De Novo Tumours After Liver Transplantation

23

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Overview
Over the last decades, the continuing amelioration of transplant surgery and the efficacy of anti-rejection therapies have greatly contributed to improve patient and graft survivals. However, the lifelong use of immunosuppressive regimens for preventing graft rejection in liver transplant recipients has increased the risk of opportunistic diseases, malignancies in particular. De novo tumours represent a major adverse outcome of liver transplantation, as are often diagnosed at advanced stages and show more aggressive behaviours than those occurring in the general population. The role of immunosuppressive treatments in the occurrence of de novo tumours, the interaction with established risk factors, the magnitude of increased cancer risk, as well as outcomes of transplant recipients after a diagnosis of cancer are important tools to help developing prevention and early detection protocols and timely management to reduce the cancer burden in this at-risk population.

23.1 Introduction

Liver transplantation has become a standard therapy for the management of end-stage liver disease, acute liver failure or hepatocellular carcinoma. According to the Global Observatory of Donation and Transplantation, approximately 30,000 of

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P. Burra (ed.), *Textbook of Liver Transplantation*,
https://doi.org/10.1007/978-3-030-82930-8_23

these procedures are performed worldwide each year (http://www.transplant-observatory.org). Over the last decades, advances in transplant surgery and immunosuppressive therapy have led to significant improvements in patient and graft survivals. However, the prolonged use of immunosuppressive regimens for preventing graft rejection has increased the risk of several opportunistic diseases, particularly infections and malignancies in liver transplant recipients [1, 2].

De novo tumours represent a major adverse outcome of liver transplantation with cumulative incidences ranging from 3% to 16% depending on the study period, geographic area and on duration of immunosuppression [2, 3]. As a result, the longer life expectancy, the enduring exposure to immunosuppressive treatments and the gradual ageing of patients undergoing liver transplantation may probably lead de novo tumours to be the leading cause of mortality in this at-risk population.

It has been estimated that liver transplant recipients have a two- to threefold excess risk of cancer compared to the age- and sex-matched general population [1, 3, 4]. Several studies have indicated that a wide range of de novo tumours—mostly those with a viral aetiology—occur at excess rate [1, 3–10]. Moreover, de novo tumours among transplant recipients tend to be more aggressive and are associated with increased mortality than in the general population [11].

This chapter provides an overview of the current evidence linking immunosuppression, persistent infections with oncogenic viruses and other risk factors with de novo tumours after liver transplantation. Moreover, epidemiologic data on cancer incidence and particular characteristics associated with different types of de novo tumours are described along with outcomes of transplant recipients after cancer diagnosis and screening recommendations for the surveillance of de novo tumours.

23.2 The Role of Immunosuppressive Treatment

Over the past few decades, a better understanding of the role of cancer immune-surveillance [12] helped investigating the role of immunosuppression in the field of de novo tumours. Indeed, immunosuppressive drugs have long been recognized as one of the causes of post-transplant malignancies and the role of different immunosuppressive protocols has been explored. Besides immune-surveillance derangement, other pathogenetic mechanisms seem to be involved. The frequency of tumours increases in parallel with a longer duration of immunosuppression, which not only compromises immune function but it also has a direct oncogenic activity [2]. Calcineurin inhibitors (CNI) show direct carcinogenic potential by inducing cancer cell invasiveness, hampering DNA repair mechanisms and apoptosis regulation, stimulating vascular endothelial growth factor synthesis and promoting functional expression of the transforming growth factor-β 1 gene, enhancing the metastatic potential of the tumour. These drugs (especially tacrolimus), together with steroids, can also promote impaired insulin secretion and induce pancreatic beta-cell apoptosis [13, 14] with 5%–27% of liver transplant recipients developing de novo diabetes mellitus, which is a recognized risk factor for neoplasms [15]. Furthermore, the use of azathioprine has been associated with DNA damage

increasing skin cell sensitivity to UV damage [16–18], requiring these patients to strictly follow protection recommendations and screening protocols.

The effect of immunosuppression on carcinogenesis appears to be also dose related. For instance, exposure to elevated concentrations of tacrolimus (>20 ng/mL) immediately after surgery increases long-term mortality due to infections, cardiovascular events and de novo tumours development [19]. Immunosuppression also increases cancer risk related to latent oncogenic virus [20], such as post-transplant lymphoproliferative disorders (PTLD), particularly when associated with Epstein-Barr virus (EBV) viraemia [21]. These tumours seem to be more immunogenic than those related to other factors and may regress once immunosuppression is withdrawn [22].

