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Master's thesis / Diplomski rad

2019

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Zagreb, School of Medicine / Sveučilište u Zagrebu, Medicinski fakultet**

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:304816>

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Download date / Datum preuzimanja: **2024-07-30**



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UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

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**VIŠESTRUKÉ PRIMARNE MALIGNOSTI
U PACIJENATA S
TRANSPLANTIRANIM BUBREGOM:
RETROSPEKTIVNA KOHORTNA
STUDIJA**

GRADUATION THESIS



Zagreb, 2019

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**MULTIPLE PRIMARY MALIGNANCIES
IN RENAL TRANSPLANT RECIPIENTS:
A SINGLE CENTRE RETROSPECTIVE
COHORT STUDY**

GRADUATION THESIS

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This graduation paper was made at University Hospital Centre Zagreb, under supervision of Professor Nikolina Basic-Jukic and it was submitted for evaluation in the academic year 2018-2019

Mentor: prof. dr. sc. Nikolina Basic-Jukic

Original Paper

Multiple Primary Malignancies in Renal Transplant Recipients: a Single Centre Retrospective Cohort Study

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Key Words

Renal transplantation • Malignant tumor • Multiple malignancies • Outcome

Abstract

Background/Aims: Renal transplant recipients are exposed to immunosuppressive treatment which may increase the risk for developing malignancies. Limited data exists concerning the occurrence of multiple primary malignancies (MPM) in renal transplant patients. **Methods:** All the patients who received a renal allograft at our institution from 1973 to 2017 were included in this investigation. Data from patients with more MPM were obtained from the charts and medical records. Malignancies were categorized as synchronous if the interval between occurrences was less than or equal to 6 months and metachronous if the interval was more than 6 months. **Results:** Out of the 1884 patients who received a renal allograft, 164 (8.7%) developed a malignant tumor. Twenty-two patients (13.4%; 6 females, 16 males) developed MPM, 7 synchronous (31.8%) and 15 metachronous types (68.2%). The most common initial primary tumors were skin cancers (8) and kidney cancers (3). Furthermore, skin cancers were the most common second primary malignancies (9). Log-rank analysis revealed significantly better survival in the synchronous group (113.3 months) than in the metachronous group (24.6 months) ($p=0.04$). **Conclusion:** MPM are more frequent in renal transplant recipients than in the general population. It is associated with a high mortality rate, especially in the metachronous group. An increased awareness and frequent screening tests are necessary when managing this condition.

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Published by S. Karger AG, Basel

Introduction

Multiple primary malignancies (MPM) are a prevalent phenomenon that are usually defined as primary malignant tumors of different histological origins in one person [1]. They are defined by the following criteria: (1) every tumor has definite features of malignant change, (2) every tumor is anatomically separate, (3) the second tumor cannot be a metastatic lesion or due to recurrence of the first tumor, and (4) the following primary malignancies have to be present in either the same or different organs [2]. Multiple primary malignancies may be classified as synchronous or metachronous. The synchronous type is defined as malignancies that are observed at the same time or within 6 months of each other, and malignancies that develop after 6-months of one another are considered as metachronous MPM [3]. The etiology of this occurrence has not been completely elucidated. It is believed to involve the patient's exposure to known carcinogens like chemotherapy and radiotherapy during the treatment of the initial tumor, genomic structural variations that can increase a patient's tumorigenic susceptibility and the functional status of a patient's immune system [4].

Current literature contains limited data concerning MPM in renal transplant recipients. In this retrospective study, we analyzed the occurrence of MPM at our renal transplant program over a 44-year study period.

Materials and Methods

This was a retrospective cohort study including a series of 1884 consecutive renal transplant patients who received a renal allograft at the University hospital centre Zagreb from 1973 to 2017. Patients were regularly followed up every three months at the outpatient clinic. Immunosuppression has changed with time. Universal induction with basiliximab was introduced in 2006, and for sensitized patients we used polyclonal antibodies. Initial maintenance immunosuppressive therapy was usually done by utilizing a triple drug regimen containing cyclosporine (640 patients) or tacrolimus (1244 patients), azathioprine (482 patients) or mycophenolate (1402 patients) and steroids. From 1999 onward we generally used mycophenolate instead of azathioprine, and from 2007 onward tacrolimus instead of cyclosporine. After January 2008, patients with a history of malignancy or with post-transplant malignancy received an mTOR inhibitor instead of a calcineurin inhibitor if they had no contraindications to the medication (proteinuria, acute rejection, side-effects, or donor-specific antibodies) (92 patients). Acute rejection was recorded in 296 patients (15.7 %). Episodes of acute rejection were treated with steroid pulses (296 patients), while 78 patients also underwent plasma exchange for treatment of humoral rejection, and 4 received ATG for treatment of steroid resistant acute rejection.

