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Incidence and Management of Colorectal Cancer in Liver Transplant Recipients

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Abstract

Liver transplant recipients are at an increased risk of developing de novo malignancies because of the prolonged immunosuppression necessary to avoid acute and chronic rejections. Skin cancers and lymphoproliferative diseases are the most common malignancies, but the overall incidence of colon cancer in this patient population does differ from that of the general population. Therefore, colorectal cancer (CRC) is a major health concern in liver transplant recipients. Furthermore, there are unique subsets of liver transplant recipients, such as those with primary sclerosing cholangitis and inflammatory bowel disease, who are at an increased risk for developing CRC after liver transplantation and might require special screening/surveillance strategies. The similar principles for management of colon cancer can be applied to transplant recipients if the adjustment to maintain the need for the long-term immunosuppression is made. Colectomy can be performed safely during the posttransplantation period. Prophylactic colectomy at the time of liver transplantation has been performed in some patients at high risk or with known premalignant conditions. Chemotherapy with 5-fluorouracil and oxaliplatin has been used in transplant recipients for the treatment of metastatic CRC; however, further research is required to examine the safety, tolerability, and efficacy of combination chemotherapy and biologic agents in this patient population. This review summarizes the incidence, risk factors, diagnosis, and management of de novo CRC in liver transplant recipients.

Keywords

Immunoregulation; Inflammatory bowel disease; Infliximab; Sclerosing cholangitis; Ulcerative colitis

Introduction

Recipients of solid organ transplants are at a particularly high risk for developing new neoplasms. This is primarily a consequence of the immunosuppressive drug regimens necessary to prevent rejection.[1] Malignancies in the posttransplantation period can be caused by infections with oncogenic viruses (such as posttransplantation lymphoproliferative disorders caused by the Epstein-Barr virus), recurrence of primary cancers in the recipients and occult malignancies not diagnosed before transplantation, donor-transmitted malignancies (known, occult, or missed), and de novo malignancies. Although transplant recipients are at increased risks for development of many different types of cancers, skin cancers and non-Hodgkin lymphomas are the most prevalent entities. Most common malignancies that are present in immunocompetent individuals (lung, breast, prostate, colon,

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uterine, and cervical carcinomas) are not particularly increased in the posttransplantation period[2–4]; however, they do require detailed attention in screening and surveillance strategies.

The prolonged survival of liver transplant recipients and the growing tendency for patients to receive transplantation at a more advanced age have added further risks to the development of cancer in the posttransplantation period because cancer, in general, is more common among the elderly population. Increased posttransplantation mortality in elderly patients is a practical concern, and some centers have limited the accepted age for transplantation. As the length of posttransplantation follow-up extends, it has become apparent that malignancies occur at distinct intervals after transplantation. Furthermore, compared with general oncogenic stimuli, immunosuppression after transplantation seems to facilitate the development of certain cancers in a relatively short period. In addition, there seems to be an impression that certain recurrent cancers might be clinically more aggressive in the posttransplantation setting than in the general population. This is certainly the case in recurrent hepatocellular carcinoma, wherein the disease readily metastasizes to multiple sites in transplant recipients even in the early stages of its progression, a feature observed only with advanced stages of the disease in immunocompetent individuals.

Colorectal cancer (CRC) is the third most common malignancy in men and women in the United States.[5] The vast majority of CRC is believed to arise from adenomatous polyps via the adenoma-carcinoma sequence. In contrast with other types of cancers, CRCs can be screened and detected at earlier stages using reliable and relatively simple methods. This review summarizes the current literature on the issue of de novo CRCs after liver transplantation.

Incidence of De Novo Cancer in Transplant Recipients

Most of the data on malignancy after transplantation comes from the Israel Penn International Transplant Tumor Registry (IPITTR), formerly the Cincinnati Transplant Tumor Registry. Since 1968, the IPITTR has collected and analyzed data on de novo cancers of various organs from transplantation centers worldwide. Several reports of the incidence of various types of lymphoid and nonlymphoid neoplasms were published.[2,6–9] Sheil and colleagues maintain registry data from transplant recipients in Australia and New Zealand.[10] Although these registries are good sources of information for a variety of de novo neoplasms that occur after transplantation, they fail to provide the true risk of such cancers in immunocompromised patients compared with the general nontransplantation population. Reporting to registries is voluntary and, therefore, subject to selection bias. Furthermore, differences in the immunosuppression regimens and schedules might become significant when comparing different centers and registries. Thus, large series from single institutions reporting consistent, long follow-up in well-defined populations with a known risk profile are likely to give more reliable data to understand the true relative risk of cancer after solid organ transplantation. This is particularly true in solid organ malignancies, which generally occur much later after transplantation than lymphoid malignancies. Longer follow-ups will clearly detect an increased incidence of malignancy. On the other hand, longer follow-up periods might be subject to bias in diagnostic technology and the continuous changes and evolution of immunosuppression concepts and protocols.

