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ARTICLE

Malignancies after Renal Transplantation during 33 Years at a Single Center

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This study provides an analysis of incidence and characteristics of malignant tumors of 2535 patients who underwent renal transplantation between 1973 and 2007 at the Transplantation Center in Budapest. One hundred ninety-three malignant diseases were found in 188 patients (7.6%). The incidence of thyroid-, renal- hepatic-, skin- and gastric cancers as well as of Kaposi sarcoma and lymphomas increased in our transplant patient cohort compared to the figures of the general population based on the data of our Cancer Registry. On the other hand, colorectal-, oral-prostate and lung cancers were underrepresented in our patient cohort. The mean time of diagnosis of malignancies following kidney transplantation was 58.5±44.8 months. One fifth of the tumors were detected within the first year. Patients with malignancies were distributed into four groups based on the immunosuppressive regimen: group I (8.5%), azathioprine + prednisone; group II (59.0%), cyclosporine + prednisone; group III (26.6%), cyclosporine + mycophenolate mofetil + prednisone; group IV (5.9%), tacrolimus + mycophenolate mofetil + prednisone. The mean age of patients was 47.3, 53.5, 55.5 and 58.1 years in group I, II, III and IV, respectively. Oncologic and immunosuppressive therapy was decided individually. Immunosuppression was switched to rapamycin-containing regimens in 63 cases. We lost 92 patients (48.9%) with a mean survival time of 25.8±39.4 months. Cumulative 1- and 5-year survivals were 69.5% and 52%, respectively. The increasing number of cancers seen early after transplantation and the increased risk of developing a cancer due to the older age of recipients draw attention to the importance of regular oncologic screening in patients on the waiting list and after transplantation. (Pathology Oncology Research Vol 13, No 1, 63–69)

Key words: immunosuppression, kidney transplantation, posttransplant malignancies, tumor risk, waiting list

Introduction

Malignant tumors occur more frequently in patients receiving immunosuppressive treatment following organ transplantation than in the non-transplanted population. The risk is 2-10-fold, and in some cases it can be even 100-fold, which means that tumors can be expected to develop in 4-18% of transplanted patients. The cumulative tumor incidence can reach 20% after 10 years and 30% after 20 years in patients receiving chronic immunosuppressive treatment.[1-4] The most frequent "de novo" tumors in adults are skin tumors and lymphomas, followed by Kaposi's sarcoma, lip, cervical, perineal, renal and hepatobiliary tumors and sarcomas.[5-8] The primary factor in tumor development is the dysfunction of the antitumoral and antiviral properties of the immune system. Oncogenic viruses, beside known carcinogenic agents, are important etiological factors. Posttransplant tumors are characterized by fast progression, unfavorable prognosis and poor response to treatment.[1,8-12] Effective immunosuppressive treatment results in prolonged graft function but also in increased tumor risk. The main therapeutic goal is to decrease tumor risk and improve graft and patient survival. Low level immunosuppres-

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sion, use of immunosuppressive drugs with antitumor effects, regular oncologic screening of transplanted patients and early treatment of precancerous conditions are essential to achieve this goal.[1,8,13]

The aim of our study was the analysis of data of posttransplant malignancies and drawing appropriate conclusions regarding the management of these conditions. The study was based on the 2852 kidney transplantations performed during the last 33 years at the Transplantation Center in Budapest.

Patients and Methods

Between 1973 and 2007, 2852 renal transplantations were performed in the Kidney Transplant Program of Semmelweis University, Budapest, Hungary: 2535 primary, 294 secondary and 23 tertiary transplantations. All our transplanted patients were followed at our out-patient care unit as long as their transplanted kidney functioned. In case of complication they were admitted to our department. The patients' data and posttransplantation complications, including malignancies, are registered in our data base. Our retrospective analysis was based on the data of this register. In January 2007, 1300 patients had a functioning graft and were regularly followed, while 2% were lost to follow-up. The mean follow-up time of tumor patients was 94.11 months.

Malignancies were found in 188 transplanted patients. The male/female ratio was 2.19:1. The mean age of patients was 53.1±10.1 years, men were significantly older than women (54.3±10.0 vs. 51.4±9.9 years; p=0.017). Tumors occurred after primary and secondary transplants in 170 and 18 cases, respectively. Mean HLA mismatch was 2.83 ±0.6.

