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Oral and lip cancer in solid organ transplant patients – A cohort study from a Swedish Transplant Centre

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SUMMARY

Objectives: Previous large studies have shown that solid organ transplant (SOT) patients have an increased risk of developing malignancies. Few studies have compared the prognosis for SOT patients who develop cancer with that of non-transplanted cancer patients. In this study we have investigated the increased risk of oral and lip cancer in SOT patients and also compared the relative survival between SOT patients and non-SOT patients with oral and lip cancer.

Patients and methods: From the patient registers at the Transplant Institute at Sahlgrenska University Hospital, records of 4604 SOT patients from 1965 to 2010 were collected. These patient records were linked to the nationwide Swedish Cancer Register and compared to those of the normal population regarding the risk of developing oral and lip cancer, and also to non-SOT patients with lip and oral cancer. A Poisson regression model was used to compare the relative survival between SOT and non-SOT patients with oral and lip cancer.

Results: We observed 17 oral cancers (expected 2.69) and 34 lip cancers (expected 0.78) in the cohort. The standardized incidence ratio (SIR) for oral cancer was 6.32 (95% CI, 3.7–10.1) and 43.7 (95% CI, 30.3–61.1) for lip cancer. Relative five-year survival for lip cancer was lower for SOT patients compared to non-SOT patients ($p < 0.001$).

Conclusion: This study shows that SOT patients have a higher risk of developing both oral and lip cancer, and in addition, that SOT patients with lip cancer have a worse prognosis.

Introduction

Previous large epidemiological studies have shown an increased risk of developing a wide range of malignant tumours following solid organ transplantation (SOT) [1–5]. Improvement in the clinical management of SOT patients leads to an increase in long-term survival, and that results in an increased risk of developing cancer over time [5].

The overall risk for malignant diseases is increased by at least twice after transplantation, but the risk varies with type of organ and type of malignancy [2,5,6]. Most of the known infection-related cancers – but also some non-infection related cancers – increase in prevalence after transplantation [7]. Tumour diseases that show the highest increase in prevalence in SOT patients are non-melanoma skin cancers and post-transplant lymphoproliferative diseases (PTLD) [2,8]. The increased risk of malignant diseases in SOT patients is assumed to be a consequence of long-standing immunosuppression that leads to impaired immunosurveillance against tumours. In addition, sun exposure is an important risk factor for non-melanoma skin cancers. The overall cancer risk in SOT patients has been shown to be higher amongst patients who received thoracic organs compared to patients receiving abdominal organ [4,6]. Also in the head-neck region there is an increase in cancer incidence [9]. Head and neck cancers have been reported to constitute 4–15% of all malignant tumours after transplantation [10–13]. An increased incidence of lip cancer has also been reported [14,15]. Treatment outcome of head and neck cancers in SOT patients seems

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to be worse than in non-SOT patients and has been ascribed to the state of immunosuppression [9,12].

Long-term survival increases for SOT patients, which is mostly attributed to improvements in the early post-transplant phase; however, malignancies in the late post-transplantation phase are an increasing problem and pose a threat to survival for SOT patients [5,16]. This warrants a close follow-up of cancer epidemiology in SOT patients. Thus, the primary aim of this study was to investigate the risk of oral and lip cancer in a Swedish patient cohort treated with SOT between 1965 and 2012. The secondary aim was to compare the prognosis for SOT patients with oral and lip cancer in this cohort with a non-SOT cohort of patients with oral and lip cancer.

Patients and methods

Study population

The study cohort was selected after a retrospective search in the register at the Transplant Institute at Sahlgrenska University Hospital. We identified 5755 patients from the register, which contain all SOT patients who were treated with transplantation between January 1965 and December 2010. After exclusion of patients with more than one transplantation ($n = 1151$), 4604 patients remained and were the foundation for the analyses. By linking data for the SOT cohort to the Swedish Cancer Registry, all patients in the cohort diagnosed with cancer both before and after SOT were identified. Patient data from the study cohort were then linked to the cause of death register and the population register to explore (1) cause of death if applicable, and (2) numbers of patients with Swedish residency and those without.

Also, patients with a history of oral and lip cancer before SOT and patients diagnosed within 30 days after SOT ($n = 2$) were excluded. Twelve patients with missing data were excluded from analysis. A cohort of 4590 SOT patients was then identified and subsequently analysed.

