Incidence and outcome of colorectal cancer in liver transplant recipients

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INCIDENCE AND OUTCOME OF COLORECTAL CANCER IN LIVER TRANSPLANT RECIPIENTS: A NATIONAL, MULTICENTRE ANALYSIS ON 8115 PATIENTS

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Main body

Manuscript containing in total: 2 Tables, 4 Figures and 2 Supplementary Figures

Abbreviations:

LT, liver transplant

CRC, colorectal cancer

PSC, primary sclerosing cholangitis

IBD, inflammatory bowel disease

RR, relative risk

NHSBT, National Health Service Blood and Transplant

UC, ulcerative colitis

SIR, standardised incidence ratio

IQR, interquartile range

IR, incidence rate

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ABSTRACT

Background and Aims: *De novo* malignancies after liver transplantation represent one of the leading causes of death in the long-term. It remains unclear if liver transplant recipients have an increased risk of colorectal cancer and if this negatively impacts on survival, particularly in those patients affected by primary sclerosing cholangitis and ulcerative colitis.

Methods: In this national multicentre cohort retrospective study, the incidence of colorectal cancer in 8115 evaluable adult patients undergoing a liver transplantation between January 1st 1990 and December 31st 2010 was compared to the incidence in the general population through standardised incidence ratios.

Results: 52 (0.6%) cases of colorectal cancer were identified at a median of 5.6 years post liver transplantation, predominantly grade 2 (76.9%) and stage T3 (50%) at diagnosis. The incidence rate of colorectal cancer in the whole liver transplant population was similar to the general UK population (SIR 0.92), but significantly higher (SIR 7.0) in the group of patients affected by primary sclerosing cholangitis/ulcerative colitis. One, five and ten-year survival rates from colorectal cancer diagnosis were 71%, 48% and 31% respectively and the majority of colorectal cancer patients died of cancer-specific causes.

Conclusions: Liver transplantation alone is not associated with an increased risk of colorectal cancer development. The primary sclerosing cholangitis/ulcerative colitis liver transplant population showed a significantly higher risk of colorectal cancer development than the general population, with a high proportion of advanced stage at diagnosis and a reduced patient survival.

Keywords: liver transplantation**,** colorectal cancer**,** primary sclerosing cholangitis**,** ulcerative colitis

KEY POINTS

1- National multicentre study on a large sample of patients transplanted over two decades

2- This study has demonstrated significantly higher risk of colorectal cancer in the primary sclerosing cholangitis/ulcerative colitis group of transplanted patients but not in unselected liver transplant recipients when compared to the general population

3- Low patient survival from colorectal cancer diagnosis (less than 50% at 5 years and 31% at 10 years), with over 20% of patients diagnosed with colorectal cancer dying from cancer-specific causes

INTRODUCTION

Liver transplant (LT) recipients have a higher risk of developing malignancies, particularly skin cancers and lymphoproliferative tumours[1, 2]. The risk of developing solid tumours is less well documented. Retrospective studies have demonstrated conflicting results regarding the risk of colorectal cancer (CRC) development and post-LT survival[1, 3-10]. According to the European Liver Transplant Register, primary sclerosing cholangitis (PSC) is

the primary indication for LT in approximately 5% of all adult recipients[11] and is associated with inflammatory bowel disease (IBD) in up to 70% of patients[12]. In comparison to the general population, patients with PSC-IBD have a 10-fold increased risk of CRC, while patients with PSC alone have a 5-fold increased risk of CRC[12-15]. Moreover, CRC in this group of patients appears to develop at a younger age and is diagnosed at a more advanced stage compared with the general population, is predominantly localised in the ascending colon and represents one of the leading causes of death[12, 14].

A recent meta-analysis on 29 selected studies (18,875 patients: 1,732 with PSC, 111 CRC cases), which aimed to analyse the risk of CRC in all post-LT patients indicated that the pooled relative risk (RR) of CRC was 2.59 in all LT recipients (7 studies were included for this analysis) and 1.8 in the non-PSC LT population (calculated on the results of 10 studies)[16]. A subsequent report on 18 studies (69 cases of CRC observed in 1987 PSC patients and 66 of them in the 1017 PSC-IBD patients, with a mean/median post-LT follow up ranging from 3 to 11 years) aiming to analyse the incidence of CRC in PSC and PSC-IBD LT recipients, showed a high incidence rate (IR) in both groups (IR 5.8 and 13.5 cases per 1000 person-years respectively)[17].

