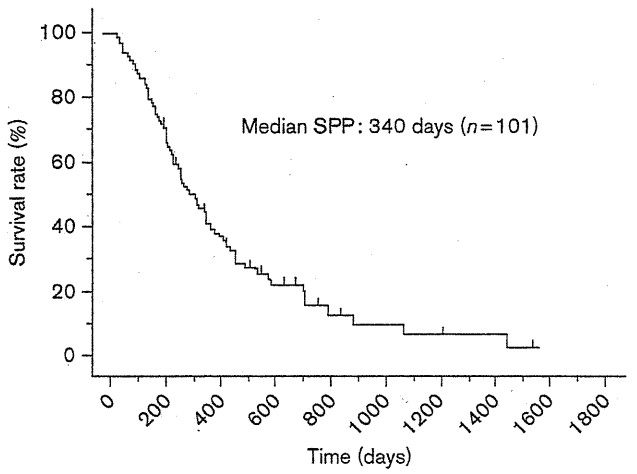
Table 2 Chemotherapy regimens

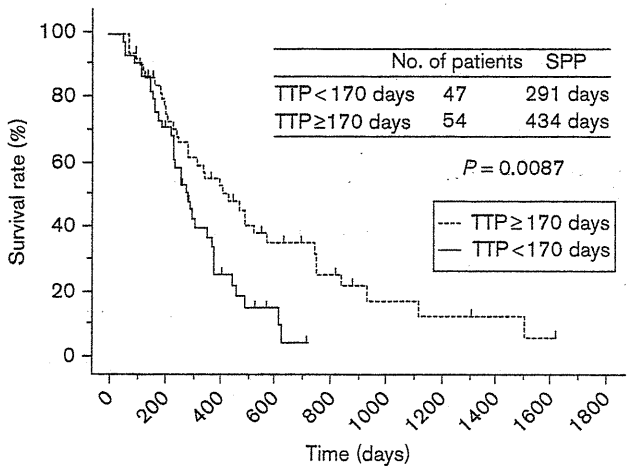
	Number of patients
First-line chemotherapy	
S-1 alone	37
S-1 + cisplatin or oxaliplatin	27
S-1 + irinotecan	9
S-1 + paclitaxel or docetaxel	15
S-1 + cisplatin + taxane	8
Irinotecan + cisplatin	5
Second-line chemotherapy	
S-1 alone	6
S-1 + cisplatin	9
S-1 + irinotecan	17
S-1 + paclitaxel or docetaxel	9
Taxane	30
Irinotecan	17
Irinotecan + cisplatin	12
Cisplatin + paclitaxel	1

Fig. 1



Survival postprogression (SPP).

Fig. 2



Survival postprogression (SPP) according to time to progression (TTP) on first-line chemotherapy.

Table 3 Prognostic factors for survival postprogression

Prognostic factors	Median SPP (days)	*P*	HR	95% CI	*P*
Sex					
Males	382	0.6839	1.491	0.738–3.013	0.2658
Females	314		1		
Age (median)					
<69 years	315	0.8443	1.076	0.596–1.943	0.8077
≥ 69 years	321		1		
Performance status					
2	262	0.4812	14.234	2.766–73.258	0.0015
0–1	351		1		
Histology					
Intestinal	314	0.4326	1.363	0.693–2.681	0.3697
Diffuse	351		1		
Primary tumor					
Present	321	0.0433	0.877	0.415–1.855	0.7315
Absent	358		1		
Measureable lesion					
Absent	340	0.8342	1.040	0.544–1.990	0.9056
Present	375		1		
Number of metastatic site					
≥ 2	178	0.0110	2.140	0.858–5.338	0.1027
0 or 1	376		1		
Albumin (g/dl)					
<3.5	246	0.0295	2.088	1.047–4.060	0.0300
≥ 3.5	401		1		
CRP (mg/dl)					
<1.0	375	0.2119	0.910	0.452–1.830	0.7905
≥ 1.0	278		1		
Hemoglobin (g/dl)					
<10	285	0.2133	0.960	0.522–1.765	0.8947
≥ 10	382		1		
TTP on the first-line chemotherapy median					
<170 days	291	0.0087	2.497	1.227–5.083	0.0116
≥ 170 days	434		1		
Response to the first-line CTX					
SD or PD	314	0.8922	1.270	0.693–2.327	0.4385
PR or CR	351		1		

CI, confidence interval; CR, complete response; CRP, C-reactive protein; CTX, chemotherapy; HR, hazard ratio; PD, progressive disease; PR, partial response; SD, stable disease; SPP, survival postprogression; TTP, time to progression.

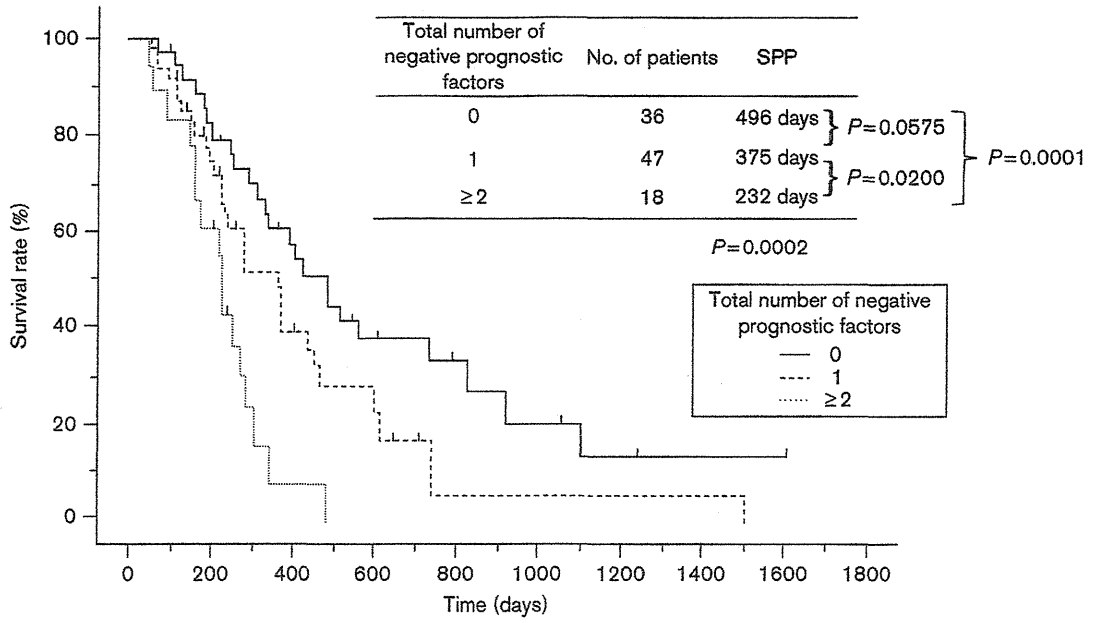
observed in 39 patients, and 18 patients had PD. When categorized by response, the median SPP was 915, 382, 302, and 261 days in patients with CR, PR, SD, and PD, respectively ($P = 0.1671$) (data not shown).

Prognostic factors

The results of univariate and multivariate analyses on the association between various factors, such as sex, age, PS, histology, presence of primary tumor, presence of measurable lesions, number of metastatic sites, TTP on first-line chemotherapy, response to first-line chemotherapy, and Alb, CRP, and Hb values at initiation of second-line chemotherapy and SPP, are summarized in Table 3. PS 2 (HR, 14.234; 95% CI, 2.766–73.258), Alb < 3.5 g/dl (HR, 2.088; 95% CI, 1.047–4.060) at initiation of second-line chemotherapy, and TTP < 170 days on first-line chemotherapy (HR, 2.497; 95% CI, 1.227–5.083) were identified as significant independent prognostic factors for shorter SPP.

