Malignancies after Liver Transplantation: A Review of the Literature

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Abstract

Background: Orthotopic liver transplant (OLT) is an established life saving procedure for both acute and chronic liver failure. A number of malignancies have been reported in liver transplant recipients over the past thirty years.

Aims:
To review the literature regarding malignancies developing in liver transplant recipients pursuant to their transplant operations.

Literature findings:
Malignancies which may develop after liver transplantation could be de novo malignancies, donor-transmitted malignancies or indolent malignancies that have undergone recrudescence in a transplant recipient. De novo malignancy is one of the leading causes of late mortality after liver transplantation. The risks of skin cancers and lymphoma are greater than 10-fold the risks in an age matched and sex-matched general population. Certain types of malignancy, for example, lung, head and neck, and colorectal cancer are more frequent in liver-transplant recipients than in an age-matched and sex matched population. The risks of other common malignancies for example, prostate, and breast cancer do not appear to be increased.

Important risks for the development of post-liver-transplantation malignancy include: Epstein-Barr virus sero-negativity (for lymphoma), sun exposure (for skin cancer), smoking, and increased age.

Recommendations:
Irrespective of the absence of evidence, the following general recommendations are important.
1. Avoidance of over-immuno-suppression
2. Sunlight protection of the liver transplant recipient would be advised
3. Cessation of smoking (The transplant recipients should be advised to stop smoking).
4. Screening protocols of potential transplant donors especially older ones by means of CT scan may help detect an incidental malignancy in a potential donor which should then lead to the exclusion from donation in order to reduce the incidence of donor transmission of cancer.

Adoption of regular screening protocols in the follow-up of recipients would lead to early detection and treatment of de novo or recurrent malignancies in the transplant recipient.

Introduction

It has been suggested that even though the etiologic factors which determine the susceptibility of malignancy have not been fully defined, it is understood or clear that complex interactions exist between environmental factors, genetic pre-disposition, oncological viral factors, and immune system status [1] Fung and associates [1] stated that the contribution of dysfunctional immune system to the risk of developing malignancy was not previously appreciated until the advent of iatrogenic immune-suppression developed for solid-organ transplantation. Starzl [2] in 1968 predicted an increased incidence in the development of de novo malignancies in immune-suppressed organ transplant recipients and this was confirmed by Penn and associates [3] in 1969 and re-affirmed by Penn [4] and associates in 1972. A number of reports [5], [6], [7], [8], [9], [10], & [11] have depicted clearly trends to increased incidence of some types of post-transplantation de novo malignancies, mainly those linked to viral cause. Depending upon the type and demographics of the transplant population, length of follow-up pursuant to transplantation and the era in which the transplantations were undertaken, the estimates of developing de novo malignancies have been reported to range from 4.1% to 16% by Penn [6] in 1990 and Penn [12] in 1993. Malignancies subsequently developing in a liver transplant recipient may be either (a) de novo malignancies, or (b) malignancies that have been transmitted from the organ donor or (c) recrudescence of innate malignancy that previously existed in the transplant recipient prior to the transplantation procedure. [2] We have reviewed in this paper the literature regarding malignancies developing in renal transplant recipients.
Literature Review

Incidence of De Novo Malignancies after Liver Transplantation:

Penn [13] summarized the Israel Penn International Transplant Tumor Registry (IPTTTR) analysis of de novo cancer occurring after liver transplantation. Penn [13] reported that three hundred and twenty four liver transplant recipients developed three hundred and twenty nine (329) cancers. In contrast to de novo malignancies seen in renal allograft recipients, lymphomas were much more common in liver allograft recipients (57% v 12% of all tumours), on the other hand skin cancers (39% v 15%), cervical carcinomas (4% v 1%), renal cancers (4% v 1%), and vulva carcinomas (3% v 0.6%) were more common in renal allograft recipients. Furthermore, liver transplant recipients appeared to develop both lymphoid (15 v 46 months) and non-lymphoid malignancies in a shorter timepursuant to liver transplantation (27 v 72 months) in comparison with renal transplant recipients. Penn [13] explained that perhaps the longer follow-up of kidney transplant recipients accounts for the greater incidence of other tumours which tended to appear rather late after transplantation. In a report for the Australian and New Zealand liver transplant Registry, Sheil [14] stated that 424 patients who survived a mean of 2 years after liver transplantation, 2% of the recipients developed de novo cancers. Sheil [14] also stated that thirteen malignancies were detected in 12 transplant recipients and the corresponding malignancies were: non-Hodgkin lymphoma 6 patients; KapoSi’s sarcoma 3 patients; leukemia 1 patient; testicular cancer 1 patient; bladder cancer 1 patient; thyroid cancer 1 patient. Sheil [15] further reported an updated version of this registry and stated that: (A) Out of 1,170 of 1,540 survivors of liver transplantation, de novo carcinomas were detected in 184 patients. (B) One hundred and thirty eight patients developed skin cancers (including 4 patients with KapoSi’s sarcoma; 19 patients with post-transplantation lymphoproliferative disorder (PTLPD); 11 patients with digestive cancers; 6 patients with genitor-urinary cancers; 5 patients with endocrine tumours; and 7 patients with other miscellaneous cancers. Sheil [15] also reported that by 10 years pursuant to liver transplantation, 30% of the liver transplant recipients had developed de novo cancers. Berenguier and associates [16] reviewed 340 liver transplant recipients who had survived more than 2 months, they reported a 4.7% incidence of de novo cancers and the mean time to the appearance of the cancers was 28 months; twenty five percent of the tumours were post-transplantation lymphoproliferative disorders; 12.5% of the tumours were colon, urinary bladder, breast, skin and oropharyngeal cancers; and 6% were of the tumours were cervical cancer and adenocarcinoma of small bowel. Kelly and associates [17] reported that out of 888 liver transplant recipients, 4.3% developed de novo cancers. They also reported a higher incidence of de novo cancers in alcoholic patients but the tumours were not more aggressive than reported for the general population. Nevertheless, Sheiner and associates [18] reported a a significant increase in the incidence of de novo cancers, with a standardized incidence ratio (SIR) of 3.94 for non-skin cancers and 3.14 for non-melanoma skin cancers in a follow-up report of long term liver transplant survivors of equal to or longer than 5 years. The standardized incidence ratio (SIR) was used to provide a comparative incidence of the observed number of cancer cases to the expected number of cases. Hence a SIR value > 1.00 indicates excess risk, and a value > 1.00 indicates a decreased risk. Sven associates [19] reported a 6% incidence of malignancy at 5 years pursuant to liver transplantation. They reported that with a median follow-up of 6 years, de Novo cancers were detected in 62 of 1,007 liver transplant recipients these included lymphoproliferative disorders, 13 patients had skin cancers, 17 patients had cervical cancers, 9 patients had lung cancers, 6 patients had breast cancers, 5 patients had oropharyngeal cancers, 12 patients had miscellaneous cancers. Levy and associates [20] reported that 25 patients (4.5%) out of 556 liver transplant recipients developed de novo cancers. Skin cancers and lymphoproliferative disorders were equally represented in these tumours and remaining tumours were single cases each of colon, prostate, breast, pancreas and liver cancer. Haagsma and associates [21] reported that out of 174 liver transplant recipients, 21 developed de novo malignancies one year after receiving their transplants. They also reported that even though skin cancers accounted for the majority of these malignancies, their surprise only one patient developed lymphoproliferative disorder. They also reported that the cumulative risks for de novo cancer were 6%, 20%, and 55% at 5, 10, and 15 years following liver transplantation respectively. Their additional reports include:

A. The overall RR compared with the general population was 4.3 (95% confidence interval, 7.4 to 7.1)
B. Significantly increased RRs were observed for non-melanoma skin cancer (RR, 70.0), non-skin solid cancer (RR 2.7), renal cell cancer (RR, 30.0) and
colon cancer (RR, 12.5).
c. Multivariate analysis showed that age older than 40
years and pre-liver transplantation use of
immune-suppression were significant risk factors. Jain
and associates [9] and [22] reported 1,000
consecutive adult and paediatric primary liver
transplant recipients who were followed up for a mean
period of 93.3 ± 11.0 months on a prospective basis.
They stated that 44 patients developed
post-transplantation lymphoproliferative disorders;
Eighty one patients developed de novo non-lymphoid
malignancies, 35 of which were skin cancers, including
2 melanomas and 2 Kaposi's sarcomas; Eleven
gastro-intestinal cancers, 9 genito-urinary cancers, 8
pulmonary cancers, 7 oro-pharyngeal cancers, 3
breast cancers, 2 metastatic cancers of unknown
primary tumours, 2 leukemias, 2 thyroid cancer, 1
brain cancer, 1 de novo hepatocellular cancer, and 1
ophthalmic malignancy. Ries and associates [23] stated
that in comparison with SIRs from the Surveillance
Epidemiologic End Results (SEER data, the incidence
of oro-pharyngeal cancer was found to be 7.6 times
greater (P>0.05) than predicted. On the other hand,
the incidence of breast cancer was 1.9 times less (P >
.05) and that of genitourinary cancer was 1.5 times
less (P > 0.05) than in their matched cohorts. They
also stated that they did not observe any difference in
risk for gastro-intestinal malignancies. Jain and
associates [24] did a sub-analysis of a high-risk group
for post-transplantation lymphoproliferative disorders
in which 353 paediatric primary liver transplant
recipients studied in order to find out the incidence of
of post-transplantation lymphoproliferative disorders.
They reported that the incidence of post-transplantation
lymphoproliferative was 13.7% with tacrolimus immune-suppression versus 8.3% with
cyclosporine (CyA), in part related to more sensitive
detecting methods in the former group. Furthermore,
they reported that in the tacrolimus group, the
diagnosis of lympho-proliferative disorders presented
at a mean age of 5.5 ± 0.7 years (range, 0.6 to 15
years), with an average time from liver transplantation
to 10.1 ± 2.1 months. Survival statistics data on de
novo malignancies after liver transplantation

