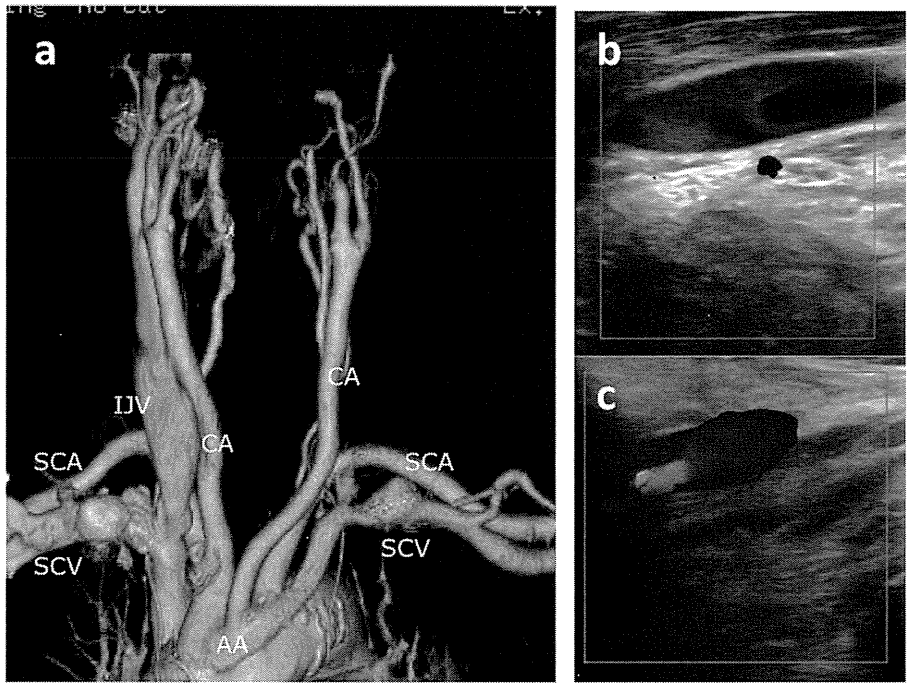

FIGURE 3 (a) MDCT venography and echo study: AP VR images. The CT-V could not identify the left IJV, the EJV, or the right EJV. The disappearance of the left IJV on CT-V image is characteristic. (b) Flow is demonstrated in the proximal section of the IJV and SCV by an ultrasound study. The Doppler color ultrasound demonstrates significantly turbulent flow with decreased flow velocity of the left IJV (c). No thrombosis was detected.

occlusion or estimation of the detailed anatomical orientation of the cervical venous plexus. The most important advantage is the absence of major complications. In regard to related patient safety, it is worth nothing that in the relatively recent past the use peripherally inserted central catheters has obviated some of the risks involved with more central access sites. Therefore, central venous access via the EJV seems to be an option to consider for vascular access in patients given our findings of a high success rate and a low complication rate [24]. The number of cases of reported is relatively small, which implies the need for a study involving a large patient population that would permit more precise assessment. Further studies are needed to determine how these advances in central access with compare to the safety profile of EJV technique.

CONCLUSIONS

Three-dimensional CT-V using MDCT clearly revealed individual vascular anatomies around EJV–SCV junction including the cervical venous plexus and could play an important role in safe cannulization. The EJV route is associated with comparable technical success and lower major procedural complication. The EJV approach with CT-V guidance is an option when central venous cannulation must be performed in patients under suboptimal conditions and patients in whom serious complications may prove to be fatal and with previous multiple central venous cannulations, especially those in hemodialysis or with long catheter indwelling periods, since because they are at higher risk of central venous occlusion.

Declaration of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of the article.

No funds supported this study. Written informed consent was obtained from the patients for publication of this manuscript and any accompanying images. Copies of the written consent are available for review by the Editor-in-Chief of this journal.

REFERENCES

[1] Gorman RC, Buzby GP. Difficult access problems. *Surg Oncol Clin North Am.* 1995;4:453–472.
[2] Trerotola SO. You are asked to place a dialysis access catheter in a patient. What is your preferred access site, and why? *J Vasc Interv Radiol.* 1997;8:75–76.
[3] Susan NW. Unconventional venous access. *Tech Vas Interv Radiol.* 2001;5:114–120.
[4] Macdonald S, Watt AJB, McNally D, et al. Comparison of technical success and outcome of tunneled catheters inserted via the jugular and subclavian approach. *JVIR* 2000;11:225–231.

[5] Schillinger F, Schillinger D, Montagnac R, et al. Post catheterization vein stenosis in haemodialysis: comparative angiographic study of 50 subclavian and 50 internal jugular access. *Nephrol Dial Transplant.* 1991;6:722–7124.
[6] Moss AH, MacLaughlin MM, Lempert KD, et al. Use of a silicone catheter with a Dacron cuff for dialysis short-term vascular access. *Am J Kidney Dis.* 1988;12:492–489.
[7] Cimochowski GF, Worley E, Rutherford WE, et al. Superior of the internal jugular over the subclavian access for temporary dialysis. *Nephron.* 1990;54:154–161.
[8] Trerotola SO, Kuhn-johnson J, Johnson MS, et al. Tunneled infusion catheters: increased incidence of symptomatic venous thrombosis after subclavian versus internal jugular venous access. *Radiology* 2000;217:89–93.
[9] Forauer AR, Brenner B, Haddad LF, et al. Placement of hemodialysis catheters through dilated external jugular and collateral veins in patients with internal jugular vein occlusions. *AJR* 2000;174:361–362.
[10] Blitt CD, Wright WA, Petty WC, et al. Central venous catheterization via external jugular vein. *JAMA* 1974;229:817–818.
[11] Cho SK, Shin SW, Do YS, et al. Use of the right external jugular vein as the preferred access site when the right internal jugular vein is not usable. *J Vasc Interv Radiol.* 2006;17: 823–829.
[12] Finley GA. A complication of external jugular vein catheterization in children. *Can J Anaesth.* 1988;35:536–537.
[13] McCowan TC, Ferris EJ, Carver DK, et al. Use of external jugular vein as a route for percutaneous inferior vena cava filter placement. *Radiology* 1990;176;527–530.
[14] Byth PL. Evaluation of the technique of central venous catheterization via external jugular vein using J-wire. *Anaeth Intens Care* 1985;13:131–133.
[15] Shih YC, Chien HL, Hao MC, et al. A safe and effective method to implantable access port in patients with synchronous bilateral mastectomies: modified femoral vein approach. *J Surg Oncol.* 2008;98:197–199.
[16] Malatinsky J, Kadlic T, Majek M, et al. Misplacement and loop formation of central venous catheters. *Acta Anaesth Scand.* 1976;20:237–247.
[17] McKenzie BJ, Hatto IP. Difficult removal of external jugular vein catheters. *Anaesth Intens Care* 1981;9:158–160.
[18] Bita FF, Obeid M, Dabbous I, et al. Acute respiratory distress associated with external jugular vein catheterization in the newborn. *Pediar Pulmonol.* 2003;36:549–550.
[19] Heye S, Maleux G, Claes K, et al. Stenosis detection in native hemodialysis fistulas with MDCT angiography. *Am J Roentgenol.* 2009;192:1079–1084.
[20] Virmani V, Khandelwal N, Kang M, et al. MDCT venography in the evaluation of inferior vena cava in Budd-Chiari syndrome. *Indian J Gastroenterol.* 2009;28:17–23.
[21] Humphrey MJ, Bitt CD. Central venous access in children via external jugular vein. *Anesthesiology* 1982;57:50–51.
[22] Jobes DR, Schwartz AJ, Greenhow DE, et al. Safer jugular vein cannulation: recognition of arterial puncture and preferential use of the external jugular route. *Anesthesiology* 1983;59:353–355.
[23] Belani KG, Buckley JJ, Gordon JR, et al. Percutaneous cervical central venous line placement: a comparison of the internal and external vein routes. *Anetsh Analg.* 1980;59:40–44.
[24] Tecklenburg FW, Cochran JB, Webb SA, et al. Central venous access via external jugular vein in children. *Pediatr Emerg Care* 2010;26:554–557.
[25] de Jonge RC, Poldermann K, Gemke RJ. Central venous catheter use in the pediatric patient: mechanical and infectious complications. *Pediatr Crit Care Med.* 2005;6:329–333.

Hindawi Publishing Corporation
BioMed Research International
Volume 2013, Article ID 879491, 5 pages
http://dx.doi.org/10.1155/2013/879491

Clinical Study

Infliximab Extends the Duration until the First Surgery in Patients with Crohn's Disease

Aki Sakatani,[1] Mikihiro Fujiya,[1] Takahiro Ito,[1] Yuhei Inaba,[1] Nobuhiro Ueno,[1] Shin Kashima,[1] Motoya Tominaga,[1] Kentaro Moriichi,[1] Kotaro Okamoto,[1] Hiroki Tanabe,[1] Katsuya Ikuta,[1] Takaaki Ohtake,[1] Toru Kono,[2] Hiroyuki Furukawa,[2] Toshifumi Ashida,[3] and Yutaka Kohgo[1]

[1] *Division of Gastroenterology and Hematology/Oncology, Department of Medicine, Asahikawa Medical University, 2-1 Midorigaoka-higashi, Asahikawa, Hokkaido 078-8510, Japan*
[2] *Division of Gastroenterological and General Surgery, Department of Surgery, Asahikawa Medical University, 2-1 Midorigaoka-higashi, Asahikawa, Hokkaido 078-8510, Japan*
[3] *Department of Gastroenterology, Sapporo Higashi Tokushukai Hospital, 3-1 North 33-jou East 14-chome East Ward, Sapporo, Hokkaido 065-0033, Japan*

Correspondence should be addressed to Mikihiro Fujiya; fjym@asahikawa-med.ac.jp

Received 16 July 2013; Revised 19 October 2013; Accepted 20 October 2013

Academic Editor: Hidekazu Kuramochi

Background/Aims. While biological drugs are useful for relieving the disease activity and preventing abdominal surgery in patients with Crohn's disease (CD), it is unclear whether the use of biological drugs in CD patients with no history of abdominal surgery is appropriate. We evaluated the effects of infliximab and other factors on extending the duration until the first surgery in CD patients on a long-term basis. *Methods.* The clinical records of 104 CD patients were retrospectively investigated. The cumulative nonoperation rate until the first surgery was examined with regard to demographic factors and treatments. *Results.* The 50% nonoperative interval in the 104 CD patients was 107 months. The results of a univariate analysis revealed that a female gender, the colitis type of CD, and the administration of corticosteroids, immunomodulators, or infliximab were factors estimated to improve the cumulative nonoperative rate. A multivariate analysis showed that the colitis type and administration of infliximab were independent factors associated with a prolonged interval until the first surgery in the CD patients with no history of abdominal surgery. *Conclusions.* This study suggests that infliximab treatment extends the duration until the first surgery in CD patients with no history of abdominal surgery. The early use of infliximab before a patient undergoes abdominal surgery is therefore appropriate.