The International Classification of Diseases was used to identify anatomical sites of tumours. Diagnoses were identified by ICD-7: oral cancer 141–144 (major salivary gland 142), and lip cancer 140.

A control group, matched for sex and age, was selected from the Cancer Registry, Region Västra Götaland, Sweden, and was used to compare the relative survival for SOT patients with that of non-SOT patients with oral and lip cancer. Oral cancer was diagnosed in 1849 non-SOT patients between 1975 and 2010, while 881 non-SOT patients were diagnosed with lip cancer during the same time frame.

In the survival analysis, one patient was excluded from the lip SOT patient group because the patient had had an oral cancer before the lip cancer, and two patients were excluded from the oral cancer SOT patient group because of a preceding lip cancer.

The Ethical Review Board at the Sahlgrenska Academy, University of Gothenburg, Sweden, approved this study.

Statistical analyses

Relative risk of cancer in SOT patients compared to the general population was expressed as standardized incidence ratio (SIR). A 95% confidence interval (CI) and a p-value < 0.05 was considered statistically significant. Incidence rates in the Swedish population, by gender, 5-year age group, and calendar year, were used to calculate the expected number of cancer cases among the SOT patients. A Poisson regression model was used to compare the relative survival between SOT patients and non-SOT patients with oral and lip cancer.

Results

Analyses of study population

A total of 4590 SOT patients proceeded to analyses. The mean and median ages at SOT were 47 years and 49 years, respectively (range: 0–77 years). Follow-up was extended to date of death or until 31 December 2010, resulting in a total of 37,270 person-years of follow-up time.

In the cohort, 2839 were men (62%) and 1751 women (38%). The study population comprised 437 heart, 359 lung, 710 liver, and 3084 kidney recipients. Patient characteristics are given in Table 1.

Oral and lip cancer in our SOT cohort

In the study cohort of 4590 single-transplanted patients we observed 17 oral cancers (0.4%) and 34 lip cancers (0.7%).

In the patient group with oral cancer the mean and median ages at diagnosis were the same, 63 years (range: 49–72 years; Table 1). In the patient group with lip cancer the mean and median ages at diagnosis were 61 and 62 years, respectively (range: 34–80 years).

The majority of the patients in the lip cancer group (56%) were diagnosed between 60 and 119 months after SOT, with a mean/median time from SOT to diagnosis of 88/79 months (range: 27–212). During the corresponding time, 47% of the SOT patients with oral cancer were diagnosed, and the mean/median time from SOT to diagnosis was 128/113 months (range: 27–289).

Standardized incidence ratio of oral and lip cancer

Among SOT patients, most oral and lip cancers were found in kidney patients (oral $n = 14$, lip $n = 24$), followed by heart (oral $n = 2$, lip $n = 6$), liver (oral $n = 1$, lip $n = 3$) and lung patients (oral $n = 0$, lip $n = 1$) (Table 2).

The expected number of oral cancers in the cohort was 0.7, but 17 patients with oral cancer were found (SIR: 6.3, CI 3.7–10.1; Table 2). The corresponding number for lip cancer was 0.8 but we observed 34 patients with that diagnosis (SIR: 43.7, CI 30.3–61.1; Table 2). Statistical comparisons show significantly increased risks for oral ($p < 0.02$) and lip cancer ($p < 0.001$) in SOT patients compared with what was expected to occur in the Swedish population. Subsite distribution of oral and lip cancers is presented in Table 3.

The highest incidence of oral cancer was found in heart transplant patients, with SIR of 8.7 (CI 1.05–31.4), followed by kidney, SIR 6.9 (CI 3.8–11.6); liver, SIR 3.1 (CI 0.08–17.4); and lung transplant patients, SIR 0 (Table 2). Lip cancer incidence was also highest among heart transplant patients, with a SIR value of 99.0 (CI 36.2–99.99) (Table 2). Lung, liver, and kidney transplant patients showed SIR values at approximately the same level: lung transplant recipients had a SIR value of 46.0 (CI 0.6–99.99); liver patients, 41.6 (CI 8.35–9.99); and kidney patients, SIR 38.5 (CI 24.7–57.3) (Table 2).