Cacciarelli and associates [25] stated that:
1. Survival with de novo cancers is on the whole poor
but this depends upon the tumour type.
2. The impact of these malignancies on survival of
patients is evolving.
3. Survival in patients with post-transplantation
lymphoproliferative disorders has improved over time.
4. Survival following the diagnosis of
post-transplantation lymphoproliferative disorders was
significantly better for tacrolimus-treated patients in
comparison with post-transplantation
lymphoproliferative disorders at 81.2% in comparison
with cyclosporine A (CyA) treated patients with
post-transplantation lympho-proliferative disorders at
50% after 5 years, in addition partly related to the
improvements in strategies for the management of this
complication.
This is favourably comparable with reports of Newell
and associates [26] and Glez Chamorro [27] on
post-transplantation lympho-proliferative disorders
which had reported the mortality rates of about 60%.
However, the development of de novo carcinomas
significantly compromises long-term survival. Sheil
[14] reported that in patients with de novo cancers, the
10-year survival was only 27%. Jain and associates [9]
reported that the one year survival rates for skin
cancer, oro-pharyngeal cancer, and lung cancer were
respectively 90.9%, 34.3%, and 37.5%.

Fung and associates [1] stated that:
1. The one-year survival rate for genitourinary and
gastro-intestinal cancers was 100% ; however, at 2
years , the survival rate had decreased to 60% and
40% respectively.
2. All the patients who had metastatic disease of
unknown primary tumour, Kaposi’s sarcoma, brain
tumour, and cancers of conjunctiva died within the first
year from the time of their diagnosis.

DONOR TRANSMISSION OF MALIGNANCY TO A
LIVER RECIPIENT:
Post transplant malignancy of donor origin is a rare
complication of organ transplantation but it has been
sporadically reported. Busuttil and Tanaka [28] in
2003 stated that quantification or calculation of the
true risk of donor transmitted malignancies have been
difficult because of under-reporting to the Organ
Procurement and transplantation Network / UNOS
registry. They also stated that despite the fact that
Israel Penn International Transplant Tumor Registry
had been collecting data on post-transplantation
malignancies since 1968, the lack of a true
denominator makes it difficult to calculate the
frequency of cancer transmission from cadaveric
donors. Thus, so far in 2003, 17 documented cases of
donor-transmitted malignancies to the liver transplant
recipient had been recorded [29] & [30]. The 17
documented cases of donor-transmitted malignancies
were as follows:
[5] liver transplant recipients who developed
melanoma died
[3] liver transplant recipients who developed
Glioblastoma died
[2] Liver transplant recipients who developed choriocarcinoma died.

[1] Liver transplant recipient developed Neuro-endocrine tumour and died.

[1] Liver transplant recipient developed Kaposi’s sarcoma and died (these add up to a total of 12 recipients who died).

[3] Liver transplant recipients who developed adenocarcinoma were alive.

[1] Liver transplant recipient who developed squamous cell carcinoma was alive (these add up to a total of 5 patients who were alive; 4 patients were re-transplanted).

Kim and associates [31] a case of donor transmission of malignant melanoma to a liver graft recipient. Post-transplant malignancy of donor origin is believed to be most likely transmitted as micro-metastases within the parenchyma of the donor organ or from circulating tumour cells contained within the organ. [31] Kim and associates [31] also stated that:

The survival of patients who have developed donor-transmitted malignancy is dependent upon early diagnosis, and differentiation of the malignancy as of donor or recipient derivation is important in developing a treatment modality. The utilization of fluorescent in situ hybridization chromosome analysis and DNA sequence analysis of the tumour cells can assist in this determination (whether the tumour is of donor or recipient origin). De Perrot and associates [32] reported that among a cohort of 3,374 patients transplanted in their institution between 1985 and 2000 (1,735 kidney recipients, 930 liver recipients, 313 heart, and 396 lung recipients), 9 patients (0.3%) had developed a bronchogenic carcinoma. Lung carcinoma occurred in 3 kidney transplant recipients, 3 liver recipients, 2 heart recipients, and 1 lung recipient. They also reported that the time to diagnosis after the transplant procedure ranged from 9 to 126 months (mean, 63 months). Aside from the lung transplant recipient, all recipients had a smoking history. Seven patients underwent thoracotomy and 6 had a complete resection. The tumours were classified as stage 1A (n=1), 1B (n=2), IIIB (n=2), IIIA (n=2), IIIB (n=1), and IV (n=1). They reported that Genotyping demonstrated donor origin recurrent malignancies can develop in recipients who were smokers rather than donor-transmitted malignancies. Foltys and associates [33] retrieved grafts from a deceased donor without any history of previous diseases. Autopsy was not performed donation. The liver transplant graft recipient presented with suspected nodules on routine abdominal ultrasound scan. After computed tomography (CT) scan, histology of biopsy from the nodules in the liver confirmed the diagnosis of small-cell carcinoma. Donor origin was unequivocally identified by DNA fingerprinting. Despite chemotherapy the patient died 7 months after orthotopic liver transplantation. All involved transplantation centres were informed immediately following the diagnosis. The male kidney recipient underwent detailed diagnostic work-up to exclude tumour transmission. One year after transplantation, liver metastases caused by a histologically proven small-cell carcinoma from the same donor were apparent. Chemotherapy was immediately started and the graft was removed. Despite continued treatment the tumour progressed and the patient died after repeated intestinal complications. The pathological examination of the explanted second kidney graft did not show any tumour infiltration. Foltys and associates [34] concluded that therapeutic regimens in recipients suffering from donor-derived carcinoma differ depending on the transplanted organ. Graft removal of non-life-sustaining organs and discontinuation of immuno-suppressive medication should result in complete tumour rejection. Minimizing the risk of tumour transmission, a CT scan might be advisable in donors of more advanced age.

LATE RECURRENTITY OF MALIGNANCY IN A POST-LIVER TRANSPLANT RECIPIENT:

Apart from de novo malignancies and donor transmitted malignancies after transplantation, recipient origin recurrent malignancies can develop after transplantation. Schreibman and associates [34] stated that hepatocellular carcinoma recurs in 10% to 60% of patients after liver transplantation and is associated with increased mortality. Schreibman and associates [34] also stated that the average time to recurrence ranges from 1 to 2 years following liver.
transplantation, and the median survival from the time of diagnosis is about one year. Schreibman and associates [34] reported a case of a 69-year old man who underwent liver transplantation for hepatitis C virus-related cirrhosis with hepatocellular carcinoma, and who was diagnosed with recurrent hepato-cellular carcinoma 6.5 years after the liver transplantation. Histological findings of biopsies from the initial and recurrent tumours showed a well-differentiated hepato-cellular carcinoma with clear cell pattern. The patient was still alive and asymptomatic 32 months after the diagnosis despite extensive tumour burden. He died 9 years, 9 months after his liver transplantation and 3 years, 2 months after the detection of recurrence. Schreibman and associates [34] concluded that:

Hepato-cellular carcinoma may recur more than 6 years after liver transplantation and may exhibit an indolent course. This case illustrates the highly variable rate of tumour growth and progression post-liver transplantation. The impact of this information on the need for long-term surveillance for recurrent hepato-cellular carcinoma post liver transplantation remains to be determined. Yoram and associates [35] evaluated the role of pre-malignant states, not associated with liver disease prior to transplantation, in the development of post-transplantation malignancy. They retrospectively evaluated one hundred and seventy patients who had undergone liver transplantation for the development of malignant conditions. Each of the patients who developed malignancy after transplantation was evaluated for the presence of pre-malignant conditions before transplantation. They identified post-liver transplantation malignancy in 13 patients (7.4%). Five patients developed non-Hodgkin lymphoma: four had post-transplantation lympho-proliferative diseases, and one had B cell lymphoma of stomach. Eight patients developed solid tumours and in five of these patients, evidence of pre-malignant state was identified including: ulcerative colitis with carcinoma of colon in 1 patient; colonic polyp in 1 patient with carcinoma of colon; Barrett oesophagus in 1 patient with oesophageal carcinoma; Caroli disease in 1 patient with anaplastic cholangiocarcinoma; and cervical atypia in 1 patient with carcinoma of the cervix. Yoram and associates [35] concluded that pre-malignant conditions existing before transplantation, which are not associated with primary liver disease, are major risk factors for post-transplantation malignancy. They recommended that screening for pre-malignant conditions should be included in pre-transplantation evaluation. Liver transplant patients with evidence of a pre-malignant state should be followed after transplantation for the detection of malignancy.

