



# HEAD AND NECK MALIGNANCIES IN CROATIAN RENAL TRANSPLANT RECIPIENTS

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## ABSTRACT

Renal transplantation is associated with increased incidence of cancer. We reviewed a large series of renal transplant recipients to determine the incidence and outcome of patients with malignant changes located at the head and neck. A total of 1232 renal transplant recipients have been followed at Department of Dialysis University Hospital Centre Zagreb from 1972 to 2009. Demographic data, localization and disease outcome were evaluated in patients who developed cancer. Twenty one patients (1,7%) developed 27 head and neck malignancies. The average time from transplantation to development of cancer was 56,8 months. The mean length of follow-up was 9,4±4,8 years. Eighteen malignancies were cutaneous in origin and 9 were noncutaneous. Of cutaneous malignancies, 88,9% were basal cell carcinoma; one patient had Merckell-cell carcinoma and one patient developed squamous cell carcinoma. Six cases of basocellular skin cancer were recorded in one fair-skin patient. Noncutaneous malignancies involved the oral cavity (2 cases of Kaposi's sarcoma and one pharyngeal cancer) and the thyroid gland in 3 patients each. Two patients had post-transplant lymphoproliferative disorder occurring at the head and neck. One patient had brain tumor. Radical surgery, radiation, and/or chemotherapy were necessary in 33,3% of patients. Immunosuppression was reduced in all patients, and 12 patients were switched from the calcineurin-based immunosuppression to sirolimus. They all have stable graft function. None of the patients died from cancer. Immunosuppression was ceased in one patient with Kaposi's sarcoma who returned to dialysis and died 10 years later from heart failure. An increased incidence of cancer occurring in the head and neck was recorded. Careful skin examination and oral examination is mandatory for discovering cancer before dissemination. Sirolimus is safe alternative to calcineurin-based immunosuppression in patients who developed head and neck malignancies.

KEY WORDS: renal transplantation, malignancy, head, neck

## INTRODUCTION

Kidney transplantation is the method of choice for treatment of patients with the end-stage renal disease (ESRD). However, prolonged immunosuppression is associated with increased incidence of malignant diseases (1). Malignancies of the head and neck may occur in kidney transplant recipients, or they may develop de novo (2). Tumors occur more often and behave clinically more aggressive in renal transplant recipients than in the general population (3). The overall incidence of different malignancies in this population ranges from 6 to 11 % (4).

Few studies have reported on the rate of head and neck malignancies in renal transplant population. In the present study we examined prevalence, clinical characteristics and outcome of head and neck malignancies occurring in renal transplant recipients in Croatia.

## MATERIALS AND METHODS

All patients who receive renal allograft at University Hospital Centre Zagreb, or were followed-up in our institution after renal transplantation in other transplant centers were included in investigation. Patients' charts and data records were evaluated to find out cases with malignancies localized at neck or head.

## RESULTS

A total of 1232 renal transplant recipients have been followed at Department of Dialysis University Hospital Centre Zagreb from 1972. to December 2008. The mean length of follow-up was  $9,4 \pm 4,8$  years. During the observed period, 21 patients (1,7%) developed 27 head and neck malignancies. The average time from transplantation to development of cancer was 56,8 months (range, 8-156 months). Eighteen malignancies were cutaneous in origin and 9 were noncutaneous.

### *Cutaneous malignancies*

Of cutaneous malignancies, 88,9% were basal cell carcinoma; one patient had Merkel-cell carcinoma and one patient developed squamous cell carcinoma. Six cases of basocellular skin cancer were recorded in one fair-skin patient. Patient with Merkel cell carcinoma had been operated, underwent irradiation and was switched to sirolimus. His graft function gradually worsened, and he is currently in the preterminal stage of renal allograft failure.

