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DE NOVO MALIGNANCIES AFTER INTESTINAL AND MULTIVISCERAL TRANSPLANTATION

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Background. **Maintenance immunosuppression required after organ transplantation creates a permissive environment in which cancer cells can proliferate because of lack of natural immunologic surveillance. With more than a decade of clinical experience, this report is the first to address the risk of de novo cancer after intestinal transplantation.**

Methods. **A total of 168 consecutive intestinal transplant recipients (86 children and 82 adults) were studied, of whom 52% were male and 91% were white. Surveillance, Epidemiology, and End Results data was used to count expected rates of de novo cancers in the general population matched for age, sex, and length of follow-up.**

Results. **With a mean follow-up of 47±41 months, 7 (4.2%) patients developed nonlymphoid de novo cancer, with a cumulative risk of 3% at 5 years and 28% at 10 years. Of these malignancies, one was donor-driven adenocarcinoma. With 0.58 being the expected rate of malignancy for the general population, the risk among intestinal recipients was 8.7 times higher ($P=0.01$). Such morbidity was significantly higher (50 times) among younger patients (<25 years), with a slight male preponderance. Induction immunosuppression was associated with early onset of de novo cancer. Patient survival after diagnosis of de novo cancer was 72% at 1 year, 57% at 2 years, and 29% at 5 years.**

Conclusion. **With conventional immunosuppression, intestinal recipients are at a significantly higher risk of developing de novo cancer when compared with the general population. Thus, a novel tolerogenic immunosuppressive strategy has been recently implemented to reduce the lifelong need for immunosuppression.**

Intestinal transplantation has recently evolved to be the standard of care for patients with irreversible intestinal failure who no longer can be maintained on total parenteral nutrition (*1*, *2*). Furthermore, survival outcomes continue to improve, with current rates comparable to thoracic and other abdominal organ transplantation (*3*, *4*). Historically, intestinal allografts have been at a higher risk for rejection compared with other solid organs, with the subsequent need for heavy immunosuppression (*5*). As a result, higher incidences of opportunistic infections and posttransplant lymphoproliferative disease (PTLD) have been reported (*2*, *6–8*). In addition, conventional immunosuppressive drug therapy provides a permissive environment for the development of de novo cancers (*9–15*).

Tacrolimus-based immunosuppression was first introduced in 1989 for solid abdominal and thoracic organ transplantation (*16*). Soon after the demonstration of its high therapeutic efficacy, in May 1990, a clinical intestinal transplantation program was established at our institution. The impact of tacrolimus-based immunosuppression on the incidence of de novo malignancies after liver transplantation has been recently reported (*15*). In this article, we report the risk of such morbidity after intestinal and multivisceral transplantation examined in comparison with the rate for the general population matched for age, gender, and length of follow-up using Surveillance, Epidemiology, and End Results (SEER) data (*17*). In addition, clinical presentation, tumor pathologic findings, recipient management, and survival outcome are fully described.

MATERIALS AND METHODS

Patient Population

Between May 1990 and June 2001, a total of 168 consecutive patients underwent primary intestinal transplantation. Of these, 70 received intestine (2 with pancreas and 1 with kidney), 74 received combined liver-intestinal (9 with pancreas), and 24 received multivisceral (stomach, duodenum, pancreas, intestine, and liver) grafts. Of the 168 recipients, 86 were children (<18 years of age) and 82 were adults, with a mean age of 21.4±19.2 years (median, 16.9 years). Eighty-eight (52%) recipients were male patients and 153 (91%) were white. The indications for transplantation were nonmalignant except in one adult patient with abdominal gastrinoma. Short-gut syndrome was the cause of intestinal failure in 81% of the cases. Indications other than the absence of bowel included dysmotility syndromes (10%), intestinal neoplasm (6%), and enterocyte failure (3%). Loss of the intestine in children was attributable most commonly to volvulus, gastroschisis, necrotizing enterocolitis, and intestinal atresia, and loss of intestine in adults was attributable most commonly to thrombotic disorders, Crohn's disease, and trauma. The medical history was significant for colorectal adenocarcinoma and anal squamous cell carcinoma in another two adult recipients 20 and 3 years before transplantation, respectively. The pretransplant workup failed to document any clinical, biochemical, or radiologic evidence of neoplastic lesions in any of the patients. The serologic studies were also negative for hepatitis C, hepatitis B, and human immunodeficiency virus. All recipients were followed through October 1, 2003, with a mean follow-up of 47±41 months (range, 0.03–161 months).

All donors were cadaveric, and brain death was primarily caused by trauma and cerebrovascular accidents, with no single example of

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primary disease that could be potentially transmitted to a recipient. With the exception of an O-blood-type liver intestine transplanted to an A-blood-type recipient under urgent circumstances, the cadaveric donor and recipient types were identical. Human leukocyte antigen matching was random and uniformly poor. The allografts were infused in situ with University of Wisconsin solution and immersed in University of Wisconsin solution for storage. Cold ischemia times ranged from 2.8 to 17.3 hr (mean, 8.9±2.5 hr).

Because of the adverse effect of positive donor cytomegalovirus (CMV) serology on outcome reported in 1995 (*2*), attempts were made, in the years after, to avoid the use of CMV-positive donors for CMV-negative intestine-alone or modified multivisceral recipients. This policy was considered impractical for patients whose need for liver intestine or full multivisceral grafts was generally too urgent to tolerate delays.

The baseline immunosuppression was tacrolimus and steroids for all recipients (*2*). Azathioprine, mycophenolate mofetil, or rapamycin was added in selected cases. With adoption of induction therapy in 1995, cyclophosphamide was used, until the clinical introduction of daclizumab in November 1998. Adjunct donor bone marrow cells were given in 50 (30%) patients (*2*). Rejection episodes were treated with steroid bolus, a 5-day dose taper, with adjustment of the daily tacrolimus dose to achieve higher trough levels. OKT3 or Thymoglobulin was used throughout to treat steroid-resistant and severe rejection episodes (*2*).

Statistical Analysis

Using the modified life table technique of OCMAP-PLUS (adapted to cancer incidence data), the person-years at risk contributed by each patient were jointly classified by gender, age group, and time period (*18*). Expected counts of malignancies were computed by multiplying average annual gender-, age-, and time-specific standard incidence rates by the person-years at risk in the corresponding gender-, age-, and time-specific intervals. Incidence rates for whites were used exclusively, because 91% of the patients were white. Standard incidence rates were obtained from the 1990 to 1991 SEER data (*18*, *19*). Because of SEER limitations, expected numbers of malignancies for the time period 1990 to 2003 were based on 1994 to 1998 incidence rates.

Excesses and deficits in malignancy incidence were expressed as standardized incidence ratios; that is, the ratio of observed counts of malignancy incidence to expected counts of malignancy incidence counts. Overall incidence of malignancy was calculated for the intestinal transplant population and compared with SEER data. Further comparisons looked at gender as well as age (≤25 years vs. >25 years) differences. The cumulative risk of cancer development and patient survival from the time of cancer diagnosis and from the time of transplant were calculated using the Kaplan-Meier method, and group comparison was performed using the log-rank test.