Survival analysis

Five-year relative survival for oral cancer patients with SOT was 30.8% (CI 7.7–60.2%; Fig. 1A), and for patients with oral cancer without SOT it was 60.1% (CI 57.6–62.6%; Fig. 1A). Outcome comparison between the groups did not show a significant difference in relative survival (Fig. 1A; $p = 0.14$). Five-year relative survival for single SOT patients with lip cancer was 66.0% (CI 44.7–82.2%; Fig. 1B) and for lip cancer without SOT 94.2% (CI 91.1–96.9%; Fig. 1B), which results in a significantly reduced

Table 1
Patient characteristics.

	All organs	Heart	Lung	Liver	Kidney
No. of patients (%)	4590	437 (9.5)	359 (7.8)	710 (15.5)	3084 (67.2)
Females	1751 (38)	105 (24)	209 (58)	269 (38)	1168 (38)
Males	2839 (62)	332 (75)	150 (42)	441 (62)	1916 (62)
Age at first transplantation (%)					
<20	5.1	14.7	4.5	7.3	3.3
20–34	15.0	11.0	12.3	10.1	16.9
35–44	18.7	14.7	13.9	14.8	20.7
45–54	26.7	28.6	31.8	25.9	26.0
55–64	27.9	28.8	32.0	33.4	26.1
⩾65	6.7	2.3	5.6	8.5	7.0
Mean/median age (range, years)	46.5/49.0 (0–77)	42.9/48.0 (0–70)	48.2/52.0 (7–73)	47.8/52.0 (0–73)	46.5/49.0 (0–77)
Year of first transplantation					
1965–69	88	0	0	0	88
1970–79	341	0	0	0	341
1980–89	726	52	0	0	674
1990–99	1362	192	130	200	840
2000–10	2073	193	229	510	1141
Follow-up time, median (range, years)	6.3 (0–43.4)	5.7 (0–23.0)	3.2 (0–20.9)	4.5 (0–17.9)	7.2 (0–43.4)
Follow-up time, total (person-years)	37,270	3192	1751	4031	28,297

Table 2
Standardized incidence ratios of oral and lip cancers in SOT patients.

	Oral cancer					Lip cancer				
Transplanted organ	Obs[a]	Exp.[b]	SIR[c]	CI[d]	*p*-value[e]	Obs.[a]	Exp.[b]	SIR[c]	CI[d]	*p*-value[e]
All organs	17	2.69	6.3	(3.7–10.1)	<0.001	34	0.78	43.7	(30.3–61.1)	<0.001
Heart	2	0.23	8.7	(1.05–31.4)	<0.05	6	0.06	99.0	(36.2–99.99)	<0.001
Lung	0	0.11	0	–	–	1	0.02	46.0	(0.6–99.99)	<0.05
Liver	1	0.32	3.1	(0.08–17.4)	n.s.	3	0.07	41.6	(8.35–9.99)	<0.001
Kidney	14	2.03	6.9	(3.8–11.6)	<0.001	24	0.62	38.5	(24.7–57.3)	<0.001

[a] No. of observed cancers.
[b] No. of expected cancers.
[c] Standardized incidence ratio.
[d] 95% confidence interval.
[e] *p*-value < 0.05 is considered significant.

Table 3
Subsite distribution of oral and lip cancers in SOT patients according to ICD-7 classification.

Localization (ICD-7)	Number of cancers
Upper lip (140.0)	3
Lower lip (140.1)	17
Lip unspecified (140.9)	14
Tongue (141)	4
Major salivary glands (142)	5
Floor of mouth (143)	3
Gingiva, palate, bucca (144)	5

relative survival for SOT patients with lip cancer (Fig. 1B; $p < 0.001$).

The observed survival rates for SOT patients were 27% and 61% alive at five years after oral and lip cancer, respectively (Fig. 2).

Discussion

Our study shows that the risk for oral cancer increased 6 times, and for lip cancer 44 times in our cohort of SOT patients. Fewer than 1% of the patients developed oral or lip cancer. The relative survival for patients who developed lip cancer following SOT was significantly decreased in comparison with non-SOT patients, but no significant difference in relative survival could be registered when comparing SOT patients who developed oral cancer with non-SOT patients. In the present study we chose to exclude patients with more than one organ transplantation. Patients with more than one SOT constitute a heterogeneous group with respect having a more complicated medical situation and a complex pharmacological treatment including immunosuppression, as well as longer duration of this treatment, compared with those having one SOT. Analysis of a single-SOT cohort thus provides a baseline level of cancer risk amongst the SOT patients.