The incidence of malignancies of the renal transplanted patients and of the Hungarian general population was compared according to data of the Hungarian National Cancer Registry.[14]

Table 1. **Type and prevalence of tumors during the observation period**

Type of malignancy	*Number of observed cases*	*Gender*		*Percentage of the total number of renal tx patients*	*Time between transplantation and detection of tumor*
	n (%)	*Male (n)*	*Female (n)*	*(%)*	*Months (mean±SD)*
Skin cancer	51 (26.4%)	36	15	2.0	55.0 ± 43.6
Renal carcinoma of the native kidney	26 (13.5%)	20	6	1.02	49.8 ± 44.9
Lung cancer	15 (7.7%)	14	1	0.60	45.8 ± 38.6
Kaposi's sarcoma	12 (6.2%)	10	2	0.47	19.6 ± 22.7
Breast cancer	12 (6.2%)	0	12	0.47	74.1 ± 56.9
Non-Hodgkin's lymphoma	10 (5.2%)	8	2	0.39	120.0 ± 52.0
Hepatic cancer	7 (3.6%)	6	1	0.27	58.1 ± 42.2
Thyroid cancer	6 (3.1%)	2	4	0.23	29.9 ± 28.2
Colorectal cancer	6 (3.1%)	4	2	0.23	42.4 ± 23.8
Malignant melanoma	6 (3.1%)	5	1	0.23	75.2 ± 25.6
Oral cavity cancer	5 (2.5%)	2	3	0.19	–
Gastric cancer	4 (2.0%)	3	1	0.15	–
Laryngeal cancer	3 (1.5%)	3	0	0.12	–
Uterine cancer	3 (1.5%)	0	3	0.12	–
Malignant brain tumor	3 (1.5%)	2	1	0.12	–
Prostate cancer	3 (1.5%)	3	0	0.12	–
Urinary bladder cancer	3 (1.5%)	3	0	0.12	–
Hodgkin's lymphoma	2 (1.0%)	2	0	0.08	–
Multiple myeloma	2 (1.0%)	2	0	0.08	–
Cancer of the transplanted kidney	1 (0.5%)	0	1	0.04	–
Acute myeloid leukemia	1 (0.5%)	0	1	0.04	–
Testicular cancer	1 (0.5%)	1	0	0.04	–
Parotid cancer	1 (0.5%)	1	0	0.04	–
Multiple metastases of unknown origin	5 (2.5%)	4	1	0.19	–
Other malignancy	5 (2.5%)	2	3	0.19	–
Total	*193 (100%)*	*133*	*60*	*7.6*	*58.5 ± 44.8*

Patients with malignancies were classified into four groups based on the type of immunosuppressive therapy: group I, azathioprine + prednisone (AP), 8.5%; group II, cyclosporine + prednisone (CP), 59.0%; group III, cyclosporine + mycophenolate mofetil + prednisone (CMP), 26.6%; group IV, tacrolimus + mycophenolate mofetil + prednisone (TMP), 5.9%.

The Hungarian kidney transplantation program started in 1973. The first group received the initial prednisone + azathioprine conventional therapy. Cyclosporine + prednisone combination was introduced in 1984 (group II). Mycophenolate mofetil was added to the previous protocol (group III) in 1997, and the administration of tacrolimus was initiated in 2000 (group IV). Induction therapy (OKT3, ATG, anti-CD25 (IL-2 receptor) monoclonal antibody) was used only in secondary transplant patients.

Fisher's exact t-test was used for comparisons between individual groups and analysis of variance (ANOVA) was used to calculate mean and standard deviations. Survival rates were calculated with the Kaplan-Meier method, and log-rank test was used to compare survival rates among these groups. $p<0.05$ was considered statistically significant. Statistical analysis was performed with SAS software version 8.2.

