

# Significantly higher incidence of skin cancer than other malignancies in patients after heart transplantation. A retrospective cohort study in the Czech Republic

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**Aims.** To perform the first study in Czech Republic on heart transplant recipients (HTRs), compare the risks for different types of cancer and provide comprehensive analysis of skin cancer and other types of cancer morbidity from which we would be able to derive an evidence-based skin cancer surveillance program.

**Materials and Methods.** A retrospective cohort study was performed to determine and compare standardized morbidity ratio (SMR) of different types of cancer developed after heart transplantation. We analysed data obtained from medical documentation of 603 HTRs transplanted between 1993 and 2010.

**Results.** 191 incident cases of malignancy occurred in 123 HTRs (20.4%). According to expectations, nonmelanoma skin cancer was the most frequent type of malignancy (119 cases) with SMR 7.6 ( $P < 0.001$ ), followed by lung cancer with SMR 2.7 ( $P < 0.001$ ). SMR for melanoma was 2.5,  $P = 0.129$ . Other types of cancer in HTRs (prostate and kidney cancer) were less frequent (SMR 2.06,  $P = 0.038$  and SMR 2.03,  $P = 0.122$ ).

**Conclusion.** The risk of malignancy development is significantly higher for HTRs compared to the general population. Squamous cell carcinoma of the skin is the most frequent type of cancer followed by basal cell carcinoma. These findings emphasise the importance of regular skin cancer screening in HTRs.

**Key words:** heart transplantation, skin cancer, immunosuppression

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## INTRODUCTION

Organ transplant recipients are at increased risk of developing malignancies compared to the general population. The risk ranges from 4% to 18% and is estimated to be more than 100 times higher than the general population<sup>1,2</sup>. According to current data, skin cancer is the most frequent malignancy among HTRs. A number of studies have also reported a higher incidence of other cancers, such as lymphoproliferative diseases, lung cancer or uterine and cervical dysplasia<sup>3,4</sup>. This study analyses the data of post-transplant malignancies among HTRs in the Czech Republic. The incidence, spectrum, risk factors and clinical impact of post transplant malignancy were investigated retrospectively in a cohort of 603 heart transplant recipients.

## MATERIALS AND METHODS

Patients who had undergone heart transplantation (HT) in the Transplant Centre at the Institute for Clinical and Experimental Medicine in Prague from 1993 - 2010 were included. Those with a history of cancer before HT and those who developed cancer within the first year after

transplantation were excluded. The study was approved by the Ethics Committee of the Institute for Clinical and Experimental Medicine.

The majority of patients were men ( $n = 493$ ; 81.8%), mean age 49.08 years ( $\pm 11.61$  years) at the time of HT. The mean age for women ( $n = 110$ , 18.1%) was 48.15 ( $\pm 13.19$  years). Besides survivors, the study included 217 (35.8%) deceased patients. HT was performed due to dilated cardiomyopathy, ischemic cardiac disease, valve disease, rheumatic fever and restrictive cardiomyopathy (Table 1). Three patients had to undergo heart re-transplantation, 18 patients after HT underwent further kidney transplantation and 2 patients underwent lung transplantation.

### Immunosuppressive regimen

The standard initial post-transplant regimen of immunosuppressives consisted of steroids, calcineurine inhibitors (cyclosporine A or tacrolimus) and antimetabolites (mycophenolatemophetil or azathioprine). Since 2006, the percentage treated with tacrolimus has gradually increased compared to cyclosporine. Mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus) have been used in the medication of HTRs since 2004/2005. 55 patients had mTOR inhibitors as part of

**Table 1.** Distribution of heart transplant recipients according to cause of transplantation.

Cause of HT	Absolute count	%
Cardiomyopathy	337	55.9%
Coronary artery disease	223	36.9%
Valve disease	22	3.6%
Retransplantation	3	0.49%
Other	18	2.9%

their immunosuppressive regimen in our cohort. Overall in 11, treatment was initiated after the formation of skin cancer. The majority of HTRs in the cohort received a combination of immunosuppressive therapy which consisted of cyclosporine A, mycophenolatemophetil and corticosteroids (CS) (Table 2).

### Data processing and analysis

Data were obtained from medical records and included gender, age at the time of HT, cause of HT, immunosuppressive regimen, rejection, type of cancer, age at the time of cancer diagnosis and cause of death.

