

# Experience of Distal Gastrectomy By Minilaparotomy With Laparoscopic-Assistance for Nonoverweight Patients With T1N0-1 Gastric Cancer

Hideyuki Ishida, Toru Ishiguro, Norimichi Okada, Kensuke Kumamoto, Keiichiro Ishibashi, Tatsuya Miyazaki, Norihiro Haga

Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Saitama, Japan

To evaluate the usefulness of laparoscopic assistance for curative distal gastrectomy by minilaparotomy, 19 patients (body mass index  $\leq 25.0 \text{ kg/m}^2$ ) with T1N0-1 gastric cancer who underwent distal gastrectomy with a minilaparotomy (skin incision  $\leq 7 \text{ cm}$ ) with laparoscopic assistance (LA (+) group) were compared with 19 historic controls who underwent equivalent surgery by minilaparotomy without laparoscopic assistance (LA (-) group). The percentage of patients with blood loss more than 300 mL tended to be lower in the LA (+) group (5.3% versus 31.6%, P = 0.09). The first flatus passage was earlier (P = 0.04), serum C-reactive protein levels on postoperative day 1 were lower (P = 0.07) in the LA (+) group. Minilaparotomy with laparoscopic assistance seems to be less invasive compared with pure minilaparotomy. This procedure is considered to be a simple alternative to standard laparoscopic-assisted distal gastrectomy in selected patients with T1N0-1 gastric cancer.

*Key words:* Minilaparotomy – Gastrectomy – Gastric cancer – Laparoscopy

L aparoscopic-assisted distal gastrectomy (LADG) has come to be widely performed in the treatment of cancer located in the middle or lower third of the stomach. LADG usually requires a small

incision (5–7 cm) for retrieval of the specimen and anastomosis.<sup>1–4</sup> The use of a small incision, compared with a full laparotomy, is believed to be associated with early recovery in patients under-

Reprint requests: Hideyuki Ishida, MD, PhD, Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, 1981 Kamoda, Kawagoe, Saitama 350-8550, Japan.

Tel.: +81 49 228 3619; Fax: +81 49 222 8865; E-mail: 05hishi@saitama-med.ac.jp

going laparoscopic-assisted colectomy.<sup>5</sup> Several surgeons<sup>6–10</sup> have advocated a minilaparotomy approach as a useful treatment alternative to laparoscopic-assisted surgery for the resection of colon cancer based on their favorable results. In 2003, Onitsuka *et al*<sup>11</sup> first reported their experience of minilaparotomy (skin incision, 7 cm) in 10 patients with gastric cancer. Subsequently, some Japanese surgeons,<sup>12–14</sup> including our group,<sup>15,16</sup> reported meticulous surgical techniques with the minilaparotomy approach for performing distal gastrectomy, pyloric-ring preserving gastrectomy, or total gastrectomy for gastric cancer. However, the feasibility, safety, and minimal invasiveness of minilaparotomy for resection of gastric cancer have not yet been fully evaluated. Compared with colectomy by minilaparotomy, which involves relatively straightforward resection of the colon, gastrectomy with minilaparotomy seems to need more complex surgical techniques, especially in relation to systematic lymph node dissection. Based on our previous experience with minilaparotomy for the resection of gastric cancer,<sup>15,16</sup> we believe that the potential difficulties of complex lymph node dissection related to minilaparotomy might be overcome with the use of laparoscopic assistance. In July 2008, we began to perform distal gastrectomy with minilaparotomy and laparoscopic assistance in patients with T1N0-1 gastric cancer. This study was undertaken to evaluate our initial experience of minilaparotomy with laparoscopic assistance for the resection of clinically (preoperatively) diagnosed T1N0-1 gastric cancer,<sup>17</sup> by comparing the results with those of patients undergoing equivalent surgery with minilaparotomy without laparoscopic assistance.

