Impact of Neoadjuvant Chemotherapy Among Patients with Pancreatic Fistula After Gastrectomy for Advanced Gastric Cancer

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Abstract. *Background: Neoadjuvant chemotherapy (NAC) has been widely adopted for patients with advanced gastric cancer; however, the safety of gastrectomy with D2 lymphadenectomy followed by NAC has not yet been evaluated. We retrospectively analyzed the influence of NAC on morbidity and mortality after gastrectomy in patients with advanced gastric cancer. Patients and Methods: A series of 364 patients with advanced gastric cancer who underwent gastrectomy without pancreatectomy between January 2008 and December 2010 at eight hospitals registered to the Yokohama Clinical Oncology Group were studied retrospectively. There were 330 patients who underwent surgical treatment immediately after diagnosis (surgery alone group) and 34 patients (NAC group) who first received NAC and then underwent surgical resection. Results: Although there were no significant differences in the morbidity rate between the two groups, postoperative pancreatic fistula was more often observed in NAC patients than in patients of the group treated with surgery alone [5 cases (14.7%) vs. 11 cases (3.3%); p=0.011]. In the univariate analysis, NAC (p=0.029), bursectomy (p<0.001) and operative bleeding (≥300 ml, p=0.002), were significantly correlated with postoperative pancreatic fistula, and NAC [odds ratio (OR)=4.901, 95% confidence interval (CI)=1.455-16.67; p=0.010] and bursectomy (OR=11.2, 95% CI=3.460-37.04; p<0.001) were independent risk factors for postoperative pancreatic fistula by multivariate analysis. The incidence of postoperative pancreatic fistula was 40.0% among patients who underwent gastrectomy with bursectomy followed by NAC. Conclusion: The incidence of pancreatic fistula in patients treated with NAC and bursectomy was significantly higher than that in other patients. Bursectomy may be discouraged for the prevention of pancreatic fistula from gastrectomy following NAC.*

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The outcome of patients with advanced gastric cancer remains poor because disease in a large proportion of these patients will recur despite curative resection. To manage micrometastasis such as lymph node metastasis, several chemotherapies in the postoperative adjuvant setting have been developed and shown survival benefit (1). However, full-dose delivery of these chemotherapies tends to be difficult due to the morbidity associated with gastric resection.

The development of new chemotherapeutic regimens for advanced gastric cancer has led to consideration in the preoperative setting since MAGIC trial reported the survival benefits of perioperative chemotherapy (2). The advantages of neoadjuvant chemotherapy (NAC), including improved tolerance of chemotherapy, increasing the R0 resection rate due to tumor down"staging and eliminating micrometastatic lesions, has been reported (3). Several studies have assessed the utility of NAC, but there are limited data regarding postoperative complications in patients undergoing chemotherapy in the preoperative setting (4, 5). If NAC is to be considered an option of treatment for patients with locally advanced gastric cancer, it is necessary to evaluate whether these patients can be treated safely without an increase in postoperative morbidity and mortality.

Herein, we undertook this retrospective study to assess the postoperative morbidity and mortality in patients with locally advanced gastric cancer receiving NAC before radical gastrectomy in comparison to patients who underwent gastrectomy alone during the same period.

Patients and Methods

A series of 364 patients with advanced gastric cancer who underwent gastrectomy between January 2008 and December 2010 were studied retrospectively. Patients included in this study had a World Health Organization (WHO) performance status of 0 or 1, pathological confirmation of gastric adenocarcinoma and underwent curative gastrectomy with D2 lymph node dissection by surgeons at the Institutes registered to the Yokohama Clinical Oncology Group (YCOG). Gastric lesions were considered to be advanced status (through the submucosa) and had no evidence of distant metastases or inoperable disease. There were 330 patients who received surgical treatment immediately after diagnosis (surgery alone group) and 34 patients who first received NAC and then underwent surgical resection (NAC group).

