

Clinical outcomes of gastric cancer surgery after liver transplantation

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Purpose: *De novo* malignancy is common after liver transplantation (LT); however, there are limited reports on the clinical outcomes of gastric cancer surgery after LT. Our study aimed to investigate the feasibility and safety of gastric cancer surgery after LT.

Methods: Seventeen patients underwent gastric cancer surgery after LT at a single institution between January 2013 and June 2021. We retrospectively collected data on surgical complications, survival, and recurrence status of these cases.

Results: Fifteen patients (88.2%) underwent curative gastrectomy, with 10 open distal (66.7%) and 5 laparoscopic distal (33.3%) gastrectomies. Surgical and severe complication rates were 3 of 15 (20.0%) and 1 of 15 (6.7%), respectively. There were no significant differences between laparoscopic (33.3%) and open surgery (66.7%) in terms of operation time and complication rate. No surgery-related mortalities occurred. Immunosuppressants could be maintained without difficulty, and no suspicious acute rejection was identified during the perioperative period. There was 1 recurrence after curative surgery (recurrence rate, 6.7%), and the 5-year cancer-specific survival rate after curative surgery was 93.3%.

Conclusion: Laparoscopic gastrectomy can be safely done even after LT in terms of postoperative complications and graft safety.

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Key Words: Gastrectomy, Liver transplantation, Stomach neoplasms

INTRODUCTION

De novo malignancies are a major cause of late mortality after liver transplantation (LT) [1,2]. Gastric cancer is the most common cancer in Korea and comprises the largest proportion of LT-associated cancers [3,4], and this has led to notable concern in LT surveillance.

Gastric cancer surgery for liver transplant patients can be more challenging than primary gastric cancer surgery because of postoperative adhesions in the abdominal cavity, anatomical diversion, and an immunosuppressed status, which can lead to potential perioperative morbidity and mortality. Nevertheless, surgical resection with lymph node (LN) dissection has been conducted for these patients because the curative treatment

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for gastric cancer is surgical resection. In 2016, a case series on open gastrectomy for gastric cancer after LT was published, showing the results of open gastrectomy in 12 patients [5].

Recent clinical trials have demonstrated the safety and feasibility of laparoscopic surgery for primary gastric cancer [6]. However, reports on the laparoscopic approach for *de novo* gastric cancer after LT are limited [7,8]. Therefore, we aimed to evaluate the surgical safety and oncological outcomes of gastric cancer surgery including open and laparoscopic approaches.

METHODS

Seventeen LT patients who underwent gastric cancer surgery afterwards at Seoul National University Hospital between January 2013 and June 2021 were reviewed. The electronic medical records were retrospectively reviewed for the following: age, sex, underlying liver disease leading to LT, age at the time of gastrectomy, immunosuppressant regimen, interval between LT and gastrectomy, approach to gastrectomy (open or laparoscopy), operation time, hospitalization day, postoperative complications, postoperative adjuvant treatment, TNM stage, pathologic characteristics, survival, and recurrence status. The TNM staging was based on the 8th edition of the American Joint Committee on Cancer/Union for International Cancer Control. Clinical stage was determined based on preoperative gastroscopy, endoscopic ultrasound findings, and CT.

Data on all surgical complications during hospitalization

were prospectively collected, and the classification of each complication, including grade, was discussed at a weekly conference. Complications were evaluated and classified according to the Clavien-Dindo (CD) classification.

Patients with pathologically confirmed stage I disease were assessed every 6 months after surgery for 5 years. Patients with advanced stages (above stage II) were followed up every 3 to 4 months for the first 2 to 3 years and every 6 months afterwards for an additional 2 to 3 years. Abdominopelvic CT or abdominal ultrasonography with laboratory tests, including those for tumor markers, was performed at every outpatient visit. Gastroscopy was performed yearly for all patients who underwent subtotal gastrectomy.

The last follow-up date and the status of survival and recurrence until June 2021 were reviewed via electronic medical records or telephone interviews.