## Patients and Methods

## Patient selection

Nineteen patients with T1N0-1 gastric cancer located in the middle or lower third of the stomach who were scheduled to undergo distal gastrectomy with minilaparotomy (skin incision,  $\leq$ 7 cm) using a laparoscope and laparoscopic instruments, Ligasure (Covidien, Mansfield, Massachusetts) or Harmonic scalpel (Ethicon Endo-Surgery, Cincinnati, Ohio) were enrolled in this prospective study between July 2008 and August 2009 at the Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University. The indications for the procedure were clinically (preoperatively) diagnosed T1N0 (stage IA) gastric

cancer other than mucosal cancer satisfying the inclusion criteria for endoscopic mucosal resection (differentiated type, 2 cm in diameter), or T1N1 (stage IB) cancer, determined according to the Guideline for the Treatment of Gastric cancer,<sup>18</sup> a tumor located in the middle or lower third of the stomach, and patient body mass index (BMI)  $\leq$ 25.0 kg/m<sup>2</sup>. Written informed consent was obtained from all the patients. Preoperative diagnosis of gastric cancer was made by histologic examination of biopsy specimens obtained at endoscopic examination. The site of the lesion and degree of invasion (T-category) were evaluated comprehensively on the basis of barium examination, endoscopic, and/or endoscopic ultrasonographic findings. All patients underwent abdominal computed tomography to determine the presence/absence of metastasis to the lymph node(s) (N-category), liver, and distant metastasis. Patients with synchronous cancer in other organs were excluded from the present study.

#### Surgical procedures

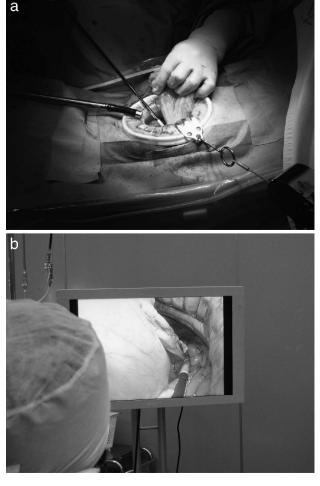
Each patient was placed on the operating table in the supine position. All the surgical procedures were performed through upper midline abdominal incision with a maximal length of 7 cm. The first author (HI) oversaw each procedure as a supervising assistant. A wound retractor, Alexis (medium size; Applied Medica, California) was applied to the edge of the wound. An assistant slid the wound into position using conventional retractors. When necessary for dissecting the lymph nodes around the celiac artery, or dissecting the gastrosplenic ligament, a Kent retractor (Takasago, Tokyo, Japan), whose bar was placed beside the patient's left-sided axilla, was used to slide the wound cephalad or laterally. This movable wound allowed direct visualization of almost the entire surgical field. The transverse colon and the greater omentum were gently pulled out of the wound, and the greater omentum was dissected about 4 to 5 cm away from the arcade of the gastroepiploic arteries. The gastroepiploic artery and vein were ligated and divided where appropriate according to the site of the primary tumor. The right gastroepiploic artery and vein were ligated and divided at their roots, and then the right gastric artery was ligated and divided. The duodenum was divided after the application of the purse-string instrument, the anvil head of PCEEA 25 mm (Covidien) or Proximate ILS (SDH25) (Ethicon Endo-Surgery) was introduced

into the lumen, and the purse-string suture was tightened. The other stump of the duodenum was closed by interrupted sutures to prevent spillage of gastric juice. With the stomach reflected cranially in the surgical field, the lymph nodes and the surrounding fat tissue along the common hepatic artery were dissected. Lymph node dissection was progressed along the root of the splenic artery and celiac axis when necessary. The left gastric artery and vein were divided at their roots. The lesser curvature was denuded, and the stomach was transected using a linear stapler, the Linear Cutter 100 (Ethicon Endo-Surgery) or GIA80 (Covidien). The body of the circular stapler was introduced into the remnant stomach by the lower cut-end of the stomach. Stapled anastomosis was performed between the posterior side of the greater curvature of the remnant stomach and the duodenum. The opened cut-end of the stomach, through which the circular stapler was introduced, was finally closed using a linear stapler.

In the present series we used Ligasure (Covidien) or Harmonic scalpel (Ethicon Endo-Surgery) to perform the lymph node dissection around the common hepatic artery and/or celiac trunk, or to divide the gastrosplenic ligament with the assistance of a laparoscope whenever necessary, to see the deep surgical field through the wound (Fig. 1a and 1b).

