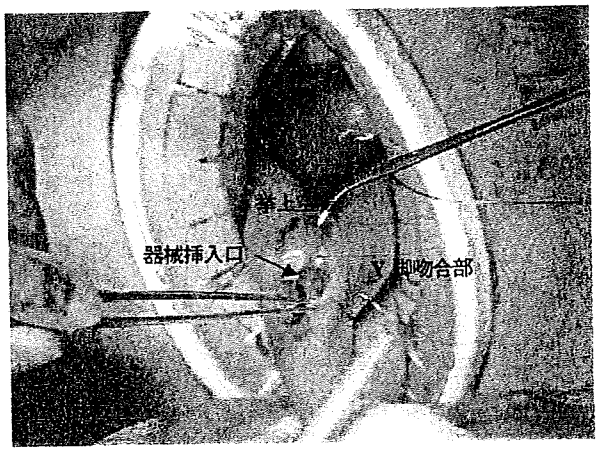


図11 Y脚吻合

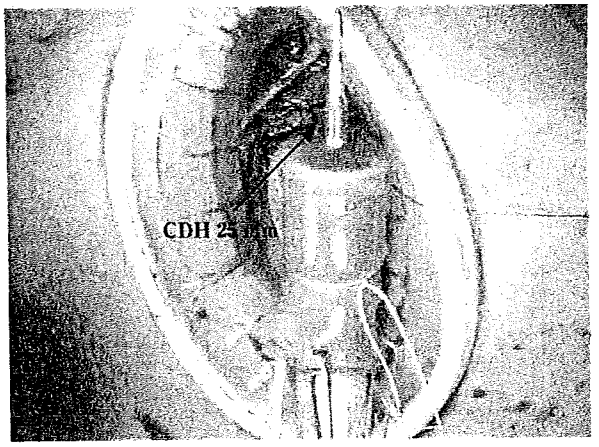


図12 食道空腸吻合

ステープラーを用いたR-Y法を概説する．

巾着縫合をかけた食道断端にサーキュラーステープラー(25 mm)のアンビルヘッドを挿入する．

次に空腸の処理を行う．通常Y脚吻合を食道空腸吻合に先立って行っている．腸把持鉗子をガイドに空腸を創外へ引き出す．Treitz靱帯から約20 cmの部位で空腸を辺縁動脈のみを処理し，リニアステープラー(45 mm)で切離する．Y脚吻合を食道空腸吻合予定部下端から約50 cmの部分で，リニアステープラー45 mmを用いて側々吻合で行う．器械挿入口は空腸の短軸方向に4-0吸収糸で全層連続1層縫合にて閉鎖する(図11)．続いて食道空腸吻合を行う．サーキュラーステープラー本体を挙上空腸断端から挿入し，吻合予定部にセンターロッドを出す．サーキュラーステープラーをドッキングし，食道空腸吻合を行う(図12)．

小開腹創からの吻合に無理があるときは，手術用手袋をサーキュラーステープラー本体に装着し再気腹し，腔内で確認しながら吻合している．空腸の挙上経路は結腸前としている．空腸断端をリニアステープラー45 mmで切離し再建を終了する．

### 13. 再気腹・ドレーン挿入・閉創

気腹した状態で，出血や，挙上空腸の捻れなどがないことを確認し，左右12 mmポートからドレーンを挿入する．ドレーンは，右はWinslow孔，左は左横隔膜下としている．

### 14. 術後管理

経鼻胃管は術直後に手術室で抜去している．

術後2日目に水分摂取，4日目に食事摂取を開始とし，三分粥，五分粥と順次食上げを行い，8日目以降に退院としている．

## おわりに

腹腔鏡下胃切除術は開腹手術と同等の技術的レベルになり，その遠隔成績においても，開腹手術と差異のないことが明らかにされつつある[5]．不十分なリンパ節郭清とならないよう，また安全な再建法となるよう留意して技術向上に努めることが重要である．

この概説が読者の手技の向上に少しでも寄与できれば幸いである．

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# Learning curve of laparoscopic surgery for gastric cancer, a laparoscopic distal gastrectomy-based analysis

**Xiaoqiao Zhang · Nobuhiko Tanigawa**

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**Abstract**
*Background* The application of laparoscopic gastrectomy in management of gastric cancer is being propagated rapidly. Training and education play important role during this process. The purpose of this study is to define the learning curve of laparoscopic gastrectomy to obtain an insight into this training process.
*Methods* All 362 cases of laparoscopic gastrectomy from January 1998 to July 2007 were enrolled and divided into 12 groups of 30 cases each in time sequence. The learning curve was defined with the split group method. Laparoscopic distal gastrectomy was extracted from the 12 groups and the means of operation time and intraoperative blood loss were compared to define the learning curve. Then general data and variables including occurrence of systematic inflammatory response syndrome (SIRS), complications, and conversion to open surgery were compared among the phases of learning curve.
*Results* A three-phase learning curve of laparoscopic gastrectomy was defined from the laparoscopic distal gastrectomy-based analysis, which included a training phase for the first 120 cases of operation, an intermediate phase for the following 90 cases, and a well-developed phase for the last 152 cases. Learning was considered to be complete after 60–90 operations in the training phase. For most variables, the differences among three phases were statistically significant except for the rate of complications.
*Conclusions* There was a significant learning curve, composed of three phases. Experience of about 60–90 cases of operation was required for completion of learning.

**Keywords** Learning curve · Laparoscopic gastrectomy · Gastric cancer

The laparoscopic technique has been introduced in surgical management of gastric cancer in the last two decades [1]. Its application is being propagated progressively and, especially this century, increasing numbers of surgeons are realizing its numerous merits. In Asian countries such as Japan and Korea, it has become a standard therapy for early-stage gastric cancer [2, 3]. However, due to the complexities of blood supply and lymphatic drainage pattern of the stomach, laparoscopic or laparoscopic-assisted gastrectomy is also recognized as a complicated and difficult procedure when compared with other laparoscopic operations. So a significant learning curve is associated with the development of these operative techniques [4]. To date, several authors have given perfect analyses of the learning curve of laparoscopic gastrectomy to obtain an insight into the progress of training, but these all focused only or mainly on the most popular procedure, laparoscopic distal gastrectomy [4, 5]. Here we aim to perform a further analysis of the learning curve of laparoscopic gastrectomy from a different point of view. We combine all laparoscopic gastrectomy procedures in order to analyze the learning curve of laparoscopic gastrectomy, because we think that different procedures may share the same pattern in terms of technique training. On the other hand, it is

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almost impossible for an institution to do only one kind of procedure, even over a short period.

## Materials and methods

### Patients

All 362 gastric cancer patients treated with laparoscopic surgery from 1st January 1998 to 31st July 2007 were enrolled in this study. Patients who accepted laparoscopic exploration only were excluded. Written informed consent was obtained from each patient before operation. To avoid the effect of manipulations besides "pure" laparoscopic gastrectomy, patients with conversion to open surgery or combined procedure for coexistent diseases were excluded in most analysis except for the conversion rate.

### Variables

#### *General data*

Sex, age, body mass index (BMI), pathological stage, and operative procedures were retrieved from medical reports and reviewed retrospectively.

#### *Operation invasiveness-related variables*

The following variables were recorded: operation time; volume of intraoperative blood loss, measured by weight difference between blood-stained gauze and dry gauze and the amount of blood in suction; and occurrence of systematic inflammatory response syndrome (SIRS) on the first postoperative day (POD1), according to the criteria by American College of Chest Physicians and Society of Critical Care Medicine [6]. All complications were recorded.

### Operative procedure and postoperative care

In general, the patient received operation under general anesthesia in a supine position with legs apart. A five-port technique was adopted, with a $CO_2$ pneumoperitoneum pressure of 8–10 mmHg. Mobilization of stomach and dissection of perigastric lymph node were performed following the Japanese Gastric Cancer Association (JGCA) gastric cancer treatment guidelines [7, 8]. Range of gastric resection and extent of lymphatic dissection were determined individually, according to the location of the primary lesion and clinical stage. The type of gastric resection included mucosectomy, wedge resection, segmental gastrectomy, laparoscopic (assisted) pyloric-preserving gastrectomy (LPPG), laparoscopic (assisted) distal gastrectomy (LDG), laparoscopic (assisted) proximal gastrectomy (LPG), and laparoscopic (assisted) total gastrectomy (LTG). Lymphatic dissection included D0, which means no lymphatic dissection or incomplete dissection of group1 lymph nodes; D1, dissection of group 1 lymph nodes; D1 + $\alpha$, dissection of group 1 lymph nodes plus nos. 7 and 8a lymph nodes if the primary lesion located in the lower third of the stomach; D1 + $\beta$, dissection of group 1 lymph nodes plus nos. 7, 8a, and 9 lymph nodes; and D2, which refers to the dissection of all group 1 and 2 lymph nodes. Reconstruction of gastrointestinal tract was performed laparoscopically or via a minilaparotomy.

