Survival after the diagnosis of *de novo* malignancy in liver transplant recipients

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In the setting of liver transplant (LT), the survival after the diagnosis of *de novo* malignancies (DNMs) has been poorly investigated. In this study, we assessed the impact of DNMs on survival of LT recipients as compared to corresponding LT recipients without DNM. A nested case–control study was conducted in a cohort of 2,818 LT recipients enrolled in nine Italian centres between 1985 and 2014. Cases were 244 LT recipients who developed DNMs after LT. For each case, two controls matched for gender, age, and year at transplant were selected by incidence density sampling among cohort members without DNM. The survival probabilities were estimated using the Kaplan–Meier method. Hazard ratios (HRs) of death and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models. The all-cancer 10-year survival was 43% in cases versus 70% in controls (HR = 4.66; 95% CI: 3.17–6.85). Survival was impaired in cases for all the most frequent cancer types, including lung (HR = 37.13; 95% CI: 4.98–276.74), non-Hodgkin lymphoma (HR = 6.57; 95% CI: 2.15–20.01), head and neck (HR = 4.65; 95% CI: 1.81–11.95), and colon-rectum (HR = 3.61; 95% CI: 1.08–12.07). The survival gap was observed for both early and late mortality, although the effect was more pronounced in the first year after cancer diagnosis. No significant differences in survival emerged for Kaposi's sarcoma and nonmelanoma skin cancers. The survival gap herein quantified included a broad range of malignancies following LT and prompts close monitoring during the post-transplant follow-up to ensure early cancer diagnosis and to improve survival.

What's new?

Solid-organ transplant recipients are at higher risk of developing several cancer types compared with the general population. The prognostic impact of *de novo* malignancies (DNMs) in these patients remain poorly investigated, however. This study shows the detrimental effect of DNMs on survival of liver transplant (LT) recipients as compared to matched LT recipients without DNM. The all-cancer 10-year survival was 43% *versus* 70% in controls. This pattern was consistent for all the most frequent cancer types, except Kaposi's sarcoma and nonmelanoma skin cancer. The findings call for close post-transplant follow-up to detect tumors at earlier stages when treatments are more effective.

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Introduction

Solid-organ transplant recipients are known to be at higher risk of developing several cancer types, mainly virus-related malignancies, compared with the general population.[1–4] The large number of investigations that have explored cancer incidence in transplant recipients has not been paralleled by investigations focused on the prognostic impact of *de novo* malignancies (DNMs).[5,6] The few studies conducted in the setting of liver transplant (LT) have suggested that the increased tumor burden among LT recipients may substantially impair their overall survival.[5,7,8] The majority of these investigations, however, have carried out external comparisons; that is, they evaluate the impact of cancer outcomes following LT with those observed in the general population.[9,10]

The use of immunosuppressive drugs and the possible limitation of treatment options in LT recipients may influence patient survival after a cancer diagnosis. As LT recipients have already been shown to be at higher risk of death than the corresponding general population,[6,11] they represent an optimal reference group to assess the impact of DNMs on survival of immune-suppressed LT recipients.

In this study, we assessed the long-term effects of developing cancer on survival among Italian LT recipients. To this end, we compared the survival of LT recipients who developed DNMs with that of corresponding cohort members without a DNM.

Material and methods

We conducted a nested case–control study taking advantage of a cohort of 3,121 individuals who underwent, between 1985 and 2014, LT in nine centers from all over Italy. LT recipients were excluded from this analysis if they met anyone of the following criteria: (*i*) history of a previous transplant (*n* = 23); (*ii*) a follow-up shorter than 30 days after LT (*n* = 232); (*iii*) missing information on age, or age at LT below 18 years (*n* = 32); (*iv*) a cancer diagnosis other than hepatocellular cancer (HCC) within the 5 years preceding transplant or within 30 days after LT (*n* = 16). Thus, a total of 2,818 LT recipients constituted the members of the cohort from which we selected cases and controls.

Trained staff gathered appropriate information from medical records and checked data for accuracy and completeness in each of the nine transplant centers. Information on patients characteristics (e.g., gender, age at transplant, area of origin, and residence), and on transplant (e.g., transplant center, date of LT, underlying disease, and donor status) were retrieved using standard data collection forms. Data regarding follow-up and vital status were actively collected.