The increased risk of tumour development amongst SOT patients has been confirmed by several large epidemiological studies [1,2,4,5]. In SOT patients long-standing pharmacological immunosuppression results in impaired function of the immune system, which is a prerequisite for good, long-term transplant function. As a consequence, the risk of spontaneously emerging cancer cells avoiding elimination by the immune system not only increases but also opens a pathway where oncoviruses like human papilloma virus and Epstein–Barr virus may induce tumours more often than otherwise. Exogenous factors like UV radiation from the sun in combination with impaired immunosurveillance have been related to the increased prevalence of skin cancers observed in SOT patients [17,18]. The loss of immunosurveillance most certainly plays an important role in development of post-transplant malignancies. Clinical evidence has been presented which suggests that the immune system plays an important role regarding the progression and the prognosis of malignant tumours in non-SOT patients [19–21].

This study focuses on investigating two nearby but different anatomical regions: the oral cavity and the lips. Immunosuppression, viruses, and environmental factors influence the oral cavity and lips in a similar manner, but the oral cavity is shielded from UV radiation, in contrast to the lips. In our patient cohort oral

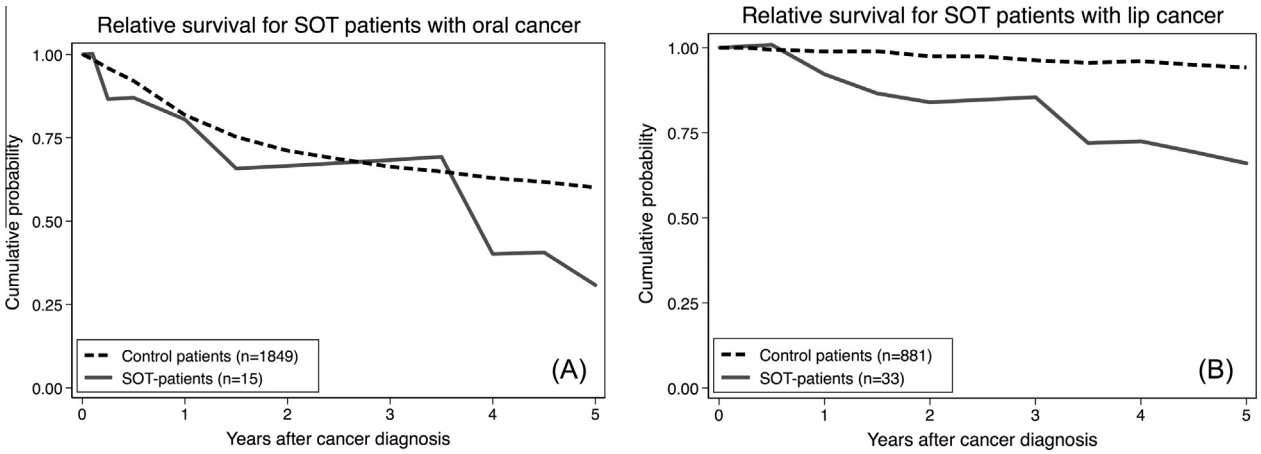

Fig. 1. Relative survival for (A) SOT patients with oral cancer (solid line) and control patients with oral cancer (dotted line), and (B) for SOT patients with lip cancer (solid line) and control patients with lip cancer (dotted line).

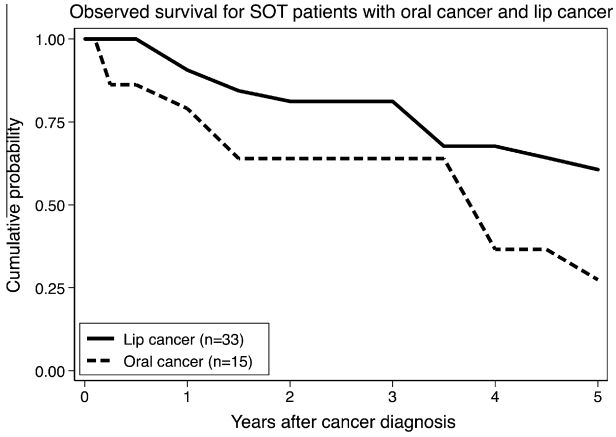

Fig. 2. Observed survival for SOT patients with oral cancer (dotted line) and lip cancer (solid line).

cancer developed six times more frequently than expected. In a Canadian SOT patient cohort there was an almost ninefold increase in oral and pharyngeal cancer [1], while a UK transplant centre reported a fourfold increase in oral cancer [3]. In a US patient cohort oral and pharyngeal cancers presented with a 2.5 times increase in risk [2]. Thus, results presented in this study are in line with and confirm that the increase in risk of oral cancer following SOT most likely lies in the range between three to eight times.

