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ORIGINAL ARTICLE

Systematic grading of surgical complications in live liver donors according to Clavien's system

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Summary

The lack of consensus on how to evaluate surgical complications of donors in live donor liver transplantation (LDLT) and incoherence of cumulative data hampers efficient comparison of the outcome worldwide. We considered that the application of the internationally validated classification system introduced by Clavien in 2004 might be beneficial. Operative complications of 243 patients who underwent live donor hepatectomy for adult LDLT between January 1996 and October 2005 at the University of Tokyo were analyzed according to the system. Definitions for each grade in the system are: grade I, deviation from the normal postoperative course but without the need for therapy; grade II, complication requiring pharmacologic treatment; grade III, complication with the need for surgical, endoscopic or radiological intervention (IIIa/b: without/with the need for general anesthesia); grade IV, life-threatening complication requiring intensive care; grade V, death. Surgical morbidity was recognized in 67 donors (28%). No deaths occurred. The numbers of patients with complications were: grade I, 36 (15%); II, 10 (4%); IIIa, 12 (5%); IIIb, 9 (4%); IV, 0; V, 0. Six in IIIb underwent surgical repair for bile leakage. Clavien's system is simple and informative. It may serve as a common tool for the quality assessment in live liver donor surgery worldwide, and we propose its application whenever surgical complication of live donor is discussed.

Introduction

In countries where organ donation from deceased donors is scarce, such as most Asian countries including Japan, live donor liver transplantation (LDLT) remains the only means of saving patients with end-stage liver disease. The first case of LDLT was performed in Brazil, in December 1988 [1]. The procedure was chosen to circumvent the serious problem of organ shortage among pediatric patients. The first successful case was reported in Australia [2]. Since then, LDLT has spread worldwide, particularly in places where organ donation from deceased donors remains uncommon. In Japan, due to the limited numbers of decreased donor organ donation, LDLT is performed as the mainstream treatment for end-stage liver disease. The first pediatric case was performed in November 1989 and the first successful adult-to-adult LDLT was performed in 1994 [3]. Over 400 cases of LDLT are now performed annually in 51 centers in Japan [http://jlts.umin.ac.jp/Registry(2004).pdf (Abstract in English)].

Although donor safety is recognized as an absolute prerequisite in LDLT, mortalities following donor surgery have been reported. Between 1998 and 2003, two healthy adult volunteers died shortly after donating a partial liver graft in the United States [4]. One death in Japan was also recently reported [5]. Currently, the mortality rate among live liver donors in the United States is estimated to be 0.2–0.5% [6].

There are a few detailed reports on donor selection criteria and the medical workup process. More importantly,

the precise outcome of donor surgery in terms of surgical morbidity and mortality is unclear. This may be due to the current lack of consensus in the field on how to describe and grade surgical outcomes of live liver donors. This shortcoming results in the incoherence of both the act of reporting and the cumulative data reported, preventing a simple comparison of outcomes among different transplant centers worldwide which would further improve the donor care.

The classification system of surgical complications introduced by Clavien *et al.* in 1992 [7] was originally intended for procedures with relatively low morbidity. Since then, the classification system has undergone modifications to better address the complications specific to organ transplant recipients [8]. Ghobrial *et al.* [9] applied the classification to describe the morbidity in a small number of LDLT cases, both recipient and donor, and suggested that it might serve as the basis to assess outcome in the field. The classification system failed to gain popularity, however, partly due to the lack of validation in a large cohort of patients for its application in different countries and cultures where definitions of negative outcome vary significantly.

The modified version of the 'Clavien classification' presented in 2004 [10] has overcome this shortcoming. The current system is based on the use of therapeutic consequences, with a major emphasis on the risk and invasiveness of the therapy used to correct a complication, which is the most readily available and objective information regarding the postoperative course. Most importantly, its simplicity and objectivity have been evaluated with a cohort of over 6000 patients, and its acceptability and reproducibility have been validated by an international survey conducted in centers from each continent, in different cultural backgrounds, including surgeons at different levels of training. Applying such an objectively validated system for describing the outcome of live liver donor surgery might facilitate international comparisons beneficial for further improvement in donor care.

We herein present our selection criteria and surgical outcome of live liver donor and describe the surgical morbidity according to the modified Clavien classification system for the consistent description of surgical complications.