Induction chemotherapy was docetaxel plus S-1 combination chemotherapy for four 4-week cycles for 18 patients (52.9%), cisplatin plus S-1 combination chemotherapy for two 5-week cycles and S-1 for two 6-week cycles for 12 patients (35.3%), and S-1 monotherapy for two 6-week cycles for four patients (11.8%). Surgery was planned for approximately 4-8 weeks after completion of administration of anticancer agents in NAC group. All gastrectomies were performed by laparotomy and in a similar fashion for both groups. Type of gastrectomy and performance of multivisceral resection were left to the discretion of the surgeon.

Postoperative complications following gastrectomy were assessed according to the medical records. Postoperative pancreatic fistula was defined according to the definition of International Study Group of Pancreatic Fistula (6). However, because this was a retrospective study, the drainage amylase levels were not measured for all patients. Hence postoperative pancreatic fistula was evaluated according to our definition (7) by which a case of pancreatic fistula must satisfy three or more of the following five criteria: dirty-appearing discharge from drain; skin redness around the drain due to amylase; an amylase concentration of 1,000 U/l or greater in the discharge from the drain; evidence of bacterial infection; and enhancement of an abscess cavity around the pancreatic stump or the main pancreatic duct.

Statistical analysis. Demographic, clinical and pathological characteristics of the two groups were analyzed. Mann–Whitney *U*-test was used to compare median values. Comparison of observed *vs*. expected results in two-by-two tables was performed with chi-square analysis. Logistic regression analysis was performed to determine factors predictive of complications. *p*-Values are reported for two-tailed tests and a *p*-value less than 0.05 was considered statistically significant. We performed these analyses using SPSS (version 15.0; SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics of the study groups are summarized in Table I. NAC patients tended to be younger than patients treated with surgery alone (62.1±12.0 years *vs*. 69.9±9.9 years; $p<0.001$) and the proportion of males (44.1% *vs*. 69.7%; $p=0.003$) and those with co-morbidity (41.2% *vs*. 59.7%; $p=0.029$) in the NAC group was smaller than in the group treated with surgery alone. There were no significant differences in body mass index, preoperative hemoglobin, or serum albumin between the two groups.

Table I. *Patients' characteristics*.

Variable	NAC (n=34)	Surgery alone (n=330)	*p*-Value
Age (years)	62.1±12.0	69.9±9.9	<0.001
Gender			0.003
Male	15 (44.1%)	230 (69.7%)	
Female	19 (55.9%)	100 (30.3%)	
BMI (kg/m^2)	21.9±2.7	22.4±3.4	0.376
Hemoglobin (g/dl)	11.4±1.4	12.2±2.2	0.065
Serum albumin (g/dl)	4.0±0.6	3.8±0.6	0.074
Comorbid disease			0.029
Presence	14 (41.2%)	197 (59.7%)	
Absence	20 (58.8%)	133 (40.3%)	

BMI: Body mass index; NAC: neoadjuvant chemotherapy.

Table II. *Clinical characteristics of patients in this study.*

Variable	NAC (n=34)	Surgery alone (n=330)	*p*-Value
Tumor location			0.616
Proximal	14 (41.2%)	116 (35.2%)	
Distal	19 (55.9%)	209 (63.3%)	
Remnant	1 (2.9%)	5 (1.5%)	
Tumor diameter (mm)	84.2±50.3	62.8±30.7	<0.001
Macroscopic appearance			0.070
Well-defined	7 (20.6%)	114 (34.5%)	
Ill-defined	27 (79.4%)	216 (65.5%)	
Histological type			0.104
Intestinal type	16 (47.1%)	212 (64.2%)	
Diffuse type	18 (52.9%)	115 (34.8%)	
Type of resection			0.040
DG	9 (26.4%)	162 (49.1%)	
TG	24 (70.6%)	163 (49.4%)	
Remnant	1 (2.9%)	5 (1.5%)	
Spleenectomy	7 (20.6%)	55 (16.7%)	0.353
Bursectomy	10 (29.4%)	75 (22.7%)	0.248
Operative time (min)	242.3±61.4	234.6±68.4	0.529
Operative blood loss (ml)	469.8±290.2	431.5±401.3	0.588
Pathological T-stage			0.302
T1-3 (M/SM/MP/SS)	20 (58.8%)	223 (67.6%)	
T4- (SE/SI)	14 (41.2%)	107 (32.4%)	
Pathological N-stage			0.515
N0	11 (32.4%)	103 (31.2%)	
N1-	23 (67.6%)	227 (68.8%)	
No. of retrieved lymph nodes	37.3±16.6	37.0±20.0	0.952

