

Original Article

Frequency and spectrum of metachronous malignancies in heart transplant recipients: a 11-year-experience at a German heart center

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Received December 23, 2012; Accepted January 21, 2013; Epub February 15, 2013; Published March 1, 2013

Abstract: Background and aim: Heart transplantation (HTX) has become an established therapy for patients with end-stage heart failure. However, cancer incidence has been shown to be increased in the context of transplant-associated immunosuppression. The objective of this study is to analyze the incidence, histological spectrum, treatment and survival of various cancer types in HTX patients. Methods: We evaluated retrospectively all patients who underwent orthotopic HTX between 2000 and 2011 at our hospital including those patients who underwent HTX in other centers, but did their routine follow-up examinations at our department because of changing residence. Results: 142 patients had HTX performed at our center in the last 11 years and another 9 patients visited our department for monitoring after HTX performed at an external center (total: 151). Ten patients (6.6%) developed a metachronous malignancy (3 non-melanoma skin cancer, 2 lung cancer and 1 each parotid gland cancer, prostate cancer, renal cancer, urinary bladder cancer and ductal pancreatic cancer). The latency between HTX and the diagnosis of the secondary neoplasm ranged from 33 to 152 months (median 76 months; mean 88 months). In all cases, surgery with or without chemoradiation was the treatment for the metachronous cancer. While most cases followed a favorable course after appropriate surgical and/or oncological treatment, four tumors (1 salivary duct carcinoma, 1 urinary bladder carcinoma, 1 ductal pancreatic cancer and 1 skin cancer) revealed a remarkable aggressiveness with wide-spread metastatic disease at the time of diagnosis or shortly thereafter. Conclusions: Incidence of various cancer types among HTX patients in this survey was consistent with previous studies, with lung and skin cancer as the commonest malignancies encountered. Regular cancer screening may be of benefit in reducing morbidity and mortality in these patients.

Keywords: Heart transplantation, secondary malignancy, immunosuppression, lung cancer, skin cancer, parotid gland cancer, urinary tract cancer, pancreatic cancer

Introduction

Heart transplantation (HTX) has become the gold standard for patients of all ages with end-stage heart failure resistant to medical or conventional surgical therapy [1, 2]. While the advances in immunosuppressive therapies have led to a concomitant decrease in cardiac allograft rejection, one uncommon but serious complication is the occurrence of malignancy after transplantation [3, 4].

Development of metachronous neoplasms is a well recognized complication in solid organ transplant recipients. The incidence and types

of immune suppression-associated neoplasia in this cohort of transplant patients varies with the extent of follow-up [5, 6]. The aetiology of metachronous neoplasms in organ transplant recipients seems to be heterogeneous and still poorly understood. Viral agents are known to play a central part in some of these neoplasms. Well documented examples of virus-related metachronous neoplasms in organ transplant recipients include human herpes virus-8 (Kaposi sarcoma-associated Herpes virus) in the development of Kaposi sarcoma [7], human papilloma viruses (HPV) in several types of non-melanocytic skin cancer [8] and Epstein Barr virus (EBV) in post-transplant lymphoprolifera-

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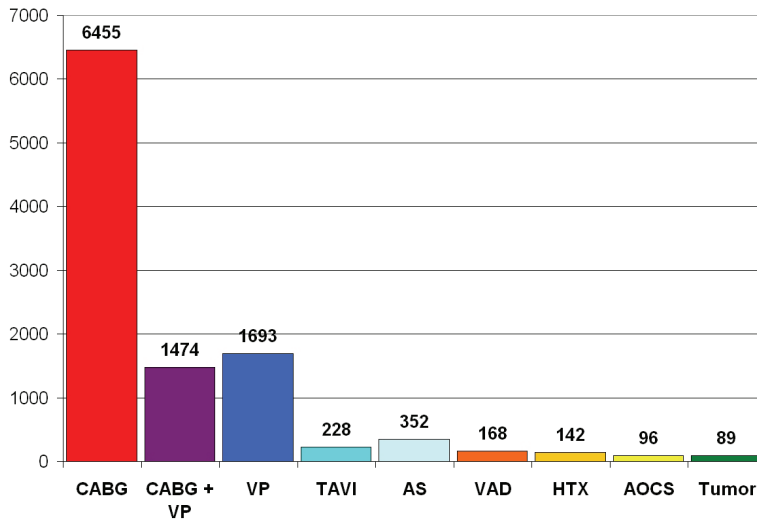