Postoperative care was performed routinely according to the clinical pathway. In brief, the nasogastric tube was withdrawn on the morning of POD1. Recovery of oral intake was initiated on POD3 with water, followed by a dietary progression from liquid to soft food and finally to solid food. Usually intravenous fluid therapy was terminated on POD5. Preventive antibiotics were administrated intravenously just before operation and continued for 2 days. Postoperative mobilization was encouraged from POD2. Blood routine examination and blood biochemical analysis were performed routinely on POD1, 3, 5, and 7.

For the purpose of standardized operative technique, most of the operations were performed by the same operator (N.T.), and usually with the same laparoscopist and assistant, in the early stage.

### Defining learning curve of laparoscopic operation for gastric cancer

Two sequential variables, time of operation and amount of intraoperative blood loss, were used to define the learning curve by using a split group method. As the procedure with the most number of cases, LDG was selected and analyzed to represent laparoscopic gastrectomy. So, all 362 patients were divided into 12 sequential groups of 30 cases each ($n = 32$ only in the last group). LDG of each group was extracted, excluding those with conversion or combined resection. The mean values of operation time and amount of blood loss of LDG in each group were calculated and compared to define the learning curve. In this step, the Student–Newman–Keuls test was used for post hoc multiple comparison of mean values of operation time and amount of blood loss. The means for groups in homogeneous subsets were displayed by this method, and the homogeneous groups in continuous time sequence were defined to form a phase of the learning curve. Then other variables such as occurrence of complications, rate of conversion to open surgery, and operative invasiveness were evaluated among the different phases of the calculated learning curve.

### Statistics

All continuous variables are expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA), least-significant difference test, and Student–Newman–Keuls test were used for comparison and post hoc multiple comparison of continuous variables. $\chi^2$ test (Pearson chi-square test) was used for analysis of categorical variables.

$p < 0.05$ (two-sided) was considered to be statistically significant. All the statistical analysis was performed with SPSS13.0 software.

## Results

### Description of patient demographics

From 1st January 1998 to 31st July 2007, 362 patients with gastric cancer were treated with laparoscopic surgery in our department. The general demographics of these 362 patients are shown in Table 1. Most of the operations (303/362, 83.7%) were performed by the same operator (N.T.). There was conversion to open surgery in 13 cases. Combined procedures for coexistent diseases were performed in 26 patients. These 39 patients were excluded from most analysis. Operation-related deaths occurred in three patients due to postoperative complication.

For the remaining 323 patients, 89 had a past history of abdominal operation and 33 of them experienced upper abdominal operations. For 157 patients, history of at least one coexistent systemic disease was recorded. The operation time of these patients was 299.4 ± 82.1 (90–600) min, and volume of blood loss was 79.2 ± 111.8 (5–800) ml. On POD1, 32 patients (9.9%) exhibited SIRS. There were 86 postoperative complications in 75 patients. Among the 86 complications, 51 cases (59.3%) were infectious, including wound infection, peritonitis or intraperitoneal abscess, cholecystitis, respiratory tract infection, and central venous catheter-related infection. Other complications mainly included delayed gastric emptying, stricture of anastomosis, intra-abdominal bleeding, and systemic complications such as liver dysfunction and cardiovascular events. Relaparotomy or interventional radiology therapy were performed 15 times, in 14 patients, for hemostasis or draining intraperitoneal infection. Among these 323 patients 2 died, on POD4 and POD15, respectively. One died from hemorrhagic shock caused by postoperative pancreatitis and anastomotic leakage; the other died from peritonitis with undefined origin on relaparotomy.

**Table 1** Clinicopathological characteristics of all the patients ($n = 362$)

| Variable | Cases (%)/mean ± SD (range) |
|---|---|
| Sex | |
| Male | 245 (67.7%) |
| Female | 117 (32.3%) |
| Age (years) | 63 ± 10.4 (32–92) |
| BMI (kg/m$^2$) | 22.7 ± 3.0 (15.4–33.9) |
| Pathological stage | |
| Stage I | 342 (94.5%) |
| Stage Ia (T1N0M0) | 299 (82.6%) |
| Stage Ib | 43 (11.9%) |
| Stage II | 13 (3.6%) |
| Stage IIIa (T3N1M0) | 5 (1.4%) |
| Stage IV (T3N3M0, T3N2P1) | 2 (0.6%) |
| Operation procedure | |
| Mucosectomy | 2 (0.6%) |
| Wedge resection | 22 (6.1%) |
| Segmental resection | 15 (4.1%) |
| LPPG | 125 (34.5%) |
| LDG | 152 (42.0%) |
| LPG | 38 (10.5%) |
| LTG | 8 (2.2%) |
| Range of lymph node dissection | |
| D0 | 18 (5.0%) |
| Sd1 | 10 (2.8%) |
| D1 | 6 (1.7%) |
| D1 + $\alpha$ | 107 (29.6%) |
| D1 + $\beta$ | 111 (30.7%) |
| sD2 | 71 (19.6%) |
| D2 | 39 (10.8%) |

### Learning curve

Among the 362 patients, 133 cases of eligible LDG were extracted from the 12 consequential groups. For cases of LDG in each group, the mean values of time of operation and volume of blood loss are shown in Fig. 1. Viewing these two variables together, three phases could be defined, with the first four groups constituting the first phase, the following three groups belonged to the second phase, and the last five groups composing the third phase. For the groups forming each phase, mean operation time was statistically homogeneous on Student–Newman–Keuls analysis (Table 2). In the first phase, time of operation of the four groups decreased gradually. On the other hand, volume of blood loss decreased significantly after the first two groups and then stayed at a relatively lower level. So learning was considered to be complete at the end of this phase. Then, after a short intermediate phase, in which time of operation increased to some degree, a well-developed phase emerged with the shortest time of operation and smallest volume of blood loss. When the means of these two variables of LDG of the three phases were compared,

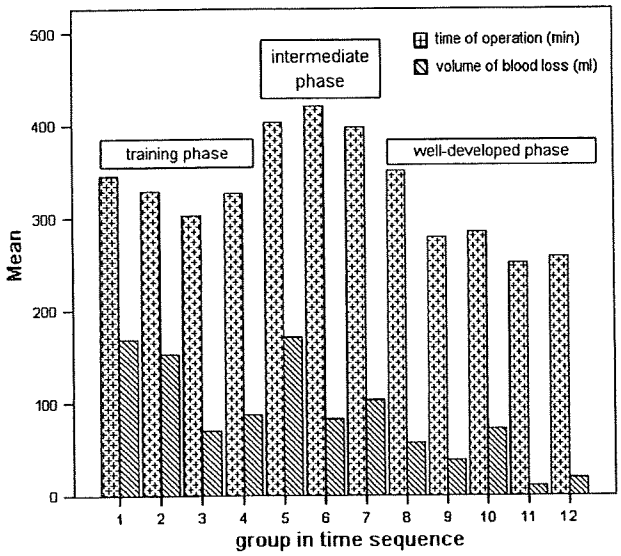


**Fig. 1** Time of operation and volume of blood loss for LDG in groups in time sequence. The 12 groups were divided into three phases: (1) the training phase, composed of the first four groups; (2) the intermediate phase, composed of the following three groups, and (3) the well-developed phase, composed of the last five groups

**Table 2** Student–Newman–Keuls analysis of time of operation of LDG among 12 groups (min)

| Group in time sequence | Groups in homogeneous subset | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| 11 | 251.15[c] | | |
| 12 | 257.86[c] | | |
| 9 | 279.00[c] | | |
| 10 | 285.00[c] | | |
| 3 | 302.69[a] | 302.69[a] | |
| 4 | 327.14[a] | 327.14[a] | 327.14[a] |
| 2 | 329.41[a] | 329.41[a] | 329.41[a] |
| 1 | 345.00[a] | 345.00[a] | 345.00[a] |
| 8 | 351.11[c] | 351.11[c] | 351.11[a] |
| 7 | | 397.78[b] | 397.78[b] |
| 5 | | | 403.33[b] |
| 6 | | | 420.88[b] |
| *p* | 0.069 | 0.050 | 0.073 |

[a] Groups defined to be in phase 1, the training phase

[b] Groups defined to be in phase 2, the intermediate phase

[c] Groups defined to be in phase 3, the well-developed phase

the differences were statistically significant, as shown in Table 3.

On further analysis, the 323 cases of laparoscopic gastrectomy were categorized by the three phases calculated based on LDG. The patients in each phase were statistically homogenous in terms of general data, including sex composition, history of abdominal operation ($\chi^2 = 1.593$, $p = 0.810$), coexistent systemic diseases ($\chi^2 = 3.889$, $p = 0.143$), pathological stage ($\chi^2 = 10.442$, $p = 0.235$), and BMI ($p = 0.262$), except for age and composition of procedures. The average age of patients of the three phases was 60.8 ± 10.4 years, 63.5 ± 9.8 years, and 64.0 ± 10.5 years respectively. The distributions of the three main procedures (LPPG, LDG, and LPG, which together accounted for about 90% of all procedures) were homogenous ($\chi^2 = 6.339$, $p = 0.175$). As shown in Table 4, operation time and volume of blood loss of the three phases of learning curve showed the same trends as for LDG. The difference among rates of SIRS was statistically significant. No difference was detected among rates of postoperative complications of the three phases.

