



A Randomized Controlled Phase III Trial to Evaluate the Effect of Preoperative Enteral Immunonutrition on the Surgical Site Infection after Total Gastrectomy (OGSG0507)

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Abstract

- Background: To investigate the effect of preoperative enteral immunonutrition on the incidence of surgical site infection (SSI) after total gastrectomy for gastric cancer, we conducted a prospective randomized controlled trial.
- Methods: Eligibility criteria included: (1) histologically proven adenocarcinoma of stomach, (2) scheduled total gastrectomy, (3) aged less than 80 years, (4) not malnourished, (5) possible to ingest liquid diet, (6) written informed consent. Eligible patients (pts) were assigned to the immunonutrition (I) group or the control (C) group. In the C group pts freely accessed to regular diet until surgery. In the I group, pts were supplemented with 1000ml/day of immunonutrient enriched with arginine, omega-3 fatty acids and RNA (IMPACT®) in addition to the regular diet for 5 days before surgery. The primary endpoint was the incidence of SSI and the secondary endpoints were other infectious complications and serum CRP level on POD 3 or 4.
- Results: From 02/2004 to 12/2009, 240 gastric cancer patients (pts) who underwent gastric surgery were enrolled. 125 pts assigned to the I group and 115 pts assigned to the C group. Age, sex, body weight, serum albumin and general nutritional status were well balanced between the two groups. 223 pts underwent total gastrectomy, 6 pts proximal gastrectomy, 4 pts distal gastrectomy, and 7 pts simple laparotomy. In terms of tumor status, there were no significant difference between the groups in histological type, T stage, and lymph node metastasis. 104 of 125 pts assigned to the I group tolerated a daily intake 1000ml of impact for 5 days. The incidence of SSI was 26 (20.8%) in the I group and 24 (20.9%) in the C group (R.R: 1.00, 95% C.I: 0.61-1.63). Postoperative morbidity was 36 (28.8%) in the I group and 30 (26.1%) in the C group. There was no difference in days of hospital stay after surgery between the groups.
- Conclusions: The oral administration of immunonutrient for 5 days before surgery did not contribute to the reduction of infectious complications after total gastrectomy in gastric cancer pts.

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Background

- Immunonutrition modulates the host immune systems and inflammatory responses. Our preliminary study demonstrated that preoperative enteral immunonutrition resulted in the changes of body composition in patients with gastrointestinal cancers (Tsujinaka, 2007).

	Before	After	p
Albumin (g/dl)	3.89 ± 0.37	3.93 ± 0.42	ns
RBP (mg/dl)	3.21 ± 1.01	3.76 ± 1.04	0.02
Arginine (mmol/ml)	91.9 ± 37.9	112.0 ± 33.4	0.01
Lipid content in WBC n3(μg/g) n3/n6	303 ± 141	378.2 ± 139	0.02
	0.24 ± 0.07	0.32 ± 0.08	0.001
Urinary uracil output (mmol/g CRE)	57.6 ± 63.3	88.9 ± 45.5	0.01

- Numbers of clinical studies demonstrated that perioperative immunonutrition improved the surgical outcomes in major abdominal surgery, but other studies failed to show the advantage of the treatment.
- There has been no large scaled multi-institutional phase III RCT focused on the immunonutrition in a specific surgery, i.e. total gastrectomy for gastric cancer.

Objective

- To investigate the effect of preoperative enteral immunonutrition on the incidence of surgical site infection (SSI) after total gastrectomy for gastric cancer, we conducted a prospective randomized controlled trial.

Methods

- Eligibility criteria
 - Histologically proven adenocarcinoma of stomach
 - Scheduled total gastrectomy
 - Aged less than 80 years
 - Not malnourished
 - Possible to ingest liquid diet
 - Written informed consent
- Exclusion criteria
 - Renal dysfunction, Hepatic dysfunction
 - Insulin dependent Diabetes Mellitus
 - Intestinal obstruction
 - Active infection
 - Other severe complications
 - Patients to whom doctors judge ineligible
- Treatment
 - Control group: Free oral ingestion of regular diet
 - Immunonutrition group: Oral ingestion of IMPACT® 1000ml/day for 5 days before surgery. NO limit for oral intake of regular diet, but priority for IMPACT.
- Composition of immunonutrients
IMPACT®, Ajinomoto Pharma, Tokyo, Japan

