n = 11) had no radiological assessment of treatment response. Radiological diagnostics and Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 response assessments were successfully completed for 67.65% of patients (23 out of 34). Progression after radiological evaluation was observed in 7 patients (20.59%), stable disease in 6 patients (17.65%), partial response in 8 patients (23.53%), and complete remission in 2 patients (5.88%). After completing treatment with the IPI-NIVO regimen, 23.53% of patients (n = 8) were eligible for subsequent lines of treatment (including cabozantinib).

The age of patients whose tumors progressed during treatment with the IPI-NIVO regimen was compared to the age of patients whose tumors did not progress. The mean age of patients at the start of systemic treatment who experienced tumor progression during treatment with the IPI-NIVO regimen was 55.14 years (range: 46 to 63 years), while the mean age of patients at the start of treatment who did not experience tumor progression during treatment with the IPI-NIVO regimen was 67.37 years (range: 44 to 80 years). A statistically higher incidence of tumor progression was observed in younger patients compared to older patients ($p < 0.001$).

The majority of patients (n = 27, 79.41%) reported adverse events during treatment with the IPI-NIVO regimen, and 19 patients (55.88%) reported more than one adverse event.

The most common grade 1 and 2 adverse events on the Common Terminology Criteria for Adverse Events (CTCAE) scale were weakness and fatigue (n = 14, 41.18%), less frequently observed were gastrointestinal toxicity (n = 12, 35.29%), thyroid dysfunction in the form of hypothyroidism or hyperthyroidism (n = 10, 29.41%), hepatic toxicity (n = 8, 23.53%), skin and mucous membrane toxicity (n = 6, 17.65%), renal toxicity (n = 4, 11.76%), significant weight loss (n = 4, 11.76%), cardiac disorders (n = 3, 8.82%), and others (n = 2, 5.88%). The most common CTCAE grade 3 and 4 adverse events included hepatic toxicity (n = 3, 8.82%), cardiac complications (n = 2, 5.88%), gastrointestinal toxicity (n = 1, 2.94%), blood count abnormalities (n = 1, 2.94%), and anaphylactic shock (n = 1, 2.94%). There was no effect of CN performed before initiation of systemic treatment on the occurrence of adverse events during systemic treatment (p = 0.677). 41.18% of patients (n = 14) required a delay of the next cycle due to adverse events (n = 11, 78.57%) or random events (n = 3, 21.43%). However, it should be noted that 58.82% of patients (n = 20) did not require an extension of the interval between IPI-NIVO cycles. Importantly, there was no effect of extending the interval between IPI-NIVO cycles on the risk of cancer progression (p = 0.410).

The study analyzed the results of basic laboratory tests and body weight at baseline and at the end of treatment with the IPI-NIVO regimen (Tab. 1). Notably, there was a statistically significant increase in liver parameters — alanine aminotransferase (ALT; p = 0.032) and total bilirubin (p = 0.001) in patients who completed treatment with the IPI-NIVO regimen compared to baseline. There were no statistically significant differences in other laboratory values or body weight between the baseline and the end of treatment with the IPI-NIVO regimen.

Table 1. Laboratory test results at baseline and at the end of ipilimumab and nivolumab (IPI-NIVO) treatment

	N	Mean	Median	Minimum	Maximum	SD	P-value
Body weight (start of treatment) [kg]	34	77.24	79.00	43.00	126.00	17.09	0.502
Body weight (end of treatment) [kg]	34	77.91	76.50	43.00	125.00	17.66	
Hemoglobin (start of treatment) [mmol/L]	34	7.69	7.70	5.20	11.1	1.06	0.456
Hemoglobin (end of treatment) [mmol/L]	34	7.59	7.70	4.60	10.80	1.30	
Hematocrit (start of treatment) [L/L]	34	0.38	0.38	0.28	0.54	0.05	0.696
Hematocrit (end of treatment) [L/L]	34	0.38	0.39	0.26	0.50	0.06	
Platelets (start of treatment) [10'9/L]	34	291.47	275.50	177.00	689.00	107.95	0.242
Platelets (end of treatment) [10'9/L]	34	280.41	250.50	128.00	593.00	116.26	
Neutrophils (start of treatment) [10'9/L]	34	5.59	5.17	1.92	13.56	2.21	0.675
Neutrophils (end of treatment) [10'9/L]	34	5.55	5.55	1.41	13.67	2.06	
Creatinine (start of treatment) [umol/L]	34	126.85	107.00	67.00	761.00	116.85	0.888
Creatinine (end of treatment) [umol/L]	34	119.56	104.00	62.00	387.00	62.83	
ALT (start of treatment) [U/L]	34	19.71	15.00	7.00	52.00	11.67	**0.032**