NAC: Neoadjuvant chemotherapy; DG: distal gastrectomy; TG: total gastrectomy.

Clinical characteristics are outlined in Table II. The mean tumor diameter in the NAC group was higher than that in the group treated with surgery alone ($p<0.001$). According to the type of resection, the proportion of NAC patients with total

Table III. *Morbidity and mortality experienced by patients in this study.*

Variable	NAC (n=34)	Surgery alone (n=330)	*p*-Value
POS median (days)	17	17	0.877
POS with complications (days)	48.9+33.8	38.0+26.6	0.262
POS with PF (days)	73.0+31.2	63.3+26.3	0.508
Complications	10 (29.4%)	105 (31.8%)	0.637
PF	5 (14.7%)	11 (3.3%)	0.011
Surgical site infection	5 (14.7%)	54 (16.4%)	0.516
Anastomotic leak	2 (5.9%)	19 (5.7%)	0.604
Anastomotic stenosis	0 (0.0%)	17 (5.1%)	0.173
Pneumonia	0 (0.0%)	14 (4.2%)	0.247
Enteritis	1 (3.7%)	6 (1.8%)	0.581
Urinary tract infection	1 (3.7%)	3 (0.9%)	0.439
Lymphorrhea	1 (3.7%)	4 (1.2%)	0.568
Re-exploration	0 (0.0%)	3 (0.9%)	0.745
Mortality	0 (0.0%)	2 (0.6%)	0.776

NAC: Neoadjuvant chemotherapy; POS: postoperative hospital stay; PF: pancreatic fistula.

Table IV. *Univariate and multivariate analysis of pancreatic fistula (PF).*

Variable	n	PF (+), n (%)	*p*-Value
Gender			0.431
Male	245	10 (4.1)	
Female	119	6 (5.0)	
Age (years)			0.190
<70	177	10 (5.6)	
>70	187	6 (3.2)	
Hemoblobin (g/dl)			0.411
<12	161	8 (5.0)	
>12	203	8 (3.9)	
Comorbidity			0.459
No	153	6 (3.9)	
Yes	211	10 (4.7)	
NAC			0.011
No	330	11 (3.3)	
Yes	34	5 (14.7)	
TG			0.126
No	176	5 (2.8)	
Yes	188	11 (5.9)	
Bursectomy			<0.001
No	279	4 (1.4)	
Yes	85	12 (14.1)	
Operative time (min)			0.355
<220	142	5 (3.5)	
>220	222	11 (5.0)	
Bleeding (ml)			0.007
<300	160	2 (1.3)	
≥300	204	14 (6.9)	
Tumor diameter (mm)			0.547
<60	188	8 (4.3)	
≥60	176	8 (4.5)	
Lauren classification			0.785
Intestinal	228	9 (3.9)	
Diffuse	129	7 (5.3)	
Macroscopic appearance			0.450
Well-defined	121	6 (5.0)	
Ill-defined	243	10 (4.1)	
p-Depth			0.120
pT1-3	243	8 (3.3)	
pT4	121	8 (6.6)	

NAC: Neoadjuvant chemotherapy; TG: total gastrectomy.

gastrectomy (70.6%) was higher than that of the group treated with surgery alone (49.4%) (p=0.040). Tumor location, macroscopic appearance, operative time, intraoperative blood loss, pathological stage and the number of retrieved lymph nodes did not differ between these groups. Splenectomy was performed for seven cases (20.6%) of the NAC group compared to 55 cases (16.7%) of the group treated with surgery alone (p=0.353). We performed bursectomy in 10 patients (29.4%) in the NAC group and in 75 patients (22.7%) of those treated with surgery alone (p=0.134).