Figure 1. Cardiac Surgery at the University of Erlangen between 2000 and 2011. CABG = Coronary Artery Bypass Grafting; VP = Valve Procedures; TAVI = Transcatheter Aortic Valve Implantation; AS = Aortic Surgery; VAD = Ventricular Assist Device; HTX = Heart Transplantation; AOCS = Any Other Cardiac Surgery.

tive diseases (PTLD) [9] and EBV-associated smooth muscle neoplasms [10].

In the study by Collett et al who analyzed a total of 37617 organ transplant recipients at a large transplantation center [11], 15% developed cancer at a median follow-up of 16 years; non-melanoma skin cancer was most common type encountered (57%). Of the group who developed non-melanoma skin cancer, 13% were reported to have developed another de novo cancer other than skin cancer. In that study, the adjusted incidence of cancer among transplant recipients in England was more than double the incidence in the general population during the same period (90/1000 vs. 36/1000). The authors noted that the overall risk of cancer among transplant recipients is almost constant from two years after transplantation. Among the different cancer types listed, lung cancer and bladder cancer showed a significant increase among transplant recipients compared to the expected frequency in the general population. Thus close monitoring of organ transplant recipients to timely diagnose malignancies after transplantation is a major challenge for all medical professions of all disciplines involved in the management of affected patients.

The aim of this study was to analyze the frequency and spectrum of metachronous neoplasms in a cohort of heart transplant recipi-

ents treated and/or followed-up at our center during the last 11 years.

Patients and methods

All patients who underwent an HTX from 2000 to 2011 at the Center for Cardiac Surgery, University Hospital of Erlangen, Germany have been included in this retrospective analysis. These were 142 cases (1.3%) of all 10693 consecutive open heart procedures performed during the same period at our department (**Figure 1**). Additionally, we included 9 patients who underwent HTX in other hospitals, but visited our center for routine follow-up examinations because of changing residence.

The majority of our recovered patients were men ($n=125$; 82.8%) with a mean age of 53.2 ± 10.0 years (range 16.4 – 68.2 years) at the time of HTX. The mean age for the 26 females was 47.4 ± 17.4 years (range 3.7 – 69.1 years). Patients characteristic are summarized in **Table 1**. Mean serum creatinine of all transplant patients was 1.4 ± 0.7 mg/dl, mean ischemic time during transplantation was 176.3 ± 51.8 min. Mean donor age for all patients was 35.7 ± 11.4 years. Among donors there were 123 male (81.5% of total). For further statistical analysis, all 151 transplant patients were divided into two groups: patients without metachronous malignancies ($n=141$) and patients with post-transplant malignancies ($n=10$, **Table 1**).

HTX was performed in most of the cases due to dilated ($n=71$, 47.0%, DCM) and ischemic ($n=70$, 46.4%, ICM) cardiomyopathy. Further underlying causes for HTX were hypertrophic non-obstructive cardiomyopathy ($n=3$, HNOCM), aortic valve disease ($n=1$, AVD), congenital heart defect ($n=2$, CHD), non-compaction cardiomyopathy ($n=1$, NCCM), sarcoidosis ($n=1$), myocarditis ($n=1$), and sarcoma ($n=1$) (**Figure 2**).

