







# Late malignant oral lesions after kidney transplantation

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## ABSTRACT

**Objective:** To review cases of oral cavity malignancies available in the literature in kidney transplant recipients. **Methods:** A search was carried out in the PubMed database using the terms “oral cancer,” “mouth neoplasms,” “renal transplantation,” and “kidney transplantation.” Regardless of the publication date, the publications were chosen by two researchers after they carefully considered the titles and abstracts and read each article in its entirety. **Results:** Twelve articles were found with cases of oral malignancies in kidney transplant recipients. In all, 31 malignant neoplasms were diagnosed in the oral cavity, of which 64.5% (20/31) were squamous cell carcinomas; Kaposi’s sarcoma represented 12.9% (4/31) of the cases. Lips and tongue were the most affected sites mentioned most frequently in the articles evaluated. Post-transplantation time ranged from 8 months to 23 years, and several immunosuppressants were used. **Conclusions:** Kidney transplant recipients should be regularly forwarded to dentists and other medical professionals who work in diagnosing malignant lesions of the oral cavity to be evaluated, and new cases of oral cancer can be recognized early to treatment. This strategy could improve the survival of patients with this threatening disease.

**Descriptors:** Mouth Neoplasms. Kidney Transplantation. Oral Diagnosis.

## *Lesões orais malignas tardias após transplante renal*

## RESUMO

**Objetivo:** Revisar casos de malignidades da cavidade oral disponíveis na literatura em receptores de transplantes renais. **Métodos:** Foi realizada uma pesquisa no banco de dados PubMed usando os termos “oral cancer”, “mouth neoplasms”, “renal transplantation” e “kidney transplantation”. Independentemente da data de publicação, as publicações foram escolhidas por dois pesquisadores após considerarem cuidadosamente os títulos e resumos e lerem cada artigo em sua totalidade. **Resultados:** Foram encontrados 12 artigos com casos de malignidades orais em receptores de transplantes renais. No total, 31 neoplasias malignas foram diagnosticadas na cavidade oral, das quais 64,5% (20/31) eram carcinomas espinocelulares; o sarcoma de Kaposi representou 12,9% (4/31) dos casos. Lábios e língua foram os artigos avaliados mais frequentemente mencionados como locais afetados. O tempo pós-transplante variou de 8 meses a 23 anos, e vários imunossuppressores foram utilizados. **Conclusões:** Os receptores de transplante renal devem ser encaminhados regularmente a dentistas e outros profissionais médicos que trabalham no diagnóstico de lesões malignas da cavidade oral a serem avaliadas, e novos casos de câncer oral são reconhecidos precocemente para tratamento. Esta estratégia poderia melhorar a sobrevivência dos pacientes com esta doença ameaçadora.

**Descritores:** Neoplasias Bucais. Transplante de Rim. Diagnóstico Bucal.

## INTRODUCTION

Renal transplantation has evolved as the best treatment option for patients with end-stage renal disease. In recent decades, significant progress has been achieved in graft and patient survival after renal transplantation. That progress was attributed to improved surgical and tissue matching techniques, advances in antirejection drug therapy, better pretransplantation cross-matching techniques, and viral infection prophylaxis, monitoring, and treatment. Post-transplantation medical management of chronic cardiovascular disease and other comorbidities also improves survival.<sup>1,2</sup> Kidney transplantations are seen to be a double-edged sword; transplantations help to restore renal function. However, it has been associated with some severe complications, including malignancy, second or third cause of death which during the first year after transplantation, became the first cause of death following the transplantation.<sup>2-4</sup>

Several reports<sup>3-8</sup> indicate that cancer incidence in patients who have undergone renal transplantation is much higher than in the normal population and hemodialyzed patients. The frequency of malignant lesions in renal transplant patients is between 14 and 500 times higher than in the general population; the incidence rises each year after transplantation. The cancer incidence ratio is different according to cancer type and population ethnicity.<sup>3-5</sup> The mortality of malignancies in renal transplant patients is at least twofold to fourfold greater than that of age and gender-matched individuals from the general population.<sup>6-8</sup>

The literature presents few studies on malignancies in the oral cavity,<sup>14,18</sup> most being case reports.<sup>5,7,11-13,15-17</sup> This paper aims to review cases of oral cavity malignancies available in the literature in kidney transplant recipients.

## METHODS

Using the Boolean operators AND and OR, a search was carried out in the PubMed database using the terms “oral cancer,” “mouth neoplasms,” “renal transplantation,” and “kidney transplantation.” Regardless of the publication date, the publications were chosen by two researchers after they carefully considered the titles and abstracts and read each item in its entirety. Only those publications that were published in English and matched the search criteria for the descriptors—malignant lesion diagnosis, patient age and gender, kidney transplantation confirmation, including post-transplantation duration, and immunosuppressive medication used—were included.

