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TOPIC HIGHLIGHT

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Donor transmitted and *de novo* cancer after liver transplantation

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Abstract

Cancers in solid organ recipients may be classified as donor transmitted, donor derived, *de novo* or recurrent. The risk of donor-transmitted cancer is very low and can be reduced by careful screening of the donor but cannot be abolished and, in the United Kingdom series is less than 0.03%. For donors with a known history of cancer, the risks will depend on the nature of the cancer, the interventions given and the interval between diagnosis and organ donation. The risks of cancer transmission must be balanced against the risks of death awaiting a new graft and strict adherence to current guidelines may result increased patient death. Organs from selected patients, even with high-grade central nervous system (CNS) malignancy and after a shunt, can, in some circumstances, be considered. Of potential donors with non-CNS cancers, whether organs may be safely used again depends on the nature of the cancer, the treatment and interval. Data are scarce about the most appropriate treatment when donor transmitted cancer is diagnosed: sometimes substitution of agents and reduction of the immunosuppressive load may be adequate and the impact of graft removal should be considered but not always indicated. Liver allograft recipients are at increased risk of some *de novo* cancers, especially those grafted for alcohol-related liver disease and hepatitis C virus infection. The risk of lymphoproliferative disease and cancers of the skin, upper airway and bowel are increased but not breast. Recipients should be advised to avoid risk behavior and monitored appropriately.

Key words: Liver transplantation; Cancer; Donor transmitted cancer; *De novo* cancer; Immunosuppression

Core tip: Cancer is an important cause of morbidity and mortality after organ transplantation. Donor transmitted cancers are rare but when they occur, they can have significant impact on the recipient outcome. Screening of donors can reduce the risk of transmission of cancer but cannot eliminate it. So this risk should be accepted by the transplant teams and the recipients. The risk of many *de novo* cancers is increased among transplant recipients. Selection of immunosuppressive agents, minimizing the intensity of immunosuppression and modification of life-style related risk factors would contribute to reduction of the risk of post-transplant cancer.

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INTRODUCTION

For donors with a known history of cancer, the risks will depend on the nature of the cancer, the interventions

given and the interval between diagnosis and organ donation. The risks of cancer transmission must be balanced against the risks of death awaiting a new graft and strict adherence to current guidelines may result increased patient death. Organs from selected patients, even with high-grade central nervous system (CNS) malignancy and after a shunt, can, in some circumstances, be considered. Of potential donors with non-CNS cancers, whether organs may be safely used again depends on the nature of the cancer, the treatment and interval. Data are scarce about the most appropriate treatment when donor transmitted cancer is diagnosed: sometimes substitution of agents and reduction of the immunosuppressive load may be adequate and the impact of graft removal should be considered but not always indicated.

Liver allograft recipients are at increased risk of some *de novo* cancers, especially those grafted for alcohol-related liver disease and hepatitis C virus infection. The risk of lymphoproliferative disease and cancers of the skin, upper airway and bowel are increased but not breast. Recipients should be advised to avoid risk behavior and monitored appropriately.

Over the last half century, successful transplantation of the liver has revolutionized the outcome for selected patients with liver failure. Adults undergoing primary liver transplant for chronic liver disease should now anticipate 1-year survival rates over 93% and 5-year survival over 60%[1]. This success has been achieved as a consequence of advances in a number of areas such as donor and recipient assessment and selection, management on the waiting list, surgical and anaesthetic techniques, intensive care and post-transplant long-term care. However, patients with liver disease and transplant teams continue to face a number of challenges before and after transplantation. One of the greatest of these challenges is the shortage of donor organs in the face of increasing demand which results in a significant mortality rate and removal from the transplant waiting list (which approaches 20% in the United Kingdom). The lack of organs poses a real dilemma for both clinicians and recipients who must decide whether to use higher risk livers such as those from older donors and donors with co-morbidities where short and/or longer term graft function may be impaired or the organs transmit infection or malignancy. Liver transplant recipients, like other patients who require long term immunosuppression, are at an increased risk of developing a number of diseases including *de novo* cancer[2,3]. Indeed, cancer, recurrence of primary disease, cardiovascular disease and infection are the four most common causes of long-term mortality after liver transplantation[4]. This review focuses on cancer in liver allograft recipients, both donor transmitted and *de novo* but does not cover recurrent cancer.

