The definition of a kidney tumour does not vary significantly from the definition of a tumour in general. It refers to new growth(s) in a tissue that stand out from the normal tissue architectonics. Robins defines neoplasm as a "new growth" [1]. Kidney cancer is the third most common cancer of the genitourinary tract after prostate and bladder cancer [2]. Of all malignancies in adults, 3% fall into the category of renal cell carcinoma (RCC). Only 4% of these tumours are considered hereditary. They can appear at any age, though they most often occur in older individuals (people in their fifties and sixties). Tumours rarely appear during the adolescence, but a few cases have been observed in patients in their twenties and thirties [3]. Nearly 30,000 new occurrences of this disease are reported every year in the United States, 12,000 of which result in death [4].

Thanks to advancements in technology, and the widespread use of diagnostic methods such as computed tomography (CT), ultrasonography, and magnetic resonance imaging (MRI), the incidence of these tumours dramatically increased during the 1970s [5,6]. At the same time, the number of patients with a five-year survival rate grew significantly. What causes the appearance of malignant tumours remains unknown. RCC is no exception, but it has been observed that RCC presents more frequently in individuals who live in urban environments, those who are of poor socioeconomic status and are obese. At this time, the only generally accepted risk factor is smoking [3].

In the widest sense, treatment of kidney tumours can be divided into:
1. surgical
2. medicamentous
3. radiation therapy
4. immunotherapy
5. hormone therapy
6. polychemotherapy (cytostatic therapy)
7. angiogenesis inhibitor therapy
8. Interferon alpha
9. Interferon beta
10. Interferon gamma
11. Interferon alpha, which is made by leukocytes
12. Interferon beta, which is made by fibroblasts
13. Interferon gamma, which is made by T lymphocytes

The clinical significance of Interferon beta and gamma in treating RCC has not been shown [10-12].

Binding of interferons to specific receptors results in the synthesis of numerous proteins and enzymes through which interferons act as modulators of biologi-
Interferon alpha and renal cell carcinoma

Interferons have a direct anti-proliferative effect on tumour cells, inhibiting their growth and prolonging each reproductive cycle. What is more, interferons have an indirect effect on tumour cells through their influence on host cells. Interferons increase the efficacy of all immune cells capable of destroying tumour cells, and improve the cytotoxicity of T lymphocytes [3,9]. Studies have shown that an increase in the number of regulatory T cells in patients who had undergone treatment with interferon alpha led to stagnation in the progression of the disease [13].

Natural interferon alpha (Sumiferon) was shown to have a positive effect on lessening the diameter of pulmonary metastases resulting from RCC [14]. Perfusion of pulmonary metastases was shown to be a good indicator of disease progression. Interferon alpha did not significantly influence tumour perfusion. Therefore, the conclusion can be drawn that interferon has poor angiogenic activity [15].

Side effects of interferon vary according to a dosage, the most common being flu-like symptoms, an elevated body temperature, gastrointestinal discomfort, myalgia, leukopenia, anorexia, asthenia, exhaustion, peripheral neuropathy, elevated liver enzymes, an increase in nitrogenous matter in the blood, and bronchial spasm [9].

Material and methods

The study included 60 patients who had undergone radical nephrectomies to treat adenocarcinomatous kidney cells. All patients had clinically enlarged local-regional lymph glands. Having been conducted over a three-year period, the study is prospective and partly retrospective.

The patients were divided into two groups:

- **Group One** consisted of 30 patients who had undergone surgery to remove adenocarcinomatous kidney cells. The pathophysiological examination revealed the existence of metastatic changes in local-regional lymph glands. All patients in this group were in the N1 stage of the disease.

- **Group Two** included 30 patients who had also undergone radical nephrectomies to treat adenocarcinomatous kidney cells, but the pathophysiological examination did not reveal metastatic changes in local-regional lymph nodes (the patients exhibited reactive lymphadenopathy).

  - thirty patients from the treatment (experimental) group received immunotherapy postoperatively.
  - thirty patients from the observation (control) group did not.

Each group was divided into two subgroups, each consisting of those who had and had not received immunotherapy. The subgroups that had not received an adjuvant immunotherapy represented the control group in the second part of the study.

Interferon alpha treatment protocol for the control group:

- A twice weekly dose of between 6–9 mil.J/m² for a total dose of 180 mil.J/m².

Recombinant interferon alpha-2a (INF-alpha-2a) was given intramuscularly or subcutaneously according to a scheme of increasing doses, from 3 MIU per day to 9 MIU per day twice or three times per week; the maximum weekly dose was 18 MIU.