## RESULTS

Twelve articles were found with cases of oral malignancies in kidney transplant recipients. In all, 31 malignant neoplasms were diagnosed in the oral cavity, of which 64.5% (20/31) were squamous cell carcinomas; Kaposi's sarcoma represented 12.9% (4/31) of the cases. In most cases, 77.4% (24/31), were male, with age mean of 48.77 years (minimum 9 years old; maximum 71 years old). Lips and tongue were the evaluated articles most frequently mentioned affected sites. Post-transplantation time ranged from 8 months to 23 years, and several immunosuppressants were used. Cyclosporine was especially identified in almost all regimens. Follow-up time ranged from 3 weeks to 5 years. Of the 20 cases with outcome information, 20% (4/20) died (Table 1).

**Table 1.** Case description of oral malignant neoplasms of renal transplant recipients.

Author and country	Sex/age	Malignant lesion	Region of the mouth	Clinical features	Post-transplant time (Immunosuppression drugs)	Follow-up time (Outcome)
Howard III et al. (2020) <sup>9</sup> USA	Male: 44 years old	Kaposi's sarcoma	Several sites: anterior maxillary gingiva, right retromolar trigone and bilateral tonsils	Asymmetric bilateral tonsillar hypertrophy with purple discoloration as well as friable exophytic lesions	16 months (mycophenolate sodium, tacrolimus, and prednisone)	15 months (alive)
Faustino et al. (2019) <sup>10</sup> Brazil	Female: 55 years old	Squamous cell carcinoma	Tongue and lower lip	White lesions on the tongue and ulcerated lesions on the lower lip	23 years (cyclosporine, mycophenolate sodium, and prednisone)	5 years (alive)
Gorsane et al. (2016) <sup>11</sup> Tunisia	Three males: 29, 37, and 41 years old	Kaposi's sarcoma	Upper gum and palate	Not specified	10, 15, and 19 years (methylprednisolone, basiliximab, mycophenolate sodium, cyclosporine, prednisone, and tacrolimus)	1, 2, and 3 years (all alive)

Continue...

Table 1. Continuation.

Author and country	Sex/age	Malignant lesion	Region of the mouth	Clinical features	Post-transplant time (Immunosuppression drugs)	Follow-up time (Outcome)
D'Antonio et al. (2015) <sup>12</sup> Italy	Male: 64 years old	Plasmablastic lymphoma	Tongue	Firm, solitary, centrally ulcerated solid lesion on the dorsum of the tongue	6 years (cyclosporine, mycophenolate sodium, and prednisone)	1 month (died)
Nolan et al. (2012) <sup>13</sup> United Kingdom	Two males: 49 and 59 years old Female: 70 years old	One carcinoma <i>in situ</i> Three squamous cell carcinoma	Lips	Not specified	30, 36, and 114 months (cyclosporine, azathioprine, tacrolimus, prednisone)	--
López-Pintor et al. (2011) <sup>14</sup> Spain	Six males: 38, 55, 57, 57, 66 and 71 years old	Five squamous cell carcinoma One basal cell carcinoma	Lower lip	Not specified	Between 27 and 116 months (cyclosporine and prednisone)	--
Darling et al. (2004) <sup>7</sup> United Kingdom	Female: 49 years old	Kaposi's sarcoma	Hard palate	Flat purple lesion	1 year (cyclosporine, azathioprine, and prednisone)	1 year (died)
King et al. (1995) <sup>15</sup> United Kingdom	Two males: 37 and 62 years old	Two squamous cell carcinoma	Lips	Not specified	The mean length of time was 69 ± 52 months. (cyclosporine, azathioprine, and prednisone)	-
Margolius et al. (1994) <sup>16</sup> South Africa	Male: 48 years old	Kaposi's sarcoma	Not specified	Not specified	8 months (cyclosporine + prednisone)	20 months (alive)
Ojha et al. (2008) <sup>17</sup> USA	Two males: 40 and 52 years old. Female: 9 years old	Three post-transplant lymphoproliferative disorder - polymorphic variant	Several sites: right lateral tongue, gum, and retromolar area, and buccal vestibule	Intraoral mass as a slightly raised purplish lesion Inflamed area with necrosis and sloughing in the anterior mandibular vestibular gingiva. Also, a large necrotic ulcer in the left lingual posterior mandible and retromolar area. Tenderness and swelling in the buccal vestibule	1, 2, and 9 years (tacrolimus, azathioprine cyclosporine, mycophenolate mofetil, prednisone)	3 weeks to 24 months (All alive)
Meng et al. (2000) <sup>5</sup> China	Three males, 40, 52, and 55 years old	Three squamous cell carcinoma	Tongue	Not specified	7 and 11 years (cyclosporin, azathioprine, and prednisolone)	2 to 3 years (one died and 2 alive)
Visscher et al. (1997) <sup>18</sup> Netherlands	Three males, 28, 47, and 51 years old. Three females, 39, 46, and 64 years old	Six squamous cell carcinoma	Lower lip	Not specified	Time not specified (cyclosporin, azathioprine, and prednisolone)	Three months to 4 years (5 alive and 1 died)