Immunosuppressive regimen

Standard initial post-HTX regimen of immunosuppression included cyclosporine A (CsA), aza-

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Table 1. HTX-Patients Characteristics

Patient Characteristics	All Patients (n = 151)	Patients Without Malignancies (n = 141)	Patients With Malignancies (n = 10)
Recipient age (years±SD)	52.2±11.8	52.0±12.0	54.9±8.8
Recipient gender (n=male/% of subgroup)	125/82.8	115/81.5	10/100
No. of treated rejection episodes, grade 2R and 3R (n/% of all biopsies of subgroup)	162/8.5	149/8.6	13/7.8
Blood group (n=O/A/B/AB)	44/69/25/13	43/62/23/13	1/7/2/0
Ischemic time (min±SD)	176.3±51.8	176.8±52.1	168.3±48.5
Serum creatinine (mg/dl±SD)	1.4±0.7	1.4±0.7	1.9±0.9
Donor age (years±SD)	35.7±11.4	35.8±11.4	33.5±10.7
Donor Gender (n=male/% of subgroup)	123/81.5	117/83.0	8/80.0

Table 2. Clinicopathological features of cardiac transplant recipients who developed metachronous malignancies

Case	Age at HTX (years)/gender	Age at neoplasm (years)	Duration after HTX (months)	Site of neoplasm	Histological type	TNM stage	Outcome
1	47/M	60	152	Skin	SCC	pT1	22 months alive and well
2	66/M	68	33	Skin	SCC	pT1	60 months alive and well
3	56/M	62	74	Lung	SCC	G2, pT2 pN0(0/28), R0	37 months alive and well
4	57/M	64	77	Lung	SCC	G3, pT2, pN1, R0	Died after 8 months
5	39/M	51	143	Parotid	Salivary duct carcinoma	G3 pT3 pN2b(26/30), R0	Recent case, alive
6	65/M	69	47	Skin	SCC	G3 pN2b(14/23), R0	Recent case, alive
7	45/M	50	65	Urinary bladder	Urothelial carcinoma	G3 pT2a pM1, R1	Died after 16 months
8	61/M	72	129	Prostate	Acinar carcinoma (3+4)	Right lobe, Gleason-score 7	18 months alive and well
9	52/M	60	100	Right kidney	2 papillary carcinomas	G1, pT1a (m=2), R0	38 months alive and well
10	56/M	61	57	Pancreas	Mucinous ductal carcinoma	Miliary lung metastases	Died shortly after diagnosis

SCC = Squamous cell carcinoma; HTX = heart transplantation; M = male.

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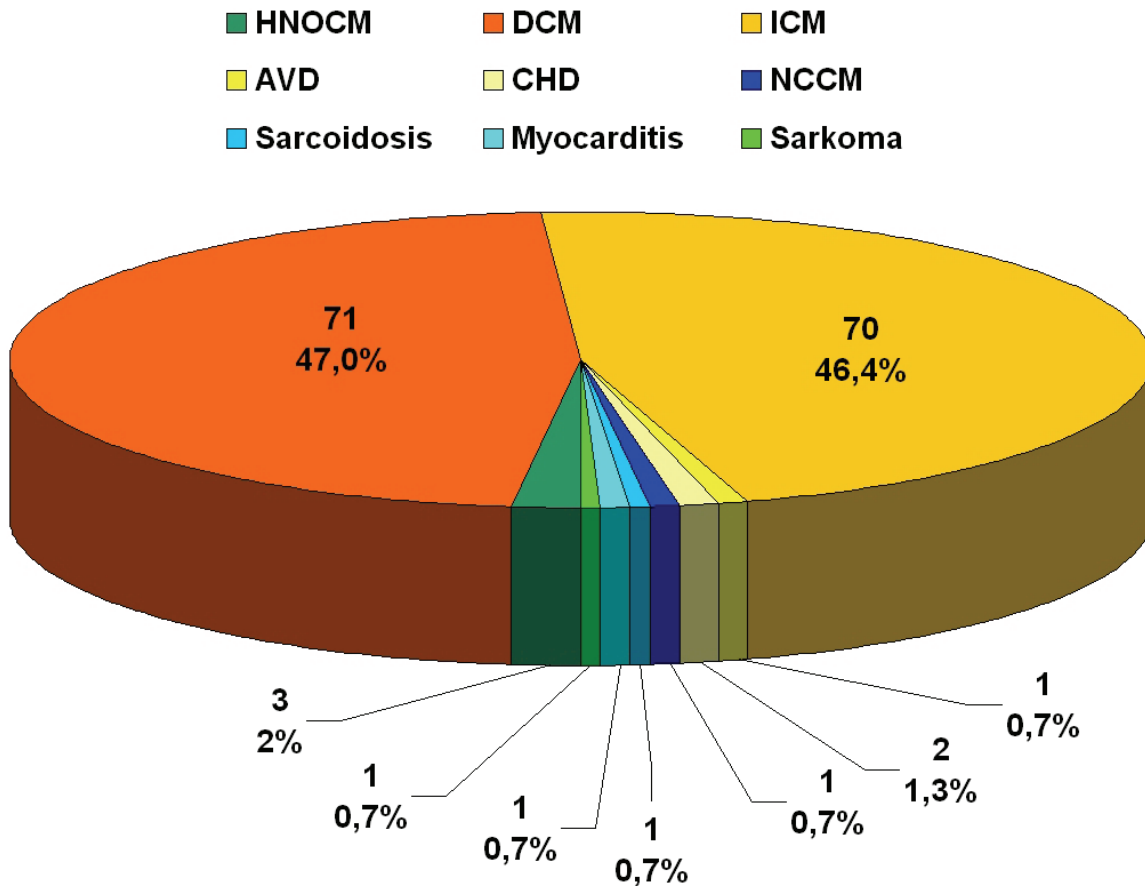


