Poor Outcomes of Solid Organ Cancers After Renal Transplantation: A Single-Center Experience

Renal Transplantasyon Sonrası Gelişen Solid Organ Kanserlerinin Kötü Sonlanımları: Tek Merkez Deneyimi

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ABSTRACT

Objective: This study aimed to describe survival and its influencing factors in post-renal transplant patients with solid organ cancers.

Material and Methods: In this retrospective, observational study overall survival was the primary endpoint.

Results: In total, 39 patients were included. The median malignancy development time after transplantation was 49 months. The median overall survival was 24 months and the median progression-free survival was 16 months. Primary tumor resection predicted better OS (p<0.001) and PFS (p=0.001). Chemotherapy was predictive of worse OS (p=0.014) and PFS (p=<0.001). An Eastern Cooperative Oncology Group Performance Status score of ≥ 2 was negatively associated with OS (p=0.038) and PFS (p=0.015). Sex, age, donor type, use of anti-thymocyte globulin , use of everolimus, use of mycophenolate mofetil, dialysis duration, malignancy development time, and human leukocyte antigen mismatch were not predictive of OS and PFS (p>.05).

Conclusion: Renal transplant patients who develop solid cancers have poorer survival and shorter treatment durations. Only primary tumor resection was found as a favorable prognostic factor. The effects of chemotherapy types and stages on survivals in renal transplanted patients are not exactly known. It was observed that chemotherapy and especially poor performance status had a negative effect on survival in all study groups but in subgroup analysis chemotherapy was found to have a positive effect on overall survival in the metastatic subgroup. Because of the retrospective limitations and the small size of the study and subgroups, the treatment should be individualized.

Keywords: Solid cancers, Renal transplant recipient, Survival

ÖZ

Amaç: Bu çalışmada, böbrek nakil sonrası solid organ kanseri gelişen hastalarda sağ kalımı etkileyen faktörlerin tanımlanması amaçlandı.

Gereç ve Yöntemler: Bu retrospektif gözlemsel çalışmada birincil sonlanım noktası genel sağ kalım idi.

Bulgular: Toplamada 39 hasta çalışmaya dahil edildi. Ortanca maligniteye kadar geçen süre 49 ay idi. Ortanca genel sağ kalım 24 aydı ve ortanca progresyonsuz sağ kalım 16 aydı. Primer tümör rezeksiyonu daha iyi OS (p<0.001) ve PFS'yi (p=0.001) öngördü. Kemoterapi daha kötü OS (p=0.014) ve PFS'yi (p=<0.001) öngördü. ECOG performans skoru ≥2 olması, OS (p=0.038) ve PFS (p=0.015) üzerine negatif etkili izlendi. Cinsiyet, yaş, donör tipi, anti-timosit globülin kullanımı, everolimus kullanımı, mikofenolat mofetil kullanımı, diyaliz süresi, malignite gelişim süresi ve insan lökosit antijen uyumsuzluğu OS ve PFS için prediktif bulunmadı (p>.05).

Sonuç: Böbrek nakil sonrası solid organ kanseri gelişen hastaları daha kısa tedavi süreleri ve daha kısa sağ kalımlara sahip izlendi. Sadece primer tümör rezeksiyonu pozitif prognostik faktör olarak bulundu. Böbrek nakli yapılan hastalarda uygulanan kemoterapi tipleri ve hastalık evrelerinin sağ kalımlar üzerindeki etkileri tam olarak bilinmemektedir. Kemoterapinin ve özellikle düşük performans durumunun tüm çalışma grubunda sağkalımı olumsuz yönde etkilediği fakat metastatik alt grupta kemoterapinin genel sağ kalım üzerine pozitif etkili olduğu bulundu. Bütün bu sınırlamalar ve çalışmanın ve subgrupların küçük sayılı olmasından dolayı, tedavinin bireyselleştirilmesi gerektiği düşünülmüştür.