## DISCUSSION

At present, it is known that several factors contribute to carcinogenesis in transplant patients, including age, gender, and end-stage renal disease etiology. Also, some viral infections are associated with increasing malignancies incidence. The cancer risk appears to differ by the type of immunosuppression used, the induction therapy drug used, and other immunological factors. It can be seen from this review that cyclosporine was used in the immunosuppression regimen for most patients. Until recently, long-term treatment with immunosuppressive agents seems to interfere with the immune state. Consequently, it is associated with the excess burden of cancer in kidney transplant recipients. However, scientific studies could not prove that some specific immunosuppressive regimens raise or reduce cancer risk. The doses and the exposition time are probably more important than the immunosuppression regimen type. Also, it needs to be considered that small differences in cancer development potential between the immunosuppressants can affect the incidence by overlapping known risk factors such as age, history of smoking, underlying kidney disease, history of previous cancers, and viral infections.<sup>5,8,19</sup>

In this review, the two most common diagnoses for malignant oral cavity lesions were squamous cell carcinomas (SCCs) and Kaposi's sarcoma. Kaposi's sarcoma, SCC, and lymphoproliferative diseases are the main diagnosis after kidney transplantation. Skin cancers account for 40–50% of all posttransplant malignancies, and the SCC is the most frequently reported. The SCC frequency in transplanted patients is between 65 and 250 times higher than in the general population, and lip cancer has an incidence up to 10 times greater than in healthy individuals.<sup>19</sup> SCCs are more aggressive in this population, and the risk of metastases in this population is higher than in the general population. Ultraviolet radiation and human papillomavirus have been associated with SCC, but it is not so clear the exact role of HPV in this condition.<sup>20,21</sup>

Kaposi's sarcoma has an incidence of up to 300 times greater than otherwise healthy individuals.<sup>19</sup> Except for squamous cell carcinoma, which prefers to show on the lips, Kaposi's sarcoma and lymphoproliferative diseases have no preference for certain anatomical regions of the mouth.<sup>7,9,11,12,16,17</sup>

Even though the literature examined for this review does not clearly identify the primary risk factors for the development of malignant lesions in the oral cavity following transplantation, it has been reported that the primary risk factors for the development of oral cancer are related to: age at transplantation, male gender, white ethnicity and extended time on dialysis before transplantation are key risk factors for the development of cancer after transplantation.<sup>8</sup>

The survival time of transplanted individuals affected by some malignant lesion in the oral cavity was not very long. It should not be underestimated, especially for a maximum follow-up of 5 years, which is the average mortality incidence time for oral squamous cell carcinoma.<sup>5,18</sup> Because the studies reviewed were all case reports or case series, it is clear that more extensive case studies in individuals undergoing organ transplantation are needed to understand the reality of these clinical manifestations of malignancy. Also, the relationship of these lesions with the use of immunosuppressants and with other risk factors. In addition, it is necessary to monitor patients for early detection of malignant lesions in the oral cavity.

## CONCLUSION

For transplant doctors, knowledge of the potential for malignant lesions of the oral cavity affects kidney transplanted patients and the consequences regarding their correct diagnosis is essential. These patients should be regularly forwarded to dentists and other medical professionals who work in diagnosing malignant lesions of the oral cavity to be evaluated, and new cases of oral cancer are recognized early to treatment. This strategy could improve the survival of patients with this threatening disease.

## CONFLICT OF INTEREST

None.

## AUTHORS' CONTRIBUTION

**Substantive scientific and intellectual contributions to the study:** Santos PSS, Sarmiento DJS and Romão EA; **Conception and design:** Santos PSS, Sarmiento DJS and Romão EA; **Data analysis and interpretation:** Santos PSS and Sarmiento DJS; **Article writing:** Santos PSS, Sarmiento DJS and Romão EA; **Critical revision:** Romão EA; **Final approval:** Santos PSS, Sarmiento DJS and Romão EA.

## AVAILABILITY OF RESEARCH DATA

All dataset were generated or analyzed in the current study.

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