Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 19 May 2019 | doi:10.4414/smw.2019.20078
Cite this as: Swiss Med Wkly. 2019;149:w20078

Solid cancer development in solid organ transplant recipients within the Swiss Transplant Cohort Study

Lengwiler Emanuel[a], Stampf Susanne[b], Zippelius Alfred[c], Salati Emanuela[d], Zaman Khalil[e], Schäfer Niklaus[f], Schardt Julian[g], Siano Marco[h], Hofbauer Günther F.L.[a], the Swiss Transplant Cohort Study

[a] Department of Dermatology, University Hospital Zurich, Switzerland
[b] Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, Switzerland
[c] Department of Biomedicine, University Hospital Basel, Switzerland
[d] Division of Oncology, University Hospital Geneva, Switzerland
[e] Department of Oncology, University Hospital Lausanne, Switzerland
[f] Division of Oncology, Inselspital Hospital Lausanne, Switzerland
[g] Division of Oncology, University Bern, Switzerland
[h] Division of Oncology, Cantonal Hospital St Gallen, Switzerland

The members of the Swiss Transplant Cohort Study are: Achermann Rita, Amico Patrizia, Aubert John-David, Banz Vanessa, Beldi Guido, Benden Christian, Berger Christoph, Binet Isabelle, Bochud Pierre-Yves, Bucher Heiner, Bühler Leo, Carell Thierry, Catana Emmanuelle, Chalandon Yves, de Geest Sabina, de Rougemont Olivier, Dickenmann Michael, Duchosal Michel, Elkrief Laure, Fehr Thomas, Ferrari-Lacraz Sylvie, Garzoni Christian, Gasche Soccal Paola, Gaudet Christophe, Giostra Emiliano, Golshayan Déla, Hadaya Karine, Halter Jörg, Heim Dominik, Hess Christoph, Hillinger Sven, Hirsch Hans H., Hofbauer Günther, Huynh-Do Uyen, Immer Franz, Klaghofer Richard, Koller MichaelHead of the data center, Laesser Bettina, Lehmann Roger, Lovis Christian, Manuel Oriol, Marti Hans-Peter, Martin Pierre Yves, Meylan PascalHead, Biological samples management group, Mohacsi Paul, Morel Philippe, Mueller Ulrike, Mueller Nicolas JChairman Scientific Committee, Mueller-McKenna HelenHead of local data management, Müller Antonia, Müller Thomas, Müllhaupt Beat, Nadal David, Pascual ManuelExecutive office, Passweg Jakob, Rick Juliane, Roosnek Eddy, Rosselet Anne, Rothlin Silvia, Ruschitzka Frank, Schanz Urs, Schaub Stefan, Schnyder Aurelia, Seiler Christian, Stampf Susanne, Steiger JürgHead, Executive Office, Stirnimann Guido, Toso Christian, Van Delden ChristianExecutive office, Venetz Jean Pierre, Villard Jean, Wick MadeleineSTCS coordinator, Wilhelm Markus, Yerly Patrick

Summary

In solid organ transplant recipients (sOTRs), 5 years after transplantation cancer is a relevant cause of death. We aimed to report cancer incidence in the Swiss Transplant Cohort Study (STCS) between 2008 and 2014 and conducted a prospective cohort study of kidney, heart, lung, pancreas and liver transplant recipients enrolled into the STCS by retrospective analysis of collected data. The STCS provided data on 2758 solid organ transplants. In total, 134 cases of cancer were observed (30 liver, 21 prostate, 18 lung, 13 kidney, 52 other cancers). Standardised incidence ratios (SIRs) were highest for liver cancer, kidney cancer, thyroid cancer, gastric cancer, bladder cancer, cancer of the oral cavity and the pharynx and for lung cancer. Cancer occurrence differed according to the transplanted organ. Cancers were mainly diagnosed at World Health Organisation (WHO) stages I and IV. Treatment received was mainly surgery and, in some cases, included also radiation and/or chemotherapy. Bladder, kidney, liver, lung and prostate cancer were detected at a younger age compared with the general population. Cumulative hazards for death were increased for transplant recipients with cancer. Solid organ transplant recipients show an organ specific increase of cancer compared with the general Swiss population.

Clinical trial registration number: NCT02333279

Keywords: *solid organ transplantation, cancer, kidney transplantation, heart transplantation, liver transplantation, lung transplantation, pancreas transplantation, non-cutaneous malignancies, immunosuppression*

Author contributions
EL was involved in concept, design, data collection, data analysis and interpretation, writing of the article. GH contributed to concept, design, data analysis and interpretation, writing of the article. SS performed data analysis and statistics. AZ, ES, KZ, MS, NS and JS contributed to data collection and critical revision of the article.

Correspondence:
Günther FL Hofbauer, MD, University Hospital Zurich, Department of Dermatology, Gloriastrasse 31, CH-8091 Zurich, Hofbauer[at]usz.ch

Introduction

There is a large body of evidence indicating that 4 to 5% of solid organ transplant recipients (sOTRs) develop a malignancy after transplantation [1], which corresponds to an approximately two- to four-fold elevated risk compared to the general population [2–5]. According to a US study, the risk for malignancies is elevated for 32 different cancer types, with the highest risk for non-Hodgkin's lym-

phoma, lung cancer, liver cancer and kidney cancer [2]. The risk for infection-related malignancies (such as liver cancer) is generally higher than for non-infection-related malignancies; however, some non-infection-related malignancies, such as lip cancer, kidney cancer, thyroid cancer and others, are also more common in sOTRs than in the general population [2] [6]. Squamous cancer of the lip, non-Hodgkin's lymphoma, kidney and bladder cancer are the most reported cancer types in kidney transplant recipients [4] [7]. In heart transplant recipients, the risk is most elevated for non-Hodgkin's lymphoma, oral cancer (comprising cancers of the oral cavity, oropharynx and lips) and lung cancer [8]. An Australian study associated lung transplantation with an increased risk for non-Hodgkin's lymphoma, Merkel cell carcinoma and cancers of the vulva, lip, lung and colorectum. The same study showed an elevated risk for non-Hodgkin's lymphoma, Kaposi sarcoma, colorectal cancer and lip cancer after liver transplantation [4].