1. Introduction

Crohn's disease (CD) is a chronic inflammatory bowel disease whose etiology remains unclear. Deep and refractory ulcers frequently develop in the small intestine in CD patients, often causing severe complications, including abdominal abscesses and ileus. Open surgery is sometimes required to relieve the patient's conditions, including ileus due to severe stricture, refractory abscesses, and fistulas, which lead to a deterioration of the general condition and quality of life in the patients, as well as severe intestinal bleeding [1]. Recent advances in therapeutic strategies have led to the development of biological agents, such as infliximab and adalimumab, that have improved the success rate of inducing remission and are useful as maintenance therapy in patients with refractory CD [2–6]. The administration of biological agents also reduces the rate of complications and extends the duration from the first to the second surgery [7–10]. Because the traditional therapeutic approach for treating CD is based on a step-up strategy [11], the administration of treatment with biological drugs is recommended in patients who fail to respond to conventional therapy, but not patients who exhibited mild to moderate disease activity without a history of abdominal surgery. Recently, D'Haens et al. reported in a 2-year randomized trial that the percentage of newly diagnosed patients without a need for corticosteroid

treatment or surgery at six and 12 months was significantly higher in the group administered infliximab [12]. This short-term observation suggests that the use of infliximab in CD patients, who were diagnosed within the past four months, can increase the duration of remission and extend the duration until the first surgery. Conversely, Jones and Finlayson evaluated the Nationwide Inpatient Sample in the US and concluded that, during the period of adoption of infliximab as a novel CD treatment, the overall rate of bowel resection either remained relatively stable or moderately decreased [13]. Domènech et al. retrospectively reviewed the clinical outcomes of newly diagnosed Crohn's disease patients before and after infliximab availability and concluded that infliximab availability did not reduce the need for surgery or the development of disease-related complications [14]. It remains unclear whether the early use of biological drugs decreases the risk of the first surgery in CD patients.

The present retrospective study investigated factors affecting the interval from the time of diagnosis to the first surgery, including patient demographics, type of disease, and treatment procedures, in CD patients with no history of abdominal surgery.

2. Methods

2.1. Patients. Written informed consent was obtained from all identified patients, and the study was approved by the institutional review board of Asahikawa Medical University. The clinical records of 104 patients who were diagnosed as having CD at Asahikawa Medical University between February 1982 and October 2011 were retrospectively investigated. The diagnosis of CD was made based on the combination of the clinical course and the colonoscopy, double balloon endoscopy, small bowel enterolysis, and histological findings. Typical lesions of CD, including longitudinal ulcers and a cobblestone appearance in the small and/or large intestine, were observed on endoscopy in all patients. Intestinal strictures, fistula formation, and abdominal abscesses were also observed in the patients. These findings were also referenced for the diagnosis of CD. Data regarding patient demographics, treatments, and operative findings were collected by A.S., who did not participate in the diagnosis, medical examination, or treatment of the patients. The onset of the disease was defined as the time of appearance of symptoms caused by CD. The date of disease onset was used to divide the patients into two groups, those treated before 2001 and those treated after 2002, because infliximab became clinically available in Japan in 2002. Patients who received infliximab four or more times, corticosteroids as remission induction therapy, or immunomodulators for one or more months were classified as belonging to the infliximab-positive, corticosteroid-positive, or immunomodulator-positive groups, respectively. These agents were administered in patients resistant to 5-aminosalicylate treatment and/or those who requested these drugs.

2.2. Cumulative Nonoperative Rate until the First Surgery. The abdominal surgeries performed in this study included intestinal resection, strictureplasty, colostomy, and ileostomy. The demographic and treatment-related factors were retrospectively compared with the cumulative nonoperative rate until the first surgery. In the patients who did not undergo surgery, the interval from diagnosis to the end of the study was defined as the nonoperative time (March 2012). In the patients who underwent either single or multiple surgeries, the interval from diagnosis to the first surgery was defined as the nonoperative time.

2.3. Statistical Analyses. The Kaplan-Meier method was used to test the cumulative nonoperative rates and the data related to each factor were statistically analyzed using the log-rank test. A Cox proportional hazards model was used to calculate the hazard ratios of the factors identified to estimate the frequency of surgery. A P value of <0.05 was considered to be statistically significant (two-sided test).

3. Results

3.1. Patient Demographics and Treatments. Seventy-one male and 33 female patients were included in this study. Sixty-seven (64%) patients exhibited lesions in both the small and large intestines (ileocolitis type), 28 (27%) patients had lesions in the small intestine only (ileitis type), and nine (9%) patients had lesions in the large intestine only (colitis type). The age at disease onset ranged from 10 to 66 years, with a median of 22 years. The date of disease onset was before 2001 in 74 patients and after 2002 in 30 patients. Corticosteroids, immunomodulators, and infliximab were administered in 33 (32%), 37 (36%), and 39 (38%) of the patients before the first surgery, respectively. A total of 16 of the 74 patients who had disease onset before 2001 and 23 of the 30 patients who had disease onset after 2002 took infliximab. Sixty-nine patients (66%) underwent one or more surgeries (Table 1). A total of 134 surgeries were performed. Ileal or jejunal resection was performed in 76 patients, strictureplasty was performed in 10 patients, and colostomy or ileostomy was performed in six patients. Combination surgeries were performed in 42 patients (Table 2).

3.2. Clinical Factors Associated with the Cumulative Nonoperative Rate. The cumulative nonoperative rate among all 104 patients is shown in Figure 1. The 50% nonoperative interval was 107 months. The relationships between the clinical factors, such as gender, the location of the lesions, the age at disease onset and treatments, and the cumulative nonoperative rate, were analyzed. The results of a univariate analysis of the cumulative nonoperative rate based on the presence or absence of each clinical factor are shown in Table 3. The analysis revealed that a female gender, the colitis type of CD, and the administration of corticosteroids, immunomodulators, or infliximab were factors estimated to improve the cumulative nonoperative rate (Figure 2). A multivariate analysis showed the colitis type of CD and the administration of infliximab to be independent factors associated with a prolonged interval until the first surgery. The hazard ratios of the colitis type of CD and the administration

Table 1: Patient demographics and treatments (104 cases).

	Number of patients (n = 104)
Sex	
Male	71 (68%)
Female	33 (32%)
Type of disease	
Ileitis	28 (27%)
Ileocolitis	67 (64%)
Colitis	9 (9%)
The age of onset	
Median	22
Range	10–66
The history of corticosteroid use until the first operation	
(+)	33 (32%)
(−)	71 (68%)
The history of immunomodulator use until the first operation	
(+)	37 (36%)
(−)	67 (64%)
The history of infliximab use until the first operation	
(+)	39 (38%)
(−)	65 (62%)
The history of enteral nutrition	
(+)	96 (92%)
(−)	8 (8%)
Bowel surgery	
(+)	69 (66%)
(−)	35 (34%)

of infliximab were 0.086 (0.011–0.657) and 0.256 (0.122–0.540), respectively (Table 4).

4. Discussion

The present study showed that the administration of infliximab extends the duration until the first surgery in CD patients who have not previously undergone abdominal surgery. This suggests that the administration of infliximab is useful in CD patients with no experience with abdominal surgery. While the usefulness of biological drugs for inducing and maintaining remission of CD and extending the duration from the first to the second surgery has been established [2, 3, 10], it remains unclear whether these biological drugs should be administered in CD patients with no history of abdominal surgery. Recently, D'Haens et al. reported in a 2-year open-label-randomized trial that the percentage of CD patients who were diagnosed within four months in clinical remission and were neither receiving corticosteroids nor requiring surgery at six and 12 months was significantly higher in the group treated with infliximab [12], thus suggesting that the early use of infliximab can improve the short-term outcomes of CD. The present study supports the notion that infliximab treatment can improve both the long-term and short-term outcomes in CD patients, even when the patient has no history of abdominal surgery.

Table 2: Surgical procedures performed in 69 patients with Crohn's disease (total: 134 operations).

	Total of 134 operations
Bowel resection	76
Strictureplasty	10
Colostomy or ileostomy	6
Bowel resection and strictureplasty	27
Bowel resection and colostomy (or ileostomy)	13
Strictureplasty and colostomy (or ileostomy)	1
Bowel resection and strictureplasty and colostomy (or ileostomy)	1

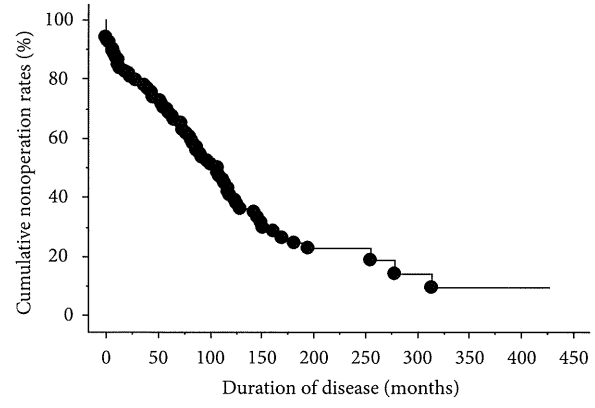

Figure 1: The cumulative nonoperative rate among all 104 patients. The nonoperative rate was inversely proportional to the duration of the disease.

Although the present study demonstrated the efficacy of infliximab treatment, the period of disease onset may have influenced the duration from disease onset to the first surgery. After 2002, the availability of infliximab treatment is not the only factor that changed from the previous era. The types and characteristics of microorganisms causing infectious colitis and the eating habits and lifestyle factors affecting the pathology of inflammatory diseases have been changed over the past two decades in Japan. Therefore, the present study investigated the influence of the date of disease onset on the duration until the first surgery, the results of which showed that the date of disease onset is not a significant factor affecting the duration until the first surgery in CD patients. An evaluation of the Nationwide Inpatient Sample conducted in the US concluded that, during the period of adoption of infliximab as a novel CD treatment, the overall rate of bowel resection either remained relatively stable or moderately decreased [13]. Domènech et al. also reviewed the clinical

Table 3: Factors associated with the nonoperative rate until the first surgery (univariate analysis).