In addition, patients were classified according to the number of these three negative prognostic factors they possessed (PS 2, Alb < 3.5 g/dl, and TTP < 170 days on

Fig. 3



Survival postprogression (SPP) according to the number of negative prognostic factors.

first-line chemotherapy) as follows: 36 patients without any negative prognostic factors were scored as 0, 47 patients with one out of three negative prognostic factors were scored as 1, and 18 cases with two or more factors were scored as 2. The median SPP was 496, 375, and 232 days in patients scored as 0, 1, and 2, respectively, with a statistically significant difference between scores of 0–1 and 2 ($P = 0.0002$), as shown in Fig. 3.

Discussion

For patients with AGC, chemotherapy plays an important role in improving survival and symptom alleviation. Even if patients with AGC initially respond to first-line chemotherapy, they ultimately have disease progression. Recently, the combined analysis of two Japanese phase III trials involving 327 patients has demonstrated that second-line chemotherapy contributes to prolonging OS in patients with AGC [25]. In addition, the efficacy of second-line chemotherapy has clearly been demonstrated for the first time in a prospective randomized phase III study, in which second-line irinotecan significantly prolonged OS over BSC in 40 patients with AGC [23]. However, it remains uncertain whether we can distinguish patients who are likely to benefit from second-line chemotherapy from those who would not.

In this study, PS 0–1 and Alb ≥ 3.5 g/dl at initiation of second-line chemotherapy as well as TTP ≥ 170 days on first-line chemotherapy were identified as positive prognostic factors for SPP. In accordance with our findings, other studies have shown that PS 0–1 and TTP greater than 5–6 months on first-line chemotherapy were significantly associated with prolonged OS in patients receiving second-line chemotherapy for AGC [26–28]. Second-line chemotherapy would not be appropriate for patients with considerable PS deterioration and rapid disease progression on first-line chemotherapy. However, data from the Surveillance, Epidemiology, and End Results registry, which enrolls large numbers of patients with metastatic gastric cancer, demonstrate that age, sex, and tumor location were significant independent prognostic factors for OS [29]. When tumor location was included in the multivariate analysis, PS 2, Alb < 3.5 g/dl, and TTP < 170 days on first-line chemotherapy were still identified as independent prognostic factors, whereas age, sex, and tumor location were not (data not shown).

As observed in other studies [26–28,30–32], PS 2 had a significantly negative impact on survival in the multivariate analysis even though only 5% of the study cohort had PS 2. Irrespective of the sample size of patients with PS 2, PS classifications of 0–1 and 2 are generally used to stratify patients in the phase III trials on AGC [5–8,10] due to its well known impact on survival.

In this study, Alb of 3.5 g/dl and CRP of 1.0 mg/dl were adopted as cut-off values because both elevated CRP (> 1.0 mg/dl) and decreased Alb (< 3.5 g/dl) were reported to be significant negative prognostic factors in various types of cancer [33,34]. Although there has been some controversy over whether serum Alb is a useful prognosticator for SPP [28,30] as opposed to PS and TTP,

Alb was independently associated with OS in our cohort. Patients who maintain their nutritional status can better tolerate second-line chemotherapy, which may lead to durable SPP.

Anemia with Hb ≤ 10 g/dl is often found in patients with AGC due to bleeding from the primary lesion, chemotherapy-induced myelosuppression, or nutritional deficiency, and its negative prognostic value has been discussed in several studies [26,27,35]. In the present study, Hb level was not identified as a prognostic factor for SPP, partly due to the comparatively well maintained Hb level at the initiation of second-line chemotherapy (median, 10.6 g/dl) compared with other studies [26,27,35] that found low Hb to be a negative prognostic factor.

Regarding the association between response to the first-line chemotherapy and SPP, positive response (CR plus PR) as assessed by CT scan was not prognostically significant (Table 3). This finding is consistent with a previous report [36] that showed no significant association between positive response to the first-line chemotherapy and longer OS in AGC, despite a moderate correlation between positive response and durable TTP. In contrast, the tumor's metabolic response to chemotherapy, which is observable by PET as a decrease in fluorine-18 fluorodeoxyglucose uptake, has recently been reported to be an independent prognostic factor for OS in patients with AGC receiving preoperative chemotherapy [37,38]. Longer TTP on first-line chemotherapy, which was identified as a positive prognostic factor for SPP in this study, might be predicted by PET scans during first-line chemotherapy.

The total number of negative prognostic factors, such as PS 2, Alb < 3.5 g/dl, and TTP < 170 days, was prognostically significant in this study (Fig. 3). Approximately four-fifths of the patients with 0 or 1 negative factor achieved SPP over 1 year, whereas patients with two or more negative factors had a median SPP of 232 days. Similar prognostic scoring models have been reported in previous studies [26,27]. Catalano *et al.* [26] incorporated five prognostic factors (PS, Hb level, carcinoembryonic antigen value, number of metastatic sites, and TTP under first-line chemotherapy) into a prognostic score. Kanagavel *et al.* [27] proposed a model composed of PS, Hb level, and TTP under first-line chemotherapy. In accordance with our findings, their models were able to differentiate patient prognosis following second-line chemotherapy in good, intermediate, and poor risk categories with a median survival of 12.7–13.5, 6.0–7.1, and 2.0–3.3 months, respectively.

The optimal indications for second-line chemotherapy in patients with AGC are less clearly defined than those for first-line chemotherapy. The present study demonstrated that second-line chemotherapy would not be beneficial in patients with two or more of the following factors: PS 2, Alb < 3.5 g/dl at initiation of the second-line chemotherapy, and TTP < 170 days on first-line chemotherapy. The limitations of this study, which include its retrospective, single-institution nature and the relatively small sample size, need to be taken into account before generalizing the results to daily clinical practice until prospective, multicenter validation is available. However, we believe that our findings will help practitioners prognosticate on the disease course and facilitate decision-making regarding second-line chemotherapy by physicians, patients, and their caregivers.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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Randomized clinical trial

Prospective randomized trial of preoperative enteral immunonutrition followed by elective total gastrectomy for gastric cancer

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Background: Perioperative enteral immunonutrition is thought to reduce postoperative morbidity in patients undergoing major gastrointestinal surgery. This study assessed the clinical effects of preoperative enteral immunonutrition in well nourished patients with gastric cancer undergoing total gastrectomy.

Methods: Well nourished patients with primary gastric cancer, fit for total gastrectomy, were randomized to either a control group with regular diet, or an immunonutrition group that received regular diet supplemented with 1000 ml/day of immunonutrients for 5 consecutive days before surgery. The primary endpoint was the incidence of surgical-site infection (SSI). Secondary endpoints were rates of infectious complications, overall postoperative morbidity and C-reactive protein (CRP) levels on 3–4 days after surgery.

Results: Of 244 randomized patients, 117 were allocated to the control group and 127 received immunonutrition. SSIs occurred in 27 patients in the immunonutrition group and 23 patients in the control group (risk ratio (RR) 1·09, 95 per cent confidence interval 0·66 to 1·78). Infectious complications were observed in 30 patients in the immunonutrition group and 27 in the control group (RR 1·11, 0·59 to 2·08). The overall postoperative morbidity rate was 30·8 and 26·1 per cent respectively (RR 1·18, 0·78 to 1·78). The median CRP value was 11·8 mg/dl in the immunonutrition group and 9·2 mg/dl in the control group ($P = 0·113$).

Conclusion: Five-day preoperative enteral immunonutrition failed to demonstrate any clear advantage in terms of early clinical outcomes or modification of the systemic acute-phase response in well nourished patients with gastric cancer undergoing elective total gastrectomy. Registration number: ID 000000648 (University Hospital Medical Information Network (UMIN) database).

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Introduction

Immunonutrition for surgical and critically ill patients, involving nutritional support with arginine, glutamine, ω-3 fatty acids and nucleotides (RNA) either alone or in combination, has been gaining increasing attention[1–4]. Immunonutrition modulates host immune systems and inflammatory responses. The ω-3 fatty acid eicosapentaenoic acid has immunomodulatory and anti-inflammatory properties. It replaces arachidonic acid, an ω-6 fatty acid, in cell membrane phospholipids, and becomes a substrate for the synthesis of the 3-series prostaglandins and the 5-series leukotrienes, which are less proinflammatory than arachidonic acid-derived 2-series and 4-series analogues respectively[5].