Table 2. **Malignancies after kidney transplantation compared to the Hungarian general population (based on 4 years of cumulative incidence)**

Type of malignancy	*Number of tumors per 100,000 population*		
	General population	*Transplanted population*	*Rate of increase*
All malignancies	2985.9	3984.2	1.33
Breast cancer (females)	584.5	501.5	0.86
Lung cancer	426.3	276.1	0.65
Skin cancer	382.2	986.2	2.58
Colorectal cancer	346.1	118.3	0.34
Prostate cancer (males)	297.6	195.0	0.65
Oral cavity cancer	148.7	78.9	0.53
Urinary bladder cancer	99.3	78.9	0.79
Gastric cancer	97.7	157.8	1.61
Kidney carcinoma	87.3	591.8	6.77
Malignant melanoma	69.3	39.4	0.57
Hepatic cancer	48.5	157.8	3.25
Non-Hodgkin's lymphoma	29.8	39.4	1.32
Thyroid cancer	22.0	197.2	8.95
Kaposi's sarcoma	NA	433.9	–

NA = not available

Results

Posttransplantation malignancies

During the last 33 years we detected 193 malignant diseases in 188 out of 2535 patients, indicating a tumor incidence of 7.6%. *Table 1* shows the type and incidence of the observed malignancies, gender distribution and the average time between transplantation and the appearance of tumor.

Malignant tumors observed in the first four years following renal transplantation were compared to the data registered between 2001 and 2004 in the National Cancer Registry. Our data show that of the common malignancies only skin- and gastric cancers (2.58- and 1.61-fold, respectively) displayed a higher incidence than in the general population, whereas the incidence of lung-, colorectal-, oral- and prostate cancers was lower than in the general population (>30%). On the other hand, the incidence of lymphomas was only slightly higher (>30%), which can be explained by the fact that, surprisingly, lymphomas occurred 5 to 10 years after transplantation in our patients. The incidence of Kaposi sarcoma (6.2%) was also high in the transplanted patient's population. The frequency of hepatic-, renal- and thyroid cancers was 3.25-, 6.77- and 8.95-fold higher, respectively, compared to the non-transplanted population (*Table 2*).

Comparison of tumor patients in the four groups with different immunosuppressive regimens

Table 3 shows the characteristics of tumor patients according to the immunosuppressive regimens received. ANOVA analysis of the data showed a significant difference in the mean age ($p<0.003$) and the time interval between transplantation and tumor detection ($p<0.0001$) in all groups. The mean age of patients increased over time both with regard to the time of transplantation and also the time of tumor detection. At the beginning of the Hungarian transplant program only young patients were transplanted (the mean age was 37.1±7.4 years, group I). Group IV included patients transplanted in and after 2000, with a significantly higher mean age at the time of transplantation (56.0±8.3 years).

We also observed a shortening of the time between the onset of the tumor and transplantation. Analysis of the data revealed a significant correlation with the changing type of immunosuppression ($p<0.0001$) but showed no significant correlation with increasing age ($p<0.14$).

Time elapsed between transplantation and the appearance of tumors

The mean time from transplantation to tumor detection was 58.5±44.8 months; 11.4% (n=22) were detected within 6 months, 20.2% (n=39) within the first year, 35.2% (n=68) within two years, 93.3% within ten years (n=180)

Table 3. **Descriptive statistics of renal transplanted patients with malignancies, receiving different immunosuppressive treatments**

	Group			
	I (n=16)	*II (n=111)*	*III (n=50)*	*IV (n=11)*
Immunosuppression	AP	CP	CMP	TMP
Age of recipients at the time of transplantation (years, mean±SD)	37.1 ± 7.4	48.7 ± 10.4	52.5 ± 9.8	56.0 ± 8.3
Age of patients at the time of tumor detection (years, mean±SD)	47.3 ± 9.0	53.5 ± 10.0	55.5 ± 9.7	58.1 ± 7.9
Time interval between transplantation and tumor detection (months, mean±SD)	107.3 ± 74.2	61.2 ± 39.2	41.4 ± 28.2	27.5 ± 44.8
1-year patient survival (%)	57.1	71.9	68.9	57.1

AP: azathioprine + prednisone; CP: cyclosporine + prednisone; CMP: cyclosporine + mycophenolate mofetil + prednisone; TMP: tacrolimus + mycophenolate mofetil + prednisone

and 6.7% (n=13) after 10 years. If we exclude the very fast progressing Kaposi's sarcoma and lymphoma cases (n=22), these numbers are 12.9% (n=22), 18.7% (n=32), 34.5% (n=59), 92.4% (n=158) and 7.6% (n=13) respectively.

In the case of more frequent tumors the ratios of detection within the first year were: cancer of the native kidney 38.46%, lung cancer 20.0%, breast cancer 33.4%, Kaposi's sarcoma 58.3%, lymphoma 0% (!).

In the four immunosuppressive groups mentioned above the percentage of tumors that were diagnosed within the first year were 12.5% (2/16) in group I, 18.9% (21/111) in group II, 22.0% (11/50) in group III and 45.5% (5/11) in group IV.