Anahtar Sözcükler: Solid kanserler, Böbrek nakli alıcısı, Sağ kalım

INTRODUCTION

Renal transplantation improves survival compared with dialysis in end-stage renal disease. Effective immunosuppressive agents and chemoprophylaxis of opportunistic diseases resulted in increased transplantation rates and graft survival (1). However, the prolonged immunosuppression and follow-up also resulted in a higher risk of post-transplant solid cancer than that in the age-matched normal population (2-5). Lymphomas, squamous skin cancers, Kaposi sarcoma, and cervical/vulvar cancers are the most frequent malignancies after renal transplantation. The risk of other common solid organ cancers, such as breast, colon, and lung cancers, is also higher in post-transplant patients than that in normal adults (2,6). Solid organ cancers in renal transplant patients mostly present in advanced stages and have poor outcomes, with a median overall survival (mOS) of < 4 months (7). Non-lymphoid de novo cancers account for 24% of all deaths after liver transplantation (8), 21% after cardiac transplantation (9), and 26% after renal transplantation (10,11).

Although immunosuppressive agents lower the risk of graft rejection, they are the most important cause of the escape of tumor cells from immune surveillance after transplantation. The type of immunosuppressive agent, duration of immunosuppression, combination drug use, previous renal replacement treatment and duration, and altered metabolic changes associated with the underlying disease leading to renal failure were reported to be risk factors for post-transplant cancer (12,13). Tacrolimus, which is a calcineurin inhibitor, replaced cyclosporine because the latter was reported to be associated with higher skin cancer risk (14). There was no reported difference in the overall cancer risk between tacrolimus and cyclosporine (14). Mycophenolate mofetil (MMF) is a nucleotide inhibitor that inhibits inosine monophosphate dehydrogenase, which suppresses lymphocyte proliferation. An analysis of two large registries also reported that MMF was not associated with a higher risk of malignancy (14,15). Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), which inhibits the proliferation of T cells in the G1 phase of the cell cycle by blocking the cellular signaling pathways generated by growth factors (16). The antiproliferative effect of everolimus is not limited to the immune system, and it also prevents vascular remodeling, invasion, and growth factor production that cause anti-neoplastic effects (17).

Patients with post-renal transplant cancers are reported to survive shorter compared with those with cancers in the general population (18-20). This study aimed to describe survival and its risk factors in post-renal transplant solid organ cancers to ultimately provide information about the optimal immunosuppressive therapy and treatment modality for post-transplant cancer.

MATERIAL and METHODS

Study Design and Patients

This retrospective study evaluated patients who developed cancer after renal transplantation and were treated at the Akdeniz University Oncology Clinic, which is a major institution for renal transplantation in Turkey. The inclusion criteria were as following: ≥18 years of age, and having histologically or cytologically confirmed malignancy after renal transplantation. Local cutaneous squamous cell carcinomas were excluded because they are followed by the dermatologist at our center unless they are metastatic. In total, 39 patients diagnosed with solid organ cancers after renal transplantation between May 2007 and May 2017 were included. The primary endpoint was OS, which was defined as the time from tumor diagnosis to death. The secondary end points were progression-free survival (PFS), response rate, duration of chemotherapy, and influencing factors of OS and PFS. PFS was defined as the date from first treatment date to documented progression or death. Malignancy development time was defined as the time from renal transplantation to time to cancer occurrence. This study (date: 26.12.2018; protocol no: 909) was approved by the Akdeniz University local ethics committee.

Assessment of Response

Radiological response was assessed every 3 cycles or in case of a clinical progression finding according to the Response Evaluation Criteria in Solid Tumors (version 1.1). All patients underwent computed tomography (CT) or positron emission tomography-CT at baseline.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY). Descriptive variables were presented using median (range) or n (%), where appropriate. The Kaplan-Meier method and log-rank tests were used to determine survival differences for nominal variables. A univariate Cox proportional hazards model was performed to identify the influencing factors of OS and PFS. A P-value of less than .05 was considered statistically significant.