ALT (end of treatment) [U/L]	34	30.94	18.50	7.00	180.00	36.69	
AST (start of treatment) [U/L]	34	20.74	18.00	8.00	44.00	8.80	0.085
AST (end of treatment) [U/L]	34	28.38	20.50	10.00	181.00	31.48	
Bilirubin (start of treatment) [umol/L]	34	8.88	7.98	4.29	21.00	4.14	**0.001**
Bilirubin (end of treatment) [umol/L]	34	9.40	8.92	3.00	25.72	4.86	
TSH (start of treatment) [uIU/mL]	34	1.67	1.53	0.62	3.70	0.84	0.321
TSH (end of treatment) [uIU/mL]	34	2.26	1.74	0.02	17.69	2.97	
FT3 (start of treatment) [pg/mL]	34	3.52	3.24	1.32	15.31	2.17	0.584
FT3 (end of treatment) [pg/mL]	34	3.67	3.22	2.00	13.63	2.27	
FT4 (start of treatment) [ng/dL]	34	1.41	1.24	0.34	5.17	0.75	0.084
FT4 (end of treatment) [ng/dL]	34	1.60	1.31	0.96	5.65	1.02	

ALT — alanine aminotransferase; AST — aspartate aminotransferase; FT3 — free triiodothyronine; FT4 — free thyroxine; SD — standard deviation; TSH — thyroid-stimulating hormone;

The influence of CN prior to systemic treatment on the efficacy of the IPI-NIVO regimen was analyzed in detail. Progression-free survival (PFS) was compared in two groups of patients – those who underwent CN (treatment group, n = 8) and those who had no prior surgical treatment (control group, n = 12). Patients who underwent CN prior to systemic treatment had a mean PFS of 381.38 days (range: 182 days to 696 days), while patients who were not eligible for CN had a mean PFS of 127.17 days (range: 20 days to 529 days). There was a statistically significant difference in the length of PFS between the two groups compared in favour of patients who underwent CN prior to starting treatment with the IPI-NIVO regimen (p = 0.004). The number of treatment cycles with the IPI-NIVO regimen was also compared between patients who underwent CN and those who did not. Patients in the treatment group received an average of 8.50 cycles of IPI-NIVO, while patients in the control group received an average of 4.58 cycles of the IPI-NIVO regimen (p = 0.149). The influence of CN prior to systemic treatment on the presence or absence of tumor progression during treatment with the IPI-NIVO regimen was also compared. There was no statistically significant effect of CN on the presence or absence of tumor progression during treatment (p = 0.619).

The influence of CN before the start of systemic treatment on the occurrence of adverse events during treatment with the IPI-NIVO regimen was analyzed. No effect of CN prior to systemic treatment was found on the occurrence of adverse events during treatment with the IPI-NIVO regimen (p = 0.629). The effect of CN on the need to extend the interval between IPI-NIVO cycles was also analyzed. There was no statistically significant effect of CN on the need to extend the interval between IPI-NIVO cycles (p = 1.00).

Discussion

Survival outcomes for patients with mRCC have improved significantly in recent years, and combination treatment regimens based on immunotherapy (i.e., a combination of ipilimumab with nivolumab) prolong survival compared to single-drug targeted therapies (e.g. sunitinib) [13]. The IPI-NIVO regimen has become the gold standard in many countries, including Poland, from 2022, when it was reimbursed for the systemic treatment of mRCC in patients with intermediate and poor prognosis, according to IMDC. The impact of CN on the results of oncological treatment of patients with mRCC has been the subject of extensive scientific discussion for many years. From antiangiogenic drugs (e.g., sunitinib) to immunological drugs (e.g., ipilimumab and nivolumab), the role of CN in the treatment of mRCC remains unclear, which is why in the modern era of immunotherapy, many ongoing clinical trials are investigating this issue in detail [14].

The results presented in the study suggest the important role CN plays in the treatment of mRCC. A statistically significant prolongation of PFS was observed in patients who underwent CN prior to IPI-NIVO treatment compared to patients who did not undergo CN. The above results are consistent with other scientific studies. Kumada et al. [15] also showed that performing CN prior to systemic treatment significantly prolonged PFS. A total of 137 patients with mRCC were included in the retrospective analysis. In the group of patients who did not undergo CN before systemic treatment (group I), the median PFS was 5 months, while in the group of patients who underwent CN before systemic treatment (group II), the median PFS was 13 months ($p = 0.006$).