To evaluate the conversion rate of different phase of learning curve, the total 362 patients were divided into three groups according to the abovementioned three phases of LDG. As a result, the rate of conversion to open surgery was significantly higher in the first training phase (7.3% versus 1.1% and 0.8% for the later two phases, respectively; $\chi^2 = 10.373$, $p = 0.006$).

## Discussion

With progress in early diagnosis and application of population screenings, the incidence of early-stage gastric cancer in Japan has increased to more than 50% of the overall morbidity of gastric cancer in past years [9, 10]. On the other hand, the application of laparoscopic surgery has also propagated at surprising speed in recent decades. Laparoscopic or laparoscopy-assisted gastrectomy was introduced into the field of surgical management of gastric cancer, especially for cases with early-stage cancer. Although its history is no longer than 20 years, laparoscopic gastrectomy for gastric cancer is being accepted by increasing numbers of surgeons and patients for its obvious merits such as less pain, earlier recovery, increased quality of life, and satisfactory short-term oncological outcome. The number of cases and its proportion in gastric cancer surgery have increased significantly, especially in the 21st century [1, 2].

However, due to the complexities of clinical anatomy for radical gastrectomy, laparoscopic or laparoscopic-assisted gastrectomy is sill quite difficult when compared with other laparoscopic operations. It is obvious that a relative longer learning progress is required to master laparoscopic gastrectomy, and that a significant learning curve is associated with this process [4]. It was believed that this learning curve would be helpful in developing strategy for training programs, evaluating the performance of a surgeon or a institution, and even optimizing patient care [5]. On the other hand, to our knowledge, to date there

**Table 3** Comparisons of time of operation and amount of blood loss of LDG among the phases of the learning curve

| Phase | *N* | Time of operation (min) | Amount of blood loss(ml) |
|---|---|---|---|
| Training phase | 52 | 324.52 ± 75.258* | 117.21 ± 144.403 |
| Intermediate phase | 35 | 410.43 ± 66.103* | 110.71 ± 157.499 |
| Well-developed phase | 46 | 279.46 ± 75.382* | 31.96 ± 47.264* |
| Total | 133 | 331.54 ± 88.690 | 86.02 ± 129.503 |
| *F* | | 32.368 | 6.683 |
| *p* | | 0.000 | 0.002 |

* $p < 0.05$ versus the values of the other two phases

**Table 4** Comparisons among the three learning-curve phases of laparoscopic gastrectomy with exclusion of conversion and combined resection

| Phase of learning curve | *n* | Time of operation (min) | Volume of blood loss (ml) | SIRS | Complications |
|---|---|---|---|---|---|
| Training phase | 101 | 304.30 ± 77.169* | 115.50 ± 126.278 | 17 (16.8%) | 23 (22.8%) |
| Intermediate phase | 80 | 343.38 ± 92.325* | 106.31 ± 143.557 | 7 (8.8%) | 25 (31.3%) |
| Well-developed phase | 142 | 271.52 ± 67.109* | 38.11 ± 51.738* | 8 (5.6%) | 27 (19.0%) |
| Total | 323 | 299.66 ± 82.145 | 79.45 ± 112.125 | 32 (9.9%) | 75 (23.2%) |
| $F/\chi^2$ value | | $F = 22.393$ | $F = 18.942$ | $\chi^2 = 8.451$ | $\chi^2 = 4.314$ |
| *p* | | 0.000 | 0.000 | 0.015 | 0.116 |

* $p < 0.05$ versus the values of the other two phases

are only two papers about the learning curve of laparoscopic gastrectomy for gastric cancer, and the objects of their analysis were only or mainly LDG. In our opinion, each case of laparoscopic operation of gastric cancer acts as a chance for training, no matter which kind of procedure it is, or whether there is conversion to open surgery or additional resection for coexistent disease or not. Also, due to the diversity of operative procedures of laparoscopic gastrectomy, it is almost impossible for an institution to do only a certain kind of operation even during a short period. So when we calculated the learning curve, instead of analyzing only a given kind of procedure, we combined all 362 cases of laparoscopic gastrectomy carried out at our institution and divided them into 12 time sequence groups.

Sophisticated approaches such as multivariate regression and the cumulative sum (CUSUM) method have been used in statistical assessment of learning curves of healthy technologies recently. Outcome-related variables, such as conversion to open surgery and occurrence of severe complications, were also evaluated. They were considered to be very useful in monitoring performance [5, 11, 12]. However, in this series, the conversion rate was less than 4%. In terms of complications, about half of them, such as port-site infection, could not be defined as performance-related events. On the other hand, severe complications which required relaparotomy or interventional radiology therapy accounted for less than 5%. As both conversions to open surgery and severe complications were too infrequent for reliable statistical analysis, we preferred to use the commonest, split group, method to define the learning curve of laparoscopic gastrectomy. Two proxies for learning, duration of operation and amount of intraoperative blood loss, were evaluated. To avoid bias caused by different procedures, we analyzed one kind of operation first. As the commonest procedure and as a surrogate for laparoscopic gastrectomy, LDG was extracted from each group and analyzed. As shown by the results of ANOVA analysis, the differences among the two variables between each time-sequential group were statistically significant. Based on this result, we divided the learning curve of laparoscopic gastrectomy into three phases: the training phase for the first four 30-case groups, an intermediate phase for the following three 30-case groups, and the well-developed phase, which began with the eighth 30-case group in the time sequence. Although such a categorization was clearly arbitrary, as shown in Fig. 1 and Table 3, average time of operation of LDG of each group in the same phase formed a homogenous subset. When the 323 "pure" laparoscopic gastrectomy were evaluated, the differences in the means of these two variables of the three phases were statistically significant also. So, we believe that such an arbitrary categorization was indeed, at least to some degree, defined objectively. As an ideal learning curve should be multidimensional and not reflect only duration of operation, other performance-related outcomes such as operative invasiveness, postoperative complication, and conversion rate were evaluated in further tests. The significantly decreased occurrence rate of SIRS and conversion rate in the latter two phases verified again the feasibility of this learning curve. So, such a learning curve,

at least to some degree, did reveal the nature of the learning process for laparoscopic surgery for stomach cancer.

During the training phase for the first 120 cases of operation, trends of decreasing volume of blood loss and shortening operative duration were clearly demonstrated. As these two variables reached a steady level in the latter half of this phase, we would like to say that learning was completed in this phase. An experience of about 60–90 cases of laparoscopic gastrectomy, which included LDG for 30–40 cases, was required for training and mastering essential techniques in this field. Blood loss of less than 100 ml was another marker of learning completion, and a further decreased amount of less than 50 ml may indicate the emergence of a well-developed phase. As described in series by other authors, about 60 operative cases for a given kind of procedure were required for completion of training [4]. When compared with these results, the completion of training in our series was slightly earlier. This may be caused by several factors such as the difference of patients' pathological characteristics, selection criteria, institutional performance in other laparoscopic surgeries, experience in open surgery of gastric cancer, etc. A strange feature of the learning curve was observed in this study: elongated duration of operation in the intermediate phase following the completion of learning in the training phase. We think that such an elevated segment of the curve may be mainly caused by the role and character of our institution. As a regional training center for laparoscopic surgery, up to 30 assistants attended the laparoscopic gastrectomy. After the termination of the training phase, education of this operation becomes an important task. In the following period, the assistants were encouraged to attend more in operation. So, such an education process resulted in the elongated duration, and only the duration of operation. After this relatively short intermediate phase, a well-developed phase with shorter operation duration and lower blood loss at a steady level soon emerged and persisted.

In spite of the aforementioned differences among the phases of learning curve, it should be noticed that, when complications of each phase were compared, no statistically significant difference in occurrence rate could be detected among the three phases. As some complications were not manipulation related and the rate of severe complications was quite low, we do not think that this indicates a failure of this learning curve to reveal surgical outcomes. On the other hand, based on our experience with gastric cancer surgery, we speculated that the occurrence of complications may be an accompanying phenomena related to the laparoscopic techniques used nowadays in gastric cancer surgery with a given rate of occurrence, but are not likely to be technique-related events. On the other hand, the rate of conversion to open surgery in the initial training phase was significantly higher than in the later two phases. This may, at least in part, be a reason for the averagely complication rate in the initial phase. So, in the training stage of laparoscopic gastrectomy, conversion to open surgery should be considered in case of difficult manipulation to avoid the occurrence of lethal complication.

Based on our analysis of the 362 cases of laparoscopic gastrectomy of our institution, we would like to conclude that there was a significant learning curve for its application, composed of three phases. Experience of about 60–90 cases of operation was required for completion of learning.