RESULTS

Patient Demographics

Of the 39 patients included, 27 were male and 12 were female. The median patient age was 54 (range, 18-80) years. The donor types were as follows: 8 (20.5%) cadaver renal transplants; 26 (66.7%) living-related transplants; and 5 (12.8%) living-unrelated transplants. The clinical and demographic characteristics of the 39 patients are presented in Table I. In total, 10 patients (25.6%) had pre-emptive renal transplantation, while 24 patients (61.5%) were on hemo-

Table I: Clinical and Demographic Data

	n=39 (%)
ECOG PS, n (%)	
< 2	33 (84.6)
≥2	6 (15.4)
Malignancy development time (month), Median (range)	49 (4-435)
Immunosuppression time (month), Median (range)	47 (4-432)
Metastatic disease, n (%)	
Liver metastases	7 (18.5)
Lung metastases	10 (26.3)
Brain metastases	4 (10.5)
Bone metastases	1 (2.6)
Primary tumor size (cm), Median (range)	2.5 (0-8)
Donor type, n(%)	
Cadaveric	8 (20.5)
Living related	26 (66.7)
Living unrelated	5 (12.8)
Renal Failure Etiology, n (%)	
Iatrogenic	2 (5.1)
Hypertensive nephropathy	12 (30.8)
Diabetic nephropathy	11 (28.2)
Polycystic renal disease	3 (7.7)
Glomerulonephritis	6 (15.4)
Nephrolithiasis	3 (7.7)
Neurogenic bladder	2 (5.1)
HLA mismatch number, n (%)	
Full match	1 (2.6)
1 mismatch	2 (5.1)
2 mismatch	8 (20.5)
3 mismatch	9 (23.1)
4 mismatch	5 (12.8)
5 mismatch	11 (28.2)
6 mismatch	3 (7.7)
Blood group, n (%)	
A+	17 (44.7)
A-	2 (5.3)
B+	8 (21.1)
AB+	4 (10.5)
0+	7 (18.4)
OS, median (95%CI)	24 (13.8-34.2)
PFS, median (95%CI)	16 (NA)

dialysis, and 5 patients (12.9%) were on peritoneal dialysis at the time of renal transplantation. The median duration of dialysis was 16 (range, 0-133) months. The median malignancy development time (MDT) after transplantation was 49 (range, 4-435) months. There were 19 patients who received early (in days) induction immunosuppressive treatment (anti-thymocyte globulin or basiliximab) after renal transplantation for acute rejection episodes. In total, 11

patients (28.2%) received anti-thymocyte globulin (ATG), and 8 patients (20.5%) received basiliximab as induction immunosuppressive treatment. At the time of cancer diagnosis, 26 patients (66.7%) were on tacrolimus; 11 patients (28.2%) were on cyclosporine; and 2 patients (5.1%) were on everolimus maintenance as a standard immunosuppressive treatment. There were 33 patients (84.6%) treated with MMF in combination with tacrolimus or cyclosporine. After the cancer diagnosis, the immunosuppressive treatment of 34 patients was switched to everolimus, while all immunosuppressive treatment was stopped in 3 patients. The types of cancer were urinary bladder urothelial cancer in 5 patients (12.8%), colorectal cancer in 5 patients (12.8%), thyroid cancer in 5 patients (12.8%), oral cavity tumors in 5 patients (12.8%), non-small cell lung cancer in 4 patients (10.3%), Kaposi sarcoma in 3 patients (7.7%), hepatocellular carcinoma in 2 patients (5.1%), gastric cancer in 2 patients (5.1%), malignant melanoma in 2 patients (5.1%), breast cancer in 1 patient (2.6%), glioblastoma multiforme in 1 patient (2.6%), non-seminomatous testicular cancer in 1 patient (2.6%), pancreatic adenocarcinoma in 1 patient (2.6%), primary unknown cancer in 1 patient (2.6%), and soft tissue sarcoma in 1 patient (2.6%). Of the 39 patients, 19 (48.7%) patients had advanced disease at the time of diagnosis. In total, 26 patients (66.7%) underwent primary tumor resection, while 18 patients (46%) received cytotoxic chemotherapy (Table II). There were 4 renal graft rejections in both groups who did and did not receive chemotherapy.