Only cancer cases and carcinomas *in situ* with histopathological verification were included. The length of the follow up period was determined as the time from the date of the first transplantation to the last examination, cancer detection or death. If malignancy was detected, the date of diagnosis and type of cancer were recorded.

The results were compared with an external control group represented by the general Czech population using data from the National Registry for Oncologic Diseases. Age, sex and calendar year were used to define the adjusted estimate of standardized morbidity ratio (SMR) with 95% confidence intervals computed.

## RESULTS

We investigated 686 patients who underwent transplantation in 1993–2010. A total of 83 patients were excluded from further analysis due to a diagnosis of cancer before HT or within the first year after HT, resulting in a final count of 603 patients (493 men and 110 women).

**Table 2.** Distribution of immunosuppressive regimen in heart transplant recipients.

Most frequent IS regimens	Therapeutic combination	n (%)
Group 1	Cyclosporine A + mycophenolatemophetil + CS	29.02
Group 2	Tacrolimus + mycophenolatemophetil + CS	27.52
Group 3	Cyclosporine A + azathioprine + CS	15.7

191 incident cases of malignancy occurred in 123 patients (20.4%). The median follow up was 6.4 years.

### Skin cancer

Skin cancer was the most frequent type of malignancy (119 cases). The median time to develop non-melanoma skin malignancy was generally 10 years. Squamous cell carcinoma (SCC) represented the most frequent type of skin malignancy (n = 62, 52.1%) followed by basal cell carcinoma (BCC) (n = 37, 31.1%). Other types of skin cancer, localisation and median time to diagnosis are shown in Table 3. The most frequent localisation of skin tumours were in the head and neck (72.53%). Multiple skin cancer developed in 29 patients, while 20 patients suffered from more than 3 tumours. An SMR for developing skin cancer was estimated to be 7.6 ( $P < 0.001$ ; 95%CI = 5.94–9.59). Melanoma occurred in three patients, giving an SMR of 2.5 ( $P = 0.129$ ) confirming no significantly increased incidence in comparison with the general population.

### Solid organ tumours and post-transplant lymphoproliferative disease (PTLD)

Lung neoplasms (n = 22) were the most frequent type of cancer after non-melanoma skin cancer (NMSC). Adjusted relative risk for lung cancer was counted (SMR = 2.79, 95% CI 1.80 – 4.15;  $P = 0.1$ ). 13 patients in our cohort developed PTLN (12 men, 1 woman), including non-Hodgkin's lymphomas as well as Hodgkin's lymphoma and MGUS. The mean time to reach the diagnosis was 8 years, median survival time was 3 years. Other types of cancer detected in our study, median times to diagnosis and SMRs are shown in Table 4.

**Table 3.** Overview of skin cancer according to frequency, median time to diagnosis and localisation.

	Absolute count	Median time to diagnosis (years)	Localisation				
			Head and neck	Upper limbs	Lower limbs	Trunk	Genitalia
BCC	37	12	21	3	2	9	-
AK	11	12	8	2	-	1	-
m.Bowen	4	6	2	-	-	2	-
SCC	62	11	44	5	2	7	2
MCC	1	5	-	1	-	-	-
KA	2	12	2	-	-	-	-
Melanoma	3	5	1	-	-	2	-

**Table 4.** Overview of other types of cancer (except for NMSC) imaging absolute count, median time to diagnosis, median survival time and standardized morbidity ratios.

Type of cancer	Men (%)	Women (%)	Median time to diagnosis (years)	Alive	Deceased	Median survival (years)	SMR (95%CI)	P value
Melanoma	2 (0.4)	1 (0.9)	5	1	2	2	2.5 (0.70 - 6.73)	0.129
Lung	19 (3.8)	3 (2.72)	5.4	6	16	2	2.79 (1.80 - 4.15)	< 0.1
Prostate	10 (2.02)	-	5.5	7	3	2	2.03 (1.05 - 3.62)	< 0.1
Kidney	4 (0.81)	1 (0.9)	2.5	4	1	3	2.06 (0.78 - 4.53)	0.122
Gastrointestinal	14 (2.8)	-	6	6	8	3	-	
PTLD	12 (2.43)	1 (0.9)	8	7	6	3	-	