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# CHALLENGES IN PERFORMING SURGICAL RANDOMIZED CONTROLLED TRIALS IN JAPAN

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SURGICAL TRIALS IN ONCOLOGY have gradually become more popular since the late 1980s. They remain a challenge, however, because of the large number of cases needed to provide adequate statistical power and the difficulty in maintaining quality control when treatment is provided by numerous participating surgeons.[1] The smaller the number of surgeons involved, the easier it is to ensure that high surgical standards are applied. However, as the number of surgeons decreases, the accrual period increases and the results become less generalizable. The optimum approach to such trials would be to use a group of surgeons with similar standards of safety and efficacy. The first section of this article lists the pitfalls of surgical trials based on the experience of the Dutch Gastric Cancer Study (DGCS), whereas the second section outlines the challenges faced by the Japan Clinical Oncology Group (JCOG) in its studies of gastric cancer and provides suggestions to surgeons who plan to carry out similar clinical trials.

## LESSONS FROM THE DGCS

The author (M.S.) was asked to take on the role of instructor in the DGCS in 1989.[2] This study was one of the first multicenter randomized controlled trials (RCT) to evaluate 2 surgical procedures for cancer. Extended lymphadenectomy (D2) was compared with limited lymphadenectomy (D1) as treatments of curable gastric cancer. This study elucidated several critical problems in running surgical trials related to cancer treatment. Most of these issues have been pointed out in other articles.[3-6]

**When to proceed to phase 3: ensuring patient safety.** Specific training is required to perform any surgical procedure, which may be particularly the case with those aimed at cancer treatment.[7] Before starting the DGCS, only 1 of the Dutch surgeons had experience performing a D2 gastrectomy. Even in Japan, where both hospital and surgeon volumes are high, this procedure carries some risk of potentially fatal complications.[8] Retrospectively, a feasibility study to confirm the safety of this procedure when performed by Dutch surgeons on Dutch patients should have been carried out. Because prior to this study, no prospective phase 2 study had been conducted to evaluate the risk and safety of D2 dissection if performed by surgeons of little experience, we did not properly estimate the risk of 1 of the treatment arms and thus began a phase 3 trial without testing feasibility. Consequently, the hospital mortality of the D2 arm was 10%, which was more than double that of the D1 arm at 4%.[2] Similar or even worse postoperative mortality (14%) was observed in the Medical Research Council trials that compared D1 with D2, which was also carried out by surgeons with little experience in United Kingdom. These results are also the highest mortality rate reported in recent years among all cancer surgeries in high-volume hospitals, including esophageal and pancreatic cancers, which usually require more aggressive operative therapy than D2 gastrectomy.[9,10]

**Defining procedural details.** In this study, the details of both procedures were decided by a few surgeons, including the author (M.S.). The author had never observed operative performance of Dutch surgeons and, therefore, was unfamiliar with the standard techniques used for upper abdominal surgery in the Netherlands. Moreover, Dutch surgeons had no experience with D2 surgery. Thus, routine use of splenectomy and pancreatectomy in the D2 procedure was adopted in this trial, but in retrospect it was not the proper choice.[11] In multicenter trials on surgical procedures, a clear, detailed definition of each procedure is mandatory. The choice of a procedure must be based on the actual experience of the participants. Training via an instructional video or textbook is obviously insufficient. Ideally, all participating surgeons should engage in the process of defining the details of the procedure to be studied.

**Quality control of treatment.** If the quality of the operation is substandard, then the results should be carefully interpreted. In the words of U. Guller, "Garbage in, garbage out."[12] The greater the number of hospitals and surgeons involved in a trial, the wider the range of quality in surgical treatment that can be expected. This point is not an important issue in medical treatment, but it is a critical issue both in radiotherapy and in operative therapy. Quality control for radiotherapy may be easier than for surgical procedures. In the SWOG9008/INT0116 trial to evaluate postoperative chemoradiotherapy as adjuvant treatment for curable gastric cancer, a central review of the irradiation plan was carried out, and modification of the initial plan was performed in more than 30% of cases.[13] By managing quality control at a central level, trial leaders could minimize morbidity and anticipate the effect of radiotherapy. This trial proved the usefulness of postoperative adjuvant chemoradiotherapy, which is now the standard of care in the United States. This kind of quality control/assurance is not possible in an operation. As mentioned, only 1 of the participating

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surgeons in the DGCS had ever carried out D2 gastrectomy before the study began. To provide a standard level of D2 dissection, 80 participating hospitals were divided into 8 regions where 1 or 2 specialists responsible for quality control always participated in D2 surgeries. The author (M.S.) remained in the Netherlands for the first 4 months of the study period to provide hands-on training to these individuals, who had had no prior experience with D2 surgery. Considering the complex nature of the procedure, this time frame was too short to afford adequate instruction, because only 33 patients were available for instruction of D2 surgery during this period. This allowed us to provide at maximum only 3 mentored exposures to D2 dissection for each quality controller. This example does emphasize the importance of quality control in surgical trials.[14]

In this trial, retrieved lymph nodes were examined in detail according to the protocol.[4] This method is useful in assessing the accuracy of lymphadenectomy. Although this method could improve the quality of operative therapy in hospitals where all dissected nodes are examined, thorough pathologic assessment of lymph nodes was seldom regarded as important in Dutch hospitals. In fact, the mean number of examined nodes from the specimens dissected by the author (M.S.) was counted as 31 if nodes were retrieved by Dutch pathologists and as 60 in other specimens from which all nodes were retrieved by the author (M.S.) himself.[15]

**Regular monitoring and termination rules.** As mentioned in the first section of this article, DGCS was started without any phase 2 studies to confirm feasibility, and no selection criteria limited hospital participation. Given this situation, rather strict termination rules should have been included in the protocol, based on hospital mortality rates, because of the uncertain safety of D2 gastrectomy performed by Dutch surgeons. A regular monitoring committee met to discuss problems in the trial, but much attention was not given to mortality issues. If an independent data and safety monitoring committee had existed, it could have recommended or ordered a temporary cease of accrual and could have changed the basic structure of the trial and minimized avoidable patient deaths. From an ethical point of view, more than double the risk of hospital mortality without certainty of an accompanying survival benefit is not acceptable in a randomized surgical study. If patients had been informed of the interim safety results, then it is doubtful that many would have accepted randomization.

**Data handling and restriction of data access.** An independent data center was implemented, but all data were accessible to investigators, and survival comparisons could have been carried out numerous times throughout the study period. In this study, there was no concept of multiplicity data analysis, and no planned interim analysis was required within the protocol. Survival analyses were carried out more than several times, the results of 2 of which were published without referring to the consumption of alpha error. Applying common sense with regard to statistical approaches should have prevented the problems in data analysis experienced in this study.

**Postoperative care.** The DGCS had many critical problems, as mentioned above, but it was still an important first step in this field. In particular, the heavy attention devoted to the quality control of an operation strongly affected studies planned afterward. However, no attention was given to the quality control of postoperative care in these patients; this issue that proved unexpectedly to be significantly related to the high hospital mortality rates that were observed. D2 surgery, which includes pancreaticosplenectomy, was expected to have high morbidity, but such high mortality after major complications was not anticipated. Hospital mortality after an anastomotic leak was greater than 40%, and that after pancreatic fistula with intra-abdominal abscess was 21%, whereas mortality rates after these events in a Japanese series in the 1980s were 14% and 3%, respectively.[16] Accumulation of experience was necessary to avoid postoperative hospital deaths after major complications. In the DGCS, the average number of D2 dissections per year was less than 2 per hospital; thus, gaining the postoperative management experience to avoid treatment related deaths was almost impossible. It has been suggested that Dutch patients might be much more fragile than those from Japan and that the high mortality rates observed might be caused by their underlying physical weakness. However, another RCT on the surgical treatment of esophagogastric junctional tumor (EGJT) performed by 2 specialized Dutch hospitals demonstrated much lower hospital mortality with a much higher incidence of potentially fatal major complications.[17] The only possible explanation is that the DGCS was carried out in 80 hospitals, which include peripheral general hospitals whose patient volume was low, whereas the EGJT study was performed in only 2 specialized centers. In the latter trial, each hospital had high volumes; thus, the requisite experience to manage potentially fatal complications and avoid treatment-related deaths was available.

## CHALLENGES IN THE JCOG

**Advantage of a cooperative group.** In Japan, several cooperative groups exist, and the JCOG was the first and is the best organized of these. This organization has a strictly independent data center and 14 organ-specific groups. It also has a steering committee (headquarters) and several other functioning committees, such as an audit committee, data and safety monitoring committee, and protocol review committee. All aspects of a trial, especially safety aspects, are strictly monitored by several committees. Peer review by statisticians, medical oncologists, surgeons, or clinical research coordinators in various fields allows protocols to be clear, scientific, and ethical. All the data are controlled by the data center, and data sets cannot be accessed by researchers individually. Most trials include planned interim analyses, which are performed by statisticians that do not belong to the specific group conducting the trial. Survival results are shown only to the independent data and safety monitoring committee, which does not include any of the group's own researchers or statisticians. A lack of this type of organization was one of the many weak points of the DGCS.