Figure 2. Distribution of underlying reasons for HTX. HNOCM = Hypertrophic Non-Obstructive Cardiomyopathy; DCM = Dilatative Cardiomyopathy; ICM = Ischemic Cardiomyopathy; AVD = Aortic Valve Disease; CHD = Congenital Heart Defect; NCCM = Non-Compaction Cardiomyopathy.

thioprine and steroids. In 2002/2003 this regimen was changed to CsA, mycophenolate mofetil (MMF) and steroids. If repeatedly severe allograft rejections appeared, CsA was substituted with tacrolimus. Mammalian target of rapamycin (mTOR) inhibitors (everolimus) were used since 2004/2005, either as calcineurin inhibitor (CNI)-free immunosuppression or combined with CNI after progressive renal insufficiency or repeated allograft rejection.

Concomitant oral prednisone was given 10 mg for the first three months, 7.5 mg for the next three months and 5 mg lifelong. In the first six months after HTX, CsA levels in combination with azathioprine or MMF were kept between 250-350 ng/ml. Thereafter CsA levels were sequentially reduced (200-250 ng/ml months 6-12, and 150-200 as of one year post transplantation. Azathioprine doses were adjusted on white blood cell count (total WBC ranging from 4000-10.000 cells/mm³). Tacrolimus lev-

els were maintained between 12-15 ng/ml within the first 6 months after HTX. Since the next six months, tacrolimus levels were kept between 10-12 ng/ml, followed by levels of 7-10 ng/ml as of one year post HTX. Everolimus was titrated to maintain a level between 4-7 ng/ml lifelong. In combination with everolimus, tacrolimus levels were a little bit lower (8-10 ng/ml in the first year, and thereafter between 6-8 ng/ml, everolimus levels were allays between 4-7 ng/ml). Particular notably, is the individual adjustment of medication for each HTX-Patient.