## DISCUSSION

Most of the available data show elevated risk of malignancy in organ transplant recipients<sup>5,6</sup>. In our study, we analysed the demographic characteristics, frequency and histopathological spectrum of tumours in 603 patients after HT. Our results confirmed that NMSC is the most frequent cancer in post-transplant period, followed by lung cancer and PTLD. In addition, a reversed SCC/BCC ratio (1.6:1) was observed in HTRs compared to the general population. Although it is thought that SCC in HTRs grows more aggressively, we recorded no patient with metastases of SCC. However, recurrence of NMSC should be considered as a serious complication (29 of 70 NMSC patients, 41.4%). Compared to other studies carried out recently, we noticed similar results in the case of risk for the development of NMSC. Jensen et al. reported an SIR of 5.6 for BCC and 113 for SCC (ref.<sup>7</sup>). In our study it was not possible to calculate adjusted risk for different types of NMSC, as data in the external group do not specify the exact type of NMSC. The relatively low incidence of skin cancer in a cohort of HTRs was recorded by Rinaldi et al. or Park et al. in a single centre in Korea<sup>8,9</sup>. Unlike most studies reported, the authors found significantly higher incidence of lung cancer (39%) and non-Hodgkin lymphomas (20%). However, the Korean authors found skin cancer in only 9% (ref.<sup>9</sup>) of HTRs.

In contrast to the report by Lanza et al. from South Africa, where 33% of skin cancer developed were Kaposi's sarcomas<sup>10</sup>, we did not observe a single case. This phenomenon can be probably attributed to different epidemiologic conditions. Moreover, the prevalence of Kaposi's sarcoma after organ transplantation varies greatly according to the prevalence of HHV-8 infection in the population<sup>11</sup>. Early detection and adequate therapy is also recommended for keratoacanthoma (2 cases in our study). Keratoacanthoma may not be clearly distinguishable from SCC histologically and in organ transplant recipients should be considered as SCC (ref.<sup>12</sup>). The incidence of melanoma in transplant recipients remains a matter of discussion. Some authors deny any increase in the incidence compared to the general population<sup>13</sup>, whereas others reported up to 8-fold increase<sup>14</sup>. According to our results, we were not able to confirm a significantly higher incidence of melanoma in HTRs.

Similar to our study, Sobieszanska-Malek et al. also demonstrated a higher incidence of lung tumours in

HTRs, even exceeding the incidence of NMSC. The high incidence rate of pulmonary cancer in the analysed group was related to smoking before transplantation. In our cohort it was not possible to assess its association due to incomplete data. Similarly, higher incidence of PTLD has been observed in some recent studies<sup>5,6</sup>. There are still only a few data in the literature evaluating other types of malignancies in HTRs.

One of the primary goals of our study was to define surveillance intervals that would allow follow up of at-risk individuals. The purpose of this post-transplant surveillance is to manage preventive strategies focusing on NMSC, although further examination is presumably required. Several studies recommend stratifying patients according to the measure of risk for developing NMSC considering skin phototype, history of NMSC, family history and other relevant risk factors. Regular skin examination by a dermatologist is recommended once a year. In patients with *in situ* carcinoma (AK, Bowen's disease) a follow up in 6 month interval is advised. Due to lack of education among patients after HT in the Czech Republic we prefer regular examination by dermatologist every 6 months with the aim of early detection of skin cancer. In case of NMSC in history, even shorter intervals (3-6 months) appear to be advisable. We emphasize the need and importance of education on the benefits of UV protection, periodic self-skin examination and regular follow up. Furthermore, post-transplant management in HTRs requires an interdisciplinary collaboration with a view to early diagnosis of malignancies and their adequate treatment. Conclusions drawn from our study should not be regarded as definitive and further detailed investigation of cancer complications in HTRs appears to be necessary.

## ABBREVIATIONS

AK, Actinic keratosis; BCC, Basal cell carcinoma; HHV8, Human herpes virus 8; HT, Heart transplantation; HTRs, Heart transplant recipients; KA, Keratoacanthoma; MB, Morbus Bowen; MCC, Merkel cell carcinoma; MGUS, Monoclonal gammopathy of undetermined significance; mTOR, Mammalian target of rapamycin; NMSC, Nonmelanoma skin cancer; PTLD, Post transplant lymphoproliferative disorders; SCC, Squamous cell carcinoma; SIR, Standardized incidence ratio; SMR, Standardized morbidity ratio

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