	Number of patients (n = 104)	50% nonoperation time (months)	P value
Sex			
Male	71	84	<0.05
Female	33	142	
Type of disease			
Ileitis/ileocolitis	95	98	<0.05
Colitis	9	Undefined	
The age of onset			
Less than 20	39	117	N.S.
20 or more	65	98	
The date of onset			
Before 2001	74	107	N.S
After 2002	30	Undefined	
Corticosteroid			
(+)	33	126	<0.05
(−)	71	91	
Immunomodulator			
(+)	37	169	<0.05
(−)	67	84	
Infliximab			
(+)	39	256	<0.05
(−)	65	78	

Undefined: nonoperation time is greater than 50% at the last time point. N.S.: not significant.

Table 4: Factors associated with the nonoperative rate until the first surgery (multivariate analysis).

		Hazard ratio	95% CI
Sex	Female	0.605	0.339–1.081
Type of disease	Colitis	0.086	0.011–0.657
Corticosteroid	(+)	0.912	0.519–1.604
Immunomodulator	(+)	1.057	0.569–1.966
Infliximab	(+)	0.256	0.122–0.540

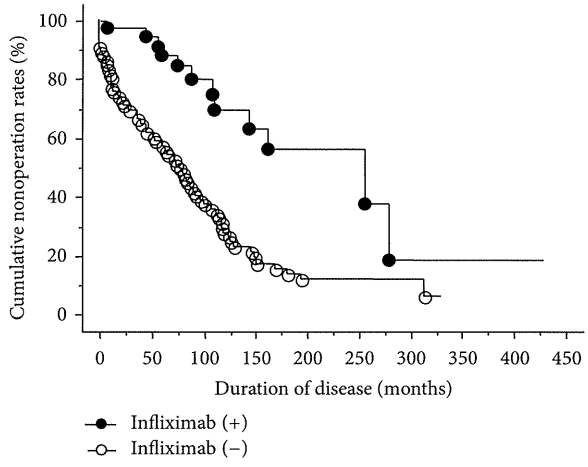

Figure 2: The results of a univariate analysis of the cumulative nonoperative rate based on the presence or absence of infliximab treatment. The univariate analysis revealed that the administration of infliximab is a factor estimated to improve the cumulative nonoperative rate.

outcomes of newly diagnosed Crohn's disease patients before and after infliximab availability in a retrospective study and concluded that infliximab availability did not reduce the need for surgery [14]. These investigations and the present study therefore indicate that the date of disease onset is not a strong factor affecting the duration until the first surgery in CD patients. Further long-term prospective studies of large numbers of CD patients with no history of abdominal surgery are needed to confirm the significance of biological agents in improving the cumulative nonoperative rate in CD patients.

In this study, while the univariate analysis revealed that the administration of corticosteroids and immunomodulators affected the duration until the first surgery, the multivariate analysis did not identify these treatments to be independent factors. Therefore, these therapies are not very useful for treating CD patients with no history of abdominal surgery in comparison to the administration of infliximab. The administration of corticosteroids has been shown to be effective for inducing remission in patients with CD [15–20]. However, it is well known that the administration of corticosteroids is associated with various side effects. Corticosteroids should be used as short-term therapy only when other treatments are ineffective. Although the administration of immunomodulators alone is useful for maintaining CD [21, 22], combination therapy with immunomodulators and infliximab has been shown to be more effective for this purpose [23]. Because immunomodulators were used in combination with infliximab in most cases in the present study,

the multivariate analysis did not identify immunomodulators to be an independent factor.

In summary, the results of the present study suggest that infliximab treatment has the potential to extend the duration until the first surgery. This implies that the administration of infliximab in CD patients with no history of abdominal surgery, even in CD patients with no experience with abdominal surgery, can improve the outcomes, including the cumulative nonoperative rate. Further randomized, controlled trials are needed to establish the appropriate timing of the initiation of infliximab treatment and determine the optimal dose, schedule, and duration of the administration of these biological drugs.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

Aki Sakatani and Mikihiro Fujiya contributed equally to this study.

References

[1] O. Bernell, A. Lapidus, and G. Hellers, "Risk factors for surgery and postoperative recurrence in Crohn's disease," *Annals of Surgery*, vol. 231, no. 1, pp. 38–45, 2000.

[2] S. B. Hanauer, B. G. Feagan, G. R. Lichtenstein et al., "Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial," *The Lancet*, vol. 359, no. 9317, pp. 1541–1549, 2002.

[3] P. Rutgeerts, B. G. Feagan, G. R. Lichtenstein et al., "Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease," *Gastroenterology*, vol. 126, no. 2, pp. 402–413, 2004.

[4] B. G. Feagan, R. Panaccione, W. J. Sandborn et al., "Effects ofadalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM Study," *Gastroenterology*, vol. 135, no. 5, pp. 1493–1499, 2008.

[5] J.-F. Colombel, W. J. Sandborn, P. Rutgeerts et al., "Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial," *Gastroenterology*, vol. 132, no. 1, pp. 52–65, 2007.

[6] S. B. Hanauer, W. J. Sandborn, P. Rutgeerts et al., "Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial," *Gastroenterology*, vol. 130, no. 2, pp. 323–332, 2006.

[7] G. R. Lichtenstein, S. Yan, M. Bala, M. Blank, and B. E. Sands, "Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease," *Gastroenterology*, vol. 128, no. 4, pp. 862–869, 2005.

[8] F. Schnitzler, H. Fidder, M. Ferrante et al., "Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort," *Gut*, vol. 58, no. 4, pp. 492–500, 2009.

[9] J. K. Bhatia, B. I. Korelitz, G. Panagopoulos et al., "A prospective open-label trial of Remicade in patients with severe exacerbation of Crohn's disease requiring hospitalization: a comparison with outcomes previously observed in patients receiving intravenous hydrocortisone," *Journal of Clinical Gastroenterology*, vol. 41, no. 7, pp. 677–681, 2007.

[10] M. Regueiro, W. Schraut, L. Baidoo et al., "Infliximab prevents Crohn's disease recurrence after ileal resection," *Gastroenterology*, vol. 136, no. 2, pp. 441.e1–450.e1, 2009.

[11] A. Dignass, G. Van Assche, J. O. Lindsay et al., "The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management," *Journal of Crohn's and Colitis*, vol. 4, no. 1, pp. 28–62, 2010.

[12] G. D'Haens, F. Baert, G. van Assche et al., "Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial," *The Lancet*, vol. 371, no. 9613, pp. 660–667, 2008.

[13] D. W. Jones and S. R. G. Finlayson, "Trends in surgery for crohn's disease in the era of infliximab," *Annals of Surgery*, vol. 252, no. 2, pp. 307–312, 2010.

[14] E. Domènech, Y. Zabana, E. Garcia-Planella et al., "Clinical outcome of newly diagnosed Crohn's disease: a comparative, retrospective study before and after infliximab availability," *Alimentary Pharmacology and Therapeutics*, vol. 31, no. 2, pp. 233–239, 2010.

[15] S. C. Truelove and L. J. Witts, "Cortisone in ulcerative colitis; preliminary report on a therapeutic trial," *British Medical Journal*, vol. 2, no. 4884, pp. 375–378, 1954.

[16] R. W. Summers, D. M. Switz, and J. T. Sessions Jr., "National cooperative Crohn's disease study: results of drug treatment," *Gastroenterology*, vol. 77, no. 4, pp. 847–869, 1979.

[17] H. Malchow, K. Ewe, and J. W. Brandes, "European cooperative Crohn's disease study (ECCDS): results of drug treatment," *Gastroenterology*, vol. 86, no. 2, pp. 249–266, 1984.

[18] G. R. Greenberg, B. G. Feagan, F. Martin et al., "Oral budesonide for active Crohn's disease," *The New England Journal of Medicine*, vol. 331, no. 13, pp. 836–841, 1994.

[19] M. Campieri, A. Ferguson, W. Doe, T. Persson, and L.-G. Nilsson, "Oral budesonide is as effective as oral prednisolone in active Crohn's disease," *Gut*, vol. 41, no. 2, pp. 209–214, 1997.

[20] O. Ø. Thomsen, A. Cortot, D. Jewell et al., "A comparison of budesonide and mesalamine for active Crohn's disease," *The New England Journal of Medicine*, vol. 339, no. 6, pp. 370–374, 1998.

[21] D. H. Present, B. I. Korelitz, and N. Wisch, "Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study," *The New England Journal of Medicine*, vol. 302, no. 18, pp. 981–987, 1980.

[22] S. Candy, J. Wright, M. Gerber, G. Adams, M. Gerig, and R. Goodman, "A controlled double blind study of azathioprine in the management of Crohn's disease," *Gut*, vol. 37, no. 5, pp. 674–678, 1995.

[23] J. F. Colombel, W. J. Sandborn, W. Reinisch et al., "Infliximab, azathioprine, or combination therapy for Crohn's disease," *The New England Journal of Medicine*, vol. 362, no. 15, pp. 1383–1395, 2010.

