厚生労働科学研究委託費

革新的がん医療実用化研究事業

患者のＱＯＬ向上をめざした胃がんに対する低侵襲標準治療確立に関する多施設共同試験

平成２６年度　委託業務成果報告書

業務主任者　森田　信司

平成２７（２０１５）年3月

本報告書は、厚生労働省の厚生労働科学研究委託事業による委託業務として、独立行政法人国立がん研究センターが実施した平成26年度「患者のQOL向上をめざした胃がんに対する低侵襲標準治療確立に関する多施設共同試験」の成果を取りまとめたものです。

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（総括）

厚生労働科学研究委託費（革新的がん治療実用化研究事業）
委託業務成果報告書（総括）

患者のQOL向上をめざした胃がんに対する低侵襲標準治療確立に関する多施設共同試験

業務主任者　　森田　信司　　国立がん研究センター中央病院　医長

研究要旨
胃癌罹患数は全がんで1位である。低侵襲治療として腹腔鏡手術が早期胃癌治療に導入されたが、安全性や長期予後に関するエビデンスはない。胃癌治療ガイドラインでも研究的治療とされている。本研究では、胃癌に対する腹腔鏡手術の有用性を、安全性・根治性の両面から検証することを目的とする。
胃癌主要術式には、幽門側胃切除、胃全摘、噴門側胃切除の3術式があるが、このうち幽門側胃切除では、根治性検証のため、primary endpointを全生存期間とする「臨床病期Ⅰ期胃癌に対する腹腔鏡下幽門側胃切除術の開腹幽門側胃切除に対する非劣性を検証するランダム化比較試験（JCOG0912）：UMIN000003319」（Jpn J Clin Oncol. 2013）を行っている。H25年11月に921例で登録完遂した症例を登録後5年間（H30年12月まで）、必要な検査、毒性評価を行い追跡中である。このうち、592例に関しては腹腔鏡手術の低侵襲性評価するため3年間のQOL調査を行っている（H28年12月まで）。
胃全摘、噴門側胃切除に関しては安全性を検証する「臨床病期Ⅰ期胃癌に対する腹腔鏡下胃全摘術および腹腔鏡下噴門側胃切除術の安全性に関する第II相試験」のプロトコール作成が終了し、H26年3月から開始する。Primary endpointは縫合不全発生割合。登録期間は3年。有効性は対象が同じJCOG0912の結果を外挿し標準治療となり得るか判断する。試験は単群であるが検証的試験となる。

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A．研究目的

胃癌罹患数は全がんで1位である。低侵襲治療として腹腔鏡手術が早期胃癌治療に導入されたが、安全性や長期予後に関するエビデンスはない。胃癌治療ガイドラインでも研究的治療とされている。本研究では、胃癌に対する腹腔鏡手術の有用性を、安全性・根治性の両面から検証することを目的とする。

胃癌主要術式には、幽門側胃切除、胃全摘、噴門側胃切除の3術式があるが、このうち幽門側胃切除では、当研究グループで「臨床病期Ⅰ期胃癌に対する腹腔鏡下幽門側胃切除術の安全性に関する第II相試験（JCOG 0703）」を実施（Jpn J Clin Oncol. 2008）、安全性を検証した。根治性検証のため、primary endpointを全生存期間とする「臨床病期Ⅰ期胃癌に対する腹腔鏡下幽門側胃切除術の開腹幽門側胃切除に対する非劣性を検証するランダム化比較試験（JCOG0912）：UMIN000003319」（Jpn J Clin Oncol. 2013）を行っている。H25年11月に921例で登録完遂した症例を登録後5年間（H30年12月まで）、必要な検査、毒性評価を行い追跡する。

腹腔鏡手術の低侵襲性評価として、限定4施設で3年間のQOL調査を行う（H28年12月まで）。対象はJCOG0912の592例。消化器癌手術RCTで500例超の調査は世界で例はない。高齢者のQOL維持が今後の課題なので、70歳未満と70歳以上に分けての比較検討もする。

胃全摘、噴門側胃切除では、安全性を検証する「臨床病期Ⅰ期胃癌に対する腹腔鏡下胃全摘術および腹腔鏡下噴門側胃切除術の安全性に関する第II相試験」をH26年度から開始する。

Primary endpointは縫合不全発生割合。登録期間は3年。有効性は対象が同じJCOG0912の結果を外挿し標準治療となり得るか判断する。試験は単群であるが検証的試験となる。

1000例規模のJCOG0912の追跡が適切になされ、腹腔鏡下胃全摘と噴門側胃切除の安全性の検証がなされることによりすべての腹腔鏡胃癌手術の評価が定まる。腹腔鏡手術の有用性が検証されれば、早期胃癌患者に早期社会復帰や術後QOLを向上させる治療手段を積極的に提供できる。

B．研究方法

胃癌罹患数は全がんで1位である。低侵襲治療として腹腔鏡手術が早期胃癌治療に導入されたが、安全性や長期予後に関するエビデンスはない。胃癌治療ガイドラインでも研究的治療とされている。本研究では、胃癌に対する腹腔鏡手術の有用性を、安全性・根治性の両面から検証することを目的とする。