Survival and Risk Factors Affecting Survival

The mOS was 24 months (95% CI: 13.8-34.2), and the median PFS was 16 months (95% CI: NA) (Figure 1,2). In univariate Cox proportional hazards model of the influencing factors of OS and PFS (Table III) sex, age, donor type, ATG induction therapy, everolimus maintenance treatment, MMF maintenance treatment, dialysis duration, MDT, and human leukocyte antigen mismatch did not affect the OS and PFS ($P > .05$). Primary tumor resection predicted better OS (HR: 0.196; 95% CI: 0.08-0.481, $p<0.001$) and PFS (HR: 0.198; 95% CI: 0.077-0.507, $p =0.001$). Chemotherapy was predictive of worse OS (HR: 3.202; 95% CI: 1.266-8.098, $p=0.014$) and PFS (HR: 8.108; 95% CI: 2.508-26.213, $p=<0.001$). An Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of ≥ 2 was negatively associated with OS (HR: 2.969; 95% CI: 1.063-8.291, $p=0.038$) and PFS (HR: 3.643; 95% CI: 1.289-10.293, $p=0.015$). Multivariate analysis showed that ECOG-PS score ≥ 2 and chemotherapy were independent negative predictive factors of PFS. Meanwhile, only primary tumor resection was the independent factor affecting OS (Table IV).

Table II: Particulars Specified for Cancer Types.

Type of cancer	No of cancer	Gender M vs F	Median OS Months (95%CI)	MDT(month) (median, range)	Chemotherapy Cycle (Median, range)
Bladder	5	4/1	18 (2.97-33)	80 (53-369)	3.5 (1-4)
CRC	5	4/1	6 (1.7-10.3)	65 (18-130)	4 (3-12)
Thyroid	5	4/1	NA (Mean:57.4)	32 (18-42)	0
Oral cavity	5	3/2	NA (Mean:82.6)	36 (8-112)	3 (0-6)
Lung	4	2/2	14 (NA)	36 (20-77)	6
KS	3	2/1	27 (NA)	18 (4-32)	-
HCC	2	1/1	3 (NA)	80.5 (51-110)	2
Breast	1	0/1	NA	46	6
Brain	1	1/0	4 (NA)	49	0
Testis	1	1/0	NA	161	3
PU	1	0/1	5 (NA)	59	0
Pancreas	1	1/0	10 (NA)	19	6
Stomach	2	1/1	20 (NA)	126 (91-161)	5
MM	2	2/0	4 (NA)	224.5 (14-435)	-
STS	1	1/0	6 (NA)	121	1

MDT: Malignancy development time, **NA:** Not applicable, **CRC:** Colorectal cancer, **HCC:** Hepatocellular carcinoma, **KS:** Kaposi Sarcoma, **PU:** Primary unknown, **MM:** Malign melanoma, **STS:** Soft tissue sarcoma.

Table III: Univariate Analysis of Risk Factors Affecting Survivals.

Variable	OS HR (95%CI)	p	PFS HR (95%CI)	p
Age	1.032 (0.996-1.07)	0.083	1.014 (0.978-1.051)	0.458
Gender	1.091 (0.423-2.813)	0.857	0.794 (0.312-2.02)	0.628
Donor type				
Cadaveric (Ref)	-	-	-	-
Living related	2.468 (0.563-10.823)	0.231	5.235 (0.689-39.762)	0.110
Living unrelated	4.74 (0.843-26.657)	0.077	6.096 (0.628-59.173)	0.119
Immunosuppressive agent				
ATG	0.935 (0.342-2.554)	0.896	0.702 (0.233-2.117)	0.530
Cyclosporine	3.039 (1.279-7.219)	**0.012**	1.93 (0.756-4.929)	0.169
Everolimus	1.203 (0.28-5.176)	0.804	2.127 (0.617-7.333)	0.232
MMF	2.438 (0.565-10.526)	0.232	4.759 (0.631-35.895)	0.130
Tacrolimus	0.342 (0.145-0.81)	**0.015**	0.529 (0.212-1.32)	0.172
Dialysis Duration	0.996 (0.984-1.009)	0.566	1.001 (0.988-1.014)	0.894
MDT	1 (0.995-1.005)	0.934	1 (0.996-1.005)	0.837
ECOG PS				
<2(Ref)	-	-	-	-
≥2	2.969 (1.063-8.291)	**0.038**	3.643 (1.289-10.293)	**0.015**
Chemotherapy	3.202 (1.266-8.098)	**0.014**	8.108 (2.508-26.213)	**<0.001**
PTR	0.196 (0.08-0.481)	**<0.001**	0.198 (0.077-0.507)	**0.001**
Mismatch				
0-1-2 (ref)	-	-	-	-
3-4	0.476 (0.134-1.693)	0.252	0.961 (0.323-2.863)	0.943
5-6	1.397 (0.516-3.782)	0.510	0.819 (0.264-2.543)	0.730