Among the cohort members, 244 patients who developed DNMs after LT were identified as cases. Cancer diagnoses were ascertained as a result of clinical follow-up, histologically confirmed, and coded according to the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10). Multiple primary tumors were included in the site-

specific survival analyses. For LT recipients diagnosed with more than one DNM within the same ICD-10 group (e.g., colon-rectum ICD-10 codes: C18–20; head and neck: C00–14, C30–32; all: C00–97), only the first one was considered. For each cancer case, two control subjects were randomly selected using incidence density sampling from members of the cohort who did not have a DNM diagnosis at the time when the case was identified. Controls were matched to each case on gender, age at transplant (<40, 40–59, ≥60 years), and calendar year at transplant (±1 year). We assigned to each control the same index date (date of diagnosis) as their matched case.

For each person time at risk was calculated as the time elapsed from the date of cancer diagnosis (or index date for controls) to the date of death, or to end of follow-up, whichever came first. The follow-up period was truncated at 10 years. The survival probabilities for all cancers combined, and for selected cancer types were estimated by means of the Kaplan–Meier method, and the log-rank test was used to compare survival rates. Hazard ratios (HRs) of death in cases compared with controls, and corresponding 95% confidence intervals (CIs) were estimated using Cox proportional hazard models stratified on the matched sets. The HRs were also examined within strata of selected variables using Cox proportional hazard models adjusted for matching factors. The Wald test was used to assess the heterogeneity of HRs by different characteristics. To evaluate differences in short-term and long-term survival, the HRs of death for 1-year and 10-year survival (conditioned to be alive at 1 year) after cancer diagnosis were estimated. The proportional hazard assumption was assessed graphically and by including interactions with follow-up time.[12]

All statistical analyses were performed using SAS software Version 9.4 (SAS Institute Inc., Cary, NC).

Results

Table 1 shows the distribution by selected characteristics of 244 LT recipients with a DNM (i.e., the cases) and corresponding 488 matched controls. The majority of study subjects were males (79.1%), between 40 and 59 years of age (69.7%), and had undergone LT between 1985 and 2000 (39.3%). Compared to controls, cases were more likely to be residents in northern Italy and more frequently reported a history of alcohol abuse. No differences emerged according to history of HBV or HCV infection, or of immunosuppressive therapy with tacrolimus or with cyclosporine. Conversely, the use of mTOR inhibitors was documented in 18% of cases and in 9% of controls.

The 244 cases were followed up for a median period of 3.7 years (interquartile range, IQR: 1.8–7.1) before cancer diagnosis, and the median length of follow-up after cancer diagnosis was 2.0 years (IQR: 0.6–5.4). Among cases, the most frequent cancer types (other than nonmelanoma skin cancers)

Table 1. Distribution of 244 cases and 488 corresponding controls, according to matching variables and selected characteristics

	Cases No. (%)	Controls No. (%)
Gender		
Male	193 (79.1)	386 (79.1)
Female	51 (20.9)	102 (20.9)
Age at transplant (years)		
‹40	27 (11.1)	54 (11.1)
40–59	170 (69.7)	340 (69.7)
60	47 (19.3)	94 (19.3)
Median (IQR)	53 (48–58)	52 (45–58)
Calendar year at transplant		
1985–2000	96 (39.3)	192 (39.3)
2001–2005	80 (32.8)	171 (35.0)
2006–2012	68 (27.9)	125 (25.6)
Area of residence		
Northern Italy	70 (28.7)	100 (20.5)
Central Italy	63 (25.8)	113 (23.2)
Southern Italy	111 (45.5)	273 (55.9)
Abroad	0 (0.0)	2 (0.4)
History of HBV infection		
No	136 (55.7)	273 (55.9)
Yes	108 (44.3)	215 (44.1)
History of HCV infection		
No	140 (57.4)	247 (50.6)
Yes	104 (42.6)	241 (49.4)
History of alcohol abuse		
No	156 (63.9)	374 (76.6)
Yes	88 (36.1)	114 (23.4)
Ever use of cyclosporine[1]		
No	124 (54.4)	248 (54.1)
Yes	104 (45.6)	210 (45.9)
Ever use of tacrolimus[1]		
No	71 (31.1)	148 (32.3)
Yes	157 (68.9)	310 (67.7)
Ever use of mTOR inhibitors[1]		
No	187 (82.0)	417 (91.0)
Yes	41 (18.0)	41 (9.0)

[1]The sum does not add up to the total because of missing values.
Abbreviation: IQR, interquartile range.

were head and neck cancer (13.9%; Table 2), non-Hodgkin lymphoma (NHL; 12.7%), bronchus and lung cancer (11.5%), colon-rectum cancer (8.6%), and Kaposi's sarcoma (KS; 6.1%).