Patients were diagnosed based on medical history, physical examination, appropriate radiographic and/or endoscopic examinations, and pathological results. The time interval to differentiate between synchronous or metachronous types required 6 months. The inclusion criteria of patients in this study were the presence of at least two neoplastic locations confirmed by histopathological examination and tumors with distinct histopathology in different locations. Patients were excluded from the investigation if they didn't have a clear histopathological confirmation of each tumor, if the second tumor was suspected to be a metastasis of the first location, as well as patients with the first malignancy being diagnosed before transplantation and the second malignancy being diagnosed after the transplantation. Patient age at the time of each tumor diagnosis, gender, site of origin, synchronous or metachronous appearance, immunosuppressive protocol, treatment regimen and outcome have been recorded.

Statistical analysis was performed using Stata/SE 11.2 for Windows (StataCorp LP, USA). Differences between these two groups were analyzed by using Fisher's exact test or the Mann Whitney U test at the level of significance $P < 0.05$, with Kaplan-Meier analysis for survival.

The study protocol was approved by the Institutional Review Board and conformed to the ethical guidelines of the Declaration of Helsinki.

Results

Patients' characteristics

Over the observed period, 1884 patients received a renal allograft (1114 male), with an average age at the transplantation of 55 years (range 18 to 77 years), and median follow-up time of 8 years. There were 673 transplantations from 1973 to 2007 and 1211 from 2007 to 2017, this abrupt increase can be attributed to Croatia entering the Eurotransplant organization during this time.

There were 164 patients who developed a malignancy, and 22 who had MPM. There was a male predominance (16 male vs. 6 female) and the median age at the time of diagnosis of the first primary malignancy was 61 (range 39-77) years. Primary kidney diseases included glomerulonephritis (7), endemic nephropathy (3), pyelonephritis (3), nephroangiosclerosis (2), diabetic nephropathy (1), polycystic kidney disease (1) and an idiopathic cause of kidney failure in 4 of the patients. The median time of dialysis vintage was 5.14 years (range 0.5-12 years). The time frame between transplantation, development of the first tumor and of the second tumor is shown in Table 1.

Four patients had two renal transplantations. Two patients had a history of malignancy before transplantation (one colon cancer and one basal cell carcinoma). Six patients were smokers. The immunosuppressive protocol included induction in 12 patients (basiliximab in 10 and antithymocyte globulin in only 2 patients). Sixteen patients received cyclosporine and 6 patients, tacrolimus. Azathioprine was used in 7, mycophenolate in 14 and everolimus in one patient. Two patients developed acute cellular rejection and were treated with steroid pulses.

Significantly more patients treated with cyclosporine or azathioprine developed MPM compared to patients treated with other immunosuppressive drugs (Fisher exact test, $p=0.007$) (Table 2).

Three patients had chronic hepatitis C virus infections, and two had CMV infection. No other viral infections were recorded.

Synchronous and metachronous malignancies

Seven patients (32%) developed synchronous and 15 (68%) metachronous MPM. The mean time from renal transplantation until the diagnosis of MPM was 10 years (range 2-20) for the synchronous and 2 years (range 1-25) for the metachronous group (Mann-Whitney $p=0.02$). Patients' characteristics based on the time of cancer occurrence are presented in Table 3.

There was no difference between the synchronous and the metachronous group regarding the type of primary kidney disease.

Table 1. Time frame between transplantation and diagnosis of the malignancies. IQR; interquartile range; Tx, transplantation

Time (years)	Median (IQR)	Range
From Tx until the 1 st tumor	4 (1 - 11)	1 - 25
From the 1 st until the 2 nd tumor	1,5 (0,3 - 3)	0 - 11
From Tx until the 2 nd tumor	7,5 (4 - 13)	2 - 26

Table 2. Development of multiple primary malignancies depending on the use of immunosuppressive drugs. Fisher exact test

Variable	Number (%) of patients			P*
	With MPM	Without MPM	Total	
Cyclosporine	16 (36,4)	624 (16,8)	640 (17)	
Tacrolimus	6 (13,6)	1146 (30,8)	1152 (30,6)	
Everolimus	1 (2,3)	91 (2,4)	92 (2,4)	0,00†
Azathioprine	7 (15,9)	475 (12,8)	482 (12,8)	
Mycophenolate	14 (31,8)	1388 (37,3)	1402 (37,2)	