TYPES OF CANCERS AFTER LIVER TRANSPLANTATION

Cancer in a liver transplant recipient can be classified into four types: (1) donor transmitted cancer (DTC), which is present within the allograft at the time of transplantation; (2) donor derived cancer (DDC), which develops within the donor cells following transplantation; (3) *de novo* cancer, which develops from the recipient cells as a long-term consequence of transplantation; and (4) recurrent cancer, which is the recurrence after transplantation of cancer that the recipient had treatment for, before transplantation.

These definitions are useful but in practice, in some cases, an accurate classification into one of these types may be difficult - for example, it may be difficult to differentiate a DTC from a DDC when the donor has no known cancer or when the cancer in the recipient is identified a long time after transplantation. Similarly, when a recipient has multiple tumours of the same type of cancer, it may be difficult to distinguish a new primary from the recurrence of a previously treated cancer. A common example would be melanoma or non-melanoma skin cancer (NMSC), which tend to develop in multiple sites over a period of time.

DONOR TRANSMITTED CANCER AFTER LIVER TRANSPLANTATION

Cancer transmission from donors was recognised initially in recipients of kidney transplantation. The initial reported cases of cancer transmission involved donors dying as a consequence of active cancer[5]. Consequent avoidance of such donors resulted in low incidence of DTC, but cases continued to be reported, both in recipients from donors with previous cancer[6-10] and in recipients from donors without a known cancer[11-15]. A recent national survey of all the organ transplant recipients in the United Kingdom reported 15 cases of DTC among 30765 recipients over 10 years, including two cases of DTC among 6645 liver recipients[16]. None of these cancers was from donors who were known to have active or past cancer. This highlights not only the rarity of this event but also the challenge in complete elimination of this risk.

A wide variety of cancers are transmitted by liver transplantation, including tumours known in the donor before donation. These are often primary tumours of the CNS, tumours diagnosed after donation at donor autopsy, tumours diagnosed on examination of stored donor tissue following identification of DTC in the recipient and tumours that were not apparent in the donor.

Table 1 shows the cases of DTC among liver allograft recipients in the published literature. Some important features associated with cancer transmission are discussed below, including interventions that can help in reducing the risk of cancer transmission.

Donors with cerebral haemorrhage

Cerebral haemorrhage is a common cause of death among donors after brain death. In some such donors, the cerebral haemorrhage may be consequent to a metastatic deposit either from an undiagnosed cancer elsewhere in the body at the time of donation, or a recur-

Table 1 Published cases of donor transmitted cancer among liver allograft recipients

Cancer type	Donor's cause of death	Cancer known in donor	Recipient outcome and cause of death	Ref.
Choriocarcinoma	Cerebral haemorrhage	Identified on autopsy	Death due to DTC	[52]
	Cerebral haemorrhage	Identified in the placenta	Death due to DTC	[53]
	NS	No	Death due to DTC	[54]
	Cerebral haemorrhage	Diagnosed retrospectively by testing the stored serum	Death due to DTC	[55]
	Cerebral haemorrhage	No	Death due to DTC	[56]
Colon	Cerebrovascular event	No	Death due to DTC	[57]
	Cerebrovascular event	No	Death due to DTC, despite re-transplant	[13]
	Cerebral haemorrhage	No	Death due to DTC	[58]
CNS-astrocytoma	Astrocytoma	Yes	Death due to DTC	[59]
CNS-glioma, GBM	GBM	Yes	Death due to liver failure	[60]
	GBM	Yes	Death due to DTC	[61]
	Malignant glioma	Yes	Death due to DTC	[62]
CNS-pinealoblastoma	Pinealoblastoma	Yes	Death due to DTC	[63]
Kaposi's sarcoma	NS	NS	Death due to DTC	[54]
Lymphoma	Suspected meningitis	Diagnosed after donation	Death due to DTC	[64]
Melanoma	Cerebral haemorrhage	No	Death due to DTC	[24]
	Cerebral haemorrhage	No	Death due to DTC	[65]
	Sub-arachnoid haemorrhage	No	Death due to DTC	[66]
	Cerebral haemorrhage	No	Death due to DTC	[67]
	NS	No	Death due to DTC	[68]
Neuroendocrine cancer	Sub-arachnoid bleed	No	Death due to DTC	[69]
	Cerebrovascular event	No	Death due to DTC	[70]
	NS	No	Alive on chemotherapy	[71]
Ovary	Anoxic brain injury	No	Death due to DTC	[15]
Pancreas	Cerebral haemorrhage	No	Alive at 1 yr following urgent re-transplant	[72]
Sarcoma	Asthma	No	NS	[73]
Unspecified adenocarcinoma	NS	NS	Alive at 8 mo following re-transplantation	[74]
Unspecified squamous carcinoma	Cerebral haemorrhage	No	Alive at 30 mo following re-transplantation	[75]
Urothelium	Sub-arachnoid haemorrhage	No	Alive at 4 yr following re-transplantation	[76]
	Sub-arachnoid haemorrhage	No	NS	[77]