Ethics statement

This study was approved by the Institutional Review Board of Seoul National University Hospital, Seoul National University College of Medicine, Korea (No. 2002-009-1097), which waived the need for informed consent.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Corp.). The open and laparoscopic gastrectomy groups were compared using the Mann-Whitney U-test. All

Table 1. Characteristics of the patients who underwent gastrectomy after LT

Patient no.	Sex	Age (yr)	Underlying liver disease	Lobe transplanted	Immunosuppressant	Diagnosed from LT (yr)	Treatment	Approach
1	Male	64	HBV-LC, HCC	Right lobe	Tacrolimus, MMF	0.6	DG-BII with D2	Open
2	Male	54	HBV-LC	Whole liver	Tacrolimus	2.3	DG-BII with D1+	Open
3	Female	60	HCV LC	Right lobe	Tacrolimus	3.8	DG-BII with D1+	Open
4	Male	52	HBV-LC	Right lobe	Tacrolimus	5.7	Palliative GJ	Open
5	Male	57	HBV-LC	Right lobe	Tacrolimus	4.7	ESD + diagnostic laparotomy	Open
6	Male	65	HBV-LC, HCC	Whole liver	Tacrolimus	10.0	DG-BI with D1+	Open
7	Female	67	PBC	Whole liver	Tacrolimus	11.3	DG-BII with D1+	Open
8	Male	75	HBV-LC	Right lobe	Tacrolimus	13.0	DG-BII with D1+	Laparoscopy
9	Male	61	HBV-LC, HCC	Whole liver	Tacrolimus	7.4	DG-BII with D2	Open
10	Male	74	HBV-LC	Right lobe	MMF	17.1	ESD + DG-BII with D1+	Open
11	Male	72	HBV-LC	Right lobe	Tacrolimus	15.6	DG-BII with D1+	Open
12	Female	77	HBV-LC, HCC	Whole liver	Tacrolimus	9.3	DG-BII with D1+	Laparoscopy
13	Male	64	HBV-LC, HCC	Right lobe	Tacrolimus	8.0	DG-BII with D1+	Laparoscopy
14	Female	54	HBV-LC	Right lobe	Tacrolimus, MMF	4.7	DG-BII with D1+	Laparoscopy
15	Male	68	Alcoholic LC	Right lobe	Tacrolimus, MMF	2.8	DG-BII with D1+	Open
16	Male	68	HBV-LC	Whole liver	Tacrolimus	13.6	DG-BII with D1+	Open
17	Male	77	HBV-LC, HCC	Whole liver	Tacrolimus, MMF	14.1	ESD + DG-BI with D1+	Laparoscopy

LT, liver transplantation; LC, liver cirrhosis; HCC, hepatocellular carcinoma; MMF, mycophenolate mofetil; DG, distal gastrectomy; ESD, endoscopic submucosal dissection; GJ, gastrojejunostomy; PBC, primary biliary cholangitis.

numerical data are reported as mean values with standard deviations or median values with ranges. A P-value less than 0.05 was considered statistically significant.

RESULTS

Demographic and clinical features

The clinical characteristics of the 17 patients who underwent gastrectomy are shown in Table 1. There were 13 male (76.5%) and 4 female patients (23.5%). The mean age of these groups was 65.3 ± 8.1 years. Seven patients (41.2%) underwent whole LT and 10 (59%) underwent right lobe transplantation. LT was performed at a single institution for 11 patients (64.7%) and outside the hospital for the other 6 (35.3%). The median duration from transplantation to gastric cancer was 9.34 years (range, 0.6–17.1 years). Except for 1 patient, 16 received a tacrolimus-based immunosuppressive regimen with or without mycophenolate mofetil (MMF).

Five patients were diagnosed with gastric cancer due to symptoms (heartburn, 1; nausea, 1; melena, 2; and anemia, 1) and the remaining patients found gastric cancer at routine esophagogastroduodenoscopy (EGD).

Surgery

As the gastric cancer lesion was in the antrum or lower body of the stomach, distal gastrectomy was planned for all patients, whose clinical stage ranged from IA to III. Fifteen patients (88.2%) underwent curative distal gastrectomy, 1 (5.9%) underwent palliative gastrojejunostomy, and the other (5.9%) underwent diagnostic laparotomy alone due to peritoneal seeding. Regarding distal gastrectomy, 10 patients (58.8%) underwent open distal gastrectomy, and 5 patients (29.4%) underwent laparoscopic distal gastrectomy (Table 2).