Table 3. Patients' characteristics based on the time of cancer occurrence are presented in Table 1. MPM, multiple primary malignancies; IQR, interquartile range). †Mann Whitney U test

Parameter	Type of MPM			P*
	Synchronous (n=7)	Metachronous (n=15)	Total (n=22)	
Gender [n(%)]				
Male	4 (57)	11 (73)	15 (68)	0,63
Female	3 (43)	4 (27)	7 (32)	
Age [years] [Median (IQR)]	54 (51 - 74)	75 (67 - 80)	73 (56 - 78)	0,02†
Dialysis vintage [years] [Median (IQR)]	6 (1 - 10)	4 (2 - 7)	4,5 (2 - 9)	0,55†

Table 4. Localization and immunosuppression at the time of occurrence and treatment of the first primary malignancy. BCC, basal cell carcinoma; SCC, squamous cell carcinoma; C, cyclosporine; T, tacrolimus; S, steroid; M, mycophenolate; A, azathioprine. *Fisher exact test

Primary malignancy	Type		P*
	Synchronous (n=7)	Metachronous (n=15)	
First tumor [n(%)]			
Kidney adenocarcinoma	2 (29)	1 (7)	
BCC	2 (29)	4 (27)	
Colon cancer	1 (14)	0	
Urinary bladder	1 (14)	1 (7)	
Thyroid	0	3 (20)	0,39
Prostatic gland	0	2 (13)	
Ovarian	1 (14)	0	
SCC	0	2 (13)	
Merkel cell cancer	0	1 (6,7)	
Breast	0	1 (6,7)	
Immunosuppression 1 [n(%)]			
C+M+S	3 (43)	6 (40)	
C+A+S	2 (29)	5 (33)	>0,99
T+M+S	2 (29)	3 (20)	
mTOR + T + S	0	1 (7)	
Treatment 1 [n(%)]			
Operative	6 (86)	8 (53)	
Operative + mTOR	1 (14)	1 (7)	
Operative+ irradiation	0	4 (27)	0,51
Operative + radioactive iodine	0	1 (7)	
Operative + tamoxifen	0	1 (7)	

Table 5. Localization and immunosuppression at the time of occurrence and treatment of the second primary malignancy. BCC, basal cell carcinoma; SCC, squamous cell carcinoma; C, cyclosporine; T, tacrolimus; S, steroid; M, mycophenolate; A, azathioprine. *Fisher exact test

Secondary tumor	Type		P*
	Synchronous (n=7)	Metachronous (n=15)	
Tumor 2 [n(%)]			
Kidney	1 (14)	1 (7)	
BCC	1 (14)	3 (20)	
Colon	3 (43)	0	
Urinary bladder	0	2 (13)	
Ovary	1 (14)	0	
SCC	1 (14)	4 (27)	0,27
Breast	0	1 (7)	
Lung	0	1 (7)	
Plasmocytoma	0	1 (6,7)	
Glyoblastoma	0	1 (6,7)	
Melanoma	0	1 (6,7)	
Immunosuppression 2 [n(%)]			
C+M+S	1 (17)	0	
mTOR + M + S	3 (50)	11 (73)	0,26
T + M + S	2 (33)	2 (13)	
C + S	0	2 (13)	
Treatment 2 [n(%)]			
Operative	5 (71)	12 (80)	
Operative + mTOR	2 (29)	0	0,07
Palliative	0	3 (20)	

Localization and immunosuppression at the time of occurrence and treatment of the first primary malignancy are presented in Table 4. The most common first primary malignancy was basal cell carcinoma in 27% of cases.

Localization and immunosuppression at the time of occurrence and treatment of the primary malignancy is presented in Table 5. The most common second primary carcinoma was squamous cell carcinoma of the skin, occurring in 23% of patients.

Tumor correlations for synchronous tumors were: colon-colon, kidney-colon, ovary-colon, urinary bladder-ovary, kidney-kidney, skin SCC- skin BCC, skin BCC- skin SCC.

Tumor correlations for metachronous tumors were: thyroid-lung, BCC-SCC (2 patients), SCC-BCC (2 patients), Merkel cell skin cancer-SCC, prostate-urinary bladder, urinary bladder-kidney, kidney-urinary bladder, prostate-SCC, BCC-plasmocytoma, BCC-glyoblastoma, thyroid-melanoma, breast-BCC, thyroid-breast.

Log-rank analysis revealed significantly better survival in the synchronous group (113, 3 months, 95% CI 79, 3 - 147, 2) than in the metachronous group (24, 6 months, 95% CI 14.7-34.5) (p=0.04) (Fig. 1).

