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Characteristics and long-term outcomes of head and neck squamous cell carcinoma after solid organ transplantation

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ABSTRACT

Introduction: Immunosuppression after solid organ transplant prevents graft rejection, but leads to increased incidence of various malignancies including head and neck squamous cell carcinoma (HNSCC). Outcomes of patients with post-transplant HNSCC are unknown.
Materials and methods: We retrospectively identified patients who developed HNSCC after solid organ transplant between 1995 and 2010. Adults with pathology-proven HNSCC and adequate follow up were included. Median overall survival and progression free survival were analyzed using the Kaplan-Meier method. The prognostic effect of variables was studied with Cox proportional hazards models.
Results: Thirty-three patients met study inclusion criteria. The median time to diagnosis of HNSCC after transplant was 5.9 years. The primary site was oral cavity in 15 patients, oropharynx in 10, larynx in 3, hypopharynx in 2, parotid in 2 and unknown in 1 patient. Eighty-eight percent underwent upfront surgical resection. Of those, sixty-six percent received adjuvant therapy. Six percent of patients had definitive chemoradiation. Treatment was well tolerated and did not lead to graft rejection. The 5-year overall survival rate was 45% and 37% for localized and locally advanced disease respectively. Seventy-five percent of patients with oropharyngeal tumors were HPV-positive and they had better outcomes (5-year overall survival rate of 67%). In multivariate analysis, age $\geq$60 years was a negative predictor of survival (HR 2.7; 95% CI, 1.1–6.5; P = 0.03).
Conclusions: Patients with post-transplant HNSCC have relatively poor survival and high risk of locoregional and distant recurrence. HPV- positive oropharyngeal tumors continue to have better outcomes in this population.

Introduction

Head and neck cancer accounts for approximately 500,000 cases annually worldwide, with over 62,000 Americans diagnosed each year and almost 13,000 dying from the disease [1,2]. It is well-recognized that the immune system plays a major role in anti-tumor surveillance in healthy individuals, a finding that is confirmed by the increased incidence of cancer diagnosis in some acquired (such as after organ transplant) or hereditary (such as GATA2 deficiency) immunodeficiency states [3]. Our understanding of the interactions between immunity and tumorigenesis is growing at a fast rate such that modulating the immune system has been the largest breakthrough in cancer therapy in the last decade [4]. Immunosuppression, which is universally required after solid organ transplant to prevent graft rejection, leads to increased incidence of various malignancies. Significant literature exists on the increased incidence and different outcomes of malignancies in the transplant population such as skin cancer and post-transplant lymphoproliferative disease (PTLD). Other post-transplant malignancies are much less well-studied including head and neck squamous cell carcinoma (HNSCC). HNSCC comprises about 15% of malignancies seen in transplant patients compared to 4% of malignancies in the general population [5].

A few limited studies have looked at post-transplant HNSCC and yielded strikingly different results. In this article, we retrospectively evaluated transplant patients treated and followed at our institution for non-cutaneous HNSCC to better define this group of patients and evaluate their long-term outcomes.

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Materials and methods

Patient selection and clinical data

This is a single institution, retrospective cohort study approved by the Mayo Clinic Institutional Review Board. We identified patients who had received a solid organ transplant (kidney, liver, heart, lung or pancreas) and were subsequently diagnosed with non-cutaneous HNSCC between January 1st 1995 and December 31st 2010.

Only adult patients older than 18 years of age who had provided consent for research purposes and received their treatment at our institution were included. All patients had complete follow up data. Only patients with pathology-proven non-cutaneous HNSCC were included. All other histologies such as non-squamous subtypes of salivary tumors, mixed-histology carcinomas, neuroendocrine tumors, esthesioneuroblastomas, sinonasal undifferentiated carcinomas, melanomas, basal cell carcinomas, thyroid gland tumors and lymphomas were excluded. Patients with superficial or invasive cutaneous squamous cell carcinomas were also excluded from this study. Patients diagnosed with HNSCC after 2010 were not included to allow for mature follow up data.