Incidence of De Novo Colorectal Cancer in Liver Transplant Recipients

When liver transplant recipients are compared with the general population matched for their age, sex, and length of follow-up, they seem to have similar relative risks of developing CRC.[11–15] Jain and colleagues have used the Surveillance Epidemiology and End Result (SEER) database from National Cancer Institute (NCI) and calculated comparative

malignancy incidence expressed as a standardized incidence ratio (SIR; ratio of the observed number of malignancies to the expected number of cases). The SIR was 1.06 for gastrointestinal malignancy after liver transplantation under tacrolimus where the value > 1 indicates excess risk.[14] This was supported by the data from the IPITTR that showed no increase in incidence of colon cancer following liver transplantation.[16] Some studies have suggested that colon cancer occurs earlier (mean age, 41 years) in liver transplant recipients compared with general population[16,17]; however, others have shown that the age at diagnosis of malignancy was similar (mean age, 55 years).[11,18] This could be explained by the adoption of less restrictive policies in transplanting patients at advanced ages. Available reported overall incidence rates of post–liver transplantation CRCs in patients from single-institution studies are listed in Table 1.[4,12,15,18–23]

Etiology and Risk Factors

Certain malignancies are more common than the others in subpopulations of transplant recipients, and these might vary depending on particular organs transplanted and patient characteristics. For example, studies demonstrated that oro-pharyngeal and lung cancer occurred more frequently in alcoholics and smokers who underwent liver transplantation,[24] and the incidence of Kaposi's sarcoma was higher in patients from Saudi Arabia who received kidney transplantation.[25] Some liver transplant recipients have preexisting risk factors for CRC, including primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD). Patients with IBD and PSC are at increased risk for colon cancer development.[26] Higher incidence of viral infections and the need for long-term immunosuppression have also been speculated to play roles in oncogenesis for transplant recipients.[11,27] The main immunosuppressive regimen using a calcineurin inhibitor (either cyclosporine or tacrolimus) is now relatively standardized among different liver transplantation centers. Steroids are withdrawn early whenever possible to ameliorate toxic complications without jeopardizing the graft. Centers adopt different policies in their use of immunosuppression induction with depleting or nondepleting antibodies, but based on our current knowledge, it is safe to assume that the differences in immunosuppression protocols among centers are unlikely to result in variations in the incidence of CRC after liver transplantation.

Ulcerative Colitis and Primary Sclerosing Cholangitis Increase the Risk of Colorectal Cancer

The association of colon cancer with ulcerative colitis (UC) and PSC is well documented.[26] Investigators have consistently found a higher incidence of colon cancer in patients with these diseases. In 1212 patients with UC who underwent total colectomy, the risk of dysplasia or cancer was 6.9 times greater in patients who had PSC.[14] Right-sided colon cancer was also more common in patients with both UC and PSC, presumably because of high levels of bile acid, a secondary carcinogenic cofactor. In another study, 45 patients with UC were compared with 45 patients with both UC and PSC for incidence of colorectal neoplasias.[28] The UC/PSC group had a significantly higher rate of colon cancer (29% vs. 9% in the UC-alone group; $P < .05$). Similarly, Brentnall et al found on colonoscopic surveillance that the risk of dysplasia was 3 times greater in UC/PSC population than in patients with UC alone.[29] In contrast with these observations, Nuako et al reported that the presence of PSC was not a significant etiologic factor in a comparison of 171 patients who had both UC and CRC with 171 UC patients who did not have CRC.[30]

Risk of Colorectal Cancer in Patients Who Undergo Liver Transplantations for Ulcerative Colitis and Primary Sclerosing Cholangitis

The coexistence of UC in liver transplant recipients potentially places these patients at increased risk for the development of colon cancer. This phenomenon has been relatively well studied. In 31 liver transplant recipients with UC/PSC, the incidence rate of colon cancer was 5.6% (2 of 36), but it was not clear whether these were de novo tumors.[31] Four patients (1 with PSC) in a University of Pittsburgh series developed de novo CRC after liver transplantation.[15,32] Using the NCI's SEER public-use database, the risk of colon cancer development for the entire transplantation population was not higher than it was for the general population.[15] Prevalence of PSC in liver transplant recipients seems higher and indicative of increased risk of CRC for this population; however, it is difficult to generalize this notion because of the limited number of patients and referral biases.