● 症 例 ●

Bevacizumab高用量の再投与にて長期生存を得た結腸癌大動脈周囲リンパ節転移の1例

海老澤良昭[*1] 千里 直之[*1] 岡山 大志[*1] 谷 誓良[*1] 河野 透[*2]
谷口 雅彦[*1] 古川 博之[*1]

〔*Jpn J Cancer Chemother* 40(10): 1401-1404, *October*, 2013〕

Long-Term Survival of a Patient with Advanced Colon Cancer and Para-Aortic Lymph Node Metastases Treated with Re-Administration of High-Dose Molecular Targeted Agent Bevacizumab: Yoshiaki Ebisawa[*1], Naoyuki Chisato[*1], Taishi Okayama[*1], Chikayoshi Tani[*1], Toru Kono[*2], Masahiko Taniguchi[*1] and Hiroyuki Furukawa[*1] ([*1]*Division of Gastroenterologic and General Surgery, Asahikawa Medical University*, [*2]*Dept. of Surgery, Sapporo Higashi Tokushukai Hospital*)

Summary

A 49-year-old woman was admitted to our hospital because of epigastralgia and abdominal distension. She was diagnosed as advanced colon cancer with para-aortic and common iliac lymph node metastases, without liver and lung metastasis. Extended right hemicolectomy was performed to remove symptoms of stenosis. Bevacizumab (BV) (5 mg/kg)+mFOLFOX6 was performed as the initial postoperative chemotherapy. The tumor marker CEA, CA19-9 decreased, and reduction in the size of distant lymph node metastasis was confirmed, which obtained PR. In July 2009, computed tomography revealed the right pulmonary hilar lymph node metastases and progressive disease was confirmed; therefore, cetuximab and FOLFIRI combination therapy was initiated. However, in October 2009, bilateral inguinal lymph node metastases was seen; therefore we changed chemotherapy to BV (10 mg/kg) and FOLFIRI. Although the abdominal lymph node was decreased slightly after 2 months, chemotherapy was changed to BV (10 mg/kg) and mFOLFOX6 since the inguinal lymph node had enlarged. Skin metastases appeared, and there was no change in the inguinal lymph node and abdominal lymph node. She was deceased due to peritonitis carcinomatosis; however, her survival time exceeded 30 months. There was a possibility that long-term survival could be obtained by increasing the quantity of BV and re-administering it in second-line chemotherapy after PD in BV+FOLFOX first-line chemotherapy. **Key words**: Colon cancer, Para-aortic lymph nodes, High-dose bevacizumab (*Received Nov. 2, 2012/Accepted Feb. 19, 2013*)

要旨 症例は49歳，女性。上腹部不快感，腹満を主訴に当科を受診し，上行-横行結腸癌，大動脈周囲リンパ節～総腸骨リンパ節転移の診断がなされた。肝・肺転移なし。狭窄症状を認めたため，2007年10月下旬に拡大右半結腸切除術を施行。術後約1か月後に全身化学療法の一次治療としてベバシズマブ（bevacizumab: BV 5 mg/kg）+mFOLFOX6を開始。腫瘍マーカーは減少，遠隔リンパ節転移も縮小しPRを得た。2009年7月に右肺門部リンパ節転移が出現しPDとなり，cetuximab+FOLFIRIに変更するも，3か月後に両側鼠径リンパ節転移出現を認めBV（10 mg/kg）+FOLFIRIに変更。2か月半後に腹部リンパ節はわずかに縮小したが，鼠径リンパ節が増大したためBVを10 mg/kgに増量したBV+mFOLFOX6に変更した。その2か月後に皮膚転移が出現するも，鼠径リンパ節，腹部リンパ節には変化を認めなかった。その後，癌性腹膜炎などを生じ死亡したが，30か月を超える生存期間が得られた。一次治療でPDとなったBV+FOLFOX療法でも，二次治療以降でBVを増量し再投与することで，長期生存が得られる可能性が示唆された。

はじめに

治癒切除不能大腸癌の一次治療としてベバシズマブ[bevacizumab (BV)]併用療法がなされており，二次治療以降でのBV再投与およびその用量についてのエビデンスも確立されてきている。今回われわれは，一次治療

[*1] 旭川医科大学外科学講座・消化器病態外科学分野
[*2] 札幌東徳洲会病院・先端外科センター

連絡先: 〒078-8510 北海道旭川市緑が丘東2条1-1-1 旭川医科大学外科学講座・消化器病態外科学分野
海老澤良昭

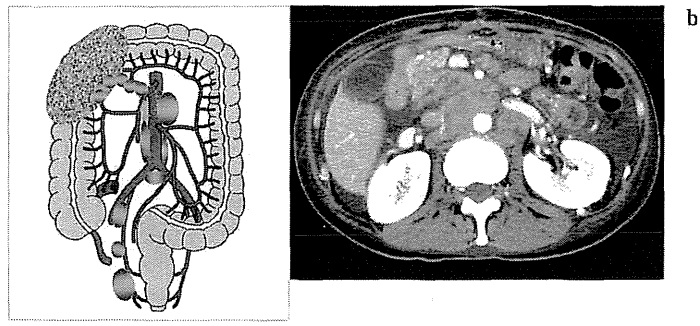

Fig. 1 a: Schema of primary tumor and lymph node metastasis. : Primary tumor, : Lymph node metastasis
b: Abdominal CT scan shows para-aortic lymph node metastasis.

で5 mg/kg，二次治療以降で10 mg/kgのBV併用療法により長期生存を得た症例を経験したので報告する。

Ⅰ．症　例

患者: 49歳，女性。

主訴: 上腹部不快感，腹満，食欲不振。

現病歴: 2007年8月下旬より，上腹部不快感，腹満，食欲不振出現。10月初旬に近医を受診し，大腸内視鏡検査にて全周性狭窄を伴う上行～横行結腸癌，CTにて大動脈周囲リンパ節～総腸骨リンパ節腫大を認め（Fig. 1a, b），手術を勧められ当科紹介となった。

既往歴: 特記すべきことなし。

家族歴: 特記すべきことなし。

臨床経過: 狭窄症状を有する転移性大腸癌であることから，手術を先行し2007年10月に拡大右半結腸切除術（D2）を施行した。肝・肺転移は認めず。術中所見として，腹膜播種を認めなかったが，傍大動脈周囲から側方リンパ節にかけて連続する著明なリンパ節腫大を認めた。病理組織学的に大腸癌は，粘液癌（muc＞tub2），pSS, ly3, v1, pN2 [#211 (4/4), #221 (9/9), #201 (0/3), #202 (0/3)], M1 [#216 (1/1), #206 (1/1)], pStage Ⅳであった。できる限り積極的な治療と仕事を続けたいという患者の意向に沿い，12月より一次治療としてBV (5 mg/kg, day 1, q2w)＋mFOLFOX6 (L-OHP 85 mg/m^2 day 1, *l*-LV 200 mg/m^2 day 1, 5-FU 400 mg/m^{2}急速静注, 5-FU 2,400 mg/m^{2}持続静注, q2w) を開始。腫瘍マーカーは減少，遠隔リンパ節転移も2サイクル後にPR in し（Fig. 2），PS 0で良好なQOLを維持しつつ，計19サイクル投与継続。有害事象は好中球減少 grade (G) 3，しびれG2であった。2009年7月に右肺門部リンパ節転移巣が出現し，CA19-9の上昇もみられPDとなり，K-ras遺伝子野生型を確認後，二次治療としてcetuximab（初回は400 mg/m^2，2回目以降は250 mg/m^{2}で毎週投与）＋FOLFIRI（CPT-11 150 mg/m^2 day 1, *l*-LV 200 mg/m^2 day 1, 5-FU 400 mg/m^{2}急速静注，5-FU 2,400 mg/m^{2}持続静注，q2w）に変更し6サイクル施行，有害事象は好中球減少G3，皮診G2，食欲不振G2であった。3か月後にCTにて両側鼠径リンパ節転移出現を認め，三次治療としてBV（10 mg/kg）＋FOLFIRIに変更し5サイクル施行，有害事象は好中球減少G3，蛋白尿G1，下痢G1であった。2か月半後に腹部リンパ節はわずかに縮小した（Fig. 3）が，鼠径リンパ節が増大したためBV（10 mg/kg）＋mFOLFOX6に変更，5サイクル施行し（Fig. 4）有害事象は蛋白尿G1であった。その2か月後に皮膚転移が出現するも，CT画像上，鼠径リンパ節，腹部リンパ節には変化なく（Fig. 5），皮膚転移，鼠径リンパ節転移に対して放射線治療（40 Gy/20 Fr）を施行した。その1か月後に右大腿部の疼痛，会陰部の帯状疱疹が出現し，抗ウイルス剤を投与した。その6か月後には腹腔内リンパ節転移増大による腸閉塞が認められ，best supportive careを施行し，術後31か月で永眠された。なお，皮膚転移，鼠径リンパ節転移に対し放射線治療を行うまで休薬などは行わず，化学療法が遂行可能であった。

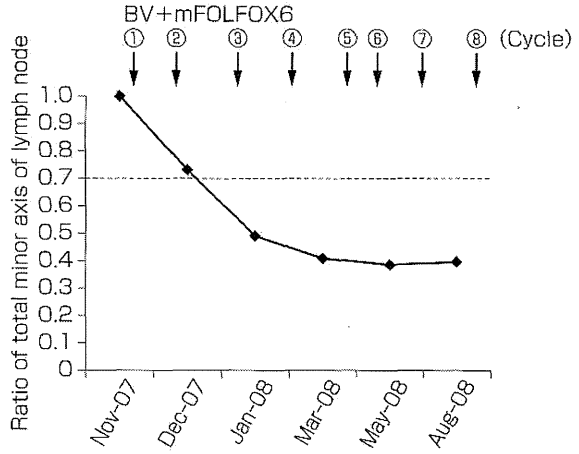

Fig. 2 Response rate in RECIST criteria
PR was achieved after 2 cycles.

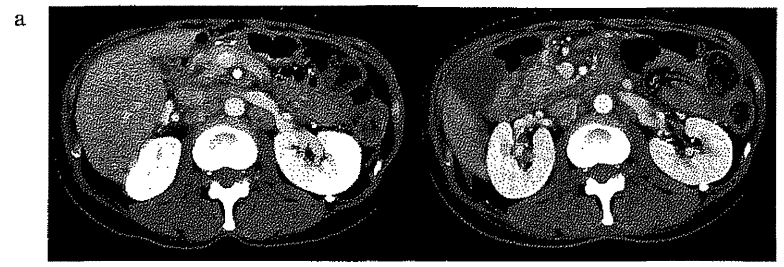

Fig. 3 Para-aortic lymph node metastasis was decreased slightly after chemotherapy.
a: Before chemotherapy [BV (10 mg/kg)+FOLFIRI].
b: After chemotherapy [BV (10 mg/kg)+FOLFIRI)].

