

Assessment of tumor risk factors in kidney transplant patients,  
oncological screening of non-functioning kidneys

Thesis booklet

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Budapest, 2022

## **I. Introduction**

The overall incidence of tumors in organ transplant recipients is 2 to 4 times higher than in the non-transplant population. This is due to the reduced antitumor and antiviral defenses of the immune system, and the uremic condition increases the risk of developing tumors. After organ transplantation, three main types of tumors can be distinguished: a tumor transmitted by a donor organ, the recurrence of a tumor that has been in remission in a previous cancer, and “de novo,” a new malignancy. The latter group can be considered as real post-transplant tumors.

Among kidney transplant recipients, the distribution of tumor types differs from the average population. The most common malignancies following organ transplantation are skin tumors, lymphomas, Kaposi's sarcoma, kidney cancer, anogenital tumors, and hepatocellular carcinoma. Post-transplant tumors typically occur at a younger age and generally have a less favorable prognosis. Thanks to effective nephrological care, the life expectancy of kidney transplants after kidney transplantation is increasing, as

well as the number of organ transplants performed at older age, and the average age of these patients is on the rise due to more potent immunosuppression. As a consequence, tumors typical of the general population, such as lung cancer, colon cancer, breast cancer, prostate cancer, pancreatic cancer, and gastric cancer, are also expected to increase in these patients. The most common post-transplant tumor that can be screened by imaging is renal cell carcinoma, which can be 5 to 15 times more common than in the general population. This disease is responsible for 10% of all cancer deaths in kidney transplant recipients. However, international recommendations for screening for tumors in the shrunken native kidneys are not uniform. Kidney Disease: Improving Global Outcomes, the American Society of Transplantation, and The Renal Association in the UK also do not recommend screening for kidney tumors. Only at increased risk does the Australian Kidney Health Australia Caring for Australians with Renal Impairment recommend screening. In contrast, the European Association of Urology recommends an annual ultrasound scan for this group of patients. What can be seen as a common point in reviewing

international guidelines is that an individual approach based on risk factors should be sought for oncology screening

## **II. Objective**

- What are the main oncological risk factors for kidney transplant patients cared for at the Department of Transplantation and Surgery, Semmelweis University?
- What conclusions can be drawn from the types and stages of tumors detected during abdominal and pelvic ultrasound examinations performed at our Institute, as well as from the factors that may influence tumor formation?
- What is the willingness to screen among kidney transplants, and what proportion of tumors detected by ultrasound are detected during screening?
- Are there any significant differences in the size, stage, or survival of tumors in the native kidneys detected by screening or other indications?

### **III. Methods**

#### **III. 1. Questionnaire survey of oncological risk factors in kidney transplant recipients**

Between October 2013 and July 2014, I conducted a questionnaire survey at the Nephrology Outpatient Clinic of the Department of Transplantation and Surgery, Semmelweis University to assess the most important risk factors. We used a self-edited questionnaire for our survey. The questions included basic anthropometric parameters of the patients, oncological risk factors, and a history of tumors. I processed a total of 530 fully completed questionnaires

#### **III. 2. Processing of ultrasound screening tests for kidney transplant recipients**

At the Department of Transplantation and Surgery, Semmelweis University, I processed the results of renal transplant patients who underwent abdominal ultrasound examination during the period from 01.01.2012 to 31.12.2016 in a retrospective manner, based on the database of the MedSol hospital IT system. Examinations

were performed on Toshiba Aplio XV and Toshiba Xario 50 ultrasound devices (Toshiba Medical Systems, Japan) using a convex probe (1-5 MHz). Due to the fact that it is not possible to list screening tests specifically, I collected the tests marked with the WHO code “Duplex UH, transplanted organ” as a first step. This represented a total of 6103 cases. Targeted ultrasound examinations of kidney grafts and liver transplant patients were considered as exclusion criteria. By reading the findings listed one by one, I selected the abdominal-pelvic and graft ultrasound examinations of the kidneys. Finally, I obtained a database of 1687 kidney recipients for further processing. I considered screening to be those that were performed on an annual basis on asymptomatic individuals. For my statistical calculations, I performed a two-sample t-test, a Mann – Whitney U-test, a Welch d-test, an analysis of variance, a Kruskal – Wallis test, and a Chi-square test. I considered  $p < 0.05$  as significance level.

