Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Screening colonoscopy and detection of neoplasia in asymptomatic, average-risk, solid organ transplant recipients: case–control study

Bret J. Spier, Andrew J. Walker, Daniel D. Cornett, Patrick R. Pfau, Richard B. Halberg and Adnan Said

Section of Gastroenterology and Hepatology, Department of Medicine, University of Wisconsin, School of Medicine and Public Health, Madison, WI, USA

Keywords
adenoma, colonoscopy, colorectal cancer, transplantation, polyp detection.

Correspondence
Adnan Said MD, MSPH, Section of Gastroenterology and Hepatology, Department of Medicine, University of Wisconsin, School of Medicine and Public Health, Madison, Wisconsin MFCB, 1685 Highland Avenue, Madison, WI 53705-2281, USA. Tel.: +1 608 263 4034; fax: +1 608 265 5677; e-mail: axs@medicine.wisc.edu

Received: 11 April 2010
Revision requested: 4 May 2010
Accepted: 20 June 2010
Published online: 19 July 2010

doi:10.1111/j.1432-2277.2010.01137.x

Summary

The aim of this study was to evaluate the detection of colonic neoplasia in an average-risk population of SOT recipients. Studies regarding colonic neoplasia in solid organ transplantation (SOT) recipients have demonstrated mixed results due to the inclusion of above average-risk patients. We performed a case–control study of 102 average-risk SOT recipients who underwent screening colonoscopy, compared with an average-risk, age and sex-matched control group ($n = 287$). Cancer rates were compared with an age-matched cohort from the National Cancer Institute's Survival, Epidemiology, and End Results (SEER) database. There was no difference in number of patients with adenomas ($P = 1.00$). There was no difference in polyps per patient ($P = 0.31$). Although the number of advanced lesions (excluding adenocarcinoma) between groups did not differ ($P = 0.25$), there were two adenocarcinomas identified in the SOT group and none in the control group ($P = 0.068$). Detection of colorectal cancer was an unexpected finding in the SOT cohort and was more likely when compared to age-matched cancer incidence generated by the SEER database. These results suggest no increased adenoma detection in SOT recipients, but with more cases of colorectal cancer than anticipated. Given previous, larger, transplant database studies demonstrating increased colorectal cancer rates, more frequent screening may be justified.

Introduction

Solid organ transplant (SOT) recipients have a higher incidence of certain neoplasms (i.e. lymphoma and skin [non-melanoma] cancer), attributable largely to the immune suppressed state. The risk for colonic neoplasia is much more ambiguous with some studies reporting an average risk and others a higher risk of colonic neoplasms after solid organ transplantation. These discrepancies remain whether evaluating for colonic adenomas [1–5] or colorectal cancers (CRC) [6–8]. The inclusion of SOT recipients at 'above average-risk' for colon neoplasms (i.e. those with symptoms, personal history or first degree relative with history of colon polyps or colon cancer, chronic inflammatory bowel disease, or primary sclerosing cholangitis) influences the risk reported in many of these studies, making definitive conclusions difficult to reach. At present no study exists examining screening for colonic neoplasia in an asymptomatic, average-risk SOT recipient population compared to a general non-transplant screening population.

The primary aim of our study was to evaluate the detection of polyps and advanced neoplasia, including cancer, in a population of asymptomatic, average-risk SOT recipients. As a secondary aim, we compared our polyp rates to an age and sex-matched average risk local

screening population, and our cancer rates to an age-matched National Cancer Institute's Survival, Epidemiology, and End Results (SEER) database [9].

Patients and methods

Study design

We performed a case–control study at the University of Wisconsin Hospital and Clinics (UWHC) from 1993 to 2007. During this period, a total of 550 colonoscopies were performed on SOT recipients (liver, lung, pancreas, kidney, heart) for various indications (Fig. 1). A proportion of these cases ($n = 102$) were average-risk for colorectal cancer and underwent colonoscopy solely for colorectal cancer screening. Patients were excluded if they were determined to be above average risk for CRC neoplasia (Fig. 1); primarily colonoscopies performed for symptoms or in those patients who had colonoscopy performed within one year of transplant (since neoplasms in these patients may represent a pre-transplant condition). A comparison group was created by a random number generator, in a 3:1 control: case ratio from an average risk, age and sex-matched non-immune suppressed control group ($n = 287$) from the same institution who underwent screening colonoscopy in this time period. Age specific colon cancer rates for the general population were obtained from the SEER database. The University of Wisconsin Institutional Review Board approved the study protocol.