In the present study, we used national data to assess the risk and outcome of CRC after LT. We therefore analysed: i) the incidence of post LT CRC and ii) whether cancer survival outcomes are comparable to the general population in LT patients with or without ulcerative colitis and with or without PSC by performing a retrospective analysis of prospectively collected national data in the UK.

MATERIALS AND METHODS

This is a national multicentre retrospective cohort study. Data from all adult patients undergoing a LT in 6 out of the 7 Liver Transplant Units of the United Kingdom between January 1st 1990 and December 31st 2010 were analysed. National ethical approval, National Health Service Blood and Transplant (NHSBT) approval and National Information Governance Board approval were obtained to perform this study. Prospectively collected liver transplant data was obtained from NHSBT. Retrospective data was obtained from electronic patient records, patient notes and hospital databases. The Yorkshire Cancer Registry, which is the lead UK registry for colorectal cancer, cross matched the datasets against the cancer registry database and provided a list of liver transplant patients with a diagnosis of CRC as well as the survival data on all colorectal cancer patients within the specified dates. Patients were followed from the first recorded liver transplant until death or 31st December 2012. Those with evidence of colectomy prior or during first transplant were excluded from the analysis.

Statistical analysis

The following populations were considered: (i) all transplanted individuals, (ii) those without either ulcerative colitis (UC) or PSC (iii), those with either UC or PSC and (iv) those with UC only. The incidence of CRC in these populations compared to that in the general population was assessed through Standardised incidence ratios (SIR). Age- and sex-adjusted estimates of the expected number of cases in each population were derived based on the rate of CRC in the UK general population in 2000. SIRs were calculated, for each population, as

the ratio of the observed/expected number of cases. People with unknown UC status were included in the group without UC/PSC for all analyses. Kaplan-Meier analyses estimated the probability of survival after CRC diagnosis for deaths from all causes. When considering only CRC-related causes of mortality, the cumulative incidence of death from CRC was estimated, treating all other causes of death as competing risks.

RESULTS

8178 patients underwent a liver transplant between 1990 and 2010 in one of 6 UK transplant centres. 63 patients (0.8%) with a colectomy prior to or at the time of transplant were excluded as they were not considered to be at risk of developing CRC, leaving 8115 for the analysis. Median survival (95% CI) following first transplant was 15.6 (15.0-16.4) years and 5 and 10-year post-LT patient survival probabilities were 72% and 62% respectively.

52 (0.6%) patients were diagnosed with CRC at a median of 5.6 years after LT. Characteristics of the whole LT cohort and patients diagnosed with CRC are shown in Table 1 and Table 2. 677 (8.3%) patients had either UC or PSC. Amongst individuals with CRC, 27 (51.9%) had either PSC or UC. The tumour localisation was equally distributed in the proximal and distal colon. The tumours were moderately differentiated (grade 2) in 76.9% of cases and were predominantly T3 tumours (50% of cases in the whole LT population, 47.6% in the PSC/UC group and 66.7% in patients without PSC/UC, Table 2).

CRC incidence in LT population compared to the general population

Whole LT population:

There were a total of 63,609 person years at risk with a median (IQR) follow up time of 6.7 (2.9-12.2) years. This gave a crude incidence rate (95% CI) of 8.2 (6.0-10.4) cases of

CRC per 10,000 person years of follow up. The SIR of CRC in the liver transplant population compared to the general UK population was 0.92 (95% CI 0.69-1.20). The probability of developing a CRC after LT increases linearly over time after transplantation and is shown in Supplementary Figure 1.

LT population with/without UC and PSC:

Among 7,438 patients without either UC or PSC, there were 25 (0.3%) diagnosed cases of CRC over a total of 58,516 person-years of follow-up, giving an incidence rate (95% CI) of 4.3 (2.6-6.0) per 10,000 years. The SIR (95% CI) in this group compared with the UK population was 0.46 (0.30-0.67).