Both sirolimus and everolimus, inhibitors of mammalian target of rapamycin (mTORi), show potential anti-proliferative properties, including inhibition of cellular growth, proliferation, metabolism and angiogenesis [23]. A lower incidence of neoplastic disease has been reported in patients with gradual reduction of CNI with the introduction of mTORi when compared to those treated with CNI monotherapy [24–26]. Few studies in mouse models and in renal or heart transplant recipients have confirmed a decreased frequency of cutaneous malignancies in those patients receiving mTORi versus CNI [23, 27–31].

In a different setting, sirolimus-based immunosuppression was associated with increased recurrence-free survival and overall survival in recipients with HCC versus mTORi-free regimens [32, 33]. Additionally, in non-transplanted patients with advanced HCC, everolimus monotherapy showed a low but significant survival benefit [34–36], suggesting that these neoplastic patients could benefit from mTORi-based therapy.

These pieces of evidence give a rationale for immunosuppression modification and minimization for de novo tumours prevention and as the first-line intervention for treatment. Nonetheless, all immunosuppression regimes could elevate cancer risk, regardless of the specific regimen [37], so that minimization of immunosuppression to the lowest tolerable level is recommended. However, the risk of rejection with the benefits of cancer prevention still needs to be carefully evaluated.

23.3 Risk Variation by Cancer Site

The overall risk of de novo tumours in liver transplant recipients is two- to threefold higher than in the general population of the same sex and age [1, 3, 4]. This augmented cancer incidence is mainly due to the intensive surveillance and to life-long immunosuppressive therapy.

Several studies have shown that a wide range of de novo tumours occur at excess rates in the post-liver transplant scenery, highlighting that the magnitude of risk varies according to cancer site [1, 3, 4]. For each cancer site, the extent of increased risk is similar between the studies, with some variations attributable to the geographic area, period and duration of the study. Malignant neoplasms, notably higher in liver transplant recipients, include those with a viral aetiology [3, 4], which liver

Table 23.1 Standardized incidence ratios for selected virus-related malignancies after liver transplantation. Data adapted from [1, 3–10]

Reference	Country	KS	NHL	HL	Liver	Cervix	Anus	Vulva
Aberg et al. [5]	Finland		13.9[a]	14.7	0.0			
Collett et al. [6]	UK	0.0	13.3[a]	8.9[a]			3.3[a]	
Ettorre et al. [7]	Italy	37.3[a]	7.1[a]	6.3	0.8			
Engels et al. [3]	US		7.8[a]		43.8[a]			
Jiang et al. [8]	Canada		20.8[a]					
Lee et al. [9]	Taiwan		28.2[a]	27.8	12.2[a]	5.3		
Na et al. [1]	Australia	290[a]	6.2[a]	7.7	1.7		9.7[a]	25.9[a]
Schrem et al. [10]	Germany		11.0[a]			2.6		23.8[a]
Taborelli et al. [4]	Italy	53.6[a]	7.1[a]	3.5	1.1	5.4[a]		

KS Kaposi's sarcoma, *NHL* Non-Hodgkin lymphoma, *HL* Hodgkin lymphoma
[a]Denotes statistical significance at level 0.05

transplant recipients are prone to develop in the setting of immunosuppression. These increases resemble the cancer risks associated with HIV infection and appear related to poor immune control of known oncogenic viruses [3].

Table 23.1 summarizes standardized incidence ratios (SIRs) for selected virus-related malignancies, taken from the largest published investigations [1, 3–10].

Among virus-related tumours, the greatest increase in incidence is seen for Kaposi's sarcoma, which occurs hundred times more often than among the general population. The very high excess risk registered for Kaposi's sarcoma in Mediterranean countries, particularly in Italy, is attributable to the high prevalence rates of infection with human herpesvirus-8 documented in that geographic area (10–30%) [2].

Risk is particularly elevated also for non-Hodgkin lymphomas, which are strongly associated with EBV (>seven fold increased risk). As seen in the HIV infection and AIDS scenery, the strong link between EBV and non-Hodgkin lymphoma highlights the important role of the immune system in controlling abnormal lymphoproliferation [22].

De novo liver cancer can develop after liver transplantation, with a > ten fold increased risk when compared to the general population. It has been shown that most liver tumours are diagnosed within the first 6 months after transplant [3]; thus, the increased incidence seems partially due to prevalent cases.

Liver transplant recipients have also an increased incidence of human papillomavirus-related cancers (vaginal, vulvar, cervical, anal, penile and oropharyngeal cancers). The SIRs are greatest for vulvar and vaginal cancers, whereas for cervical cancer, the incidence seems increased only slightly [4].