Morbidity and mortality are summarized in Table III. Complications occurred in 115 patients (31.5%) in the present study. Although there were no significantly differences between the two groups in the morbidity rate [10 patients (29.4%) in the NAC group and 105 patients (31.8%) in the group treated with surgery alone], pancreatic fistula was more often observed in patients of the NAC group than in those of the group treated with surgery alone (5 cases: 14.7% *vs*. 11 cases: 3.3%; p=0.011). Three patients (0.9%) in the group treated with surgery alone underwent re-exploration, two patients underwent reoperation for postoperative leak and an another patient for pancreatic fistula. There were two deaths within 30 postoperative days due to an acute cardiac disorder on postoperative day 23, acute renal disorder and deep surgical site infection on postoperative day 26. There was no operative mortality in the NAC group. Regarding the clinical factors distinguishing postoperative pancreatic fistula, NAC (p=0.011), bursectomy (p<0.001) and bleeding (≥300 ml, p=0.007) were significantly correlated with postoperative pancreatic fistula (Table IV). Logistic regression analysis revealed that bursectomy (p<0.001) and NAC (p=0.010) were independent risk factors for postoperative pancreatic fistula (Table V). The incidence of postoperative pancreatic fistula was 40.0% in the patients who underwent gastrectomy with bursectomy following NAC (Table VI).

Discussion

The prognosis of patients with advanced gastric cancer is dismal worldwide; 5-year survival is still less than 30% (8). Since the publication of results from the MAGIC trial (2), the benefits of perioperative chemotherapy for locally advanced gastric cancer have been recognized. Several clinical trials of

Table V. *Multivariate analysis for pancreatic fistula.*

Variable	OR (95% CI)	*p*-Value
NAC (no *vs.* yes)	4.910 (1.455-16.67)	0.010
Bursectomy (no *vs.* yes)	11.24 (3.460-37.04)	<0.001
Age (<70 y.o. *vs.* >70 y.o.)	1.481 (0.256-2.415)	0.675
TG (no *vs.* yes)	1.387 (0.236-2.717)	0.721
p-Depth (p1-3 *vs.* p4)	1.739 (0.477-4.219)	0.529

NAC: Neoadjuvant chemotherapy; OR: odds ratio; CI: confidence interval.

Table VI. *Incidence of pancreatic fistula.*

NAC	Bursectomy	n	Pancreatic fistula, n (%)
Yes	Yes	10	4 (40.0%)
	No	24	1 (4.2%)
No	Yes	75	8 (10.6%)
	No	255	3 (1.2%)

NAC are now in progress and finding a better choice of regimen for NAC is undoubtedly of much note in this area (4, 5). However, there are limited data concerning postoperative morbidity and mortality in patients with gastric cancer treated with NAC. Most studies regarding NAC for gastric cancer noted that this treatment did not significantly increase the incidence of postoperative complication, the morbidity rate was from 23.1 to 34.8% and mortality from 0.0 to 7.2%, hence most reports claimed that gastrectomy followed by NAC can be performed safely (9-11). In contrast, An *et al.* reported the incidence of surgical complications in patients with NAC was high (12); the morbidity and mortality rates were 29.3% and 1.6%, respectively. However, this was a retrospective single-arm cohort study and there was no comparison with patients with gastric cancer without NAC. In this regard, there are few studies comparing the surgical results of gastrectomy followed by NAC and surgery alone, and whether NAC increases morbidity or not is controversial. In the present study, postoperative morbidity occurred in 29.4% of the NAC group and 31.8% of the group treated with surgery alone; this was not a significant difference between these two groups. These results were similar to studies mentioned above.