The STCS aims at a comprehensive and structured data collection for all solid organ transplant recipients in Switzerland since May 2008 [9]. Our objective is to report the aggregated results of solid cancer cases occurring in this Swiss Transplant cohort. With the hypothesis of increased cancer incidence, we compare their incidence to the general population and report on treatment and outcome.

Methods

Swiss transplant registry and collection of data

The STCS collects data from all six transplantation centres in Switzerland and started enrolment of patients in May 2008. Patients' base-line data are collected at the time of transplantation and the transplantation centres provide follow-up data on recipients' vital status, health issues and graft function 6 and 12 months after transplantation, followed by yearly follow-ups. There was no specific screening procedure beyond the public screening programmes. Once a cancer became apparent in clinical follow-up, this date was entered into the data base. Each cancer was checked for histological findings to differentiate between primary and metastatic cancers. A detailed description of the design and methodology of the STCS is provided by Koller et al. [10].

For our report, the following inclusion criteria were applied: all kidney, liver, heart, lung, pancreas, islet cell and small bowel transplant recipients who were included in the STCS data base between May 2008 and September 2014. Patients with multiple organ transplantation were included as well. Patients contributed to the study observation time until death or end of follow-up for other reasons, up to the censoring date of 31 December 2014. Patients with graft loss remained in the study population and were assessed in the subgroup of their original transplanted organ, since they remained at risk for cancer development. Transplant recipients with pre-existing malignancies were included to adequately assess the overall cancer risk in our study population. In these patients, no pre-emptive modification in immunosuppression regimens or post-transplant screening strategies was pursued. There was no age restriction for inclusion. Exclusion criteria were: withdrawal of consent, a non-solid organ transplantation (such as haematopoietic stem cell transplantation) as these transplant types are not registered in the STCS, and if the information in the STCS was insufficient for detailed analysis of cancer development. Haematological malignancies (such as post-transplant lymphoproliferative disorder) and skin cancers were excluded from this analysis, as they will be addressed separately in another STCS report. All World Health Organization (WHO) stage 0 cases were excluded because of limited duration of follow up, limited biological relevance in comparison with invasive cancers and inherent validation uncertainty on data capture.

The two main points to avoid bias were: no selection of specific sOTR, but all sOTRs in Switzerland included, thus avoiding selection bias; the data collected in a prospective manner and with uniform data collection protocols in all centres in order to avoid bias of retrospective studies. The cancer data for the reference group was provided by the National Institute for Cancer Epidemiology and Registration (NICER). NICER compiles and aggregates data that are collected by the different cantonal and regional cancer registries of Switzerland and provided a corresponding reference group, since the NICER registry covers most of the Swiss population [11].

Our study was approved by the respective local ethics committee of all involved centres: ethics committee Bern, ethics committee of northwest and central Switzerland, ethics committee St Gallen, ethics committee Vaud, ethics committee Geneva and the lead ethics committee Zurich (Swiss national clinical trial portal number SNCTP000000587).

Statistical analysis

For patients with multiple cancers, each cancer was treated as a separate event for the statistical analysis. The expected number of cancer cases in the SCTS was calculated as the NICER Swiss cancer rate multiplied by observation time in the STCS. Relative risks of cancer in transplant recipients compared to the general population were expressed as standardised incidence ratios (SIRs) per 100,000 person-years, i.e., observed/expected cases. The SIRs were calculated indirectly with the Swiss general population as reference population. Further, there was no stratification of our population. Exact confidence intervals and p-values were calculated based on the Byar formula [12] often applied in similar studies [2].

We also calculated the median age at cancer diagnosis with interquartile range (IQR), as well as the time from trans-

ABBREVIATIONS:

CI	confidence interval
HBV	hepatitis B virus
HCV	hepatitis C virus
IQR	interquartile range
NICER	National Institute for Cancer Epidemiology and Registration
SEER	Surveillance, Epidemiology and End Results Program
SIR	standardised incidence ratio
sOTR	solid organ transplant recipient
STCS	Swiss Transplant Cohort Study
WHO	World Health Organization

plantation to first cancer occurrence with IQR. We applied the Wilcoxon signed rank test to check for any difference in median age at cancer detection in transplant recipients compared with the general Swiss population with the respective cancer type. The cumulative hazard function was used to find any difference for the cumulative hazards for death in transplant recipients with cancer compared with those without cancer as described by Cleves et al. [13]. If patients developed multiple cancers, the time of the first cancer incidence was used to calculate the cumulative hazards for death.

Results

The characteristics of our patient cohort are shown in table 1. Between May 2008 and September 2014, the STCS included 2758 patients with a solid organ transplant, with a median follow-up of 3 years, yielding 8563 person-years. They received 1557 (56.5%) kidney transplants, 557 (20.2%) liver transplants, 278 (10.1%) lung transplants, 208 (7.5%) heart transplants and 158 (5.7%) other or combined transplants (i.e., single pancreas, small bowel, islet cells or combined, e.g. kidney-lung). The majority of transplant recipients were male (63.9%). As shown in table 2, the infection rates for hepatitis B virus (HBV) and hepatitis C virus (HCV) were reported to be higher for liver transplant recipients, as HBV and HCV often lead to liver cirrhosis and therefore to liver transplantation. The number of malignancies before STCS inclusion was also higher in patients with liver transplant, since previous liver cancer made the patients eligible for a liver transplant. Most transplant recipients were treated with an immunosuppressive regimen comprising calcineurin inhibitors (95.5%) and mycophenolate mofetil (90.7%).

All post-transplant cancer findings (141 patients) registered in the STCS data base were verified by reviewing the patient files in the respective hospitals. Eighteen patients were excluded. In 13 patients, each with one cancer, cancer diagnosis could not be validated (e.g., a benign tumour was registered as cancer or the cancer occurred before transplantation). In another five patients, the transplant was before May 2008 and thus did not meet inclusion criteria. No patient had to be excluded because of insufficient data. In the remaining 123 patients, a total of 134 malignancies were noted (66 malignancies in kidney transplant re-

Table 1: Patient characteristics.