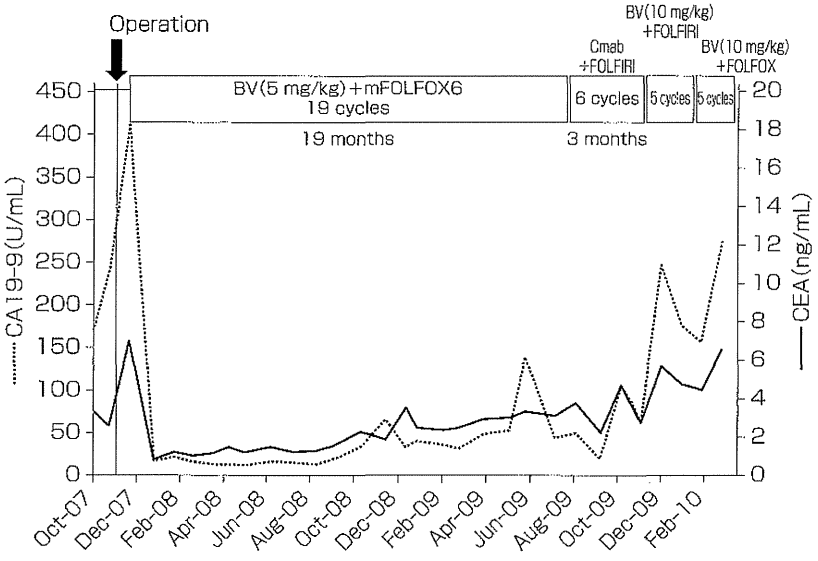

Fig. 4 Therapeutic course and CEA and CA19-9 level after operation

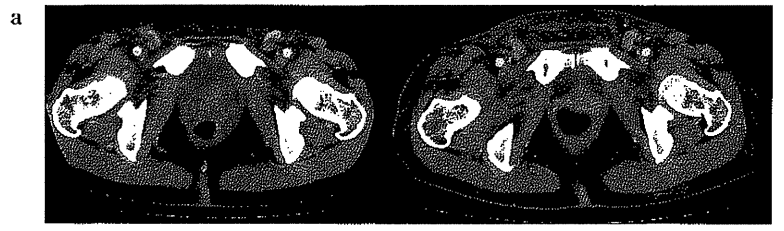

Fig. 5 Bilateral inguinal lymph node metastasis was no change after chemotherapy.
a: Before chemotherapy [BV (10 mg/kg)+FOLFOX].
b: After chemotherapy [BV (10 mg/kg)+FOLFOX].

Ⅱ. 考　察

大腸癌における遠隔リンパ節は領域外リンパ節に相当し，その転移は大腸癌取扱い規約（第7版）ではM1と定義される。遠隔リンパ節転移の頻度（1998年）は3.5%（190例/5,364例）[1]と比較的まれであり，CTV，MRI，PET/CTなどにて診断される。1997年の第44回大腸癌研究会アンケート調査によると#216転移率はS状結腸癌2.1%，直腸癌1.9%であり，それらの症例の臨床的特徴としては壁深達度が深く，低分化型腺癌・粘液癌・印環細胞癌の頻度が高く，高度脈管侵襲やリンパ節転移個数も多く認められ，さらに肝転移31%，腹膜播種は21%に認められ，57%が根治度Cであった。このことから#216郭清効果の意義はほとんどないと考えられ，化学療法を中心とした集学的治療が有効であると考えられるが，それを結論付けるためには症例の集積，RCTが必要である[2]。進行・再発大腸癌に対する化学療法は5-FU，L-OHP，CPT-11をkey drugとし，この3剤を使うこ

とにより20か月以上のMSTが得られるとされ[3]，これに分子標的薬を組み合わせることにより，さらに長い25か月以上のMSTが得られることが報告されている。BV併用療法は一次治療[4]，二次治療[5]としてOS延長が確認され，本邦の大腸癌治療ガイドライン2010年版[6]においても推奨されており，最近ではML18147試験で一次治療PD後の二次治療継続投与によりOSおよびPFSの有意な延長が確認された[7]。一方，二次治療以降でのBV再投与の際の用量増量についてのエビデンスは現在のところ確立しておらず，本邦においてL-OHP，BV既治療進行再発大腸癌に対する二次治療BV併用FOLFIRI療法におけるBV至適投与量の第Ⅲ相ランダム化比較試験（EAGLE study）が行われており，その結果が待たれるところである。本症例は結腸癌大動脈周囲リンパ節転移という遠隔リンパ節のみに転移が認められた，予後不良の比較的まれな症例であるが，一次治療でPDとなったBV＋FOLFOX療法でもBVを増量し再投与することで，31か月という長期生存を得た。これは一次治療が19か月継続できたこと，またその後も腫瘍血管形成における促進因子であるVEGFを継続的に阻害したことが寄与したと考えられる。二次治療以降のBV増量投与による重篤な副作用（高血圧，蛋白尿，出血，消化管穿孔，血栓など）の発現を認めなかったことから，二次治療以降でもBV増量による再投与は検討される治療法の一つになると考えられる。本症例では腫瘍のK-ras遺伝子が野生型であったことから，二次治療として抗EGFR抗体薬を選択したが，今後はML18147試験の結果を踏まえて，K-ras遺伝子変異の有無にかかわらずBVの一次，二次継続治療も考慮される。皮膚転移は血行性，リンパ行性に生じる末期癌の一症状であるが，最後まで仕事を続けたいという患者の希望がかなえられ，終末期でも治療ができた貴重な症例と考えられた。

本論文の要旨は第48回日本癌治療学会総会（2010年10月，京都市）にて報告した。

文　献

1) 大腸癌研究会/編：大腸癌取扱い規約．改訂第7版，金原出版，東京，2010.
2) 正木忠彦，武藤徹一郎，安富正幸：大動脈周囲リンパ節転移の実態：第44回大腸癌研究会アンケート調査報告．日本大腸肛門病会誌　**50**(5)：318-330，1997.
3) Grothey A, Sargent D, Goldberg RM, *et al*: Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol*　**22**(7)：1209-1214，2004.
4) Hurwitz H, Fehrenbacher L, Novotny W, *et al*: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*　**350**(23)：2335-2342，2004.
5) Giantonio BJ, Catalano PJ, Meropol NJ, *et al*: Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol*　**25**(12)：1539-1544，2007.
6) 大腸癌研究会/編：大腸癌治療ガイドライン．医師用2010年版，金原出版，東京，2010，p26.
7) Arnold D, Andre T, Bennouna J, *et al*: Bevacizumab (BEV) plus chemotherapy (CT) continued beyond first progression in patients with metastatic colorectal cancer (mCRC) previously treated with BEV plus CT: results of a randomized phase Ⅲ intergroup study (TML study). *2012 ASCO Annual Meeting, J Clin Oncol*　**30**(18s)：abstr #CRA3503，2012.

LIVER TRANSPLANTATION 20:298–310, 2014

ORIGINAL ARTICLE

Risk Factors for Alcohol Relapse After Liver Transplantation for Alcoholic Cirrhosis in Japan

Hiroto Egawa,[1] Katsuji Nishimura,[2] Satoshi Teramukai,[3] Masakazu Yamamoto,[1] Koji Umeshita,[4] Hiroyuki Furukawa,[5] and Shinji Uemoto[6]

[1]Departments of Surgery and [2]Psychiatry, Tokyo Women's Medical University, Tokyo, Japan; [3]Innovative Clinical Research Center, Kanazawa University, Kanazawa, Japan; [4]Department of Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan; [5]Department of Surgery, Asahikawa Medical University, Asahikawa, Japan; and [6]Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Alcoholic liver cirrhosis (ALC) is an established indication for liver transplantation (LT). Most LT procedures in Japan are living donor liver transplantation (LDLT) because of an extreme shortage of deceased donors. Social circumstances enabling LDLT could be favorable for preventing relapse. The aims of this retrospective study were to analyze the outcomes of LDLT for ALC and to evaluate risk factors for relapse in this cohort. One hundred ninety-five subjects underwent LT [LDLT (n = 187), deceased donor LT (n = 5), or domino LT (n = 3)] for ALC in Japan from November 1997 to December 2011. Risk factors for alcohol relapse and the impact of relapse on outcomes were analyzed for 140 patients after the exclusion of 26 patients who died in the hospital and 29 patients without information about alcohol relapse. The incidence of alcohol consumption after LT was 22.9%. The risk factors for patient survival were a donor age $\geq$ 50 years ($P < 0.01$) and a Model for End-Stage Liver Disease score $\geq$ 19 ($P = 0.03$). The 10-year patient survival rates were 21.9% and 73.8% for patients who had relapsed and patients who had not relapsed 18 months after LT, respectively ($P = 0.01$). The relapse rates were 50.0%, 34.5%, 13.3%, 19.7%, and 14.3% for patients who had received livers from parents, siblings, spouses, sons/daughters, and deceased or domino donors, respectively. A history of treatment for psychological diseases other than alcoholism before LT was a significant indicator for the risk of recidivism ($P = 0.02$), and noncompliance with clinic visits after LT and smoking after transplantation were promising indicators for the risk of recidivism ($P = 0.06$, and $P = 0.05$, respectively). Preoperative alcohol consumption was not a risk factor. In conclusion, rather than selecting patients on the basis of preoperative alcohol use, we should provide sociomedical support to improve adherence after LT for ALC in Japan. ***Liver Transpl 20:298-310, 2014.*** © **2013 AASLD.**

Received August 9, 2013; accepted November 17, 2013.

See Editorial on Page 255

Alcoholic liver cirrhosis (ALC) is the second most common indication for deceased donor liver transplantation (DDLT) for chronic liver disease in the Western world. In Japan, following cholestatic liver diseases and viral cirrhosis, ALC is the third most common indication.[1] Most liver transplantation (LT) in Japan involves living donors because of an extreme shortage of deceased donors.

Medical professionals have made considerable efforts to prevent graft loss secondary to the recurrence of the original disease; for example, they provide antiviral therapies to patients with hepatitis B or

Abbreviations: ABO-I AMR, ABO blood type incompatibility–related antibody-mediated rejection; ALC, alcoholic liver cirrhosis; CI, confidence interval; CTP, Child-Turcotte-Pugh; DIC, disseminated intravascular coagulation; DDLT, deceased donor liver transplantation; GRWR, graft/recipient weight ratio; HRAR, high-risk alcohol relapse; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; SLVR, standard liver volume ratio.

The authors of this article have no conflicts of interest to disclose as described by *Liver Transplantation.*

Address reprint requests to Hiroto Egawa, M.D., Ph.D., Department of Surgery, Tokyo Women's Medical University, 8-1 Kawada-Cho, Shinjuku-Ku, Tokyo 162-8666, Japan. Telephone: +81-(3)-3358-8111; FAX: +81-(3)-5269-7508; E-mail: egawa@ige.twmu.ac.jp

DOI 10.1002/lt.23797
View this article online at wileyonlinelibrary.com.
LIVER TRANSPLANTATION.DOI 10.1002/lt. *Published on behalf of the American Association for the Study of Liver Diseases*

hepatitis C, and they modify patient selection and organ distribution for patients with hepatocellular carcinoma. A patient with ALC may return to a pattern of alcohol consumption, which potentially can damage the transplanted liver and affect compliance with the immunosuppressive regimen and follow-up appointments; this may put the graft at risk.[2] Hence, selection criteria for predicting alcohol relapse from preoperative data and postoperative education and support to keep patients away from recidivism have been strengthened.[2-12]

In 1990, Bird et al.[3] reported the usefulness of an abstinence period of at least 6 months. Since then, the 6-month rule has been the most widely used criterion.[4-8] However, the length of abstinence before transplantation has not predicted alcohol relapse in some studies.[2,9,10] DiMartini et al.[11] found that each additional month of pretransplant sobriety lowered the risk of posttransplant drinking by 33%; however, they could not identify a specific length of pretransplant sobriety that predicted abstinence. Tandon et al.[12] obtained similar results in 2009.