Those patients who tolerated the treatment well were given a total of 180 MIU.

All patients who had undergone surgery were treated at the Department of Urology of the Clinical Centre in Novi Sad. The data sources were the disease histories of these patients.

In our study, the patients were observed over a three-year period. The appearance of metastases was verified by regularly scheduled examinations; the survival rate was also recorded.

- RTG diagnostics meant postoperative observation after 3, 6, 12, 24, and 36 months, aimed at verifying possible metastases.
- U/S diagnostics was conducted after 3, 6, 12, 24, and 36 months, postoperatively, to verify the existence of metastatic changes.
- CT diagnostics was conducted postoperatively after 6, 12, 24, and 36 months to verify the existence of metastatic changes.

- In all cases, a pathohistological examination was done at the Institute of Pathology of the Clinical Centre in Novi Sad.

- In all of the described cases, immunotherapy was conducted at the Institute of Oncology in Srem'ska Kamenica.
Results

The analysis of the overall survival rate in the group of patients with positive lymphocytes (PH+) regarding receiving/not receiving immunotherapy, expressed in months.

Since p=.047, it may be said that there was a difference in the length of survival, i.e. the patients who had received immunotherapy had a shorter survival rate than those in the control group (Graph 1).

The analysis of the overall survival rate in the patients with negative lymphocytes (PH-) regarding receiving/not receiving immunotherapy, expressed in months.

- Since p=.235, it may be said that there was no difference between the length of survival in the two groups, i.e. that immunotherapy had no significant influence on the survival rate in the experimental group of patients when compared to that of those in the control group (Graph 2).

The analysis of the survival rate without metastases in the group of patients with positive lymphocytes regarding receiving/ not receiving immunotherapy, expressed in months

- Since p=.035, it may be said that there was a difference between the groups regarding the length of survival without metastases, i.e. that the experimental group of patients who had received immunotherapy, on average, had a shorter survival rate without metastases in comparison to the control group (Graph 3).

The analysis of the survival rate without metastases in the patients with negative lymphocytes regarding receiving/not receiving immunotherapy, expressed in months.

Since p=.235, it can be said that there was no difference in the length of survival among the groups, i.e. that immunotherapy did not significantly influence the survival rate in the experimental group of patients when compared to that of those in the control group (Graph 4).

Discussion

RCC is the most representative of malignant kidney diseases. Over the last fifty years, the number of incidence of this disease has grown. RCC is the third-most-frequent of all urogenital tumours, and this type of tumour accounts for 3% of all malignant diseases.

Radical nephrectomy is the "gold standard" in the treatment of this disease. Its goal is the complete removal of the tumour. The preoperative evaluation of the patient should include RTG diagnostics of the lungs, an U/S and CT of the abdomen in order to de-
termine the current phase of the disease and detect possible development of metastases [16].

Traditional methods of treating malignant diseases (radiation and chemotherapy) had a negligible efficacy rate in the treatment of RCC, only 2–6%.

During the observation of spontaneous remission of advanced-stage RCC, immune mechanisms were supposed to play a significant role in the developmental process of the tumour itself. Today, numerous kinds of non-specific cytokines are used to treat advanced-stage RCC. The most common among them are interferon alpha and interleukin-2. They are used individually, or in combination with 13-cis-retinoic acid and 5-fluorouracil. Since the objective clinical response was on average 15%, this type of therapy has attained significant status in the treatment of RCC. At the same time, it is important to mention that the toxic effect of this medicine is also significant [17].

Edward et al. (2003) published a study in which a group of 294 patients had been observed following radical nephrectomies, without verification of further metastases. All of the patients were in the T2, T3, or T4a stages of the disease, with or without local-regional metastases in their lymph glands (N0, N1). The experimental group underwent immunotherapy with interferon alpha-NL, over a five-day period every three weeks for a total of 12 cycles [18].

The study covered a period of 10 years in which both the overall survival rate and the appearance of further metastases were observed. On average, the group of patients who had not received immunotherapy had an overall two-year survival rate of 77%, and a five-year survival rate of 62%, while the group of patients who had received immunotherapy had a 70% overall two-year survival rate, and a five-year survival rate of 51%.

After two years, 56% of the patients in the first group were without metastases, after five years, this number was 41%. In the second group (which had received immunotherapy), 51% of the patients were without metastases after two years, and 37% were without metastases after 5 years.

They came to the conclusion that patients who had received adjuvant immunotherapy did not have a longer survival rate, nor was the appearance of metastases less frequent in comparison with the control group [19,20].

We obtained similar results in our study, in which we had observed survival rates regarding receiving/ not receiving immunotherapy postoperatively.