	Transplanted organ					
	Kidney	Liver	Lung	Heart	Other	Total
Patients, n (%)	1557 (56.5)	557 (20.2)	278 (10.1)	208 (7.5)	158 (5.7)	2758 (100.0)
Male sex, n (%)	1010 (64.9%)	365 (65.5%)	138 (49.6%)	156 (75%)	94 (59.5%)	1763 (63.9%)
Age at transplantation (years), median (IQR)	53.9 (41.7–62.9)	54.4 (43.9–61.2)	54.2 (37.7–60.6)	51.7 (38–59.8)	46.1 (38.4–54.8)	53.5 (41.4–61.8)
Previous transplantations, n (%)	264 (17%)	25 (4.5%)	10 (3.6%)	1 (0.5%)	40 (25.3%)	340 (12.3%)
Re-/second transplantations, n (%)	29 (1.9%)	37 (6.6%)	8 (2.9%)	1 (0.5%)	19 (12%)	94 (3.4%)
– Re-transplantations, n	24	31	8	1	15	79
– Second transplantations (different organ), n	5	6	0	0	4	15
Cancer before transplantation, n (%)	165 (10.6%)	223 (40%)	26 (9.4%)	8 (3.8%)	13 (8.2%)	435 (15.8%)
Time of follow-up (years), median (IQR)	3.3 (1.6–5)	2.7 (1.2–4.5)	2.6 (1.1–3.8)	2.6 (0.9–4.3)	3 (1.4–4.8)	3 (1.4–4.8)
Primary non-function, n (%)	15 (1%)	11 (2%)	1 (0.4%)	3 (1.4%)	5 (3.2%)	35 (1.3%)
Graft loss, n (%)	96 (6.2%)	43 (7.7%)	31 (11.2%)	14 (6.7%)	34 (21.5%)	218 (7.9%)
Dropout, n (%)	11 (0.7%)	3 (0.5%)	1 (0.4%)	1 (0.5%)	4 (2.5%)	20 (0.7%)
Death, n (%)	104 (6.7%)	90 (16.2%)	75 (27%)	38 (18.3%)	15 (9.5%)	322 (11.7%)

IQR = interquartile range There were 8 patients with both primary non-function and graft loss for different organ transplants. The baseline for immunosuppressive medication was defined as medication start within 7 days before and 7 days after transplantation. Other transplanted organs included multiple transplantations of different organs, single pancreas, small bowel or islet cells transplantation.

Table 2: Serostatus and immunosuppressive medication at baseline.

	Transplanted organ					
	Kidney	Liver	Lung	Heart	Other	Total
Serostatus at baseline						
EBV positive, n (%)	1466 (94.2%)	475 (85.3%)	246 (88.5%)	188 (90.4%)	148 (93.7%)	2523 (91.5%)
– missing, n	7	26	2	1	3	39
CMV positive [n, (%)]	913 (58.6%)	384 (68.9%)	144 (51.8%)	110 (52.9%)	92 (58.2%)	1643 (59.6%)
– missing, n	6	0	0	0	4	10
HBV positive, n (%)	20 (1.3%)	55 (9.9%)	2 (0.7%)	3 (1.4%)	2 (1.3%)	82 (3%)
– missing, n	5	6	2	0	2	15
HCV positive, n (%)	49 (3.1%)	153 (27.5%)	5 (1.8%)	2 (1%)	9 (5.7%)	218 (7.9%)
– missing, n	6	4	2	0	2	14
Immunosuppressive medication at baseline						
Calcineurin inhibitors, n (%)	1508 (96.9%)	511 (91.7%)	275 (98.9%)	184 (88.5%)	155 (98.1%)	2633 (95.5%)
Mycophenolate mofetil, n (%)	1520 (97.6%)	383 (68.8%)	268 (96.4%)	184 (88.5%)	146 (92.4%)	2501 (90.7%)
mTOR-inhibitors, n (%)	17 (1.1%)	17 (3.1%)	1 (0.4%)	16 (7.7%)	10 (6.3%)	61 (2.2%)
Azathioprine, n (%)	12 (0.8%)	4 (0.7%)	4 (1.4%)	45 (21.6%)	4 (2.5%)	69 (2.5%)

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; mTOR = mammalian target of rapamycin Other transplanted organs included multiple transplantations of different organs, single pancreas, small bowel or islet cells transplantations.

cipients, 53 in liver, 7 in lung, 6 in heart and 2 in combined transplant patients) (table 3). High numbers were found for liver cancer in liver transplant recipients (n = 29, a total of 30 liver cancers), of whom 27 patients had liver malignancy before transplantation. In kidney transplant recipients, high numbers of prostate (n = 18), kidney (n = 13), lung (n = 8), bladder (n = 5) and thyroid cancers (n = 5) were noted. In total, in 4.5% of all transplant recipients included in our analysis cancer was observed, and the incidence was especially high in liver transplant recipients (8.8%).

The cancer incidence within the STCS was compared with the general Swiss population by calculation of the SIR. For kidney transplant recipients, an elevated SIR was found for kidney, thyroid, brain, bladder and prostate cancer. In liver transplant recipients, higher incidences were reported for liver, oral cavity and pharyngeal, pancreas, gastric and lung cancer (table 4). In the remaining transplant recipients, a higher risk for lung cancer in lung transplant recipients and for testicular cancer in heart transplant recipients was detected.

In our analysis of the median age at cancer diagnosis, we detected an earlier occurrence of bladder, kidney, liver, lung and prostate cancer. For the other cancer types, no difference was detected (fig. 1).

As shown in table 5, most cancer cases were diagnosed at either WHO stage IV (n = 56) or stage I (n = 40). More specifically, of 30 liver cancers, 25 were WHO stage IV at the time of diagnosis. Kidney cancers were more likely to be diagnosed at earlier stages as 13 out of 14 kidney cancers were registered at WHO stage I.

Patients' files were searched to capture all treatments patients received related to their cancers. The treatments are reported in table 6, according to affected organ and histological subtype. Treatment was grouped for patients who received surgery (total n = 73), chemotherapy (total n = 22), radiotherapy (total n = 24) and other therapies (total n = 126), such as transurethral resection of the prostate or hormonal therapy.

Figure 2 shows the cumulative hazards for death within the STCS for transplant recipients with cancer compared to those without cancer. The hazards for death in the population with cancer increase early after transplantation and become less common after 2 years of follow-up, whereas for the population without cancer the hazards for death increases only slowly over time.

Discussion

In this first analysis of the Swiss Transplant Cohort Study, we found 134 cancers, corresponding to 4.5% of all transplant recipients, with a median follow-up time of 3 years. An increased risk was seen for a wide range of malignancies.