De Gottardi et al.[13] applied a high-risk alcohol relapse (HRAR) scale,[14] which was originally designed to predict recidivism in nontransplant patients after alcohol rehabilitation, to the prediction of alcohol relapse after transplantation, and they found that an HRAR score > 3 was associated with harmful relapse. However, the independent predictive ability of the HRAR score for posttransplant recidivism remains controversial.[15] Familial and social support has also been reported to be important for preventing alcohol relapse.[10,16]

In DDLT, organs are considered to be a public resource that should be shared fairly and effectively. Hence, alcohol relapse could be considered a reason for transplant units and public opinion to deny transplantation. In living donor liver transplantation (LDLT), healthy relatives donate their organs to the patients. The conditions for alcohol relapse may be different after LDLT versus DDLT. For example, the relapse rate might be lower when patients are being watched by relatives, including donors; in such cases, LDLT might be favorable. The only report on LDLT for ALC came from a single-center study that showed a low recidivism rate for 13 patients selected according to very strict criteria.[7] No studies of recidivism after LDLT have been performed with a large cohort.

The aims of this study were (1) to analyze the outcomes of LDLT for ALC, (2) to find risk factors for patient survival, and (3) to evaluate risk factors for alcohol relapse in this cohort.

PATIENTS AND METHODS

LT for ALC was performed for 197 patients at 38 institutions according to the registry of the Japanese Liver Transplantation Society. These 38 institutions were sent questionnaires that asked about institutional policies for patient selection, patient characteristics, the preoperative alcohol consumption status of patients, treatments, postoperative living conditions, and clinical courses after transplantation for patients who underwent LT for ALC. Patient characteristics included the following: disease, age, sex, and blood types of the recipient and donor; relationship between the recipient and the donor; Model for End-Stage Liver Disease (MELD) score[17]; Child-Turcotte-Pugh (CTP) score[18]; hepatitis C, hepatitis B, and hepatocellular carcinoma status; smoking status; living or not living with the family or donor; occupational status; and marital status. The alcohol consumption status before transplantation included the duration of drinking, the amount of ethanol per day, the number of inpatient treatments for alcoholism, a history of psychiatric problems other than alcoholism, and the length of abstinence before transplantation. Treatment data included the graft/recipient weight ratio (GRWR), the standard liver volume ratio (SLVR), and follow-up by psychiatrists. Postoperative living conditions included the smoking status, living with family, living with the donor, and occupational status. The clinical course included alcohol relapse as well as rejection, surgical and infectious complications, renal dysfunction, malignancies, noncompliance with clinic visits (3 absences without notice), and follow-up by psychiatrists. Liver biopsy was performed on demand. Histological findings of liver biopsy specimens were collected from medical records. Data on mortality and causes of death were also collected. This retrospective, multicenter study was approved by the human ethics review board of Tokyo Women's Medical University (2417 on February 29, 2012) as the place of data collection and analysis in accordance with the Declaration of Helsinki (as revised in Seoul, Korea in October 2008).

Selection Criteria for LT for ALC

The indication for LT for ALC was based on a patient's history of alcohol consumption and clinical and laboratory findings determined before LT at each institution. At all institutions, psychiatrists interviewed the patients and their families and confirmed the absence of substance abuse, including alcohol abuse and dependence, and the presence of an agreement indicating the intention of lifetime abstinence after LT. Since 1997, the Assessment Committee of Indication for Transplantation has assessed patients and determined their priority on the waiting list for DDLT in Japan. Currently, this committee accepts only patients with ALC for DDLT who score 2 or lower on the HRAR scale.[14]

Pretransplant Alcohol Use and Other Psychosocial Variables

A history of alcohol intake was also obtained, and this included the duration of drinking, types and amounts of alcohol consumed, and previous treatment history. The HRAR score was calculated. This score consists of 3 variables: the duration of heavy drinking, the number of drinks per day, and the number of earlier inpatient treatments for alcoholism.[14] Other demographic and psychosocial information collected during the

pretransplant evaluation included the current or prior use of other substances, the diagnosis of substance use disorders and depressive or anxiety disorders, and treatment for psychiatric disorders. Pretransplant abstinence was defined as the time between the last consumption of alcohol and the date of the transplant.

Posttransplant Alcohol Use Outcomes

The diagnosis of alcohol relapse was based on patient self-reports, reports by the patient's relatives and friends, comments by the primary care physician, and relevant laboratory or histological findings, and relapse was divided into 2 stages: recidivism and harmful relapse. Recidivism was defined as any alcohol intake after transplantation, and the onset time was reported. Harmful relapse was defined as declared alcohol consumption associated with the presence of alcohol-related damage, either physical (including histological features of alcohol liver injury on liver biopsy specimens and abnormal values on biochemical examinations for which etiologies other than ethanol were ruled out) or mental.[13] The diagnosis of harmful relapse was made at the last follow-up during this study, and the onset time was not available.

Three alcohol relapse patterns were defined [adapted from a study by DiMartini et al.[11]]: (1) relapse within 6 months of transplantation, (2) frequent use (4 drinking days per week), and (3) binge use (72 g of ethanol or more for men and 48 g of ethanol for women per day).

Statistical Analysis

Survival curves were constructed with the Kaplan-Meier method. In univariate and multivariate analyses, the log-rank test and Cox proportional hazards regression analysis were used to evaluate the association between patient characteristics and overall survival. Receiver operating characteristic curves were plotted, and areas under the curve were calculated to assess the optimal cutoff values for the MELD score, GRWR, and SLVR in the analysis of prognostic factors for patient survival.

The log-rank test and Cox proportional hazards regression analysis were also used to evaluate the association between patient characteristics and the incidence of recidivism in univariate and multivariate analyses. The incidence of harmful relapse was compared by means of the chi-square test, and multivariate logistic regression analysis was used to evaluate the association between patient characteristics and harmful relapse.

JMP 10.0 (SAS Institute, Inc., Cary, NC) was used for the statistical analysis.

RESULTS

Patients

Clinical and laboratory data were available for 195 patients who underwent LT at 36 of 38 institutions between November 1997 and December 2011. Among the 195 patients, 26 patients died before discharge after transplantation. Among the 169 patients who were discharged, information about alcohol relapse was available for 140 patients, and information about harmful relapse was available for 139 patients. The length of the follow-up period ranged from 3 to 4962 days with a median of 1319 days.

An analysis of prognostic factors for survival was performed for 195 patients. An analysis of risk factors for recidivism and the impact of recidivism on patient survival was performed for 140 patients, and an analysis of risk factors for harmful relapse and the impact of harmful relapse on patient survival was performed for 139 patients (Fig. 1).

Demographic data for the 195 patients are shown in Table 1. The MELD score ranged from 6 to 48 with a median value of 20. For most patients, the CTP score was C. The recipients' ages ranged from 25 to 69 years with a median age of 35 years. The donors' ages ranged from 17 to 65 years with a median age of 52 years. The blood type combination was identical for 127 patients, compatible for 49 patients, incompatible for 17 patients, and unknown for 2 patients. Six patients had a hepatitis C infection, 4 patients were positive for hepatitis B DNA, and 47 had hepatocellular carcinoma. GRWR ranged from 0.44% to 2.4% with a median value of 0.88%. SLVR ranged from 23.6% to 126% with a median value of 46.0%. Sixty-nine patients were male, and 195 patients were female. One hundred eighty-seven patients underwent LDLT, 5 patients underwent DDLT, and 3 patients had domino LT.

Institutional Policy of Patient Selection for LT for ALC in the Setting of LDLT

A period of abstinence of at least 6 months before LT was absolutely mandated at 21 institutions, was not required at all at 4 institutions, and was preferred but ignored in life-threatening cases at 11 institutions. The HRAR score was used for patient selection for LDLT at 13 institutions and was not used at 23 institutions.

Analysis of Prognostic Factors for Patient Survival

In univariate analyses, prognostic factors that were significantly and favorably associated with patient survival were a low MELD score (<19 versus ≥ 19) and a low donor age (<50 years versus ≥ 50 years). Both the MELD score and the donor age were also significant factors in the multivariate analysis (Tables 1 and 2).

Morbidity and Mortality

Postoperative comorbidities are shown in Table 3. The major complications were biliary complications (n = 41), cytomegalovirus infections (n = 38), bacterial infections (n = 37), acute cellular rejection (n = 34), and intra-abdominal hemorrhaging (n = 26). The causes of deaths before discharge for 26 patients are shown in Table 4. The most common causes were