## Level of lymph node dissection

The type of lymph node dissection (D1+ $\alpha$  or D1+ $\beta$ ) for T1N0 cancer was selected in accordance with the Guideline of the Treatment of Gastric Cancer.<sup>18</sup> Mucosal cancer not meeting the criteria for endoscopic mucosal resection was treated by modified gastrectomy A with D1+ $\alpha$  lymph node dissection. Modified gastrectomy A was also performed to differentiate submucosal cancer less than 1.5 cm in diameter. The D1+ $\alpha$  dissection included removal of lymph nodes classified into group 1 lymph nodes (1, 3, 4sb, 4d, 5, and 6) and 7 (along the left gastric artery) lymph nodes. Submucosal cancer, which did not satisfy the criteria for modified gastrectomy A, was treated by modified gastrectomy B with  $D1+\beta$ lymph node dissection, which included removal of the group 1 lymph nodes plus 7, 8a (along the common hepatic artery), and 9 (around the celiac trunk) lymph nodes. The D1 lymph node dissection included removal of all or part of the group 1 lymph nodes comprising the right paracardial lymph nodes (1), nodes along the lesser curvature (3), nodes along



**Fig. 1** Intraoperative findings of minilaparotomy with laparoscopic assistance. Ligasure is introduced through the small incision under illumination from a laparoscope (a). The surgeon is dissecting the vessels near the spleen while observing the video monitor (b).

the left gastroepiploic vessels (4sb), nodes along the right gastroepiploic vessels (4d), the suprapyloric lymph nodes (5), and the infrapyloric lymph nodes (6), which varied according to the site of the primary tumor. In cases of cancer involving the lower third of the stomach, modified gastrectomy A included dissection of the 8a lymph nodes.

## Factors evaluated

The age, sex, BMI (in kilograms per meter squared) of the patients, the American Society of Anesthesiologists classification, location of the tumor, pathologic stage, type of gastrectomy, number of harvested lymph nodes, duration of surgery, blood loss, postoperative complications, postoperative changes in the serum C-reactive protein (CRP) levels,

Factors	Laparoscopic assistance (+) (n = 19)	Laparoscopic assistance $(-) (n = 19)$	<i>P</i> value
Age (y)	65 (48-84)	65.5 (49–79)	0.57
Sex (male:female)	10:9	12:7	0.74
Body mass index $(kg/m^2)$	21.3 (16.5-25.0)	21.3 (16.6-25.0)	0.81
ASA classification (I:II:III)	7:10:2	7:6:6	0.71
Tumor location (middle third:lower third)	6:13	12:7	>0.99
Lymph node dissection $(D1+\alpha:D1+\beta)$	6:13	13:6	0.052
Number of lymph nodes harvested	33 (14-64)	29 (16-51)	0.23
Pathologic stage (IA:IB:II)	16:3:0	15:2:2	0.33
Duration of surgery (min)	150 (115–190)	155 (105–170)	0.57
Blood loss (mL)	150 (80–320)	180 (25–520)	0.22
Postoperative complication (%)	1 (5.3)	2 (10.5)	>0.99

Table 1 Demographic, clinicopathologic, and surgical factors

leukocyte counts, postoperative use of analgesic use (pentazocine, 15 mg, by intramuscular injection), first passage of flatus, time to start of oral intake, and postoperative length of hospital stay were prospectively recorded on the medical charts of the patients undergoing minilaparotomy with laparoscopic-assistance (LA (+) group). These parameters were compared with those of the patients (LA (-) group, n = 19) who underwent equivalent gastrectomy (D1+ $\alpha$  or D1+ $\beta$  lymph node dissection) by minilaparotomy, but without laparoscopic assistance, between July 2006 and June 2008.

#### Statistical analysis

A statistical software package (Statview version 5.0; SAS Institute, Cary, North Carolina) running on a Windows personal computer was used to conduct the analysis. Continuous data were expressed as median and range. Mann-Whitney's U-test, Fisher's exact probability test, and the  $\chi^2$  test were used where appropriate. P < 0.05 was considered to denote statistical significance.

#### Results

The minilaparotomy approach with laparoscopic assistance was successful in all the patients. There were no significant differences between the two groups in terms of the patient age, male-to-female ratio, location of the tumor, pathologic stage, number of harvested lymph nodes, American Society of Anesthesiologists classification, duration of surgery, or blood loss. In terms of the postoperative complications, 1 patient in the LA (+) group developed a wound infection, whereas in the LA (-) group, 1 patient developed a wound infection and 1 patient developed enteritis. The frequency of post-

operative complications did not differ between the two groups. In terms of the type of lymph node dissection, the percentage of patients undergoing D1+ $\beta$  lymph node dissection tended to be higher in the LA (+) group than in the LA (-) group (*P* = 0.052) (Table 1). Although the blood loss was not significantly different between the two groups, the percentage of patients with blood loss more than 300 mL tended to be lower in the LA (+) group than



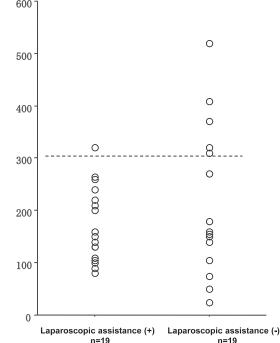


Fig. 2 The percentage of patients with blood loss of more than 300 mL tended to be lower in the patients undergoing gastrectomy with laparoscopic assistance than in those without laparoscopic assistance (P = 0.09).