Among 677 patients with either UC or PSC, there were 27 (4.0%) diagnosed cases of CRC over a total of 5094 person-years of follow-up, giving an incidence rate (95% CI) of 53.0 (33.0-73.0) per 10,000 years. The rate of CRC among those with UC or PSC was therefore 12.3 (95% CI= 7.20-21.4) times the rate in those without UC or PSC ($p<0.001$). When compared with the UK population, the rate of CRC was 7 times higher in those with UC or PSC (SIR, (95% CI)= 7.00, (4.71-10.04)).

Among 354 patients with UC, there were 23 diagnoses of CRC in 2908 person-years of follow-up, giving an incidence of 79.1 (46.8-111.4) cases per 10000 person-years. When compared with the rate of CRC in the UK population, the SIR was 10.90 (95% CI=(7.08-16.10)). The probability of developing a CRC after LT in patients with UC appears to be increasing linearly and is shown in Supplementary Figure 2.

Patient survival from CRC diagnosis

Whole LT population (n=8,115)

Thirty-one (59.6%) patients with CRC died. Median (95% CI) survival from cancer diagnosis was 4.7 (2.1-8.0) years. One, five and ten-year survival rates from CRC diagnosis were 71%, 48% and 31% respectively (Figure 1A). The probability of death due to CRC at 1, 5 and 10 years was 17.4%, 17.4% and 23.8% (Figure 1B).

Population with UC or PSC (n=677)

There were 27 patients diagnosed with CRC who also had either UC or PSC. Of these, 13 (48.2%) died during follow up. Median survival time was 8.0 years. One, five and ten-year survival rates from CRC diagnosis were 81%, 59% and 47% respectively (Figure 2).

Population without UC or PSC (n=7,438)

There were 25 patients with CRC that did not have either UC or PSC. Of these, 18 (72%) died during follow up. Median survival time was 3.1 (0.7-6.4) years. One and five year survival rates from CRC diagnosis were 60%, 37% respectively (Figure 3A). The probability of death due to CRC at 1, 5 and 10 years was 32%, 32% and 46.6% respectively (Figure 3B).

Population with UC (n=354)

There were 23 patients in this population with CRC. Of these, 11 (47.8%) died during follow up. Median survival time was 8.0 years (CI couldn't be estimated). One, five and ten-year survival rates from CRC diagnosis were 82%, 61% and 46% respectively (Figure 4).

DISCUSSION

Our study has demonstrated significantly increased risk of CRC in the PSC/UC group of transplanted patients (SIR 7.0) but not in the whole LT group (SIR 0.92), when compared with the general population. It has further shown that probably tumours are frequently diagnosed at an advanced stage, despite increased awareness and vigilance.

De novo malignancies after LT adversely affect patients' outcome, representing the second most common cause of death in transplant recipients (and the first from non-hepatic causes), accounting for over the 20% of deaths especially in the long-term after transplant[18-21]. While the increased risk of tumour development after transplant in comparison with the general population has been extensively documented for malignancies such as post-transplant lymphoproliferative diseases or skin cancer[22-25], analysis aimed to investigate the incidence of post-LT colorectal cancer have shown conflicting results[1-10, 26]. Engels et al[27], in a large cohort study analysing data from the US Scientific Registry of Transplant Recipients from 1987 to 2008, observed an overall cancer risk significantly higher than the general population (SIR 2.10). The CRC SIR was 1.24 (CI 1.15-1.34), but this rate referred to a mixed population of liver, kidney, pancreas, heart and lung transplant recipients, with liver transplants representing only the 22.6% of the total. The discrepancy in the results from our study might be due to the relatively lower immunosuppression doses required by liver transplant recipients