MDT: Malignancy development time; **PTR:** Primary tumor resection.

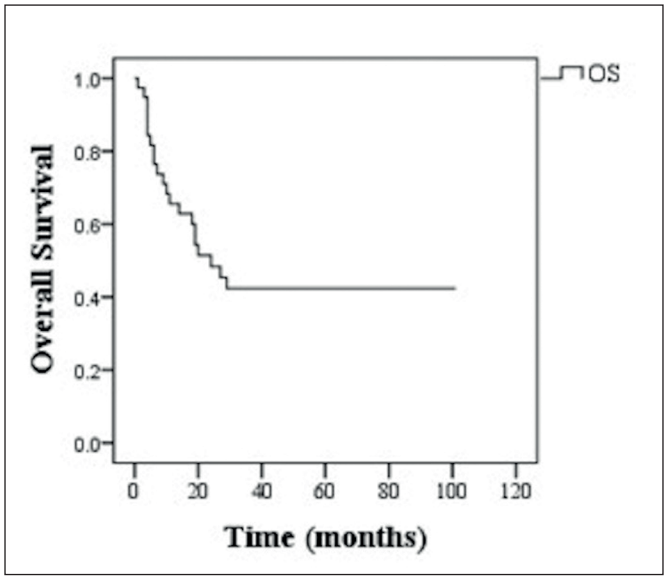

Figure 1: Overall Survival.

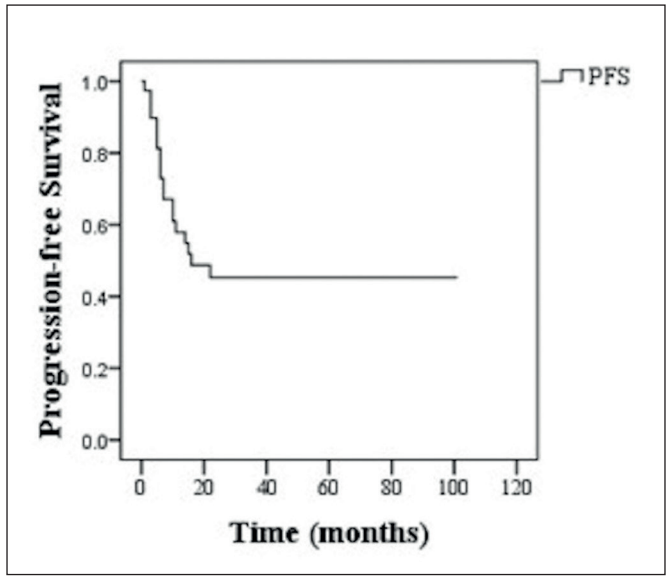

Figure 2: Progression-free Survival.

Table IV: Multivariate Analysis of Risk Factors Affecting Survivals.

Variable	OS HR (95%CI)	p	PFS HR (95%CI)	p
Cyclosporine	0.802 (0.089-7.254)	0.845	-	-
Tacrolimus	0.345 (0.042-2.855)	0.324	-	-
ECOG PS				
<2(Ref)	-	-	-	-
≥2	1.902 (0.595-6.077)	0.278	3.184 (1.071-9.461)	**0.037**
Chemotherapy	1.741 (0.59-5.135)	0.315	5.966 (1.602-22.21)	**0.008**
PTR	0.251 (0.09-0.702)	**0.008**	0.446 (0.153-1.297)	0.138

PTR: Primary tumor resection.