Overall, 100 cases out of 244 (41.0%) and 65 controls out of 488 (13.3%) died during the follow-up period. Figure 1 illustrates the Kaplan–Meier estimates of overall survival probabilities after cancer diagnosis for all cases, as compared to their matched control subjects. Controls showed a higher overall

Table 2. Distribution of 244 cases according to cancer types

Cancer type[1]	ICD-10 codes	No.	%
		Cases	
Kaposi's sarcoma	C46	15	6.1
PTLD		37	15.2
Non-Hodgkin lymphoma	C82−85, C96	31	12.7
Leukaemia	C91−95	3	1.2
Hodgkin's lymphoma	C81	2	0.8
Multiple myeloma	C90	1	0.4
Solid tumours		147	60.2
Head and neck	C00−14, C30−32	34	13.9
Bronchus and lung	C34	28	11.5
Colon-rectum	C18−20	21	8.6
Bladder	C67, D09.0, D30.3,D41.4	9	3.7
Oesophagus	C15	8	3.3
Stomach	C16	7	2.9
Skin melanoma	C43	7	2.9
Liver	C22	6	2.5
Breast female	C50	4	1.6
Kidney	C64	4	1.6
Thyroid gland	C73	4	1.6
Pancreas	C25	3	1.2
Cervix uteri	C53	3	1.2
Prostate	C61	2	0.8
Testis	C62	2	0.8
Small intestine	C17	1	0.4
Bone and articular cartilage	C41	1	0.4
Mesothelioma	C45	1	0.4
Corpus uteri	C54−55	1	0.4
Penis	C60	1	0.4
Other/unspecified urinary organs	C68	1	0.4
Brain	C71	1	0.4
Adrenal gland	C74	2	0.8
Unspecified sites	C76-C80	3	1.2
Skin nonmelanoma	C44	50	20.5
All but skin nonmelanoma		197	80.7
All		244	100.0

[1]The sums can exceed the total because some patients were diagnosed with more than one malignancy. For LT recipients diagnosed with more than one malignancy within the same ICD-10 group (e.g., colon-rectum ICD-10 codes: C18−20; head and neck: C00−14, C30−32; all: C00−97), only the first one was considered.
Abbreviations: LT, liver transplant; PTLD, post-transplant lymphoproliferative diseases.

survival rate than cases (the 5- and 10-year survival probabilities were 89% and 70% for controls; 54% and 43% for cases, $p < 0.01$). In cases, the poorest survival was observed for lung cancer (Fig. 2*f*): all cases died within 5 years after diagnosis
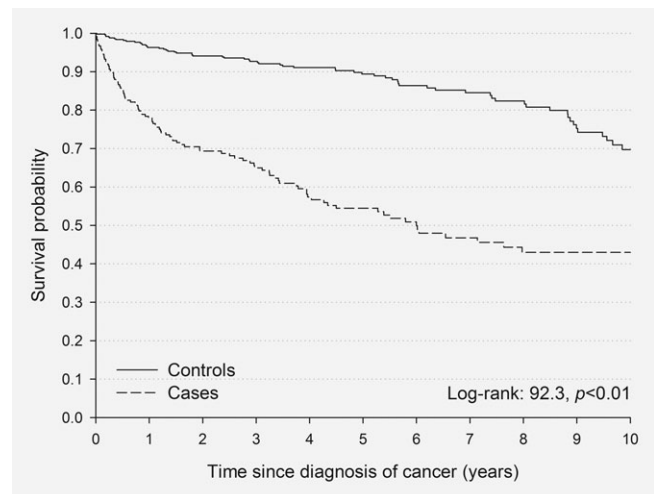

Figure 1. Kaplan−Meier estimates of survival probabilities for all cases and corresponding controls.