Variables collected

The cases and controls underwent review of their electronic medical record to gather data on polyp detection, size and histopathology. Polyp detection (yes/no) and size determination (millimeters [mm]) was provided by the performing endoscopist (all trained gastroenterologists) at the time of the procedure. Histopathology of the polyps was reported as hyperplastic, tubular adenoma, tubulovillous, villous, inflammatory, containing high-grade dysplasia or carcinoma. An adenoma was defined as a glandular, non-invasive, neoplastic polyp found in the colon which if not removed, has the potential of progressing to adenocarcinoma. Advanced lesions were defined as any adenoma ≥10 mm, any adenoma with villous features, high-grade dysplasia or carcinoma. Procedural data including complications and completion of the colonoscopy to the cecum was recorded.

Data on immune suppressive regimens was collected. Generally, prednisone burst/taper was reserved for the early post-transplant period and episodes of rejection. Maintenance immune suppression (single or multi-agent) included the following: mycophenolic acid derivative, cyclosporine, tacrolimus, sirolimus or azathioprine. Data regarding years of immune suppression use and type of immune suppression preceding the colonoscopy was recorded. In addition, data regarding indication for, and type of organs transplanted was recorded.

Statistical analysis

The proportion of patients with polyps between SOT cases and controls were compared using chi-square and Fisher's exact tests. Average polyp detection rates per patient were compared using the Student's *t*-test.

The cancer incidence in SOT cases per person years of follow up was calculated from the time of transplant since this was the period of immune suppression. This was compared with age matched cancer incidence in our local screening population as well as to age matched cancer incidence rates in the general US population extracted from the SEER database.

A linear regression model was created to examine the influence of the following variable on adenomas per patient: Years of immune suppression (IS) and number of immunosuppressive agents used. A regression model was also used to compare detection rates of adenomas and

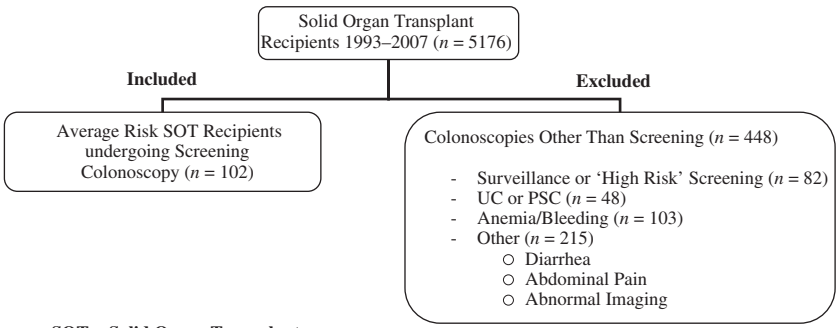

Figure 1 Analysis of 550 colonoscopies performed on SOT recipients from 1993 to 2007.

advanced lesions between SOT cases and controls controlling for age.

Results

Patient and procedure characteristics

The SOT group consisted of 102 patients (72 males; liver alone recipients = 24, kidney alone = 46, liver-kidney = 2, kidney-pancreas = 12, lung = 16, heart = 2) with an average age of 55 years at time of the index colonoscopy. These were compared to an age and sex matched, non-immunosuppressed control group of 287 patients (193 males) with average age of 57 years at time of index colonoscopy (Table 1).

Immune suppression

The SOT recipients were exposed to an average of 9.9 years (SD 7.4) of immune suppression at time of colonoscopy. Their maintenance immune suppression regimen consisted of a single agent ($n = 5$), two agents ($n = 31$), or three agents ($n = 66$) as defined above. Of the 66 patients on triple therapy, steroids were part of the regimen in each patient as well as a Calcineurin-inhibitor (Cyclosporine [CsA] in 44, Tacrolimus [FK] in 22) and an anti-metabolite. Of the 31 patients on dual therapy, 17 patients were on Calcineurin-inhibitors (10 on CsA, 7 on FK) and the rest were on either steroid in combination with Azathioprine or Mycophenolate. There were five patients on monotherapy (three on steroids and two on FK).

Polyp, adenoma and advanced lesion detection (Table 1)

Patients with polyps

There were 37 (36%) SOT recipients with polyps of any type compared to 133 (46%) controls ($P = 0.10$). There was also no difference in SOT recipients and controls regarding polyps categorized by size: polyps ≥10 mm ($P = 0.66$), 6–9 mm ($P = 0.88$) or <6 mm ($P = 0.28$).

Adenomas were identified in 28 (27%) SOT recipients (both patients with adenocarinomas had concomitant adenomas) compared to 79 (28%) controls ($P = 1.00$). Similarly, the detection of advanced adenoma was not different between SOT recipients and controls ($n = 5/102$ [5%] vs. $n = 24/287$ [8%]; $P = 0.25$).