D1+ or D2 LN dissection was performed in all the patients (Table 1). The mean number of retrieved LNs was 22.5 ± 9.8 (range, 8–45) (Table 3). No difference in the number of dissected

Table 2. Comparison of postoperative outcomes between open vs. laparoscopic gastrectomy (n = 15)

Variable	Open	Laparoscopy	P-value
Patients	10 (66.7)	5 (33.3)	
Pathologic stage			
IA	4	4	
IB	2	0	
IIA	2	0	
IIB	1	1	
IV	1	0	
Age (yr)	65.3 ± 5.9	69.4 ± 10.2	0.269
Sex			
Male	8	3	
Female	2	2	
Lobe transplanted			
Right lobe	5	3	
Whole liver	5	2	
Transplant to gastrectomy (yr)	$8.5 \pm 5.9^{a)}$	$9.9 \pm 3.8^{a)}$	0.624
Operative time (min)	$205.3 \pm 44.7^{a)}$	$252.0 \pm 106.3^{a)}$	0.391
No. of dissected lymph nodes	23.6 ± 11.9	20.4 ± 3.4	0.902
Resection margin positive	0	0	
Resection margin (cm)			
Proximal margin	6.5 ± 3.3	3.6 ± 1.8	0.500
Distal margin	2.2 ± 1.9	4.2 ± 3.7	0.297
Reconstruction type			
Billroth I	1	1	
Billroth II	9	4	
Complication	3 (30.0)	0 (0)	
CD grade II	1 ^{b)}	0	
CD grade IIIA	2 ^{c)}	0	
Postoperative hospitalization (day)	16.5 ± 19.2 (9–71) ^{d)}	9.0 ± 1.0 (8–10) ^{d)}	
Mortality	0	0	

Values are presented as number (%), number only, mean \pm standard deviation (SD), ^{a)}median \pm SD, or ^{d)}median \pm SD (range). CD, Clavien-Dindo classification.

^{b)}Pneumonia; ^{c)}pleural effusion, chyle leak.

Table 3. Clinicopathologic findings of the gastrectomy in patients after liver transplantation

Patient no.	Operation name	Operation time (min)	Blood loss (mL)	Complication	Postoperative stay (day)	TNM stage	No. of involved LNs	No. of resected LNs	Postoperative treatment
1	Open DG	165	450	None	9	T2N1M0, IIA	2	42	Adjuvant TS-1
2	Open DG	265	800	None	11	T1bN1M0, IB	1	8	None
3	Open DG	240	250	Pneumonia (CD grade II)	10	T1bN0M0, IA	0	18	None
4	Open palliative GJ	118	20	None	9	T3NxM1, IV	NA	NA	Palliative XELOX
5	Diagnostic laparotomy	50	0	None	11	T1aNxM1, IV	NA	NA	None
6	Open DG	148	100	None	9	T1aN0M0, IA	0	19	None
7	Open DG	175	150	None	11	T1bN0M0, IA	0	25	None
8	Laparoscopic DG	440	0	None	9	T1aN0M0, IA	0	16	None
9	Open DG	170	70	None	11	T3N1M0, IIB	2	17	Adjuvant TS-1 → XP
10	Open DG	275	220	Pleural effusion (CD grade IIIa)	13	T1bN1M0, IB	2	15	None
11	Open DG	180	100	None	9	T1aN0M0, IA	0	29	None
12	Laparoscopic DG	185	270	None	8	T2N2M0, IIB	4	18	Adjuvant TS-1
13	Laparoscopic DG	215	100	None	10	T1aN0M0, IA	0	23	None
14	Laparoscopic DG	225	300	None	8	T1aN0M0, IA	0	24	None
15	Open DG	205	150	Chyle leakage (CD grade IIIa)	71	T4aN3bM1, IV	17	45	Adjuvant XELOX
16	Open DG	230	400	None	11	T3N0M0, IIA	0	18	Adjuvant TS-1
17	Laparoscopic	195	110	None	10	T1bN0M0, IA	0	21	None
	Mean ± SD				13.5 ± 14.9		1.9 ± 4.4	22.5 ± 9.8	

LN, lymph node; DG, distal gastrectomy; TS-1, tegafur, gimeracil and oteracil potassium; CD, Clavien-Dindo classification; GJ, gastrojejunostomy; NA, not applicable; XELOX, capecitabine and oxaliplatin; XP, capecitabine and cisplatin; SD, standard deviation.