(median survival: 0.7 years, 95% CI: 0.3–2.4), whereas the 5-year survival for their matched controls was 89%. Five-year overall survival in cases was 64% for NHL (median survival: 6.5 years, 95% CI: 0.5–10.0; Fig. 2*a*), 45% for colorectal cancer (median survival: 3.3 years, 95% CI: 1.9–10.0; Fig. 2*e*), and 42% for head and neck cancer (median survival: 4.0 years, 95% CI: 1.1–10.0; Fig. 2*d*), although it remained significantly worse than in their respective control group. Survival did not differ significantly between the two groups for nonmelanoma skin cancers (Fig. 2*c*) and KS (Fig. 2*b*).

Table 3 shows the HRs of death in cases *versus* their matched controls, according to selected cancer types. A 4.7-fold higher risk of death (95% CI: 3.17–6.85) was documented for all cancer sites, and the exclusion of patients with non-melanoma skin cancers did not substantially modify this risk estimate (HR = 5.51, 95% CI: 3.59–8.46 for cases *vs* controls). The highest HR was found for cancer of bronchus and lung (HR = 37.13, 95% CI: 4.98–276.74), followed by NHL (HR = 6.57, 95% CI: 2.15–20.01), head and neck cancers (HR = 4.65, 95% CI: 1.81–11.95), and colorectal cancer (HR = 3.61, 95% CI: 1.08–12.07). Conversely, no statistically significant difference in risks emerged for KS or nonmelanoma skin cancer. The HR of death for cases of all cancer types was significantly higher than for controls considering both early (i.e., at 1-year after cancer diagnosis) and late mortality (i.e., at 10-year after cancer diagnosis, conditioned to be alive after 1 year) (Table 3). However, the negative prognostic effect of DNMs was particularly evident in the early mortality period (HR = 5.93, 95% CI: 3.37–10.43). In particular, for cases with NHL (HR = 20.00, 95% CI: 2.56–156.24) or head and neck cancer (HR = 5.44, 95% CI: 1.46–20.21), the survival gap was restricted to the first year after diagnosis. Conversely, for cases with colon-rectum (HR = 29.85, 95% CI: 3.26–273.07) and bronchus and lung (HR = 17.41, 95% CI: 4.56–66.52) cancers, the differences in the death risk emerged only after one year