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Primary endpointは縫合不全発生割合。登録期間は3年。有効性は対象が同じJCOG0912の結果を外挿し標準治療となり得るか判断する。試験は単群であるが検証的試験となる。

1000例規模のJCOG0912の追跡が適切になされ、腹腔鏡下胃全摘と噴門側胃切除の安全性の検証がなされることによりすべての腹腔鏡胃癌手術の評価が定まる。腹腔鏡手術の有用性が検証されれば、早期胃癌患者に早期社会復帰や術後QOLを向上させる治療手段を積極的に提供できる。

C．研究結果

①臨床病期Ⅰ期胃癌に対する腹腔鏡下幽門側胃切除術の開腹幽門側胃切除に対する非劣性を検証するランダム化比較試験
（JCOG0912: UMIN000003319）

a．登録患者の6か月ごと退院後評価
（全身状態、血液検査、画像検査、毒性評価、生存確認）

b．記録用紙を用いた6か月ごとのデータ収集

c．定期モニタリングレポートの作成（H26年8月）（資料として添付）

d．班会議の実施
（H26年5月、9月、H27年1月）

e．「臨床病期Ⅰ期胃癌に対する腹腔鏡下幽門側

胃切除術の安全性に関する第 II 相試験（JCOG 0703）」の secondary endpoint を American Society of Clinical Oncology で発表。

②JCOG0912 登録患者での調査票による QOL 調査

a．調査票(EORTC QLQ-C30、STO22）の発送と回収手術３年後まで１患者計５回）
回収:手術１年後調査 573/592 例　３年後調査の終了予定は H28 年 11 月

b．QOL 調査状況レポートの作成
（H26 年５月、９月、H27 年１月）

c．班会議の実施
（H26 年５月、９月、H27 年１月）

③臨床病期Ｉ期胃癌に対する腹腔鏡下胃全摘術および腹腔鏡下噴門側胃切除術の安全性に関する非ランダム化検証的試験（JCOG1401）

a．JCOG プロトコール・コンセプト（PC1401）作成（H26 年５月）

b．JCOG コンセプト検討会提出と JCOG 運営委員会でのコンセプト承認（H26 年６月）

c．プロトコール（JCOG1401）承認
（H27 年２月）（資料として添付）

d．班会議の実施
（H26 年５月、８月、H27 年１月）

D．考察

胃癌に対する郭清を伴う腹腔鏡下手術の安全性と有効性が証明され、この手術の評価が定まれば、内視鏡切除適応外の早期胃がん患者に早期社会復帰や術後患者 QOL を向上させうる、新しい治療手段を積極的に提供できる。早期社会復帰や術後患者 QOL の向上は、社会的活動の向上、精神的安定、雇用機会の増加、経済的な改善などの成果をもたらすこととなりうる。

腹腔鏡手術は、手術器具やロボティックシステムの開発により、さらなる低侵襲性を患者に提供可能である。この手術手技が一般化し、社会的な認知度が上がることにより、手術関連企業の開発への参画、市場の拡大などの多くの経済効果も期待できる。

E．結論

胃癌主要術式には、幽門側胃切除、胃全摘、噴門側胃切除の３術式がある幽門側胃切除に関する JCOG0912 登録患者のデータ収集および JCOG0912 登録患者での調査票による QOL 調査の発送と回収は、予定通り順調に行われている。胃全摘、噴門側胃切除では、安全性を検証する「臨床病期Ｉ期胃癌に対する腹腔鏡下胃全摘術および腹腔鏡下噴門側胃切除術の安全性に関する第 II 相試験」の患者登録が開始される。本研究は、予定通り順調に進んでいる。

F．健康危険情報

なし。

G．研究発表

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H.　知的財産権の出願

なし。

学 会 等 発 表 実 績

様式第１９

学 会 等 発 表 実 績

委託業務題目「患者のＱＯＬ向上をめざした胃がんに対する低侵襲標準治療確立に関する多施設共同試験」

機関名　独立行政法人　国立がん研究センター

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
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発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
鏡視下幽門保存胃切除術における幽門下静脈温存の有効性に関する研究(口頭)	高木　航，三木友一朗，大森隼人，平田史子，辰林太一，本田晋策，幕内梨恵，徳永正則，谷澤　豊，坂東悦郎，川村泰一，絹笠祐介，上坂克彦，寺島雅典	第27回日本内視鏡外科学会総会	2014.10	国内（盛岡市）

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Surgical treatment of non-early gastric remnant carcinoma developing after distal gestrectomy for gastric cancer	Ohashi M, Morita S, Fukagawa T, Kushima R, Katai H	J Surg Oncol	2015	海外
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掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
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（注１）発表者氏名は、連名による発表の場合には、筆頭者を先頭にして全員を記載すること。

（注２）本様式はexcel形式にて作成し、甲が求める場合は別途電子データを納入すること。

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Surgical Treatment of Non-Early Gastric Remnant Carcinoma Developing After Distal Gastrectomy For Gastric Cancer

