ORIGINAL ARTICLE

Voriconazole increases the risk for cutaneous squamous cell carcinoma after lung transplantation

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SUMMARY

Lung transplant recipients (LTR) are at high risk of cutaneous squamous cell carcinoma (SCC). Voriconazole exposure after lung transplant has recently been reported as a risk factor for SCC. We sought to study the relationship between fungal prophylaxis with voriconazole and the risk of SCC in sequential cohorts from a single center. We evaluated 400 adult LTR at UCLA between 7/1/2005 and 12/22/2012. On 7/1/2009, our center instituted a protocol switch from targeted to universal antifungal prophylaxis for at least 6 months post-transplant. Using Cox proportional hazards models, time to SCC was compared between targeted ($N = 199$) and universal ($N = 201$) prophylaxis cohorts. Cox models were also used to assess SCC risk as a function of time-dependent cumulative exposure to voriconazole and other antifungal agents. The risk of SCC was greater in the universal prophylaxis cohort (HR 2.02, $P < 0.01$). Voriconazole exposure was greater in the universal prophylaxis cohort, and the cumulative exposure to voriconazole was associated with SCC (HR 1.75, $P < 0.01$), even after adjustment for other important SCC risk factors. Voriconazole did not increase the risk of advanced tumors. Exposure to other antifungal agents was not associated with SCC. Voriconazole should be used cautiously in this population.

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complications (lung clinical), fungal (infection), quality of life (quality of life, ethics, economics), solid tumor (malignancy and long-term complications)

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Introduction

Invasive fungal infection remains a significant threat to survival after lung transplantation [1]. Furthermore, Aspergillus colonization, which affects approximately 1/3 of lung transplant recipients (LTR) in the first post-transplant year, may increase the risk of chronic lung allograft dysfunction (CLAD) [2,3]. Given the relatively high incidence and poor outcomes associated with fungal infections after lung transplant, use of antifungal prophylaxis and pre-emptive treatment of Aspergillus colonization is increasingly widespread [4]. Given the ease of administration and efficacy against Aspergillus, voriconazole is a common choice for prophylaxis (off label) and treatment [5]. However, voriconazole is also associated with significant toxicity and side effects.

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Vision changes, hallucinations, and hepatic enzyme abnormalities are well described [6]. Photosensitivity is also common and may range from mild sunburn-like erythema to blistering pseudoporphyria [7]. More recently, several reports have described an increased risk of cutaneous squamous cell carcinoma (SCC) among lung transplant recipients receiving prolonged courses of voriconazole [8–11]. However, another study found no increased risk of SCC in LTR treated with voriconazole [12], thus the relationship remains controversial.

On July 1, 2009, our center instituted a protocol shift from targeted to universal antifungal prophylaxis for the first 6 months post-transplant. The sequential cohorts offer a unique opportunity to compare the impact of antifungal prophylaxis protocols on risk of SCC. While voriconazole was used most commonly for prophylaxis and treatment in each cohort, some patients in each cohort received alternative antifungal medications. This scenario offers the additional opportunity to compare the risk of SCC associated with exposure to voriconazole versus other antifungal medications. In this retrospective single-center study, we sought to determine whether universal antifungal prophylaxis, and whether the cumulative exposure to voriconazole or other antifungals, is a risk factor for SCC.

Methods and materials

Study population

We performed a retrospective cohort study of all adult recipients of a first single or bilateral lung transplant at UCLA between 7/1/2005 and 12/22/2012 who survived to hospital discharge. Data were collected through 12/31/2013. We recorded demographic and clinical data including date of birth, date of transplant, gender, race, underlying lung disease, type of transplant, induction type, acute rejection episodes, and date of death if applicable. This study was approved by the University of California, Los Angeles Institutional Review Board.