Follow-up

All transplant-patients were routinely followed up at the heart failure and transplantation ambulance, University Hospital Erlangen. After initial hospital stay for the transplantation, patients were seen on a routine surveillance protocol for endomyocardial biopsies (EMB) or

in cases with clinically suspected allograft dysfunction or rejection. The normal biopsy schedule was: weekly for the first month, every 2 weeks for the next month, once for the next 4 weeks, once for the next 6 weeks, then every 3 months for the next two years, and afterwards every 6 months for the next years. Allograft rejection was diagnosed according to the International Society for Heart and Lung Transplantation (ISHLT) guidelines [12, 13]. After all EMB procedures, a transthoracic echocardiogram (TTE), a conventional chest x-ray in two planes and a complete blood screening were performed. Additionally, all cardiac transplant recipients underwent right and left heart catheterization once every year after HTX. Tumor screening included a dermatological, urological, gynaecological, gastroenterological or any other medical examination whenever clinically indicated. From all 151 patients who underwent HTX in the last 11 years, a total follow-up of 607.8 patient years was created (mean 4.0 years). The follow-up varied from one day to 11 years. Two patients from this study have been published previously as case reports [14, 15] and were summarized in a recently published paper [16], respectively.

Results

General frequency of malignant neoplasms in HTX patients

Ten of the 151 patients (6.6%) developed a metachronous malignant neoplasm during the follow-up period (**Table 2**). The latency between HTX and the diagnosis of the secondary neoplasm ranged from 33 to 152 months (median 76 months; mean, 88 months). Taken by histological type, the mean time to diagnosis of the neoplasm was 77 and 109 months for squamous cell carcinoma (SCC) and the non-squamous neoplasms, respectively. Taken by site, SCC of the lung developed earlier than SCC of the skin (75.5 versus 92.5 months respectively). However, the frequency of neoplasms would be higher if recent cases with <2 years follow-up are excluded (10.6%) and would even rise to 21.2% if only patients who have reached the mean follow-up (91 months, i.e. 7.6 years) for those who developed malignancy were taken into consideration.

All of the 10 patients were males with a mean age at the time of HTX of 54.9 ± 8.8 years

(range 39.2 – 66.0 years). Their age at the time of diagnosis of the malignant neoplasm ranged from 51.1 – 72.6 years (mean 63.2 years) (**Table 2**). In comparison to patients without malignancies, patients with neoplasms were not significantly older at time of transplantation (52.0 years versus 54.9 years respectively, **Table 1**). However, the percentage of male recipients was significantly higher among patients with malignancies (n=10, 100% of subgroup) than in the group without neoplasms (115 men = 81.5% of subgroup). Concerning underlying reasons for HTX, five of the ten patients suffered from DCM and 5 from ICM, respectively.

Effects of immunosuppression

Interestingly, the number of treated rejection episodes, grade 2 and 3, scored by the International Society for Heart and Lung Transplantation (ISHLT) guidelines [12], and revised in 2005 [13], were not significantly different between patients with and those without metachronous malignancies (8.6% versus 7.8% respectively, **Table 1**). Repeated moderate or severe allograft rejection required modification of immunosuppressive therapy in 44 of the 151 cardiac transplant patients (29.1%), in the malignancy group, 4 of the 9 patients (44.4%) received a switch of immunosuppression protocol. Furthermore, no statistically significant correlation between development of metachronous malignancies and the use of different immunosuppressive drugs as cyclosporine A (CsA), azathioprine, mycophenolate mofetil (MMF), tacrolimus or mTOR inhibitor (everolimus) could be established during the follow-up period (data not shown).

The mortality rate after diagnosis of malignancy during follow-up was 33.3% (3 of 10 patients with malignancies). Clinicopathological features and outcome of these 10 cardiac transplant recipients who developed metachronous malignancies are summarized in **Table 2**. Additionally, no statistically significant correlation between diagnosis of malignancy and serum creatinine pre-HTX, ischemic time during HTX or donor age as well as donor gender was seen (**Table 1**).