**The Role of Immunosuppression in the potentiating or enhancement of the aggressive nature of de novo malignancies:**

A number of authors (36; 37; 38) have stated that antirejection medications induce a state of iatrogenic depression of immune surveillance, suggested to be a condition permissive for the development of malignancy. It has also been suggested that such immunosuppressive agents as azathioprine [39], [40] and cyclosporine (CyA) [41] have intrinsic properties that favour the establishment of de novo malignancies. The potential mechanisms range from inherent carcinogenic properties of antiproliferative agents to alterations in the cytokine milieu associated with CyA (and may be tacrolimus) to an independent effect on cell-adhesive properties. Some authors (Dalton and associates)[42] and Singhal and associates [43] have stated that antiproliferative and alkylating agents can initiate and / or potentiate DNA damage and act synergistically with other carcinogens. It has been suggested that Azathioprine has a role in the development of skin cancer; a study by Lennard and associates [44] revealed that renal transplant recipients on azathioprine therapy who developed skin cancer had higher levels of metabolite 6-thioguanine than those who did not develop skin cancer. On the other hand, schoeffner and Thorgeirsson [45] reported that large-animal models failed to show excessive cancer rates when they were chronically administered either cyclophosphamide or azathioprine. Hojo and associates [41] suggested that cyclosporine (CyA) heightens the risk for carcinogenesis in autonomous fashion. Hojo and associates [41] also illustrated that cyclosporine (CyA) induces phenotypic changes in cells, including non-transformed cells, with increased membrane ruffling, cell locomotion, and extracellular matrix-independent growth. Mooradian and associates [46] stated that this effect would appear to be mediated by transforming growth factor-β (TGF-β) in view of the fact that monoclonal antibodies to TGF-β prevent metastasis in an experimental model. Fung and associates [1] stated that TGF-β is a potent cell-growth modulator and this affects cell-extra-cellular matrix interactions in a dose-dependent manner. It has been stated that both cyclosporine (Shin and associates [47]) and tacrolimus (Khanna and associates [48]) increase TGF-β transcription rates in humans in vivo. Mohammed and associates [49] stated that comparative studies suggest that this may be more prevalent with cyclosporine (CyA).
Discussion

Flattery [50] stipulated that the reported incidence of de novo malignancies following liver transplantation ranged from 4% to 16%, depending on the length of follow-up, age distribution of patients who underwent liver transplantation, and the nature of immunosuppressive regimens used. Flattery [50] highlighted that, a point incidence for the risk for de novo malignancies will not be accurate, in view of the fact that the longer a transplant recipient survives, the greater is the cumulative-risk. Flattery [50] also noted that actuarial risk for de novo cancer among cardiac transplant recipients increased from 2.7% ± 1.9% at 1 year to 25.6% ± 11% at 5 years. Fung and associates [1] also noted that in their own series the overall frequency of de novo non-lymphoid cancers increased as further follow-up accrued. Fung and associates [1] reported that majority of studies addressing the development of de novo cancers in liver transplant recipients observed that a significant proportion of patients have post-transplantation lympho-proliferative disorders. Post-transplantation lympho-proliferative disorders comprise of a spectrum of abnormal entities of lymphocyte proliferation which occur in the setting of iatrogenically induced immune-deficiency following organ transplantation. Starzl and associates in 1968 [2] were the first to observe the susceptibility of transplant recipients to the development of lymphomas. Paya and associates [51] confirmed the relationship between post-transplantation lympho-proliferative disorders and a viral cause when Epstein-Barr virus was observed to be associated with most cases of post-transplantation lympho-proliferative disorders. Devarbhavi and associates [52] stated that majority of post-transplantation lympho-proliferative disorders arise within the first 1 to 2 years after transplantation but recent evidence has shown that the proportion of Epstein-Barr virus negative post-transplantation lympho-proliferative disorders increases in late presentations. Nalesnik and associates [53] and Malatack and associates [54] observed that the actuarial one-year incidence of post-transplantation lympho-proliferative disorders is approximately 2%, even though the incidence is up to ten times greater in children younger than 5 years (more likely to be Epstein-Barr virus sero-negative) in comparison with adults (usually Epstein-Barr virus sero-positive). Hezode and associate [55] and Buda and associates [56] reported an increased incidence of post-transplantation lympho-proliferative disorders in patients with hepatitis C virus co-infection, not only in liver transplant recipients, but also in cardiac transplant recipients.

Paya and associates [51] stated that:
1. The pathophysiological course of post-transplantation lympho-proliferative disorders is not completely understood.
2. The treatment of post-transplantation lympho-proliferative disorders has been controversial.
3. For patients with disease which fails to respond to a reduction in immune-suppression, a variety of systemic therapies have been used as a second step of treatment. These include interferon alfa, chemotherapy regimens, anti-B-cell monoclonal antibodies, and cell-based therapies. No clinical trial has delineated which therapeutic approach is best.