Clinical management

Clinical protocols at UCLA have been described elsewhere [2]. Briefly, induction immune suppression included rabbit antithymocyte globulin (ATG) or a CD25 antagonist (age ≥60 years, prior malignancy, or chronic infection). Thereafter, patients were maintained on triple immunosuppression with tacrolimus, mycophenolate, and corticosteroids. Surveillance bronchoscopies and transbronchial biopsies were performed at 1, 3, 6, and 12 months, and as clinically indicated. Acute rejection diagnosis required histopathology on transbronchial biopsy and was graded according to ISHLT criteria [13]. Asymptomatic episodes of A1 AR were usually treated with a prednisone burst (0.5 mg/kg daily) for 1 week and tapered by 5 mg/week down to the previous dose. Symptomatic A1 and grade A2 or greater AR were treated with methylprednisolone 0.5–1 g QD for 3 days, with subsequent augmentation of prednisone to 0.5 mg/kg daily for 1 week and tapered by 5 mg per week down to the previous dose. Protocol dictated a referral for a baseline visit with a transplant dermatologist in the first year after transplant. Thereafter, further evaluations were determined by transplant dermatology as needed.

Antifungal prophylaxis and treatment

All patients received antifungal prophylaxis with nebulized amphotericin B lipid complex 50 mg/day for 3 days and then weekly plus intravenous caspofungin 50 mg/day for the duration of the postoperative hospitalization. Prior to 7/1/2009, patients targeted for long-term antifungal prophylaxis included those with a history of fungal infection prior to transplant, those with fungal infections identified in explant pathology, and those with cystic fibrosis. Patients transplanted on or after 7/1/2009 universally received long-term antifungal prophylaxis. Long-term antifungal prophylaxis (targeted or universal) consisted of oral voriconazole 200 mg twice daily started prior to hospital discharge and continued for at least 6 months post-transplant. Voriconazole therapeutic drug monitoring was not routinely performed. In the case of suspected voriconazole toxicity or side effects, or when voriconazole was otherwise not feasible, choice of an alternative triazole (posaconazole oral suspension 200 mg 3 times daily or itraconazole 400 mg daily) was at the discretion of the treating physician. Post-transplant-positive fungal cultures were treated similarly with voriconazole or other triazole antifungal therapy. For the purpose of cumulative exposure determination for this study, start and stop dates of triazole antifungal therapies were abstracted from the medical record until the patient death, or last follow-up through 12/31/2013.

Squamous cell carcinoma determination

Medical records were reviewed to determine the details of each skin cancer diagnosis. Information for each cancer included the following: date of biopsy, location,

vascular invasion, neural invasion, metastatic disease, and stage of tumor. Advanced tumors were defined as stage T2 or greater according to the alternative cutaneous squamous cell carcinoma staging system [14].

Statistical methods

Demographic and clinical characteristics were compared between targeted and universal antifungal prophylaxis cohorts using *t*-tests for continuous variables and chi-square tests for categorical variables. Incidence rates of SCC per 10 person-years within the targeted antifungal prophylaxis (TAP) and universal antifungal prophylaxis (UAP) cohorts were calculated separately for each of the first 5 years post-transplant, and compared between cohorts for each year with chi-square tests. This was calculated as the sum of SCC event observed divided by the person-years observed. Cumulative incidence of SCC at years 1, 2, and 3 post-transplant were calculated and used to describe the SCC burden for each cohort. Cumulative incidence curves also present the SCC incidence in both cohorts for the full observation periods. Cumulative incidence curves were computed using the nonparametric estimator described in (Hosmer, Lemeshow, and May 2008) [15] using the SAS macro %CIF (Lin, So, and Johnston 2012) [16]. Comparisons between cumulative incidence curves were performed using Gray's test, also implemented using the %CIF macro.

The association between SCC and fungal prophylaxis exposure was assessed through a series of univariable and multivariable death-censored proportional hazard (PH) models. Patients' SCC experience was measured in three ways: (i) time to the first SCC event; (ii) time to the first advanced SCC event; and (iii) recurrence of SCC events. Exposure to fungal prophylaxis was measured in two ways: (i) targeted and universal prophylaxis groups and (ii) cumulative time-dependent exposure to specific medications (voriconazole, posaconazole, itraconazole). Patients' time to first SCC and advanced SCC were evaluated as outcomes in PH regression models, and their recurrent SCC events were evaluated as outcomes in repeated events PH regression models, using the fungal prophylaxis exposure group variable and the time-dependent cumulative medication-specific variables in separate models. Patients' age at transplant, gender, race (White, non-White), diagnosis (COPD/A1ATD, CF/bronchiectasis, restrictive parenchymal lung disease, other), transplant type (single lung, double lung), induction type (basiliximab, ATG/Campath), and time-dependent cumulative AR score were considered as potential covariates and included in multivariable models where significant in the corresponding univariable model. As a sensitivity analysis, Fine and Gray's method was applied to account for the competing risk of death in the cumulative incidence of SCC, which includes anyone who had a competing event before a given time point in estimations of the hazard ratio and significance levels. All statistical analyses were performed using SAS v. 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of the study cohort