Risk is also increased for certain malignancies without established links to viral infections but that are associated with unhealthy behaviours, such as tobacco smoking, alcohol abuse or sun exposure [1, 3–10]. Examples are lung cancer (approximately double risk), head and neck cancer (>fourfold increased risk), oesophagus (sevenfold increased risk) and melanoma (twofold increased risk). The incidence of colorectal cancer appears to be greater in liver transplant recipients than in the general population (approximately double risk). Although most of this difference may be explained by the increased risk of colorectal cancers associated with liver

Table 23.2 Standardized incidence ratios for selected virus-unrelated malignancies after liver transplantation. Data adapted from [1, 3–10]

Reference	Country	HN	Lung	CR	Oesophagus	Melanoma	Breast	Prostate
Aberg et al. [5]	Finland	14.8[a]	0.0	1.6		2.1	0.3	1.2
Collett et al. [6]	UK	10.0[a]	1.6[a]	2.3[a]			0.8	
Ettorre et al. [7]	Italy	4.5[a]	1.1	1.2		3.1	0.7	
Engels et al. [3]	US		2.0[a]			2.4[a]		
Jiang et al. [8]	Canada	2.5	1.4	2.6[a]			0.6	1.0
Lee et al. [9]	Taiwan	82.9[a]	1.3	2.9	6.7[a]		2.2	2.9
Na et al. [1]	Australia		0.5	2.4[a]	2.5		1.3	0.6
Schrem et al. [10]	Germany		1.9[a]	1.4[a]	1.9		0.8	0.7
Taborelli et al. [4]	Italy	4.4[a]	1.4	1.3	6.7[a]	2.6[a]	0.5	0.1[a]

HN Head and neck, *CR* Colon-rectum
[a]Denotes statistical significance at level 0.05

transplantation for primary sclerosing cholangitis (PSC) with associated inflammatory bowel disease [38], a recent meta-analysis found a 1.8-fold higher risk of colorectal cancers after liver transplantation even excluding PSC patients [34]. Other cancers, including thyroid, kidney and bladder, have also been reported to be elevated in comparison with the general population, although they are infrequent in most series of liver transplant recipients. Cancers of the breast and, to a lesser extent, of the prostate are the established malignancies not showing an increased risk for liver transplant recipients.

Non-melanoma skin cancers are common after liver transplantation. As for immune competent individuals, prior exposure to solar ultraviolet radiation is a principal risk factor, with squamous cell carcinomas most likely to occur at sun-exposed areas and in recipients with a history of high sun exposure [2]. Nevertheless, most national cancer registries do not record skin cancers; thus, accurate estimates of risk in relation to the general population are not straightforward.

A summary of the estimated SIRs for the most frequently reported virus-unrelated malignancies according to major studies is provided in Table 23.2.

23.4 Survival in Liver Transplant Recipients with Cancer

The use of immunosuppressive drugs and the possible limitation of treatment options in liver transplant recipients may compromise patient survival after a diagnosis of de novo tumour. Indeed, the continuous immunosuppression may give rise to an increase in cancer proliferation and spread, which results into more advanced stages at disease occurrence, precluding surgical or chemo-radiotherapeutic options [39].

In spite of the large number of studies that have explored cancer incidence in the context of liver transplantation, the survival after the diagnosis of de novo malignancies has been poorly investigated. Nevertheless, the available epidemiologic evidence has suggested that the prognosis of liver transplant recipients diagnosed with de novo malignancies is much worse than in patients with transplant or just cancer [11, 40, 41].

The majority of the studies on survival after cancer in liver transplant recipients have compared cancer outcomes to those seen in the general population [11, 41]. Although the survival probability for liver transplant recipients with cancer depends on the specific diagnosis, it is generally worse than that for a non-transplant patient with the same cancer. Overall, survival rates of liver transplant recipients after the diagnosis of any de novo tumours (excluding non-melanoma skin cancers) are reportedly 72%, 50% and 38% after 1, 5 and 10 years respectively [40]. For certain types of cancer, survival rates are particularly low, reaching only 64% for non-Hodgkin lymphoma, 45% for colorectal cancer and 42% for head and neck cancer at 5 years after diagnosis [40]. Lung cancer tends to have the worst prognosis, while non-melanoma skin cancer is associated with a much better survival rate than other cancers.

The mortality risk due to de novo tumours in liver transplant recipients has been shown to be significantly elevated compared to the general population (twofold increased risk) [42], regardless of the recipient's sex and age at transplantation. Data from the Israel Penn International Transplant Tumor Registry have shown that certain malignancies arising in transplant recipients, including lung, colon, prostate, breast and bladder cancers, are associated with adverse outcomes because they are often more aggressive and developed at a much later stage than the general population [11]. Unexpectedly, a study from Germany reported that 5-year survival was slightly better in the transplant population compared with the general population for renal cell carcinoma, lung, colorectal and thyroid cancers, whereas other cancers were associated with similar or inferior survival rates after their diagnosis [10].