Colorectal cancers occurred in 3 of 27 (11%) patients with IBD who underwent transplantation for PSC.[26] Interestingly, however, these patients developed cancers rather rapidly, ie, within 9–13 months after transplantation. In a retrospective study of 1085 liver transplant recipients, the incidence of CRC was found to be 8% in patients with IBD versus 0.1% in recipients without IBD.[22] Among 57 patients with intact colons who underwent transplantation for PSC with coexistent UC, the risk of CRC was increased 4-fold, but this difference was not statistically significant.[33] Coinciding with this data, Vera et al have reported higher incidence rates of CRC in liver transplant recipients with PSC (5.3%) compared with non-PSC counterparts (0.6%; $P < .001$).[18] On multivariate analysis, colonic dysplasia after liver transplantation, duration of colitis > 10 years, and presence of pancolitis were related to the risk of CRC development. In selected high-risk patients with long-standing severe colitis, aggressive colonic surveillance and strong consideration for prophylactic colectomy were advocated.

Role of Immunosuppression in Inflammatory Bowel Disease Activity and Development of De Novo Colorectal Cancer in Liver Transplant Recipients

Posttransplantation rejection prophylaxis includes cyclosporine- or tacrolimus-based immunosuppression, along with low-dose steroid therapy, which is usually tapered with an aim to stop several months after transplantation.[15,18] Some patients also receive azathioprine. Rejection episodes are usually treated with bolus high-dose steroids. It is tempting to speculate that the development of CRC is stimulated with immunosuppression in patients with underlying IBD activity, which presumably provides a permissive environment for malignant growth, possibly precipitating an accelerated course of cancer progression. However, the postoperative course of IBD activity is variable and largely unpredictable, with some reports indicating improvement[34,35] or no change[36,37] and the others reporting disease flare.[38–41] It has been suggested that depressed T-cell function with advanced liver disease improves after new liver grafting, possibly creating a new balance in immunoregulation.[38] In general, patients with IBD receiving infliximab seem to have a comparable frequency of new neoplasia diagnoses; however, a subset of patients who have undergone liver transplantation might be in a different risk group.[42] There has been a single case report of de novo CRC after infliximab therapy in a patient with Crohn's disease who underwent transplantation for PSC.[43]

It is speculated that immunosuppressive regimens might play a significant role in the development of CRCs in liver transplant recipients; however, the precise mechanisms involved possible earlier presentation and aggressive behavior of these malignancies are currently not defined.[11,27] Further characterization with careful documentation from registry data and large series from transplantation centers are eagerly awaited.

Colorectal Adenomas in Liver Transplant Recipients

Limited data are available for the prevalence or incidence of colorectal adenomas in liver transplant recipients. The adenoma-carcinoma sequence is well established as pathogenesis of CRC development; however, whether immunosuppressed post–liver transplant recipients might follow this scheme is still unknown. In a retrospective study of 25 patients with posttransplantation colonoscopy, 7 patients (28%) were found to have colorectal adenoma as opposed to 4 patients (8%) in the control group (n = 50; $P = .049$).[44] Patients aged < 45 years, those who survived < 3 years after liver transplantation, and those with a history of IBD or colonic tumors were excluded from this study. No malignant polyps were detected in either group. Patients with a history of PSC were included. It is difficult to generalize the finding of 1 retrospective study; however, authors have cautioned about an increased risk of colorectal adenoma in posttransplantation populations and advocated early screening colonoscopy in this group.[44]

Clinical Presentations and Diagnosis

During the early stages of CRC, patients might be asymptomatic and the cancer could be discovered at surveillance colonoscopy, or they could present with vague abdominal complaints. Alternatively, patients might complain of changes in bowel habits or of hematochezia. Right-sided colon cancer presents with anemia resulting from chronic blood loss with associated abdominal mass, weight loss, and vague abdominal pain. Left-sided lesions, on the other hand, classically present with obstructive symptoms or constipation alternating with diarrhea.

Clinical presentations could be similar to CRC in immunocompetent patients; however, the differential diagnoses in the posttransplantation period would be broader and include posttransplantation complications such as rejection, intestinal ischemia, biliary complications, bowel obstructions caused by adhesions, internal hernias, and volvulus. Therefore, they require careful and extensive workup. In addition to CRCs, neoplastic bowel obstructions in this population might also be secondary to posttransplantation lymphoproliferative disease.[42,45] Diarrhea is common after liver transplantation, and common etiologies include bacterial and viral infections, side effects of immunosuppression, and flare of IBD. However, in rare occasions, lymphoproliferative disorder and de novo CRC have been recognized to present in this fashion.[46] A systematic approach for posttransplantation diarrhea could be applied, and endoscopy (esophagogastro-duodenoscopy and colonoscopy) with biopsy might play a significant role in the workup and management of diarrhea. Colorectal cancers in patients with IBD, especially in UC, could have different presentations, and their lesions tend to be flat, with characteristic infiltrating growth. Imaging with computed tomography scans might have an important role in the evaluation of suspected colorectal neoplasia and its potential metastatic diseases.