Site distribution of the malignant neoplasms

Squamous cell carcinoma (SCC) of skin and lung: Distribution of malignant neoplasms is

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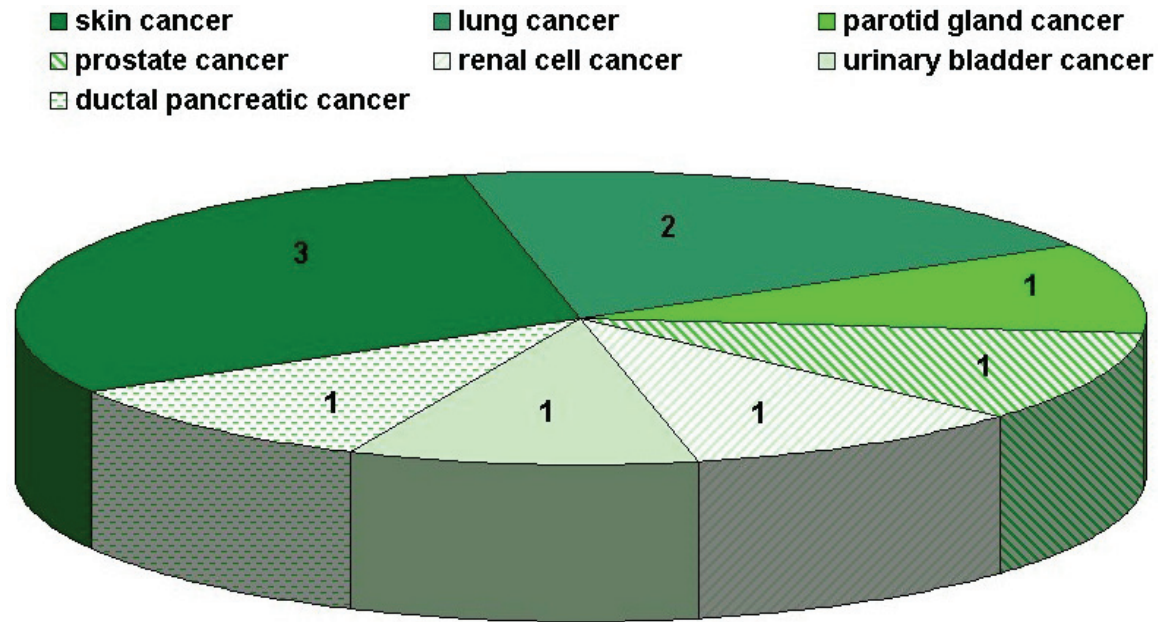


Figure 3. Distribution of second malignancies in heart transplant recipients.

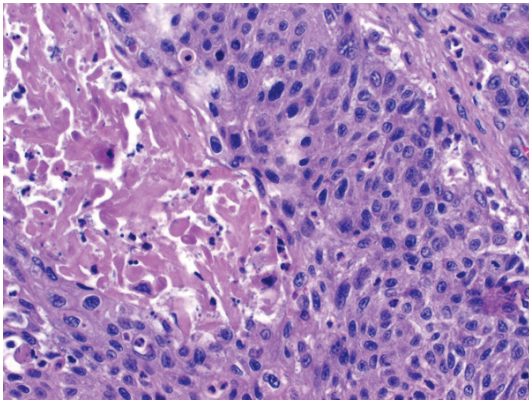


Figure 4. Example of keratinizing squamous cell carcinoma of the lung after HTX (original magnification x400).

summarized in **Figure 3**. There were 3 non-melanocytic skin cancers, 2 lung cancers, 1 parotid gland cancer, 1 prostate cancer, 1 renal cancer, 1 ductal pancreatic cancer and 1 urinary bladder cancer. Well differentiated SCC was diagnosed in the head and neck skin (eye, cheek and ear) in two patients. One patient had two distinct SCC of the skin and one Bowen disease. This patient developed extensive cervical lymph node metastasis and parotid gland metastasis 3 months after diagnosis of skin cancer. Two patients developed SCC of the lung; both had involved the right lower lobe of the lung (in addition to the right middle lobe in