Discussion

The frequency of MPM ranges between 2.4% and 20% based on the definition in literature and is increasing with longer patient follow-up [5]. The incidence of MPM has increased significantly due to improvements in diagnostic methods and with the discovery of new treatments, which allows for more patients to survive long enough to develop additional primary tumors [6]. Attributing factors involve improved screening, advances in diagnostic testing, more sophisticated anticancer treatment regimens, an improved overall surveillance of patients with cancer and better nutritional support. Cancer survivors may be more susceptible to developing second primary malignancies due to many factors which include a genetic predisposition towards cancer, environmental exposures, specific

characteristics of some tumors, and adverse effects of treatment with chemotherapy and/or radiotherapy. Increased risk for MPM was found to correlate with family history, race, younger age at the time of diagnosis, a lower tumor stage and with indolent cancer behavior which enables prolonged survival [7]. Although there are numerous reports addressing the clinical features of MPM in the general population, literature on this topic in the renal transplant population is scarce.

Therefore, this retrospective study was designed to evaluate the clinical

characteristics and outcomes of MPM involving renal transplant patients. The incidence of MPM in our study was 1.16% among all renal transplant recipients and 13.4% among renal transplant patients with malignancies. Of the 22 cases (6 females, 16 males) diagnosed with MPM, 7 were synchronous (31.8%) and 15 were the metachronous variant (68.2%). In the study of Bisof et al. from our institution, the incidence of MPM in the general population of oncology patients was 2.4%. Among 103 patients, 83 cases were metachronous (80.5%), and 20 cases (19.5%) were synchronous malignancies. The frequency was higher in females than males. The most common tumor combinations in males were: prostate cancer-digestive system malignancy (especially colorectal cancer) and vice versa, and hematological malignant tumors-digestive system malignancy. While in women the most frequent were: breast cancer-cancer of contralateral breast and hematological malignant tumors (especially lymphoma non Hodgkin)-breast cancer [8]. In the transplanted population from our institution, the most common tumor combinations were different skin malignancies. Based on this comparison, it is obvious that the incidence of MPM was higher in renal transplant recipients (13.4%) than in the general population (2.4%). Additionally, in the general population MPM was more common in female and renal transplant populations than in male patients, with a diverse spectrum of localizations.

Our results are in contrast with previously reported data. Santangelo et al. did not find a higher risk for development of MPMs as compared to the corresponding general population. Their explanation is based on the fact that kidney-transplanted patients probably die before a new "second primary malignancy" appears or due to interruptions of immunosuppressive therapy, thus limiting the exposure to oncogenic effects of such drugs over time while they return to dialysis. In their practice, it was hard to find transplanted patients who survived the first malignancy and then continued immunosuppressive treatment long enough to develop a second primary cancer as a consequence of iatrogenic immune deficiency [9]. Taioli et al. investigated the incidence of a MPM in 7,636 patients who underwent a kidney, liver, lung or heart transplant between 1970 and 2004. They did not find an increased risk of MPM in transplanted patients with a previous malignancy [10]. To our knowledge, only these two reports have specifically examined the incidence of MPMs in transplanted patients. Tessari et al. reported an increased risk for the development of primary and second cancers in the renal transplant population, with the type of second cancer being dependent on the type of the primary. Patients with nonmelanoma skin cancer developed a second nonmelanoma skin cancer, and patients with nonskin cancer developed a second nonskin cancer [11]. Our

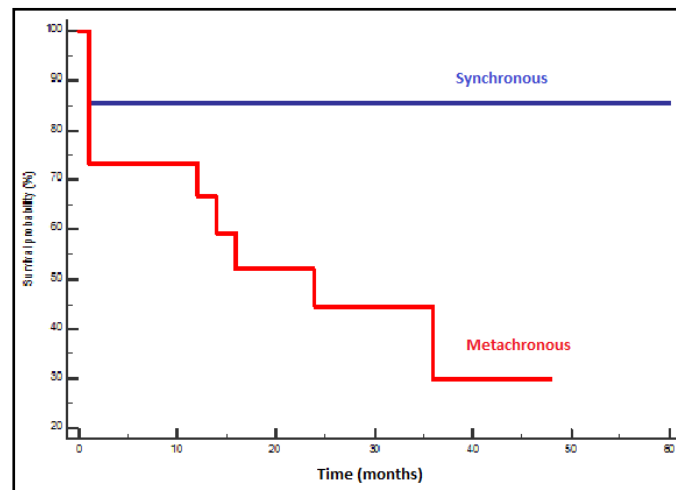


Fig. 1. Kaplan-Meier survival analysis comparing survival of patients with synchronous and metachronous multiple primary malignancies.

results demonstrate that all types of tumors may occur in various possible combinations, and are not limited to skin or nonskin localizations.