Data that were collected from patients' electronic medical records included age at diagnosis, gender, type of transplant, date of transplant, date of cancer diagnosis, primary tumor location, stage at diagnosis, histologic grade, smoking and alcohol use (current or past use), primary treatment modality, radiation dose and modality, chemotherapy regimen, treatment related mortality, immunosuppression at diagnosis (tacrolimus or cyclosporine), date of recurrence if any, type of recurrence (locoregional or distant or both), date of death or last follow up and the cause of death for deceased patients. Survival end-points and follow-up was documented through January 2016.

For staging purposes, the 7th edition of the American Joint Committee of Cancer (AJCC) was used and patients were grouped into three categories: localized disease (Stages I and II), locally advanced disease (Stages III, IVa and IVb) and metastatic disease (stage IVc) [6]. Tumor histologic grade was obtained from pathology reports either from biopsy or surgical samples. Human papilloma virus (HPV) status was determined based on standard immunohistochemistry staining for P16 on biopsy or surgical samples.

Statistical analysis

The JMP statistical software (version 10.0.0, SAS Institute Inc., Cary, NC) was used to conduct statistical analysis. Variables were expressed as medians (range) or frequencies. Overall survival (OS) was calculated from the date of cancer diagnosis to the date of death or last follow up and analyzed using the Kaplan-Meier method. Log-rank tests were used to compare survival distributions. Progression free survival (PFS) was calculated from the date of cancer diagnosis to the date of locoregional or distant relapse or death using the Kaplan-Meier method. Time to relapse (TTR) was calculated from the date of diagnosis to the date of locoregional or distant relapse. Patients were followed from the date of diagnosis to the earliest date for each endpoint, or were censored at last follow up. The prognostic effect of pertinent clinical variables was studied using multivariate Cox proportional hazards models. All variables with $p < 0.05$ in the univariate analysis were subsequently entered into a multivariate model with backward elimination. All tests of statistical significance were two-sided and $P < 0.05$ was considered significant.

Results

Patient characteristics

We identified 33 patients with history of a solid organ transplant who developed de novo HNSCC and met all the study inclusion criteria. The baseline clinical features of these patients are summarized in Table 1. Patients with kidney transplant were the most common (n = 17, 52%) followed by liver transplant (n = 11, 33%). The median age at HNSCC diagnosis was 58 years (range 38–76 years). There were 21 males (64%) and 12 females (36%). More than half of the patients (n = 17, 52%) had a smoking history while (n = 9, 27%) had a history of alcohol use. No history of

Table 1
Baseline characteristics for patients diagnosed with squamous cell carcinoma of the head and neck after a solid organ transplant.

Variable	N = 33	%
Age		
<60 years	17	52
≥60 years	16	48
Gender		
Males	21	64
Females	12	36
Type of transplant		
Kidney	17	52
Liver	11	33
Heart	2	6
Kidney-Pancreas	2	6
Liver-Kidney	1	3
Immunosuppression		
Tacrolimus	20	61
Cyclosporine	8	24
Other	5	15
Time from transplant to cancer diagnosis		
≤5.9 years	17	52
>5.9 years	16	48
Smoking		
Yes	17	52
No	16	48
Alcohol		
Yes	9	27
No	24	73
Primary location of tumor		
Oral cavity	15	46
Oropharynx	10	30
Larynx	3	9
Hypopharynx	2	6
Salivary glands	2	6
Unknown	1	3
Stage at diagnosis		
Localized (I–II)	13	39
Locally advanced (III–IVa–IVb)	19	58
Metastatic (IVc)	1	3
Grade		
I	1	3
II	11	33
III	13	39
IV	1	3
Unknown	7	21
Treatment modality		
Surgery alone	10	30
Surgery with adjuvant radiation	11	33
Surgery with adjuvant chemoradiation	8	24
Definitive chemoradiation	2	6
Patient refused	2	6
Chemotherapy		
Cetuximab-based	6	60
Platinum-based	3	30
Both	1	10