**Setting up phase 3 trials in the JCOG.** In the JCOG, the first step in setting up a trial is to write a protocol concept. When the researchers in an organ-specific group agree to undertake a clinical trial, one of them writes a protocol concept to explain the background, methods, and feasibility of the study. With the help of the group's associated statistician, statistical aspects such as alpha, beta, and sample size are also discussed. A committee, which is composed of statisticians, medical oncologists, surgeons, and clinical research coordinators, peer reviews the protocol and then reports their evaluation along with any questions they might have. This report is discussed by the steering committee, and a vote is held to decide whether the study is worth performing in the JCOG. Any lack of safety information or lacking of experience of the participants involved in the study is usually pointed out, and the review committee sometimes recommends that the researchers carry out a feasibility study or a phase 2 study instead of proceeding immediately to phase 3. Especially in cases of surgical trials, hospital mortality should be maintained below 5% even with multidisciplinary treatment such as extended operative therapy after neoadjuvant chemotherapy. At the moment, a mortality rate higher than 5% is no longer acceptable in Japan for any cancer operation.

After approval by the steering committee, a full protocol is written by researchers together with coordinating physicians who are specialists at compiling protocols for clinical studies. This process takes a rather long time, especially in surgical trials, because the details of each surgical technique used in the study must be defined clearly and agreed on by all trial participants so as to minimize the variation in procedural implementation. Occasionally, selection of the participants is debated, especially in studies that require learning of new techniques, such as laparoscopic cancer surgery. The nature of the surgical technique also influences the decision of how to evaluate the results of the procedure performed in each case.

**Actual trials in the Gastric Cancer Surgical Study Group (GCSSG) of the JCOG.** In the GCSSG of the JCOG, 5 surgical trials have been conducted since 1995. The first trial, JCOG9501, was a phase 3 trial among 24 Japanese hospitals that compared D2 gastrectomy with superextended D3 gastrectomy, which is a D2 gastrectomy plus para-aortic nodal dissection, for T2b-T4 gastric cancer. Between July 1995 and April 2001, we randomized 523 patients intraoperatively to either the D2 arm (263 patients) or the D3 arm (260 patients). No adjuvant therapy was permitted until recurrence. The primary endpoint was overall survival. We paid careful attention to this initial surgical trial because of the experience of DGCS as previously mentioned. This trial selected surgeons who had experience with more than 100 gastrectomies with D2 dissection, or hospitals with an annual gastrectomy volume of more than 80 cases. During the study planning stages, all participating surgeons agreed to the technical details of both types of operations. In addition to reviewing the semiannual monitoring report, several participating surgeons presented videos of 1 or both procedures of arbitral patients to ensure uniformity of treatment and the procedures' technical details were discussed. To assess compliance with the specified type of lymphadenectomy, node retrieval in all regional nodal stations and number of dissected nodes in the para-aortic area were recorded on case report forms, which were also monitored. As a result, both surgical arms showed permissible complication rates and low hospital mortalities (0.8% in each arm).[8] Unexpectedly, no significant difference was observed in either overall survival or recurrence-free survival between the 2 groups. In conclusion, this first JCOG surgical phase 3 trial demonstrated that superextended D3 gastrectomy should not be used to treat this target population.[18]

In parallel with JCOG9501, another phase 3 trial was conducted to compare the effects of a left thoracoabdominal (LTA) approach with a abdominal-transhiatal (TH) approach in the treatment of gastric cancers with an esophageal invasion of 3 cm or less (corresponding mainly to tumors classified as Siewert type 2 or 3). Following a similar quality control procedure as JCOG9501, the JCOG9502 trial selected 27 specialized hospitals for participation. Only 3 patients died in hospital after LTA and none after TH. Morbidity was less favorable after LTA than after TH. Nevertheless, the survival of the LTA arm was diminished compared with the TH arm at the first interim analysis.[19] We therefore closed the accrual and opened the results according to the recommendation of the independent data and safety monitoring committee. Thus, the JCOG9501 and JCOG9502 trials demonstrated the ineffectiveness of more extensive surgeries and led to the establishment of standard surgeries in the field of gastric cancer.

Through the experience of these initial trials, other surgical trials were planned and are now ongoing in the GCSSG of the JCOG. JCOG0110 is a trial to evaluate the role of splenectomy in total gastrectomy for proximal gastric cancer in terms of survival benefit and postoperative morbidity.[20] Because this trial was designed in a noninferiority fashion, we have managed quality control more strictly than in previous trials, using a superiority-based approach so as not to affect the final results inappropriately. For example, the details of the planned surgical procedures were specified and described more clearly in the trial protocol before the study began. The number of dissected nodes in all stations was recorded on case report forms to be used for assessing the quality of operative therapy. We made a termination rule regarding hospital mortality in advance. If the number of deaths caused by surgical complications reached 10, the accrual would be stopped temporarily to wait for a judgment from the data and safety monitoring committee. The randomization to either gastrectomy with or without splenectomy was performed during operation after intraoperative confirmation of the eligibility criteria. Recruitment of the planned sample of 500 patients was accomplished in March 2009, after which all patients will be followed for 5 years.

We have also conducted a phase 2 trial of laparoscopy-assisted distal gastrectomy (LADG). Recently, this laparoscopic surgery technique has been established in specialized institutions. Although the technical difficulties of LADG have been solved gradually, some retrospective studies have reported that LADG is associated with a higher risk of surgical morbidities, such as anastomotic leak, stenosis, and pancreatic fistula, compared with open gastrectomy. The aim of the JCOG0703 trial is to evaluate the safety of LADG in clinical stage I gastric cancer. The primary endpoints are incidence of anastomotic leak and pancreatic fistula. If the incidence of these 2 postoperative complications is as low as expected (3% in total), then a subsequent phase 3 trial will be started to evaluate noninferiority of LADG compared with open gastrectomy in terms of long-term survival. Only surgeons with experience of more than 30 LADG and 30 open distal gastrectomies were allowed to participate in this trial. In addition to monitoring the number of dissected nodes in all stations with a case report form, we performed a central review of the surgical procedure by photographs of all patients and by videotaping of arbitrarily selected patients. This trial would have stopped accrual if treatment related deaths or life-threatening complications had reached 6.[21]

The latest JCOG phase 3 trial has just started with the international collaboration of the Korean Gastric Cancer Association. The prognosis of patients who suffer from incurable gastric cancer with hepatic or peritoneal metastases is poor. To investigate the role of gastrectomy in advanced gastric cancer with a single noncurable factor, 43 specialized hospitals (33 Japanese and 10 Korean) are conducting this REGATTA (JCOG0705) trial. Patients are randomized to either gastrectomy plus chemotherapy or to chemotherapy alone. The primary endpoint is overall survival, and the planned sample size is 330 with 2 years of follow-up after 4 years of accrual. The JCOG data and safety monitoring committee will independently perform the interim analysis and will consider stopping the trial early on behalf of both countries. Central monitoring is performed by the respective data center in each country to ensure data submission, patient eligibility, protocol compliance, safety, and on-schedule study progress. The monitoring reports are submitted to and reviewed by the respective data center independently every 6 months. The monitoring summary is exchanged between the 2 countries semiannually. Audits of the participating facilities are also carried out independently in each country, and brief summaries are exchanged. In this trial, if the number of treatment-related deaths reaches 9 in the chemotherapy-alone arm or 14 in the gastrectomy-plus-chemotherapy arm, the accrual will be stopped temporarily. Prior to its initiation, we had all expected significant difficulties in starting this international trial because of the many differences in medical culture and customs, as well as language, between Japan and Korea. Furthermore, most surgical trials are initiated by investigators without industrial sponsors, which requires them to obtain governmental or other competitive grants. Fortunately, the above challenges have been overcome, and the trial has been launched thanks to all the investigators' sincere efforts. Thus, the key to success in conducting high-quality surgical clinical trials is the investigators' enthusiasm and commitment to providing the best possible treatment to all future patients worldwide.

In conclusion, many issues in surgical oncology clinical trials are not relevant to medical oncology trials. If the treatment provided in surgical trials is not marked by the high quality afforded by specialists, the resulting benefits will not be appreciated by either patients or their providers. Establishing a cooperative group of specialists whose technical variance is minimal is therefore of paramount importance in performing meaningful clinical trials in surgical oncology.