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Background and Objectives: The optimal surgical procedure for gastric remnant carcinoma (GRC) remains debatable. The aim of this study was to retrospectively evaluate the surgical treatments for T2-4 GRC developing after distal gastrectomy for gastric cancer.
Methods: Between 1970 and 2012, a total of 50 patients underwent R0 resection for T2-4 GRC. The clinicopathologic features, therapeutic methods, and follow-up data of these patients were reviewed.
Results: The tumor was located at a non-anastomotic site of the remnant stomach in 43 of the 50 patients. Total gastrectomy was performed in 48 patients and partial gastrectomy was in two patients. Lymph node metastasis was found in 19 patients. Major postoperative complications occurred in 16 patients. The overall 1-, 3-, and 5-year survival rates of the 50 patients were 90%, 66%, and 44%, respectively. Presence of small intestinal or esophageal infiltration and postoperative complications was independently associated with poorer survival. Dissection of the perigastric and splenic hilar/artery nodes was found to have potential therapeutic benefit.
Conclusions: Surgical resection for T2-4 GRC developing after distal gastrectomy for gastric cancer can be invasive, but is feasible and effective. Total gastrectomy with splenectomy is one of the recommendable procedures for this disease.
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KEY WORDS: **surgical treatment; remnant gastric cancer; outcome; gastrectomy; splenectomy**

INTRODUCTION

With the advances in diagnostic and therapeutic techniques, the outcomes of patients with primary gastric cancer have improved over time in Japan [1–3]. Consequently, gastric remnant carcinoma (GRC), arising from the remnant stomach after surgery for gastric cancer, has become an important clinical issue [4]. Despite the steady increase in the incidence of proximal gastric cancer, including cancer of the cardia [5], distal gastric cancer has been and will, for some time to come, remain the most common type of primary gastric malignancy in Eastern Asia [6]. In the late 1980s, pylorus-preserving gastrectomy (PPG) was introduced in Japan as a function-preserving procedure for early cancer located in the middle-third of the stomach, besides conventional distal gastrectomy (DG) which was employed as the standard procedure [7]. A large-scale retrospective study showed that PPG is a safe and radical operation [8].

As the epidemiologic and clinicopathologic features of GRC developing after DG for cancer and after DG for benign gastroduodenal disease are distinct [4,9–12], they should be investigated separately. We previously reported the trends in the clinicopathologic features, diagnosis and treatment of GRC developing after DG for gastric cancer [4]; our study revealed that patients with T1 GRC showed favorable outcomes after endoscopic resection or modified surgical treatments such as spleen-preserving gastrectomy, while those with T2-4 GRC showed a poor prognosis even after radical operations. Thus, the optimal surgical procedure for T2-4 GRC remains under debate. The aim of this study was to retrospectively evaluate the surgical treatments for T2-4 GRC developing after DG or PPG for gastric cancer.

MATERIALS AND METHODS

Patients

Between 1970 and 2012, a total of 15,063 patients underwent surgery for gastric cancer at our institution. They included 139 patients with GRC developing after surgery for benign gastroduodenal disease and 208 patients with GRC developing after surgery for gastric cancer. Of the latter 208 patients, 117 had T1 GRC and 91 had T2-4 GRC. In this study, the data of 50 patients who had no distant metastasis and underwent R0 resection for T2-4 GRC developing after curative DG or PPG for gastric cancer were extracted and analyzed.

Description of Data

The depth of tumor invasion, nodal status, and the disease stage were recorded according to the International Union Against Cancer (UICC) TNM Staging System [13]. The histologic type, macroscopic tumor type, and lymph node stations were recorded according to the Japanese Classification of Gastric Carcinoma [14]. Papillary adenocarcinoma and well- or moderately differentiated tubular adenocarcinoma were described as differentiated-type carcinoma, while poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma

Abbreviations: GRC, gastric remnant carcinoma; DG, distal gastrectomy; PPG, pylorus-preserving gastrectomy; UICC, Union Internationale Contre le Cancer (International Union Against Cancer).

Conflicts of interest: All authors report no conflicts of interest relevant to this article.

This article is not based on any previous communication to any society or meeting.

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were classified as undifferentiated-type carcinoma. The main location of the tumor was categorized as anastomotic site, non-anastomotic site, or total remnant stomach. When multiple carcinomas were found in the remnant stomach, only the largest and most deeply invasive lesion was considered for the analysis.

The extent of lymph node dissection was defined on the basis of the Japanese gastric cancer treatment guideline [15]. In total gastrectomy for GRC, D2 was defined as dissection of any remaining stations among 1–7, 8a, 9, 10, 11, and 12a. In partial gastrectomy for GRC, D2 was defined as dissection of any remaining stations among 1, 3–7, 8a, 9, 11p, and 12a. For tumors invading the esophagus, D2 also included dissection of stations 19, 20, 110, and 111. For tumors involving the gastrojejunal anastomotic site, D2 also included dissection of the mesojejunal nodes (station J) [16]. The postoperative complications were recorded according to the Clavien–Dindo classification [17].

Principles of Treatment

Our consistent policy on surgery for GRC is mentioned below. Total gastrectomy with splenectomy (≥D2) is the first treatment of choice for potentially curable T2-4 tumors. In patients with poor operative risk, splenectomy may be omitted. For small tumors confined within the anastomotic site, partial gastrectomy can also be indicated. Combined resection of adjacent organs is considered in case direct tumor invasion is suspected.