Patients and methods

Selection of live liver donor for LDLT at the University of Tokyo

Donation should be absolutely voluntary. Candidates must be between 20 and 65 years of age and either ABO blood type compatible or identical. Also, the potential donor should be within three degrees of consanguinity, or a spouse. Nondirected donation, the so-called 'Good Samaritan' or 'donor swap' in cases of ABO blood type incompatibility, is not accepted in any case. The majority of the donors, 146 (60%), were males. The most common familial relationship to the recipient recognized in the donor population was a son in 69 cases (28%), followed by a daughter in 36 cases (15%), wife in 30 cases (12%), brother in 29 cases (12%), sister in 20 cases (8%), husband in 17 cases (7%), father in 12 cases (5%), mother in 11 cases (5%) and nephew in 10 cases (4%). The mean age of the donors was 37 years (17–66 years) and the average body mass index was 22 [11–26].

The medical evaluation at our institution of live liver donors has been described in detail elsewhere [27]. To summarize, a computed tomography (CT) scan for preliminary volumetry is obtained and estimation of the available graft size is evaluated [28]. For the recipient, the standard liver volume is calculated as previously described using Urata's equation: standard liver volume $(cm^3) = 706.2 \times$ body surface area $(m^2) + 2.4$ [29]. Appropriate graft type is determined according to the algorithm previously described by Kokudo *et al.* [11]. Estimated graft volume must be <70% of total liver volume of the donor and it should be at least 40% of the recipient's estimated standard liver volume, or at least 35% when the Model for End-Stage Liver Disease score is 15 or less [11]. Indocyanine green retention test is then performed to confirm the hepatic reserve for major hepatectomy [12]. When eligibility is confirmed by the above preliminary evaluations, triple-phase abdominal CT scan with contrast medium is then acquired to obtain a three-dimensional reconstruction image of the vascular anatomy of the liver. The digital data are further analyzed to obtain the segmental volume drained by each tributary of the middle hepatic veins and portal veins with virtual hepatectomy simulation software (Hitachi Image Processing System, Version 0.7a, Patent no. 283191; Hitachi Ltd., Tokyo, Japan) [13], using a region-growing technique [14]. Graft type is determined according to the anatomical variations and the expected graft volume is estimated by the simulation.

Liver biopsy is performed when a fatty liver is suspected but not routinely. When the donor age is 40 years or older, additional cardiac evaluation and additional gastrointestinal workup are performed.

Surgical technique for LDLT

The surgical techniques for various types of donor operation have been described in detail previously [11,15–18]. In 83 (43%) cases, left lobe grafts were obtained, of which 78 (32%) were left hemi-liver graft with caudate lobe. In the remaining 160 (66%) cases, right lobe grafts were

obtained. Right hemi-liver graft without the middle hepatic vein was selected in 107 (44%) and right lateral sector graft was selected in 19 (8%). The mean graft size procured was 551 g, which corresponded to an average of 48% of the total liver volume of the donor. The average time for procurement, not including waiting time, was 8 h (range 4–12 h) with an estimated blood loss of 500 ml (range 100–1500 ml). The sum of intermittently performed vascular occlusion procedure, Pringle's maneuver [19], during parenchymal transaction averaged 66 min. Autologous blood for transfusion was prepared prior to surgery or by hemodilution immediately after the induction of general anesthesia in most cases. No patients required transfusion of packed red blood cells either intra- or postoperatively.

Analysis and classification of surgical complications

Between January 1996 and October 2005, 348 cases of LDLT were performed at the University of Tokyo. Among them, 243 patients underwent live donor hepatectomy for adult-to-adult LDLT. Clinical records of these patients were retrospectively analyzed. The surgical complications observed after live donor hepatectomy were graded according to the classification system proposed by Clavien and colleagues [10]. The system consists of five major grades with subdivisions as summarized in Table 1.

Table 1. Classification of surgical complications by Clavien and colleagues [10].

Grade	Definitions
I	Any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens: use of drugs such as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy
II	Requiring pharmacologic treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
III	Requiring surgical, endoscopic, or radiological intervention a. Intervention not under general anesthesia b. Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management a. Single organ dysfunction b. Multi-organ dysfunction
V	Death of a patient

CNS, central nervous system; IC, intermediate care; ICU, intensive care unit; TIA, transient ischemic attacks.
*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding TIA.

Results

Complications and grade according to Clavien's classification system are summarized in Table 2. Surgical morbidity was recognized in 67 patients (28%) in this series. No donor deaths occurred. In brief, 46 cases (19%) were classified as grade I to II complications, and 21 cases (9%) were classified as grade IIIa to IIIb complications. Bile leakage, the most characteristic complication in hepatectomy, occurred in 11 cases (5%), of which six (2%) required surgical repair and were classified as grade IIIb. Three other cases required surgical intervention under general anesthesia, two for intra-abdominal abscess drainage and one for perforated duodenal ulcer, all of which were also classified as grade IIIb. Altogether, nine (4%) were classified as having grade IIIb complications.