RESULTS

This study provided the data on 168 patients that accounted for 510.2 total person-years of follow-up. With a mean follow-up of 47±41 months, de novo nonlymphoid cancer developed in seven (4.2%) patients, with none having more than one malignancy. Four were adults and three were children, with an incidence of 4.9% and 3.5%, respectively. The organs transplanted to the seven recipients were isolated intestine (n=2), liver-intestine (n=4), and multivisceral (n=1), with 2.8%, 4.4%, and 4.1% risk of de novo cancer after each type of intestinal transplant procedure, respectively. The overall cumulative risk was 1% at 1 year, 3% at 5 years, 15% at 8 years, and 28% at 10 years (Fig. 1). With a median time of 79.8 months (range, 10.9–101.6 months) from the date of transplantation to tumor diagnosis, there was no significant correlation between the time of cancer diagnosis, tumor pathologic findings, and type of intestinal allograft.

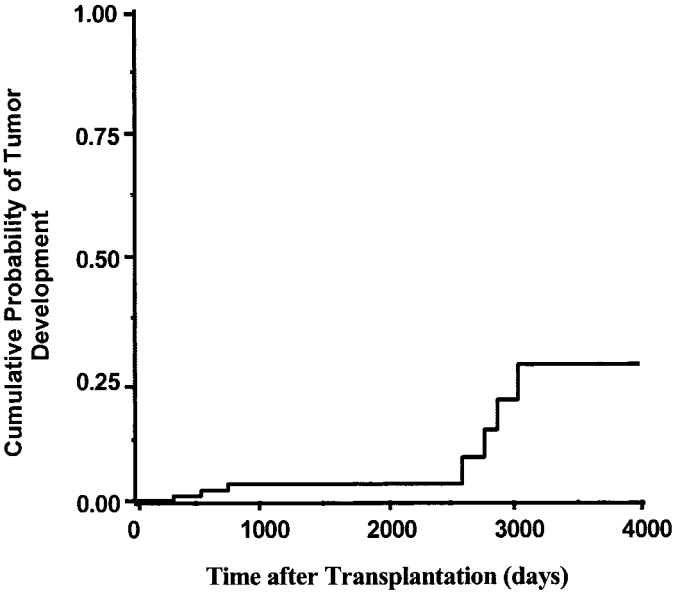

FIGURE 1. Cumulative probability of de novo cancer development after intestinal and multivisceral transplantation.

The development of de novo cancer did not correlate with any of the known generic risk factors associated with transplantation, including indications, donor characteristics, CMV status, and cold ischemia time. The distribution of donor-recipient CMV match and mismatch was similar between the seven patients who developed de novo malignancy and the remaining 161 recipients who continued to be cancer free. Similarly, there was no significant difference (P=0.3) in the mean (±SD) cold ischemia time, with 9.3±1.9 and 8.9±2.5 hr, respectively.

The observed neoplasms were nonmelanotic skin cancers (n=2), testicular seminoma (n=1), donor-driven adenocarcinoma (n=1), T-large granular lymphocyte leukemia (n=1), lung squamous cell carcinoma (n=1), and metastatic adenocarcinoma of unknown origin (n=1). Patient demographics, indication for transplant, type of allograft, primary cancer site, and histopathologic type of the seven malignancies are summarized in Table 1. It is noteworthy that the development of PTLD (not shown in Table 1) in four of these patients (patients 1–4) occurred at different time periods after transplantation and before the development of de novo cancer. All PTLD lesions were completely resolved with prompt reduction of immunosuppression and aggressive antiviral treatment.

Expected counts for malignancy excluding nonmelanotic skin cancer was 0.58 in the general population and 5.0 in this study. Accordingly, it was 8.7 times higher among the small bowel transplant recipients. When the data were examined by gender, there were three malignancies among male patients and two among female patients (Table 1), with expected counts of 0.26 and 0.32, respectively. Thus, male patients showed an incidence 11.5 times higher, and female patients were 6.25 times higher. When recipients were stratified according to age, there were three malignancies in the cohort younger than 25 years of age and two in those above the age of 25 years, with expected counts of 0.06 and 0.516,

TABLE 1. De novo cancer after intestinal and multivisceral transplantation: patient and tumor characteristics

Patient	Gender	Age at transplant (yr)	Indication for transplant	Type of allograft	Time of cancer diagnosis after transplant (mo)	Site of malignancy	Histopathology
1	M	0.8	Microvillus inclusion	L/I	98.5	Allograft intestine and liver	Adenocarcinoma (donor driven)
2[a]	F	10.9	Pseudo-obstruction	MV	90	Blood	T-large granular lymphocyte leukemia
3	M	15.5	Volvulus	L/I	103	Testicle	Seminoma
4	F	26.7	SMA thrombosis	L/I	93.3	Skin (multiple sites)	Basal cell squamous carcinoma
5	F	46.5	Radiation enteritis	L/I	18.2	Chest wall, liver, lung, brain	Adenocarcinoma of unknown origin
6[b]	M	49.8	Volvulus	I	11.1	Skin (arm)	Basal cell carcinoma
7	M	58.6	SMA thrombosis	I	25.1	Lung	Squamous cell carcinoma

[a] Patient received a liver transplant 4.2 yr before the intestinal transplant.
[b] Patient received a kidney transplant 5 mo after the intestinal transplant.
I, Isolated intestine; L/I, liver and intestine; MV, multivisceral; SMA, superior mesenteric artery.

respectively. Thus, the standardized incidence ratio was 50 times higher for recipients less than 25 years of age and 3.9 times higher for recipients greater than 25 years of age. Details of these incidence ratios with confidence intervals are shown in Table 2.

The causes of intestinal failure and indications for transplantation were nonneoplastic except in one patient (patient 5), who developed radiation enteritis after successful treatment of early anal squamous cell carcinoma 3 years before transplantation using the standard Nigro protocol (combined radiation and chemotherapy). In addition, the lung cancer recipient (patient 7) was a heavy smoker for nearly 30 years who continued to smoke after transplantation.

Induction therapy with cyclophosphamide or daclizumab was used for patients 5 and 6, respectively, and was associated with early development of de novo cancer (Table 1). The need for posttransplant heavy immunosuppression to treat acute rejection was observed in all of the seven recipients with de novo cancer. Steroid bolus and a 5-day dose taper was used to treat multiple episodes of intestinal or liver allograft rejection in patients 1, 2, 4, 5, and 7 (Table 1). In addition to steroids, monoclonal (OKT3) or polyclonal (Thymoglobulin) antilymphocyte antibodies were used to treat intractable rejection episodes in patients 3 and 6. Of interest, patient 6 was treated for rejection of a living kidney allograft that was transplanted 7 months after a cadaveric intestine that never experienced allograft rejection.

The diagnosis of cancer was established, in all cases, on the basis of comprehensive histopathologic examination of the tissue specimen. The in situ hybridization technique using a dual color X-Y chromosome probe or the cytochemical staining against donor-recipient human leukocyte antigen using specific antibodies was performed to determine the cell origin of the tumor, particularly in cases with adenocarcinoma of abdominal or unknown origin. With these tools, the de novo cancer was of recipient origin in six patients and was donor driven in the remaining case.