Recently, Sint Nicolaas et al[16] and Singh et al[17] conducted meta-analyses in order to estimate RR and incidence rate (IR) of CRC in LT recipients, specifically in the PSC and non-PSC groups. They concluded that the whole LT population (RR 2.59, 95% CI 2.12-5.24), the non-PSC group (RR 1.8, 95% CI 1.1-2.9), and the PSC-IBD group (IR 13.5 cases per 1000 person-years) all carry an increased risk of CRC development, although no transplant-

related risk factors had been identified. However, both these analyses had several limitations, such as evidence of publication bias (statistically significant Egger's test with p=0.07[16] and p=0.01[17]), inclusion of only a small proportion of high-quality studies (6/29 in Sint Nicolaas and 7/18 in Singh's reviews respectively), considerable heterogeneity (moderate in Singh's review, with p=0.03 (Cochran's Q), I^2=41%) and the inclusion of several studies variably accounting for the competing risk of post-LT early mortality and colectomy, that could significantly underestimate the CRC IR.

To the best of our knowledge, we describe in the present study the results from both the largest European LT and LT-PSC/UC cohort published in the literature (8115 and 677 patients respectively). Although solid organ malignancies have been reported to occur in about 11% of LT recipients[21], and several studies[1, 8, 28-30] report a high incidence of post-LT CRC, we observed no increased incidence in the whole LT population, with a crude incidence rate (95% CI) of 8.2 (6.0-10.4) cases of CRC per 10,000 person years of follow up and SIR 0.92. This finding is in contrast with what has been observed in the meta-analysis by Sint Nicolaas and colleagues[16], where the CRC IR in the overall post-LT patients was 11.9 cases per 10,000 person years (data calculated on 9620 patients from 15 studies, with a statistically significant Egger's test (p=0.07), indicating a possible publication bias). In order to calculate the RR in overall post-LT patients, the authors compared the results of 7 studies (6200 patients) with data from the United States NCI SEER database, which showed a lower CRC IR (7.8 cases per 10,000 person years of follow up) when compared with our control general UK population, and results in a RR of 2.59 in overall post-LT patients.

Patients with PSC/UC have been reported to have an increased risk of CRC development[12-15], potentially with a greater risk after LT due to a possible contribution of other factors such as the immunosuppressive therapy or a more aggressive course of the IBD after transplant[31-34].

Our analysis identified the PSC/UC group as at significantly increased risk for CRC development after LT either when compared to the general population (SIR 7) or the non-PSC/UC LT recipients (SIR 12.3). Moreover, patients with UC showed a risk of CRC development over 10 times higher than the general population (SIR 10.9). These results are similar to those of a recent study on the whole US transplant population[35] where PSC and IBD LT recipients showed an increased CRC risk.

We estimated a SIR of 7, which is higher than the SIR of 5 reported by Boonstra and colleagues[12] in a PSC population not undergoing LT. Comparing these results it is important to consider that these populations are not matched for the time from PSC diagnosis. The CRC risk distribution in PSC/IBD patients increases with time[2] as the duration and the extent of the disease represent the predominant risk factors for tumour development[36, 37]. Therefore the greater SIR after LT could just reflect a longer duration of the underlying disease in this population. Our results have shown a linear increase of probability of developing a CRC after LT in the whole LT population and in patients with UC (Supplementary Figures 1 and 2). The LT recipients are also burdened by the possible role of the drug-induced immunosuppression in the carcinogenesis[28, 35, 38]. The mechanisms involved in CRC development in PSC patients are still unclear. Multiple factors, such as alteration in bile acids pool, increased concentration of secondary bile acids, microbiome dysbiosis, Farnesoid X Receptor downregulation and colonic mucosal inflammation, may play a central role in carcinogenesis[14, 39].

Most previous series[12, 14, 40] demonstrate a predominance of right-sided tumour distribution (up to 76%) unlike our series which shows an equal distribution across all locations with <50% of tumours in the right colon, but unfortunately data on tumour location were missing in about 34% of patients.

When compared with the general UK population[41], we report CRC being diagnosed at a more advanced stage with 65% of tumours being T3-T4. We also found that patient survival from CRC diagnosis was less than 50% at 5 years and 31% at 10 years. Over 20% of patients diagnosed with CRC died from cancer-specific causes during the follow-up. Our results demonstrated superior patient survival from CRC diagnosis in the PSC/UC population than in the whole LT population and in patients without PSC/UC (Figures 1A, 2 and 3A).