Cause and time of death

Ninety-two out of 188 patients (48.9%) died during the observation period. Their mean age was 54.8±10.4 years at the time of death. Mean survival time after the diagnosis of the tumor was 25.8±39.4 months in the deceased population; 36.9% (n=34) died within 6 months, 55.4% (n=51) within 12 months, 70.6% (n=65) within 24 months and 84.7% (n=78) within 60 months. The cause of death was tumor progression in 32.6% (n=30), while 30.4% (n=28) died of infection (pneumonia and sepsis). Cardiac complications, lung embolism, cerebrovascular accidents, liver cirrhosis, hepatic failure, acute pancreatitis and tuberculosis were the causes of death in the remaining 37% (n=34). The mean follow-up time of the 96 patients who were alive at the end of this study was 65.7±46.6 months.

Patient survival data

The cumulative survival rate of the 188 tumor patients according to the Kaplan-Meier method was 69.5% at 1 year, 61.8% at 2 years, 57.3% at 3 years and 52% at 5 years. Survival was best in the skin cancer subgroup: 90.2% at 1 year and 75.9% at 5 years. The prognosis of other types of cancer was much worse: 59.2% at 1 year and 38% at 5 years. Overall survival was 81.3% at 1 year and 60.4% at 5 years in women, and 63.8% at 1 year and 46.3% at 5 years in men. Survival rate was significantly higher in women (p =0.0138; *Fig. 1*). *Table 4* shows the survival data of patients with the most frequent tumor types.

Discussion

We analyzed the data of 33 years of kidney transplantation and assessed the fate of patients who developed malignant tumors after transplantation. We would like to draw the attention to the following important observations.

Changes in the incidence of tumors after renal transplantation

Tumors following renal transplantation were compared to the Hungarian general population based on the data of the Hungarian National Cancer Registry. *Table 5* shows the order of incidence of the most frequent types of malignancies in the two populations. It can be concluded that the transplantation procedure does not simply increase tumor incidence compared to the general population, but the posttransplantation cancer profile is fundamentally different from that of the general population. In accordance with previous findings,[2,3,5] a remarkably high incidence was observed for skin and renal cancers as well as non-Hodgkin's lymphoma. Interestingly, the prevalence of hepatic carcinoma and Kaposi's sarcoma was higher only in male patients, while that of thyroid carcinoma only in females. We have also noted that several common cancer types of the general population, as colorectal-, prostate- and lung cancer, occurred less frequently in our transplanted patient cohort, while the incidence of oral cancer

decreased only in the male patients with a simultaneous increase in females. The explanation of these findings awaits further studies.

Shortened time interval before tumor manifestation

The comparison of four groups receiving different immunosuppressive regimens suggests a shortening of the time between transplantation and tumor detection. Our observation may be due to the different immunosuppressive treatments, however, it is more likely that this shortened time interval before tumor manifestation is the consequence of the different case number and follow-up time in the different immunosuppressive groups. A larger study group and a longer follow-up time are needed to justify or disprove our observation.