The clinical features of each case including tumor staging, treatment, and outcome are fully described in Table 3. The malignancy was detected at a relatively advanced stage except for the testicular and skin cancers. Despite sophisticated biochemical, radiologic, and tissue immunocytochemical studies, the primary site of the adenocarcinoma in recipient 5 was never defined. The management of each individual case was determined on the basis of the type and extent of cancer, as shown in Table 3. Surgery was performed for diagnostic and therapeutic purposes, and immunosuppression was significantly reduced or discontinued, particularly in cases with advanced adenocarcinoma. The skin cancer patients were treated with repeated surgical excisions. Aggressive systemic chemotherapy was used for the hematologic malignancy and advanced carcinoma.

Of great interest is the development of allograft adenocarcinoma. The recipient was a male child who received a com-

TABLE 2. SEER: expected counts, standardized incidence ratios, confidence intervals, and *P* values

	Observed malignancies[a]	Expected	SIR	95% confidence interval	*P* value
Overall	5	0.58	8.7	2.8–20.2	<0.05
Male	3	0.26	11.63	2.4–34.0	<0.05
Female	2	0.32	6.3	0.8–22.7	NS
Age <25 yr	3	0.06	50	10.3–146.0	<0.05
Age >25 yr	2	0.516	3.9	0.5–14.0	NS
Male ≤25 yr	2	0.032	61.9	7.5–223.6	<0.05
Female ≤25 yr	1	0.028	35.7	0.9–199.0	<0.05
Male >25 yr	1	0.226	4.4	0.1–24.7	NS
Female >25 yr	1	0.29	3.4	0.1–19.2	NS

[a] Excluding nonmelanotic skin cancers.
SIR, Standardized incidence ratio; NS, not significant.

TABLE 3. De novo malignancy after intestinal transplantation: presentation, histopathology, treatment and outcome (May 1990–October 2003)

Patient	Presenting symptoms	Staging	TNM	Treatment	Status at last follow-up (10/01/03)	Tumor-free	Survival after cancer diagnosis (mo)
1	Abdominal mass	IV	T3N1M1	Surgery, chemotherapy (carboplatin, VP-16) stop immunosuppression	Dead	No	18.2
2	Persistent anemia and thrombocytopenia	NA	NA	Chemotherapy (methotrexate)	Dead	No	10.3
3	Painful mass of the right testicle	1	T2NXNX	Right radical orchiectomy	Alive	Yes	27.8
4	Skin lesion	NA	NA	Surgical excision	Alive	Yes	66.9
5	Subcutaneous mass of the left anterior chest wall	IV	T3N1M1	Radiation/chemotherapy (carboplatin, paclitaxel, etoposide)	Dead	No	3.2
6	Skin lesion	NA	NA	Surgical excision	Alive	Yes	28.0
7	Right upper abdominal discomfort	IV	T3N1M1	Chemotherapy (Taxol, carboplatin)	Dead	No	5.9

TNM, Tumor, node, metastasis; NA, not applicable.

bined liver and intestine from a female donor at the age of 9 months because of microvillus inclusion disease and total parenteral nutrition-induced liver failure. Ninety-seven months after transplantation and at the age of 8.9 years, he presented with a large abdominal mass. Because the patient was treated 7 months earlier for Epstein-Barr virus–related polymorphic PTLD that involved the intestinal allograft, the initial presumptive diagnosis was PTLD recurrence. With the radiologic identification of multiple bilobar allograft hepatic lesions in addition to a large tumor located in the intestinal allograft mesentery (Fig. 2A), a percutaneous biopsy of the hepatic lesions was performed that revealed a relatively undifferentiated tumor suggestive of carcinoma. Accordingly, an exploratory laparotomy was performed and

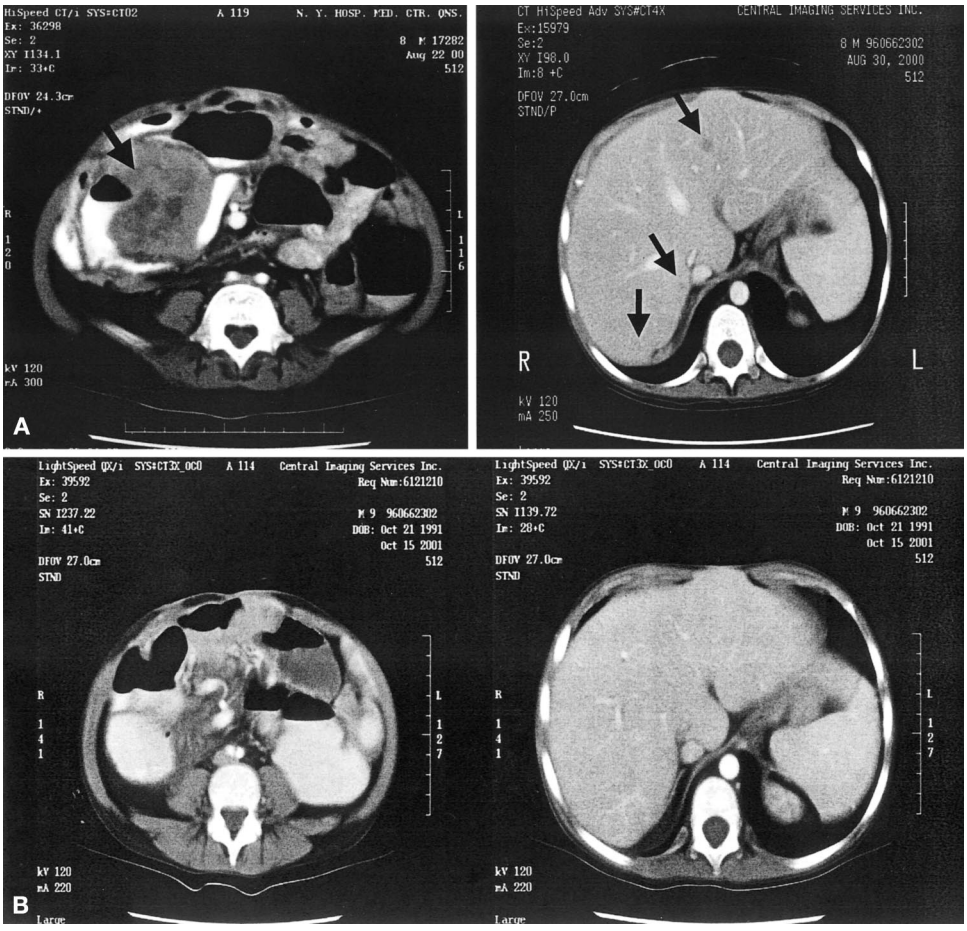

FIGURE 2. Abdominal computed tomographic scan obtained (A) at the time of diagnosis with a large mesenteric mass (*left*) and multiple hepatic lesions (*Right*) and (B) 14 months later, with no evidence of local recurrence and complete resolution of the hepatic metastatic lesions.

the mesenteric tumor was successfully resected en bloc with a segment of the intestinal allograft. The histopathologic examination of the resected specimen showed small intestinal carcinoma of pleomorphic histology with neuroendocrine-undifferentiated components and multiple lymph node metastasis. The donor origin of the malignant cells was confirmed using the in situ hybridization technique. Targeted hybridization of 203 cells showed 99.5% of the malignant cells containing two chromosome X centromeres, suggesting that the tumor tissue was of a female donor genotype. Complete resolution of the malignancy including the hepatic metastasis (Fig. 2B) was achieved with withdrawal of immunosuppression and a single course of chemotherapy (Table 3). Sixteen weeks after withdrawal of immunosuppression, the patient developed intestinal allograft rejection that required restoration of his baseline tacrolimus and steroid maintenance immunosuppression. Unfortunately, the patient died of unknown cause 18 months from the time of cancer diagnosis but free of tumor.