Disease Management

Although liver transplant recipients require long-term immunosuppression, the same basic principles for management of CRC and IBD could be applied. Available data on individual CRC treatments in liver transplant recipients are listed in Tables 2A and 2B.[4,12,15,18–23,26,33,43,47–51]

Colectomy in Liver Transplant Recipients with Inflammatory Bowel Disease

Colectomy can be performed relatively safely in liver transplant recipients. Vera et al reported on 152 patients from a series of 1336 liver transplant recipients between 1986 and 2000 with a diagnosis of PSC.[52] Patients with a > 10-year history of UC before liver

transplantation had a 30% risk of developing cancer by 6 years posttransplantation. Ten patients underwent colectomy posttransplantation; 17 had colectomy performed before (n = 13) or during (n = 4) liver transplantation. Patients who underwent prophylactic colectomy before or during transplantation had superior 10-year survival of 87% versus 60% in patients with an intact colon, but the difference was not statistically significant. Five-year survival was 55% in patients with CRC compared with 75% in patients without CRC. In addition, right-sided CRCs were more common in older patients and those who had UC for a longer period of time. Risk factors associated with decreased survival time in this series were age > 45 years, diagnosis of PSC, an intact colon, and presence of colonic polyps. The risk factors for increased incidence of de novo CRCs are considered to be age > 45 years, diagnosis of PSC, an intact colon, colonic polyps, and a longer duration of UC. One could consider prophylactic colectomy at the time of or after liver transplantation if recipients have > 2 risk factors, including long-term IBD (> 10 years before liver transplantation), severe colitis (pancolitis, severe dysplasia), and age > 40 years to reduce the risk of CRC development in the posttransplantation period.[18,52] Further prospective studies are eagerly awaited before the treatment recommendations can be made.

Chemotherapy for Colorectal Cancer in Liver Transplant Recipients

Recently reported characteristics of de novo CRC after liver transplantation are shown in Table 1.[4,12,15,18–23] The majority of de novo CRCs were treated with colectomy or other surgical resection, and available information regarding the use of chemotherapy in liver transplant recipients is limited. However, there are a few reported cases of CRCs in the posttransplantation period treated with chemotherapy (Table 1).[4,12,15,18–23] Haagsma et al reported on 2 patients who received prolonged 5-fluorouracil (5-FU) treatment (9 months and 10 months, respectively) for metastatic CRCs after liver transplantation.[4] Adjuvant chemotherapy including oxaliplatin has shown to be well tolerated in patients with liver dysfunction and has been used in the setting of CRC in a liver transplant recipient.[53] One patient who had undergone liver transplantation received oxaliplatin 60 mg/m^2. Current standard chemotherapeutic agents for CRC include combinations of 5-FU, oxaliplatin, and irinotecan with biologic agents (bevacizumab, cetuximab, and panitumumab). It is conceivable that those agents could have reasonable activity in the post–liver transplantation setting. However, further delineations of specific dosing, drug interactions with immunosuppressive agents, and safety on graft tolerance should be carefully reviewed and are eagerly awaited.

Radiation Therapy for Rectal Cancer in Liver Transplant Recipients

Currently, no data are available for the use of radiation therapy in colon or rectal cancer treatment in liver transplant recipients. It is reasonable to consider radiation therapy for palliation of symptoms in this patient population. The role of chemoradiation therapy for rectal cancer in liver transplant recipients will be defined in the future studies.

Surveillance

Most transplantation centers advocate pretransplantation screening colonoscopy to age-appropriate potential candidates or patients with risk factors for development of CRCs. In liver transplant recipients with no history of PSC, the relative risk of developing CRC compared with general population matched for age, sex, and length of follow-up is similar.[11–15] Parikshak et al examined the role of endoscopic surveillance over 3 years in solid organ transplant recipients. There was no difference in the polyp size or histology between the group of transplant recipients compared with the age- and sex-matched control group.[47] Non-PSC post–liver transplant recipients should follow general surveillance strategy for an age-matched population. On the other hand, in 7% of patients with IBD who underwent transplantation for PSC, CRC developed within the first few years after

transplantation.[54] Many have advocated annual surveillance colonoscopy in this subset of liver transplant recipients.[26,31,33,39,54–56] The British Society of Gastroenterology recommends an annual surveillance colonoscopy after transplantation for PSC for recipients with IBD.[55] A full examination should be performed during colonoscopy, with careful inspection of the entire mucosa, and random biopsy specimens should be taken at regular intervals. Dysplasia is generally considered to be a premalignant condition, and whenever a dysplasia is identified, this should serve as a strong indication for colectomy. If patients are reluctant to undergo colectomy, they should be aware of the increased risk of CRC, and they will require at least an increase in the surveillance frequency (eg, colonoscopy every 6 months until 2 consecutive negative examinations with no evidence for dysplasia or cancer).