Starzl and associates [57] stated that:
1. Most of post-transplantation lympho-proliferative disorders are of B cell origin (>90%), on the other hand, the remainder is of T cell origin, and only rarely of null cell, i.e., without identifiable T- or B- markers.
2. Epstein-Barr virus is believed to play a role in the development of majority of post-transplantation lympho-proliferative disorders, by binding to the Epstein Barr virus-specific receptor found on B cells and providing a growth signal to the infected B cell.
3. Expression of viral proteins could lead to a number of immune consequences. For example, the viral product bcl-2 protects Epstein-Barr virus infected B cells from the normal process of apoptosis.
4. The role of exogenous immune-suppression, believed to be related to suppression of host defences (primarily T cells, which normally provide surveillance and protection from out-growth of viral-infected cells) is the underlying commonality in the development of post-transplantation lympho-proliferative disorders. This role of immune-suppression supports the finding that reduction or withdrawal of immune-suppression leads to regression of post-transplantation lympho-proliferative disorders in many cases. Fung and associates [1] stated that with the unavailability of anti-CD21 and anti-CD24 monoclonal antibodies as stated by Benkerrous and associates [59], anti-CD20 monoclonal antibody therapy has been used instead and recently this was reported to be of some benefit in post-liver-transplantation lympho-proliferative disorders as reported by Zompi and associates [59], and Chemotherapy may be necessary for refractory post-transplantation lympho-proliferative disorders as reported by McCarthy and associates [60]. Kelly and associates [17] as well as Jain and
associates [22] reported that alcohol related liver disease was associated with a higher incidence of de novo cancers than in patients who did not undergo liver transplantation for alcoholic liver disease. Fung and associates [1] reported that in their series at five years following liver transplantation, the overall patient survival rates for the alcoholic liver disease and non-alcoholic liver disease groups were similar (72.0% v 66.5%). Nevertheless, after 5 years patient survival for the alcoholic disease group was significantly less (P=0.001) in comparison with the non-alcoholic disease group. Despite the fact that rates of post-transplantation lympho-proliferative disease in the alcoholic liver disease (3.2%) and non-alcoholic liver disease groups (2.6%) were similar, mortality in the alcoholic liver disease group with post-transplantation lympho-proliferative disease was significantly higher (83%) in comparison with the non-alcoholic liver disease group (17.6%; P = 0.002). Fung and associates [1] also stated that even though there are a number of reports of post-transplantation lympho-proliferative disease in liver transplantation populations, there are no reports of increased mortality caused by post-transplantation lympho-proliferative disease in liver transplant recipients with alcoholic liver disease.

Ethanol has been reported to do the following:
1. Increase karyotypic chromosomal aberrations (reported by Matsushima [61]; and Huttner and associates [62].
2. Increase the expression of TGF-ß in a variety of cells, including macrophages (as reported by Singhal and associates [63], and liver cells (as reported by Kamimura and Tsukamoto [64].
3. Increase suppression of immunity toward cancer and infections in experimental models (as reported by Hunt and associates [65]; and Jerrells and associates [66] Thun and associates [67] reported that rates of de novo malignancies after liver transplantation in their study were as follows:
1. Oropharyngeal and lung cancers 25.5 and 3.7 times greater in the alcoholic liver disease group in comparison with the general population matched for age, sex, and length of follow-up using SEER data respectively.
2. Incidence of de novo cancers for the non-alcoholic liver disease group was similar to that of the general population.
3. The rates of genitor-urinary cancers were 2.2 times higher in the alcoholic population, but not in the non-alcoholic group; nevertheless this difference was not statistically significant.
4. The increased incidence of oral, oesophageal, pharyngeal, laryngeal and hepatic malignancies was documented in non-immuno-suppressed middle aged and elderly individuals with moderate to large amounts of alcohol consumption.

Fung and associates [1] stated that in their experience, 70% of patients who developed oro-pharyngeal, lung, and gastro-intestinal malignancies in their study had an alcoholic history prior to their liver transplantations. Majority of these patients were fully rehabilitated and free from alcohol consumption before liver transplantation and were believed to be sober after their liver transplantations. It is not known whether or not abstinence from alcohol and tobacco use can reverse this susceptibility, even though reports suggest this in the non-transplantation population. Castelli and associates [68]. Castellsague and associates. [69] Castellsague and associates [69] reported that cessation of smoking and drinking reduced the risk factor for oesophageal cancer by 70% within 5 to 9 years.

Fung and associates [1] stipulated that skin cancers represent the single largest non-lymphoid class of de novo cancers. The pathophysiological cause for the development of skin is multi-factorial with the following noted as implicated causes: sun exposure, age, race, and viral causes. Human papilloma virus is a large class of DNA viruses which have been shown to play a critical role in the development of cervical intra-epithelial neoplasms and cervical cancer. McGregor and Proby [70] as well as Bavinck and associates [71] have implicated Human papillomavirus, especially, types 5 and 8 as a co-factor in the development of skin cancers (primarily squamous cell carcinoma) in immuno-suppressed patients.