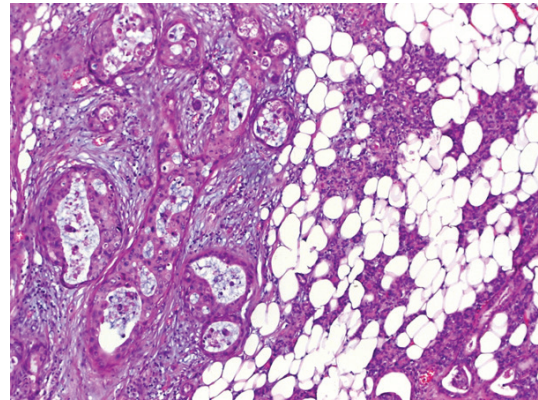


Figure 5. This highly infiltrative salivary duct carcinoma developed 10 years after HTX and showed advanced disease at the time of diagnosis (recent case). The tumors showed extensive intraductal spread (left) at the periphery of the salivary gland tissue (right).

one) (**Figure 4**). Lymph node involvement was seen in one of the two patients, but there was no histological or clinical evidence of increased tumor aggressiveness. One patient was alive 37 months after diagnosis of lung cancer, the other died 8 months later due to progressive cardiopulmonary failure.

Salivary gland cancer: One patient had poorly differentiated (high-grade) salivary duct carcinoma. The tumor in this patient (recent case)

showed extensive permeation of the lymphatics and venous channels in the soft tissue of the head and neck with more than 20 regional lymph node metastases (**Figure 5**). A few months later he developed liver metastasis and received radiation and chemotherapy. At last follow-up (currently), he is alive with disease under palliative treatment. As mentioned above, the parotid gland was also involved by metastatic disease from SCC of skin in another patient.

Other miscellaneous neoplasms: One patient developed acinar carcinoma of the prostate that was diagnosed by core needle biopsy because of elevated PSA (PSA: 15.8 ng/ml; Gleason score: 3+4=7) [17]. The tumor was limited to the right lobe of the gland. Another patient was diagnosed with high-grade widely invasive sarcomatoid transitional cell carcinoma of the urinary bladder, shortly followed by metastatic disease (**Figure 6**). Another patient who developed end-stage vascular renal disease that necessitated renal transplantation was diagnosed with two small well differentiated papillary renal cell carcinomas contained within the explanted right kidney. The last patient developed a widely metastatic pancreatic ductal adenocarcinoma that presented with miliary bilateral pulmonary metastasis. This patient was a recent case diagnosed during preparation of this manuscript. He died short after diagnosis due to cancer-related progressive cardiopulmonary failure.

Discussion

In this study, we have analyzed the frequency, histological spectrum, treatment and outcome of metachronous malignant neoplasms in patients with a history of HTX. We found 10 patients (6.6%) with a malignant neoplasm that developed after HTX. This rate of metachronous malignancies in cardiac transplant recipients is consistent with previously published series with a range of 4.1% to 46.1% up to 15 years after HTX [18-21]. However, it is well recognized that the incidence and types of immune suppression-associated neoplasia usually vary with the extent and completeness of follow-up. Our patients had a mean follow-up period of 4 years. The metachronous malignancy developed at a range of 33 to 152 months (median, 76; mean, 88 months). However, the frequency of neoplasms would be higher if recent cases

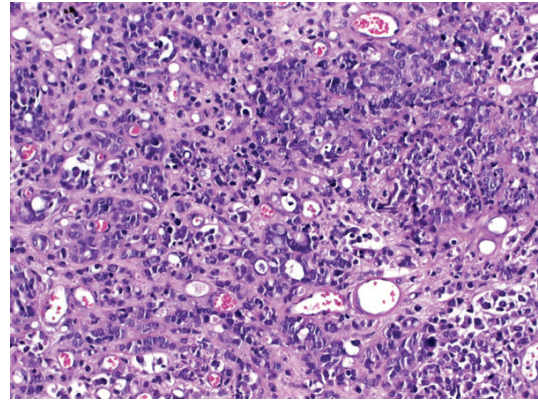


Figure 6. This poorly differentiated aggressive transitional cell carcinoma of the urinary bladder developed 65 months after HTX and lead to rapid death of the patient 16 months after cancer diagnosis.

with < 2 years follow-up are excluded (10.6%) and would even rise to 21.2% if only those who reached the mean follow-up for metachronous cancer were considered. In the study by Collett et al, 15% of solid organ transplant recipients developed cancer at a median follow-up of 16 years. The authors noted that the overall risk of cancer among transplant recipients is almost constant from two years after transplantation. However, 13% of those who initially developed a skin cancer suffered later from another non-cutaneous malignancy.