The typical abnormality in liver function tests encountered after donor hepatectomy was elevation of aminotransferase levels 1 week after surgery, which resolved spontaneously. In one case, however, the prothrombin time was prolonged to 29% on postoperative day 1, and

Table 2. Summary of operative morbidity following live donor hepatectomy.

	Grade according to Clavien's classification system			
	I	II	IIIa	IIIb
Hepatectomy-related complications				
Bile leakage*	1		4*	6
Abnormal liver function tests	10	1		
Pleural effusion/ascites	2		5†	
Hepatic vein thrombosis		1‡		
Intra-abdominal abscess		2		2
Wound infection		1		
General surgical complications				
Psychiatric	3§			
Fever	7	1		
Pain	4	1¶		
Respiratory	1	2		
Gastrointestinal	5	1	3**	1
Others	3			
Total (%)	36 (15)	10 (4)	12 (5)	9 (4)

*Bile leakage requiring prolonged placement of drainage tube.
†Pleural effusion requiring thoracocentesis.
‡Partial hepatic thrombosis discovered by intraoperative ultrasound, treated aggressively with anticoagulation postoperatively.
§Two cases of *de novo* episode of depression, and one case of delirium immediately postsurgery.
¶Wound pain requiring intercostal neural block.
**A case of gastric torsion requiring endoscopic repair, a case of gastric ulcer bleed treated endoscopically, and a case of long tube placement under fluoroscopy for paralytic ileus.

fresh frozen plasma was transfused to secure hemostasis; this case was classified as grade II. All five cases with pleural effusion treated with thoracocentesis were classified as grade IIIa. Either a right hemi-liver or a right lateral sector graft was procured in these five patients. The procedure was performed under ultrasound guidance by a surgeon, and there were no secondary complications such as uncontrollable bleeding or pneumothorax.

Fever above 38 °C without apparent infectious cause was noted in eight cases. In seven cases, the fever resolved after a short duration of time without the use of antibiotics or further intervention, and was classified as grade I. In one case, however, antibiotics were administered preemptively and therefore the case was classified as grade II. Wound pain requiring an intercostal neural block was also classified as grade II.

The two cases of respiratory complications classified as grade II were a case of pneumonia treated with antibiotics and a case of acute asthma attack. The event of asthma attack took place in the recovery unit within few hours following surgery and treated successfully with immediate administration of intravenous aminophylline and methylprednisolone. The patient was a 22-year-old woman with a history of intermittent asthma since childhood. Her disease has been under control with oral theophylline with the occasional use of inhaled short-acting bronchodilator. Latest symptomatic exacerbation had occurred 6 months prior to the surgery which resolved with the use of inhaled bronchodilator and did not require any clinic visit. Respiratory workups prior to surgery including pulmonary function testing were within normal limits. Her postoperative course after the event remained uneventful.

Discussion

Our criteria for safe hepatic resection for malignant diseases were previously described [12]. Over 1000 hepatic resections have been performed for hepatocellular carcinoma according to the criteria, with zero mortality at our institution [20]. Based on this experience in hepatic resection for malignant disease, we developed surgical techniques and an algorithm to achieve safe donor hepatectomy [11]. Applying these experiences to carefully selected candidates according to the criteria described above, our series presented with a morbidity of 28% without mortality.

Several transplant centers worldwide have reported the morbidity of live donor hepatectomy for adult-to-adult LDLT at their institutions [9,21–26,30–34]. These reports ranged from 7 to 331 cases of live donor hepatectomy per center, with morbidity ranging between 8% and 67%. When limited to centers that reported more than 50 cumulative cases, the rate of morbidity within each series varied from 8% to 35% (Table 3). Because medical evaluation protocols from various institutions aimed at securing donor safety do not seem to differ greatly [34–39], the varying outcomes concerning morbidity following live donor hepatectomy suggest that there is either incoherence in the data collection and evaluation process, or significant differences in the technical aspects of live donor surgery and postoperative care. Differences in the results between centers and the need for uniform reporting have been noted [34–36,40,41]. Various approaches have been used, including the application of the previous Clavien classification system with some modifications [9,34–36]. These approaches, however, lack international validation and the problems of incoherence and heterogeneity among reports from different transplant centers worldwide remain unsolved. Use of the modified version of the 'Clavien classification' presented in 2004 [10], which has been validated by a large cohort and many medical centers from different continents, has the potential to overcome this issue. Any deviation from the cumulative data according to the system may provoke questions as to why and how such deviation occurred, providing useful information to improve surgical care of live liver donors, regardless of the region.