Numerous clinical studies on the effects of perioperative immunonutrition following surgery or trauma have shown beneficial effects, reducing postoperative morbidity after major abdominal surgery[6,7]. Before initiating the present

study the authors showed that 5 days of preoperative enteral immunonutrition with 1000 ml/day Impact® (Ajinomoto Pharmaceutical Company, Tokyo, Japan) could alter the cell membrane composition of peripheral blood mononuclear cells and change the ω-3 to ω-6 ratio in membrane phospholipids from 0·24 to 0·32 in patients undergoing elective abdominal major surgery for gastrointestinal cancer[8].

Surgical resection is the mainstay of curative treatment for gastric cancer. Total gastrectomy is associated with postoperative catabolism, and perturbations in the metabolic, endocrine, neuroendocrine and immune systems that contribute to high postoperative morbidity rates in more than 40 per cent of patients[9,10]. Immunonutrition seems a promising treatment option to modify metabolic and immune responses in such patients, reducing the incidence of postoperative complications and shortening hospital stay.

This prospective randomized clinical trial was undertaken to investigate the impact of preoperative enteral immunonutrition on the incidence of postoperative complications and C-reactive protein (CRP) values (as a marker of inflammatory response) in patients undergoing elective total gastrectomy for gastric cancer.

Methods

This study was conducted in accordance with the international ethical recommendations stated in the Declaration of Helsinki. Preoperative staging included chest X-ray, abdominal computed tomography and endoscopy within 4 weeks of entry into the trial, and full blood cell count, liver and renal function tests within 2 weeks before trial entry. Entry criteria were: histologically proven resectable primary gastric adenocarcinoma; fit for elective total gastrectomy with adequate bone marrow function (white blood cell (WBC) count 4000–12 000/mm^3, platelet count at least 100 000/mm^3, haemoglobin 8·0 g/dl or more), hepatic function (total bilirubin no more than 25·65 μmol/l, serum aminotransferases 100 units/l or less) and renal function (serum creatinine no more than the upper institutional limit); performance status 0 or 1 on the Eastern Cooperative Oncology Group scale; age no more than 80 years; bodyweight (BW) loss of 10 per cent or less within 6 months before entry; tolerance of oral feeding; no other severe medical conditions including insulin-dependent diabetes mellitus; no concurrent active infection; no known allergy to any of the ingredients of immunonutrition; no preoperative chemotherapy or radiotherapy; and provision of written informed consent.

The study was approved by the institutional review and ethics board of each hospital involved and was registered in the University Hospital Medical Information Network (UMIN) database (ID 000000648).

Study design and enteral regimens

This study was designed to test the hypothesis that preoperative enteral immunonutrition given orally would reduce the incidence of postoperative infectious complications in a population of comparatively well nourished patients after elective total gastrectomy. Patients who met eligibility criteria were randomized into two groups, stratified by institution. Randomization was carried out by data centre staff using the minimization method, with an algorithm that balanced institution. The immunonutrition group received 1000 ml/day of preoperative oral supplementation in the form of an immunonutrient-enriched enteral feed (Impact®) added to normal diet for 5 consecutive days before surgery. The control group had access to a regular diet without any nutritional supplementation. The constituents of Impact® are shown in *Table 1*. Even when patients were unable to take the 1000 ml/day of Impact® orally, it was not administered via an enteral feeding tube. Antibiotic prophylaxis was given routinely at least 30 min before operation and repeated every 3 h during surgery. Postoperative wound management was according to each participating institution's standard.

Outcome measures

Surgical and non-surgical complications from surgery to hospital discharge were documented prospectively. The primary outcome was surgical-site infection (SSI). SSIs were categorized as superficial incisional, deep incisional, and organ or space SSI, as defined in the Centers for Disease Control guidelines[11]. Other complications analysed were abdominal abscess (collection of pus confirmed by percutaneous drainage), pancreatic fistula

Table 1 Composition of Impact®

	Amount (per 100 ml)
Energy (kcal)	101
Protein (g)	5·6
Fat (g)	2·8
Eicosapentaenoic acid (g)	0·20
Docosahexaenoic acid (g)	0·14
n-6 : *n*-3 ratio	4 : 5
Carbohydrate (g)	13·4
Arginine (g)	1·28
RNA (mg)	0·13

(drain output of any measurable volume of fluid on or after the third day after surgery, with an amylase content greater than three times the serum amylase level[12]), anastomotic leakage (positive contrast swallow test), wound infection (purulent exudate in the wound with positive bacterial culture), drain infection (purulent exudate around a percutaneous drainage tube), pneumonia (clinical signs of pneumonia with radiographic evidence and positive sputum culture or bronchoalveolar lavage), venous catheter infection (local signs of inflammation or the isolation of pathogenic organisms in culture), bleeding (need for blood transfusion of at least 2 units), respiratory failure (presence of dyspnoea and respiratory rate over 35 breaths/min or arterial partial pressure of oxygen less than 70 mmHg), pleural effusion, heart failure (unstable blood pressure requiring use of additional intravenous fluids or cardiac stimulants) and ileus.

Systemic inflammatory response syndrome (SIRS) was diagnosed as the clinical manifestation of two or more of the following features in the first week after operation: temperature exceeding 38°C or less than 36°C; heart rate more than 90 beats/min; respiratory rate over 20 breaths/min or arterial partial pressure of carbon dioxide less than 32 mmHg; WBC count over 12 000/mm^3, less than 4000/mm^3 or more than 10 per cent immature (band) forms.

Serum levels of CRP were measured on day 3 or 4 after surgery. The prognostic nutritional index (PNI) was calculated as 10 × albumin (g/dl) + 0·005 × lymphocyte counts (per mm^3), based on albumin levels measured within 2 weeks before trial entry.

Statistical analysis

This study was designed as a multi-institutional prospective randomized clinical trial. The primary endpoint was the incidence of SSI. Secondary objectives were rates of postoperative infectious complications, overall morbidity and highest CRP value on day 3 or 4 after surgery. A *post hoc* subgroup analysis was performed to explore the effects of preoperative nutritional intervention according to the baseline clinical and nutritional status of the patients. Based on an overall rate of SSI following gastrectomy of between 9 and 21 per cent[13–16] and an estimated 10 per cent decrease in the incidence of SSI (5 per cent in the immunonutrition group *versus* 15 per cent in the control group), with a power of 0·80 and a two-sided α of 0·05, it was calculated that the trial required 120 patients in each treatment group.

The χ^2 test or Fisher's exact test was used to compare categorical variables. The Wilcoxon signed-rank test was used for data that were not normally distributed. All statistical tests were two-sided, and $P < 0{\cdot}050$ was