Similar to our series, the histological types of metachronous malignant neoplasms in organ transplant recipients in previous studies seem quite heterogeneous. However, it is remarkable that among the different cancer types encountered in previous studies, lung cancer and bladder cancer showed a significant increase among transplant recipients compared to the expected frequency in the general population [11]. Our results are consistent with these observations with bladder cancer and lung cancer being overrepresented in the same range as skin cancer (2 cases each). The etiology of these different cancer types at different locations is unclear. It is possible that specific oncogenic HPV strains may play a role in SCC of skin and lung in our cases but unfortunately no data were available on the HPV status in these patients. The patient with 2 small papillary renal cell carcinomas has end-stage renal disease, a condition known to be frequently complicated by renal epithelial neoplasms, particularly papillary carcinoma [22]. Thus, it is likely

that this patient had incidental papillary renal carcinoma associated with his end-stage renal disease but unrelated to his immunosuppression.

Three neoplasms in our cases showed remarkable tumor aggressiveness with wide-spread metastasis and/or extensive permeation of lymphatic and blood vessels. Although both neoplasms were of histological types well known to display a highly aggressive clinical course, it is not completely excluded that the long-term immunosuppression might have influenced the tumor behaviour. Remarkably, all three neoplasms have developed after more than 5 years from HTX. Of note, two of these neoplasms were histogenetically related; both were ductal adenocarcinoma of salivary-type tissue (parotid gland and pancreas). Both developed more than 10 years after immunosuppression and presented initially with extensive local or widely metastatic disease. These features in both cases suggest a possible common pathogenesis and enhanced aggressiveness but this remains currently unclear. The remaining patients did not follow an aggressive course and both have survived well after appropriate surgical and/or oncological treatment.

Of note, we did not observe a higher frequency of non-melanocytic skin cancer (SCC and Bowen disease) in our cases, thus contrasting with some previous studies [4, 6]. This may be due to limited extent of follow-up after HTX in some of our patients, variation in regimens used for immunosuppression by different centers, age of the cohort analyzed in different studies, presence or absence of additional risk factors predisposing to skin cancer (actinic skin damage, HPV infection, etc.), missing diagnoses of skin lesions treated at external hospital and denied by the patients or various combinations of the above. Likewise, post-transplant lymphoproliferative disorder (PTLD) has not been recorded in our cases. This might be due to the rarity of early-onset PTLD as most cases developed after long-term immunosuppressive therapy at a mean of 128 months [9]. Interestingly, the incidence of different types of metachronous malignant neoplasms varied with the organ transplanted [11]. Moreover, further prospective clinical studies are presently underway to test the concept that different immunosuppressive drugs reduce cancer while

simultaneously inhibiting allograft rejection [23, 24].

In summary, we reported our experience with metachronous malignancies in HTX patients, illustrating the histological heterogeneity of recorded neoplasms, variation of anatomic sites affected and the increasing frequency with the extent of follow-up after HTX. Overrepresentation of some organ systems (urinary tract, lung and salivary glands) in our study and some previous reports underlines the possibility of and the need for establishing a screening program for early detection of these aggressive malignancies in HTX patients.

The unusually aggressive course of some of these neoplasms underscores the need for studying their biological distinctness from their sporadic counterparts in non-transplant patients to allow for conceptualizing more appropriate therapeutic regimens for them.

Acknowledgement

We thank all colleagues at our heart failure and transplantation ambulance, University Hospital Erlangen, for their untiring assistance and supervision of all heart transplant recipients.

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