Four hundred total lung transplant recipients were included in this study; 199 in the targeted antifungal prophylaxis cohort and 201 in the universal antifungal prophylaxis cohort. The clinical characteristics of the two cohorts were similar except that recipients in the universal antifungal prophylaxis cohort were less likely to receive a bilateral lung transplant (40% vs. 55%, $P = 0.003$), and more likely to receive basiliximab (71% vs. 49%, $P < 0.001$) as opposed to ATG induction (Table 1). The median post-LT observation period is 1.43 (IQR 0.82–2.59) years in the universal antifungal prophylaxis cohort and 2.88 (IQR 1.47–5.33) years for the targeted antifungal prophylaxis cohort (Figure S1). The universal antifungal prophylaxis cohort had a higher percent of patients who were ever exposed to antifungal medications than the targeted antifungal prophylaxis cohort (98% vs. 74%) (Table 2). The percent of total follow-up time observed on voriconazole nearly doubled in the universal prophylaxis group (41% vs. 22%) (Table 2). The median percent of time each patient was observed on voriconazole during the first year post-transplant was 57% (IQR 26–95%) in the universal prophylaxis cohort versus 0% (IQR 0–73%) in the targeted prophylaxis cohort. There were 149 deaths observed (37% of patients) in the follow-up period.

Cumulative Incidence of SCC

Cumulative incidence curves demonstrate a shorter time to first SCC in the universal prophylaxis cohort ($P < 0.01$) (Fig. 1). The 1-, 2-, and 3-year cumulative incidence of SCC was 1% 6%, and 14%, respectively, for the targeted antifungal prophylaxis cohort, and 6%, 18%, and 28%, respectively, for the universal antifungal prophylaxis cohort.

Table 1. Demographics and clinical characteristics.

	Targeted antifungal prophylaxis *N* = 199	Universal antifungal prophylaxis *N* = 201	*P*-value
Age at transplant (years), mean (SD)	58.8 (10.9)	59.0 (10.6)	0.87
Age >65 years, *N* (%)	66 (33)	49 (25)	0.07
Male gender, *N* (%)	126 (63)	120 (60)	0.46
Race, *N* (%)			
White	147 (74)	151 (75)	0.96
Hispanic	24 (12)	27 (13)	
Black	12 (6)	10 (5)	
Asian	9 (5)	7 (4)	
Other	7 (4)	6 (3)	
Diagnosis, *N* (%)			
Restrictive parenchymal lung disease	123 (62)	137 (68)	0.40
COPD/A1ATD	51 (26)	43 (21)	
CF/bronchiectasis	14 (7)	9 (4)	
Other	11 (6)	14 (7)	
Bilateral transplant, *N* (%)	110 (55)	81 (40)	0.003
Induction type, *N* (%)			
ATG	101 (51)	58 (29)	<0.001
Basiliximab	98 (49)	143 (71)	

Table 2. Fungal prophylaxis exposure.

	Targeted antifungal prophylaxis *N* = 199		Universal antifungal prophylaxis *N* = 201	
	N (%) ever exposed	% Observed time on specific drug	*N* (%) ever exposed	% Observed time on specific drug
Any antifungal	148 (74)		198 (98)	
Voriconazole	118 (59)	22	184 (91)	41
Posaconazole	30 (15)	5	32 (16)	6
Itraconazole	28 (14)	8	11 (5)	5

The incidence rate of SCC episodes per 10 person-years was higher in each of the first five post-transplant years in the universal antifungal prophylaxis cohort, but this was statistically significant only in years 1 and 2 (Table 3). At 1-, 3-, and 5- year post-transplant, the incidence rates of SCC episodes per 10 person-years of follow-up were 0.28, 11.35, and 8.30, respectively, for the targeted antifungal prophylaxis group, and 1.23, 13.81, and 19.91, respectively, for the universal antifungal prophylaxis group.