NS: Not specified; DTC: Donor transmitted cancer; CNS: Central nervous system; GBM: Glioblastoma multiforme.

rence of a cancer that was treated in the past. If such metastasis is mis-diagnosed as a benign cerebral haemorrhage, the cancer transmission risk from such donor will be underestimated. Cases of transmission of cancer of colon, pancreas, melanoma and choriocarcinoma have been reported in these circumstances. So in donors with cerebral haemorrhage, in addition to standard donor assessment with investigation into cancers that may have been treated years or decades ago, consideration should also be given to additional tests such as cross-sectional imaging of brain, thorax, abdomen and pelvis or tumour markers. Some tumours are diagnosed during the retrieval process but the priorities of speedy retrieval, minimization of ischemic times and respect for the dignity of the donor and feelings of the family, means that full examination is not always appropriate. It is sometimes worthwhile considering a full post-mortem examination of the donor following organ procurement, as an early identification of donor cancer will influence the management of the recipients of organs from this donor.

Donors with a history of cancer

Existing guidelines from the Council of Europe (CoE)[17] and the organ procurement and Transplantation network/United Network for Organ Sharing (OPTN/UNOS)[18], summarized in Table 2, are useful for assessment of the risk of cancer transmission when a donor has a history of cancer, either treated in the past or active at the time of donation. These guidelines help in risk stratification and hence enable a detailed assessment of risks and benefits of accepting an organ from such a donor and also form the basis for informed consent. The relative rarity of DTC among transplant recipients is likely to be attributable to exclusion of donors deemed as high-risk, such as those described in these guidelines. These guidelines are based on evidence from case series and retrospective registry reports, which often do not include detailed data on the donor cancer such as histological grade of cancer, the details of treatment of cancer in the donor or post-treatment cancer surveillance. The relative risk of cancer transmission from a multi-organ donor with a history of cancer will be different for the recipients of different organs and the guidelines do not give comprehensive guidance on such relative risks. For example, when a donor has a history of colon cancer, the chance of the liver (a common site of metastasis) containing occult cancer cells will be higher than in the heart. Similarly, when a donor has a history of breast cancer, the relative risk of cancer transmission to the recipients of heart or lungs is likely to be higher than the risk to the recipients of abdominal organs. In practice, it is difficult to grade accurately the cancer transmission risk for each

Table 2 Summary of council of europe and organ procurement and transplantation network/united network for organ sharing guidelines for donor with cancer history