## **IV. Results**

### **IV.1 Results of the questionnaire**

Post-transplant tumors were significantly more common in men ( $p = 0.04$ ). 67.8% of the respondents who mentioned a tumor after transplantation were men during the completion of the questionnaire. As the age progressed, both the number and proportion of tumors showed a significant ( $p < 0.01$ ) increasing tendency. According to the WHO classification, 38.3 percent of the respondents were in the normal body mass index (BMI: 18.5–24.99) range. The most commonly used immunosuppressive drug combination was the combined use of a calcineurin inhibitor and an antimetabolite, with 62% of responding subjects. The mean time since kidney transplantation was  $88.27 \pm 71.52$  months for all patients. This value averaged  $127.38 \pm 75.08$  months in patients who developed a post-transplant tumor. The incidence and relative proportion of tumors increased significantly ( $p < 0.01$ ) in parallel with the time since transplantation.

51,8 % of the respondents have smoked or smoked before (11.5% are active smokers and 40.3% have been smokers

before). 4% of respondents (n = 22) were affected by neoplastic disease prior to transplantation. The most common of these was kidney cancer (n = 5). 10.4% (n = 55) of the renal recipients who completed the questionnaire developed a post-transplant tumor. The most common were non-melanoma skin tumors, which accounted for 38% (n = 21) of cancers. The second most common was cervical kidney cancer, which was reported in 18% (n = 10) of tumor patients. Abdominal ultrasound showed 83.8% (n = 440) within one year for oncological screening. 83.5% (n = 193) of women over 18 years of age used to be screened for cervical cancer each year. Among the relevant risk factors, 28.6% (n = 66) have ever smoked or are still smokers. 29.9% (n = 159) of patients participated in dermatological screening. 23% (n = 46) of women aged 45 years and over participate in mammography screening every two years. Risk factors for breast cancer: 30.2% (n = 61) of women in this age group are diabetic and 53.7% (n = 81) are overweight or obese.

## **IV.2. Processing the results of abdominal and pelvic ultrasound examinations**

During the 5 years of the study period, the number of abdominal and pelvic ultrasound examinations performed on kidney transplant recipients was 1687, of which 1444 (85.6%) were screening examinations. In the case of screening tests, malignancy was confirmed in 17 cases during the further examination, which accounted for 1.2 percent of all oncology screening ultrasound examinations. Of the 17 tumor patients mentioned above, 12 patients were diagnosed with tumor of the shrunken kidney, representing nearly 71 percent of all tumors detected by ultrasound.

An average of  $8.04 \pm 6.19$  (min: 0, max.: 20) years elapsed between transplantation and tumor recognition. Abdominal and pelvic ultrasound were performed for an average of  $27.8 \pm 23.89$  (min: 7, max.: 77) months prior to tumor-induced ultrasound. The proportion of those who underwent ultrasound within one year was 28.6%. By processing the results of ultrasound examinations in other

indications, a total of 9 tumors could be confirmed, of which 6 were kidney cancer.

For a total of 18 patients diagnosed with kidney tumors, the following findings can be made: mean age was  $52.8 \pm 12.46$  (min: 25, max: 74) years. The male - female ratio was 5: 1 ( $p = 0.029$ ). Renal graft was derived from cadaveric donation in 15 cases (83%) and 3 (17%) from living donor donations. Histological type: 10 papillary tumors with 4 clear cells, 2 tumors with clear cell and papillary elements, 1 chromophobic renal cancer, 1 patient with confirmed papillary and chromophobic renocellular carcinoma. The mean tumor size was  $25.83 \pm 11.9$  mm (min: 10 mm, max.: 55 mm). 17 patients had stage I disease and one patient had stage IV disease. All tumors were well differentiated: 8 tumors were Fuhrman grade I and 10 were grade II. The mean time to dialysis was  $37.73 \pm 24.37$  (min: 3, max: 84) months. Acquired cystic kidney disease (ACKD) was confirmed in 33% ( $n = 6$ ) of patients. The mean time between transplantation and tumor recognition was  $7.9 \pm 6.29$  (min: 0, max.: 20) years. 1 patient was treated for acute rejection. The most

commonly used immunosuppressive treatment was a combination of a calcineurin inhibitor, antimetabolite therapy, and steroid given to 12 patients (66%).