Our patients showed characteristics similar to populations in similar studies. Other cohorts have included 175,732 [2], 193,905 [5] and 5931 [14] patients, whereas our study oversees 2758 sOTRs. A higher proportion of male than female sOTRs was reported by Engels et al. (60.9% male), Sampaio et al. (53.9–80.6%, depending on transplant type) and Adami et al. (61%) [2, 5, 14]. The median age at transplantation for our population was higher than documented by Engels et al. (47 years) and Adami et al. (46

Table 3: Solid cancers by organ affected.

	ICD-10	Transplanted organ					
		Kidney	Liver	Lung	Heart	Other	Total
Cancer by organ affected							
Oral cavity and pharynx	C00-14	1	4	0	0	0	5
Oesophagus	C15	1	0	0	0	0	1
Stomach	C16	2	2	1	0	0	5
Small intestine	C17	1	0	0	0	0	1
Colon, rectum	C18–20	1	2	1	0	0	4
Anus, anal canal	C21	0	1	0	0	0	1
Liver	C22	1	29	0	0	0	30
Extrahepatic bile duct	C23–24	1	0	1	0	0	2
Pancreas	C25	0	4	0	0	0	4
Vocal cord	C32	0	1	0	0	0	1
Lung	C33–34	8	5	4	1	0	18
Connective tissue	C47, C49	1	0	0	0	0	1
Breast	C50	3	0	0	0	0	3
Prostate	C61	18	0	0	2	1	21
Testis	C62	0	0	0	2	0	2
Kidney	C64	13	0	0	0	0	13
Bladder	C67	5	0	0	1	0	6
Brain	C70–72	3	0	0	0	0	3
Thyroid	C73	5	0	0	0	1	6
Endocrine system	n.a.	1	2	0	0	0	3
Vascular system	n.a.	1	2	0	0	0	3
Unknown primary	n.a.	0	1	0	0	0	1
Total n of cancers (% of transplant recipients)		**66 (3.8%)**	**53 (8.8%)**	**7 (2.5%)**	**6 (2.9%)**	**2 (1.3%)**	**134 (4.5%)**
Time to cancer (months), median (IQR)		**24.5 (13.1–41.5)**	**18 (6.3–28.4)**	**22.3 (12.7–49.9)**	**25.3 (22.2–39.2)**	**5.3 (3.3–7.3)**	**21.1 (9.8–34.5)**

ICD-10 = International statistical classification of diseases and related health problems (Version 10, 2016); IQR = interquartile range. Other transplanted organs included multiple transplantations of different organs, single pancreas, small bowel or islet cells transplantations.

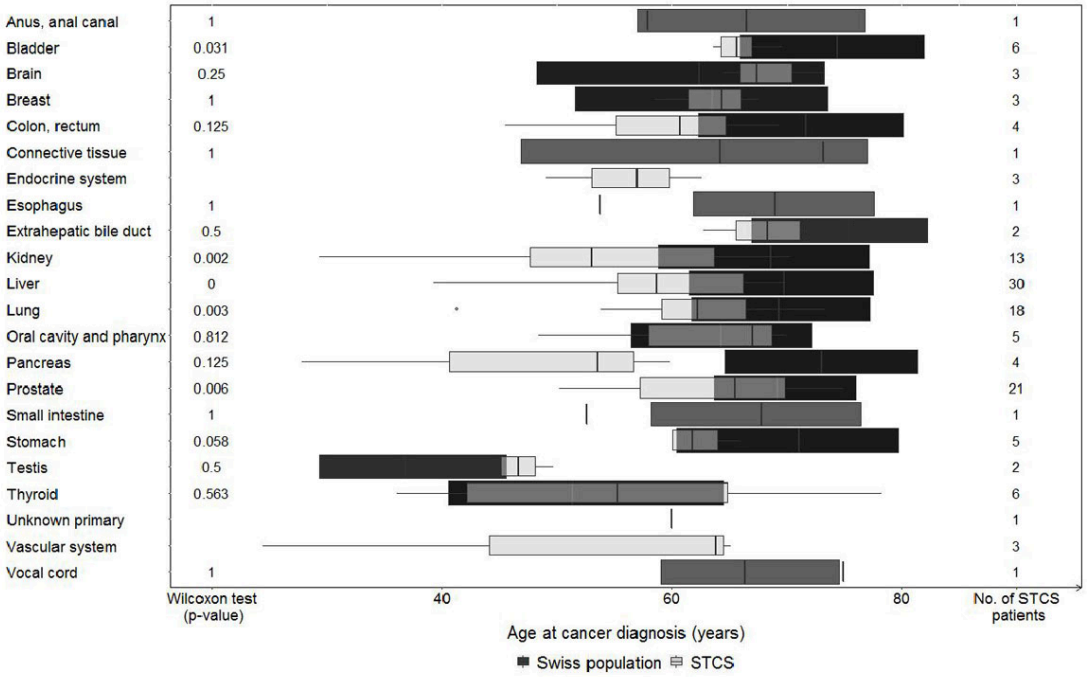
years) [2, 14]. Our population included a small proportion of patients with re-transplants, who have less exposure to immunosuppression than patients with previous transplants. Our follow-up time was relatively short compared

Table 4: Cancer risk by transplanted organ type.