Fung and associates [1] stated that Kaposi’s sarcoma is a viral-associated skin cancer which is significantly greater in the transplantation population than in the general population. According to Penn [72] as well as Bismuth and associates [73] the reported incidence of Kaposi’s sarcoma in the transplant population ranges from 0.18% to 6%, with a latency of 20 to 24 months. The SEER age-adjusted incidence rate (adjusted to the 1970 USA population) for men of all races was 5.8 cases/100,000 population per year.

Sheldon and associates [74] stipulated that human herpes virus 8 is involved in the cause of this disease. Afflicted patients tend to be men of Mediterranean descent, in whom the prevalence of human herpes virus 8 is greatest. Fung and associates stated that even though the instances of regression of even visceral disease have been reported with cessation or
reduction in immunosuppressive drugs, but their experience with Kaposi's sarcoma has been poor, with high mortality.

Marchesa and associates [75], Leidenius and associates [76] as well as Brentnall and associates [77] stated that some conditions are associated with a greater risk for the development of cancer. Higashi and associates [78] reported an incidence of colon cancer in 6.5% in 31 patients with ulcerative colitis and primary sclerosing cholangitis who underwent liver transplantation.

Jain and associates [9], reported that 2 patients out of 35 with ulcerative colitis and primary sclerosing cholangitis developed de novo colon cancer after liver transplantation; but compared with SEER estimates, this risk was not considered to be greater than in the general population in comparison with the entire transplant population at risk.

Bleday and associates [79] reported that colorectal carcinoma occurred in 3 of 27 patients (11%) with inflammatory bowel disease who underwent liver transplantation, and these patients developed their cancer rapidly, within 9 to 13 months after liver transplantation.

Fabia and associates [80] reported the incidence of colon to be 8% in patients with inflammatory bowel disease versus 0.1% in transplant recipients without inflammatory bowel disease.

Loftus and associates [81], reported that among 57 patients with intact colons who underwent liver transplantation for primary sclerosing cholangitis with ulcerative colitis, the risk for carcinoma of colon was increased four-fold, however, this difference was not statistically significant.

Hanaway and associates [82] reported on 21 patients with de novo carcinoma of colon, of whom 10 patients (48%) had a diagnosis of primary sclerosing cholangitis and 10 patients had metastatic lesions at the time of diagnosis. They observed that as expected survival was better in patients who had localized disease than among those with metastatic disease.

Vera and associates [83] studied 152 patients with primary sclerosing cholangitis who underwent liver transplantation. They observed that patients with more than a 10-year history of ulcerative colitis pre-liver transplantation had a 30% risk for developing cancer by 6 years post liver transplantation. They reported that ten patients underwent colectomy post-transplantation; 17 patients had a colectomy performed either before (13 patients) or during (4 patients) liver transplantation. They also observed that patients who underwent prophylactic colectomy before or during liver transplantation had superior ten-year survival rate (87%) versus 60% in patients with an intact colon; but the difference was not found to be statistically significant. The five-year survival rate was 55% in patients with colon cancer versus 75% in patients without colon cancer. Vera and associates [84] concluded that risk factors for increased incidence of de novo colon cancers were age older than 45 years, diagnosis of primary sclerosing cholangitis, length of time with ulcerative colitis, and presence of colonic polyps.

A number of authors (Bani Hani and associates [84], Caygill and associates [85], Weston and associates [86] have considered Barrett's oesophagus to be a premalignant condition with a 30- to 50-fold increase in the risk for the development of cancer. Caygill and associates [80] observed that over a twenty-year period, 11.1% of Barrett’s oesophagus degenerated into oesophageal cancer. The risk for the development of adenocarcinoma in patients with Barrett’s oesophagus ranges from 1 in 72 (Weston and associates) [86] to 1 in 227 person-years of follow-up (Provenzale and associates) [87]. A number of authors ([Jain and associates] [9], (Kaiser ) [88], (Ilan and associates) [89], Trotter [90] have stated that whether this risk is increased in liver transplantation recipients has not been shown, nevertheless, their experience suggests that this risk is greater than in the general population.

Fung and associates [1] stated that myeloproliferative disorders constitute another coexistent premalignant condition as an indication for liver transplantation, which contributes as a leading cause of Budd-Chiari syndrome, frequently resulting in end-stage liver failure necessitating liver transplantation. They also stated that it has been reported that up to 10% of patients with myeloproliferative diseases progress to acute leukemia. There is therefore, concern that immunosuppression after liver transplantation may increase this risk.