There was no significant difference between tumors detected during screening or in examinations with other indications considering tumor size ( $p = 0.815$ ), time between the last two ultrasound examinations ( $p = 0.274$ ), and length of dialysis treatment ( $p = 0.882$ ), neither the type of dialysis ( $p = 0.433$ ), the type of donation ( $p = 0.838$ ), nor the five-year survival ( $p = 0.065$ ). The Kaplan-Meier cumulative survival was 94.5% at one year, the three-year survival was 83.4%, and the five-year cumulative survival was 66.6% in patients diagnosed with kidney cancer. The mean follow-up was  $63.83 \pm 28.91$  months. Of the 18 patients, 6 died during the follow-up period. It is important to point out that only one of them died of the underlying cancer – the patient with IV. stage renal disease.

## **V. Conclusions**

1. I was the first in Hungary to conduct a questionnaire survey to assess the oncological risk factors of kidney transplant patients. Among my results, the high incidence of post-transplant tumors should be highlighted: more than one-tenth of the study participants had malignancy. The most common cases were non-melanoma skin tumors and kidney cancer in the native kidneys. Male gender, older age, and longer time since transplantation were significantly associated with the development of malignancies. The high number of smokers and overweight individuals and the low participation in mammography screening should be highlighted.

2. For the first time in my work, I measured the results of an annual ultrasound screening program for kidney transplant recipients at the Department of Transplantation and Surgery, Semmelweis University. Based on one thousand six hundred and eighty-seven findings, only slightly more than half of the abdominal tumors detected during the 5-year period were detected by screening. In

average, the time between the last two examinations was almost two and a half years.

3. Two-thirds of the tumors identified by ultrasound were renal cell carcinoma, which was significantly more common in men. ACKD was also confirmed in a third of kidney tumors. There were no significant differences in tumor size, stage, and survival for renal tumors identified by screening or other indications for ultrasound. However, the effectiveness of ultrasound is shown by the fact that, with one exception, all kidney tumors were detected in stage I, and a total of one mortality associated with kidney cancer occurred during the observation period.

4. Based on the results of my research, I formulated a recommendation for screening for renal cancer in kidney transplant patients, according to which biennial screening is considered safe, however, patients affected by risk factors for cirrhosis should be monitored annually.

## **VI. List of own publications**

### **VI. 1. Publications related to the dissertation**

1. Kiss G, Szalontai L, Wagner L, Mathe Z, Vegso G. (2015) Survey About the Cancer Risk of Renal Transplant Recipients. *Transplant Proc*, 47: 2196-2197.

2. Kiss G, Korda D, Szabo G, Juhasz R, Wagner L, Mathe Z, Doros A, Vegso G. (2019) Oncological Screening of Kidney Transplant Patients: The Role of Ultrasound Examination. *Transplant Proc*, 51: 1231-1233.

3. Korda D, Deak PA, Kozma V, Kiss G, Doros A. (2016) Role of Contrast-Enhanced Ultrasound in the Follow-up of Kidney Transplant Patients. *Transplant Proc*, 48: 2544-2547

4. Farkas AZ, Throat S, Kovacs JB, Red L, Vegso G, Kiss G, Korda D, Bibok A, Hartmann E, Deak AP, Doros A. (2019) Diagnosis and Management of De Novo Urothelial Carcinoma in a Kidney Allograft: A Case Report. *Transplant Proc*, 51: 1281-1285.

## **VI. 2. Publications not related to the dissertation**

5. Korda D, Deak PA, Kiss G, Gerlei Z, Kobori L, Gorog D, Fehervari I, Piros L, Mathe Z, Doros A. (2017) Management of Portal Hypertension After Liver Transplantation. *Transplant Proc*, 49: 1530-1534
6. Nagy G, Dezső K, Kiss G, Gerlei Zs, Nagy P, Kóbori L (2018) Modern diagnosis and treatment principles of benign liver tumors. *Hungarian Oncology* 62: 5-13
7. Pásti K, Kiss G, Tóth R, Szabó A. (2010). Childhood sleep disorders Part I. *Medicina Thoracalis*, LXIII. 5,336-343.
8. Pásti K, Kiss G, Tóth R, Szabó A. (2010). Childhood sleep disorders Part II. *Medicina Thoracalis*, LXIII. 6. 397-402