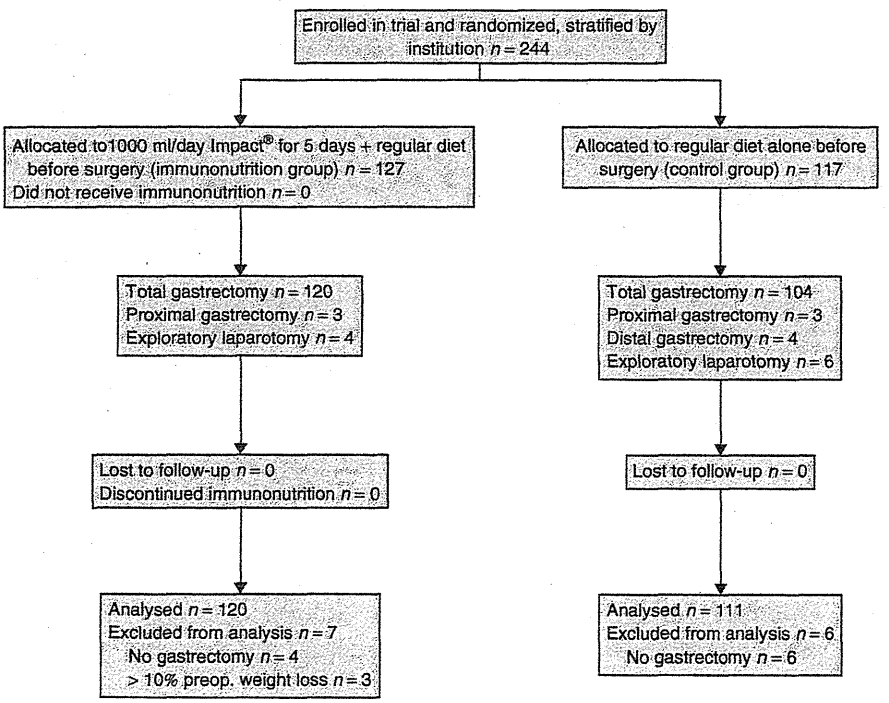

Fig. 1 CONSORT diagram for the trial

Table 2 Clinical and nutritional characteristics

	Immunonutrition ($n = 127$)	Control ($n = 117$)	P†
Age (years)*	64 (26–78)	65 (30–79)	0·323‡
Sex ratio (M : F)	97 : 30	84 : 33	0·465§
Weight (kg)*	60·9 (38·0–97·0)	60·0 (40·1–92·2)	0·182‡
Body mass index (kg/m^2)*	22·8 (15·1–33·8)	22·6 (17·8–33·1)	0·780‡
Weight loss (%)*	0 (0–16·9)	0 (0–10·0)	0·780‡
Nutritional status			0·372§
Well nourished	123 (96·9)	116 (99·1)	
Malnourished	4 (3·1)	1 (0·9)	
Albumin (g/dl)*	4·2 (2·5–4·8)	4·1 (2·4–5·3)	0·447‡
Total lymphocyte count (/mm^3)*	1880 (800–5952)	1765 (700–4446)	0·248‡
CRP (mg/dl)*	0·1 (0–7·2)	0·1 (0–10·3)	0·818‡
Type of surgery			0·155
Total gastrectomy	120 (94·5)	104 (88·9)	
Proximal gastrectomy	3 (2·4)	3 (2·6)	
Distal gastrectomy	0 (0)	4 (3·4)	
Exploratory laparotomy	4 (3·1)	6 (5·1)	
Node dissection			0·223
D0	1 (0·8)	3 (2·7)	
D1	22 (17·9)	20 (18·0)	
D2	100 (81·3)	85 (76·6)	
D3	0 (0)	3 (2·7)	
Combined resection			0·179
Gallbladder	80 (65·0)	77 (69·4)	
Spleen	42 (34·1)	23 (20·7)	
Pancreas	3 (2·4)	5 (4·5)	
Transverse colon	4 (3·3)	2 (1·8)	
Pathological characteristics	$n = 123$	$n = 111$	
Tumour status			0·349
T1	44 (35·8)	42 (37·8)	
T2	36 (29·3)	37 (33·3)	
T3	38 (30·9)	24 (21·6)	
T4	5 (4·1)	8 (7·2)	
Node status			0·382
N0	58 (47·2)	61 (55·0)	
N1	35 (28·5)	24 (21·6)	
N2	29 (23·6)	23 (20·7)	
N3	1 (0·8)	3 (2·7)	
Resection type			0·138§
R0	111 (90·2)	106 (95·5)	
R1–2	12 (9·8)	5 (4·5)	

Values in parentheses are percentages unless indicated otherwise; *values are median (range). General nutritional status at baseline was diagnosed on subjective global assessment. CRP, C-reactive protein. †χ^2 test, except ‡Wilcoxon signed-rank test and §Fisher's exact test.

considered significant. Statistical analysis was performed with SPSS® version 14 (SPSS, Chicago, Illinois, USA).

Results

Between 16 February 2006 and 25 December 2009, 244 patients were recruited and randomized to immunonutrition (127) or control (117) groups (*Fig. 1*). Three patients with more than 10 per cent preoperative BW loss were incorrectly randomized to the immunonutrition group and excluded from the analysis. No patient was withdrawn from the study.

The clinical and nutritional characteristics of the groups are shown in *Table 2*. They were well matched for age, sex, BW, extent of BW loss within the 3 months before surgery, body mass index (BMI), general nutritional status at baseline, preoperative albumin level, total lymphocyte count and CRP level. Most patients in both groups were well nourished. Twenty-one patients in the immunonutrition group and 13 in the control group were mildly malnourished based on 5·1–10·0 per cent preoperative BW loss.

Two hundred and twenty-four patients underwent total gastrectomy, six proximal gastrectomy, four distal gastrectomy and ten had exploratory laparotomy alone

Table 3 Endpoints according to treatment

	Immunonutrition ($n = 120$)	Control ($n = 111$)	Risk ratio*
Surgical-site infection	27 (22·5)	23 (20·7)	1·09 (0·66,1·78)
Superficial incisional	8 (6·7)	7 (6·3)	
Deep incisional	5 (4·2)	1 (0·9)	
Organ or space	17 (14·2)	15 (13·5)	
Infectious complication	30 (25·0)	27 (24·3)	1·11 (0·59, 2·08)
Any complication	37 (30·8)	29 (26·1)	1·18 (0·78, 1·78)
CRP value on day 3 or 4 (mg/dl)†	11·8 (2·3–38·1)§	9·2 (1·1–38·9)	

Values in parentheses are percentages unless indicated otherwise; *values in parentheses are 95 per cent confidence intervals; †values are median (range). Infectious complications include abdominal abscess, infectious pancreatic fistula, anastomotic leakage, wound infection, drain infection, pneumonia and venous catheter infection. CRP, C-reactive protein. §$P = 0·113$ *versus* control (Wilcoxon signed-rank test).

owing to unresectable disease. There were no significant differences between the groups in terms of the surgical procedure, including extent of lymph node dissection, degree of combined resection, or pathological tumour or node status according to the classification of the Japanese Gastric Cancer Association[17].

Even when patients were unable to take the 1000 ml/day of Impact® orally, it was not administered via an enteral feeding tube. No patient received parenteral nutrition before surgery. Compliance with oral Impact® was 91·7, 95·2, 96·6, 96·6 and 92·3 per cent of planned volume over the 5 days before surgery, with an overall rate of 94·5 per cent.

Outcomes were measured in 231 patients, excluding ten patients who had exploratory laparotomy alone and three with more than 10 per cent preoperative BW loss who did not fulfil the entry criteria. SSI occurred in 27 patients (22·5 per cent) in the immunonutrition group and 23 (20·7 per cent) in the control group (risk ratio (RR) 1·09; 95 per cent confidence interval 0·66 to 1·78) (*Table 3*). Infectious complications occurred in 30 patients (25·0 per cent) in the immunonutrition group and 27 (24·3 per cent) in the control group (RR 1·11, 0·59 to 2·08). The overall postoperative morbidity rate was 30·8 per cent (37 patients) and 26·1 per cent (29 patients) respectively (RR 1·18, 0·78 to 1·78). The median CRP value on day 3 or 4 after surgery was 11·8 mg/dl in the immunonutrition group and 9·2 mg/dl in the control group ($P = 0·113$).

Postoperative complications are detailed in *Table 4*. There were no differences in the incidence of abdominal abscess, pancreatic fistula, anastomotic leakage and wound infection or dehiscence between the groups. No significant differences between the groups were found with respect to other postoperative complications or SIRS. There were no reoperations or in-hospital deaths, and median hospital stays were similar.