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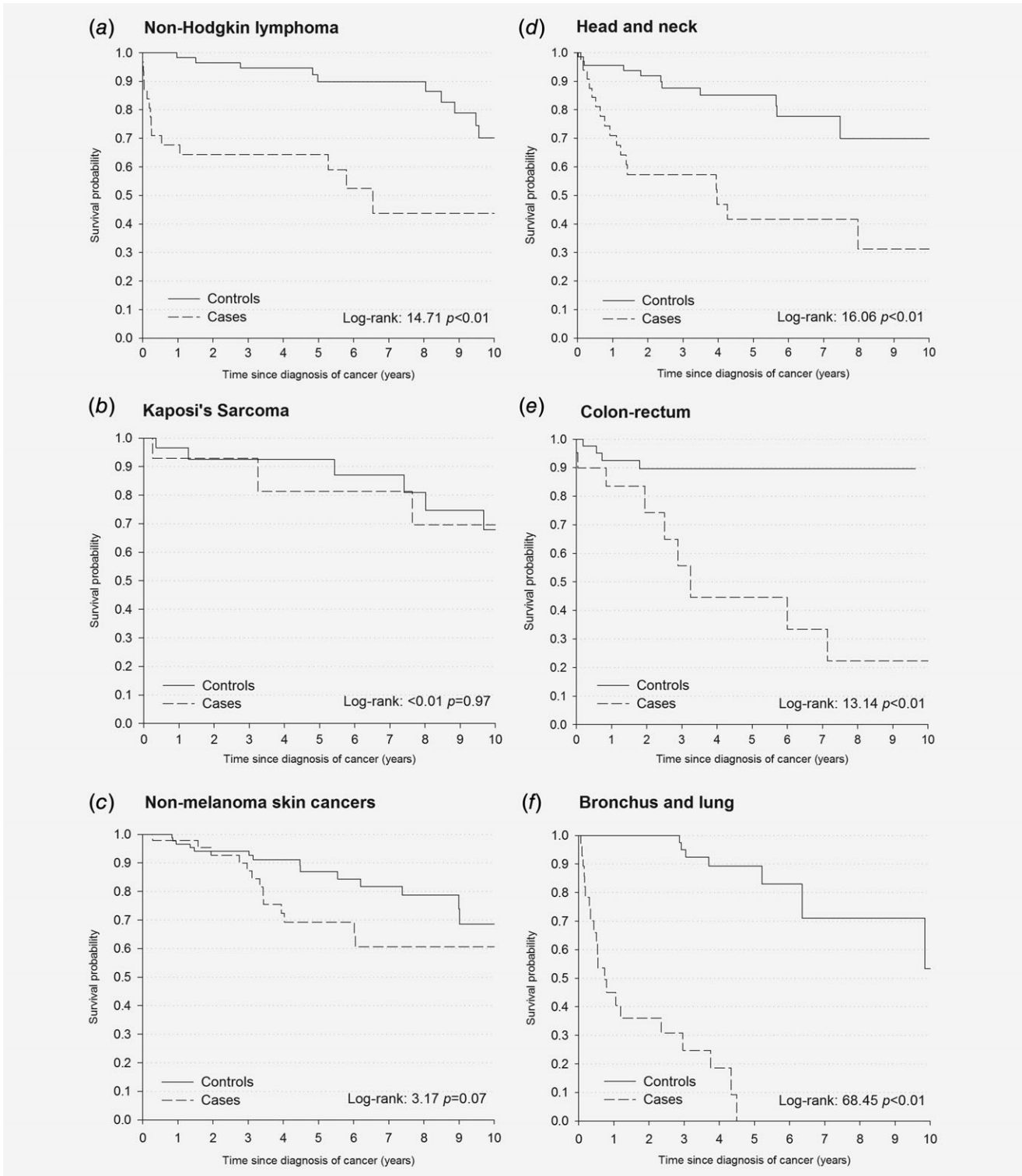
Figure 2. Kaplan–Meier estimates of survival probabilities for cases of (*a*) non-Hodgkin lymphoma, (*b*) Kaposi's sarcoma, (*c*) nonmelanoma skin, (*d*) head and neck, (*e*) colon-rectum, and (*f*) bronchus and lung cancers, and corresponding controls.

following diagnosis. No statistically significant differences in survival were observed for KS and for nonmelanoma skin cancer throughout the entire follow-up period.

No heterogeneity in HRs of death in cases of all cancer sites *versus* controls was detected across strata of gender, age at LT, year at transplant, area of residence, history of HBV or

Table 3. Hazard ratios (HRs) of death with corresponding 95% confidence intervals (CIs) in cases versus controls, according to selected cancer types and time since cancer diagnosis

Type/site	10-year survival					1-year survival	10-year survival, conditioned to be alive at 1 year
	Cases		Controls[3]				
	No. deaths	% death	No. deaths	% death	HR (95% CI)[1]	HR (95% CI)[1]	HR (95% CI)[2]
Kaposi's sarcoma	3	20.0	6	20.0	1.23 (0.27–5.57)	2.00 (0.13–31.97)	0.43 (0.05–3.69)
PTLD	18	48.7	12	16.2	6.85 (2.54–18.49)	13.00 (2.93–57.60)	2.11 (0.68–6.56)
Non-Hodgkin lymphoma	14	45.2	10	16.1	6.57 (2.15–20.01)	20.00 (2.56–156.24)	1.45 (0.41–5.09)
Solid tumors	70	47.6	36	12.2	6.28 (3.76–10.48)	6.76 (3.35–13.66)	4.79 (2.85–8.06)
Head and neck	17	50.0	11	16.2	4.65 (1.81–11.95)	5.44 (1.46–20.21)	2.75 (0.99–7.60)
Bronchus and lung	21	75.0	7	12.5	37.13 (4.98–276.74)	-	17.41 (4.56–66.52)
Colon-rectum	9	42.9	4	9.5	3.61 (1.08–12.07)	1.79 (0.36–8.97)	29.85 (3.26–273.07)
Skin nonmelanoma	13	26.0	14	14.0	2.23 (0.89–5.61)	0.55 (0.06–5.39)	2.26 (0.98–5.21)
All but skin nonmelanoma	89	45.2	52	13.2	5.51 (3.59–8.46)	7.35 (3.99–13.55)	3.41 (2.17–5.34)
All	100	41.0	65	13.3	4.66 (3.17–6.85)	5.93 (3.37–10.43)	3.01 (2.02–4.49)