In contrast, lip cancer developed 44 times more frequently than expected amongst our patients. Earlier studies have also reported a more than 10-fold increase in lip cancer following SOT, which parallels the general risk increase in risk for non-melanoma skin cancers in these patients [1,2,22]. In a US cohort a 17 times increase in lip cancer was registered, but in contrast, in a UK cohort lip cancer occurred 66 times more frequently than expected [2,3]. The range in lip cancer frequencies between the cohorts may possibly be explained by differences in exposition to sunlight and skin constitution.

Several centres have confirmed an organ-specific, significant difference in overall cancer incidence in SOT patients. Transplantation of heart or/and lung has the highest risk of cancer development [4,6]. This fact has been attributed to the higher level of immunosuppressive treatment in this group in comparison with regimens applied in transplantation of other organs. Despite the relatively low numbers of oral and lip cancers the standard incidence rates in heart or lung SOT patients in our cohort surpassed what was registered in liver and kidney SOT patients. Thus, this study presents further evidence that heart and lung SOT patients are at high risk of tumour development in comparison with other organ transplantation patients. It can be speculated whether this is a result of the level of immunosuppression; however, this we cannot answer, since the level of immunosuppression was not monitored in our database. New regimens of immunosuppressive treatment following SOT may influence tumour development, which in the future certainly will influence cancer risk in SOT patients [24]. In our study we cannot address the impact of new regimens because of the relatively low number of patients contracting oral or lip cancer.

In the general population it is well investigated that exposure to tobacco and alcohol increase the risk for oral cancer [25], and UV exposure has been shown to be the main risk factor for both melanoma and non-melanoma skin cancers, including cancers of the facial skin [26]. Globally, oral cancer has the highest incidence in parts of Asia, in Eastern Europe, and in parts of Latin America [23]. However, to our knowledge no large cohort studies from centres in those regions have been presented, which makes comparison of a global variation in cancer incidence in SOT patients difficult.

Few studies have specifically evaluated survival outcome of SOT patients who develop oral or lip cancer. In a recent study, Nelissen and co-workers reported the overall five-year survival for head and neck tumours in a Belgian SOT patient cohort to be slightly more than 50% [9]. In an Israeli cohort the five-year overall survival rate was 74% for head and neck malignancies [13]. In a nationwide study of all SOT patients transplanted in Sweden between 1970 and 1997 Adami and collaborators [27] report standard incidence ratios for oral and lip cancer in accordance with our findings. However, our single centre study has longer follow up time and also addresses survival outcome for SOT patients that contracted oral or lip cancer in our cohort. We evaluated survival outcome for SOT patients who contracted oral or lip cancer in our cohort. The relative survival for patients who contracted lip cancer was significantly decreased in comparison with lip cancer patients without SOT. In SOT patients with oral cancer no statistically significant difference was observed when these were compared with non-SOT patients with oral cancer, although data in our statistical analysis may indicate a trend.

Many factors may be involved in the worse outcome of SOT patients with lip and possibly oral cancer in our cohort compared to a matched group of non-SOT patients with these diagnoses. A principal cause, as pointed out by several groups, is the longstanding immunosuppression that SOT patients are subjected to and the

comorbidity that transplantation adds. Standard protocols for treatment of head-neck cancers may have to be modified because of the patient's medical condition in general, which influences treatment efficacy. The worldwide trends in incidence of oral and oropharyngeal cancer show a changing pattern with an increase in oropharyngeal cancers during the last two decades, while oral cancer incidence displays a more heterogeneous pattern [28]. This calls for close monitoring of changes in incidence of head and neck cancers also in SOT patients.

Conclusion

The present study verifies an increased risk of oral and lip cancer in SOT patients. We also report a decrease in relative survival for lip cancer and possibly also for oral cancer.

Conflict of interest statement

The authors Jenny Öhman, Helena Rexius, Lars Mjörnstedt, Helena Gonzales, Erik Holmberg, Göran Dellgren and Bengt Hasséus declare no conflict of interest.

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