Factors	Laparoscopic assistance (+) (n = 19)	Laparoscopic assistance (-) (n = 19)	P value
First pass of flatus (d)	1 (1–3)	2 (1–5)	0.04
Start of fluid diet (d)	4 (4-6)	4 (4–7)	0.17
Start of solid diet (d)	9 (7–14)	10 (7–23)	>0.99
Use of pentazocine (15 mg, IM)	1 (0-6)	1 (0-9)	0.82
Postoperative stay (d)	10 (8–14)	10 (8–41)	0.12

Table 2Postoperative recovery and analgesic use

IM, intramuscular.

in the LA (-) group (5.3% versus 31.6%, P = 0.09) (Fig. 2). First passage of flatus was significantly earlier in the LA (+) group than in the LA (-) group (P = 0.04). There were no significant differences in the time to start of fluid diet and solid diet, postoperative analgesic use, or postoperative length of hospital stay between the two groups (Table 2). The postoperative changes in the serum CRP levels are shown in Fig. 3. The serum level of CRP on postoperative day (POD) 1 was significantly lower in the LA (+) group than in the LA (-) group (P =0.04). The serum levels of CRP on POD 4 and POD 7 did not differ significantly between the two groups. The white blood cell count on POD 1 tended to be lower in the LA (+) group than in the LA (-) group (P = 0.07). The white blood cell counts on POD 4 and POD 7 did not differ significantly between the two groups (Fig. 4). There has been no recurrence after a median follow-up period of 18 months (range, 12-33 months) in the LA (+) group and 37 months (range, 26–50 months) in the LA (-) group.

#### Discussion

The underlying rationales for minilaparotomy with laparoscopic assistance for the resection of gastric cancer are twofold. First, as small an incision as necessary is done to extract the resected stomach



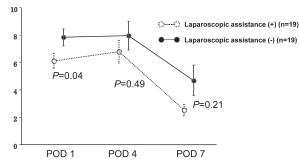


Fig. 3 Postoperative changes in serum levels of C-reactive protein.

and perform anastomosis safely right from the beginning of the surgical procedure. Second, the laparoscopic assistance enables an easier and safer lymph node dissection and division of vessels in the deeper surgical fields.

It is noteworthy that minilaparotomy with laparoscopic assistance has several advantages compared with minilaparotomy without laparoscopic assistance, especially in relation to the technical feasibility and minimal invasiveness. Factors related to the surgical technique, such as blood loss volume, duration of surgery, and number of harvested lymph nodes, did not differ between the two groups. However, the percentage of patients with excessive blood loss (i.e., >300 mL) tended to be lower in the LA (+) group. Considering that the percentage of patients undergoing D1+ $\beta$  lymph node dissection, which needs slightly more extended and complex procedures than D1+ $\alpha$  lymph node dissection, tended to be higher in the LA (+) group, laparoscopic assistance seems to be useful for decreasing the blood loss. In addition, objective parameters of minimal invasiveness, such as first passage of flatus, serum CRP level on POD 1, and leukocyte count on POD 1, were more favorable in the LA (+) group. Although the exact reasons for these results are unclear, it is possible that local tissue trauma related to lymph node dissection is lesser when a bipolar sealing device (Ligasure) or

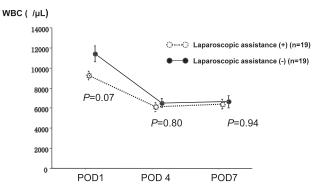


Fig. 4 Postoperative changes in white blood cell (WBC) counts.

when an ultrasonically activated device (Harmonic scalpel) is used than when a monopolar electrocoagulation device is used, as demonstrated by experimental studies.<sup>19,20</sup>