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# INVESTIGATIONS USING CLINICAL DATA REGISTRIES: OBSERVATIONAL STUDIES AND RISK ADJUSTMENT

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OUTCOMES RESEARCH has progressed a great deal in the past several years with the increasing availability of population-based data sources as well as other types of data registries. Also, the increasingly powerful and menu-driven statistical packages have made analyses of such data sets common, place, and have contributed to the increasing numbers of such publications. In this regard, however, there are a number of issues that an investigator needs to understand and address when performing such analyses. This article will review the following approaches to observational studies, with particular comments relevant to the use of clinical registry data:

- No risk adjustment
- Cohort study
- Case-control study
- Stratified study
- Regression-based risk adjustment
- Matching
- Propensity scores
- Instrumental variables

Following these observations, a few additional topics that are critical to the most common approaches will be briefly discussed:

- Sensitivity analysis
- Adjusting for exogenous and endogenous factors
- Regression to the mean
- Average treatment effect versus treatment effect on the treated
- The use of administrative data for risk adjustment

## BACKGROUND: RANDOMIZED CONTROLLED TRIALS VERSUS OBSERVATIONAL STUDIES

The experiment is a critical element of the scientific method:

*In the scientific method, an experiment (Latin: ex periri "of (or from) trying") is a set of observations performed in the context of solving a particular problem or question, to retain or falsify a hypothesis or research concerning phenomena. The experiment is a cornerstone in the empirical approach to acquiring deeper knowledge about the physical world.*[1]

There are some critical and desirable features in the design of experiments. First, only one factor or treatment, referred to as the *experimental, treatment* or *independent variable,* should vary systematically across the experiment's groups. When this is true, the experiment is considered a *controlled experiment.* In controlled experiments, other factors that might also affect the outcome being studied do not vary systematically between groups. This method enables strong conclusions about the isolated effect of the experimental variable. A second major desirable feature in the design of experiments is for the outcome being studied (the *dependent variable*) to actually reflect an influence of the independent variable and for the measurement of that outcome to be possible without error or with describable error.

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Clinical Trial Note

# A Phase II Trial of Combined Treatment of Endoscopic Mucosal Resection and Chemoradiotherapy for Clinical Stage I Esophageal Carcinoma: Japan Clinical Oncology Group Study JCOG0508

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Standard treatment for clinical stage I esophageal cancer with submucosal invasion (T1b) has been surgical resection. We conducted a Phase II trial to evaluate the efficacy and the safety of combined treatment of endoscopic mucosal resection (EMR) and chemoradiotherapy for clinical stage I (T1b) esophageal cancer. Patients diagnosed as having clinical stage I (T1b) esophageal cancer which is considered to be resectable by EMR are eligible. When pathological examination of the EMR specimen confirms T1b tumor with negative or positive resection margin, the patient undergoes chemoradiotherapy. The study continues until 82 patients with T1b tumor with negative resection margin are enrolled from 20 institutions. The primary endpoint is 3-year overall survival (OS) in pT1b cases with negative resection margin. The secondary endpoints are 3-year OS and progression-free survival in all eligible cases, OS in pT1a-MM cases with margin-negative, complications of EMR and adverse events of chemoradiotherapy. The data from this trial will be expected to provide a non-surgical treatment option to the patients with clinical stage I (T1b) esophageal cancer.

*Key words: superficial esophageal cancer – endoscopic mucosal resection – chemoradiotherapy*

## INTRODUCTION

According to the Japanese Classification of Esophageal Cancer by the Japan Esophageal Society, T1 esophageal tumors defined by the TNM system (6th edition) is further divided into T1a (mucosal) and T1b (submucosal) tumors by the Japanese Classification of Esophageal Cancer (1). Endoscopic mucosal resection (EMR) is usually indicated for T1a tumor, whereas the standard treatment for T1b tumors has been a surgical resection with adequate lymph node dissection in Japan because of the high incidence of lymph node metastasis (~40%) (2). However, surgical resection often deteriorates patient's general condition. Some patients with clinical T1b esophageal cancer are over-treated by surgery with a result of pathological T1a tumor, because the accuracy of diagnosis of T1b esophageal cancer is not high.

Recent advance in techniques of EMR including endoscopic submucosal dissection (ESD) enables us to remove the clinical T1b tumor and gives us accurate diagnosis of depth of invasion. However, the patients with T1b are at risk of lymph node metastasis (3) and therefore EMR alone cannot be considered as curative.

Chemoradiotherapy is one of the effective modalities for both early and advanced esophageal tumors. Since chemoradiotherapy is less toxic than surgical resection, the usefulness has been tested in several clinical trials (4,5). In Japan,

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a Phase II trial (JCOG9708) was conducted to evaluate the efficacy and the safety of concurrent chemoradiotherapy using 5-fluoraouracil (5-FU) plus cisplatin (CDDP) for T1 tumors (6). However, 22% of patients showed minor relapses that needed to be removed by endoscopic treatment. We have therefore conducted a pilot study of EMR followed by chemoradiotherapy and have reported promising results (7). Thus, the Japan Clinical Oncology Group initiated this multi-institutional Phase II trial (JCOG0508) to evaluate the efficacy and the safety of combined treatment of EMR and chemoradiotherapy for clinical stage I (cT1bN0) esophageal cancer.

The Protocol Review Committee of JCOG approved the protocol in October 2006 and the study was activated in December 2006.

## JCOG0508 PROTOCOL

### Purpose

The aim of this study is to evaluate the efficacy and the safety of combined treatment of EMR and chemoradiotherapy for clinical stage I (T1b) esophageal cancer.

### Study Setting

The study is a multi-institutional (20 centers), single-arm Phase II trial.

### Resources

This study is supported by the Grants-in-Aid for Cancer Research (17S-3, 17S-5, 20S-3, 20S-6) and Health and Labour Sciences Research Grant for Clinical Cancer Research (17-12) from the Ministry of Health, Labour and Welfare, Japan.

### Endpoints

The primary endpoint is 3-year overall survival (OS) in pT1b cases with negative resection margin (comment 4). The secondary endpoints are 3-year OS and progression-free survival (PFS) in all eligible cases, OS in pT1a-MM (muscularis mucosa) cases with negative resection margin, complications of EMR and adverse events of chemoradiotherapy.

In this trial, resection margin is diagnosed from endoscopic findings immediately after mucosal resection for horizontal margin and from pathological findings for vertical margin. OS is defined as the time from registration to death from any cause, and it is censored at the last contact day for living patient. PFS is defined as the time from registration to either the first event of progression or death from any cause, and it is censored at the latest day when patient is alive without progression.

### Inclusion Criteria

Patients are included in this trial if they meet all of the following criteria: (i) histologically proven squamous cell carcinoma of the esophagus by endoscopic biopsy, (ii) tumors located within the thoracic esophagus, (iii) depth of tumor invasion is diagnosed as T1b by endoscopy and endoscopic ultrasonography, (iv) the number of multiple intra-esophageal tumors is less than three, and the depths of invasion of them are diagnosed as cT1a-EP (carcinoma *in situ*) or cT1a-LPM (tumor invades lamina propria mucosa), (v) clinically node-negative (cN0) and no metastasis to other organs (cM0), (vi) size of main tumor is $\leq$5 cm, and circularity of esophageal lumen is less than three-fourths, (vii) no ulcerative lesion in the tumors, (viii) no intra-esophageal metastasis, (ix) no prior treatment of chemotherapy or radiation therapy against any other malignancies, except for previous curative EMR for pT1 esophageal cancer, (x) aged between 20 and 75 years old, (xi) performance status of 0 or 1, (xii) sufficient organ functions and (xiii) written informed consent.

### Exclusion Criteria

Patients are excluded if they meet any of the following criteria: (i) iodine allergy, (ii) enable to discontinue anticoagulant or antiplatelet medications, (iii) synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*, (iv) pregnant or breast-feeding women, (v) severe mental disease, (vi) systemic administration of corticosteroids, (vii) HBs antigen positive, (viii) active bacterial or fungous infection, (ix) concurrent unstable angina or myocardial infarction within 3 months before registration, (x) unstable hypertension, (xi) diabetes mellitus, uncontrolled or controlled with insulin, or (xii) interstitial pneumonia, lung fibrosis or severe emphysema.

### Registration

After confirming the inclusion/exclusion criteria by telephoning or faxing the JCOG Data Center, the patients are registered into this JCOG0508 trial.

### Quality Control of EMR

Twenty institutions among the Gastrointestinal Oncology Study Group of the JCOG participate in this trial. All participating physicians have agreed to the technical details for EMR. For quality control of EMR technique and endoscopic diagnosis, we perform central review of the photographs in all patients at the semi-annual investigators meeting. Regarding an ESD procedure, we permit it only for expert physicians who have significant experiences in ESD and EMR, and they are registered by the primary investigator (M.M.). The minimum request for ESD permission is the experience of EMR $\geq$ 50 and ESD $\geq$ 10 for esophageal

carcinoma, ESD $\geq$ 50 for gastric cancer and perforation rate $\leq$2% in total.

### Treatment Methods

#### Endoscopic Mucosal Resection

EMR is performed against esophageal tumors within 30 days from registration. The technical methods of EMR approved in this trial are a two-channel method, a cap method or an esophageal endoscopic mucosal resection-tube method (8). Only the registered physicians are allowed to perform ESD in this trial. After EMR, it should be confirmed endoscopically that no iodine-unstained area is left. Physicians need to take pictures before and after EMR and submit them to the primary investigator for quality control of EMR technique and endoscopic diagnosis.

#### Chemoradiotherapy

In cases of pT1a tumor with negative resection margin and no vascular invasion, no additional treatment after EMR is given. In other cases, chemoradiotherapy was started at 29–70 days after EMR. The chemotherapy regimen is continuous 5-FU (700 mg/m$^2$/day, days 1–4 and 29–32) and CDDP (70 mg/m$^2$/day, days 1 and 29). The dose of radiotherapy is 41.4 Gy/23 Fr/5 weeks (5 days/week) for cases with negative resection margin and 50.4 Gy/28 Fr/5 weeks (5 days/week) with boost on the primary site for the case with positive resection margin, respectively.