Conclusion

The majority of patients who develop de novo CRC after liver transplantation have PSC with UC as their indications for the transplantation. Colorectal cancer after liver transplantation is more often a right-sided lesion, is aggressive, and is associated with a higher rate of metastasis and poor survival. Patients who undergo liver transplantation for PSC should have annual follow-up screening examination with colonoscopy and random colorectal mucosal biopsies for early detection of CRC. When a dysplasia is found on the colonic biopsy specimen, early colectomy should be strongly considered for patients. Although the removal of colon before or during transplantation in patients with underlying PSC appears to enhance survival, prospective studies are necessary before recommendations can be made for prophylactic colectomy. Only limited information for chemotherapy options in liver transplant recipients is currently available, and further study is warranted.

References

1. Trivedi MH, Agrawal S, Muscato MS, et al. High grade synchronous colon cancers after renal transplantation: were immunosuppressive drugs to blame? Am J Gastroenterol. 1999; 94:3359–61. [PubMed: 10566744]
2. Penn I. The changing pattern of posttransplant malignancies. Transplant Proc. 1991; 23:1101–3. [PubMed: 1899153]
3. Di Tondo U, Berloco P, Trombetta G, et al. Incidence of tumors in organ transplants. Transplant Proc. 1997; 29:3623–4. [PubMed: 9414863]
4. Haagsma EB, Hagens VE, Schaapveld M, et al. Increased cancer risk after liver transplantation: a population based study. J Hepatol. 2001; 34:84–91. [PubMed: 11211912]
5. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. CA Cancer J Clin. 2007; 57:43–66. [PubMed: 17237035]
6. Penn I, Hammond W, Brettschneider L, et al. Malignant lymphomas in transplantation patients. Transplant Proc. 1969; 1:106–12. [PubMed: 4944206]
7. Penn I. Neoplastic complications of transplantation. Semin Respir Infect. 1993; 8:233–9. [PubMed: 8016484]
8. Penn I. Incidence and treatment of neoplasia after transplantation. J Heart Lung Transplant. 1993; 12:S328–36. [PubMed: 8312352]
9. Penn I. Posttransplantation de novo tumors in liver allograft recipients. Liver Transpl Surg. 1996; 2:52–9. [PubMed: 9346628]
10. Sheil AG, Disney AP, Mathew TH, et al. Lymphoma incidence, cyclosporine, and the evolution and major impact of malignancy following organ transplantation. Transplant Proc. 1997; 29:825–7. [PubMed: 9123543]
11. Saigal S, Norris S, Muiesan P, et al. Evidence of differential risk for posttransplantation malignancy based on pretransplantation cause in patients undergoing liver transplantation. Liver Transpl. 2002; 8:482–7. [PubMed: 12004349]