Council of Europe guidelines[17]: Donors with unacceptable risk of transmission	
Features applicable to cancer of any histological type at any time prior to donation	
Presence of metastasis - lymphatic or distant	
Absence of curative surgical treatment or missed follow-up (except low-grade prostate cancer under surveillance)	
Palliative therapy for cancer	
Non-CNS cancer at any time prior to donation	
Breast	
Ovary	
Choriocarcinoma	
Malignant melanoma, including carcinoma-*in-situ*	
Sarcoma	
Chronic Leukaemia	
Thyroid (except capsulated papillary or minimally invasive follicular type)	
Non-CNS cancer diagnosed during donor procurement	
All cancers, except:	
Renal cell cancer < 2.5-4.0 cm (pT_{1a}), tumour free resection margin and Fuhrman grade Ⅰ or Ⅱ	
Localised low grade (Gleason score ≤ 6) prostate cancer	
Small gastrointestinal stromal tumours	
Localised non-melanoma skin cancer	
Cancers of the CNS	
WHO grade Ⅳ cancers	
WHO grade Ⅲ cancers with following features:	
Presence of ventriculo-peritoneal or ventriculo-atrial shunts	
Craniotomy	
Systemic chemotherapy	
Radiotherapy	
OPTN/UNOS guidelines[18] - intermediate or high risk of transmission	
Intermediate risk of transmission (1%-10%)	High risk of transmission (> 10%)
Breast cancer, stage 0	Breast cancer, stage > 0
Colon cancer, stage 0	Colon cancer, stage > 0
Renal cell cancer (resected, solitary): 4-7 cm, well differentiated, stage I	Renal cell cancer: > 7 cm or stage Ⅱ-Ⅳ
Treated non-CNS malignancy (≥ 5 yr prior) with cure rate 90%-99%	Choriocarcinoma
	Leukaemia
	Lymphoma
	Small cell cancer: lung/neuroendocrine
	Metastatic carcinoma
	Sarcoma
	Lung cancer: stage Ⅰ-Ⅳ
	Any CNS tumour with ventriculo-peritoneal or ventriculo-atrial shunt, surgery (other than uncomplicated biopsy), irradiation or extra-cranial metastases
	CNS tumour of WHO grade Ⅲ or Ⅳ
	Any other cancer with insufficient follow-up or probability of cure < 90%

OPTN/UNOS: Organ Procurement and Transplantation Network/United Network for Organ Sharing Guidelines; CNS: Central nervous system; WHO: World health organization.

organ from a donor because of lack of data and the inevitable reliance of selected case histories.

Donors with a primary CNS tumour: Factors influencing the risk of transmission of a CNS tumour by transplantation include the histological grade of the tumour and interventions that breach the blood-brain barrier and hence may increase the probability of extracranial metastases; such interventions include cerebrospinal fluid shunts, craniotomy, systemic chemotherapy and radiotherapy. Tumours classified as grade Ⅲ or Ⅳ by the world Health Organization (WHO) classification[19] are considered to impose a rate of transmission of more than 10% as in the OPTN/UNOS recommendations[18]. However, not all studies have replicated these results. A study of transplant recipients by Watson *et al*[20] showed no cases of transmission among 448 recipients from 177 donors with a primary CNS cancer, including 33 donors with high-grade malignancies. While it is important to take all reasonable precautions to reduce the risk of cancer transmission, it is crucial that the waste of donated organs is avoided. Hence a careful risk-benefit assessment must be performed when a donor has a history of a high grade CNS cancer, balancing the risk of harm from cancer transmission against the risk of death while waiting for another graft. Thus, a liver from a high-risk donor might be accepted for a recipient with a growing liver cell cancer but declined for a recipient whose main indication is intractable itching or recurrent encephalopathy.

Thus, a sub-group of such donors may be a valuable source of additional organs, especially when an urgent life-saving transplantation is required. The risks of death

awaiting another offer must be balanced against the risk of inadvertent cancer transmission. Therefore, transplantation of organs from such donors must always be preceded by an informed consent.

Donors with a history of a non-CNS cancer: Even from the donors with a past history of a non-CNS cancer, the transmission of cancer to the organ recipients is very rare. The largest study[21] is from the UNOS/OPTN registry which included 39455 deceased donors between 2000 and 2005, of whom 1069 donors with a history of cancer donated to 2508 recipients (1866 from donors with non-CNS cancers and 642 from donors with CNS cancers). Two donor cancers were transmitted to four recipients a glioblastoma to 3 recipients and one case of melanoma. The glioblastoma was present in the donor at the time of donation but the melanoma in the donor was treated 32 years prior to donation with no apparent evidence of recurrence. Although these data are useful, they did not show the degree of selection of donors with a known cancer, *i.e.*, the number of potential donors with previous cancer whose organs were rejected after assessment of cancer transmission risk. Considering the rarity of DTC even after accepting organs from donors with previous cancer, it is possible that the process of donor assessment and exclusion of donors with past cancer based on the perceived risk of cancer transmission may result in wastage of some donor organs and so lead to loss of life.