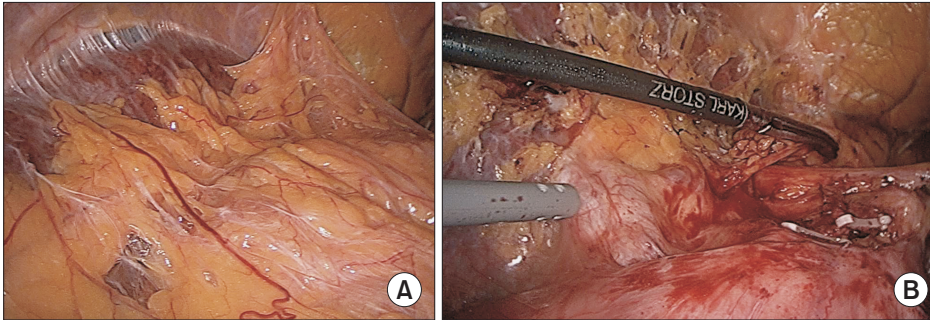


Fig. 1. (A) Adhesion to the abdomen wall. (B) Adhesion around the liver.

LN was found between the open and laparoscopic groups (23.6 ± 11.9 vs. 20.4 ± 3.4 , $P = 0.902$) (Table 2). As LN dissection around hepatoduodenal ligament can affect graft safety, if there is severe adhesion around hepatic hilum, surgeon performed D1+ LN dissection instead of D2 dissection.

The reconstruction method was determined by the surgeon for distal gastrectomy. Most patients underwent reconstruction with Billroth II anastomosis (13 of 15, 86.7%) rather than Billroth I. In laparoscopic group, 1 patient (patient 17) had Billroth I anastomosis and 4 patients (including patient 12) had Billroth II anastomosis. Patient 17 with severe adhesions had a Billroth I anastomosis according to the surgeon's preference. On the other hand, patient 12 with severe adhesions had adhesiolysis and Billroth II anastomosis (Table 2).

Laparoscopic surgery (5 of 15, 33.3%) was performed in the early clinical stage, and open gastrectomy was performed in advanced stages or according to the patients' condition, such as the probability of severe adhesion due to a previous operation. After LT, as after other abdominal surgeries, there were some adhesions, but no serious adhesions were found that would make the operation difficult in our case. After adhesiolysis from adjacent organ including hilum area, laparoscopic gastrectomy was performed successfully (Fig. 1). No intraoperative conversion from laparoscopy to laparotomy occurred.

Three endoscopic submucosal dissection (ESD) procedures were performed before gastrectomy. Two patients underwent gastrectomy because of incomplete ESD, and 1 patient (patient 5) was diagnosed with advanced gastric cancer (AGC) at the annual EGD follow-up after 3 years later from curative ESD. Patient 5 had gastric cancer at the different site (mid antrum, lesser curvature) from ESD (proximal antrum, great curvature).

Hospital course and outcome

In the open gastrectomy group, there were 2 cases of CD grade \geq IIIA complications (1 pleural effusion and 1 chyle leak) and 1 case of CD grade II complication (pneumonia). In the laparoscopic gastrectomy group, there were no perioperative complications of CD grade \geq II. The mean hospitalization duration was 9.9 ± 1.3 days, excluding 1 patient who was hospitalized for 71 days due to lymphatic leakage. In addition,

most patients had a routine hospitalization course, and there was no surgery-related mortality.

Complete tumor resection (R0 resection) was achieved in all patients who underwent gastrectomy. The resection margins were negative for microscopic cancer spread in all patients, and there was no difference in the mean lengths of the proximal and distal margins. The mean number of resected LNs was similar in the laparotomy group vs. laparoscopic group (23.6 ± 11.9 vs. 20.4 ± 3.4) (Table 2).