Our results may differ from the results of Santangelo [9] and Taioli [10] for the following reasons: after malignancy diagnosis our patients are allowed (after detailed information) to choose between three different approaches: cessation of immunosuppression and graftectomy, minimization of existent immunosuppressive therapy or switching to an mTOR based immunosuppressive regimen (instead of the calcineurin inhibitor). So far, none of the patients have decided to stop immunosuppression and return to dialysis. Additionally, an exponential increase in the number of transplantations performed in Croatia has enabled transplantations for very old patients who are prone to develop malignancies. Based on a combination of factors (improved diagnosis, improved treatment, demographics), it may be expected that this aging transplant population will lead to an increased prevalence of MPM.

Our study observed a higher number of the metachronous subtype versus synchronous malignancies. This contrasts the results of Santangelo et al. but is in agreement with a large observational study [9, 12]. While our results show a significant mortality advantage of synchronous over metachronous malignancies, the observational study revealed the opposite with a median survival time that was greater for the metachronous subtype, 96 months from diagnosis compared to 12 months. Their study showed that an interval time of less than 60 months was a positive prognostic factor for patients with metachronous cancer [12].

In contrast to the healthy population, squamous cell carcinoma of the skin is more common than basal cell carcinoma in immunosuppressed patients. However the limited number of skin cancer occurrences in this study limits the support of this conclusion in renal transplant recipients with MPM [9].

Survival of patients with MPM in the general population depends on the cancer type and stage at diagnosis, but also on comorbidities, behavioral and genetic factors. In renal transplant recipients, allograft dysfunction can cause lymphocyte attenuation and the immunosuppression may affect survival by altering the immune response. This along with immunosuppressive therapy can have direct oncogenic effects by inhibiting apoptosis, increasing the expression of transforming growth factor-beta (TGF-beta) and vascular endothelial growth factor (VEGF) (cyclosporine and tacrolimus), inducing DNA damage and negatively influencing DNA repair (azathioprine), or by promoting genetic mutations (polyclonal antibodies). On the contrary, it has been shown that some tumor types may regress with the use of mTOR inhibitors [13] and mycophenolate [14]. In our cohort, we did not find any difference between the type of immunosuppression and time-frame of cancer occurrence, or with survival. However, a significantly higher proportion of patients treated with cyclosporine or with azathioprine developed MPM than those who received tacrolimus, mycophenolate or everolimus. The small number of patients limits further statistical analysis to reveal the role of prolonged exposure to immunosuppression in general (which is present in patients who receive cyclosporine or/and azathioprine).

Renal transplant patients who are smokers, alcoholics, have a hereditary predisposition or with a primary malignancy before transplantation have an increased risk for the development of MPM. Additionally, the number of octogenarians receiving allografts is increasing. All these factors may contribute to the problem of MPM in the renal transplant population. As a preventive strategy, renal transplant recipients should be encouraged to stop the use of alcohol and tobacco, exercise regularly and adopt a healthy diet in order to regulate body weight. Regular dermatological examinations are mandatory. Studies have shown that the immunocompromised state of dialysis patients leads to a significant increase in malignancies due to uremic and dialysis prompted lymphocyte dysfunction, and several metabolic misbalances. However, there has not been a comprehensive study of MPM in this population [15].

There are some limitations of our study. During the observed period, the changing landscape of recipient demographics and comorbidities may influence our results. For

different reasons many patients have changed their initial immunosuppressive protocol during the post-transplant follow-up. The small number of patients on T cell depleting agents and with viral infections prevent an analysis about their possible roles in oncogenesis, which are well known drivers of post-transplant neoplasia [15].

Conclusion

Multiple primary malignancies were not uncommon in our cohort and occurred synchronously or metachronously. With regular follow-up of patients with a primary malignancy, most of the metachronous second primary malignancies could be detected at an earlier stage.

Acknowledgements

The authors contributed to this paper in the following: Nikolina Basic-Jukic: design, performed research, wrote the paper; Jason Kirincich: collected data, wrote the paper; Bojan Jelakovic: data analysis, final approval; Zeljko Kastelan: performed research, wrote the paper.

Disclosure Statement

We have no conflicts of interest.

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Ethics: The research paper was a retrospective cohort. According to this definition, research was performed by searching electronic medical records. There was no direct intervention on patients. Patients' identities were kept confidential. An ethical committee appointed by the hospital approved the research plan, which was developed and orchestrated by my mentor (and Head of Department) Professor Nikolina Basic-Jukic.