In principle, adjuvant chemotherapy was not given to the patients until 2006. In 2007, S-1 started to be used routinely as postoperative adjuvant chemotherapy in patients with stage II or III disease [3]. From 2008, neoadjuvant chemotherapy has been considered for tumors with extensive lymph node metastasis [18].

Statistics

The IBM SPSS Statistics 20.0 (IBM, Corp., Armonk, NY) was used for the statistical analyses. The chi-square test was applied for assessment of the correlation between the occurrence of postoperative complications of ≥grade III severity and necessity of combined resection of adjacent organs. The Kaplan–Meier method was used to present the survival data. Univariate and multivariate Cox regression analyses were performed to identify the prognostic factors for overall survival. P values <0.05 were considered to indicate statistical significance. The significant prognostic factors identified by the univariate analysis were used as the covariates in the multivariate analysis. The incidence of metastasis at each lymph node station was calculated by dividing the number of patients with metastasis at the station by the number of patients who underwent dissection of that station.

RESULTS

Clinicopathologic Features

The clinicopathologic features of the 50 patients are summarized in Table I. Twenty-eight patients were asymptomatic and were diagnosed as having GRC by a screening examination. The median time interval between the initial gastrectomy and surgery for GRC was 10 (range, 1–40) years. All the initial gastrectomies had been performed via laparotomy, with the extent of lymph node dissection being <D2 in 13 patients and ≥D2 in 37 patients. Billroth I anastomosis was the most common reconstruction method during the initial surgery, employed in 29 patients. Twenty-four patients had pT4 GRC, of which 14 had pT4b GRC. Lymph node metastasis was found in 19 of the 50 patients. The disease stage was I in 9 patients, II in 21 patients and III in 20 patients. The main location of the tumor was a non-anastomotic site in 43 patients. Esophageal infiltration was identified in 14 patients and small intestinal (duodenal or jejunal) infiltration in 8 patients.

TABLE I. Clinicopathologic Features

	Number of patients[a]
Gender	
Male	38
Female	12
Age (years) (median, range)	67 (36–84)
Symptom	
Absent	28
Present	22
Interval[b] (years) (median, range)	10 (1–40)
Method of initial gastrectomy	
Billroth I	29
Billroth II	14
Roux-en-Y	4
Pylorus-preserving	3
Initial lymph node dissection	
<D2	13
≥D2	37
Tumor size (cm) (median, range)	5.2 (1.2–18)
Depth of tumor invasion	
pT2	10
pT3	16
pT4a	10
pT4b	14
Lymph node metastasis	
pN0	31
pN1	7
pN2	6
pN3	6
Stage	
I	9
II	21
III	20
Histologic type	
Differentiated	18
Undifferentiated	32
Macroscopic type	
0	11
1, 2	16
3–5	23
Location of tumor	
Anastomotic site	3
Non-anastomotic site	43
Total remnant stomach	4
Esophageal infiltration	
Absent	36
Present	14
Small intestinal infiltration[c]	
Absent	42
Present	8

[a]Unless indicated otherwise.
[b]Time interval between the initial gastrectomy and surgery for GRC.
[c]Duodenal or jejunal infiltration.

Therapeutic Methods and Short-Term Outcomes

The therapeutic methods and short-term outcomes of the 50 patients are shown in Table II. All the surgeries for GRC were performed via laparotomy alone. Total gastrectomy with (≥D2) or without (<D2) splenectomy was performed in 48 patients and partial gastrectomy (D2) was in two patients. The median number of retrieved lymph nodes was 14.5 (range, 4–50). Combined resection of adjacent organs other than the spleen and gall bladder was needed in 18 patients. The resected organs included the liver in 11 patients, distal pancreas in six patients, transverse colon in five patients, left adrenal gland in four patients, pancreatic head with duodenum in one patient, and diaphragm in one patient with some overlap. Blood transfusion was needed in 24 patients. In 16 patients,

TABLE II. Therapeutic Methods and Short-term Outcomes

	Number of patients[a]
Type of gastrectomy	
Total gastrectomy with splenectomy (≥D2)	39
Total gastrectomy without splenectomy (<D2)	9
Partial gastrectomy (D2)	2
Number of retrieved lymph nodes, median (range)	14.5 (4–50)
Combined resection of adjacent organs[b]	
No	32
Yes	18
Duration of operation (min), median (range)	328 (183–685)
Blood loss (ml), median (range)	637 (119–3239)
Intraoperative or postoperative blood transfusion	
No	26
Yes	24
Postoperative complication (≥grade III[c])	
No	34
Yes	16
Adjuvant chemotherapy	
No	33
Yes	17

[a]Unless indicated otherwise.
[b]Excluding spleen and gall bladder.
[c]According to the Clavien–Dindo classification.

postoperative complications of ≥grade III severity occurred, including pancreatic fistula formation in seven patients, anastomotic leakage in four patients, bleeding in two patients, aspiration pneumonia in two patients, and small bowel obstruction in one patient. Ten of the 18 patients who underwent combined resection developed a complication of ≥grade III severity ($P = 0.012$). Postoperative adjuvant chemotherapy was given to 17 patients, of whom three also received neo-adjuvant chemotherapy.