Risk factors for SCC

Univariable PH regression identified universal prophylaxis as a risk factor for time to first SCC (HR 1.99, 95% CI 1.19–3.33, $P = 0.008$). In addition, age at transplant, male gender, Caucasian race, and basiliximab induction were significantly associated with time to first SCC in univariable PH regression (Table 4). Universal prophylaxis remained a significant risk factor for SCC after multivariable adjustment for these other important SCC risk factors (HR 2.00, 95% CI 1.18–3.37, $P = 0.01$). Of note, induction type was not found to be an independent predictor of time to first SCC on multivariable analysis.

Univariable repeated events PH regression also identified universal prophylaxis as a risk factor for recurrent SCC (HR 2.48, 95% CI 2.03–3.02, $P < 0.001$) (Table S1). Universal prophylaxis remained a significant risk factor for recurrent SCC after multivariable adjustment for other important SCC risk factors (HR 2.22, 95% CI 1.82–2.71, $P < 0.001$) (Table S1).

Voriconazole cumulative exposure and risk of SCC

To determine whether specific fungal prophylaxis drugs were associated with SCC outcomes, the cumulative time-dependent exposures of the different antifungal

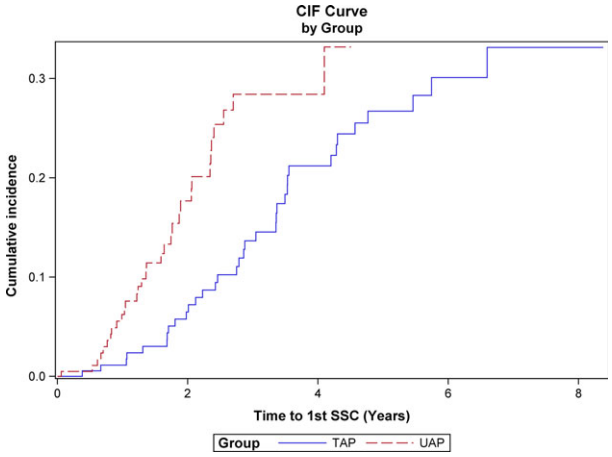

Figure 1 Cumulative incidence estimate of time to first squamous cell carcinoma (SCC) for targeted antifungal prophylaxis (TAP) and universal antifungal prophylaxis (UAP) cohorts. The TAP cohort had a shorter time to first SCC when compared to the UAP cohort.

drugs were analyzed in PH models for time to first SCC. Voriconazole was the only triazole antifungal associated with time to first SCC (HR 1.62, 95% CI 1.27–2.09, $P < 0.001$) (Table 4). Voriconazole remained a significant risk factor for SCC after multivariable adjustment for other known risk factors (HR 1.71, 95% CI 1.33–2.20, $P < 0.001$) (Table 4). When accounting for the competing risk of death, voriconazole remained a significant risk factor in univariate and multivariate analyses (Table S2). Similarly, repeated events PH regression demonstrated that the time-dependent cumulative exposure to voriconazole was associated with recurrent SCC (HR 1.12, 95% CI 1.06–1.19, $P < 0.001$) (Table S1). Voriconazole remained a significant risk factor for recurrent SCC after multivariable adjustment (HR 1.16, 95% CI 1.09–1.24, $P < 0.001$) (Supplemental Digital Content Table 1).

Advanced SCC between cohorts

There was no difference between the two cohorts in the cumulative incidence of first advanced SCC, defined as stage T2 or greater ($P = 0.87$) (Fig. 2). Likewise, in univariable PH regression, neither the prophylaxis cohort nor time-dependent exposure to voriconazole was associated with time to first advanced SCC (Table S3). Only age greater than 65 years at the time of transplant was associated with advanced SCC (HR 2.99, 95% CI 1.26–7.09, $P = 0.01$).