When we performed subgroup analysis for metastatic and non-metastatic groups, age (p=0.62), sex (p=0.21), ECOG PS (p=0.17), and PTR (p=0.15) were not effective on OS, but chemotherapy (p=0.01) was found to be effective on OS in the metastatic subgrup.The patients who had chemotherapy in the metastatic subgroup had lower death risk (HR: 0.2; 95% CI: 0.16-1.35, p=0.019). In the non-metastatic subgroup, age (p=0.149), sex (p=0.36), ECOG PS (p=0.29), PTR (p=0.36), and chemotherapy (p=0.13) were not found to be effective on OS.

DISCUSSION

The majority of post-transplantation solid organ cancers occur within the first 3 years after transplantation (19). Several clinical studies have reported an increased risk of cancer in renal transplant patients (2-4,11,15,16). Although lymphomas, squamous skin cancers, Kaposi sarcoma, and cervical/vulvar cancer are the most frequent cancers after renal transplantation, the incidence of breast, colon, and lung cancers has also increased in this population compared with that in normal adults (2,6,21). However, despite the increased risk of malignancy, the prognosis, optimal treatment modality, and the treatment efficacy are not well-understood, also known as "unmet medical need" (19). In general, 2%-13% of patients develop cancer after renal transplantation (4,8,19,22-25), which is 3-8-fold higher than that in the normal population (23). The varying incidence rates between studies may be due to the differences in follow-up and duration of immunosuppression (25). Kauffman et al. reported that the incidence of post-transplantation cancer is negatively associated with the duration of pre-transplantation dialysis (26). Kasiske et al. reported that a pre-transplantation dialysis duration of > 3 years is associated with higher risk of cancer (6). However, in the current study, the duration of pre-transplantation dialysis was not predictive of survival.

Renal allograft recipients have significantly poorer survival after cancer diagnosis than the general population (19,21). Farrugia et al. evaluated 19103 renal transplant recipients in a population-based cohort study in England and reported that 18% of deaths after renal transplantation was due to malignancy (21). The Australia and New Zealand Dialysis and Transplant Registry also showed higher mortality in transplant recipients with breast cancer and lower survival in male renal transplant patients with colorectal cancers compared to the general population (18). Lim et al. reported that 1-, 5-, and 10-year survival rates were 73.4% (95% CI: 70.8-75.9), 51.7% (95% CI: 48.6-54.7) and 39.5% (95% CI: 36.0-43.0) after cancer development in kidney transplant recipients (19). In our study, survival rates of patients after de novo malignancy were markedly lower than those reported in the literature (22). The mOS after cancer development was 2 years, similar with that in the Netherlands Organ Transplant Registry (median 2.1 years vs 8.3 years in the control group without cancer; P < .001) (20).

MDT in our study was 49 months. MDT differs between different cancers and different studies (27). The median duration of immune suppression was 47 months, which was shorter than that reported in previous reports (20,22,23). Chapman and Webster reported that the duration and intensity of immunosuppression, not the type of immunosuppressive agent increases the overall cancer risk (25). In vitro studies showed calcineurin inhibitors (tacrolimus and cyclosporine) contribute to carcinogenesis and metastases by producing tumor growth factors such as TGF-ß (25,26). Apel et al. observed an insignificant tendency toward slightly improved survival for renal transplant recipients who received cyclosporine treatments compared with those who did not (P = .46) (23). mTOR inhibitors such as sirolimus showed antitumor effect by causing cell cycle arrest and reducing the production of tumor growth factors

such as VEGF-A and TGF-ß (26). In our study, the type of immunosuppressive agent also did not influence survival, consistent with previous studies (12,23-25).