All sixty patients included in our study had enlarged local-regional lymph glands, which were identified during a surgical procedure. Each patient underwent a radical nephrectomy, followed by a lymphadenectomy to treat RCC.

In the group of patients with positive local-regional lymph glands, a significant statistical difference compared to the survival rate of the existing groups (p=0.047) was observed. The patients who did not receive adjuvant immunotherapy had a better survival rate than those patients who had. The three-year survival rate in the group of patients who had received immunotherapy was 47.1%, while the three-year survival rate of the control group was 61.5%.

In the group of patients with negative local-regional lymph glands, there was not a statistically significant difference (p=0.235) in the overall survival rate compared to the existing groups. Despite postoperative immunotherapy, there was no difference in the survival rate. In the first group (the patients who had not received the adjuvant immunotherapy), 82.4% were still alive after 3 years, while in the control group, that percentage was 76.9%.

In a study published in 2003, Messing et al. attempted to justify the application of adjuvant immunotherapy in the patients having the T3 and T4 stages of RCC with or without metastases. The study included 283 patients, and followed the appearance of metastases as well as the overall survival rate over a ten-year period after the radical nephrectomy. The average survival rate of patients in the experimental group was 5.1 years compared to 7.4 in the control group. The authors concluded that immunotherapy did not have a positive effect on the patients’ survival rates [21].

In 2005, J. Atzpodian et al. published a study in which they had observed patients over the course of 10 years following a radical nephrectomy. The study included 203 patients in stages T3b/c and T4, with or without metastases in local-regional lymph glands (N0, N1). This study observed the overall survival rates as well as the appearance of additional metastases regarding receiving/ not receiving immunotherapy postoperatively. As in the previous study, the adjuvant immunotherapy did not prove to be beneficial. The authors concluded that the group of patients who had not received immunotherapy had a better survival rate than those in the experimental group [22].

By following two experimental groups of patients over a two-year period, this study attempted to answer the question of whether or not postoperative immunotherapy (i.e. treating or not treating with immunotherapy) influenced the development of additional metastases, and if so, to what extent.

In the group of patients with positive lymph glands, it was evident that those patients who had received postoperative immunotherapy had earlier instances of verified metastases than those who had not.

In the experimental group, the average survival rate without metastases was 20.29 months, whereas in the control group, this rate was 23.77 months. This means that only 23.5% of patients in the experimental group were without metastases after 3 years, whereas in the control group, the same was true of 38.5% of the patients. One can clearly see that the overall survival rate within the control groups of patients follows these statistics as well. In addition, a statistically significant difference (p=0.04) confirms that the prognosis for the experimental group was worse than that for the control group.

In the group of patients with negative lymph glands, immunotherapy did not influence the survival rate without metastases. The group of patients who had received immunotherapy had an average survival rate of 34.15
months, while the survival rate in the control group was 34.59 months. The three-year survival rate in the experimental group was 76.9% compared to 52.4% in the control group (p = 0.433).

According to these results, it could be concluded that patients did not benefit from postoperative immunotherapy. This is true of all of the control groups, including those patients in the T stages of RCC. It is important to mention that postoperative immunotherapy even proved to be counterproductive in patients in the N1 phase, because metastases appeared more frequently than in the controls.

Conclusions

Treating N0- and N1-stage patients with adjuvant immunotherapy is not justified, it may even be counterproductive.

This study did not confirm any later or earlier occurrence of metastases in N0-stage patients who had received immunotherapy, and immunotherapy proved to be counterproductive in N1-stage patients.

Considering the above-mentioned conclusions, and keeping in mind the chemo-resistance of these tumours, it becomes apparent that surgery is still the treatment of choice when the disease is detected early.

References


Uvod

Ispitivana je opravdanost davanja imunoterapije bolesnicima nakon radikalne nefrektomije u N1 i N0 stadijumu.

Materijal i metode

Studiija je obuhvatila 60 bolesnika, koji su podvrgnuti radikalnoj nefrektomiji radi lečenja adenokarcinoma bubrežnih čelija. U studiju su uključene dve grupe bolesnika: Prva grupa od 30 bolesnika u N1 i N0 stadijumu bolesti, koja je primala imunoterapiju (po 15 bolesnika u oba stadijuma) i druga grupa od 30 bolesnika u N1 i N0 stadijumu bolesti, koja nije primala imunoterapiju (po 15 bolesnika u oba stadijuma).

Ključne reči: Interferon alfa; Karcinom bubrežnih čelija; Nefrektomija; Imunoterapija; Ishod lečenja