Cancer by organ system affected	Transplanted organ											
	Kidney		Liver		Lung		Heart		Other		Total	
	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI
Oral cavity and pharynx	1.38	0.02–7.69	**17.72**	**4.77–45.36**	–		–		–		**4.17**	**1.34–9.73**
Oesophagus	2.76	0.04–15.38	–		–		–		–		1.67	0.02–9.28
Stomach	3.52	0.4–12.7	**11.28**	**1.27–40.71**	12.47	0.16–69.37	–		–		**5.31**	**1.71–12.39**
Small intestine	8.06	0.11–44.86	–		–		–		–		4.87	0.06–27.07
Colon, rectum	0.37	0–2.04	2.34	0.26–8.47	2.59	0.03–14.43	–		–		0.88	0.24–2.26
Anus, anal canal	24.81	0.32–139.02	24.81	0.32–138.02	–		–		–		4.67	0.06–25.99
Liver	1.95	0.03–10.87	**181.67**	**121.64–260.91**	–		–		–		**35.39**	**23.87–50.52**
Extrahepatic bile duct	4.96	0.06–27.6	–		35.17	0.46–195.67	–		–		5.99	0.67–21.62
Pancreas	–		**15.70**	**4.22–40.2**	–		–		–		2.96	0.8–7.57
Vocal cord	–		18.24	0.24–101.48	–		–		–		3.43	0.04–19.11
Lung	2.99	1.29–5.9	**6.00**	**1.93–14**	**10.61**	**2.85–27.17**	3.50	0.05–19.48	–		**4.07**	**2.41–6.43**
Connective tissue	5.69	0.07–31.66	–		–		–		–		3.43	0.04–19.11
Breast	0.78	0.16–2.27	–		–		–		–		0.47	0.09–1.37
Prostate	**4.47**	**2.64–7.06**	–		–		4.64	0.52–16.76	2.56	0.03–14.24	**3.14**	**1.95–4.81**
Testis	–		–		–		**90.57**	**10.17–327**	–		6.77	0.76–24.43
Kidney	**22.26**	**11.84–38.07**	–		–		–		–		**13.43**	**7.15–22.98**
Bladder	**6.67**	**2.15–15.57**	–		–		12.49	0.16–69.47	–		**4.83**	**1.76–10.52**
Brain	**7.44**	**1.5–21.74**	–		–		–		–		4.49	0.9–13.12
Thyroid	**10.75**	**3.46–25.09**	–		–		–		22.18	0.29–123.42	**7.79**	**2.84–16.95**
Endocrine system		n.a.		n.a.		n.a.		n.a.		n.a.		n.a.
Vascular system		n.a.		n.a.		n.a.		n.a.		n.a.		n.a.
Unknown primary		n.a.		n.a.		n.a.		n.a.		n.a.		n.a.

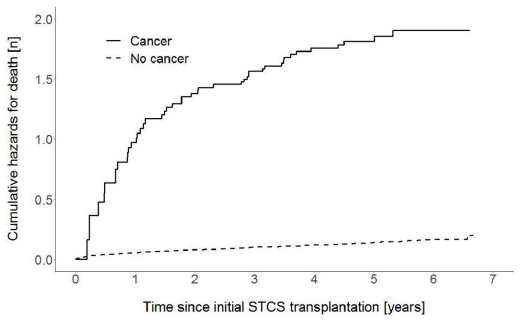
CI = confidence interval; n.a. = not applicable; SIR = standardised incidence ratio Other transplanted organs included multiple transplantations of different organs, single pancreas, small bowel or islet cells transplantations. "-" means that there were no cancer cases. Significantly different SIR are printed in bold type. "n.a." means that there was no data for the general population available and thus no SIR could be calculated..

Figure 1: Comparison of age at cancer diagnosis. Black bars represent the Swiss population. White bars represent the Swiss transplant cohort study population. Differences in age were calculated using the Wilcoxon test, with respective p-values shown for each cancer. Right column shows number of patients. The single dot at lung cancer represents a statistical outlier. No. = numbers; STCS = Swiss Transplant Cohort Study



with Adami et al. (6.8 years) and Engels et al., who included patients from as early as 1987 [2] [14]. The proportion of graft failures within our follow-up was smaller than that reported by Kim et al. (approximately 20% for liver transplants) and Hart et al. (approximately 8% for kidney transplants) [15, 16]. In comparison with other cohorts, our study group seems similar in composition, although smaller. The serostatus for HBV and HCV was more commonly positive in liver transplant recipients than non-liver transplant recipients and was comparable to the findings of Hoffmann et al. (5.7% HBV positive in liver transplant recipients versus 1.4% in non-liver transplant recipients; 36.8% HCV positive versus 3.9%, respectively) [17].

Figure 2: Cumulative hazards for death within the Swiss Transplant Cohort Study (STCS) cohort. Cumulative hazard function after time of transplantation expressed as the number of events to be expected for any solid organ transplant recipients at the corresponding time of follow-up.



We observed incidence rates of malignancies in our cohort higher than in the general population for eight cancer types, namely cancer of the liver, kidney, thyroid, stomach, bladder, oral cavity and pharynx, lung and prostate. Our findings are for the most part consistent with Engels et al. who also found an increased risk for the cancer types mentioned previously (liver: SIR 11.56, 95% CI 10.83–12.33; kidney: SIR 4.65, 95% CI 4.32–4.99; thyroid: SIR 2.95, 95% CI 2.58–3.34; stomach: SIR 1.67, 95% CI 1.42–1.96;

Table 5: Cancer WHO stage at detection.

Cancer by organ system affected	Histological type	n	WHO stage				
			I	II	III	IV	n.a.
Oral cavity and pharynx	Squamous cell carcinoma	5	2	0	2	1	0
Oesophagus	Squamous cell carcinoma	1	0	0	1	0	0
Stomach	Adenocarcinoma	4	0	1	0	3	0
	Signet-ring cell carcinoma	1	1	0	0	0	0
Small intestine	Neuroendocrine carcinoma	1	0	1	0	0	0
Colon, rectum	Adenocarcinoma	2	0	0	2	0	0
	Sarcoma	1	1	0	0	0	0
	Unknown	1	0	0	0	0	1
Anus, anal canal	Squamous cell carcinoma	1	0	0	1	0	0
Liver	Cholangiocarcinoma	5	0	0	0	5	0
	Hepatocellular carcinoma	25	0	4	1	20	0
Extrahepatic bile duct	Cholangiocarcinoma	2	0	2	0	0	0
Pancreas	Adenocarcinoma	1	0	0	0	1	0
	Neuroendocrine carcinoma	2	0	0	0	2	0
	Pancreatoblastoma	1	0	0	0	1	0
Vocal cord	Squamous cell carcinoma	1	1	0	0	0	0
Lung	Small cell carcinoma	5	0	0	1	4	0
	Adenocarcinoma	12	2	3	3	4	0
	Squamous cell carcinoma	1	0	0	0	1	0
Connective tissue	Chondrosarcoma	1	1	0	0	0	0
Breast	Invasive ductal carcinoma	2	0	1	0	1	0
	Tubular carcinoma	1	1	0	0	0	0
Prostate	Adenocarcinoma	21	7	8	3	3	0
Testis	Mixed germ cell tumour	1	1	0	0	0	0
	Seminoma	1	1	0	0	0	0
Kidney	Clear cell renal cell carcinoma	4	4	0	0	0	0
	Mucinous tubular spindle cell carcinoma	1	1	0	0	0	0
	Papillary renal cell carcinoma	8	7	0	1	0	0
Bladder	Urothelial carcinoma	6	4	1	0	1	0
Brain	Astrocytoma	1	1	0	0	0	0
	Glioblastoma	1	0	0	0	1	0
	Meningioma	1	0	1	0	0	0
Thymus	Papillary adenocarcinoma	6	4	0	0	2	0
Endocrine system	Neuroendocrine carcinoma	3	1	0	0	2	0
Vascular system	Angiosarcoma	1	0	0	0	1	0
	Kaposi sarcoma	2	0	0	0	2	0
Unknown primary	Unknown	1	0	0	0	1	0
Total		**134**	**40**	**22**	**15**	**56**	**1**

n.a. = not applicable. Tumors in WHO stage 0 were not included for analysis, see methods.