#### Follow-up

Patients are followed with blood tests, upper gastrointestinal endoscopy and computed tomography at least every 4 months for 3 years.

### Study Design and Statistical Methods

This trial determines the efficacy and the safety of combined treatment of EMR and chemoradiotherapy for cT1b esophageal cancer in terms of 3-year OS. Additionally, 3-year OS in all eligible patients are evaluated as the most important secondary endpoint. The sample size is 82 for pT1b cases with negative resection margin with the power of 90%. In case this hypothesis rejected, the secondary hypothesis for all eligible patients can be tested using hierarchical method keeping trial-wise $\alpha$ error nominal level, one-sided 5%, with the power of 80%. To test the hypothesis, 3-year OS estimated by Kaplan–Meier method and its confidence interval by Greenwood's formula is used. The total number of registered patients is estimated as 137, because the proportion of pT1b cases with margin-negative among all eligible patients is predicted as ~60%.

This study was registered with UMIN-CTR [www.umin.ac.jp/ctr/], identification number UMIN000000553.

### Interim Analysis and Monitoring

Interim analysis is not planned. If the number of cases with treatment-related death, severe (Grade 4) bleeding or severe (Grade 4) perforation reaches seven, the registration will be suspended unless the JCOG Data and Safety Monitoring Committee approves to continue this trial. The JCOG Data Center is responsible for data management, central monitoring and statistical analysis. This center also provides semi-annual monitoring reports, each of which is submitted to and reviewed by the JCOG Data and Safety Monitoring Committee on demand of the JCOG Data Center. None of physicians administering the interventions are involved in the data analysis. For quality assurance, site-visit audits, not for a specific study basis but for the study group basis, are done by the JCOG Audit Committee.

## Acknowledgements

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## Conflict of interest statement

None declared.

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## Appendix

The initially participating hospitals are as follows: Iwate Prefectural Central Hospital, Ibaragi Prefectural Central Hospital, Tochigi Cancer Center Hospital, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Showa University Hospital, Cancer Institute Ariake Hospital, Kitasato University East Hospital, Kanagawa Cancer Center Hospital, Ishikawa Prefectural Central Hospital, Saku Central Hospital, Shizuoka Cancer Center Hospital, Aichi Cancer Center Central Hospital, Kyoto University Hospital, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka City Medical Center, and Osaka Medical College Hospital.

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ORIGINAL ARTICLE

# Laparoscopy-Assisted Distal Gastrectomy with D2 Lymph Node Dissection Following Standardization—A Preliminary Study

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**Abstract**
*Background* Laparoscopy-assisted distal gastrectomy (LADG) with standard D2 dissection is a complex procedure usually performed only by experienced surgeons, and the feasibility of this procedure still remains unclear.
*Method* Patients who underwent LADG at the Cancer Institute Hospital between April 2006 and October 2008 were recruited for this study. Early surgical outcomes were compared between patients who underwent complete D2 dissection (complete D2 group; $n$=42) and those who underwent D1 + beta dissection (D1 + beta group; $n$=179) to determine the feasibility of laparoscopic D2 lymph node dissection.
*Results* In complete D2 group, the operation time was longer (253±10 vs 224±4 min; $P$=0.005), and the number of retrieved lymph nodes was larger (41±2 vs 35±1; $P$=0.002) compared with those in D1 + beta group. The other early surgical outcomes monitored for the two groups were not different between groups.
*Conclusions* LADG with complete D2 lymph node dissection can be performed safely if the procedure is standardized and an experienced laparoscopic surgeon performs the surgery. To be accepted as a standard treatment for advanced gastric cancer, well-designed prospective trial is necessary.

**Keywords** Laparoscopy-assisted gastrectomy · Gastric cancer · D2 lymph node dissection

## Introduction

Laparoscopy-assisted gastrectomy (LAG) is increasingly performed in Japan since the first case of laparoscopy-assisted distal gastrectomy (LADG) with Billroth I reconstruction was reported.[1] Several advantages of LAG compared with conventional open gastrectomy have been documented,[2–8] including reductions in bleeding and pain and reduced disturbance of respiratory function. However, LAG has limitations for lymph node dissection,[7] and at present in Japan, generally accepted laparoscopic lymph node dissection is D1 and D1 + beta lymph node dissection (D1 + station 7, 8a, 9 lymph nodes dissection), while complete laparoscopic D2 lymph node dissection is performed by experienced surgeons.[7,9–13]

A large randomized controlled trial conducted in Europe failed to prove the efficacy of conventional open gastrectomy with D2 lymph node dissection due to the high morbidity and mortality rate.[14–17] By comparison, in Japan, the procedure for conventional open gastrectomy with complete D2 lymph node dissection (D1 + station 7, 8a, 9, 11p, 12a, 14v lymph node dissection) is well established and accepted as a standard practice for the treatment of advanced gastric cancer.[18–20] Therefore, the feasibility of LAG with D2 lymph node dissection should be investigated so that LAG is accepted as a standard treatment for advanced gastric cancer.

It is difficult to perform LAG with complete D2 lymph node dissection since this type of surgery involves major vessel and pancreatic tissue exposure, and there is, therefore, an increased risk of major vessel injury and postoperative

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pancreas-related infections associated with the procedure. Therefore, the establishment of standardized procedures for D1 + beta lymph node dissection might be an initial step towards the introduction of complete laparoscopic D2 lymph node dissection. In our institute where these procedures have been standardized,[21] the number of laparoscopic D2 lymph node dissections is gradually increasing. In the present study, the early surgical outcomes of laparoscopic D2 lymph node dissection was investigated, and these surgical outcomes were compared with those following D1 + beta lymph node dissection. The feasibility of laparoscopic D2 lymph node dissection following standardization of LAG with D1 + beta lymph node dissection was thereby determined.

## Patients and Methods

Patients who were treated with LADG with extraperigastric lymph node dissection performed by one of the two specialists (F.T. or H.N.) at the Cancer Institute Hospital between April 2006 and October 2008 were included in the study. All patients had histologically proven adenocarcinoma prior to surgery, and all surgeries were conducted with a curative intent.

Patients' characteristics, including gender, age, body mass index, and preoperative comorbidity, were collected from their respective clinical records. Information on the operation procedure, operation time, intraoperative bleeding, intraoperative complications, degree of lymph node dissection, and number of retrieved lymph nodes were collected from surgical charts. The postoperative clinical course, such as the day of first flatus, the day of first oral intake, postoperative morbidity, mortality, and the duration of the postoperative hospital stay were also collected from clinical records. All data collection was performed retrospectively.

## Indication for LADG with D2 Lymph Node Dissection

Laparoscopy-assisted distal gastrectomy with D2 lymph node dissection is indicated in patients with cT2N0 or cT1N1 gastric cancer. LADG with D2 lymph node dissection is also indicated even in patients with cT1N0 early gastric cancer if tumor invasion to proper muscle layer (T2a) or first tier lymph node metastasis was suspected intraoperatively.

## Numbering of Lymph Node Station and Degree of Lymph Node Dissection

The number of each lymph node station was assigned according to the Japanese Classification of Gastric Carcinoma.[22] Stations 1 to 6 were perigastric lymph nodes while 7, 8a, 9, 11p, 12a, and 14v were second-tier lymph nodes and were located along the left gastric artery, the common hepatic artery, the celiac axis, the proximal half of the splenic artery, the proper hepatic artery, and the surface of the superior mesenteric vein at the lower border of the pancreas, respectively. D1 + beta lymph nodes were defined as regional lymph nodes with some additional second-tier lymph nodes (stations 7, 8a, and 9). Conversely, all second-tier lymph nodes were dissected during complete D2 lymph node dissection (Fig. 1).

## Conversion from LADG to Conventional Open Gastrectomy

Laparoscopy-assisted distal gastrectomy was converted to conventional open gastrectomy if intraoperative findings showed (1) advanced gastric cancer was obviously exposed the serosal membrane, (2) positive second-tier lymph nodes following frozen examination of retrieved lymph nodes, (3) uncontrollable bleeding or adhesion, and (4) any other difficulties in performing laparoscopic surgery.