Discussion

In this retrospective study, we explored the risk factors for SCC in a relatively large cohort of lung transplant recipients. While lung transplant recipients are known to be at high risk of SCC, recently several centers have reported that treatment with the antifungal medication, voriconazole, increases SCC risk [8–11]. A novelty of our study is that we investigate this relationship in sequential cohorts, before and after a shift in antifungal prophylaxis. More specifically, we compared the era of targeted antifungal prophylaxis to the era of universal antifungal prophylaxis, where voriconazole was the first line agent. Importantly, we found that SCC incidence was increased in the universal prophylaxis cohort, suggesting that voriconazole may increase the risk of SCC. However, because voriconazole treatment was relatively common even in the targeted prophylaxis cohort, and because a sizable number of patients were treated with antifungal medications other than voriconazole, we investigated the relationship with specific antifungals and SCC. Importantly, the cumulative exposure to voriconazole was the only antifungal drug that was associated with the time to first SCC. Voriconazole was also the only antifungal drug which was a predictor of recurrent SCC.

In addition to the cumulative exposure to voriconazole, other risk factors for time to first SCC were age at transplant, male gender, and Caucasian race. These are well-described SCC risk factors and demonstrate the validity of our methods. In this study, basiliximab induction was associated with SCC risk in univariable PH models for time to first SCC, but this relationship did not persist in adjusted models. Basiliximab induction remained a risk factor for SCC in the multivariable repeated events models. However, the statistical collinearity between basiliximab and age ($r = 0.3$,

Table 3. Rates of squamous cell carcinoma (SCC) per 10 person-years by year post-transplant (actual number of cases/person-years observed).

	Year 1	Year 2	Year 3	Year 4	Year 5
Targeted antifungal prophylaxis	0.28 (5/180.8)	3.83 (58/151.3)	11.35 (144/126.9)	11.68 (119/101.8)	8.30 (70/84.3)
Universal antifungal prophylaxis	1.23 (21/170.6)	5.86 (68/116.0)	13.81 (98/71.0)	17.49 (62/35.4)	19.91 (12/6.0)
P-value	<0.01	0.05	0.32	0.11	0.09

Table 4. Proportional hazards regression models predicting time to first squamous cell carcinoma (SCC).

	Univariable		Multivariable model 1		Multivariable model 2	
	HR	95% CI	HR	95% CI	HR	95% CI
Group, UAP versus TAP	1.99	1.19–3.33*	2.00	1.18–3.37*	N/A	
TD voriconazole exposure (years)	1.62	1.27–2.09**	N/A		1.71	1.33–2.20**
TD posaconazole exposure (years)	0.51	0.15–1.67				
TD itraconazole exposure (years)	0.70	0.38–1.29				
Age at transplant, >65 years	2.02	1.22–3.33**	1.53	0.86–2.72	1.33	0.74–2.38
Gender, male versus female	1.74	1.03–2.93*	1.75	1.03–2.99*	1.85	1.08–3.18*
Race, white versus non-white	5.04	1.84–13.86*	5.45	1.98–15.06*	5.59	2.02–15.49**
Diagnosis versus restrictive						
COPD/A1ATD	1.00	0.57–1.76				
CF/bronchiectasis	1.23	0.49–3.11				
Other	0.80	0.29–2.25				
Induction, basiliximab versus ATG	1.83	1.09–3.08*	1.25	0.69–2.26	1.33	0.74–2.41
TD acute rejection	1.00	0.87–1.14				

UAP, universal antifungal prophylaxis; TAP, targeted antifungal prophylaxis; TD, time dependent.
*$P < 0.05$, **$P < 0.001$.

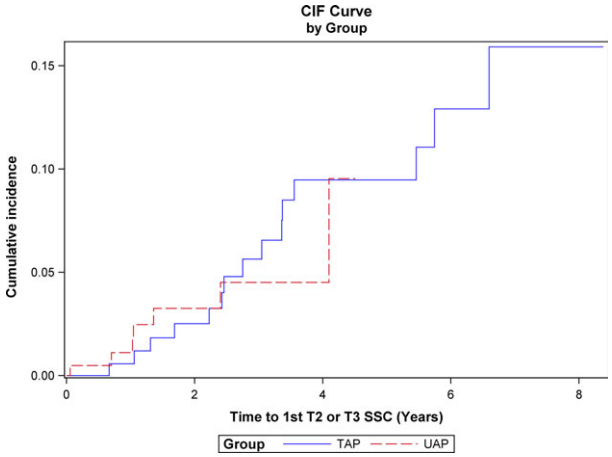

Figure 2 Cumulative incidence estimate of time to first advanced squamous cell carcinoma (SCC) (T2 or T3) for targeted antifungal prophylaxis (TAP) and universal antifungal prophylaxis (UAP) cohorts. There was no difference in time to first SCC between cohorts.