Limitations of the present study include the retrospective nature of data collection that were incomplete for some parameters, such as LT indication and CRC characteristics. The heterogeneity of the different centres' policies regarding post-LT colonoscopy did not allow evaluation of whether a screening protocol might be able to improve earlier diagnosis. However, liver transplant candidates and recipients are likely to have undergone colonoscopy (and possibly polypectomy) more frequently than the general population as part of the pre-LT evaluation or post-LT follow up, and this might have resulted in a reduction of the risk of CRC development. This further strengthens the finding of increased CRC risk in patients transplanted for PSC. In the UK, there is a nationwide screening for CRC development with faecal blood assays every 2 years offered to all men and women aged 60 to 74. Moreover, due to the small number of patients developing a post LT CRC, it was not possible to perform a uni- and multivariate analysis to identify independent risk factors for CRC development.

In conclusion, our results suggest that LT in unselected patients is not associated with an increased risk of CRC development. The PSC/UC LT population showed a significantly increased risk of CRC development (7 times higher than the general population). Considering the patient survival and the possible high proportion of advanced CRC stage at diagnosis, a long-term post LT screening program would be advisable in patients with PSC/UC and an intact colon. In this scenario, prophylactic colectomy could play a role, since it has been demonstrated that PSC patients who had a pre-LT colectomy or don't suffer from UC carry a

significantly lower risk of recurrent PSC when compared to patients with UC and no colectomy, which is strongly associated to an increased rate of graft failure and patient death[42].

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Table 1: Whole LT Population Patient Characteristics

	Whole LT population
Years of follow-up, median (IQR)	6.8 (2.9-12.3)
Age at transplant, median (IQR)	51 (41-59)
Male, n (%)	4327 (53.3)
Main indication, n (%)	
PSC	605 (7.5)
PBC	981 (12.1)
alcoholic liver disease	1414 (17.4)
HCV-related cirrhosis	980 (12.1)
HBV-related cirrhosis	325 (4)
autoimmune hepatitis	296 (3.7)
cryptogenic cirrhosis	395 (4.9)
alpha-1 antitrypsin deficit	79 (1)
urgent/fulminant liver failure	962 (11.9)
HCC	294 (3.6)
haemocromatosis	62 (0.8)
metabolic	83 (1)
polycystic liver disease	53 (0.7)
all other indications/unknown	1587 (19.6)
Total, n	8115

LT= liver transplant, IQR= interquartile range, PSC= primary sclerosing cholangitis, PBC= primary biliary cirrhosis, HCV= hepatitis C virus, HBV= hepatitis B virus, HCC= hepatocellular carcinoma

Table 2: CRC Patient Characteristics

	CRC population
Age at transplant, median (IQR)	56 (48-61)
Male, n (%)	35 (67.3)
Transplant for PSC, n (%)	24 (46.2)
Presence of UC, n (%)	23 (44.2)
Time to diagnosis (years), median (IQR)	5.6 (3.8-8.8)
Tumour location, n (%)*	
caecum/ascending/hepatic flexure	13 (38.2)
transverse	4 (11.8)
splenic flexure/descending/sigmoid	9 (26.5)
rectum	8 (23.5)
Type of surgery, n (%)**	
right/extended right hemicolectomy	14 (33.3)
left/sigmoid colectomy	4 (9.5)
subtotal colectomy	2 (4.8)
panproctocolectomy	14 (33.3)
anterior resection	9 (21.4)
Tumour grade, n (%)[§]	
1	2 (7.7)
2	20 (76.9)
3	4 (15.4)
Tumour Stage, n(%)[§§]	
Tis	2 (6.1)
T1	2 (6.1)
T2	6 (18.2)
T3	18 (50)
T4	5 (15.2)
Nx	1 (3)
N0	20 (60.6)
N1	9 (27.3)

N2	3 (9.1)
M0	24 (72.7)
M1	9 (27.3)
Total, n	52

CRC= colorectal cancer, IQR= quartile range, PSC= primary sclerosing cholangitis, UC= ulcerative colitis, *n=34, **n=42, §=26, §§=33

Figure 1: (A) Kaplan-Meier plot of patient survival from diagnosis of CRC in those with liver transplant. (B) Cumulative Incidence for death due to colorectal cancer amongst LT population with CRC. CRC= colorectal cancer, LT= liver transplant.