According to the 8th edition of TNM stage, there were 10 early gastric cancer (EGC) patients (58.8%) and 7 AGC patients (41.2%). Five of 7 AGC patients received adjuvant chemotherapy, 1 patient received palliative chemotherapy after palliative gastrojejunostomy, and 1 patient did not receive chemotherapy. The patients in the pathological stage II or III received S-1 as the first-line adjuvant chemotherapy regimen. Two patients (patients 5 and 9) were lost to follow up at 5 months and 1.6 years after gastrectomy, respectively; and their cancer-related death was confirmed by telephone interview (patient 5 had diagnostic laparotomy alone due to peritoneal seeding and patient 9 was transferred to a nursing hospital after progression). Other causes of death were traffic accidents after 9 months (patient 1), acute pyelonephritis after 2.6 years (patient 8), and unknown causes after 7 months (patient 10).

Except for 2 cases of noncurative surgery, 1 case of recurrence was observed 19.5 months after open distal gastrectomy for T3N1M0 gastric cancer (recurrence rate, 6.7%). The 5-year cancer-specific survival rate after curative surgery was 93.3%.

Immunosuppressant

All patients were administered a triple combination immunosuppressant regimen, including tacrolimus, MMF, and steroids at the point of LT, which was tapered off within 3 to 6 months after LT. At the time of gastrectomy, 4 patients maintained a dual regimen, 1 patient maintained MMF alone, and the remaining patients maintained tacrolimus alone. The average immunosuppressant-off period during hospitalization for gastric cancer surgery was 2.35 days, and patients resumed their immunosuppressants when the oral diet was started. There were no dose adjustments during hospitalization,

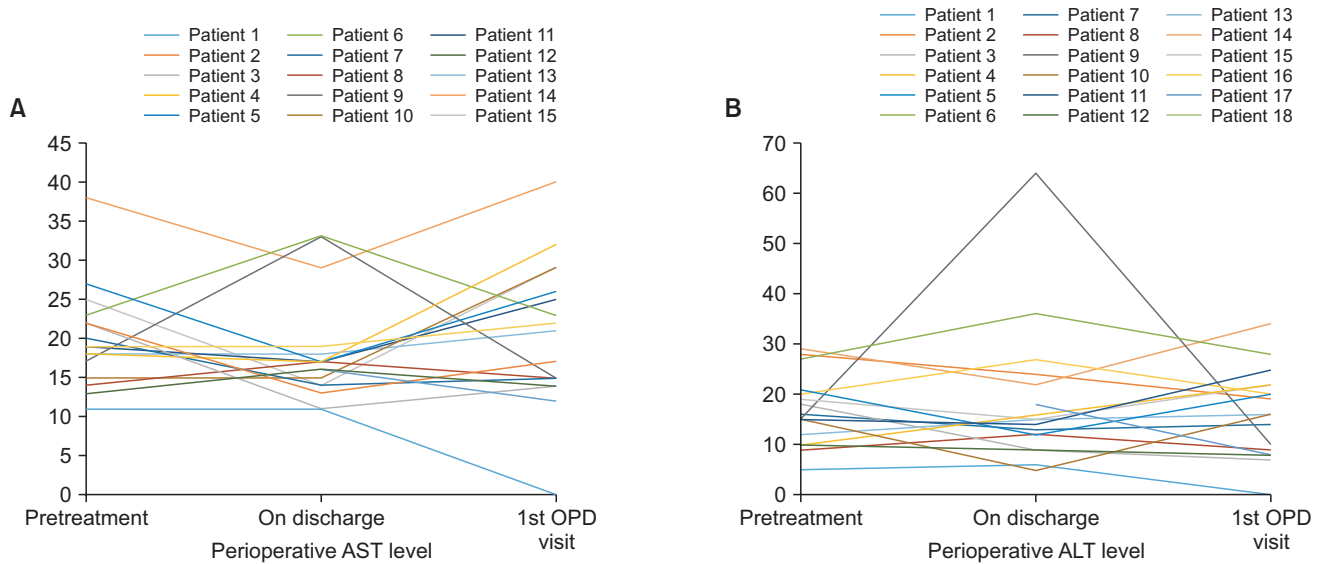


Fig. 2. Perioperative AST (A) and ALT (B) levels. OPD, outpatient department.

except for 3 patients (patients 8, 16, and 17). The MMF level was not monitored; however, the dosage was 0.5 to 1.5 g/day. No suspicious acute graft rejection or failure was identified during the perioperative period, and proper liver function was noted. All but 1 patient had normal AST and ALT (Fig. 2). ALT of patient 9 increased to 64 IU/L (normal range, 0–40 IU/L) at discharge and normalized again at the first outpatient clinic.