Survival and Prognostic Factors

During the median follow-up period of 29.5 (range, 0–447) months, 26 patients died, including 18 of tumor recurrence, one of postoperative aspiration pneumonia, six of other disease, and one of unknown cause. The one in-hospital mortality occurred in 1975. The sites of recurrence were peritoneum in nine patients, lymph node in six patients, liver in three patients, and others (lung, bone, pleura, or loco-regional) in four patients with some overlap. The overall 1-, 3-, and 5-year survival rates of the 50 patients were 90%, 66%, and 44%, respectively. The overall 5-year survival rates of the patients with disease stage I, II, and III were 58%, 56%, and 25%, respectively.

The results of the univariate and multivariate analyses and the 5-year survival rates according to each variable are shown in Table III. The univariate analysis showed that presence of serosal invasion, lymph node metastasis, small intestinal or esophageal infiltration, and postoperative complications of ≥grade III severity was associated with poorer survival. The multivariate analysis showed that presence of small intestinal or esophageal infiltration and postoperative complications of ≥grade III severity was independently associated with poorer survival.

Therapeutic Benefit of Lymph Node Dissection

The two patients who were treated by partial gastrectomy had no pathologic lymph node metastasis. We assessed the potential therapeutic benefit of lymph node dissection in the remaining 48 patients who were treated by total gastrectomy. The incidence of metastasis in the perigastric (station 2 or 4), celiac/hepatic artery (station 8, 9, or 12), splenic hilar/artery (station 10 or 11), mesojejunal (station J) and paraesophageal/diaphragmatic (station 19, 20, 110, or 111) nodes, and the respective 5-year survival rates are presented in Table IV. Dissection of the perigastric and splenic hilar/artery nodes was found to have potential therapeutic benefit. The mesojejunal nodes were not involved in any of the patients in this series. All the six patients with celiac/hepatic artery or paraesophageal/diaphragmatic node metastasis also had multiple perigastric node involvement and died within 5 years of the surgery.

DISCUSSION

Surgical procedures for T2-4 GRC are potentially highly invasive because of the presence of adhesions or direct tumor invasion. In addition, the adhesions could be denser and direct invasion occur more easily after surgery for gastric cancer than after that for benign gastroduodenal disease, because the initial operation for cancer includes lymph node dissection and often, bursectomy or omentectomy [19]. In the present study, 18 patients needed combined resection of an adjacent organ, and 14 of these patients had pT4b tumors. The frequencies of blood transfusions and of major postoperative complications were apparently high as compared to those after surgery for primary gastric cancer [20]. Nevertheless, there were no mortalities since 1975 and surgical resection for T2-4 GRC may be considered feasible.

Previous studies have reported higher incidences of metastasis in the splenic artery/hilar nodes in patients with GRC than in patients with

TABLE III. Univariate and Multivariate Analyses to Identify Prognostic Factors for Overall Survival

			Multivariate	
Variable	5-year survival rate	Univariate *P* value	Hazard ratio	*P* value
Gender, male vs. female	36% vs. 67%	0.126	—	
Age (years), ≥65 vs. <65	43% vs. 45%	0.748	—	
Time of surgery for GRC, 1970–1991 vs. 1992–2012	33% vs. 49%	0.457	—	
Method of initial gastrectomy, Billroth I/pylorus-preserving vs. Billroth II/Roux-en-Y	34% vs. 58%	0.221	—	
Depth of tumor invasion, pT4 vs. pT2-3	25% vs. 63%	0.050	1.726 (0.685–4.352)[a]	0.247
Nodal status, pN1-3 vs. pN0	23% vs. 57%	0.036	0.762 (0.268–2.168)[a]	0.611
Tumor size (cm), >5.0 vs. ≤5.0	28% vs. 60%	0.056	—	
Histologic type, undifferentiated vs. differentiated	43% vs. 45%	0.821	—	
Macroscopic type, 3–5 vs. 0–2	30% vs. 58%	0.471	—	
Small intestinal or esophageal infiltration, yes vs. no	17% vs. 59%	0.015	2.842 (1.215–6.652)[a]	0.016
Number of retrieved lymph nodes, ≥15 vs. <15	32% vs. 56%	0.131	—	
Postoperative complication (≥grade III[b]), yes vs. no	15% vs. 60%	<0.001	4.585 (1.677–12.536)[a]	0.003
Adjuvant chemotherapy, yes vs. no	17% vs. 60%	0.084	—	

[a]Values in parentheses are the 95% confidence intervals.
[b]According to the Clavien–Dindo classification.