Few investigations have shown that developing cancer after liver transplantation leads to a poor prognosis even compared to other transplant recipients. In a single-centre study conducted in the United States, only patients with non-cutaneous cancers after liver transplantation had a significantly lower survival when compared to control patients without cancer [41]. Similar results were suggested by a Spanish case-control study, although patients with and without cancer were not matched by age and gender [43]. In our series of 2832 adult recipients undergoing liver transplantation—within which a matched cohort study was conducted—the survival of patients who had been diagnosed with cancer was significantly lower than that of matched liver transplant recipients without cancer [40]. Liver transplant recipients with cancer had an almost fivefold higher risk of death than controls, with the highest risks found in cases with cancers of lung, non-Hodgkin's lymphoma, head and neck and colon-rectum. Moreover, the survival gap was observed at 1 year after cancer diagnosis and at 10 years after cancer diagnosis, conditioned to be alive after 1 year.

23.5 Post-Transplant Follow-Up

Prevention and screening protocols are recommended in order to ensure early detection of cancer, to increase the probability of appropriate treatment and to improve prognosis. A summary of some proposed preventive measures is provided in Table 23.3.

Table 23.3 Screening recommendations proposed for the surveillance of de novo neoplasms in liver transplant population [44–53]

Neoplasms	Suggested post-transplant screening
Skin cancer	Low-risk patients: annual skin examination High-risk patients[a]: skin examinations every 3 months
PTLD	No specific recommendations for EBV monitoring of adult liver recipients, nor the use of antiviral prophylaxis in high-risk EBV-naive patients
Lung cancer	Yearly thoracic CT scan in active smokers Annual chest radiography in other recipients
Colorectal cancer	Consider a baseline colonoscopy in patients younger than 50 years. Perform baseline colonoscopies in patients 50 years old and older. Screening colonoscopy 2 years after transplant Annual screening colonoscopies are recommended in PSC patients with inflammatory bowel diseases
Head and neck cancers	Ears, nose and throat examination in patients transplanted for ALD, particularly if positive smoking history
Renal cancer	Yearly abdominal ultrasound
Prostate and breast cancers	Based on the routine health maintenance recommendations, but compliance should be monitored
De novo HCC	Abdominal imaging every 6 months if recurrence of liver disease in the allograft, especially development of cirrhosis
Anogenital cancers	Annual Papanicolaou test and pelvic examination, inspection of anal, vaginal and vulvar regions Potential benefit: HPV vaccine before transplant

CT Computed tomography, *PSC* Primary biliary cholangitis, *ALD* Alcoholic liver disease
[a]Older age at transplantation, phototype II-III, cyclosporine- or azathioprine-based immunosuppression

▶ Tips

- Pre-transplant risk assessment should be routinely conducted, and should include screening for unhealthy lifestyle habits, such as tobacco smoking, alcohol abuse or sun exposure.
- Post-transplant de novo neoplasms screening should be individualized on the basis of known associated risk factors. New risk factors should be investigated to further guide surveillance planning.
- Minimization of immunosuppression to the lowest tolerable level is recommended for de novo tumours prevention. However, immunosuppressive protocols must be balanced to minimize graft rejection and avoid unwanted complications.
- Survival probability for liver transplant recipients with cancer depends on the specific diagnosis, with the worst outcomes for those patients diagnosed with non-Hodgkin lymphoma, lung, colorectal and head and neck cancers. High-risk liver transplant recipients must be strictly screened for these neoplasms to allow early diagnosis and prompt treatment.

Key Points

- The prolonged use of immunosuppressive treatments increases the risk of de novo tumours in liver transplant recipients and the effect on carcinogenesis appears to be also dose-related.
- Liver transplant recipients have a two- to threefold excess risk of de novo tumours compared to the general population of the same age and sex.
- Immunosuppression increases cancer risk related to latent oncogenic virus, such as non-Hodgkin lymphomas, Kaposi's sarcoma and liver cancer.
- Risk is also increased for certain malignancies associated with unhealthy behaviours, such as tobacco smoking, alcohol abuse or sun exposure.
- The prognosis of liver transplant recipients diagnosed with de novo malignancies is much worse than in patients with transplant or just cancer.
- De novo tumours among transplant recipients tend to be more aggressive and develop at a much later stage.
- Prevention and screening protocols are recommended in order to reduce the cancer burden in liver transplant recipients.

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