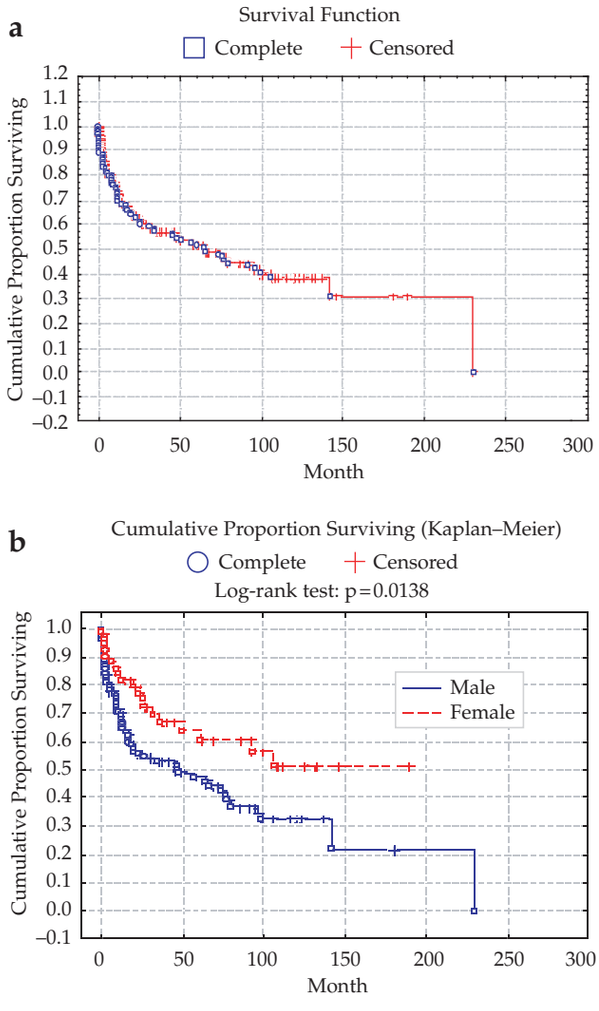

Figure 1. (a) *Cumulative patient survival rate of all patients (n=188) analyzed by Kaplan-Meier test.* ***(b)*** *Cumulative patient survival rate of female (n=59) and male patients (n=129) analyzed by long-rank test*

Early tumor manifestation in recipients

It is well known that posttransplant malignancies can derive both from the organ donor and can develop in the transplant recipient.[1,15] In the first case the tumor is transmitted unnoticed at the time of transplantation with the transplanted organ. In most cases, however, tumors arise in the recipient. They can already be present at the time of transplantation but not detected, or develop later, "de novo", in the "tumor-free" recipient; the term posttransplant tumor refers to this latter case. Apart from Kaposi's sarcoma and lymphomas, which are characterized by early manifestation and rapid progression, it is likely that tumors detected very early after transplantation are already present in the patients at the time of transplantation. This presumption may be difficult to prove, nevertheless, it is the most plausible explanation in case of tumors detected weeks or months after transplantation.

If we exclude tumors that were detected within the first 12 months from the "de novo" group, we can state that nearly 20% of our patients had an unknown tumor developing at the time of their transplantation.

It is important to note that immunosuppressive treatments promote the development of tumors. Therefore, tumor screening and early diagnosis is essential both before and after transplantation. This means that tumors should be diagnosed while patients are on the waiting list. The importance of this problem is supported by the well-known fact that the incidence of tumors is higher in patients with chronic renal failure than in the normal population. The cause for this difference can be explained with immunological abnormalities.[4,16,17]

Increasing age of kidney recipients

The mean age of kidney recipients is increasing steadily. The risk of developing malignant tumor is also increasing with the age. The average age of kidney transplantation recipients in 1970 was 20 years lower than at present in Hungary. This difference comes from improving management of patients suffering from renal diseases, and the higher standard of care in the nephrological network as well as the wide availability of dialysis treatment. As a result, nearly 50% of the patients on dialysis are over 60 years in Hungary. There are approximately 1000-1100 patients on the waiting list, their mean age is 50.1 years, 20% of them are over 60 years. Other publications report a similar phenomenon, i.e. the aging of patients awaiting kidney transplantation. Buell reported a 10-year increase in the age of recipients in the US in the last decade.[1]

The importance of oncologic screening

In our view regular oncologic screening of the patients on the waiting list for kidney transplantation is essential for the following reasons: increased incidence

Table 4. **Survival data of renal transplanted patients with different types of malignancies**

Type of malignancy	*Number of tumors*	*Age of patients*	*1-year survival*	*5-year survival*	*Survival time*
	(n)	*years (mean±SD)*	*(%)*	*(%)*	*months (mean±SD)*
Skin cancer	51	53.5 ± 6.8	90.2	75.9	116.8 ± 11.9
Native kidney cancer	26	53.0 ± 12.2	73.4	51.4	126.6 ± 35.2
Lung cancer	15	55.5 ± 7.0	42.4	20.4	9.6 ± 2.0
Kaposi's sarcoma	12	52.6 ± 12.1	25.0	16.0	14.7 ± 5.6
Breast cancer	12	57.1 ± 6.1	100.0	31.0	42.4 ± 5.5
Non-Hodgkin's lymphoma	10	48.6 ± 12.0	28.6	14.3 (at 48 months)	11.9 ± 5.2
Hepatic cancer	7	48.2 ± 7.8	16.7 (at 4 months)	–	1.8 ± 0.8
Thyroid cancer	6	50.9 ± 7.3	83.3	83.3	111.0 ± 10.3
Colorectal cancer	6	56.6 ± 3.8	62.0	23.0 (at 42 months)	14.4 ± 3.8
Total	*193*	*53.1 ± 10.1*	*69.5*	*52.0*	*99.9 ± 10.5*

of tumors that are detected early after transplantation, aging of patients with renal insufficiency and uremia, which again is associated with an increased risk of tumors.