Table 3. Summary of outcome of live liver donor surgery for adult live donor liver transplantation.

Author (reference)	Year	City	*n*	Morbidity (%)
Lee *et al*. [25]	2002	Seoul, Korea	331	2*
Ito *et al*. [26]	2003	Kyoto, Japan	200	35
Fan *et al*. [31]	2003	Hong Kong, China	93	26
Tan *et al*. [32]	2003	Rochester, NY, USA	95	8
Malago*et al*. [30]	2003	Essen, Germany	74	41
Shackleton *et al*. [34]	2005	Los Angeles, CA, USA	42	31
Bak *et al*. [22]	2001	Denver, CO, USA	41	17
Marcos *et al*. [21]	1999	Richmond, VA, USA	25	16
Ghobrial *et al*. [9]	2002	Los Angeles, CA, USA	20	20
Pomfret *et al*. [23]	2001	Boston, MA, USA	15	67
Beavers *et al*. [40]	2001	Chapel Hill, NC, USA	14	64
de Carlis *et al*. [33]	2003	Milan, Italy	7	43

*Only major morbidity such as postoperative bleeding requiring re-exploration, biliary strictures, and portal vein stenosis or thrombosis requiring invasive interventions were reported.

Conclusion

The classification system introduced by Clavien and colleagues in 2004 [10] is simple and informative. We believe it could serve as a useful tool for the evaluation

and grading of donor morbidity enabling worldwide quality assessment in live liver donor surgery. Its use should be considered whenever surgical complications of live liver donor are discussed.

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References

1. Raia S, Nery JR, Mies S. Liver transplantation from live donors. *Lancet* 1989; **2**: 497.
2. Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful liver transplantation from a living donor to her son. *N Engl J Med* 1990; **322**: 1505.
3. Hashikura Y, Makuuchi M, Kawasaki S, *et al.* Successful living related partial liver transplantation to an adult patient. *Lancet* 1994; **343**: 1233.
4. Anonymous. Adult-to-adult living donor liver transplantation cohort study (A2ALL). *Hepatology* 2003; **38**: 792.
5. Tanaka K, Yamada T. Living donor liver transplantation in Japan and Kyoto University: what can we learn? *J Hepatol* 2005; **42**: 25.
6. Shiffman ML, Brown RS Jr, Olthoff KM, *et al.* Living donor liver transplantation: summary of a conference at The National Institutes of Health. *Liver Transpl* 2002; **8**: 174.
7. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. *Surgery* 1992; **111**: 518.
8. Clavien PA, Camargo CA, Croxford R, Langer B, Levy GA, Greig PD. Definition and classification of negative outcomes in solid organ transplantation. Application in liver transplantation. *Ann Surg* 1994; **220**: 109.
9. Ghobrial RM, Saab A, Lassman C, *et al.* Donor and recipient outcomes in right lobe adult living donor liver transplantation. *Liver Transpl* 2002; **8**: 901.
10. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205.
11. Kokudo N, Sugawara Y, Imamura H, Sano K, Makuuchi M. Tailoring the type of donor hepatectomy for adult living donor liver transplantation. *Am J Transplant* 2005; **5**: 1694.
12. Makuuchi M, Kosuge T, Takayama T, *et al.* Surgery for small liver cancers. *Semin Surg Oncol* 1993; **9**: 298.
13. Saito S, Yamanaka J, Miura K, *et al.* A novel 3D hepatectomy simulation based on liver circulation: application to liver resection and transplantation. *Hepatology* 2005; **41**: 1297.
14. Zahlten C, Jurgens H, Peitgen HO. Reconstruction of branching blood vessel from CT data. In: Gobel M, Muller H, Urban B, eds. *Visualization in Scientific Computing*. Wien: Springer, 1995: 41–52.
15. Takayama T, Makuuchi M, Kubota K, Sano K, Harihara Y, Kawarasaki H. Living related transplantation of left liver plus caudate lobe. *J Am Coll Surg* 2000; **190**: 635.
16. Sugawara Y, Makuuchi M, Takayama T, Imamura H, Kaneko J. Right lateral sector graft in adult living-related liver transplantation. *Transplantation* 2002; **73**: 111.
17. Makuuchi M, Kawasaki S, Noguchi T, *et al.* Donor hepatectomy for living related partial liver transplantation. *Surgery* 1993; **113**: 395.
18. Kokudo N, Sugawara Y, Imamura H, Sano K, Makuuchi M. Sling suspension of the liver in donor operation: a gradual tape-repositioning technique. *Transplantation* 2003; **76**: 803.
19. Imamura H, Kokudo N, Sugawara Y, *et al.* Pringle's maneuver and selective inflow occlusion in living donor liver hepatectomy. *Liver Transpl* 2004; **10**: 771.
20. Imamura H, Seyama Y, Kokudo N, *et al.* One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg* 2003; **138**: 1198.
21. Marcos A, Fisher RA, Ham JM, *et al.* Right-lobe living donor liver transplantation. *Transplantation* 1999; **68**: 798.
22. Bak T, Wachs M, Trotter J, *et al.* Adult-to-adult living donor liver transplantation using right-lobe grafts: results and lessons learned from a single-center experience. *Liver Transpl* 2001; **7**: 680.
23. Pomfret EA, Pomposelli JJ, Lewis WD, *et al.* Live donor adult liver transplantation using right lobe grafts. *Arch Surg* 2001; **136**: 425.
24. Beavers KL, Sandler RS, Fair JF, Johnson MW, Shrestha R. The living donor experience: donor health assessment and outcomes after living donor liver transplantation. *Liver Transpl* 2001; **7**: 943.
25. Lee SG, Park KM, Hwang S, *et al.* Adult-to-adult living donor liver transplantation at Asan Medical Center, Korea. *Asian J Surg* 2002; **25**: 277.
26. Ito T, Kiuchi T, Egawa H, *et al.* Surgery-related morbidity in living donors of right-lobe liver graft: lessons from the first 200 cases. *Transplantation* 2003; **76**: 158.
27. Yamashiki N, Sugawara Y, Tamura S, *et al.* Selection of liver-transplant candidates for adult-to-adult living donor