[1]Estimated using Cox proportional hazard models stratified on the matched sets.
[2]Adjusted for gender, age at transplant, and year at transplant.
[3]Reference category.
Abbreviation: PTLD, post-transplant lymphoproliferative diseases.

HCV infection, history of alcohol abuse, or use of immuno-suppressive drugs (Table 4).

Discussion

The results of this study showed a detrimental effect of DNMs on the risk of death of LT recipients, as compared to corresponding LT recipients without DNM. This pattern was consistent for all the most frequent cancer types, with the exception of KS and nonmelanoma skin cancer. The survival gap was observed during both the early and the late mortality periods, even though the effect was more pronounced in the early period.

The majority of previous investigations on survival after cancer in LT recipients showed a worse survival in LT population by comparing their observed results with those documented in the general population.[9,10] However, LT recipients differed from the general population for a wide spectrum of risk factors. Indeed, several risk factors are transplant-specific, and a substantial role is played by immunosuppressive regimens used to prevent the organ rejection.[13] This study evidenced that, even compared with corresponding LT recipients, the occurrence of a DNM after LT carried a poor prognosis, with almost 50% of LT recipients dying within 5 years from diagnosis.

Although DNM has been reported in some investigations as a major cause of late mortality after LT,[7,14,15] few studies have evaluated the effects of cancer on survival comparing LT recipients who developed DNMs with corresponding LT recipients who did not.[8,16,17] Moreover, none of these investigations has assessed cancer outcomes starting from the date of cancer diagnosis. In agreement with our findings, a previous report

conducted in United States found that patients with a malignancy had a significantly lower survival after LT than control patients without neoplasm.[16] These results were further supported by a Spanish case–control study, though patients with and without cancer were not matched for gender and age.[8] In addition, a recent investigation reported that patient survival was diminished only in the subset of patients with DNM excluding nonmelanoma skin cancer, compared with patients without cancer.[17]

In the present type-/site-specific analyses, the probability of survival was impaired in LT recipients with DNM for a broad range of malignancies. In accordance with other studies,[16,18] the lowest survival probability was found for lung cancer patients—a neoplasm known for a generally poor prognosis. Nonetheless, the survival gap emerged also for other cancers that frequently occur after LT, for instance, NHL and colon-rectum cancer.

Our findings are in substantial agreement with prior evidence from studies on cancer outcomes among LT recipients.[9,10,16] A population-based analysis comparing outcomes of *de novo* cancer cases from the Israel Penn International Transplant Tumor Registry with those of the general population found a worse survival in transplant patients for several cancer types, including colorectal, lung, breast, prostate, and bladder cancers.[10] There is substantial variability in reported survival after post-transplant lymphoproliferative disease (PTLD), with median survival as low as two months in one report,[19] likely due to heterogeneity in risk characteristics of PTLD. On the other hand, longer median survival intervals were noted in other LT investigations,[7,20] with survival rates

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Table 4. Hazard ratios (HRs) of death with corresponding 95% confidence intervals (CIs) in cases versus control across strata of selected characteristics