In view of tumor frequency, we made a recommendation for the national nephrological departments for regular dermatological screening, chest X-ray and abdominal sonography. It can help with the detection of kidney and liver

Table 5. **Order of incidence of malignant tumors following renal transplantation and in the Hungarian general population**

	Type of malignancy					
	Total		*Male*		*Female*	
	General population[a]	*Transplanted population*[b]	*General population*[a]	*Transplanted population*[b]	*General population*[a]	*Transplanted population*[b]
1.	Lung	Skin	Lung	Skin	Breast	Skin
2.	Skin	Kidney	Large intestine	Kidney	Skin	Breast
3.	Large intestine	Lung	Skin	Lung	Large intestine	Kidney
4.	Breast	Kaposi's sarcoma	Prostate	Kaposi's sarcoma	Lung	Thyroid gland
5.	Oral cavity	Breast	Oral cavity	Non-Hodgkin's lymphoma	Hematological malignancies	Oral cavity
6.	Prostate	Non-Hodgkin's lymphoma	Urinary bladder	Liver	Uterus	Uterus
7.	Hematological malignancies	Liver	Hematological malignancies	Malignant melanoma	Ovary	Non-Hodgkin's lymphoma
8.	Urinary bladder	Thyroid gland	Stomach	Large intestine	Cervix	Large intestine
9.	Stomach	Large intestine	Kidney	Stomach	Stomach	Lung
10.	Kidney	Malignant melanoma	Larynx	Larynx	Kidney	Liver

[a]Based on incidence according to data from National Cancer Registry[14]

[b]Based on the cumulative incidence of tumors during the observation period (*Table 1*)

tumors, which occur more frequently in patients with hepatitis B or C virus positivity or in patients with chronic liver disease. Oncological screening of the oral cavity, gynecological examination, mammography and the detection of occult blood in the feces is also very important. We believe that all the above mentioned tests should be performed prior to putting the patient on the waiting list, and they should be repeated annually after transplantation. These tests can discover precancerous conditions and their treatment may prevent the development of malignant tumors. If any kind of malignancy is found, the patient will be excluded from kidney transplantation at a given time.

We believe that the oncologic screening of patients on the waiting list is extremely important for nephrologists. Regular screening of transplanted patients for tumors is also essential.

Survival of the transplanted patients with malignant tumors

The principles of tumor treatment are identical both in the transplanted and non-transplanted population. A unique problem in transplanted patients is immunosuppression: the decision to taper or discontinue immunosuppression or to switch to a different drug must be made on a case-by-case basis.

Since rapamycin was introduced at our Center three years ago, 63 patients with malignancies were converted to this drug. Rapamycin can maintain the function of the transplanted kidney, and it has antiproliferative effects as well.[8,13,18-20]

Despite all efforts, malignant diseases in transplanted patients have a poor prognosis.[1,4,5,8,11,12] It is common that the tumor is already at an advanced stage at the time of diagnosis. 48.9% of our tumor patients died and the average survival time from tumor diagnosis was 25.8±39.4 months. The majority of the tumors had a rapid progression: more than 50% of the deaths occurred in the first year after diagnosis.

Based on the 1- and 5-year survival of different tumors, skin and thyroid tumors have a significantly better survival rate than Kaposi's sarcoma, lung and liver cancer and lymphomas, which have a very bad prognosis. The cumulative survival rate in female patients is significantly better than in male patients. Survival is determined by many factors, tumor grade and tumor stage being the most important ones, however, general condition of patients and response to therapy also play a role. Different survival rates in women and men can be explained by the fact that tumors with a very bad prognosis (such as lung cancer, Kaposi's sarcoma, lymphoma, malignant melanoma, hepatic, laryngeal, colorectal and gastric carcinoma) occurred in female patients with a lower frequency than in males.

The age of kidney transplanted patients developing a tumor has increased during the last 33 years. The risk of an undetected tumor at the time of transplantation is also increasing due to the increasing age of the recipients, resulting in early manifesting tumors. Our data underlines the importance of oncologic screening in patients on the waiting list and also in transplanted patients.

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