$P < 0.0001$) warrants caution in interpreting this finding. In our center, age greater than 60 is an indication for basiliximab induction, as is history of prior malignancy or chronic infection. Exclusion of induction type from multivariable models did not change interpretation of fungal prophylaxis cohort, voriconazole exposure, or other variables (data not shown).

Our study is the first to look at cutaneous tumor stage in lung transplant recipients. The prophylaxis cohort and cumulative exposure to voriconazole were not associated with time to the first advanced-stage SCC (stage T2 or greater). However, the numbers of advanced SCC were relatively small, limiting the evaluation. In fact, there were no characteristics found to be associated with risk of advanced SCC in this study. However, it is noteworthy that our program includes protocol baseline and follow-up assessment by dermatology to prevent late-stage diagnoses. This vigilance likely played a role in limiting the number of advanced-stage SCC diagnoses in this study. Thus, the combination of voriconazole treatment with a vigilant SCC surveillance protocol may mitigate some of the risk of SCC morbidity, although this will require further study.

The strengths of our study include the relatively large cohort of 402 patients. We also uniquely show risk of SCC by prophylaxis era, as well as by time-dependent cumulative exposure to antifungal drugs. While the cumulative exposure to voriconazole has been examined by other groups, we are the first to examine SCC risk with other antifungals in this manner as well and we show that the increased risk of SCC is specific to voriconazole.

The limitations of our study are inherent in the single-center retrospective design. As a result, we lack information on Fitzpatrick skin type and prior sun exposure history. Furthermore, without a true randomized study, the link between voriconazole and SCC is not definitive. The targeted prophylaxis and universal prophylaxis cohorts did differ significantly by transplant type and induction treatment. However, in multivariable models, neither covariate affected the risk

of SCC. Finally, the exposures to posaconazole and itraconazole were considerably less than voriconazole in this study, and thus, the lack of significance that we observed for posaconazole and itraconazole may be a result of inadequate power rather than true difference. It is also worth noting that posaconazole use in this study was entirely the suspension form of the drug, as posaconazole delayed-release tablets were not available during the period in which these patients were studied.

In summary, our study validates and expands upon the existing literature indicating that voriconazole is risk factor for SCC in lung transplant recipients. We make the novel observation that other triazole antifungal agents do not increase the risk of SCC. As a result, we now consider other agents for antifungal prophylaxis in our center, or when voriconazole is required, we attempt to limit the duration of exposure. A strategy of regular dermatologic surveillance and cautious use of voriconazole, especially in patients at high risk of SCC, is warranted to limit the incidence SCC and related morbidity after lung transplantation.

Authorship

NAK: collected data, drafted initial manuscript, edited the manuscript and approved the final manuscript. ED: performed statistical analysis, edited the manuscript and approved the final manuscript. AZ, ML, DTB and MC: collected data and approved the final manuscript. TS, JH, VN, RS, DMS, AD, MYS, JPL, BMK, AA, DJR and JAB: contributed to the conception of the work and interpretation of results, edited and approved manuscript. DE: contributed to the conception of analysis plan, performed statistical analysis, edited manuscript and approved final manuscript. RS and SSW: contributed to the conception of the work and analysis plan, drafted manuscript, revised and approved final manuscript.

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Conflicts of interest

The authors declare no conflict of interests.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Reverse Kaplan-Meir estimate of follow-up times for targeted antifungal prophylaxis (TAP) and universal antifungal prophylaxis (UAP) cohorts where the outcome of interest is being censored.

Table S1. Repeat events proportional hazards regression models predicting recurrent squamous cell carcinoma (SCC) events.

Table S2. Computing cumulative incidence of squamous cell carcinoma (SCC) accounted for the competing risk of death.

Table S3. Univariate PH regression models predicting time to first T2 T3 SCC: UAP/TAP and covariates.

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