Using the Kaplan-Meier method, patient actuarial survival after the diagnosis of de novo cancer was 72% at 1 year, 57% at 2 years, and 29% at 5 years (Fig. 3). Three of the seven de novo cancer recipients died because of disease progression 3.2, 5.9, and 10.3 months after the diagnosis of cancer (Table 3). The pediatric recipient who developed donor-driven adenocarcinoma (patient 1) died as a result of unknown cause free of tumor 18.2 months after the diagnosis of cancer. The remaining three were alive as of October 1, 2003, with a follow-up of 70, 29, and 31 months from the onset of diagnosis of skin cancer (n=2) and seminoma (n=1), respectively (Table 3). Interestingly, the development of de novo cancer did not significantly (P=0.38) affect the overall posttransplant actuarial survival of the morbid cases compared to recipients who remained cancer free, as shown in Figure 4.

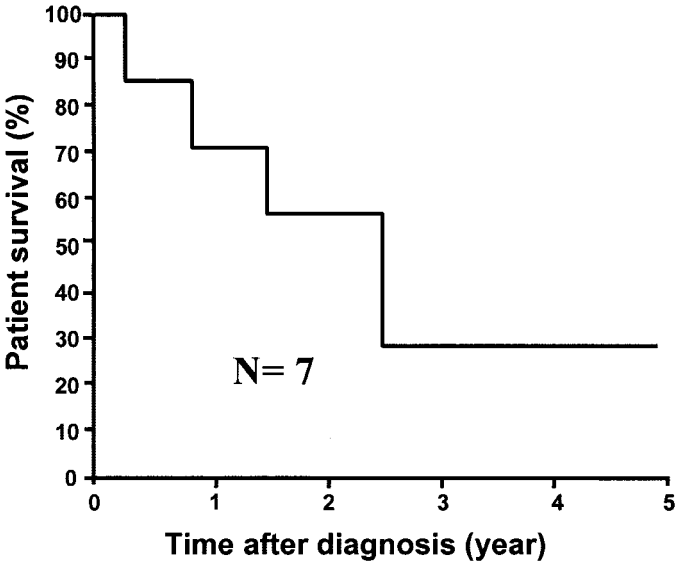

FIGURE 3. Actuarial survival of the intestinal and multivisceral recipients from the time of cancer development.

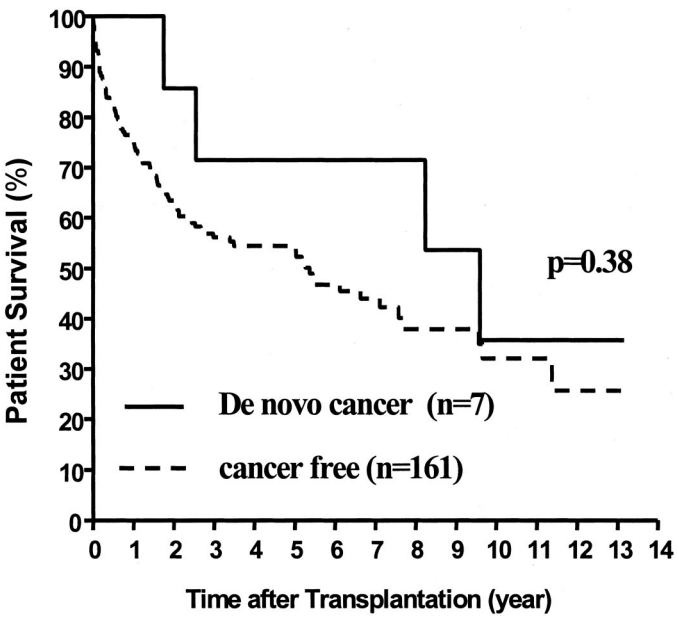

FIGURE 4. The overall posttransplant actuarial survival of the intestinal and multivisceral recipients who developed de novo cancer compared with those who remained cancer-free.

DISCUSSION

Advances in surgical techniques, use of better immunosuppressive regimens, and improvement of postoperative care have steadily increased the survival advantages of intestinal and multivisceral transplantation (*2*, *3*). The cumulative improvement in survival granted us the opportunity to study the risk of developing de novo malignancy in this unique population and its negative impact on the therapeutic benefits of the procedure. The transplantation of massive gut-associated lymphoid tissue and its high alloimmunogenicity with the subsequent need for high maintenance immunosuppression are expected to relatively increase the potential risk of both lymphoid and nonlymphoid de novo malignancy in comparison with other abdominal solid organ transplantation.

The risk of de novo lymphoid malignancy, namely, PTLD, after intestinal transplantation has been previously published (*8*) and recently updated (*2*). PTLD is a significant morbid event among intestinal recipients, with an incidence ranging from 12% to 20% (*20*). Young age (children), type of intestinal transplant (multivisceral), and recipient splenectomy are three major significant risk factors for development of PTLD. Simultaneous donor bone marrow augmentation does not increase the risk of the disease (*2*). The recent use of a quantitative competitive polymerase chain reaction technique to serially monitor serum Epstein-Barr viral replication with prompt initiation of preemptive therapy has significantly reduced the risk of the disease (*21*). A new management strategy to prevent the chronic need for heavy immunosuppression without the penalty of rejection has been recently implemented at our institution to further ameliorate such a morbid event. The scientific background of the therapeutic principles, the details of the tolerogenic immunosuppression protocol, and summary of the preliminary results with different abdominal organs including 11 intestinal recipients (not included in this study) were recently published by Starzl et al. (*22*).

This report is the first to address the risk of de novo nonlymphoid malignancy after intestinal transplantation.

The risk was measured by comparing the posttransplant rate with SEER data matched for age, gender, and length of follow-up. With a mean 3-year follow-up, the overall risk among the reported intestinal and multivisceral transplant recipients was 8.7 times higher, with a striking difference particularly noted between the younger cohort. As clearly demonstrated in this study and in comparison with the SEER data, the risk of de novo cancer was 50 times higher among recipients younger than 25 years old and only 3.9 times higher for the older age group. With gender, the ratio of observed to expected malignancies was only 1.8 times higher for male patients than for female patients.

A complex interaction between the host immune status, environmental factors, genetic predisposition, and oncogenic viruses is believed to be responsible for the increased susceptibility of the allograft transplant recipients to malignancy (*23*). Most immunosuppressive agents induce a state of suppressed immune surveillance, with the establishment of a condition permissive for the development of cancer. In addition, some of these drugs, including calcineurin inhibitors, have intrinsic properties that favor the establishment of de novo neoplasm (*23*). The success of reducing or eliminating the long-term need of these agents may significantly reduce the risk of tumor development, particularly those associated with high mortality (*22*).