Polyp detection rate

There were an average of 0.76 polyps of any type per SOT recipient screened compared to 0.92 polyps per control ($P = 0.31$). There was also no difference in polyps per patient that were ≥10 mm in SOT recipients compared to controls ($P = 0.96$).

There were on average 0.49 adenomas identified per SOT recipient screened compared to 0.48 in the control group ($P = 0.96$). There was no difference in SOT recipients and controls regarding specific size criteria of adenomas per patient: ≥10 mm ($P = 0.42$), 6–9 mm ($P = 0.76$) or <6 mm ($P = 0.66$).

In SOT recipients, a regression model revealed no relation between years of immune suppression ($P = 0.64$) and number of immune suppressive agents ($P = 0.59$) on adenomas found per patient. Also, in a regression model

Table 1. Comparison of colon neoplasia rates between SOT recipients and controls.

	SOT recipients ($n = 102$)	Control ($n = 287$)	*P* value
Gender (M/F)	74 male/28 female	193 male/94 female	0.54
Age at colonoscopy (avg. years)	55	57	0.39
Number of patients >55	47 (46%)	148 (52%)	
Years of immune suppression at colonoscopy	9.9 (SD 7.4)	NA	
Patients with polyps (n)			
Patients with any polyps (including hyperplastic and neoplastic)	37	133	0.10
Patients with non-advanced adenomas*	21	55	0.87
Patients with advanced adenomas† (excluding adenocarcinoma)	5	24	0.25
Patients with adenocarcinoma	2	0	0.068
Polyp detection rate (avg. per patient)			
Polyps per patient	0.76	0.92	0.31
Polyps per patient ≥10 mm	0.08	0.08	0.96
Adenomas per patient	0.49	0.48	0.96
Adenomas per patient ≥10 mm	0.04	0.06	0.42
Adenomas per patient 6–9 mm	0.16	0.17	0.76
Adenomas per patient <6 mm	0.27	0.24	0.66

*Non-advanced adenomas are adenomas <10 mm without villous features or high grade dysplasia.

†Advanced adenomas include those with tubulovillous or villous features, adenomas ≥10 mm. In our cohort, there were no patients with high grade dysplasia.

corrected for age, SOT recipients were not more likely to have adenomas ($P = 0.73$), advanced polyps ($P = 0.63$) or adenomas ≥10 mm ($P = 0.30$), found on screening colonoscopy exam when compared to controls.

Advanced lesion and carcinoma detection (Table 1)

A total of 12 advanced lesions were detected in 7 of the 102 SOT recipients. Of these 12 advanced lesions, 2 (17%) were carcinomas (both adenocarcinomas). One patient with adenocarcinoma (male, 65 years, 6–9 mm polyp) had undergone lung transplant 3 years prior to colonoscopy, while the other patient (male, 67 years, ≥10 mm polyp) had received a kidney transplant 34 years prior to colonoscopy. None of these patients had a colonoscopy prior to transplantation.

In the screening control group of 287 patients, there were no carcinomas detected. To facilitate comparison with a larger general population cancer rate we compared our SOT cancer rate to age matched cancer rates in the national SEER database. Both cancer patients in the SOT population were between the ages of 60–70 at time of diagnosis/colonoscopy (65, 67 years). There were 27 SOT recipients screened in this age group with 189 patient years of immune suppression exposure giving a cancer rate, or incidence, of 2/189, or 1050 cases of cancer per 100 000 years of follow up in the 60–70-year old SOT recipient group. SEER cancer incidence from ages 65–74 for 2000–2006 is 180 per 100 000, making a cancer diagnosis 5.8 times higher in the SOT group. SEER cancer incidence from 60 to 64 from 2000 to 2006 is 119 per 100 000, making a cancer diagnosis 8.8 times as likely in the SOT group when compared to this age group [9].

Discussion

Our study demonstrated no difference in polyp or adenoma detection, regardless of size or polyp pathology, when comparing asymptomatic, average-risk SOT recipients to the non-transplant average risk patients undergoing a screening colonoscopy. However, the detection of colorectal cancer, albeit a rare event in a small sample size, was 5.8 to 8.8 times more likely when compared to the age-matched cancer incidence generated from the national SEER database. The results of this study cannot provide a mechanistic explanation for unexpected increased colorectal cancer rates detected. Previous explanations for an increased adenoma-carcinoma sequence in SOT patients include impairment of immune surveillance, increased susceptibility to potentially oncogenic viruses (i.e. Epstein–Barr Virus or [Polyoma] JC virus), chronic stimulation of the lymphoreticular system, or neoplastic effects of immune suppression medications [10,11].