The poor outcomes of cancer treatment in renal transplant recipients may be due to the unconvinced approaches for intensive chemotherapeutics and surgical procedures or the reluctance to lower immunosuppression because of the fear of potential renal allograft loss (19,26). In a French retrospective study, there was no difference in median survival after disseminated lung cancer diagnosis between those who did and did not undergo renal transplantation (27). However, renal transplant recipients had less first-line (68% vs 90%; P = .06) and second-line chemotherapy (46% vs 58%; P = .043) compared with the control group (27). In our study, 46% of patients received cytotoxic chemotherapy, which is also lower than that in a previous study (27). Another Korean study of renal recipients reported localized gastric cancers treated with surgical approaches, but three metastatic gastric cancers were not treated (28). Treatment durations and chemotherapy cycles in our study were also shorter than that in the general population due to adverse events such as myelosuppression and infections or pre-transplantation comorbidities such as diabetes and heart failure.

Oncologists traditionally assess ECOG PS for cancer treatment and follow up because it was associated with survival in primary lung cancer, gastrointestinal cancers, breast cancers, gynecological cancers, head & neck cancers, and genitourinary cancers (29,30). There is no data about ECOG PS and patient survival after the diagnosis of cancer in renal transplanted patients. In our study, an ECOG PS of ≥ 2 was negatively associated with OS and PFS as in the previous cancer research patients who had not undergone renal transplantation (29,30).

In this study, we describe the survival and its influencing factors in post-renal transplant patients with solid organ cancers. We believe that our study makes a significant contribution to the literature because it shows instrumental evidence that renal transplant patients who consequently develop solid organ cancers have poorer survival outcomes and shorter treatment duration than the general population of cancer patients. This finding can alert clinicians on the necessary precautions needed before transplantation.

Although patients with different cancers are studied, we reported real-life data from a population representing the renal transplanted group.

The major limitations of this paper are the very small number, and the lack of adequate controls. The incidence and prevalence of malignancy in renal transplant recipients could not be evaluated since the study was performed in the oncology department and some patients transplanted at our center were followed-up at different centers. We did not have any gynecological cancer patients and could not include them in the study although they are commonly seen in the post-transplant period. Another limitation of this study is that survival interpretation could not be performed because the number of patients was very small when grouped by stage or chemotherapeutics.

CONCLUSION

This study of solid organ cancers in renal transplant patients showed poorer survival outcomes and shorter treatment durations compared with those in the general population of cancer patients. Physicians should be aware of the poor prognosis of patients who develop solid organ cancer after renal transplantation. The efficacy and safety of therapeutic options for solid cancer remain unclear in patients who have undergone renal transplantation, but individualized treatment that considers not only the patient's risk of allograft rejection but also survival risk factors should be investigated.

OS after cancer diagnosis in renal transplant patients is too short to investigate the effect of treatment modalities. Our study found only primary tumor resection as a favorable prognostic factor. Malignancies other than the most common tumours were also included in this retrospective analysis. The effects of chemotherapy types and stages on survivals in renal transplanted patients are not exactly known. It was observed that chemotherapy and especially poor performance status had a negative effect on survival in all study groups, but in subgroup analysis chemotherapy was found to have positive effect on overall survival in the metastatic subgroup. Because of the retrospective limitations and the small size of the study and subgroups, the reliability of the results is doubtful. Cancer treatment in renal transplanted patients should therefore be individualized. Malignancies developing after renal transplant may be worse than in other cancer patients because optimal chemotherapy (right time and right/full dose) approaches may not be applied (due to ongoing immunosuppression and infections) or other systemic therapies including immunotherapy may not be available. In this population, it will be better to define risk factors influencing survival in order to understand the progress of the immunosuppressed cancer patient and to guide the tailored therapies.

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Author Contributions: **DKS:** Concept, **DKS, HŞC:** Design, **HŞC:** Supervision, **DKS, SSG, HK:** Resources, **DKS:** Materials, **DKS:** Data Collection and/or Processing, **DKS:** Analysis and/ or Interpretation, **DKS:** Literature Search, **DKS:** Writing Manuscript, **DKS, SSG, HK, HŞC:** Critical Review.

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