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Effects of Neoadjuvant Intraperitoneal / Systemic Chemotherapy on Lymph Node Metastasis from Advanced Gastric Cancer with Peritoneal Metastasis

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Summary

Background: Neoadjuvant Intraperitoneal/ Systemic Chemotherapy (NIPS) is considered effective method to treat Peritoneal Metastasis (PM) from Gastric Cancer (GC). The objective of the present study is to verify the effect of NIPS on Lymph Node Metastasis (LNM).

Methods: During the last 18 years, we enrolled 107 and 136 patients who underwent D2-gastrectomy after NIPS and D2-gastrectomy alone (non-NIPS group), respectively.

Results: The total number of LNMs in the non-NIPS group and NIPS group was 14.8 ± 13.9 and 4.6 ± 5.9, respectively (P<0.0001), and is significantly lower in those with histologic response at the primary tumor site (3.4± 6.6) than in those with no histologic response (5.9 ±6.6) (P<0.03). The incidence of N0 cases was significantly higher in the NIPS group (37/107; 34.6% vs. 14/136; 10.3%) (P<0.0001). Survival after NIPS plus Cytoreductive Surgery (CRS) was significantly better than that of non-NIPS group.

Conclusion: NIPS is a very effective method to control LNM from GC. After intraperitoneal administration of chemotherapeutic drug, extremely higher concentrations of chemotherapeutic drug are absorbed through omental milky spots, and the efferent lymphatic fluid drain into the regional lymph nodes of stomach. As a result, regional LNM of stomach are exposed with extremely higher concentrations of chemotherapeutic drugs than systemic chemotherapy. This feature of the lymphatic circulation accounts for the much greater effects of NIPS on LNM.

Synopsis: Neoadjuvant intraperitoneal/systemic chemotherapy is effective not only peritoneal metastasis but also lymph node metastasis from gastric cancer.

Keywords: Gastric cancer; Lymph node metastasis; Neoadjuvant intraperitoneal/systemic chemotherapy

Introduction

The Peritoneal Cancer Index (PCI) cut-off level, completeness of cytoreduction and the effects of neoadjuvant chemotherapy are independent prognostic factors after the comprehensive treatment for Gastric Cancer (GC) with Peritoneal Metastasis (PM) [1-3]. Recently, Neoadjuvant Intraperitoneal/Systemic Chemotherapy (NIPS) was adopted as Neoadjuvant Chemotherapy (NAC) for GC with PM. NIPS is also called bidirectional chemotherapy, because administration is via two routs: intraperitoneal and systemic. NIPS enhances the area of PM treatment, delivering chemotherapeutic agents not only to the peritoneal surface but also

through the subperitoneal blood capillaries [4]. Accordingly, the histologic response of the PMs and cytologic response after NIPS were significantly higher than those after systemic chemotherapy alone [4,5]. However, no study has reported the effects of NIPS on lymph node metastasis of gastric cancer with PM. The main objective of the present study was to verify the effects of NIPS on lymph node metastasis

Patients and Methods

Patients and Treatments

Between January 2000 and January 2018, 243 GC-patients with PM underwent gastrectomy plus D2 lymph node dissection. Patients' characteristics, pathologic findings, and treatment-related data were obtained from a prospective database. Among 243 patients, 107 patients underwent gastrectomy after NIPS and laparotomy was performed 4 to 6 weeks after the last cycle of NIPS (NIPS group). The other 136 patients underwent D2 gastrectomy without neoadjuvant chemotherapy (non-NIPS group).

The eligibility criteria included: (1) histologically or cytologically proven PM from GC; (2) absence of hematogenous metastasis and remote lymph node metastasis; (3) Eastern Clinical Oncology Group scale of performance status 3 or less; (4) good bone marrow, liver, cardiac, and renal function; (5) absence of severe adhesion in the peritoneal cavity; and (6) absence of other severe medical conditions or synchronous malignancy.

The numbers of males and females were 82 and 54 in non-NIPS group and 53 and 54 in NIPS group, respectively. The average age was 59.7 and 51.3 years old in the non-NIPS group and NIPS group, respectively Table 1.