In July 2001, a new tolerogenic protocol with peritransplant lymphocyte depletion and posttransplant tacrolimus monotherapy was clinically introduced at our institution, with the intestinal recipients being the first to be enrolled in the protocol. The preliminary current (December 2003) results of a total of 89 consecutive intestinal recipients showed a 1-year patient and graft survival of 92% and 89%, respectively. Such a high survival index with the striking ability to wean immunosuppression in nearly half of these cases is unprecedented and is expected to significantly reduce the risk of lymphoid and nonlymphoid de novo malignancy. With a mean follow-up of 11 months, none of these patients developed nonlymphoid de novo malignancy, and only one child was diagnosed with PTLD (1.1%). This patient was successfully treated with reduction of immunosuppression and long-term specific antiviral therapy.

Under the conventional immunosuppressive regimen, the observed relative risk of de novo nonlymphoid cancer after intestinal and multivisceral transplantation was higher, as expected, than that published for solid abdominal organ transplant recipients. With liver transplantation, the risk was 1.33 times higher than SEER data, with a mean follow-up of 6 years (*15*). Interestingly, none of the liver recipients below the age of 35 years developed de novo cancer, with nearly one third of the total population in the same age group (*24*). However, both the liver and intestinal transplant population showed a male preponderance for development of de novo cancer. The overall higher probability of de novo cancer development observed after intestinal and multivisceral transplantation could be related to the necessity for chronic heavy immunosuppression, particularly during the early phase of our series. In addition, the inevitable massive transfer of donor endodermal and mesodermal tissues including gut-associated lymphoid tissue could be another risk factor distinctive for intestinal and multivisceral transplantation.

With the limited sample size, this study is not qualified to statistically address the risk factors that precipitate the development of de novo cancer after intestinal and multivisceral transplantation, particularly indications for transplantation, donor characteristics, CMV status, cold ischemia time, and type of intestinal allograft. Similarly, no particular type of de novo cancer appeared to be of significance, as previously observed after liver replacement resulting from certain hepatic diseases (*24*). Of great interest, however, is the development of donor-driven adenocarcinoma in a combined liver and intestine pediatric transplant recipient that was diagnosed more than 8 years after transplantation. The donor-recipient sex mismatch made the diagnosis certain by using the in situ hybridization technique. The long interval between date of transplantation and time of diagnosis excludes the possible transmission at the time of transplantation. With the failure to identify the primary origin of any abdominal or metastatic malignancy among allograft recipients, the donor origin of the tumor should be entertained. Of major concern in this study is the late diagnosis of the internal de novo cancer, particularly of the adenocarcinoma and its rapid progression despite the very aggressive combined surgical and medical approach.

CONCLUSION

The documented relatively high risk of de novo lymphoid and nonlymphoid malignancy among the immunocompromised intestinal and multivisceral transplant recipients emphasizes the clinical importance of our recently adopted tolerogenic protocol for transplant recipients receiving intestinal and other abdominal organs. In addition, preoperative screening including risk factors for malignancy and postoperative preventive measures with cessation of smoking and avoidance of excessive sun exposure may reduce the risk of internal as well as external de novo cancer. Careful long-term follow-up, with conduction of clinically relevant studies, particularly for high-risk patients, is strongly recommended to achieve early diagnosis, prompt intervention, and better outcome.

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REFERENCES

1. Reyes J, Bueno J, Kocoshis S, et al. Current status of intestinal transplantation in children. Pediatr Surg 1998; 33: 243–254.
2. Abu-Elmagd K, Reyes J, Bond G, et al. Clinical intestinal transplantation: A decade of experience at a single center. Ann Surg 2001; 234(3): 404.
3. Grant D. Intestinal transplantation: 1997 report of the international registry. Intestinal Transplant Registry. Transplantation 1999; 67: 1061–1064.
4. Abu-Elmagd K, Bond G, Reyes J, et al. Intestinal transplantation: A coming of age. Adv Surg 2002; 36(4): 65–101.
5. Abu-Elmagd KM. History of organ and cell transplantation. In: Hakim NS, Vassilios Papalois V, eds. History of intestinal transplantation. London, Imperial College Press 2003.
6. Kusne S, Furukawa H, Abu-Elmagd K, et al. Infectious complications after small bowel transplantation in adults: An update. Transplant Proc 1996; 28(5): 2761–2762.
7. Manez R, Kusne S, Green M, et al. Incidence and risk factors associated with the development of cytomegalovirus disease after intestinal transplantation. Transplantation 1995; 59(7): 1010.
8. Nalesnik M, Jaffe R, Reyes J, et al. Post-transplantation lymphoproliferative disorders in small bowel allograft recipients. Transplant Proc 2000; 32(6): 1223–1224.
9. Murray JE, Wilson RE, Tilney NL, et al. Five years' experience in renal

transplantation with immunosuppressive drugs: Survival, function, complications, and the role of lymphocyte depletion by thoracic duct fistula. Ann Surg 1968; 168(3): 416.
10. Penn I, Hammond W, Brettschneider L, et al. Malignant lymphomas in transplantation patients. Transplant Proc 1969; 1(1): 106.
11. McKhann CF. Primary malignancy in patients undergoing immunosuppression for renal transplantation. Transplantation 1969; 8(2): 209.
12. Penn I. The changing pattern of post transplant malignancies. Transplant Proc 1991; 23(1 suppl 2): 1101.
13. Penn I. Incidence and treatment of neoplasia after transplantation. J Heart Lung Transplant 1993; 12(6 suppl 2): S328.
14. 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 (1–2): 825.
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(9): 1193.
16. Starzl TE, Todo S, Fung J, et al. FK 506 for human liver, kidney and pancreas transplantation. Lancet 1989; 2: 1000–1004.
17. Ries LAG, Eisner MP, Kosary CL, et al. SEER cancer statistics review 1973–1998. Bethesda, MD, National Cancer Institute 2001.
18. Marsh GM, Youk AO, Stone RA, et al. OCMAP-PLUS: A program for the comprehensive analysis of occupational cohort data. J Occup Environ Med 1998; 40(4): 351.
19. Kauffman HM, McBride MA, Delmonico FL. First report of the United Network for Organ Sharing Transplant Tumor Registry: Donors with a history of cancer. Transplantation 2000; 70(12): 1747.
20. Abu-Elmagd K, Reyes J, Fung JJ. Clinical intestinal transplantation: Recent advances and future consideration. Primer on transplantation [ed 2]. Malden, Blackwell 2001, 610–625.
21. Green M, Bueno J, Rowe D, et al. Predictive negative value of persistent low Epstein-Barr virus viral load after intestinal transplantation in children. Transplantation 2000; 70(4): 593–596.
22. Starzl TE, Murase N, Abu-Elmagd K, et al. Tolerogenic immunosuppression for organ transplantation. Lancet 2003; 361: 1502–1510.
23. 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 1): S109.
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(9): 1335.