bladder: SIR 1.52, 95% CI 1.33–1.73; oral cavity and pharynx: SIR 2.56, 95% CI 2.17–3.01; lung: SIR 1.97, 95% CI 1.86–2.08), whereas the risk for prostate cancer was not increased. Engels et al. were, however, able to report a higher risk for multiple other cancer types thanks to a larger study population, potentially also due to other factors, such as medication or difference in genetic background [2].

Hoshida et al. showed an increased relative risk for malignancies in the kidney (SIR 79.96, 95% CI 39.98–114.95) and the thyroid (SIR 12.43, 95% CI2.38–33.70) in kidney transplant recipients, which is in line with our findings. They, however, did not find a higher risk for bladder, prostate and brain cancer as our study did [18]. In larger studies, Cheung et al. and Li et al. reported a greatly increased risk for kidney cancers (SIR 12.5, 95% CI 8.51-18.36 and SIR 44.29, 95% CI 36.24–54.06) and bladder cancers (SIR 8.22, 95% CI 4.67–14.47 and SIR 42.89, 95% CI 34.08–53.98) in kidney transplant recipients, both being attributed to multiple factors including immunosuppressive status, underlying renal diseases, genetic background and environmental factors [7, 19]. An often cited reason for the elevated risk of kidney cancer in kidney transplant recipients is the malignant transformation of cysts that develop in end-stage renal disease [2, 7]. Lung cancer risk was increased in lung transplant recipients. This can probably be attributed to smoking-related lung diseases, such as chronic obstructive pulmonary disease, as indication for the lung transplant. Minal et al. and Dickson et al. reported an increased risk for lung cancer, mostly in single-lung recipients who develop lung cancer in the remaining native lung [20, 21]. Increased liver cancer risk in liver transplant recipients is probably mainly due to two factors. Firstly, liver transplantion is a common treatment for hepatocellular cancer, with the risk for residual cancer after the initial treatment. Thus, the post-transplant liver cancers are not *de novo* but rather relapses of pre-existing cancers. The second reason might be the high prevalence of carcinogenic infections such as HBV or HCV. Frequently these infections drove the initial liver cancer that needed liver transplantation in first place [2].

Table 6: Cancer treatment following diagnosis.

Cancer by organ affected	Histological type	n	Surgery	Chemotherapy	Radiotherapy	Other therapy
Oral cavity and pharynx	Squamous cell carcinoma	5	5	1	1	1
Oesophagus	Squamous cell carcinoma	1	1	0	0	0
Stomach	Adenocarcinoma	4	0	2	0	0
	Signet-ring cell carcinoma	1	1	0	0	0
Small intestine	Neuroendocrine carcinoma	1	1	0	0	0
Colon, rectum	Adenocarcinoma	2	2	2	1	0
	Sarcoma	1	1	0	0	0
	Unknown	1	0	0	0	0
Anus, anal canal	Squamous cell carcinoma	1	0	0	0	0
Liver	Cholangiocarcinoma	5	0	3	1	0
	Hepatocellular carcinoma	25	7	4	4	6
Extrahepatic bile duct	Cholangiocarcinoma	2	2	0	0	0
Pancreas	Adenocarcinoma	1	0	0	0	0
	Neuroendocrine carcinoma	2	1	0	0	1
	Pancreatoblastoma	1	0	1	0	0
Vocal cord	Squamous cell carcinoma	1	1	0	0	0
Lung	Small cell carcinoma	5	0	3	1	0
	Adenocarcinoma	12	8	3	4	0
	Squamous cell carcinoma	1	0	1	0	0
Connective tissue	Chondrosarcoma	1	1	0	1	0
Breast	Invasive ductal carcinoma	2	1	0	0	2
	Tubular carcinoma	1	1	0	0	0
Prostate	Adenocarcinoma	21	8	1	9	5
Testis	Mixed germ cell tumor	1	1	0	0	0
	Seminoma	1	1	0	0	0
Kidney	Clear cell renal cell carcinoma	4	4	0	0	0
	Mucinous tubular spindle cell carcinoma	1	1	0	0	0
	Papillary renal cell carcinoma	8	8	0	0	0
Bladder	Urothelial carcinoma	6	5	1	0	0
Brain	Astrocytoma	1	0	0	0	0
	Glioblastoma	1	1	0	1	0
	Meningioma	1	1	0	0	0
Thymus	Papillary adenocarcinoma	6	6	0	1	2
Endocrine system	Neuroendocrine carcinoma	3	3	0	0	0
Vascular system	Angiosarcoma	1	0	0	0	0
	Kaposi sarcoma	2	1	0	0	0
Unknown primary	Unknown	1	0	0	0	0
Total		**134**	**73**	**22**	**24**	**18**

For therapies multiple options were possible. Some cancers were treated with multiple modalities.

In general, the most cited reason for the increased cancer risk in sOTRs is prolonged immunosuppressive therapy. Long-term immunosuppression increases the risk of oncovirally driven malignancies substantially [7]. A second important mechanism is the nonspecific mode of action of most immunosuppressive agents leading to impaired tumour immunosurveillance. Third, some immunosuppressive drugs have pro-oncogenic properties themselves in addition to their immunosuppressive properties. It has been shown that calcineurin inhibitors such as ciclosporin, and to a lesser extent azathioprine and prednisolone, cause a significant impairment of DNA repair mechanisms or drive cancer formation directly, leading to elevated cancer risk in sOTRs [2] [22] [23]. Additionally, ciclosporin is linked to promoting angiogenesis and invasiveness of non-transformed cells *in vitro* by inducing transcription and expression of the *TGF-β1* gene [7] [8].