Components	Per 100ml
Total energy (kcal)	101
Protein (g)	5.6
Arginine (g)	1.28
Lipids (g)	2.8
EPA (g)	0.20
DHA (g)	0.14
Carbohydrates (g)	13.4
RNA (mg)	0.13

- End points
 - Primary: Ratio of SSI
 - Secondary: Postoperative Infectious Complications
Serum CRP level on POD 3 or 4
- Study Design
Multi institutional prospective randomized controlled trial, Phase III
- Sample size
 - Control group: N=120
 - Immunonutrition group: N=120

Results

Patient Characteristics

	Control (N=115)	Immunonutrition (N=125)
Age, median (range)	66 (30-79)	63.5 (29-78)
Gender, M : F	85 : 32	96 : 30
Body weight (kg), median	60.0 (40.1-92.2)	60.9 (38.0-97.0)
Weight loss(%), median	0 (0-10.0)	0 (0-16.9)
Nutritional Status Well : Malnourished	116 : 1	122 : 4
Albumin (g/dL), median	4.1 (2.4-5.3)	4.2 (2.5-4.8)
TLC* (/mL), median	1792 (700-4446)	1880 (800-5952)
CRP, preop. (mg/ml)	0.1 (0-10.3)	0.1 (0-7.2)
Type of surgery		
Total gastrectomy	104	119
Proximal gastrectomy	3	3
Distal gastrectomy	4	0
Simple laparotomy	4	3
Node dissection D0 : D1 : D2 : D3	4 : 20 : 85 : 3	4 : 22 : 99 : 0
Tumor stage (pathologic)	(N=122)	(N=111)
pT1 : T2 : T3 : T4	43 : 36 : 24 : 8	43 : 36 : 38 : 5
pN0 : N1 : N2 : N3	62 : 24 : 22 : 3	57 : 35 : 29 : 1

* TLC: Total Lymphocyte Count

Ingestion of Immunonutrient: IMPACT®

	Total (/day)	Day 1	Day 2	Day 3	Day 4	Day 5
Intake (ml), mean	945	917	952	966	966	923

Postoperative Complications

	Control (N=115)	Immunonutrition (N=125)
Overall (%)	30 (26.1%)	36 (28.8%)
Abdominal abscess	7 (6.1)	11 (8.8)
Pancreatic fistula	7 (6.1)	8 (6.4)
Anastomotic leakage	3 (2.6)	3 (2.4)
Pneumonia	0 (0.0)	5 (4.0)
Wound Infection	8 (7.0)	7 (5.6)
Drain infection	1 (0.9)	3 (2.4)
IV cath. Infection	1 (0.9)	2 (1.6)
Pleural effusion	1 (0.9)	1 (0.8)
Postop. Bleeding	0 (0.0)	3 (2.4)
Bowel obstruction	1 (0.9)	2 (1.6)
SSI	24 (20.9)	26 (20.8)
SIRS*	34 (29.6)	46 (36.8)

*Presence of SIRS (Systemic Inflammatory Response Syndrome) during postoperative period

End Points

	Control (N=115)	Immunonutrition (N=125)	R.R. (95% C.I.)
Surgical Site Infection (SSI)	24 (20.9%)	26 (20.8%)	1.00 (0.61-1.63) P=1.000
Superficial incisional Deep incisional Organ/space	8 (7.0%) 1 (0.9%) 15 (13.0%)	7 (5.6%) 5 (4.0%) 17 (11.2%)	
Total Morbidity	30 (26.1%)	36 (28.8%)	1.10 (0.73-1.67) P=0.667
CRP on POD 3 (or 4)	9.2 (0.8-33.9)	11.0 (1.4-38.1)	P=0.114

Conclusions

- The oral administration of immunonutrient for 5 days before surgery did not contribute to the reduction of infectious complications after total gastrectomy in gastric cancer patients.

Participating Institutions

- OGSG:
Osaka Gastrointestinal Cancer Chemotherapy Study Group

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 Osaka Medical Center for Cancer and Cardiovascular Disease
 Sakai Municipal Hospital
 NTT West Osaka Hospital
 Kinki Central Hospital
 Osaka Seamen's Insurance Hospital
 Yao Municipal Hospital
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 Hoshigaoka Kosei-Nenkin Hospital
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