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FAVORABLE OUTCOMES AMONG RECIPIENTS OF LIVING-DONOR NEPHRECTOMY USING VIDEO-ASSISTED MINILAPAROTOMY

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Background. **Minimally invasive, living-donor nephrectomy (LDN) is an attractive procedure for the donor in kidney transplantation (KTx). Its advantages include better cosmesis, shorter hospital stay, and rapid recovery. The most commonly performed, minimally invasive nephrectomy is done laparoscopically. However, the technical challenges, a steep learning curve for the surgeon, the risk of impaired early graft function, and the high cost of the procedure, have prevented minimally invasive LDN from gaining wide acceptance. To overcome these problems, we have developed a new surgical procedure named video-assisted minilaparotomy (VAM) for LDN. VAM-LDN is performed entirely with a small retrieval incision. Moreover, it does not require the induction of pneumoperitoneum, thereby avoiding potential vascular and renal complications.**

Methods. **We evaluated the outcome of transplant recipients receiving kidneys with the VAM-LDN procedure by retrospectively comparing the surgical outcomes of patients who underwent KTx with the conventional open nephrectomy (group I, n=382) and VAM-LDN (group II, n=170) procedures from March 1, 1997, to June 30, 2002, at our institution. We compared postoperative complications, patient and graft survival, and graft functions between these two groups during a 12-month follow-up period.**

Results. **There were no differences in demographic data, ABO compatibility, degree of human leukocyte antigen matching, or method of immunosuppression between the two groups ($P>0.05$). No significant difference was observed in complications such as delayed graft function, acute rejection, ureter complication, graft failure, or patient's mortality. There was no difference in graft function between the two groups, as determined by serum creatinine level measured during the 12-month follow-up.**

Conclusion. **The short-term recipient outcome was favorable in patients who underwent KTx with the VAM-LDN procedure.**

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The open approach to donor nephrectomy is known as the safest and most reliable method of performing living-donor kidney transplantation (KTx). However, this approach inevitably causes great pain and discomfort to the donor. Recently, laparoscopic nephrectomy has increased in popularity because it offers less postoperative pain, improved cosmesis, faster recovery, and shorter hospital stay (*1–10*). Nonetheless, this approach has certain drawbacks, such as a steep learning curve for the surgeon, compromised renal perfusion because of pneumoperitoneum, and high risk of early renal dysfunction because of the longer warm ischemic period (*4*, *9–11*). Other challenges associated with laparoscopic donor nephrectomy are the involvement of relatively short or multiple renal arteries, a short renal vein, especially in the right kidney, the higher incidences of ureteral injury, and the high cost of laparoscopic equipment (*11–13*). Therefore, we developed a procedure termed video-assisted minilaparotomy (VAM), which we have been using for kidney procedures since 1991, and which we have applied to living-donor nephrectomy (LDN) since 1993 (*14*, *15*). Using a special retractor system, we have been able to perform VAM-LDN through a small minilaparotomy incision of 6 to 8 cm in length without cutting the abdominal muscles. This technique has given us an excellent and secure surgical field, through both the main minilaparotomy incision (direct vision) and a magnified view through a telescope (video-assisted). In addition, if it becomes necessary, the conversion to an open procedure is both possible and simple to accomplish. In LDN, donor safety and recipient outcomes are equally important (*8–11*,*16–19*). We evaluated the recipient outcome after VAM-LDN by comparing the complication rates, patient and graft survival, and functions of the grafted kidneys of renal transplant recipients who received kidneys with the conventional open nephrectomy procedure with those of recipients who received kidneys with the VAM-LDN procedure.

MATERIALS AND METHODS

We retrospectively analyzed the medical records of 552 of 608 patients who underwent KTx at Severance Hospital, Yonsei University College of Medicine, between March 1, 1997, and June 30, 2002. Excluded were patients who underwent cadaveric KTx (n=13), patients with diabetes (n=19) or viral hepatitis B (n=10) before transplantation, and children aged less than 15 years (n=14). The recipients were divided into two groups according to the surgical approach. Patients who received kidneys harvested with the conventional open nephrectomy procedure were included in group I (n=382), and those who received kidneys harvested with the VAM procedure were included in group II (n=170). Video-assisted surgery was performed with a specially designed retractor set, which is now commercially available, including piercing abdominal retractors (Fig. 1) and long, bent forceps (Thompson Surgical, Travers City, MI). Prognostic factors after transplantation, such as age, gender, ABO Rh blood group compatibility, degree of human leukocyte antigen matching, kidney weight to body weight ratio (*20*), and immunosuppressive regimens, were compared between the two groups. The complication rates and renal function indices were measured. The complication rates after renal transplantation were measured in terms of delayed graft function, acute rejection, ureteral complications (e.g., ureteral stricture, stenosis, and fistula), 1-year graft failure rate, and patient mortality rate.

Delayed graft function was defined as no change in the serum creatinine (SCr) level after transplantation or a change in the SCr level of less than 10% per day during the first week after transplantation (*21*). Acute rejection was defined as a significant decrease in urine output accompanied by more than a 20% increase in SCr level. The diagnosis of acute rejection was confirmed by sonography and renal biopsy. Graft functions were evaluated by measuring the serial SCr level up to 1 year after transplantation.

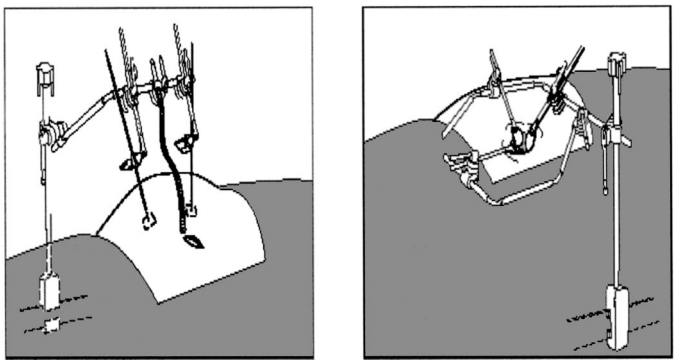

FIGURE 1. Video-assisted minilaparotomy (VAM) for living-donor nephrectomy (LDN). Abdominal wall elevators combined with conventional table mount retractors are used to create ample retroperitoneal surgical space.

All statistical analyses were performed using the Statistical Package for the Social Sciences version 10.0 (SPSS Inc., Chicago, IL). The clinical characteristics of the two groups were compared using the Student *t* test, complication and mortality rates were compared using the chi-square test, and graft functions were compared using analysis of variance repeated measures. A *P* value of less than 0.05 was considered significant.

RESULTS

Comparison of Demographic Data Between the Two Groups

No significant difference was found between the two groups in terms of age, gender, ABO blood group compatibility, degree of human leukocyte antigen matching, kidney weight to body weight ratio, or use of immune suppressants (Table 1) ($P>0.05$).