12. Kelly DM, Emre S, Guy SR, et al. Liver transplant recipients are not at increased risk for nonlymphoid solid organ tumors. Cancer. 1998; 83:1237–43. [PubMed: 9740091]
13. Penn I. The problem of cancer in organ transplant recipients: an overview. Transplant Sci. 1994; 4:23–32. [PubMed: 7804694]
14. Penn I. Malignancy after immunosuppressive therapy: how can the risk be reduced. Clin Immunother. 1995; 9:207–8.
15. Jain AB, Yee LD, Nalesnik MA, et al. Comparative incidence of de novo nonlymphoid malignancies after liver transplantation under tacrolimus using surveillance epidemiologic end result data. Transplantation. 1998; 66:1193–200. [PubMed: 9825817]
16. Penn I. Cancer in the immunosuppressed organ recipient. Transplant Proc. 1991; 23:1771–2. [PubMed: 2053149]
17. Fung JJ, Jain A, Kwak EJ, et al. De novo malignancies after liver transplantation: a major cause of late death. Liver Transpl. 2001; 7(11 suppl):S109–18. [PubMed: 11689783]
18. Vera A, Gunson BK, Ussatoff V, et al. Colorectal cancer in patients with inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. Transplantation. 2003; 75:1983–8. [PubMed: 12829898]
19. Frezza EE, Fung JJ, van Thiel DH. Non-lymphoid cancer after liver transplantation. Hepatogastroenterology. 1997; 44:1172–81. [PubMed: 9261620]
20. Silva MA, Jambulingam PS, Mirza DF. Colorectal cancer after orthotopic liver transplantation. Crit Rev Oncol Hematol. 2005; 56:147–53. [PubMed: 16140543]
21. Oo YH, Gunson BK, Lancashire RJ, et al. Incidence of cancers following orthotopic liver transplantation in a single center: comparison with national cancer incidence rates for England and Wales. Transplantation. 2005; 80:759–64. [PubMed: 16210962]
22. Fabia R, Levy MF, Testa G, et al. Colon carcinoma in patients undergoing liver transplantation. Am J Surg. 1998; 176:265–9. [PubMed: 9776156]
23. Sanchez EQ, Marubashi S, Jung G, et al. De novo tumors after liver transplantation: a single-institution experience. Liver Transpl. 2002; 8:285–91. [PubMed: 11910575]
24. Jain A, DiMartini A, Kashyap R, et al. Long-term follow-up after liver transplantation for alcoholic liver disease under tacrolimus. Transplantation. 2000; 70:1335–42. [PubMed: 11087149]
25. al-Sulaiman MH, al-Khader AA. Kaposi's sarcoma in rental transplant recipients. Transplant Sci. 1994; 4:46–60. [PubMed: 7804697]
26. Bleday R, Lee E, Jessurun J, et al. Increased risk of early colorectal neoplasms after hepatic transplant in patients with inflammatory bowel disease. Dis Colon Rectum. 1993; 36:908–12. [PubMed: 8404380]
27. Hojo M, Morimoto T, Maluccio M, et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature. 1999; 397:530–4. [PubMed: 10028970]
28. Leidenius MH, Färkkilä MA, Kärkkäinen P, et al. Colorectal dysplasia and carcinoma in patients with ulcerative colitis and primary sclerosing cholangitis. Scand J Gastroenterol. 1997; 32:706–11. [PubMed: 9246712]
29. Brentnall TA, Haggitt RC, Rabinovitch PS, et al. Risk and natural history of colonic neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis. Gastroenterology. 1996; 110:331–8. [PubMed: 8566577]
30. Nuako KW, Ahlquist DA, Sandborn WJ, et al. Primary sclerosing cholangitis and colorectal carcinoma in patients with chronic ulcerative colitis: a case-control study. Cancer. 1998; 82:822–6. [PubMed: 9486569]
31. Higashi H, Yanaga K, Marsh JW, et al. Development of colon cancer after liver transplantation for primary sclerosing cholangitis associated with ulcerative colitis. Hepatology. 1990; 11:477–80. [PubMed: 2312061]
32. Jain A, Reyes J, Kashyap R, et al. What have we learned about primary liver transplantation under tacrolimus immunosuppression? Long-term follow-up of the first 1000 patients. Ann Surg. 1999; 230:441–8. [PubMed: 10493490]
33. Loftus EV Jr, Aguilar HI, Sandborn WJ, et al. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis following orthotopic liver transplantation. Hepatology. 1998; 27:685–90. [PubMed: 9500695]