Table 4 Operative morbidity and mortality

	Immunonutrition ($n = 120$)	Control ($n = 111$)	P†
Any complication	37 (30·8)	29 (26·1)	0·468
Abdominal abscess	11 (9·2)	7 (6·3)	0·469
Pancreatic fistula	8 (6·7)	7 (6·3)	1·000
Anastomotic leakage	3 (2·5)	3 (2·7)	1·000
Wound infection or dehiscence	13 (10·8)	8 (7·2)	0·369
Drain infection	3 (2·5)	1 (0·9)	0·623
Pneumonia	5 (4·2)	0 (0)	0·061
Venous catheter infection	2 (1·7)	1 (0·9)	1·000
Pleural effusion	1 (0·8)	1 (0·9)	1·000
Postoperative bleeding	3 (2·5)	0 (0)	0·248
Ileus	2 (1·7)	1 (0·9)	1·000
SIRS	46 (38·3)	34 (30·6)	0·268
Reoperation	0 (0)	0 (0)	
Hospital death	0 (0)	0 (0)	
Hospital stay (days)*	18 (9–85)	17 (10–88)	0·395‡

Values in parentheses are percentages unless indicated otherwise; *values are median (range). SIRS, systemic inflammatory response syndrome. †Fisher's exact test, except ‡Wilcoxon signed-rank test.

When patients were divided into subgroups based on BW loss (less than 5 per cent *versus* 5 per cent or more), BMI (less than 25 kg/m^2 *versus* 25 kg/m^2 or more), CRP (under 0·2 mg/dl *versus* at least 0·2 mg/dl), albumin (below 4·0 g/dl *versus* 4·0 g/dl or over) and prognostic nutritional index (less than 50 *versus* 50 or more) as indicators of malnutrition, a significant interaction was found between treatment effect and preoperative BW loss (*Fig. 2*). Among 34 patients with at least 5 per cent BW loss in the 3 months before surgery, SSI occurred in 10 of 21 patients in the immunonutrition group and 11 of 13 in the control group. The RR for SSI in the immunonutrition group was 0·56 (0·34 to 0·93; $P = 0·031$). Contrary to the favourable effect of immunonutrition in patients with BW loss of at least 5 per cent, preoperative nutritional intervention seemed unfavourable in patients with a BMI of 25 kg/m^2 or more (RR 2·86, 0·68 to 12·12; $P = 0·149$).

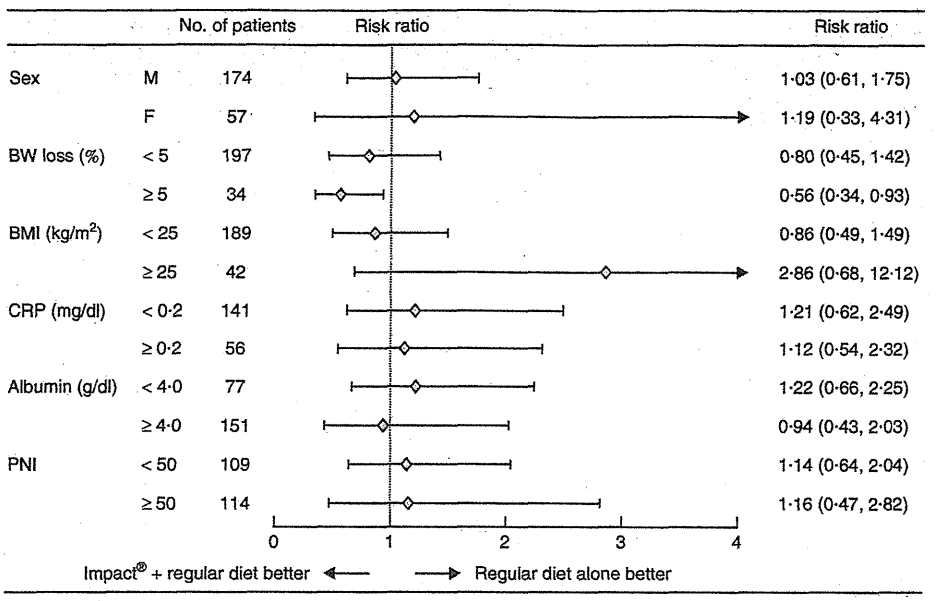

Fig. 2 Effect of enteral nutrition on risk of development of surgical-site infection, in relation to clinical and nutritional characteristics. BW, bodyweight; BMI, body mass index; CRP, C-reactive protein; PNI, prognostic nutritional index

Discussion

The primary goal of nutritional care has changed from the provision of necessary calories to cover a patient's needs to approaches aimed at restoring optimal metabolic and immune responses. Dietary components, such as arginine, glutamine, ω-3 fatty acids and nucleotides, have been shown to provide beneficial effects beyond their nutritional value. Immunomodulatory formulas supplemented with such components have gained increasing attention because of their ability to reduce the rate of postoperative complications compared with standard nutritional formulas[1–4].

Some authors, however, have questioned the importance of immunonutrition[2,18] because perioperative nutritional support reduces the rate of postoperative complications only in selected populations, such as severely malnourished patients and those undergoing major surgical procedures such as oesophagectomy and pancreatectomy[7,19,20]. Although evidence-based guidelines recommend preoperative nutritional intervention for 7–14 days in moderately or severely malnourished patients undergoing major gastrointestinal surgery[21,22], the benefits of nutritional support in well nourished subjects are controversial. This uncertainty regarding the routine use of immunonutrition might be attributed to the heterogeneity of individual studies with regard to definitions of malnutrition and the incidence of malnutrition and other co-morbidities[23,24], as well as inadequate numbers of patients in previous trials. The present study was therefore undertaken to overcome some of these inconsistencies.

Despite adequate patient compliance with Impact®, there were no significant differences in any clinical outcomes between the immunonutrition and control groups. A clear effect of immunonutrition on the systemic acute-phase response to major surgery was absent. Klek and colleagues[25] also failed to demonstrate any clear advantage for routine postoperative immunonutrition, whether enteral or parenteral, in well nourished patients undergoing elective upper gastrointestinal surgery. Heslin and co-workers[26] reported that early postoperative enteral immunonutrition did not reduce rates of postoperative complications or length of hospital stay after upper gastrointestinal surgery for malignancy compared with intravenous crystalloid therapy.

Contrary to these findings, a recent meta-analysis of 13 randomized trials involving 1269 patients demonstrated that perioperative immunonutrition significantly reduced rates of postoperative infection, shortened hospital stay and improved various parameters of immune function in patients undergoing gastrointestinal surgery[4]. Nearly all of these trials, however, involved patients with various degrees of malnutrition, and the proportion of malnourished patients with more 10 per cent weight loss from their preillness BW reached almost 60 per cent in some studies[6,27–32]. It is not clear whether the benefits reported in the meta-analysis by Zheng *et al.*[4] could be generalized

to well nourished patients. In addition, when patients undergoing upper gastrointestinal surgery were stratified by BMI before randomization to minimize the impact of nutritional status on outcomes, patients on immunomodulatory enteral diets had similar rates of postoperative complications to those on standard enteral diets[18]. Taken together with the present findings, well nourished patients undergoing upper gastrointestinal surgery seem unlikely to benefit from immunonutrition, whether administered before or after surgery.

In the present study preoperative immunonutrition significantly decreased the risk of SSI in patients who had at least 5 per cent preoperative BW loss within the 3 months before surgery. This seems to confirm the effectiveness of perioperative immunonutrition in moderate or severely malnourished patients undergoing major gastrointestinal surgery reported elsewhere[4,21,22]. Although immunonutrition appeared to be beneficial in patients with at least 5 per cent BW loss, it seemed unfavourable in those with a BMI of 25 kg/m^2 or more. However, it is acknowledged that BMI has been shown to be an independent risk factor for the development of postoperative surgical complications in patients undergoing gastrectomy[33–35].

Differences in the outcomes of immunonutrition between well nourished and malnourished surgical patients may be attributed to the impact of surgical stress on immune function, which may be much smaller in the former population[24]. Severity of risk associated with surgery or trauma and nutritional status are therefore likely to be key elements affecting the efficacy of immune-enhancing diets.

Uncertainty over the use of enteral immunonutrition can also be attributed to the considerable heterogeneity of individual studies in terms of the timing, duration and composition of nutritional intervention[2,24,27,28,31,32,36,37]. As it is reasonable to assume that immunonutrients should reach suitable tissue and plasma concentrations to exert their maximum effects, preoperative feeding seems logical to achieve this goal in the early postoperative period. Although there is no clear evidence about the exact length of the optimum preoperative feeding period, 5–7 days is commonly used[6,36,38–40].