TABLE 1. Demographic and clinical data

	Group I (n=382) Open nephrectomy	Group II (n=170) VAM-LDN	*P* value
Age (mean±SD)	37.72±10.74	38.10±9.73	0.87
Sex (M:F)	235:147	115:55	0.73
KW/BW ratio	4.01±0.96	4.05±0.96	0.54
ABO match			0.08
Identical	298 (78.0%)	139 (81.8%)	
Compatible	84 (22.0%)	31 (18.2%)	
HLA match			0.11
Identical	72 (18.8%)	29 (17.1%)	
Haploidentical	208 (54.5%)	75 (44.1%)	
Unrelated	102 (26.7%)	66 (38.8%)	
Immunosuppression			0.70
Double[a]	101 (26.4%)	40 (23.5%)	
Triple[b]	281 (73.6%)	130 (76.5%)	

[a] Double: cyclosporine or FK506+steroid.

[b] Triple: cyclosporine or FK506+steroid+AZA or MMF.

KW/BW, kidney weight/body weight; AZA, azathioprine; MMF, mycophenolate mofetil; HLA, human leukocyte antigen; VAM, video-assisted minilaparotomy; LDN, living-donor nephrectomy; SD, standard deviation.

Rates of Complications, Graft Failure, and Patient Mortality

No significant difference was noted between the two groups in terms of the overall rate of complication, graft failure, or mortality ($P>0.05$). Delayed graft function with oliguria immediately after KTx was observed in one patient in each group. These two recipients showing delayed graft functions both recovered within 1 month of their KTx. Acute rejection episodes were noted in 96 patients (25.1%) in group I and in 42 patients (24.7%) in group II, showing no statistically significant difference between the two groups ($P=0.37$). The majority of these patients were treated with intravenous steroid pulse therapy (0.5 g/day for 4 days), followed by oral steroids. However, five patients (1.3%) in group I and 1 patient (0.6%) in group II did not respond to these treatments, and their renal functions were eventually lost. No complications related to ureteral injury were noted in either group.

Ten kidney grafts were lost within 1 year of transplantation. In group I, five patients experienced irreversible acute rejection, one patient died of posttransplant lymphoproliferative disorder, one patient experienced recurrence of the original kidney disease, and one patient died of myocardial infarction. In group II, one patient did not recover from acute rejection, and one patient died of fungal infection (Table 2) ($P>0.05$).

Comparison of Grafted Kidney Functions

There were no statistically significant differences in the SCr level, which was measured to compare the graft function between the two groups, at 1 week, 4 weeks, 6 months, and 1 year postoperatively (Table 3) ($P>0.05$).

DISCUSSION

Cadaveric KTx is rarely performed in Korea, and living-donor kidneys are used in most KTx cases. In living-donor KTx, donor safety and comfort are important during the perioperative period. For recipient benefit, the length of the renal artery, vein, and ureter should be sufficient and the warm ischemia time should be minimized to decrease the amount of renal tubular damage and prevent delayed graft function after transplantation (*4*, *11–13*). Open-donor nephrectomy through a retroperitoneal approach satisfies these requirements for living-donor KTx. Nonetheless, this method of nephrectomy causes various problems for the donor, such as pain from a long incision, long recovery period after surgery, and cosmetic problems. Therefore, the availability of a non-invasive and safer nephrectomy procedure for the donor should significantly increase the number of living kidney donors (*22*). Although laparoscopic LDN is an attractive, minimally invasive alternative, it has certain limitations related to safety and graft kidney functions. We initially developed VAM for kidney procedures and later extended its use to LDN, resulting in a procedure that combines the advantages of open nephrectomy and laparoscopic nephrectomy. This technique offers a double view of the surgical field: direct vision and magnified viewing on a video monitor. The use of a "piercing abdominal wall retractor" provides sufficient space to secure the same surgical field as in the conventional retroperitoneal approach, enabling the safe dissection of longer length of the renal artery (Fig. 2). In addition, the use of disposable equipment is minimized with this technique, thereby reducing the cost of surgery. Furthermore, problems related to vascular damage, which frequently occur during laparoscopic nephrectomy, can be dealt with immediately and conveniently by applying direct pressure to the hemorrhage site through the minilaparotomy incision. A plastic retrieval bag is introduced through the minilaparotomy incision to retrieve the kidney. The warm ischemic time is usually restricted to less than 3 min, which is comparable to that in conventional open retroperitoneal donor nephrectomy and shorter than that in laparoscopic nephrectomy. The average total surgery time with VAM-LDN was approximately 130 min, which is significantly shorter than that in laparoscopic LDN and comparable to the average of 138 min for open LDN at our center (*14*, *15*).

Increased intraperitoneal pressure when performing laparoscopic donor nephrectomy can decrease renal blood flow, which in turn can result in delayed graft function. However, these complications can be prevented by VAM-LDN inasmuch as this procedure does not induce renal artery spasm because carbon dioxide gas is not required to induce pneumoperitoneum (*14*, *15*). In an animal study, Kouwenhoven et al. (*23*) reported that delayed graft function can promote early acute rejection and is closely related with ischemia time. Boom et al. (*21*) reported that delayed graft function is a factor inducing early acute rejection and eventual graft failure. Therefore, the ischemia time, which varies from one surgical method to another, seems to be the most important factor determining the prognosis of graft function after KTx.

The rate of ureteral complications in kidney donors is high during the early stage after transplantation according to studies at Johns Hopkins (10.3%) and the University of Maryland (10.5%). Ratner et al. (*24*) reported that the rate of

TABLE 2. Recipient complications

	Group I (n=382) Open nephrectomy	Group II (n=170) VAM-LDN	*P* value
Delayed graft function	1 (0.3%)	1 (0.6%)	1.00
Acute rejection	96 (25.1%)	42 (24.7%)	0.37
Urinary complication	0	0	1.00
Graft failure (within 1 yr)			0.87
Acute rejection	5 (1.3%)	1 (0.6%)	
Patient death	2 (0.5%)	1 (0.6%)	
Disease recurrence	1 (0.3%)	0	
Patient mortality			0.58
PTLD	1 (0.3%)	0	
Myocardial infarct	1 (0.3%)	0	
Fungal infection	0	1 (0.6%)	

PTLD, posttransplant lymphoproliferative disorder.

TABLE 3. Graft function

	Group I (n=382) Open nephrectomy	Group II (n=170) VAM-LDN	*P* value
1 wk	1.86±0.45	1.68±0.46	0.57
1 mo	1.58±0.42	1.55±0.41	0.53
6 mo	1.33±0.38	1.28±0.36	0.47
1 yr	1.46±0.40	1.35±0.37	0.55