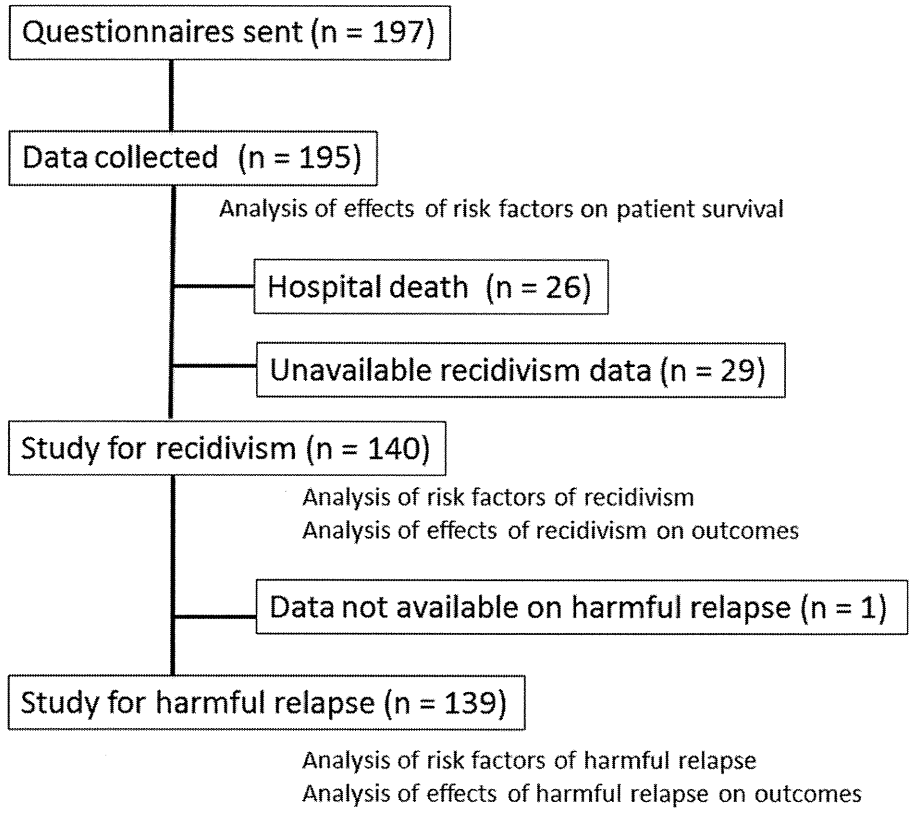

Figure 1. Patient enrollment and inclusion in our analysis. Questionnaires were sent to 38 centers for 197 patients. Clinical data were collected for 195 patients from 36 centers, and risk factors for patient survival were analyzed for these patients. Risk factors for recidivism and the impact of recidivism on patient survival were analyzed for 140 patients after 55 patients were excluded (26 who died in the hospital and 29 without data about recidivism). Data on harmful relapse were obtained and analyzed for 139 patients.

infectious complications (n = 10), small-for-size syndrome (n = 3), acute cellular rejection (n = 3), and hepatic artery thrombosis (n = 2).

The causes of death after discharge for 23 patients and their survival periods are shown in Table 5. Six patients died because of infectious complications; 7 died because of malignancies, including recurrent hepatocellular carcinoma; 2 died because of cerebral or myocardial vascular complications; and 1 died because of chronic rejection. Two patients died because of ALC on postoperative days 2526 and 4641.

There were 5 de novo tumors, including 2 gastric cancers and 3 squamous cell cancers. All 5 patients with these malignancies were abstinent and did not smoke after transplantation. Interestingly, however, all 5 patients had smoked before transplantation and quit after LT. The incidence of de novo malignancies increased as the quantity of daily drinking before transplantation increased on the HRAR scale [2.4% (1/41) with 108 g of ethanol or less each day, 6.1% (2/33) with >108 g-<204 g of ethanol each day, and 9.1% (2/22) with 204 g of ethanol or more each day], although there was no significant relationship ($P = 0.50$).

Risk Factors for Alcohol Relapse

The significant risk factors for recidivism were a positive history of treatment for psychological diseases other than alcoholism before transplantation, an absence of a marital history, noncompliance with clinic visits after transplantation, and smoking after transplantation according to univariate analyses adjusted by the time of onset (Table 6). The significant risk factors for harmful relapse were living alone before LT, no marital history before LT, and noncompliance with clinic visits after LT (Table 6). The HRAR score had no relationship with the incidence of recidivism or harmful relapse. Six months of abstinence before LT had no significant impact. Abstinence for 24 months or longer decreased the incidence of harmful relapse (to 3.3%), but this difference was not significant. The occupational status had no impact on the incidence.

Risk factors for recidivism and harmful relapse that were significant ($P < 0.05$) in the univariate

TABLE 1. Influence of Pretransplant Risk Factors on Patient Survival in 195 Patients With ALC: A Log-Rank Analysis

		Patient Survival (%)				
Characteristic	Patients (n)	1 Year	3 Years	5 Years	10 Years	Log-Rank *P* Value
Entire cohort	195	82.5	78.4	74.5	50.4	
MELD score						0.04*
≥19	103	76.5	72.0	72.0	40.1	
<19	84	89.2	86.7	82.6	49.5	
Unknown	8	—	—	—	—	
CTP score						0.17
A	5	80.0	80.0	53.3	—	
B	43	83.7	83.7	79.0	67.7	
C	141	82.2	77.4	76.2	40.5	
Unknown	6	—	—	—	—	
Recipient age						0.96
≥50 years	117	82.0	77.1	75.7	66.0	
<50 years	78	81.9	80.3	78.3	39.5	
Donor age						0.01*
≥50 years	44	81.5	72.8	67.9	—	
<50 years	151	83.0	80.0	78.0	64.0	
Blood type combination						0.17
Identical	127	83.4	79.6	76.6	46.3	
Compatible	49	83.6	79.3	76.5	41.2	
Incompatible	17	68.2	64.2	64.2	—	
Unknown	2	—	—	—	—	
Hepatitis C						0.65
Yes	6	83.3	83.3	—	—	
No	186	81.6	77.9	75.2	52.3	
Unknown	3	—	—	—	—	
Hepatitis B DNA–positive						0.65
Yes	4	100.0	100.0	100.0	—	
No	190	81.4	77.8	75.1	51.4	
Unknown	1	—	—	—	—	
Hepatocellular carcinoma						0.97
Yes	47	87.1	77.7	74.1	60.5	
No	148	81.0	78.6	76.2	49.2	
GRWR						0.16
≥0.7%	156	84.5	80.4	77.6	5.4	
<0.7%	34	70.6	67.4	67.4	—	
Unknown	5	—	—	—	—	
SLVR						0.08
≥30%	179	82.6	78.8	75.9	50.2	
<30%	7	57.1	57.1	57.1	—	
Unknown	9	—	—	—	—	

*$P < 0.05$.

TABLE 2. Multivariate Analysis of Pretransplant Risk Factors for Patient Survival in 195 Patients With ALC: A Proportional Hazards Analysis

Risk Factor	Risk Ratio	95% CI	*P* Value
Donor age ≥ 50 years	2.33	1.28-4.13	<0.01*
MELD score ≥ 19	1.91	1.07-3.55	0.03

*$P < 0.05$.

analysis were chosen for the multivariate analysis. A history of treatment for psychological diseases other than alcoholism before transplantation was a significant indicator of the risk of recidivism, and noncompliance with clinic visits after transplantation and smoking after transplantation were promising indicators of the risk of recidivism ($P = 0.06$ and $P = 0.05$, respectively; Table 7). Noncompliance with clinic visits was a significant indicator of the risk of harmful relapse.

The rates of recidivism were similar for patients living with donors (22.9% before LT and 27.9% after LT) and patients not living with donors (26.4% before LT and 25.9% after LT). Recidivism was high when the donors were parents (50.0%) or siblings (34.5%), but it was much lower when the donors were children (19.7%), spouses (13.3%), or nonrelatives (14.3%), although the difference was not

significant (Table 6). Similarly, the incidence of harmful relapse was much higher, but not significantly so, when the donors were parents or siblings versus when the donors had other relationships with the recipients (Table 6).

TABLE 3. Comorbidities After Transplantation in 195 Patients

Comorbidities	Patients (n)
Biliary complications	41
Cytomegalovirus diseases	38
Bacterial infection	37
Acute cellular rejection	34
Intra-abdominal hemorrhage	26
Malignancies*	13
Vascular complications	12
Fungal infection	12
Permanent dialysis	8
Steroid-resistant acute cellular rejection	5
Chronic rejection	2

*Recurrence of hepatocellular carcinoma (n = 8), gastric cancer (n = 2), lung squamous cell cancer (n = 1), tongue squamous cell cancer (n = 1), and frontal sinus squamous cell cancer (n = 1).

TABLE 4. Causes of Hospital Deaths

Cause of Death	Patients (n)
Infection	10
Small-for-size syndrome	3
Acute cellular rejection	3
Chronic rejection	1
Hepatic artery thrombosis	2
Portal vein flow insufficiency	1
Cerebral hemorrhage	1
ABO-I AMR	1
Graft-versus-host disease	1
Multiorgan failure	1
Biliary stenosis	1
Graft injury	1

Impact of Alcohol Consumption After LT on Patient Survival

The survival rates were compared for recidivist patients and abstinent patients 18 months after LT. Five patients for whom the time of relapse was not obtained and 10 patients who had died within 18 months of LT were excluded from this analysis. The survival rates were 100.0%, 94.7%, 89.5%, 65.7%, and 21.9% at 1, 3, 5, 7, and 10 years, respectively, for recidivist patients and 100.0%, 98.6%, 96.4%, 92.7%, and 73.8% at 1, 3, 5, 7, and 10 years, respectively, for abstinent patients. There was a significant difference in survival ($P = 0.01$; Fig. 2).

Impact of Alcohol Consumption Status on Harmful Relapse

The impact of an early onset of drinking, frequent drinking, and the consumption of large amounts of alcohol after LT on the incidence of harmful relapse was analyzed in 32 recidivist patients. The incidence of harmful relapse was higher for patients who consumed alcohol 4 days or more per week (88.9%) versus patients who drank less frequently (35.7%, $P = 0.008$; Table 8), and it was higher for patients who binged (100%) versus patients who drank less (25%, $P = 0.002$; Table 8). One patient showed all 3 patterns of harmful drinking, and 5 patients showed 2 of the 3 patterns.