Hoshida et al. described earlier cancer development in their kidney transplant recipients. The median age of all their cancer patients was 40.0 years, whereas for renal and bladder cancer it was 41.0 years and 43.5 years, respectively. This corresponds to a clearly younger age at cancer development compared with the general population in Japan (64 years) [18]. This study analysed only kidney transplant recipients, but their findings conform to our results on the subgroup of kidney transplant recipients in the STCS.

Cancer stages at diagnosis for lung cancer were comparable to the data for the general Swiss population. According to the Surveillance, Epidemiology, and End Results Program (SEER) database, lung cancers are most often detected in WHO stage IV (57%) and less often in regional (22%) or localised (16%) stages [24]. Liver cancers are commonly found in a localised stage (44%) and less frequently in regional (27%) or metastasised (18%) stages [25]. Our high proportion of WHO stage IV at diagnosis for liver cancer is probably caused by the high prevalence of liver cancer in liver transplant recipients before transplantation. Kidney cancers are mostly diagnosed at localised stages (65%) and less so at regional (16%) or metastasised stages (16%), whereas in our population the cancers were almost exclusively found in WHO stage I, potentially related to closer follow-up in kidney transplant recipients [26]. For prostate cancer, our findings are comparable to the findings of Rohrmann et al., who reported cancer detection mostly in stage I (38.4%) and stage II (22.7%) and less often in stage III (13.1%) and stage IV (10.8%) [27]. In summary, cancer stage at diagnosis for prostate and lung cancer were comparable to the general Swiss population, whereas liver and kidney cancers showed a different pattern.

We found that kidney cancers in the STCS cohort received surgical treatment only, potentially because of rather limited disease. For other common cancer types, such as liver, lung and prostate cancer, the treatment often included serial and multi-modal therapies, as would be expected for these kinds of cancer. Zhou et al. described a 5-year overall mortality of 30.4% for liver recipients with *de novo* malignancies after transplantation and 31.4% mortality for liver recipients without malignancy [28]. The higher mortality for sOTRs without cancer does not support our findings of an increased cumulative hazard of death for sOTRs with cancer. We observed a higher incidence of all-cause death for sOTRs with cancer in the first 2 years compared with later years after transplantation. We speculate that by the onset of immunosuppression at transplantation, the natural course of disease for cancer would be accelerated. Thus, patients with incipient and as yet undiagnosed cancer at transplantation would fare worse under immunosuppression, contributing to all-cause death in the first 2 years more than in later years.

Although our study gives an overview of the cancer risk in sOTRs, it is limited by the relatively small population size and therefore small number of incident cancers, which does not yet allow any detailed analysis owing to the limited follow-up time, as cancer incidence probably increases with prolonged immunosuppressive treatment. As the STCS as a prospective cohort will continue to collect data, later studies will provide longer-term data. Also, some patients had prior transplantations in some of which different organs were transplanted. These patients had been exposed to potentially cancer-inducing risk (immunosuppression) prior to inclusion in our study. Because there were only a few patients with prior transplantations, we did not calculate the SIRs for them separately. Additionally, there was no uniform protocol for cancer screening prior to transplantation across all centres, which may have led to an overestimation of cancer incidence. Further limitations include potential divergences between cancer at diagnosis and staging, as full staging was only performed several weeks or months after cancer diagnosis, which may cause an overestimation of initial cancer stages. For the evaluation of cancer treatment, we searched patient files outside of the structured cohort data that are prospectively gathered. Therapies may not all have been registered for patient charts outside the cohort; this may have caused an underestimation of cancer treatments.

The strengths of our study include the inclusion of all sOTRs in Switzerland during the study period, as every transplantation centre in Switzerland has to provide minimum data to the STCS. Even patients moving within Switzerland were usually not lost to follow-up as they continued to be monitored by a different transplantation centre that is an active member of the STCS. Also, the relatively limited number of cancers allowed us to double-check all the findings by source verification in patient files. Therefore, incorrectly entered malignancies could be eliminated for our analysis.

In conclusion, we were able to give an overview of the cancer risk in Swiss sOTRs, who are susceptible to a wide range of cancer types. Depending on the transplant, sOTRs were at increased risk for different cancers. Kidney transplant recipients were at an increased risk for renal cell carcinoma, and prostate, bladder, thyroid and brain cancer; liver transplant recipients were more likely to develop hepatocellular carcinomas, gastric, pancreas and lung cancers, and cancer of the oral cavity and pharynx. For lung transplant recipients we observed an increased risk of lung cancer, whereas in heart transplant recipients risk was increased for cancer of the testis. Building on the results of our study, with a short follow-up but a reliable cohort, extended studies will help to improve cancer surveillance and prevention strategies in sOTRs.

Acknowledgments
We thank all patients, doctors, nurses associated with the STCS for their co-operation.

Financial disclosure
This observational study was not supported by external funding sources.

Potential competing interests
Not all author forms received

All authors had full access to all data in the study and take final responsibility for the decision to submit for publication. The authors of this manuscript have no conflict of interest to disclose.