The study showed no effect of CN on the incidence of adverse events during systemic treatment ($p = 0.629$). This means that CN does not reduce the quality of life of patients with mRCC who underwent CN compared to patients who did not undergo surgical treatment. There are few literature reports describing the impact of CN on the quality of life of patients with mRCC. Larcher et al. [16] analyzed the treatment history of 317 patients with mRCC between 1988 and 2019. It was shown that 43% of patients who underwent CN reported complete relief of symptoms, and 71% of patients reported an improvement in their overall health after the procedure [16]. To draw reliable conclusions about the impact of CN on patients' quality of life, a prospective assessment is needed immediately after the procedure and several weeks and months after surgery.

Renal cancer is an important source of antigens that can stimulate the immune system, thereby increasing the efficacy of immune checkpoint inhibitors (such as IPI-NIVO). Studies have shown that renal cancer is highly immunogenic, meaning it has a high ability to induce

an immune response due to the presence of multiple tumor-specific antigens. These antigens can activate immune cells and increase their ability to target and destroy cancer cells. The presence of tumor-associated antigens can lead to increased infiltration of immune cells, such as T-cells, which are key to the anti-tumor response. This immune activation is further modulated by immune checkpoints such as PD-1/PD-L1, which can be targeted by immune checkpoint inhibitors (such as IPI-NIVO) to enhance the immune response against the tumor [17, 18]. The above arguments argue against performing CN in patients treated with IPI-NIVO because the presence of the tumor as a source of antigens is crucial for stimulating the immune system, and improving the results of treatment with IPI-NIVO in the treatment of mRCC.

Patients diagnosed at a younger age had a statistically higher rate of mRCC progression during treatment compared to patients diagnosed at an older age ($p < 0.001$). Due to the small number of patients included in the study, these results should be interpreted with caution. Literature reports show that the prognosis of older patients with mRCC is worse compared to younger patients, mainly due to more frequent comorbidities, poorer physical condition, as well as potentially higher toxicity of drugs used in older patients [19, 20]. Clarification of the issue of age in the context of treatment planning seems to be a very important aspect. Perhaps the age of patients should become an independent prognostic factor on which the qualification for certain systemic therapies should depend. This requires further prospective and randomized scientific analyses. Further research is needed to refine therapeutic strategies and improve survival rates in different age groups of patients eligible for systemic treatment of mRCC.

The results obtained in this study are promising, but need to be continued in order to draw more precise conclusions. Due to limited literature data, further studies are needed to evaluate the role and validity of performing CN in patients with mRCC treated with the IPI-NIVO regimen. From a clinical point of view, it is also important to find the best time to perform CN (before or after starting IPI-NIVO therapy). If it is determined that systemic therapy prior to CN is optimal, the duration of systemic therapy prior to CN needs to be determined. This will allow for further prospective randomized trials to evaluate the role of CN in the treatment of patients with mRCC.

The conducted study is not without limitations. The main limitation is its retrospective nature and the small number of patients included in the study. In addition, all patients were treated at a single center, which also reduces the scientific value of the study. What is more, there was no comparative analysis between patients who underwent CN prior to systemic

treatment and patients who underwent CN after initiation of systemic treatment with IPI-NIVO.

Conclusions

There is no clear effect of CN on the course of mRCC treatment. The decision to perform CN should always be made by a multidisciplinary oncology team, including a urologist, oncologist, and radiation therapist, after discussing the potential benefits and risks of the procedure with the patient. Appropriate selection of patients suitable for CN is critical to achieving optimal outcomes of cancer treatment.

The results obtained in this study are promising, but need to be continued in order to draw more precise conclusions. Due to limited literature data, further studies are needed to evaluate the role and validity of performing CN in patients with mRCC treated with the IPI-NIVO regimen. From a clinical point of view, it is also important to find the best time to perform CN (before or after starting IPI-NIVO therapy). If it is determined that systemic therapy prior to CN is optimal, the duration of systemic therapy prior to CN needs to be determined. This will allow for further prospective randomized trials to evaluate the role of CN in the treatment of patients with mRCC.

Article information and declarations

Data availability statement

The data that support the findings of this study are available on reasonable request from the corresponding author, Maciej Michalak.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki. The opinion of the Ethics Committee was obtained that there were no features of a medical experiment.

Author contributions

Maciej Michalak — conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization, writing — original draft preparation.

Anna Kopczyńska — conceptualization, formal analysis, methodology, writing — original draft preparation.

Andrzej Antczak — conceptualization, formal analysis, investigation, supervision, writing — review & editing.

Tomasz Milecki — formal analysis, methodology, writing — original draft preparation.

Piotr Tomczak — conceptualization, formal analysis, investigation, methodology, project administration, supervision, writing — review & editing.

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Conflict of interest

None declared.

Supplementary material

None.

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