In 2003, Onitsuka *et al*<sup>11</sup> first reported their experience with minilaparotomy (7 cm) in 10 patients with early gastric cancer. They performed 5 distal gastrectomies and 5 pyloric ring-preserving gastrectomies, one of which required the extension of the incision to accomplish the procedure. In their series, D2 or near complete D2 lymph node dissection<sup>17</sup> was performed in all patients with a mean operative time of 175 minutes, although the blood loss was not documented. Subsequently, some Japanese surgeons<sup>12–16</sup> reported their experience of using the minilaparotomy approach with or without laparoscopic assistance for the resection of gastric cancer, focusing on the surgical techniques. To the best of our knowledge, this is the first report comparing minilaparotomy with and without laparoscopic assistance for the resection of gastric cancer in terms of the feasibility, safety, and minimal invasiveness.

The definition of minilaparotomy appears to be a matter of personal opinion. Some Japanese surgeons<sup>11–16</sup> reported a maximal incision length used for distal gastrectomy with a minilaparotomy of 6 to 7.5 cm. Hyodo *et al*<sup>21</sup> defined minilaparotomy as a 5to 6-cm incision through which gasless laparoscopyassisted distal gastrectomy was performed using an abdominal wall lift. Practically, 6 to 7 cm is the shortest incision that would allow the surgeon to insert his or her hand into the operative field for prompt control of unexpected bleeding. Rino  $et al^{22}$ reported that an incision of 3 cm or longer was needed to perform stapled gastroenterostomy safely in LAGD for early gastric cancer. Important, surgeons should note that distal gastrectomy can be accomplished through smaller incisions than is generally believed. The length of our minilaparotomy (<7 cm) is considered to be not any longer than the incision used for LADG when multiple incisions are made to insert trocars. Because the incision for our minilaparotomy is no longer than the length of the incision used for LADG, it will be less painful than a conventional open gastrectomy incision and comparable with that in patients undergoing LADG, although such comparisons were not performed in the present study and deserve further investigations.

Morbid obesity is generally considered to be a relative contraindication to LADG. Noshiro *et al*<sup>1</sup> reported that LADG for early gastric cancer in patients with BMI more than 24.2 kg/m<sup>2</sup> resulted in

significantly more technical difficulties, longer operative times, and delayed recovery of bowel activity than in those with lower BMI. Even conventional open gastrectomy may be more difficult to perform in obese patients than in slender patients. Bearing this in mind and our experience with the minilaparotomy approach for curative colectomy,<sup>9</sup> we tentatively excluded patients with a BMI of more than 25.0 kg/ m<sup>2</sup>, which is the cutoff value for internationally recognized overweight.<sup>23</sup> Further studies are needed to determine whether the indications of minilaparotomy with laparoscopic assistance could be expanded to more obese patients.

In institutions where surgeons are specialized in laparoscopic gastric procedures, LADG has been performed with wider acceptance, and it is considered to be the most useful treatment alternative to minimally invasive modalities for the treatment of early gastric cancer. However, even at present, we are not ready for the wide expansion of LADG in all institutions. However, we do not propose any restriction to expanding LADG. Unlike LADG, distal gastrectomy through minilaparotomuy with laparoscopic assistance is not associated with longer operative time. In addition, it does not require highly trained skills or a high cost. Thus, we believe that this surgical procedure should continue to be used as a minimally invasive treatment alternative in the future.

In conclusion, this study demonstrated that the use of minilaparotomy with laparoscopic assistance for distal gastrectomy might overcome the technical difficulties and invasiveness issues associated with minilaparotomy without laparoscopic assistance. In addition, this procedure seems to be a simple alternative to standard laparoscopic distal gastrectomy in selected patients with T1N0-1 gastric cancer. To validate the usefulness of this approach, a prospective randomized trial comparing this approach with LADG, in terms of the attribute of minimal invasiveness, cosmetic results, cost, and long-term oncologic outcomes, is needed.