### *Noncutaneous malignancies*

Noncutaneous malignancies involved the oral cavity (2 cases of Kaposi's sarcoma and one pharyngeal cancer) and the thyroid gland in 3 patients each. Thyroid cancers were all papillary carcinomas incidentally found during regular parathyroid glands examination. Two patients had post-transplant lymphoproliferative disorder (PTLD) occurring at the head and neck. One case of rare T-cell lymphoma arose at the forehead. One patient had brain tumor. It was meningioma.

### *Treatment and outcome*

Radical surgery, radiation, and/or chemotherapy were necessary in 33,3% of patients. Immunosuppression was reduced in all patients, and 12 patients were switched from the calcineurin-based immunosuppression to sirolimus. They all have stable graft function. None of the patients died from cancer. Immunosuppression was ceased in one patient with Kaposi's sarcoma (KS) who returned to dialysis and died 10 years later from heart failure. Patients with PTLD received chemotherapy. Patients with thyroid cancer underwent total thyroidectomy followed by radioiodine ablation and thyroid hormones substitution.

## DISCUSSION

Increased cancer incidence after organ transplantation is well documented but few studies have reported on the rate of head and neck malignancies among these patients. In the present study we evaluated malignancies occurring in the area of head and neck in Croatian renal transplant recipients. Post-transplantation KS is a well-known complication after renal transplantation with a possible negative impact on the patient's and graft long-term survival. According to the Cincinnati Transplant Tumor Registry (CTTR), KS accounts for 5,7% of all neoplasms arising after renal transplantation (4). Finnish data from the National Kidney Transplant Registry found 113 non-lymphomatous head and neck malignancies among 2884 kidney transplant patients. The standardized incidence ratio (SIR), as compared with the general population, was 13,6, with a 95% confidence interval (CI) of 11,2-16,2. The SIR was significantly elevated for cancers of the skin (47,3; 95% CI 36,3-60,7), lip (31,8, 95% CI 20,8-46,6), oral cavity (6,5, 95% CI 2,4-14,0) and thyroid (5,8, 95% CI 3,0-10,2) (5). Skin cancer is the most common malignancy encountered in the transplant population, especially

in areas of high sun exposure, where as many as 80% of patients may be affected. Neoplastic disorders in this patient population tends to present at a younger age compared with the general population, with a more aggressive course and less favourable.

Merkel cell carcinoma (MCC) is a rare aggressive skin cancer originally described in 1972 as the trabecular cell carcinoma (6,7). There are less than 50 cases of MCC reported after renal transplantation. Optimal therapeutic approach has still not been determined. Its highly aggressive behaviour demands radical therapeutic approach that should be determined by the clinical stage at presentation. Wide local excision of the lesion with the 2-cm margin should be performed in suspected cases. Local irradiation is recommended to decrease the rate of recurrence, while the tumour is

considered to be radiosensitive. In general, the radiation fractionation schemes were 45 to 50 Gy in 10 to 25 fractions over 2 to 5 weeks, depending on the size of affected area. Positive lymph node scintigraphy demands nodal dissection accompanied by local irradiation. It is a difficult task to treat patients with post-transplant malignancy. The risk of death from dissemination of malignancy should be weighed against the risk of graft rejection. Reduction of immunosuppression may be sufficient to treat less aggressive malignancies. Sirolimus and everolimus may become the first choice immunosuppressant drugs in renal transplant recipients with malignancy especially in patients with Kaposi's sarcoma while they provide optimal immunosuppression and may inhibit the progression of malignancy (8,9). It still remains to be determined which malignancies are sensitive to action of mTOR inhibitors.

## CONCLUSION

An increased incidence of cancer occurring in the head and neck was recorded. Careful skin examination and oral examination is mandatory for discovering cancer before dissemination. Sirolimus is safe alternative to calcineurin-based immunosuppression in patients who developed head and neck malignancies.

### List of Abbreviations

ESRD - end stage renal disease  
 CTTR - Cincinnati Transplant Tumor Registry  
 PTLD - post-transplant lymphoproliferative disorder  
 SIR - standardized incidence ratio  
 MCC - Merkel cell carcinoma  
 KS - Kaposi's sarcoma

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