However, detailed analysis revealed that the incidence of pancreatic fistula in NAC patients (5 cases; 14.7%) was higher than that in the group treated only with surgery (11 cases; 3.3%), although there was no significant difference in the rate of splenectomy (NAC: 7 cases; 20.6%, SURG: 55 cases; 16.7%) and bursectomy (NAC: 10 case; 29.4%, SURG: 75 cases; 22.7%). Due to the limitation of this being a retrospective study, the ratio of patients who underwent total gastrectomy in the NAC group (70.6%) was higher than that in the group treated only with surgery (49.4%). Komatsu *et al.* reported the surgical outcomes of 1,341 patients undergoing gastrectomy (including total, distal proximal and remnant gastrectomy) and the incidence of severe pancreatic fistula was 2.6% (35/1341) (13). In these series, patients treated with total, proximal and remnant gastrectomy (71%: 25/35) were higher than those with distal gastrectomy (29%: 10/35). Miki *et al.* reported that the incidence of severe postoperative pancreatic fistula following total gastrectomy with D2 lymphadenectomy was 22.1% (23/104) (14). From the results of these studies, the proportion of patients with pancreatic morbidities after total gastrectomy tended to be higher than those after distal gastrectomy. However, we confirmed that total gastrectomy did not affect the incidence of postoperative pancreatic fistula in the univariate analysis.

This retrospective study revealed that bursectomy (p=0.012) and NAC (p=0.010) were independent risk factors for postoperative pancreatic fistula by multivariate analysis. The incidence of postoperative pancreatic fistula in patients who underwent gastrectomy with bursectomy followed NAC was high (40.0%). Standard surgical treatment of advanced gastric cancer is gastrectomy with D2 lymph node dissection and bursectomy, which covers resection of the omentum, the anterior membrane of transverse mesocolon and the anterior pancreatic capsule (15). These procedures were also standard surgical treatment at our Institutes, but actually adopted for 108 patients (27.8%) in the present study due to the discretion of the surgeon. If NAC acts on the peripancreatic tissues, consumption of the anatomical layer around the pancreas may occur due to tissue denaturation by chemotherapeutic response (12). Especially during the retrieval of no.6 lymph node with exposure of the roots of right gastroepiploic vessels at the ventral side of pancreatic head and the removal of the anterior pancreas capsule and peripancreatic lymph nodes (no. 8a, 9, and 11p), the borderline between the fat and the pancreas was unclear in cases with fibrotic changes derived from anticancer agents and these conditions render lymph node dissection and bursectomy more difficult. These maneuvers seeming to lead to potential pancreatic complications occurred especially in NAC patients. The Japan Clinical Oncology Group 1001 prospective study with the recruitment of 1,000 patients with cT3-4 tumors of gastric cancer is now ongoing to clarify the survival benefit of bursectomy and there is a randomized controlled trial to clarify the survival benefit of bursectomy in gastric cancer surgery (15). However, there are some articles that skeptically mention the survival value of bursectomy (16-18). The indication of bursectomy in patients with gastric cancer treated with NAC should be considered carefully because of high risk of pancreatic morbidity after bursectomy following NAC.

The survival benefits of preoperative chemotherapy including the improvement of the R0 resection rate and recurrence rate has been reported. However the surgical morbidity and mortality rates are unsatisfactory. Tissue denaturing and fibrotic changes due to chemotherapeutic response may contribute to increased difficulty of surgical maneuvers. A high pancreatic morbidity rate was observed after gastrectomy with bursectomy following NAC. Therefore, gastrectomy after NAC should be performed carefully and surgical complication should be analyzed in detail in a prospective, randomized and large-scale study of NAC for advanced gastric cancer.

Conclusion

The incidence of surgical complications in patients who underwent gastrectomy after preoperative chemotherapy was comparable to those in patients treated with surgery alone, however, the incidence of pancreatic fistula was significantly higher. The indication of bursectomy in patients with gastric cancer treated with NAC should be considered carefully.

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