34. Stephens J, Goldstein R, Crippin J, et al. Effects of orthotopic liver transplantation and immunosuppression on inflammatory bowel disease in primary sclerosing cholangitis. Transplant Proc. 1993; 25:1122–3. [PubMed: 7680144]
35. Befeler AS, Lissoos TW, Schiano TD, et al. Clinical course and management of inflammatory bowel disease after liver transplantation. Transplantation. 1998; 65:393–6. [PubMed: 9484758]
36. Gavaler JS, Delemos B, Belle SH, et al. Ulcerative colitis disease activity as subjectively assessed by patient-completed questionnaires following orthotopic liver transplantation for sclerosing cholangitis. Dig Dis Sci. 1991; 36:321–8. [PubMed: 1995269]
37. van de Vrie W, de Man RA, van Buuren HR, et al. Inflammatory bowel disease and liver transplantation for primary sclerosing cholangitis. Eur J Gastroenterol Hepatol. 2003; 15:657–63. [PubMed: 12840678]
38. Papatheodoridis GV, Hamilton M, Mistry PK, et al. Ulcerative colitis has an aggressive course after orthotopic liver transplantation for primary sclerosing cholangitis. Gut. 1998; 43:639–44. [PubMed: 9824344]
39. Knechtle SJ, D'Alessandro AM, Harms BA, et al. Relationships between sclerosing cholangitis, inflammatory bowel disease, and cancer in patients undergoing liver transplantation. Surgery. 1995; 118:615–9. [PubMed: 7570313]
40. Miki C, Harrison JD, Gunson BK, et al. Inflammatory bowel disease in primary sclerosing cholangitis: an analysis of patients undergoing liver transplantation. Br J Surg. 1995; 82:1114–7. [PubMed: 7648169]
41. Shaked A, Colonna JO, Goldstein L, et al. The interrelation between sclerosing cholangitis and ulcerative colitis in patients undergoing transplantation. Ann Surg. 1992; 215:598–603. [PubMed: 1632681]
42. Biancone L, Orlando A, Kohn A, et al. Infliximab does not increase the risk of newly diagnosed neoplasia in Crohn's disease: a multicentre matched-pair study. Gut. 2006; 55:228–33. [PubMed: 16120759]
43. Peyrin-Biroulet L, Bressenot A, Chone L, et al. Colon cancer after infliximab therapy for Crohn's disease in a young patient transplanted for primary sclerosing cholangitis. Am J Gastroenterol. 2006; 101:2664–5. [PubMed: 17090288]
44. Atassi T, Thuluvath PJ. Risk of colorectal adenoma in liver transplant recipients compared to immunocompetent control population undergoing routine screening colonoscopy. J Clin Gastroenterol. 2003; 37:72–3. [PubMed: 12811214]
45. Blachar A, Federle MP. Bowel obstruction following liver transplantation: clinical and CT findings in 48 cases with emphasis on internal hernia. Radiology. 2001; 218:384–8. [PubMed: 11161150]
46. Ginsburg PM, Thuluvath PJ. Diarrhea in liver transplant recipients: etiology and management. Liver Transpl. 2005; 11:881–90. [PubMed: 16035068]
47. Parikshak M, Pawlak SE, Eggenberger JC, et al. The role of endoscopic colon surveillance in the transplant population. Dis Colon Rectum. 2002; 45:1655–60. [PubMed: 12473890]
48. MacLean AR, Lilly L, Cohen Z, et al. Outcome of patients undergoing liver transplantation for primary sclerosing cholangitis. Dis Colon Rectum. 2003; 46:1124–8. [PubMed: 12907911]
49. Goss JA, Shackleton CR, Farmer DG, et al. Orthotopic liver transplantation for primary sclerosing cholangitis. A 12-year single center experience. Ann Surg. 1997; 225:472–83. [PubMed: 9193175]
50. Narumi S, Roberts JP, Emond JC, et al. Liver transplantation for sclerosing cholangitis. Hepatology. 1995; 22:451–7. [PubMed: 7635412]
51. Papaconstantinou HT, Sklow B, Hanaway MJ, et al. Characteristics and survival patterns of solid organ transplant patients developing de novo colon and rectal cancer. Dis Colon Rectum. 2004; 47:1898–903. [PubMed: 15622583]
52. Vera, A.; Gunson, BK.; Candinas, D., et al. Inflammatory bowel disease and colorectal cancer in patients with primary sclerosing cholangitis following liver transplantation. Presented at: The Joint American Transplant Meeting; May 11–16, 2001; Chicago, IL. p. Abstract 517
53. Levin B. Risk of cancer in ulcerative colitis. Gastrointest Endosc. 1999; 49:S60–2. [PubMed: 10049450]

54. Doroshow JH, Synold TW, Gandara D, et al. Pharmacology of oxaliplatin in solid tumor patients with hepatic dysfunction: a preliminary report of the National Cancer Institute Organ Dysfunction Working Group. Semin Oncol. 2003; 30(4 suppl 15):14–9. [PubMed: 14523790]

55. Gow PJ, Chapman RW. Liver transplantation for primary sclerosing cholangitis. Liver. 2000; 20:97–103. [PubMed: 10847476]

56. Eaden JA, Mayberry JF, et al. British Society for Gastroenterology. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. Gut. 2002; 51(suppl 5):v10–2. [PubMed: 12221032]

Table 1

Incidence of Post–Liver Transplantation Colorectal Cancer in Patients from Large Studies

Study/Country	Period	Number of Patients	Number of CRCs	Incidence Rate (%)
Haagsma et al, Netherlands[4]	1979–1986	174	3	1.7
Kelly et al, UK[12]	1988–1996	888	3	0.33
Jain et al, US[15]	1989–1992	1000	4	0.4
Vera et al, UK[18]	1986–2000	1336	15	1.1
Frezza et al, US[19]	1982–1992	1657	3	0.18
Silva et al, UK[20]	1986–2004	1593	18	1.1
Oo et al, UK[21]	1982–2004	1778	18	1
Fabia et al, US[22]	1984–1995	1085	6	0.55
Sanchez et al, US[23]	1985–1999	1421	7	0.49

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Table 2A

Clinical Characteristics of Recently Reported De Novo Colorectal Cancer in Liver Transplant Recipients