	Cases		Controls[2]			
	No. deaths	% death	No. deaths	% death	HR (95% CI)[1]	χ^2 for heterogeneity
Gender						
Male	83	43.0	52	13.5	4.42 (3.11–6.28)	
Female	17	33.3	13	12.8	3.14 (1.51–6.53)	p = 0.40
Age at transplant (years)						
<40	8	29.6	4	7.4	6.04 (1.77–20.61)	
40–59	78	45.9	50	14.7	4.08 (2.85–5.83)	
60	14	29.8	11	11.7	3.82 (1.67–8.74)	p = 0.80
Calendar year at transplant						
1985–2000	47	49.0	39	20.3	3.20 (2.09–4.91)	
2001–2005	34	42.5	21	12.3	4.03 (2.30–7.04)	
2006–2012	19	27.9	5	4.0	11.56 (4.18–31.93)	p = 0.07
Area of residence						
Northern Italy	30	42.9	12	12.0	5.64 (2.71–11.72)	
Central Italy	28	44.4	11	9.7	6.04 (2.96–12.33)	
Southern Italy	42	37.8	42	15.4	3.55 (2.30–5.48)	p = 0.31
History of HBV infection						
No	49	36.0	37	13.6	3.45 (2.24–5.31)	
Yes	51	47.2	28	13.0	4.76 (2.99–7.60)	p = 0.32
History of HCV infection						
No	55	39.3	25	10.1	4.93 (3.05–7.96)	
Yes	45	43.3	40	16.6	3.77 (2.45–5.80)	p = 0.38
History of alcohol abuse						
No	69	44.2	50	13.4	4.94 (3.41–7.15)	
Yes	31	35.2	15	13.1	3.11 (1.65–5.85)	p = 0.18
Ever use of cyclosporine[3]						
No	40	32.3	20	8.1	5.19 (3.02–8.92)	
Yes	48	46.2	30	14.3	4.31 (2.71–6.85)	p = 0.60
Ever use of tacrolimus[3]						
No	38	53.5	15	10.1	6.74 (3.69–12.30)	
Yes	50	31.9	35	11.3	3.79 (2.44–5.87)	p = 0.13
Ever use of mTOR inhibitors[3]						
No	76	40.6	45	10.8	4.73 (3.26–6.88)	
Yes	12	29.3	5	12.2	6.25 (1.92–20.35)	p = 0.58

[1]Adjusted for gender, age at transplant, and year at transplant.
[2]Reference category.
[3]The sum does not add up to the total because of missing values.

similar to those documented in the present study. As shown also in our previous work,[21] survival after head and neck cancer ranked among the least favorable in our LT population. We could not conduct analysis according to head and neck cancer subtype due to an insufficient number of cases, but there is a chance that the impaired survival reflected the predominance of types with poor prognosis. The survival analyses revealed that—for NHL and head and neck cancer—the survival gap was concentrated in the first year after diagnosis,

pointing to the possibility of later stage diseases or less effective treatment protocols. In this study, nonmelanoma skin cancers represented the most common DNM, a finding that is generally consistent among published reports.[8,22] We found no differences in survival rates between LT recipients with and without DNM over the entire period. Similarly, a case–control study showed that patients with skin cancer after LT had similar long-term survival when compared with patients without neoplasm.[16] In addition, another study reported that

the survival after diagnosis of post-transplant DNM was better for skin cancer cases as compared to those with other DNMs.[8]

The worse survival related to DNMs among LT recipients is thought to be the consequence of continuous immunosuppression that may give rise to increased proliferation and spread of the tumor, which results in more advanced stages of disease at occurrence, precluding surgical or chemoradiotherapy options.[7,23] Close monitoring during the post-transplant follow-up year in this population is worth considering to detect tumors at earlier stages, allow more effective treatments, and improve survival.

Some study limitations need to be mentioned. The lack of completeness of cancer case ascertainment was possible as diagnoses were registered on the basis of medical records. We could not perform a linkage with population-based cancer registries for all LT recipients. However, the strict clinical follow-up of these patients is likely to limit the lack of completeness of cancer ascertainment. Furthermore, despite the relatively large sample size, the study has still limited power to detect associations for specific cancer types and results should be interpreted with caution. Despite these limitations, this is

the only study that compared the survival of LT recipients with and without DNM starting from the date of diagnosis. The choice of this approach allowed us to provide an important perspective on evaluation of post-transplant cancer outcomes on long-term survival among LT recipients. Moreover, all study participants were derived from a defined cohort over a defined time window and controls were matched to cases by age, gender and year at transplant. Other important strengths include the relatively large sample size that allowed analyses by cancer type, the length of follow-up period, and the multicentric nature of the study.

In conclusion, the findings of this study further support the negative impact of DNM on survival among LT recipients. Targeted efforts to reduce the burden of post-transplant malignancies may improve long-term outcomes, and the implementation of specific interventions for this population as an attempt to ensure early cancer diagnosis should be considered.

Acknowledgement

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