Histological Changes in the Liver After LT

Liver biopsy was performed for 20 recidivist patients and 53 abstinent patients. Results from biopsy samples obtained before hospital discharge were included. The incidence of fatty changes was greater in the recidivism group (45.0%) versus the abstinent group (13.2%; Table 9). In contrast, the incidence of rejection was greater in the abstinent group (30.6%) versus

TABLE 5. Causes of Death After Discharge

Cause of Death	Patients (n)	Survival Period (Days)
Infection	6	3802, 2256, 662, 517, 328, 295
Hepatocellular carcinoma recurrence	5	2588, 2057, 422, 357, 300
Gastric cancer	1	2309
Lung cancer	1	195
Cholangitis	2	3302, 1414
Alcoholic cirrhosis	2	2526, 4641
Arachnoid hemorrhage	1	246
Myocardial infarction	1	2983
DIC/lung edema	1	1990
Chronic rejection	1	528
Accident	1	3361
Intra-abdominal hemorrhage	1	373

TABLE 6. Univariate Analysis of Risk Factors for Recidivism and Harmful Relapse After Transplantation

Risk Factor	Patients (n)	Recidivism: Log-Rank Test [n/N (%)]*	*P* Value	Patients (n)	Harmful Relapse: Chi-Square Test [n/N (%)]†	*P* Value
Before transplantation						
HRAR score			0.48			0.24
0	8	1/8 (12.5)		8	1/8 (12.5)	
1	25	8/25 (32.0)		25	6/25 (24.0)	
2	40	8/40 (20.0)		40	4/40 (10.0)	
3	16	4/16 (25.0)		15	3/15 (20.0)	
4	9	1/9 (11.1)		9	0/9 (0.0)	
Unknown	42	—		42	—	
Duration of heavy drinking			0.41			0.50
≥25 years	41	9/41 (22.0)		41	4/41 (9.8)	
<11->25 years	32	7/32 (21.9)		31	6/31 (19.4)	
≤11 years	31	9/31 (29.0)		31	7/31 (22.6)	
Unknown	36	—		36	—	
Daily alcohol consumption‡			0.96			0.47
≤9 g	43	11/43 (25.6)		43	9/43 (20.9)	
<9->17 g	36	8/36 (22.2)		36	4/36 (11.1)	
≥17 g	23	5/23 (21.7)		22	3/22 (13.6)	
Unknown	38	—		38	—	
Pretransplant abstinence			0.39			0.68
≥6 months	100	19/100 (19.0)		99	13/99 (13.1)	
<6 months	31	9/31 (29.0)		31	5/31 (16.1)	
Unknown	9	—		9	—	
Pretransplant abstinence			0.77			0.19
≥24 months	31	5/31 (16.1)		30	1/30 (3.3)	
12-24 months	20	3/20 (15.0)		20	3/20 (15.0)	
6-12 months	49	11/49 (22.4)		49	9/49 (18.4)	
<6 months	31	9/31 (29.0)		31	5/31 (16.1)	
Unknown	9	—		9	—	
History of treatment for psychiatric diseases other than alcoholism			<0.01‡			0.17
Yes	9	5/9 (55.6)		9	3/9 (33.3)	
No	125	27/125 (21.6)		125	18/125 (14.4)	
Unknown	6	—		5	—	
Recipient sex			0.16			0.73
Male	88	23/88 (26.1)		88	14/88 (15.9)	
Female	52	9/52 (17.3)		51	7/51 (13.7)	
Smoking			0.12			0.43
Smoking	46	15/46 (32.6)		46	10/46 (21.7)	
No history	24	5/24 (20.8)		24	3/24 (12.5)	
Quit	59	8/59 (13.6)		58	6/58 (10.3)	
Unknown	11	—		11	—	
Living			0.08			0.03‡
With family	122	27/122 (22.1)		121	16/121 (13.2)	
Alone	9	4/9 (44.4)		9	4/9 (44.4)	
Unknown	9	—		9	—	
Marital status			0.04‡			0.04‡
Stable partner	106	24/106 (22.6)		105	15/105 (14.3)	
Widowed/divorced	10	1/10 (10.0)		10	1/10 (10.0)	
No marital history	13	6/13 (46.2)		13	5/13 (38.5)	
Unknown	11	—		11	—	
Living with donor			0.99			0.28
Yes	70	16/70 (22.9)		69	8/69 (11.6)	
No	53	14/53 (26.4)		53	11/53 (20.8)	
Unknown	17	—		17	—	
Occupational status			0.41			0.85
No	42	9/42 (21.4)		41	7/41 (17.1)	
Part time	13	2/13 (15.4)		13	1/13 (7.7)	
Full time	64	16/64 (25.0)		64	10/64 (15.6)	
Unknown	21	—		21	—	

TABLE 6. *Continued*

Risk Factor	Patients (n)	Recidivism: Log-Rank Test [n/N (%)]*	*P* Value	Patients (n)	Harmful Relapse: Chi-Square Test [n/N (%)]†	*P* Value
After transplantation						
Noncompliance with clinic visits			<0.01‡			0.03§
Yes	8	4/8 (50.0)		7	4/7 (57.1)	
No	131	8/131 (6.1)		131	17/131 (13.0)	
Unknown	1	—		1	—	
Followed by psychiatrists			0.78			0.78
Yes	29	7/29 (24.1)		29	5/29 (17.2)	
No	108	25/108 (23.1)		107	16/107 (15.0)	
Unknown	3	—		3	—	
Smoking			<0.01‡			0.09
Yes	24	11/24 (45.8)		24	7/24 (29.2)	
No	73	12/73 (16.4)		72	7/72 (9.7)	
Unknown	43	—		43	—	
Living			0.25			0.07
With family	107	25/107 (23.4)		107	17/107 (15.9)	
Alone	8	4/8 (50.0)		8	3/8 (37.5)	
Unknown	25	—		24	—	
Living with donor			0.46			0.07
Yes	43	12/43 (27.9)		43	7/43 (16.3)	
No	58	15/58 (25.9)		57	12/57 (21.1)	
Unknown	39	—		39	—	
Occupational status			0.18			0.34
No	51	14/51 (27.5)		50	8/50 (16.0)	
Part time	14	4/14 (28.6)		14	4/14 (28.6)	
Full time	38	9/38 (23.7)		38	6/38 (15.8)	
Unknown	37	—		37	—	
Donors			0.07			0.07
Parent	6	3/6 (50.0)		6	3/6 (50.0)	
Sibling	29	10/29 (34.5)		29	8/29 (27.6)	
Son/daughter	61	12/61 (19.7)		61	4/61 (6.6)	
Nonrelative	7	1/7 (14.3)		7	1/7 (14.3)	
Spouse	30	4/30 (13.3)		29	3/29 (10.3)	
Nephew	3	1/3 (33.3)		3	1/3 (33.3)	
Cousin	1	0/1 (0.0)		1	0/1 (0.0)	
Brother-in-law	2	1/2 (50.0)		2	1/2 (50.0)	
Nephew-in-law	1	0/1 (0.0)		1	0/1 (0.0)	

*32/140 (22.9%).
†21/139 (15.1%).
One drink = 12 g of ethanol.
‡$P < 0.05$ (chi-square test)

the recidivism group (25.0%; Table 9). Alcoholic damage was found in 3 patients with recidivism.

Information on the presence or absence of acute cellular rejection after discharge was obtained from 130 patients. The incidence of rejection was 6.9% (2/29) for recidivist patients and 5.0% (5/101) for patients who were abstinent.

Patients for Whom Information on Alcohol Relapse Was Not Available

Twenty-nine patients for whom information on alcohol relapse was not available were excluded from the statistical analysis of alcohol relapse. To understand the impact of this exclusion on the results, we analyzed the overall survival and frequency of risks for recidivism for the 29 patients. There was no significant difference in overall survival between abstinent patients, relapsing patients, and patients of an unknown status (data not shown; $P = 0.09$, log-rank test). For abstinent patients, relapsing patients, and patients of an unknown status, the frequency of noncompliance with clinic visits was 3.7%, 12.5%, and 15.4%, respectively ($P = 0.03$); the frequency of smoking after LT was 17.5%, 47.8%, and 100.0%, respectively ($P < 0.001$); the frequency of no marital history was 7.1%, 19.3%,

TABLE 7. Multivariate Analysis of Risk Factors for Recidivism and Harmful Relapse

		Proportional Hazards Analysis	
Risk Factors for Recidivism	Risk Ratio	95% CI	*P* Value
History of treatment for psychiatric diseases other than alcoholism: yes versus no	5.15	1.26-17.78	0.02*
Marital status			
Stable partner	1.00	—	
Widowed/divorced	0.45	0.02-2.46	0.41
No marital history	1.24	0.34-4.99	0.75
Noncompliance with clinic visits: yes versus no	4.36	0.92-15.43	0.06
Posttransplant smoking: yes versus no	2.67	0.97-7.00	0.05

		Logistic Regression Analysis	
Risk Factors for Harmful Relapse	Odds Ratio	95% CI	*P* Value
History of treatment for psychiatric diseases other than alcoholism: yes versus no	5.15	1.26-17.78	0.02*
Marital status			
Stable partner	1.00	—	
Widowed/divorced	0.45	0.02-2.46	0.41
No marital history	1.24	0.34-4.99	0.75
Noncompliance with clinic visits: yes versus no	4.36	0.92-15.43	0.06
Posttransplant smoking: yes versus no	2.67	0.97-7.00	0.05
Pretransplant living: alone versus family	3.21	0.43-23.46	0.25
Pretransplant marital status			
Stable partner	1.00	—	
Widowed/divorced	0.31	0.01-2.32	0.28
No marital history	2.41	0.38-11.76	0.32
Noncompliance with clinic visits: yes versus no	16.32	2.56-149.34	0.004*

*$P < 0.05$.

and 4.2%, respectively ($P = 0.14$); and the frequency of a history of treatment for psychiatric diseases other than alcoholism was 3.9%, 15.6%, and 6.9%, respectively ($P < 0.001$). Although these 29 patients were less compliant with clinic visits than abstinent patients, 21 of the 29 patients visited the clinic regularly, 4 patients fell into noncompliance, 1 patient died, 1 patient changed hospitals, and the data for 2 patients were unknown. However, for 28 of the 29 patients (including 1 deceased patient), data for smoking as well as relapse data were not available.

Interactions Between Recipients Who Returned to Harmful Drinking and Related Donors

We hypothesized that interactions between a recipient who returns to harmful drinking and the family member who donated the liver might affect outcomes. Although we were not able to examine this directly, we compared the survival rates between recipients living with their donors and recipients who lived separately from their donors. The survival rates were 95.2%, 86.4%, 86.4%, 71.2%, and 63.3% at 1, 3, 5, 7, and 10 years, respectively, for recipients living with donors and 100.0%, 98.2%, 92.0%, 83.5%, and 41.8% at 1, 3, 5, 7, and 10 years, respectively, for recipients living without donors ($P = 0.66$). Although this result does not address the existence or absence of a change in the relationship after the onset of harmful drinking, if such changes do occur, they do not affect survival.

DISCUSSION

Patients undergoing LT for ALC must pledge to remain sober in order to protect the transplanted liver. However, not all recipients are able to maintain sobriety. Alcohol relapse can have a number of negative impacts, including (1) liver dysfunction secondary to alcohol toxicity, (2) noncompliance with medications or clinic visits, (3) rejection secondary to noncompliance, (4) graft failure secondary to rejection or alcohol toxicity, and (5) malignancies and cardiovascular diseases possibly related to smoking (which is highly associated with alcohol relapse). The perception that recipients will relapse may also decrease the willingness of others to donate organs.

Harmful Drinking and Impact

Reports have differed in both the definitions used for harmful drinking and its effects after LT. Schmeding