liver transplantation as the only surgical option for end-stage liver disease. *Liver Transpl* 2006; **12**: 1077.
28. Kawasaki S, Makuuchi M, Matsunami H, *et al.* Preoperative measurement of segmental liver volume of donors for living related liver transplantation. *Hepatology* 1993; **18**: 1115.
29. Urata K, Kawasaki S, Matsunami H, *et al.* Calculation of child and adult standard liver volume for liver transplantation. *Hepatology* 1995; **21**: 1317.
30. Malago M, Testa G, Frilling A, *et al.* Right living donor liver transplantation: an option for adult patients. Single institution experience with 74 patients. *Ann Surg* 2003; **238**: 853.
31. Fan S-T, Lo C-M, Liu C-L, Wang W-X, Wong J. Safety and necessity of including the middle hepatic vein in the right lobe graft in adult-to-adult live donor liver transplantation. *Ann Surg* 2003; **238**: 137.
32. Tan HP, Madeb R, Kovach AJ, *et al.* Hypophosphatemia after 95 right-lobe living-donor hepatectomies for liver transplantation is not a significant source of morbidity. *Transplantation* 2003; **76**: 1085.
33. de Carlis L, Giacomoni A, Sammartino C, Lauterio A, Slim AO, Forti D. Right lobe living-related liver transplant: experience at Niguarda Hospital. *Transplant Proc* 2003; **35**: 1015.
34. Shackleton CR, Vierling JM, Nissen N, *et al.* Morbidity in live liver donors: standards-based adverse event reporting further refined. *Arch Surg* 2005; **140**: 888.
35. Salvalaggio PR, Baker TB, Koffron AJ, *et al.* Comparative analysis of live liver donation risk using a comprehensive grading system for severity. *Transplantation* 2004; **77**: 1765.
36. Broering DC, Wilms C, Bok P, *et al.* Evolution of donor morbidity in living related liver transplantation: a single-center analysis of 165 cases. *Ann Surg* 2004; **240**: 1013.
37. Trotter JF, Wachs M, Trouillot T, *et al.* Evaluation of 100 patients for living donor liver transplantation. *Liver Transpl* 2000; **6**: 290.
38. Valentin-Gamazo C, Malago M, Karliova M, *et al.* Experience after the evaluation of 700 potential donors for living donor liver transplantation in a single center. *Liver Transpl* 2004; **10**: 1087.
39. Chen YS, Cheng YF, De Villa VH, *et al.* Evaluation of living liver donors. *Transplantation* 2003; **75**(3 Suppl.): S16.
40. Beavers KL, Sandler RS, Shrestha R. Donor morbidity associated with right lobectomy for living donor liver transplantation to adult recipients: a systematic review. *Liver Transpl* 2002; **8**: 110.
41. Lo CM. Complications and long-term outcome of living liver donors: a survey of 1508 cases in five Asian centers. *Transplantation* 2003; **75**(3 Suppl.): S12.