Dousser and associates [91] reported two patients who had myeloproliferative disorders and Budd-Chiari syndrome who underwent liver transplantation and developed leukemia relatively late after liver transplantation (29 and 31 months). Saigal and associates [92] reported six patients with myeloproliferative disorders, one patient developed...
acute leukemia six years after liver transplantation. Saigal and associates [92] were of the opinion that this suggests that leukemia transformation follows the natural history of the disease, rather than an effect of immunosuppression.

Post-transplantation de novo malignancies are apparently rarely found in bone, however, Zhen Qi and associates [93] described a patient with a low-grade, aggressive fibrous histiocytoma of the scapula. The patient had undergone liver transplantation 6 years earlier. En bloc resection of the tumour and limb salvage was performed. At the 2-year follow-up the patient had no signs of local recurrence or metastatic spread. The patient had a musculoskeletal Tumor Society (MSTS) score of 87. From the literature there was no previously clearly documented case of de novo malignancy developing in bone therefore they stated that their case may be the first reported case of de novo malignancy developing in bone after liver transplantation.[94]. Cagatay and associates [95] stated that while the most common cancers following liver transplantation include skin cancers, lymphoma and Kaposi’s sarcoma, gastric cancer is uncommon. Cagatay and associates [94] reported a case of gastric adenocarcinoma developing three years after cadaveric liver transplantation, in a patient with autoimmune hepatitis. The patient was successfully operated. The patient did not receive any adjuvant therapy, and was free of disease at 9 months’ follow-up. Apart from de novo malignancies that could develop after liver transplantation, donor transmitted malignancies can develop. Martin and associates [95] stated that donor-transmitted malignancies should be considered in the differential diagnosis. Fung and associates [1] stated that inadvertent cancer transmission through organ transplantation has been documented by correlation of donor autopsy findings or medical history with subsequent development of a malignancy in the transplant recipient. Jain and associates [9] reported that one patient in their liver transplantation population developed carcinoma in the liver as a result of donor transmission. Penn [96] stated 117 of 270 recipients of organs from donors with malignancies developed cancer. Jonas and associates [97] reported the transmission of a single glioblastoma multiforme out of 49 organs transplanted from donors with central nervous system malignancies.

Some authors (Castellsague and associates [69], Otley and associates, [98]) have stated that:
1. Measures for the prevention and early detection of malignancies developing after liver transplantation are critical to reduce the impact of de novo malignancies
2. Risks can be reduced by cessation of risk factors such as alcohol consumption, smoking, photo-damage

Fung and associates [1] suggested that early detection with routine colonoscopy for high risk individuals such as those with inflammatory bowel disease and follow-up endoscopy for those with Barrett’s metaplasia of oesophagus will allow early detection.

Jain and associates [9] stated that:
1. Only 20% of non-skin malignancies were found on routine screening in their study.
2. Almost half of the patients with non-skin non-lymphoid de novo cancers presented with advanced disease at the time of diagnosis
3. Rapid dissemination of the cancer in a setting of reduced immune surveillance could account for the presentation at an advanced stage as well as accelerated progression.

Barrett and associates [99] reported that malignancies in renal transplant patients had had an aggressive behaviour. However, Strazl and associates [100] noted instances of tumour regression with cessation or reduction of in the immunosuppressant regimen in post-transplant lympho-proliferative disorders, and that most non-lymphoid de novo non-skin cancers follow a virulent course un-checked by return to normal immune surveillance.

Conclusions

Malignancies which may develop after liver transplantation could be de novo malignancies, donor-transmitted malignancies or indolent malignancies that have undergone recrudescence in a transplant recipient. Recurrent and De novo malignancies are the second leading causes of late death in liver transplant recipients, following age-related cardiovascular complications. [1] The increased incidence rate of de novo malignancies in liver transplant recipients in comparison with the general population reflects their demographic makeup, known pre-existing risk factors for malignancy, greater rate if chronic viral infection, and actions of exogenous immune-suppression. [1] The greatest incidence of de novo cancers is seen in malignancies associated with chronic viral infections, for example, Epstein-Barr virus-associated post-transplant lymphoproliferative disease, and skin cancers, including squamous cell carcinoma and Kaposi’s sarcoma. [1] Even though a greater incidence of such malignancies as
oropharyngeal malignancy and colorectal cancer was noted, there did not appear to be an increased risk for recipients of liver transplant matched for age, sex, length of follow-up using modified life-table technique and Surveillance Epidemiology End Result data with a similar at-risk group. [1] An increased incidence of de novo malignancy in chronically immunocompromised recipients of liver transplant requires careful long-term screening protocols to help facilitate diagnosis at an earlier stage of disease. [1] In order to avoid or minimise donor to recipient transmission of cancer, the policy of careful screening of potential liver transplant donors by means of scans (CT-scan; MRI-Scan; ultrasound scan would be useful. Recipients of liver transplant who have previously had a malignancy before should have careful regular follow-up screening in order to detect recurrent tumours early.

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