Donors without a history of cancer

The risk of cancer transmission from a donor with no past history of cancer nor any evidence of active cancer at the time of donation is very low, but not absent. This applies both to deceased donors and living donors. As shown in Table 1, there have been several instances where donors with no evidence of cancer on standard donor assessment have resulted in cancer transmission. Some such cancers were never identified in the donors and some others were identified on the post-mortem examination of the donor. Therefore, as discussed above, the retrieving surgeon should perform a complete examination of the thoracic and abdominal cavity looking for occult cancer and an autopsy should be considered for donors with a past history of cancer. In reality, following such advice may be a challenge, especially in donors after circulatory death where there retrieval must be rapid.

In the survey of the transplant centres in the United Kingdom, 15 DTCs from 13 donors were identified and in none of these cases the donor was known, at the time of donation, to have a cancer[16]. Of these, one donor was identified to have a lymphoma on post-mortem examination resulting in investigation of the recipients and the subsequent identification of transmitted lymphoma. These data demonstrate that further reduction of cancer transmission risk from organ donors is difficult and a small risk is unavoidable. Therefore, informed consent of all the prospective recipients is important, which should be undertaken at the time of listing for transplantation; where donors have an increased risk of tumour transmission (such as those with a recent history of cancer) the potential recipient should be counseled and give specific consent, although it is recognized that there are possible issues in having such a difficult discussion at a stressful time for the transplant candidate.

While there has been no report of transmitted cancers from living liver donors, but living kidney donation has shown that a donor without evidence of cancer at the time of donation can transmit a cancer, which is subsequently identified in both the donor and the recipient[22]. In cases of living donation, the donor should be followed up for a minimum period of 1 year after donation.

MANAGEMENT OF RECIPIENTS WITH DTC

Management of recipients with DTC should be individualised depending on several factors including the time of diagnosis of DTC following transplantation, type of cancer, the extent of DTC, organ transplanted, comorbidities and wishes of the recipient. When the transplanted organ is a kidney or a pancreas, urgent explantation should be considered, as this would enable removal of the graft responsible for cancer transmission and also cessation of immunosuppression. Even in cases where explantation is not performed, reduction, change or even cessation of immunosuppression should be considered, as the reconstitution of immune system following cessation of immunosuppression has been shown in some cases to reject the cancer cells resulting in complete clearance of cancer[23,24], although this would depend, in part, on the degree of mismatch between the donor and the recipient and the degree of differentiation of the cancer cells. The chances of the recipient's immune system rejecting the cancer cells are higher with a greater mismatch between the donor and the recipient and for a cancer that is well differentiated and is able to express its human leukocyte antigens.

For recipients of liver or cardiothoracic transplantation, the risks of re-transplantation must be compared against the risks of treating the cancer without re-transplantation. In all cases, the immunosuppression should be minimized and a switch to mammalian target of rapamycin (mTOR) inhibitors should be considered as these agents have shown efficacy against certain types of cancers[25,26].

Considering the rarity of DTCs and the variety in the types of cancers transmitted and their management, each transplant regulatory authority should make efforts to record the data of all cases of DTC in a national registry as such data will be useful in guiding the management of future recipients with DTCs.

The outcome is more favourable for cancers diagnosed at the time of transplantation or soon after (within 6 wk) as compared to those diagnosed later, and also for cancers localised to the allograft as compared to those,

Table 3 Increased risk of cancer after liver transplantation compared with general population adjusted for age, gender and year

Cancer type	Standardised incidence ratio
All cancers	2-3
Kaposi's sarcoma	37-144
Non-melanoma skin cancer	6-38
Lip	20
Lymphoma	7-13
Upper aero-digestive tract	10-15
Anus	3-10
Kidney	2-4
Colorectal (PSC-IBD)	3
Melanoma, lung	2
Colorectal (non PSC-IBD)	Not increased
Myeloma	Not increased
Breast	Not increased
Prostate	Not increased

PSC-IBD: Primary sclerosing cholangitis inflammatory bowel disease.

which have metastasised[16].