	Non NIPS	NIPS	
Mean age	59.7 (24-82)	51.3 (25-75)	P<0.0001
Gender			
Male	82	53	
Female	54	54	NS
CCR (completeness of cytoreduction			
CCR-0 (complete cytoreduction)	78 (57.5%)	81 (75.7%)	0.0044
CCR-1 (incomplete cytoreduction)	58	26	
Mean PCI (peritoneal cancer index)	2.9 (0-6)	5.8 (0-32)	P<0.0001
Histologic type			
differentiated	33	5	
Poorly differentiated	103 (75.7%)	101 (95.2%)	P<0.0001
T (wall invasion)			
T1a (m)	0	2 (1.9%)	
T1b (sm)	0	3 (2.8%)	
T2 (mp)	1 (0.7%)	4 (3.8%)	P=0.00118
T3 (ss)	38 (27.9%)	13 (12.1%)	
T4a (se)	79 (58.0%)	56 (52.2%)	
T4b (si)	18 (13.2%)	29 (27.1%)	
N (lymph node metastasis)			
pN0	14 (10.3%)	37 (34.6%)	
pN1	13 (9.6%)	20 (18.7%)	

pN2	23 (16.9%)	22 (20.5%)	
pN3a	39 (28.6%)	22 (20.6%)	
pN3b	47 (34.6%)	6 (5.6%)	
Ly (lymphatic invasion)			
Ly0	6 (5.9%)	29 (27.1%)	
Ly1	42 (30.9%)	26 (24.3%)	P<0.0001
Ly2	45 (33.1%)	21 (19.6%)	
Ly3	41 (30.1%)	31 (19.0%)	
V (venous invasion)			
V0	47 (34.6%)	81 (75.7%)	
V1	59 (43.4%)	23 (21.5%)	
V2	16 (15.8%)	3 (2.8%)	P<0.0001
V3	13 (9.6%)	0	
Retrieved lymph node number	51.9 (5~295)	19.2 (3~71)	P<0.0001
Total No. of metastatic nodes	14.8 (1~82)	4.6 (1~29)	P<0.0001
	136	107	

Table 1: Clinicopathological factors of non-NIPS and NIPS group.

Methods of Neoadjuvant Intraperitoneal/Systemic Chemotherapy (NIPS)

Under general anesthesia, exploratory laparoscopy was done [6]. Biopsy specimens were routinely taken from peritoneal nodules to histologically confirm the diagnosis. Lesion size in the 13 abdominal sectors was quantitatively evaluated and peritoneal cancer index (PCI) was determined in each case [7]. Then, a peritoneal port system (Hickman Subcutaneous port; BARD, Salt Lake City, UT, USA) was introduced into the abdominal cavity.

Two weeks after exploratory laparoscopy, a series of 3-week cycles of NIPS was performed [6]. Specifically, S1 was administered orally twice daily at a dose of 60mg/m^2/day for 14 consecutive days, followed by 7 days' rest. Docetaxel and cisplatin were administered Intraperitoneally (IP) at a dose of 30 mg/m^2 on day 1. Docetaxel and cisplatin was diluted in 500 ml of normal saline and administered through the peritoneal port system. The same doses of docetaxel and cisplatin were administered Intravenously (IV) on day 8 after standard premedication. The treatment course was repeated every 3 weeks for 3 courses.

Cytoreductive Surgery

Four weeks after the last NIPS cycle, laparotomy for cytoreductive surgery (CRS) was performed. Then, CRS consisting of total gastrectomy, splenectomy, cholecystectomy, D2 lymph adenectomy and peritonectomy was done in the NIPS group (n=107), and the same surgical procedures were performed in non-NIPS group (n=136).

Histologic Investigation

The resected specimens were evaluated according to the Japanese classification of gastric carcinoma [8]. All harvested lymph nodes were stained with hematoxylin and eosin, and were examined for metastasis by two pathologists.