DISCUSSION

Several studies have reported that liver transplant recipients have a high risk of *de novo* malignancy due to the suppression of the immune system. Kim et al. [3] in 2021 reported that gastric cancer is the most common cancer that develops after LT in Korea, but not many cases of laparotomy and laparoscopic gastrectomy for gastric cancer after LT have been reported. If gastric cancer develops in a patient who has undergone LT, gastrectomy can be performed in the same manner as for gastric cancer in patients without a history of LT.

Previously, the first (KLASS-01) and the second multicenter randomized clinical trial of the Korean Laparoscopic Gastrointestinal Surgery Study Group (KLASS-02) indicated that laparoscopic distal gastrectomy was an oncologically safe alternative to open surgery for EGC and AGC with better short-term outcomes [6,9]. Our study also showed that laparoscopic gastrectomy was comparable to open gastrectomy in terms of operation time, number of LNs dissected, and complications. Compared with other data published in 2014, the complication rate (CD grade of >IIIa) in our study was the same as noted in a previous study of patients with a surgical history who underwent gastrectomy (13.3% vs. 13.3%) [10]. There was no surgery-related mortality in our study, whereas the

postoperative mortality reported by the Korean Gastric Cancer Association was 1.0% [11].

The mean number of retrieved LNs was 22.5 ± 9.8 , and 86.7% of the patients met the National Comprehensive Cancer Network recommendation for harvesting LNs (≥ 16 LNs).

With the advancement of laparoscopic instruments and improved surgical skills and experience, laparoscopic surgery has become safer for patients who have undergone previous abdominal surgeries [12]. In our experience, open or laparoscopic gastrectomy can be safely performed even if the patient has undergone LT.

Several reports have suggested that the long-term use of immunosuppressants weakens the immune surveillance system and leads to *de novo* malignancy. To prevent *de novo* malignancies or recurrence of hepatocellular cancer in LT patients, mammalian target of rapamycin (mTOR) inhibitor-based immunosuppression, which has anticancer effects, is considered to delay tumor recurrence [13]. In our study, mTOR inhibitors were administered to 6 patients during the postoperative outpatient follow-up period, and no cancer recurrence was reported.

There are concerns regarding the discontinuation of immunosuppressive agents during the perioperative period of gastrectomy after LT [14]. The period of discontinuation of immunosuppressant medication after surgery was as short as 2.35 days on average, and the adjustment of immunosuppressant concentration for 3 patients (patients 8, 16, and 17) was minor. Graft rejection or failure was not observed.

The proportion of EGC in the overall gastric cancer of the general population has been reported to range from 67.9% up to 75% in 2019, including cases of ESD [11]. In our study, the rate of EGC after LT was 58.8%, which was lower than that in

the general population. According to Kim et al. [3], the EGC rate after LT was 46.7%, which was also lower than that in the general population. The lower rates of EGC in patients undergoing LT compared to general patients may be due to immunosuppressants. Immunosuppressant use may not only increase the incidence of new malignancies but may also accelerate cancer progression due to weakened immunity.

The Korean National Health Insurance Service recommends regular basic cancer screening, including endoscopy every 1 to 2 years, depending on the examination. As *de novo* malignancies are more common following LT when compared to the general population due to immunosuppression, more intensive screening, including annual EGD and CT, should be performed in this population [15,16]. As the number of LTs increases and their use as immunosuppressants increases, surgeons will need to pay special attention to cancer screening after LT.

One of the limitations of this study is that it utilized a retrospective medical chart review. Because the patient's clinical information is based on medical records, it is difficult to completely rule out selection bias owing to the possibility of omission or incorrect information.

Second, the number of target patients included in the study was insufficient, and the follow-up period was short (range, 100–3,025 days). In the future, prospective multicenter studies involving larger numbers of patients and longer-term follow-up data may yield more reliable and useful results.

Laparoscopic gastrectomy can be safely done in terms of postoperative complications and graft safety. In the case of EGC, laparoscopic surgery might be safe. However, further studies investigating benefit of the laparoscopic surgery are required with large number of cases.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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