TRENDS IN ORGAN DONATION AND THEIR IMPACT ON THE RISK OF CANCER TRANSMISSION

The gap between the supply of and demand for donated organs has remained wide in spite of increasing donation rates[1]. The average donor is getting older, more obese and the proportion of donors following circulatory death is increasing[1]. With increasing waiting times for transplantation and the consequent morbidity and mortality for patients on the transplant waiting-list, organs from donors with previous cancer and other co-morbidities, history of tobacco and alcohol use are being offered for transplantation. In the United Kingdom, the rates of adults continuing to smoke and drink harmful amounts of alcohol remain high[27,28], in spite of the measures such as minimum age limit for sale of alcohol and tobacco, banning of smoking in public places and restrictions on advertising. Therefore, the chances of a donor having an occult cancer and transmitting it to the recipient are likely to increase.

DE NOVO CANCER AFTER LIVER TRANSPLANTATION

Long-term survival of liver transplant recipients is related to sustained functioning of the graft, which nearly always depends on effective immunosuppression. Although different immunosuppressive agents block different intra-cellular pathways, the end-result of post-transplant immunosuppression is the blocking of T-cell activation when presented with an alloantigen. As this is not specific to allograft, the immune response to other foreign antigens is also suppressed, resulting in an increased risk of some infections and malignancies. Liver transplant recipients are at an increased risk of cancer as compared with matched general population and cancer is one of the leading causes of long-term mortality after liver transplantation. Table 3 summarises the standardised incidence ratio (SIR, ratio of the observed incidence of cancer to the expected incidence in an age, gender and year matched immunocompetent population) as reported in the liver transplant recipients in the United Kingdom[2], United States of America[29,30], Australia[31], Germany[32], Netherlands[33], Finland[34] and Italy[35,36]. The risk of all cancers is increased 2-3 fold following liver transplantation. The relative increase in incidence is higher for Kaposi's sarcoma, non-melanoma skin cancer and lymphoma whereas the risk of cancers of the breast, prostate and multiple myeloma is not increased.

RISK FACTORS FOR POST LIVER TRANSPLANT CANCER

Several factors contribute to the increased risk of cancer following liver transplantation. Factors such as age of the recipient, time since transplant (which represents the duration of immunosuppression) and intensity of immunosuppression are associated with an increased overall risk of cancer. Different immunosuppressive agents are likely to influence the cancer risk differently. Immunosuppressive agents are often used in combination, and for most recipients, depending on their co-morbidities and the risk of rejection, the choice and dose of immunosuppressive agents vary during their post transplant period, and this makes it difficult to estimate the risk of cancer with individual agents. Some types of cancers are associated with specific risk factors and these are discussed below.

Non-melanoma skin cancer

Non-melanoma skin cancer (NMSC) comprise the most common group of cancer seen after liver transplantation with a highest increase in risk among all cancers as compared against matched non-transplant population. NMSC are often a late complication of liver transplantation with a mean time from transplant to diagnosis of 50 mo[37]. Apart from widely recognised risk factors such as sun exposure, lighter skin colour and intensity of post transplant immunosuppression, increased risk of NMSC is also noted to be associated with higher age at transplantation, male gender[38] and excess alcohol consumption[39].

Post-transplant lymphoproliferative disorder

Post transplant lymphoproliferative disorder (PTLD) is unique for a number of reasons. It is a cancer that is entirely caused by medical intervention (*i.e.*, transplantation), is one of the few cancers which can develop *de novo* in the early post transplant period and is often fatal. It is also highly responsive to immunosuppression and is attributable to a viral infection. The risk of PTLD is increased in patients who are not exposed to Epstein-Barr virus (EBV) before transplantation[40] more so in paediatric recipients and in the early post transplant period. The impaired T lymphocyte activation as a result of post transplant im-

munosuppression results in uncontrolled proliferation EBV-infected B cells[41,42]. The overall immunosuppressive burden is an important factor in determining the risk of development and also the outcome of PTLD and the epidemiological evidence indicated that the risk is particularly related to use of anti-thymocyte globulin (ATG) and OKT3[43]. Liver transplantation for certain indications such as hepatitis C[44-46] and alcoholic liver disease[44,45] is also shown to be associated with an increased risk of PTLD. Reasons for this are not clear.