References

1 Rashti SL. Themes in Literature Related to Incidence, Risk, and Prevention of Cancer in Solid-Organ Transplantation Recipients on Immunosuppressive Therapy. Cancer Nurs. 2019;42(1):E28–35. doi: http://dx.doi.org/10.1097/NCC.0000000000000558. PubMed.
2 Engels EA, Pfeiffer RM, Fraumeni JF, Jr, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA. 2011;306(17):1891–901. doi: http://dx.doi.org/10.1001/jama.2011.1592. PubMed.
3 Miao Y, Everly JJ, Gross TG, Tevar AD, First MR, Alloway RR, et al. De novo cancers arising in organ transplant recipients are associated with adverse outcomes compared with the general population. Transplantation. 2009;87(9):1347–59. Available at: https://journals.lww.com/transplantjournal/Fulltext/2009/05150/De_Novo_Cancers_Arising_in_Organ_Transplant.14.aspx. doi: http://dx.doi.org/10.1097/TP.0b013e3181a238f6. PubMed.
4 Villeneuve PJ, Schaubel DE, Fenton SS, Shepherd FA, Jiang Y, Mao Y. Cancer incidence among Canadian kidney transplant recipients. Am J Transplant. 2007;7(4):941–8. doi: http://dx.doi.org/10.1111/j.1600-6143.2007.01736.x. PubMed.
5 Sampaio MS, Cho YW, Qazi Y, Bunnapradist S, Hutchinson IV, Shah T. Posttransplant malignancies in solid organ adult recipients: an analysis of the U.S. National Transplant Database. Transplantation. 2012;94(10):990–8. doi: http://dx.doi.org/10.1097/TP.0b013e318270bc7b. PubMed.
6 Chapman JR, Webster AC, Wong G. Cancer in the transplant recipient. Cold Spring Harb Perspect Med. 2013;3(7):a015677–015677. doi: http://dx.doi.org/10.1101/cshperspect.a015677. PubMed.
7 Cheung CY, Lam MF, Chu KH, Chow KM, Tsang KY, Yuen SK, et al. Malignancies after kidney transplantation: Hong Kong renal registry. Am J Transplant. 2012;12(11):3039–46. doi: http://dx.doi.org/10.1111/j.1600-6143.2012.04209.x. PubMed.
8 Jiang Y, Villeneuve PJ, Wielgosz A, Schaubel DE, Fenton SS, Mao Y. The incidence of cancer in a population-based cohort of Canadian heart transplant recipients. Am J Transplant. 2010;10(3):637–45. doi: http://dx.doi.org/10.1111/j.1600-6143.2009.02973.x. PubMed.
9 Swiss Transplant Cohort Study. http://www.stcs.ch/about/study-description. Accessed January 24, 2018.
10 Koller MT, van Delden C, Müller NJ, Baumann P, Lovis C, Marti HP, et al. Design and methodology of the Swiss Transplant Cohort Study (STCS): a comprehensive prospective nationwide long-term follow-up cohort. Eur J Epidemiol. 2013;28(4):347–55. doi: http://dx.doi.org/10.1007/s10654-012-9754-y. PubMed.
11 National Institute for Cancer Epidemiology and Registration. Switzerland | NICER. http://www.nicer.org/. Accessed January 24, 2018.
12 Breslow NE, Day NE, Davis W. Statistical Methods in Cancer Research. Vol 2. Lyon: International Agency for Research on Cancer; 1987.
13 Cleves M. W. Gould W, G. Gutierrez R, Marchenko Y. An Introduction To Survival Analysis Using Stata. College Station, TX: Stata Press; 2010.
14 Adami J, Gäbel H, Lindelöf B, Ekström K, Rydh B, Glimelius B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer. 2003;89(7):1221–7. doi: http://dx.doi.org/10.1038/sj.bjc.6601219. PubMed.
15 Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Harper AM, et al. OPTN/SRTR 2016 Annual Data Report: Liver. Am J Transplant. 2018;18(1, Suppl 1):172–253. doi: http://dx.doi.org/10.1111/ajt.14559. PubMed.
16 Hart A, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Robinson A, et al. OPTN/SRTR 2016 Annual Data Report: Kidney. Am J Transplant. 2018;18(Suppl 1):18–113. doi: http://dx.doi.org/10.1111/ajt.14557. PubMed.
17 Hoffmann CJ, Subramanian AK, Cameron AM, Engels EA. Incidence and risk factors for hepatocellular carcinoma after solid organ transplantation. Transplantation. 2008;86(6):784–90. doi: http://dx.doi.org/10.1097/TP.0b013e3181837761. PubMed.
18 Hoshida Y, Tsukuma H, Yasunaga Y, Xu N, Fujita MQ, Satoh T, et al. Cancer risk after renal transplantation in Japan. Int J Cancer. 1997;71(4):517–20. doi: http://dx.doi.org/10.1002/(SICI)1097-0215(19970516)71:4<517::AID-IJC3>3.0.CO;2-X. PubMed.
19 Li W-H, Chen Y-J, Tseng W-C, Lin MW, Chen TJ, Chu SY, et al. Malignancies after renal transplantation in Taiwan: a nationwide population-based study. Nephrol Dial Transplant. 2012;27(2):833–9. doi: http://dx.doi.org/10.1093/ndt/gfr277. PubMed.
20 Minai OA, Shah S, Mazzone P, Budev MM, Sahoo D, Murthy S, et al. Bronchogenic carcinoma after lung transplantation: characteristics and outcomes. J Thorac Oncol. 2008;3(12):1404–9. doi: http://dx.doi.org/10.1097/JTO.0b013e31818e1259. PubMed.
21 Dickson RP, Davis RD, Rea JB, Palmer SM. High frequency of bronchogenic carcinoma after single-lung transplantation. J Heart Lung Transplant. 2006;25(11):1297–301. doi: http://dx.doi.org/10.1016/j.healun.2006.09.009. PubMed.
22 Burra P, Shalaby S, Zanetto A. Long-term care of transplant recipients: de novo neoplasms after liver transplantation. Curr Opin Organ Transplant. 2018;23(2):187–95. doi: http://dx.doi.org/10.1097/MOT.0000000000000499. PubMed.
23 Gutierrez-Dalmau A, Campistol JM. Immunosuppressive therapy and malignancy in organ transplant recipients: a systematic review. Drugs. 2007;67(8):1167–98. doi: http://dx.doi.org/10.2165/00003495-200767080-00006. PubMed.
24 Lung and Bronchus Cancer - Cancer Stat Facts. https://seer.cancer.gov/statfacts/html/lungb.html. Accessed May 13, 2018.
25 Liver and Intrahepatic Bile Duct Cancer - Cancer Stat Facts. https://seer.cancer.gov/statfacts/html/livibd.html. Accessed May 13, 2018.
26 Kidney and Renal Pelvis Cancer - Cancer Stat Facts. https://seer.cancer.gov/statfacts/html/kidrp.html. Accessed May 13, 2018.
27 Rohrmann S, Bouchardy C, Mousavi M, Lorez M, Arndt V, NICER Working Group. Effects of age and stage on prostate cancer survival in Switzerland. Schweizer Krebsbulletin. 2016;4:354–9.
28 Zhou J, Hu Z, Zhang Q, Li Z, Xiang J, Yan S, et al. Spectrum of de novo cancers and predictors in liver transplantation: analysis of the scientific registry of transplant recipients database. PLoS One. 2016;11(5):. doi: http://dx.doi.org/10.1371/journal.pone.0155179. PubMed.