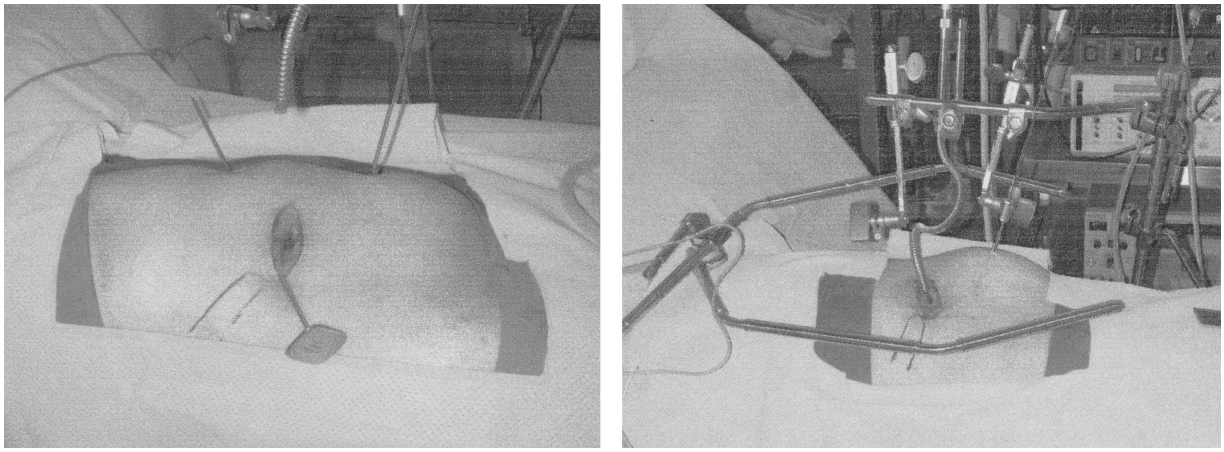

FIGURE 2. A piercing retractor is introduced between the peritoneum and the abdominal wall, which is attached to the retractor system.

ureteral complications can be as much as 66% higher in laparoscopic nephrectomy than in open nephrectomy with the retroperitoneal approach. The rate of ureteral complications in open nephrectomy with the retroperitoneal approach was reported to be 0.6% to 6.3% (*25*). We did not encounter any cases of ureteral complication in our study, suggesting that VAM-LDN does not increase the frequency of ureteral complications (*14*, *15*). We did not observe any difference in the rates of graft failure or patient mortality between open nephrectomy and VAM-LDN; however, further studies are required to confirm our findings. We followed the SCr levels of our patients for 1 year after KTx, assuming that functional changes in the grafted kidney can serve as an index to predict graft function (*26*, *27*), and found no significant difference in this index between the two groups.

CONCLUSION

Minimally invasive VAM-LDN not only offers the advantages of donor safety and convenience but also produces similar morbidity and mortality rates and renal functions in the KTx recipient as those that are obtained in conventional open nephrectomy. At our institution, VAM-LDN has recently become a viable option in the selection of minimally invasive methods for living-donor kidney procurement. Long-term follow-up studies will help to further evaluate this novel technique.

REFERENCES

1. Ratner LE, Ciseck LJ, Moore RG, et al. Laparoscopic live donor nephrectomy. Transplantation 1995; 60: 1047.
2. Ratner LE, Kavoussi LR, Sroka M, et al. Laparoscopic assisted live donor nephrectomy-a comparison with the open approach. Transplantation 1997; 63: 229.
3. Ratner LE, Hiller J, Sroka M, et al. Laparoscopic live donor nephrectomy removes the disincentive with the open approach. Transplant Proc 1997; 29: 3402.
4. Brown SL, Biehl TR, Rawlins MC, et al. Laparoscopic live donor nephrectomy: a comparison with the conventional open approach. J Urol 2001; 165: 766.
5. Lennerling A, Blohme I, Ostraat O, et al. Laparoscopic or open surgery for living donor nephrectomy. Nephrol Dial Transplant 2001; 16: 383.
6. Beull JF, Alverdy J, Newell K, et al. Hand-assisted laparoscopic live-donor nephrectomy. J Am Coll Surg 2001; 192: 132.
7. Stefelman MD, Hull D, Sosa RE, et al. Hand assisted laparoscopic donor nephrectomy: a comparison with the open approach. J Urol 2001; 166: 444.
8. Merlin TL, Scott DF, Rao MM, et al. The safety and efficacy of laparoscopic live donor nephrectomy: a systematic review. Transplantation 2000; 70: 1659.
9. Hawasli A, Boutt A, Cousins G, et al. Laparoscopic versus conventional live donor nephrectomy: experience in a community transplant program. Am Surg 2001; 67: 342.
10. Jacobs SC, Cho E, Dunkin BJ. Laparoscopic donor nephrectomy: current role in renal allograft procurement. Urology 2000; 55: 807.
11. Nakache R, Szold A, Merhav H, et al. Kidney graft loss after laparoscopic live donor nephrectomy. Transplant Proc 2000; 32: 683.
12. Ratner LE, Kavoussi LR, Chavin KD. Laparoscopic live donor nephrectomy: technical considerations and allograft vascular length. Transplantation 1998; 65: 1657.
13. Rajasekar MR, Rajakumari V, Rehmani B, et al. Challenges in laparoscopic donor nephrectomy and technical innovation to make it cost effective. Transplant Proc 2000; 32: 1581.
14. Yang SC, Ko WJ, Byun YJ, et al. Retroperitoneoscopy-assisted live donor nephrectomy: the Yonsei experience. J Urol 2001; 165: 1099.
15. Yang SC, Rha KH, Kim YS, et al. Retroperitoneoscopy-assisted living donor nephrectomy: 109 cases. Transplant Proc 2001; 33: 1104.
16. Rudich SM, Marcovich R, Magee JC, et al. Hand-assisted laparoscopic live-donor nephrectomy: comparable donor/recipient outcomes, costs, and decreased convalescence as compared to open donor nephrectomy. Transplant Proc 2001; 33: 1106.
17. Montgomery RA, Kavoussi LR, Su LM, et al. Improved recipient results after 5 years of performing laparoscopic donor nephrectomy. Transplant Proc 2001; 33: 1108.
18. Koffron A, Herman C, Gross O, et al. Laparoscopic donor nephrectomy: analysis of donor and recipient outcomes. Transplant Proc 2001; 33: 1111.
19. Jacobs SC, Cho E, Dunkin BJ, et al. Laparoscopic live donor nephrectomy: the University of Maryland 3-year experience. J Urol 2000; 164: 1494.
20. Kim YS, Moon JI, Kim DK, et al. Ratio of donor kidney weight to recipient body weight as an index of graft function. Lancet 2001; 357: 1180.
21. Boom H, Mallat MJ, de Fijter JW, et al. Delayed graft function influences renal function, but not survival. Kidney Int 2000; 58: 859.
22. Schweitzer EJ, Wilson J, Jacobs S, et al. Increase rates of donation with laparoscopic donor nephrectomy. Ann Surg 2000; 232: 392.
23. Kouwenhoven EA, de Bruin RW, Bajema IM, et al. Prolonged ischemia enhances acute rejection in rat kidney grafts. Transplant Proc 2001; 33: 361.
24. Ratner LE, Montgomery RA, Cohen C, et al. Laparoscopic live donor nephrectomy: the recipient. Transplantation 1998; 85: S109.
25. Novick AC. Laparoscopic live donor nephrectomy: con. Urology 1999; 53: 668.
26. Woo YM, Jardine AG, Clark AF, et al. Early graft function and patient survival following cadaveric renal transplantation. Kidney Int 1999; 55: 692.
27. Sund S, Reisaeter AV, Fauchald P, et al. Living donor kidney transplantation: a biopsy study 1 year after transplantation, compared with baseline changes and correlation to kidney function at 1 and 3 years. Nephrol Dial Transplant 1999; 14: 2445.