## Operation Procedures of LAG with Complete D2 Lymph Node Dissection

We previously reported our standardized laparoscopic procedure for LAG with D1 + beta lymph node dissection;

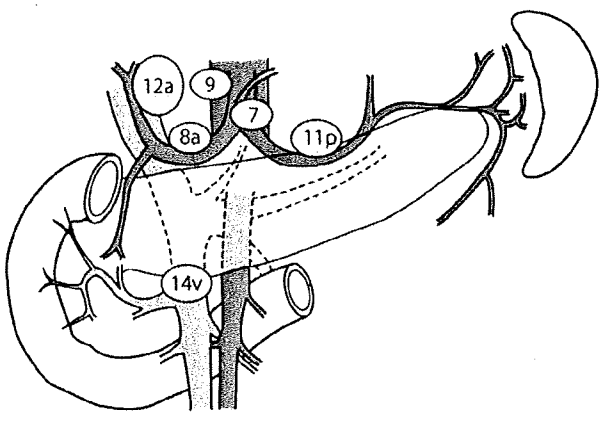


**Figure 1** Extragastric lymph node station. D1 + beta lymph node dissection includes station 7, 8a, and 9 lymph node (*open oval*) retrieval. In distal gastrectomy with D2 lymph node dissection, station 11p and 12a lymph node (*shaded oval*) have to be dissected as well as station 7, 8a, and 9 lymph nodes. Moreover, station 14v lymph node (*shaded oval*) should also be dissected in patient with lower third gastric cancer.

thus techniques for station 11p, 12a, and 14v lymph node dissection were highlighted in this manuscript.[21]

Dissection of Station 6 and 14v Lymph Nodes

The origin of the right gastroepiploic vein and the surface of the superior mesenteric vein at the lower border of the pancreas were exposed for the dissection of station 14v lymph nodes. The right gastroepiploic artery and vein were divided separately at its origin using a clip (Lapro-Clip™; single absorbable ligating clip cartridge, Covidien) and Ligasure (Covidien), then station 6 and 14v lymph node dissection were completed.

Dissection of Station 5 and 12a Lymph Nodes

The origin of the right gastric artery and vein was exposed using AutoSonix™ ULTRA SHEARS™. The left border of the proper hepatic artery and portal vein was also exposed, and station 12a lymph nodes were completely dissected. The right gastric artery and vein were then divided using clips and Ligasure at its origin.

Dissection of Station 7, 8a, 9, and 11p Lymph Nodes

The pancreatic capsule was dissected using AutoSonix™ ULTRA SHEARS™ at the line of the superior pancreatic border. The splenic artery and its origin were exposed, and the surface of splenic vein was also exposed toward the pancreatic tail as far as the root of the posterior gastric artery, then station 11p lymph node was completely retrieved. Next, the left gastric artery and vein were divided at their origins, respectively. Subsequently, common hepatic artery and celiac axis were exposed; thus, station 7, 8a, and 9 lymph node dissection were also completed.

## Comparison of Early Surgical Outcomes

In the present study, operation time, intraoperative bleeding, the number of retrieved lymph nodes, the day of first flatus, the day of first oral intake, postoperative morbidity, mortality, and the duration of the postoperative hospital stay were compared between patients who underwent LADG with complete D2 lymph node dissection (complete D2 group) and patients who underwent LADG with D1 + beta lymph node dissection (D1 + beta group). Surgery-related complications included intra-abdominal bleeding, anastomotic leakage, anastomotic bleeding, enteric injury, pancreas related infection, intra-abdominal abscess, and other complications related to the surgical procedure itself. Complications unrelated to surgery included respiratory and cardiovascular complications.

## Statistic Analyses

All continuous data are presented as the mean ± standard error. Statistical analyses were performed using the chi-square test, Fisher's exact test, Student's $t$ test, and Mann–Whitney $U$ test. $P<0.05$ was considered significant.

## Results

Between April 2006 and October 2008, 221 patients underwent LADG with lymph node dissection performed by one of the two specialists (F.T. or H.N) at the Cancer Institute Hospital. Of these, 179 patients underwent LADG with D1 + beta lymph node dissection (D1 + beta group), and 42 patients underwent LADG with complete D2 lymph node dissection (complete D2 group).

The patients' characteristics and operative findings are given in Tables 1 and 2. Younger patients were more frequently observed in the complete D2 group. The operation time was significantly longer, and the number of retrieved lymph nodes was significantly larger for the complete D2 group compared to the D1 + beta group (253± 10 vs 224±4 min; $P=0.005$ and 41±2 vs 35±1; $P=0.002$,

**Table 1** Characteristics of Patients

| | Complete D2 | D1 + beta | $P$ value |
|---|---|---|---|
| Number of patients | 42 | 179 | |
| Gender | | | |
| Male/Female | 29/13 | 118/61 | 0.699 |
| Age (years) | | | |
| Mean | 56±2 | 64±1 | 0.001 |
| Range | 36–78 | 37–90 | |
| Body mass index (kg/m2) | 22±0 | 24±1 | 0.403 |
| Pathological stage | | | |
| IA | 17 (40) | 147 (82) | |
| IB | 13 (31) | 19 (11) | |
| II | 9 (21) | 10 (6) | |
| IIIA | 2 (5) | 2 (1) | |
| IIIB | 1 (2) | 1 (1) | <0.001 |
| Preoperative complication | | | |
| Hypertension | 5 (14) | 49 (27) | 0.077 |
| Diabetes | 3 (7) | 21 (11) | 0.390 |
| Ischemic heart disease | 0 | 4 (2) | 0.328 |
| Asthma | 0 | 11 (6) | 0.099 |
| Cerebral infarction | 1 (2) | 4 (2) | 0.954 |
| Previous laparotomy | | | |
| Yes | 5 | 56 | |
| No | 37 | 123 | 0.012 |

Data are presented as mean ± SE

**Table 2** Operative Data of Patients

| | Complete D2 | D1 + beta | *P* value |
|---|---|---|---|
| Operation time (min) | 253±10 | 224±4 | 0.005 |
| Bleeding (ml) | 73±5 | 57±7 | 0.392 |
| Number of retrieved lymph nodes | 41±2 | 35±1 | 0.002 |
| Conversion | 1 (2) | 6 (3) | 0.746 |
| Transfusion, *n* (%) | 0 | 0 | – |

Data are presented as mean ± SE

respectively). Intraoperative bleeding was not different between groups, and intraoperative transfusion was not required in any of the patients in the present study. Conversion to open gastrectomy was required in six patients of D1 + beta group (three patients for further lymph node dissection, two patients due to severe intra-abdominal adhesion, and one patient for total gastrectomy due to positive proximal margin). In complete D2 group, one patient required conversion to open surgery due to uncontrollable bleeding from the gastrocolic trunk, which happened during station 14v lymph node dissection.

The postoperative clinical course of patients in both groups is given in Table 3. The incidence of surgery-related complication was similar, and postoperative mortality was not observed. Re-operation was not required in any patient in this study.

## Discussion

Open gastrectomy with D2 lymph node dissection is a standard surgical procedure for advanced gastric cancer. The procedure is widely accepted in Japan despite a large randomized controlled study conducted in Europe that failed to prove the efficacy of D2 lymph node dissection.[14,16,17] LAG has been widely accepted as a treatment for early gastric cancer, and many advantages, including reduced pain and bleeding, less postoperative respiratory disturbance, early bowel movement, and short postoperative hospital stay, have been reported.[2–8] Nevertheless, laparoscopic D2 lymph node dissection has not been widely investigated since it is considered to be technically difficult. LAG with D2 lymph node dissection is performed only in a few institutes by highly experienced surgeons.[7,9–12,23,24] Furthermore, the quality of lymph node dissection differs between institutes, and the operation time for LAG with D2 lymph node dissection was generally longer than that for conventional open gastrectomy with D2 lymph node dissection.[7,9,11]

Approximately 50 operations are required to complete a surgeons' learning curve in LAG.[2,25,26] Moreover, we previously reported that standardization of each laparoscopic procedure resulted in favorable early surgical outcomes such as shortened operation time or less intraoperative

**Table 3** Postoperative Clinical Course

| | Complete D2 | D1 + beta | P value |
|---|---|---|---|
| Postoperative complications | | | |
| Surgery-related complications, *n* (%) | 2 (5) | 16 (9) | 0.373 |
| Intraabdominal bleeding, *n* (%) | 0 | 1 (1) | 0.627 |
| Anastomotic leakage, *n* (%) | 0 | 2 (1) | 0.491 |
| Anastomotic bleeding, *n* (%) | 1 (2) | 1 (1) | 0.262 |
| Pancreas related infection, *n* (%) | 1 (2) | 3 (2) | 0.758 |
| Intraabdominal abscess, *n* (%) | 0 | 5 (3) | 0.273 |
| Bowel obstruction, *n* (%) | 0 | 0 | – |
| Superficial surgical site infection, *n* (%) | 0 | 3 (2) | 0.398 |
| Others, *n* (%) | 0 | 1 (1) | 0.627 |
| Surgery unrelated complications | 0 | 6 (3) | 0.229 |
| Respiratory complications, *n* (%) | 0 | 2 (1) | 0.491 |
| Cardiovascular complications, *n* (%) | 0 | 1 (1) | 0.627 |
| Others, *n* (%) | 0 | 3 (2) | 0.398 |
| Re-operation | 0 | 0 | – |
| Postoperative hospital stay (days) | 12±1 | 13±1 | 0.346 |
| Time until start of oral intake (days) | 2±0 | 2±0 | 0.471 |
| Time until first flatus (days) | 3±0 | 2±0 | 0.549 |

Data are presented as mean ± SE