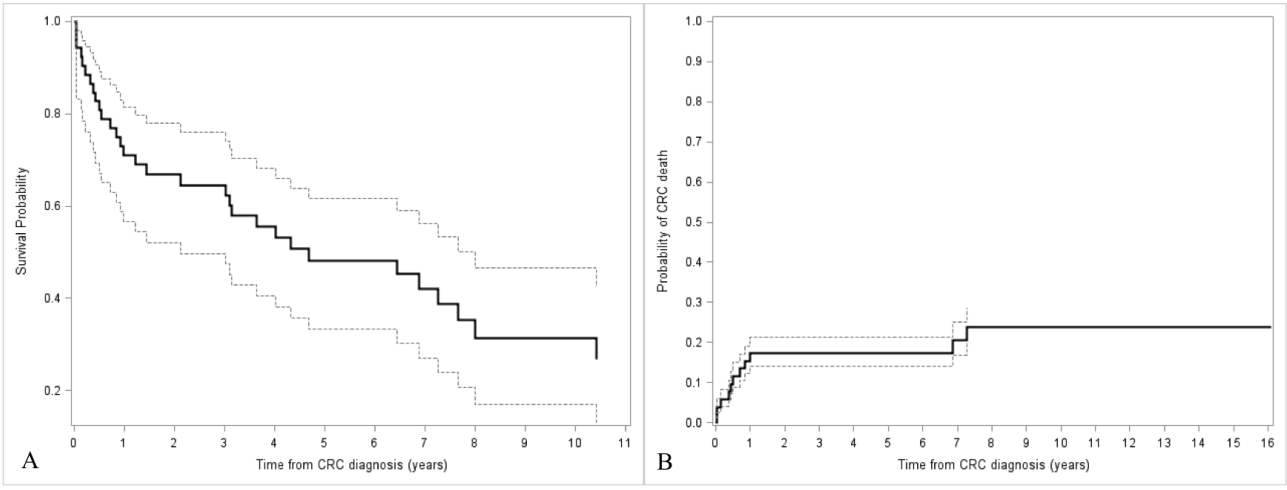

Figure 2: Kaplan Meier plot of survival from CRC diagnosis in population with UC and PSC. CRC= colorectal cancer, PSC= primary sclerosing cholangitis, UC= ulcerative colitis.