Regarding the composition of immunomodulatory formulations, a number of studies have been conducted with Impact®[6,26–32]. There are no adequate clinical trials comparing various immune-enhancing formulas. It is not possible to estimate how differences in composition could affect results.

Routine preoperative use of immunonutrition in well nourished patients having gastric cancer resections cannot be recommended.

Acknowledgements

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Disclosure: The authors declare no conflict of interest.

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Snapshot Quiz 12/08

Question: A 24-year-old male intravenous drug user presented with this lesion on his right thigh. What is the most likely diagnosis? How this condition is treated?

The answer to the above question is found on p. 636 of this issue of *BJS*.

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Significance of Surgical Treatment of Liver Metastases from Gastric Cancer

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Abstract. *Background/Aim: The optimal treatment of liver metastases from gastric cancer (LMGC) remains uncertain. We retrospectively compared surgical treatment with chemotherapy alone and identified prognostic determinants. Patients and Methods: We reviewed the records of 50 consecutive patients with LMGC: 25 patients with gastrectomy plus hepatic resection (group A), 13 patients with palliative gastrectomy (group B), and 12 patients with chemotherapy alone (group C). We compared the overall survival among these three groups, and assessed prognostic factors. Results: Median survival time in groups A, B, and C was 33.4, 10.5, and 8.7 months, respectively. Univariate analysis found T stage, number of liver metastases, and treatment group to be significant prognostic factors. In the multivariate analysis, T stage was shown to be an independent prognostic determinant, while gastrectomy plus hepatic resection was of marginal significance compared with chemotherapy alone. Conclusion: T Stage was a significant prognostic determinant, and gastrectomy plus hepatic resection could be a promising treatment for patients with LMGC.*

Liver metastases from gastric cancer (LMGC) occur in approximately 3.5 to 14% of patients with primary gastric cancer (1-16). Chemotherapy is the most common treatment option for LMGC, since surgical treatment is rarely indicated due to the presence of numerous liver metastases and/or extrahepatic disease, such as peritoneal dissemination and extensive lymph node metastasis. Although chemotherapy for metastatic gastric cancer has recently evolved, the prognosis of patients with LMGC is still disappointing, with a median survival time (MST) of approximately 12 months and a 3-year survival rate of around 5% (17) when treated with chemotherapy alone.

Although palliative gastrectomy was reported to be prognostically beneficial for selected patients with a single non-curative factor including LMGC (18), the efficacy of palliative gastrectomy in patients with liver-only metastases remains uncertain. However, this might be clarified by the results of an ongoing prospective randomized controlled trial investigating the role of palliative gastrectomy for patients with advanced gastric cancer (AGC) with a single non-curative factor (19).

On the other hand, complete resection of the primary gastric tumor and LMGC has resulted in MST of approximately 23 months and a 5-year survival rate of 11-42% (1-16). Hepatic resection provides a potential opportunity for cure, although the complete resection rate for LMGC has been reported to be approximately 20% due to frequently associated peritoneal dissemination or advanced lymph node metastasis.

No standard treatment has yet been established for patients with LMGC, partly because there has only been one report (1) concurrently comparing the three treatment options, and partly because of the variability in patients' background non-curative factors in the literature (1–16). Therefore, in this study, we retrospectively compared these three treatment options and identified prognostic determinants through univariate and multivariate analyses for patients with LMGC as the sole non-curative factor that is considered crucial for better survival (18, 19).

Patients and Methods

Patient inclusion criteria. We retrospectively reviewed the records of 50 consecutive patients with LMGC treated at Osaka National Hospital between January 1, 1995 and December 31, 2009. In this study, patients diagnosed with synchronous or metachronous liver metastasis as a single non-curative factor were included. Those who met any of the following criteria were excluded: (i) any other non-curative factor except for liver metastasis, such as T4 tumor (tumor infiltrating to adjacent organs), para-aortic lymph node metastasis,

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Key Words: Gastric cancer, liver metastasis, hepatic resection, gastrectomy, chemotherapy, prognostic factor.

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Table I. *Patient characteristics.*

	Group A (n=25)	Group B (n=13)	Group C (n=12)	*P*-value
Male/female	23/2	11/2	11/1	0.77
Age (years), median (range)	72 (47-80)	70 (49-78)	67 (54-80)	0.71
Primary tumor				
Intestinal/diffuse	17/8	9/4	7/5	0.81
T Stage: 1/2/3	1/7/17	0/0/13	0/2/10	0.08
N Stage: 0/1/2	7/7/11	2/6/5	4/5/3	0.62
Liver metastasis				
Synchrounous/metachronous	16/9	13/0	12/0	<0.01
Unilobar/bilobar	20/5	4/9	1/11	<0.01
Solitary/multiple	18/7	1/12	1/11	<0.01
Diameter (mm), median (range)	20 (5-98)	20 (10-57)	40 (20-100)	0.02

peritoneal dissemination, positive abdominal lavage cytology, or distant metastasis; (ii) *linitis plastica*; (iii) other concurrently active malignancy; (iv) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or more at initial diagnosis; and (v) any prior chemotherapy or radiation therapy.

Data collection. Data collected retrospectively include patient characteristics, such as age and gender, pathological characteristic of the primary gastric cancer, clinicopathological characteristics of metastasis, and treatment modality used. The histology of the primary gastric cancer was based on the Lauren classification. T and N stage were classified according to the Japanese Classification of Gastric Carcinoma (20). Clinicopathological characteristics of liver metastasis included timing of emergence, intrahepatic distribution, number of nodules, and maximum diameter of each nodule.

Survival analysis. The therapeutic course of each patient was censored at death or on February 11, 2010. Twelve patients in the gastrectomy plus hepatic resection (group A, n=25), two patients in the palliative gastrectomy (group B, n=13), and three patients in chemotherapy alone (group C, n=12) were alive on February 11, 2010, and treated as censored cases for survival analyses. Overall survival (OS) was defined as the time from the date of diagnosis of liver metastasis to the date of death from any cause or the last follow-up, and was compared among the three treatment options. Univariate analysis was used to assess the association between each clinicopathological factor and OS. A multivariate analysis was performed to identify variables independently associated with OS.

Statistical analysis. With regard to the associations between treatment options and clinicopathological characteristics, the chi-square test was used for categorical variables, and Student's *t*-test or the Wilcoxon test was used for continuous variables as appropriate. OS curves were estimated by the Kaplan–Meier method and compared using the log-rank test. Multivariate Cox's regression analyses were performed to identify prognostic factors for survival by adjusting potential confounding factors. Variables achieving a *p*-value less than 0.05 in the univariate analysis were subsequently introduced into the multivariate analysis. All statistical analyses were performed with JMP software, version 8.0 (SAS Institute, Cary, NC, USA). *P*-values less than 0.05 were considered statistically significant, and all tests were two-sided.

Results

Patient characteristics. The clinicopathological characteristics of the 50 patients are presented in Table I. There were 45 males and 5 females with a median age of 70 (range 47-80) years. These 50 patients were categorized into three groups according to the treatment modality performed. Twenty-five patients in group A underwent complete resection of both the primary gastric cancer and liver metastasis with D2 lymphadenectomy, and 13 patients in group B received D1 gastrectomy with liver metastasis untouched, while 12 patients in group C underwent chemotherapy alone without any surgical intervention. Histologically, approximately two-thirds of the patients had intestinal-type adenocarcinoma and one-third had diffuse-type adenocarcinoma. Most patients had an advanced primary cancer of T3 or deeper, with positive lymph node metastases. There were clear imbalances among the groups with respect to clinicopathological features of liver metastasis. Metachronous metastasis was observed only in group A. The median disease-free interval from primary surgery to the detection of metachronous liver metastasis was 645 (range 240-1682) days. Both unilobar metastasis and solitary metastasis were also more frequent in group A than in groups B and C ($p<0.01$). The maximum tumor diameter was significantly higher in group C than in groups A and B ($p=0.02$). In group A, 10 out of 25 patients received adjuvant chemotherapy, however, this treatment had no impact on OS (data not shown). After hepatectomy, relapse of disease was found in 18 patients, with a median recurrence-free interval of 154 days, involving the remnant liver in 15 patients, lymph nodes in 2 patients, and pleura in 1 patient.