TABLE IV. Incidence of Metastasis at Each Lymph Node Station and the Overall 5-year Survival Rate of Patients With Metastasis at the Respective Stations

Lymph node station	Incidence of metastasis	5-year survival rate of patients with metastasis
Perigastric (2 or 4)	17/48 (35%)	17%
Splenic hilar/artery (10 or 11)	10/39 (26%)	13%
Celiac/hepatic artery (8, 9 or 12)	4/13 (31%)	0%
Mesojejunal (J)	0/10 (0%)	Not evaluable
Paraesophageal/diaphragmatic (19, 20, 110, or 111)	2/14 (14%)	0%

primary proximal gastric cancer [9,21,22]. The incidence of metastasis to these nodes was 26% (10/39) in the present study, which also tended to be higher than that seen in patients with primary cancer [9,22]. The preceding lymph node dissection possibly causes relative increase of lymphatic flows from the remnant stomach to these nodes [9,21,22]. We could not reliably evaluate the incidence of mesojejunal or paraesophageal/diaphragmatic node metastasis because of the small sample size. However, the observed low incidence of mesojejunal node metastasis might be attributable to the relative rarity of anastomotic tumors, unlike in cases of GRC developing after surgery for benign disease [4,9].

The pT and pN stages reliably reflected the outcomes of GRC, and the most common mode of postoperative recurrence was peritoneal seeding, the same as in cases of non-early primary gastric cancer [23]. The 5-year survival rate of the patients with pT4 or pN1-3 tumors was very poor, being 25% or less. GRCs of these stages seem particularly intractable. On the other hand, GRCs of pT2-3 and pN0 stage appear to show a high likelihood of being cured. Half of the current patients were diagnosed as having GRC more than 10 years after the initial gastrectomy. Therefore, life-long periodic surveillance should be considered for earlier detection and improvement in the outcomes of GRC after gastric cancer surgery [4].

GRCs with small intestinal or esophageal infiltration also showed dismal outcomes, which might reflect the higher malignant potential and/or additional difficulty in surgical control of these types of tumor. Mesojejunal, paraesophageal/diaphragmatic, hepatoduodenal ligament, retropancreatic, or more distant nodes may often be involved and it is always difficult to obtain sufficient surgical margins in the treatment of these tumors. Previous investigators have suggested worse outcomes of GRCs arising at the anastomotic site [24]. We have not routinely performed dissection of the posterior pancreatic head nodes in the treatment of GRC, but this procedure may be an option in patients with duodenum-infiltrating tumors developing after Billroth I reconstruction [25].

Correlation between postoperative complications and poorer long-term outcomes has been shown for several gastrointestinal malignancies, including gastric cancer [26–30]. Our findings are consistent with these reports. The exact reason for this correlation is unclear, but it is supposed that immunosuppression and/or intracorporeal cancer cell implantation caused by the complications could negatively affect the patient survival [26–29]. Meticulous surgical technique to minimize postoperative complications might improve the long-term oncologic outcomes in GRC. In the present study, the occurrence of complications was closely associated with necessity of combined resection of adjacent organs, again suggesting the importance of earlier detection of GRC.

To the best of our knowledge, this is the first study to exclusively evaluate the outcomes of surgical treatment for T2-4 GRC developing after DG or PPG for gastric cancer. Surgical resection for this disease appears to be effective. Despite the small sample size and dismal outcomes of the node-positive cases, we found a potential therapeutic benefit of dissection of the perigastric (station 2 or 4) and splenic hilar/artery (station 10 or 11) nodes. Splenectomy is considered to be necessary for complete removal of the splenic hilar/artery nodes [31]. Thus, total gastrectomy with splenectomy is one of the recommendable procedures for this disease. As perioperative chemotherapy is a promising strategy in patients with primary gastric cancer with extensive lymph node metastasis [32], this therapy may also deserve evaluations in the treatment of GRC with similar condition.

This single-institutional retrospective study over a 42-year period has several limitations. First, the methods of patient care, including perioperative adjuvant therapy and surgical technique, have greatly changed during the study period. Second, the surgical procedures employed, including the type of gastrectomy and extent of lymph node dissection, could be influenced by each attending surgeon's decision, leading to substantial bias. Third, the number of patients enrolled was small, albeit mostly attributable to the rarity of the disease. The similar 5-year survival rates of the patients with disease stage I and II, observed in the present study, may partly be due to the small sample size. In consideration of these limitations, the study results should be interpreted with caution.

CONCLUSIONS

Surgical treatment for T2-4 GRC developing after DG or PPG for gastric cancer can be invasive, but is feasible and effective. Earlier tumor detection and minimization of postoperative complications may provide better long-term outcomes. Total gastrectomy with splenectomy is a recommendable procedure, although further studies are needed to evaluate the optimal extent of lymph node dissection, for this relatively rare disease.

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Randomized Comparison of Surgical Stress and the Nutritional Status Between Laparoscopy-Assisted and Open Distal Gastrectomy for Gastric Cancer

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ABSTRACT

Background. Laparoscopy-assisted distal gastrectomy (LADG) for gastric cancer may prevent the development of an impaired nutritional status due to reduced surgical stress compared with open distal gastrectomy (ODG).

Methods. This study was performed as an exploratory analysis of a phase III trial comparing LADG and ODG for stage I gastric cancer during the period between May and December of 2011. All patients received the same perioperative care via fast-track surgery. The level of surgical stress was evaluated based on the white blood cell count and the interleukin-6 (IL-6) level. The nutritional status was measured according to the total body weight, amount of lean body mass, lymphocyte count, and prealbumin level.