Parikshak and colleagues found higher incidence of CRC in a cohort of SOT recipients who had a personal history of polyps as compared to that observed in a control group with a personal history of polyps [1]. While the tubular adenoma, tubulovillous adenoma and villous adenoma rates was similar between groups in that study ($P = 0.63$, $P = 0.83$, and $P = 0.61$ respectively), the SOT group did have 1 colorectal cancer detected (out of 74 patients). A limitation of this study was that the SOT recipients were not mandated to be asymptomatic and were above average-risk (personal history of polyps). Similar deficiencies in study protocol (i.e. including above average risk patients) holds for other studies of polyp detection in SOT recipients making results difficult to interpret[2–4].

Given the low number of adenocarcinomas and the small sample size with a cumulative of 189 patient years of follow up in our study, it is possible that the cancer risk has been overestimated in our SOT recipients compared to the general population. While it is difficult to make strong conclusions of cancer risk on studies with a small sample size, our results demonstrating higher CRC rates are consistent with reviews of large transplant databases that have documented increased CRC rates when compared to the general population. A study utilizing a kidney-liver transplant database demonstrated a 2.6 incidence ratio when comparing the rate of adenocarcinoma to an age-adjusted annual CRC incidence derived from the SEER database [8]. Another study in living donor kidney transplantations showed that the rate of malignancy for colon cancer was roughly two times higher than in the general population [12]. These, along with other studies suggesting a similar increased risk of CRC in SOT recipients [7,13] further substantiate the need to systematically study the effect that chronic immune suppression has on the adenoma-carcinoma sequence in colorectal cancer. The effect of immune suppression on colorectal neoplasia has already been suggested in patients following renal transplantation by a study from Australia, where more advanced stage colorectal cancer was reported in those after renal transplantation compared to hemodialysis patients [14]. Our study demonstrated no particular immunosuppressive regimen to be associated with CRC or polyp detection rates. Animal data have demonstrated that use of Rapamycin use may be associated with anti-tumor effects [15]. The number of patients with Rapamycin in our study was too small to allow meaningful comparisons but this is an area that warrants further research.

The acceleration of the typical adenoma-carcinoma sequence in transplant patients could have several explanations. One possibility is that the cancers arise from aberrations in signaling pathways other than the Wnt

pathway associated with APC gene mutations found in most sporadic CRC [16], i.e. the cancers arise from a new pathway in transplant patients. Alternatively, tumors may arise in the same way as in controls but aberrations in genes that favor progression may accumulate more rapidly because newly arising mutant cells are not defeated by the immune system. These possibilities could be tested by profiling tumors from transplant patients and controls. Molecular differences occurring either early or late that affect progression will likely dictate outcome.

We compared incidence between SOT recipients and generally healthy controls (SEER database and local controls); these are clearly different populations in terms of life expectancy over a 10 year period. Even within the SOT cohort, lung transplant patients have a higher mortality compared to kidney transplant recipients. This attrition from death in the SOT cohort may influence the incidence of colon cancer and colon polyp detection. However, in the absence of data to suggest whether transplant patients that die from other causes would have had a higher or lower risk of developing colon neoplasia, it is difficult to state if this would result in an over or underestimation of colon neoplasia in SOT recipients when compared to the general population.

The current guidelines for outpatient surveillance of CRC in renal transplant recipients is for renal transplant recipients 50 years of age or older to undergo screening for CRC with flexible sigmoidoscopy every 5 years or colonoscopy every 10 years which is not different than the recommendations for the general population. Despite there being a two to fourfold increase for male and female renal transplant recipients this 2000 consensus statement concluded that, 'there is no reason to think that evidence-based recommendations for the general population would be any less effective for renal transplant recipients' [17]. Our study is the first study to examine screening colonoscopy in average risk SOT patients, demonstrating no increased rate of adenoma detection. These findings coupled with the fact that large transplant database studies have found greater CRC rates in SOT patients suggest the possibility of an altered adenoma-carcinoma pathway to one that is perhaps more accelerated. Therefore, we recommend considering more frequent surveillance from 10 to every 5 years with colonoscopy in the average risk SOT population. Further longitudinal and multi-center studies may be needed to enact change to current guidelines.

Authorship

Bret Spier: study concept and design, acquisition of data, drafting of the manuscript; Andrew Walker: study concept and design, acquisition of data, drafting of the manuscript; Daniel Cornett: acquisition of data; Patrick Pfau: critical revision of the manuscript for important intellectual content; Richard Halberg: drafting of the manuscript; Adnan Said: study concept and design, drafting of the manuscript, statistical analysis.

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