Study	Number of Patients	Age (Years)	Sex	Duration of IBD (Years)	Preoperation Diagnosis	Time from Transplantation to Cancer Diagnosis
Haagsma et al[4]	3	67, 55, 68	3 Women	–	3 PSCs	16.7, 5.9, and 8.8 Years
Kelly et al[12]	3	–	–	23 Years (Crohn's disease)	PSC, Crohn's disease	7 Months (Crohn's disease)
Jain et al[15]	4	60, 48, 60, 62	4 Women	–	1 PSC	24, 11, 53, and 75 Months
Vera et al[18]	7	> 45	–	–	Non-PSC	Mean, 52.4 months (range, 6–108 months)
Vera et al[18]	8	Mean, 56.5 (range, 47–64)	5 Men, 3 women	–	8 PSCs, 8 IBDs	Mean, 43.6 months (21, 26, 35, 37, 47, 57, 58, and 68 months)
Frezza et al[19]	3	Range, 38–58	–	–	–	830, 1280, and 2100 days
Silva et al[20]	18	–	–	–	10 PSCs, 10 IBDs	–
Oo et al[21]	18	All males and 7 of 8 females aged > 40	10 Men, 8 women	–	10 PSCs, 6 UCs	Mean, 60 months
Fabia et al[22]	1	–	–	–	Laennec's cirrhosis	4 Years
Fabia et al[22]	4	Mean, 45.9 (range, 42–48)	4 Men, 1 woman	1–23 (4 Patients > 7)	4 PSCs, 4 UCs	Mean, 48 months (range, 22–66 months)
Sanchez et al[23]	7	–	–	–	–	Mean, 50.6 months
Bleday et al[26]	3	39, 40, 50	2 Men, 1 woman	9, 22, 27	3 PSCs, 3 UCs	9, 12, and 13 Months
Loftus et al[33]	3	–	–	–	3 PSCs, 3 UCs	3.5 Months, 1.1 year, 10 months
Peyrin-Biroulet et al[43]	1	23	Man	12	Crohn's disease, PSC	18 Months
Parikshak et al[47]	2	55, 56	–	–	–	1 Year, 2 years
MacLean et al[48]	4	49, 56, 69, 76	3 Men, 1 Woman	16–29 (2 Patients)	4 PSCs, 2 IBDs	Mean, 4.7 years
Goss et al[49]	6	–	–	–	6 PSCs	–
Narumi et al[50]	1	69	Woman	30	PSC, UC	27 Months
Papaconstantinou et al[51]	27	Mean, 53.6	–	–	–	Mean, 2.9 years

Dashes indicate data not available.

Table 2B

Clinical Characteristics of Recently Reported De Novo Colorectal Cancer in Liver Transplant Recipients

Study	Number of Patients	Treatment	Location	Stage	Outcome
Haagsma et al[4]	3	Left colectomy with 9 months of 5-FU; another with 10 months of 5-FU	–	2 Metastases	1 Cancer-related death (metastasis)
Kelly et al[12]	3	Colectomy; 1 patient treated with chemotherapy	–	–	–
Jain et al[15]	4	Surgery	2 Right-sided, 1 rectum, 1 sigmoid	T3 N0 (3 cases) and T3 N1	2 Cancer-related deaths
Vera et al[18]	7	–	–	–	–
Vera et al[18]	8	–	3 Right-sided, 3 transverse, 2 left-sided	3 Stage I, 1 stage II, 2 stage III, 2 stage IV	3 Cancer-related deaths (4, 21, and 7 months); 1 chronic rejection
Frezza et al[19]	3	Surgery	Right, left, rectum	T3 N2 M1; T4 N1; T3 N0 (rectum)	Alive
Silva et al[20]	18	–	–	–	–
Oo et al[21]	18	–	–	–	2 Cancer-related deaths
Fabia et al[22]	1	Hemicolectomy	–	–	2 Years disease free
Fabia et al[22]	4	Colectomy	–	–	2 Developed metastasis 1–2 years after surgery; 2 deaths
Sanchez et al[23]	7	–	6 Colon, 1 rectal	–	–
Bleday et al[26]	3	Colectomy; (1 with history of subtotal and ileorectal)	Hepatic flexure, rectosigmoid junction	2 Dukes B	–
Loftus et al[33]	3	Colectomy	–	–	–
Peyrin-Biroulet et al[43]	1	Coloproctectomy; chemotherapy planned but not reported	Cecum, right side	T4 N2 M0 (19/126 LNs)	–
Parikshak et al[47]	2	Colectomy; local excision	Sigmoid (2 patients)	Stages I, II	–
MacLean et al[48]	4	Colectomy	Rectum, ascending, cecum, splenic flexure	–	–
Goss et al[49]	6	–	–	4 Dukes A, 2 Dukes C	–
Narumi et al[50]	1	Proctocolectomy; irradiation	Rectal	Dukes B	Cancer-related death
Papaconstantinou et al[51]	27	–	–	–	–

Dashes indicate data not available.

Abbreviation: LNs = lymph nodes