#### References

- Noshiro H, Shimizu S, Nagai E, Ohuchida K, Tanaka M. Laparoscopy-assisted distal gastrectomy for early gastric cancer: is it beneficial for patients of heavier weight? *Ann* Surg 2003;238(5):680–685
- Kim MC, Kim KH, Kim HH, Jung GJ. Comparison of laparoscopy-assisted by conventional open distal gastrectomy and extraperigastric lymph node dissection in early gastric cancer. J Surg Oncol 2005;91(1):90–94

- Huscher CGS, Mingoli A, Sgarzini G, Sansonetti A, Di Paola M, Recher A *et al*. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial. *Ann Surg* 2005;241(2):232–237
- Sakuramoto S, Kikuchi S, Kuroyama S, Futawatari N, Katada N, Kobayashi N *et al.* Laparoscopy-assisted distal gastrectomy for early gastric cancer experience with 111 consecutive patients. *Surg Endosc* 2006;**20**(1):55–60
- Fleshman JW, Fry RD, Birnbaum EH, Kodner IJ. Laparoscopicassisted and minilaparotomy approaches to colorectal diseases are similar in early outcome. *Dis Colon Rectum* 1996;39(1):15–22
- Fürstenberg S, Goldman S, Machado M, Järhult J. Minilaparotomy approach to tumors of the right colon. *Dis Colon Rectum* 1998;41(8):997–999
- 7. Nakagoe T, Sawai T, Tsuji T, Ayabe H. Use of minilaparotomy in the treatment of colonic cancer. *Br J Surg* 2001;**88**(6):831–836
- Takegami K, Kawaguchi Y, Nakayama H, Kubota SY, Nagawa H. Minilaparotomy approach to colon cancer. *Surg Today* 2003;33(6):414–420
- Ishida H, Nakada H, Yokoyama M, Hayashi Y, Ohsawa T, Inokuma S *et al*. Minilaparotomy approach for colonic cancer: initial experience of 54 cases. *Surg Endosc* 2005;**19**(3):316–320
- Hsu TC. Feasibility of colectomy with mini-incision. *Am J Surg* 2005;**190**(1):48–50
- Onitsuka A, Katagiri Y, Miyauchi T, Yasunaga H, Mimoto H, Ozeki Y. Minilaparotomy for early gastric cancer. *Hepatogas*troenterology 2003;50(51):883–885
- Takahashi S, Kojima N, Bandou E, Kawamura Y, Yonemura Y. Distal gastrectomy performed via 6-cm laparotomy for early gastric cancer [in Japanese]. *Syujyutu (Operation)* 2005;**59**(8): 1161–1165
- Yasumoto K, Watanabe M, Mai M, Kouda W, Takahashi Y. Gastrectcomy via 3-inch (7.5 cm) incision [in Japanese]. Syujyutsu (Operation) 2007;61(3):315–321

- 14. Kimura Y, Kubo N, Noguchi T. Useful minilaparotomy approach for pyloric-ring preserving gastrectomy. *Geka-Chiryou (Surgical Treatment)* 2008;**98**(2):216–219
- Ishiguro T, Sakimoto T, Kubo N, Miyazaki T, Ishibashi K, Ishida H. Minilaparotomy (6–7 cm) for gastric cancer [in Japanese]. Syujyutsu (Operation) 2008;62(5):607–612
- Ishida H, Ishiguro T, Miyazaki T, Okada N, Kumamoto K, Ishibashi K *et al.* Distal gastrectomy via minilaparotomy for non-overweight patients with T1N0-1 gastric cancer: Initial experience of 30 cases. *Int J Surg* 2010;8(8):643–647
- Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma, 2nd English edition. *Gastric Cancer* 1998;4(1):10–24
- Japanese Gastric Association. *Therapeutic Guideline for Gastric Cancer* [in Japanese]. Tokyo: Kanehara, 2001
- Diamantis T, Kontos M, Arvelakis A, Syroukis S, Koronarchis D, Papalois A *et al*. Comparison of monopolar electrocoagulation, bipolar electrocoagulation, Ultracision, and Ligasure. *Surg Today* 2006;**36**(10):908–913
- Lantis JC II, Durville FM, Connolly R, Schwaltzberg SD. Comparison of coagulation modalities in surgery. J Laparoendosc Adv Tech A 1998;8(6):381–394
- Hyodo M, Hosoya Y, Yokoyama T, Arai W, Yasuda Y, Nagai H et al. Gasless laparoscopy-assisted distal gastrectomy for early cancer via mini-laparotomy using an abdominal wall lift. *Hepatogastroenterology* 2003;50(54):2279–2281
- 22. Rino Y, Ashida A, Harada H, Kawamoto M, Inagaki D, Yukawa NS *et al.* Laparoscopy-assisted distal gastrectomy with 3-cm laparotomy, left hepatic lobe compression technique, and selection of automatic anastomosis device. *Hepatogastroenterology* 2007;**54**(73):4–9
- 23. WHO expert consultation. Appropriate body mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;**363**(9412):157–163