Results. Twenty-six patients were randomized to receive ODG (13 patients) or LADG (13 patients). The baseline characteristics and surgical outcomes were similar between the two groups. The median IL-6 level increased from 0.8 to 36.3 pg/dl in the ODG group and from 1.5 to 53.3 pg/dl in the LADG group. The median amount of lean body mass decreased from 48.3 to 46.8 kg in the ODG group and from 46.6 to 46.0 kg in the LADG group. There are no significant differences between two groups.

Conclusions. The level of surgical stress and the nutritional status were found to be similar between the ODG and LADG groups in a randomized comparison using the same perioperative care of fast-track surgery.

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The use of laparoscopy-assisted distal gastrectomy (LADG) to treat gastric cancer was first described by Kitano.[1] Since then, the number of cases of gastric cancer treated with LADG has been increasing gradually. The advantages of this procedure, compared with open distal gastrectomy (ODG), include reduced amounts of operative blood loss and pain, earlier recovery of bowel activity, and resumption of oral intake and shorter hospital stays.[2,3] Adachi et al.[4] evaluated 102 early gastric cancer patients and compared the level of surgical stress between patients undergoing ODG and those undergoing LADG. The authors reported lower levels of surgical stress and a lower incidence of impaired nutrition in the LADG group than in the ODG group.

Once surgical stress occurs, immune cells produce cytokines that act as mediators of both immune and systemic responses to injury.[5] Interleukin (IL)-6, IL-1, tumor necrosis factor (TNF), and interferon gamma (IFN-γ) are important mediators of the integrated host response.[6] These cytokines are synthesized from amino acids supplied by muscle catabolism. In addition, the response of skeletal muscle during critical illness is characterized by a rapid decrease in protein content and accelerated amino acid release.[7,8] Low relative muscularity and/or low overall levels of lean body mass are reportedly related to a poor quality of life and the severity of toxicity induced by chemotherapy.[9,10] Theoretically, less invasive surgical

procedures inhibit muscle catabolism during surgery, which may reduce the incidence of an impaired nutritional status and improve the quality of life after surgery.

Based on this background, we hypothesized that the use of LADG reduces the incidence of an impaired nutritional status, including decreases in lean body mass, induced by surgical stress. To confirm our hypothesis, we evaluated the levels of surgical stress and the nutritional status after surgery in a randomized comparison of patients undergoing ODG and LADG. To minimize variability in perioperative care, all patients received the same fast-track surgery program in this study.

PATIENTS AND METHODS

This study was performed as an exploratory analysis of the Surgical Invasion and Nutrition in ERAS protocol after Gastrectomy (SINEG) study and the Japan Clinical Oncology Group (JCOG)-0912 trial. The SINEG is an in-house prospective cohort study performed to evaluate surgical stress and nutrition in patients who undergo gastrectomy for gastric cancer and receive perioperative care based on the enhanced recovery after surgery (ERAS) protocol at Kanagawa Cancer Center. The details of the perioperative ERAS protocol have been previously described.[11] The SINEG study was initiated in May 2011 and terminated in December 2011. The JCOG-0912 trial is a multicenter phase III trial comparing ODG and LADG for clinical stage I gastric cancer disease diagnosed according to the 14th edition of the general rules for gastric cancer published by the Japanese Gastric Cancer Association (UMIN-ID 000003319).[12] The details of the JCOG-0912 trial have been previously reported.[13] The JCOG-0912 trial was initiated in March 2010 and is currently ongoing. The institution was selected as a stratification factor for randomization in the JCOG-0912 trial. The institutional review board of our hospital approved both the SINEG and JCOG-0912 studies. The primary investigators of the JCOG-0912 trial, the representative director of the JCOG Gastric Cancer Study Group and the chairman of the JCOG, approved the exploratory study of the JCOG-0912 trial. The primary investigator of the SINEG trial also approved this study.

A total of 26 patients who were enrolled into both the SINEG and JCOG-0912 studies were examined in this study. The 26 patients were randomly assigned to undergo either ODG or LADG and received the same perioperative care based on the ERAS protocol.

Surgical Procedure

All patients received distal gastrectomy with nodal dissection. D1 or more nodal dissection was applied for clinical stage IA tumors and D2 dissection was applied for clinical stage IB tumors, regardless of the approach.

For the laparoscopic surgery, one of two certified laparoscopic staff surgeons was responsible for the surgical quality following the protocol of the JCOG-0912 trial. Five or six ports were used. Lymph node dissection was performed in the laparoscopic field. The omentum was preserved except where resection was necessary for lymph node dissection along the right gastroepiploic artery. A small abdominal incision ($\leq$6 cm) was made in the upper abdomen for removal of the specimen and reconstruction. In principle, reconstruction was performed using Billroth-I gastroduodenostomy and all reconstruction procedures were performed extracorporeally using circular staplers.[14]

For the open surgical procedure, an upper abdominal median incision extending from the xiphoid to the navel was created. The nodal dissection and reconstruction procedure was the same as that used in the laparoscopic approach.