Prognostic factors. The MST ranged from 33.4 months in group A to 8.7 months in group C. The 1-, 3-, and 5-year survival rates were 73.9%, 42.8%, and 36.7% in group A; 46.2%, 23.1%, and 15.4% in group B; and 36.7%, 12.2%, and 0% in group C, respectively. OS in group A was

Table II. *Univariate analysis of prognostic factors for overall survival.*

	No. of patients	MST (months)	Survival rate			HR (95% CI)	*P*-value
			1-Year	3-Year	5-Year		
Gender							0.74
Male	45	15.0	56.8	30.7	23.7	1	
Female	5	19.1	66.7	33.3	NA	0.79 (0.13-2.62)	
Age, years							0.83
<70	25	16.0	58.4	30.3	19.0	1	
>70	25	14.0	57.1	31.7	31.7	1.04 (0.50-2.39)	
Histological type							0.92
Intestinal	33	16.5	62.5	28.1	NA	1	
Diffuse	17	12.0	47.8	39.8	39.8	1.04 (0.50-2.39)	
T Stage							<0.01
1, 2	10	NA	100.0	83.3	83.3	1	
3, 4	40	12.0	47.6	20.6	13.2	12.7 (2.73-226.42)	
N Stage							0.34
0, 1	31	16.0	56.8	36.4	30.3	1	
2, 3	19	14.0	59.4	20.8	NA	1.41 (0.69-2.81)	
Timing							0.15
Synchrounous	9	35.1	100	42.9	28.6	1	
Metachronous	41	12.0	48.9	29.5	23.6	1.92 (0.80-5.68)	
Distribution							0.05
Unilobar	25	35.1	72.6	39.3	26.2	1	
Bilobar	25	10.2	44.0	22.0	17.6	2.00 (1.00-4.14)	
Number							0.03
Solitary	20	36.8	70.8	50.1	41.7	1	
Multiple	30	10.8	50.0	19.2	15.4	2.27 (1.09-5.19)	
Size							0.35
<50	38	16.7	59.5	35.6	25.6	1	
>50	12	12.9	50.5	13.4	NA	1.49 (0.62-3.19)	
Treatment group							
A	25	33.4	73.9	42.8	36.7	1	
B	13	10.5	46.2	23.1	15.4	1.93 (0.84-4.33)	0.12
C	12	8.7	36.7	12.2	NA	2.65 (1.07-6.29)	0.04

MST: Median survival time; HR: hazard ratio; CI: confidence interval.

Previous studies demonstrated an MST of 8.8–34 months and a 5-year survival rate of 0-42% after hepatic resection, as shown in Table IV. In the present study, a relatively favorable MST of 33.4 months and a 5-year survival rate of 36.7% were obtained after hepatic resection. The wide difference in OS among studies is partly due to patient selection bias with small sample sizes, although most of the studies adopted liver-only metastasis as a common indication for hepatic resection.

To date, various prognostic factors have been proposed. As shown in Table IV, the number of liver metastases was found to be a significant prognostic factor in five reports, timing of liver metastasis (synchronous or metachronous), lymphatic and venous invasion and T stage of primary gastric cancer in two reports; and intrahepatic distribution of liver metastases, size of hepatic nodules, tumor differentiation, and negative surgical margins in the liver specimen, each in one report with univariate or multivariate analyses. In accordance with these findings, the number of liver metastases and T stage of the primary gastric tumor were significant prognostic factors found in the univariate analysis of this study. In addition, when incorporating treatment modality into the multivariate analysis, hepatic resection was shown to be independently associated with

Table III. *Multivariate analysis of prognostic factors for overall survival.*

Variable	HR	95% CI	*P*-value
T Stage (3, 4 vs. 1, 2)	13.90	2.82-251.70	<0.01
Multiple vs. solitary	1.09	0.37-3.09	0.88
Treatment, B vs. A	1.18	0.43-3.44	0.75
Treatment, C *vs.* A	2.83	0.93-9.26	0.07

HR: Hazard ratio, CI: confidence interval.

Table IV. *Summary of survival outcomes and prognostic indicators for patients undergoing hepatic resection for liver metastasis from gastric cancer.*

First author (ref)	Year	No. of pts. with liver metastasis	No. of pts who underwent hepatic resection	Median survival time (months)	Survival after resection			Prognostic factors	
					1-Year	3-Year	5-Year	Univariate	Multivariate
Okuyama *et al.* (1)	1985	9	9	24	NA	NA	NA		NA
Ochiai *et al.* (2)	1994	21	21	19	NA	NA	NA	T stage, ly, v	NA
Miyazaki *et al.* (3)	1997	21	21	NA	NA	NA	NA	Number, surgical margin	NA
Elias *et al.* (4)	1998	11	11	NA	90	35	NA	NA	NA
Ambiru *et al.* (5)	2001	40	40	12	NA	NA	18	Timing, surgical margin	Timing
Imamura *et al.* (6)	2001	17	17	NA	47	22	0	NA	NA
Saiura *et al.* (7)	2002	10	10	25	50	30	20	NA	NA
Okano *et al.* (8)	2002	90	19	21	77	34	34	Number, differentiation, timing, fibrous pseudocapsule	NA
Zackerl *et al.* (9)	2002	NA	15	8.8	35.7	14.3	0	None	NA
Sakamoto *et al.* (10)	2002	228	22	21	73	38	38	Number, distribution	Number
Shirabe *et al.* (11)	2003	NA	36	NA	64	26	26	ly, v, N stage, number	Ly, v, number
Roh *et al.* (12)	2005	NA	11	19	72.7	NA	27.3	NA	
Sakamoto *et al.* (13)	2007	182	37	31	NA	NA	11	Distribution, v, tumor size	Distribution, tumor size
Koga *et al.* (14)	2007	247	42	34	76	48	42	Number	Number, serosal invasion
Cheon *et al.* (15)	2008	1013	41	17.9	75.3	31.7	20.8	NA	None
Makino *et al.* (16)	2010	63	16	16.0	82.3	46.4	37.1	Stage, distribution, number, hepatic resection, chemotherapy,	Hepatic resection

ly, Lymphatic invasion; v, venous invasion; number, number of liver metastasis; distribution, hepatic distribution; timing, timing of metastasis (synchronous or metachronous); NA, not applicable; pts, patients.

longer survival by Makino *et al.* (16), which is consistent with our findings that gastrectomy plus hepatic resection was of marginal significance as a prognostic factor. T3/4 primary gastric cancer was chosen as an independent prognostic factor in the current study. Although T3/4 disease portends a potential risk for peritoneal seeding, the most frequent cause of death of our patients with T3/4 stage disease was liver metastasis, even after complete resection of the hepatic nodules. It is uncertain to what degree peritoneal seeding affected OS of our patients since accurate diagnosis of peritoneal dissemination was not possible in every case.

As for treatment options, the current study demonstrates the possibility that complete resection of both the primary gastric tumor and liver metastasis might contribute to a better prognosis than chemotherapy alone; however, this finding was of marginal statistical significance in the multivariate analysis. In contrast, there was no prognostic difference between gastrectomy plus hepatic resection and palliative gastrectomy. At present, a prospective randomized controlled trial is underway in Korea and Japan (19) comparing palliative gastrectomy with chemotherapy alone for patients with AGC including those with liver-only metastasis. The treatment option with better outcomes from this trial should be prospectively compared with gastrectomy plus hepatic resection for patients with liver-only metastasis in order to clarify which treatment strategy is optimal.