Upper aero-digestive tract cancers

This group includes cancer of the oral cavity, pharynx, larynx and oesophagus. The risk is increased up to 15 times after liver transplantation, particularly in recipients whose indication for transplantation was alcoholic liver disease[32]. Higher association of cigarette smoking with excess alcohol consumption is considered as a significant factor in several studies[30,39,44] but an increased risk of oral and pharyngeal cancers with alcohol consumption independent of smoking has also been demonstrated in non-transplant population[47]. Several mechanisms by which alcohol may increase the risk of cancer have been described including impaired ability of cells to repair DNA resulting in increased expression of oncogenes, carcinogenic alcohol metabolites such as acetaldehyde, alcohol-mediated induction of CYPP450 family of enzymes which enhance the metabolism of tobacco into carcinogenic free radicals, decreased levels of retinoic acid which has anti-carcinogenic effect and decreased methylation of certain oncogenes resulting in their increased expression[48].

Colorectal cancer

The risk of colorectal cancer is increased in non-transplant patients with primary sclerosing cholangitis (PSC), much more so in patients with PSC and inflammatory bowel disease (PSC-IBD)[49]. After liver transplantation, the risk of colorectal cancer is increased up to 3 times in patients with PSC-IBD[31,50]. This increased risk has been attributed to a combined effect of post transplant immunosuppression and IBD related colorectal mucosal inflammation.

PREVENTION AND MANAGEMENT OF CANCER AFTER LIVER TRANSPLANTATION

Risk reduction

All the transplant recipients should be counseled regarding the benefits of cessation of smoking and alcohol consumption. This should ideally be started at the time of listing for transplantation and continued for as long as needed even after transplantation. Screening for EBV should be performed in all recipients and where possible, the benefits of matching the donor and the recipient status for their EBV status should be considered, particularly in paediatric recipients. Avoidance of sun exposure and protection against prolonged sun exposure should be advised to all the recipients. As a general rule, the intensity of immunosuppression should be kept to a minimum and in particular combining several risk factors which increase the risk of post transplant cancer should be avoided, for example, induction using ATG or OKT3 should be avoided in a EBV seronegative recipient receiving a liver from a EBV seropositive donor. Liver recipients (who are not infected with hepatitis B) should be routinely vaccinated against hepatitis B. Information should be provided regarding the risk factors which may be pre-existing (such as viral infections, past smoking) or non-modifiable (such as age, gender, ethnicity, skin colour) including their influence on the risk of post transplant cancer. Early symptoms of common cancers should also be discussed in order to facilitate early detection. There is limited evidence demonstrating the benefits of specific screening protocols after liver transplantation. The risk of cancers which are common in the general population and which are routinely screened such as cancer of breast, colon, prostate and cervix is not uniformly elevated in all recipients of liver transplantation. Therefore, it is advisable to use for liver recipients, the same screening guidelines that are used for non-transplant population. With regards to screening for other cancers, high quality evidence is lacking. Some studies suggest modified screening recommendations in specific sub-groups[37] such as annual colonoscopies for liver recipients with PSC-IBD. Other screening interventions such as annual dermatological examination, annual chest X-ray and laryngological examination for patients with history of alcohol and tobacco consumption have been recommended[51] but in absence of strong evidence of benefit, these should be used in accordance with policies of individual transplant centres and the assessment of benefit to individual patients. Management of post liver transplant cancers should be along the lines of cancers in non-transplant population with specific attention to minimalisation of immunosuppression in such recipients.

In summary, cancer is a significant challenge in recipients of liver transplantation and is one of the leading causes of late mortality. Donor transmitted cancer is rare but is frequently associated with poor outcome. Detailed assessment of donors should be performed before accepting the livers for transplantation and informed consent of the recipients should be obtained in all cases. Strategies for managing *de novo* cancer following liver transplantation should include intensive approach to eliminate or reduce risk factors such as smoking and alcohol and judicious use of screening techniques.

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