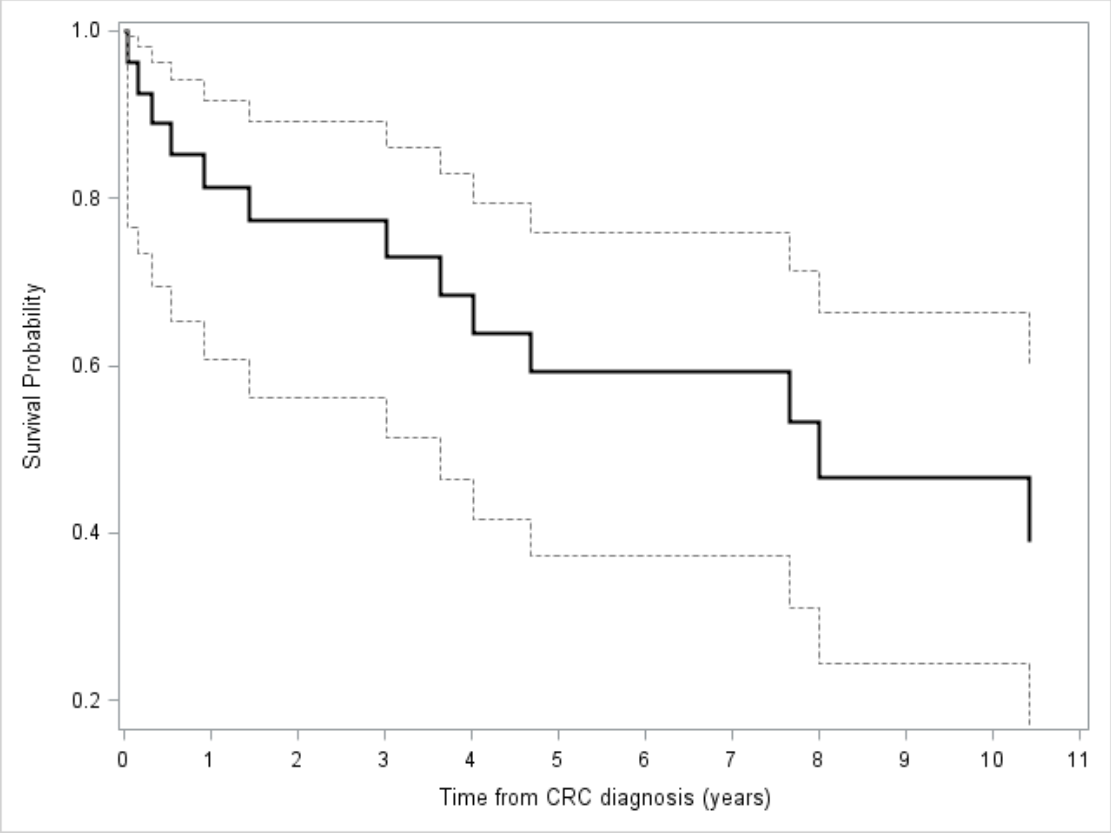

Figure 3: (A) Kaplan Meier plot of survival from CRC diagnosis in LT population without PSC or UC. (B) Probability of CRC death amongst CRC patients without UC or PSC. CRC= colorectal cancer, LT= liver transplant, PSC= primary sclerosing cholangitis, UC= ulcerative colitis.

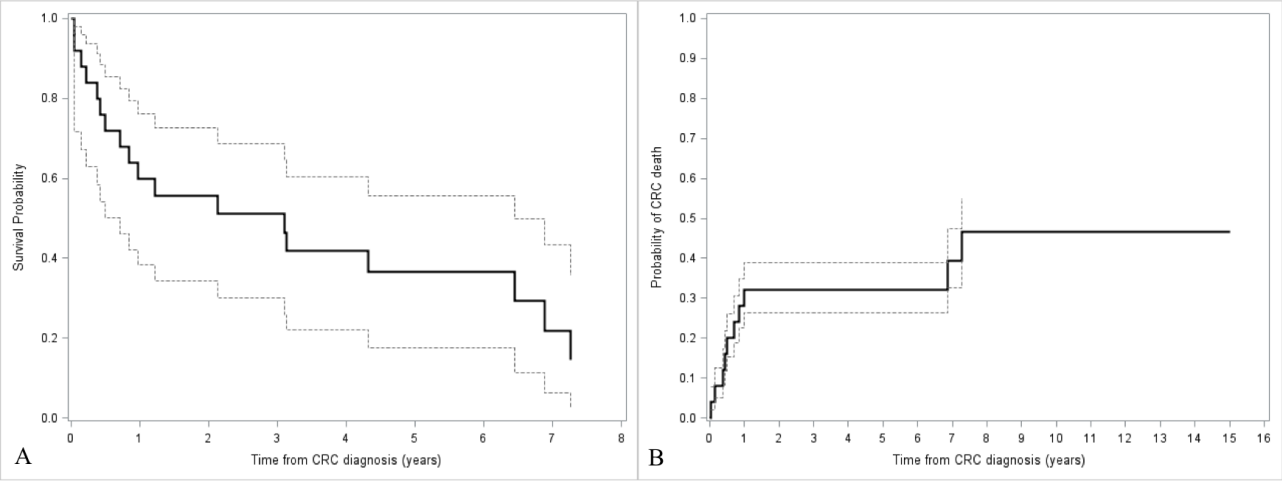

Figure 4: Kaplan Meier plot of survival from CRC diagnosis in LT population with UC. CRC= colorectal cancer, LT= liver transplant, UC= ulcerative colitis.