In conclusion, we believe that this is the first report comparing three different treatment options (gastrectomy plus hepatic resection *versus* palliative gastrectomy *versus* chemotherapy alone) for patients with LMGC as a single non-curative factor. T Stage of the primary gastric tumor was shown to be an independent prognostic factor for patients with LMGC. Limitations of this study, such as its retrospective nature correlating with selection bias between the treatment groups and small sample size, should be taken into account. Although gastrectomy plus hepatic resection might be a promising treatment option, with longer survival for patients with LMGC, further study is needed in a prospective, multi-institutional fashion to establish its role and clarify what constitutes optimal indications for hepatic resection in patients with LMGC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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Long-term Outcome after Proximal Gastrectomy with Jejunal Interposition for Gastric Cancer Compared with Total Gastrectomy

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Abstract

Background Proximal gastrectomy (PG) has been widely accepted as treatment for early gastric cancer located in the upper third of the stomach. Reconstruction by jejunal interposition has been known to reduce reflux esophagitis for PG patients. The aim of this study was to compare the long-term outcomes of patients who underwent PG with jejunal interposition with those treated by total gastrectomy (TG).

Methods Data on 102 cases of PG with jejunal interposition and 49 cases of TG with Roux-Y reconstruction for gastric cancer were analyzed retrospectively in terms of overall survival, weight maintenance, anemia and nutritional status, and endoscopic findings.

Results Median follow-up time was 59 months in the both groups. There was no significant difference in the overall 5-year survival rate between the PG group (94 %) and the TG group (84 %). The PG group showed significantly better body weight maintenance at the first year. The laboratory blood tests showed that the PG group had a significantly better red blood cell count and hemoglobin and hematocrit levels at the second and third year. However, postoperative endoscopic surveillance detected reflux esophagitis (3 %), peptic ulcer (9 %), and metachronous gastric cancer (5 %) in the PG group.

Conclusions Proximal gastrectomy maintains comparable oncological radicality to TG and is preferred over TG in terms of preventing postoperative anemia. However, periodic endoscopic follow-up is necessary to monitor the upper gastrointestinal tract.

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Introduction

Gastric cancer is one of the most common types of solid tumor, and it is estimated to be the fourth most common in terms of morbidity and the second most frequent cause of cancer death in the world [1]. In recent years, the frequency of cancers in the upper third of the stomach has been increasing in both Western and Asian countries [2–4]. As a function-preserving operation for such lesions, proximal gastrectomy (PG) has been widely accepted because it maintains comparable oncological radicality to total gastrectomy (TG), the standard operation for the lesions [5–8]. Although reflux symptoms and esophagitis had been major postoperative problems for patients who underwent PG [9, 10], a sphincter-substituting reconstruction called "jejunal interposition" has minimized these symptoms and improved the long-term outcome [11–13]. There has been one meta-analysis [14] and several reports comparing the long-term outcomes of TG and those of PG with jejunal interposition [15, 16], PG with jejunal pouch interposition [17] and PG with esophagogastrostomy [5, 8, 16, 18]. Because these reports differ in their conclusions, it remains controversial whether PG provides a better long-term outcome than TG. We conducted a large-scale comparison study with the aim of clarifying the long-term outcome of PG with jejunal interposition by comparing it to that of TG with Roux-Y reconstruction in terms of overall survival, weight maintenance, anemia and nutritional status, and endoscopic findings.

Patients and methods

All clinical diagnoses and pathological examinations of the resected specimens in this study were classified according

to AJCC/UICC cancer staging guidelines (7th ed.) [19]. The indication for PG in our institute is gastric cancer located in the upper third [20] of the stomach with it clinically staged as T1-2N0M0. The techniques for PG with jejunal interposition have already been described [11]. From January 1999 to December 2008, we performed PG with jejunal interposition on 107 patients with gastric cancer at the Shikoku Cancer Center and experienced no postoperative deaths (Fig. 1). None of these patients had prophylactic cholecystectomy or other combined resections. From this PG group, we selected 102 patients for this study who underwent postoperative surveillance at the Shikoku Cancer Center for more than 1 year.

We compared the long-term outcomes after PG to outcomes seen after TG. In the same period (1999–2008), there were 321 cases of TG performed for gastric cancer at the Shikoku Cancer Center. From this group we selected the 51 patients who were clinically diagnosed as having T1-2N0M0 gastric cancer [19] and underwent TG with Roux-Y reconstruction. Although most of these TG patients underwent prophylactic cholecystectomy, no other combined resection such as splenectomy was carried out in these patients. The final selection criteria involved those who underwent postoperative surveillance at the Shikoku Cancer Center for more than 1 year, resulting in 49 TG patients (Fig. 1).

R0 resection was achieved for all patients in this study. Following surgery, prophylactic antireflux medications such as camostat mesilate, H2-blocker, or proton pump inhibitor were not given to any patient. Prophylactic antianemia medication such as a vitamin B12 injection or oral iron supplements was also not administered to any patient. The patients underwent laboratory examinations, chest X-rays, and CT scans every 6 months. Surveillance by upper endoscopy was done annually for PG patients and every 2–3 years for TG patients. In surveillance endoscopy, the reflux esophagitis was graded using the Los Angeles classification system [21]. The patients with residual food grade ≥ 3 by the RGB classification [22] were diagnosed as having residual food. The definition for metachronous gastric cancer in the remnant stomach was described previously [23]. The red blood cell count, hemoglobin level, and hematocrit level were used as indicators of postoperative anemia. Total protein, serum albumin, and total cholesterol were used as indicators of postoperative nutritional status.

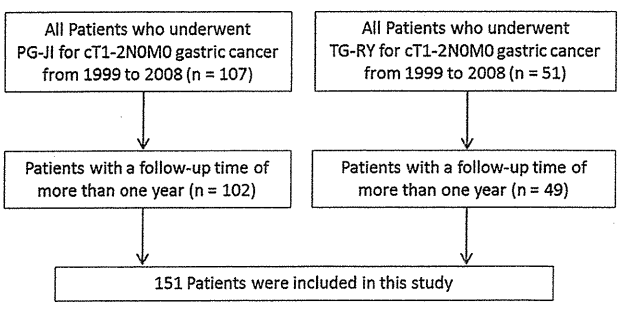

Fig. 1 Study design. *PG-JI* proximal gastrectomy with jejunal interposition, *TG-RY* total gastrectomy with Roux-Y reconstruction. Staging was classified according to the 7th edition of AJCC/UICC cancer staging system [19]

JMP 9 statistical software (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses. The overall survival was calculated by the Kaplan–Meier method and analyzed by the log-rank test. Pearson's χ^2 test or Wilcoxon test was used to compare the two groups. The level of significance was set at $p < 0.05$.

Results

The characteristics of the groups are given in Table 1. The age and sex distribution were similar in the two groups. Although a less extensive lymphadenectomy was carried out during the operation in the PG group, there was no significant difference between the two groups. Vagal nerve preservation was carried out in 75 PG patients (74 %), while no patients underwent vagal preservation in TG group. Tumor size was significantly larger in the resected specimen in the TG group, and the TG group had significantly more cases with undifferentiated type cancer upon histological examination. In the pathological examination, a significantly more advanced T factor and stage were seen in the TG group.

After median follow-up periods of 59 months (range = 12–147) in the PG group and 59 months (range = 14–116) in the TG group, there have been nine deaths in the PG group and eight deaths in the TG group. Figure 2 shows the overall survival curves for both groups. The 5-year survival rate was 94 % for the PG group and 84 % for the TG group, and the log-rank test showed no significant difference between the two groups. In the PG group, two patients died from cancer recurrence, two patients died from cancers other than gastric cancer, three patients died from benign disease, and two patients died from unknown causes. In the TG group, six patients died from cancer recurrence, one patient died from cancers other than gastric cancer, and one patient died from benign disease.

The PG group showed better body weight maintenance until the third year, with the difference during the first year being statistically significant (Fig. 3). The percent preoperative body weight at the third year was 88 % in the PG group and 86 % in the TG group and was not significantly different between the two groups.

In the postoperative laboratory examination of blood, we used the red blood cell count, hemoglobin level, and