For the both procedure, in principal, no drain was used in both laparoscopy and open distal gastrectomy. If the surgeon need drain placement for postoperative bleeding or pancreatitis, a low-vacuum drainage system was left in the subhepatic area for peritoneal fluid collection.

Perioperative Care

The patients received ERAS protocol after both ODG and LADG. Figure 1 shows the details of this protocol, which have been previously reported.[11] In brief, the patients were allowed to eat until midnight on the day before the surgery and were required to drink the contents of two 500-ml plastic bottles containing oral rehydration solution until 3 h before surgery. The nasogastric tube was removed immediately after surgery. Oral intake was initiated on POD 2, beginning with water and an oral nutritional supplement. The patients began to eat solid food on POD 3, starting with rice gruel and soft food on POD 3 and advancing in three steps to regular food intake on POD 7. The patients were discharged when they had achieved adequate pain relief and soft food intake, had returned to their preoperative mobility level, and exhibited normal laboratory data on POD 7.

Evaluation of Operative Morbidity and Mortality

The surgical and nonsurgical complications were assessed prospectively and classified according to the Clavien–Dindo classification.[15] Operative mortality was defined as postoperative death from any cause within 30 days after surgery or during the same hospital stay.

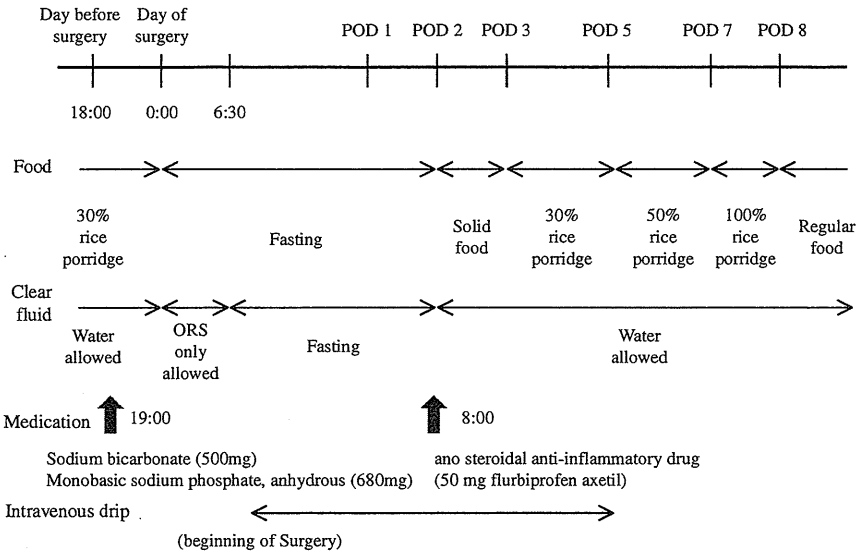

FIG. 1 Details of enhanced recovery after surgery protocol used in this study

Surgical Stress and Nutritional Status

The response induced by systemic surgical stress was assessed by measuring the white blood cell (WBC) count and IL-6 levels. The nutritional status was assessed by measuring the serum prealbumin level, lymphocyte count, and body composition. The segmental body composition was analyzed using the Tanita MC-190EM bioelectrical impedance analyzer (Tanita, Tokyo, Japan), which provides relative information regarding the amount of lean and fat tissue in the trunk area and each limb, as well as the overall body composition and hydration status.

The body composition was measured 3–4 days before and 8 or 9 days after surgery. Previous, Kiyama et al.[16] clarified that body composition dramatically changed during the immediate postoperative period of only 14 days. Although the period for the weight change was only 8 or 9 days in this study, we considered that the change of the body weight or body composition could be detectable. The IL-6 level was measured before surgery and 12 h after surgery. The WBC count was examined before and on the day after surgery. The prealbumin level and lymphocyte count also were evaluated before and 7 days after surgery. Rapid-turnover protein of prealbumin was considered to be a marker for the nutritional status of the short-term period, because half-life of prealbumin was only 2 days. We considered that the change of prealbumin could be detectable before the change of the body weight or composition. We measured total lymphocyte count as one of the general marker for the nutritional status. We considered that total lymphocyte count might be different if weight loss is different.

Evaluation and Statistical Analyses

The values are expressed as the median and range. The statistical analyses were performed using the χ^2 test or the Wilcoxon signed-rank test. $P < 0.05$ was considered to indicate statistical significance. The SPSS software package (v12.0 J Win, SPSS, Chicago, IL) was used for all statistical analyses.

RESULTS

Background

Among the 26 patients, 13 were assigned to receive ODG and 13 were assigned to receive LADG. The background characteristics and baseline data were well randomized to both groups (Table 1). No patients had any history of weight loss, appetite loss, or food intake loss before surgery. No patients had a past history of diabetes mellitus or metabolic or mental disorders.

Surgical and Pathological Outcomes

No patients assigned to receive LADG underwent conversion to open surgery The median duration of surgery was significantly longer in the LADG group than in the ODG group ($P = 0.005$). On the other hand, the median amount of bleeding was significantly less in the LADG group than in the ODG group ($P = 0.009$; Table 2). No differences were observed between the groups in terms of pathological outcomes.

No mortalities occurred in either group. The surgical morbidities are shown in Table 3. No patients had grade 1