The histologic effect of NIPS on the primary tumor was graded according to Becker [9]: Grade 1, complete or subtotal tumor regression (10% residual tumor per tumor bed); Grade 2, partial tumor regression (10-50% residual tumor per tumor bed), and Grade 3, minimal or no tumor regression (>50%) residual tumor per tumor bed). In the present study, patients with Grade 1 or Grade 2 specimens were considered to be histologic responders [9]. Figure 1 shows a photograph of a Grade 1 specimen.

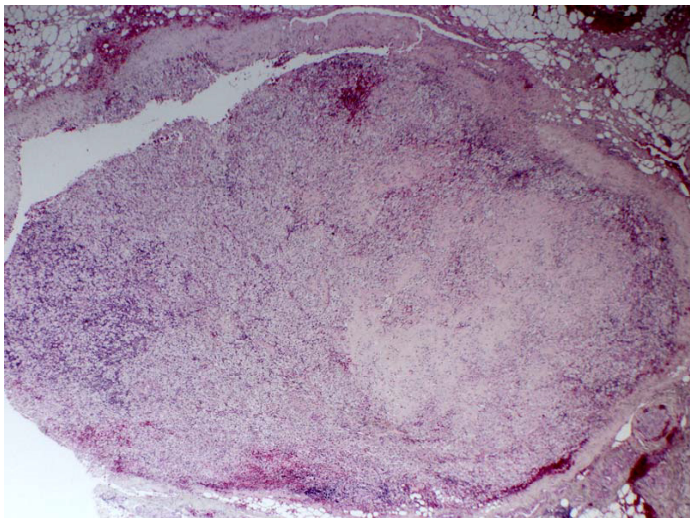

Figure 1: Histological findings of lymph node in station 9. Metastasis is replaced by foamy cells (*: higher magnification).

Ethical Standards

All patients were informed about the adverse events of the procedure and gave their written informed consents to participate. The present study was approved by ethical committee of Kishiwada Tokushukai Hopsital (Number, H19-1)

Follow-up

Follow-up consisted of physical examination and serum tumor marker level determination every 3 months until 2 years after surgery, and every 6 months after 2 years. Patients also underwent contrast-enhanced computed tomography (ceCT) every 6 months or when recurrence was suspected. Recurrence was diagnosed, when ceCT showed an abnormality typical of recurrence, and/or when there was a progressive increase in Carcinoembryonic Antigen (CEA) or Cancer Antigen (CA) 19-9 serum levels.

Data Analysis

The survival was analyzed by using the Kaplan-Meier method and compared between groups by using by the log rank test. Categorical variables were compared by X^2 analysis or the Fischer's exact test. Statistical analyses were performed by using SPSS version 11.5 (SPSS Inc., Chicago, IL). The confidence of interval was considered and a $P<0.05$ was considered significant.

Result

The mean PCI was 2.9 and 5.8 in the non-NIPS and NIPS group, respectively. Cytoreduction of the primary tumor, lymph node metastasis and PM was complete (CCR-0) in 78 (57.5%) and 81 (75.7%) patients in the non-NIPS and NIPS group, respectively. A significantly higher mean ± SD total number of lymph nodes (tLNs) was removed from the non-NIPS (51.9 ± 37.4) than the NIPS group (19.2 ± 11.1) ($P<0.0001$). The number of T3 and T4 tumors was 135 (99.2%) in the non-NIPS group and 98 (91.5%) in the NIPS group ($P=0.001$).

There was no lymphatic invasion in 6 (5.9%) and 29 (27.1%) non-NIPS and NIPS patients ($P=0.005$), respectively, and venous invasion in 47 (34.6%) and 81 (75.7%), respectively ($P<0.0001$). The total number of lymph node metastasis (TNLNM) in the non-NIPS and NIPS group was 14.8 ± 13.9 (range 1-82) and 4.6 ± 5.9 (range 1-29), respectively ($P<0.0001$) (Table 1), and significantly lower in those with a histologic response of the primary tumor than those with no histologic response (grade 3) (3.4± 6.6 vs. 5.9 ±6.6) ($P<0.03$). Figure 1 shows the complete disappearance of lymph node metastasis. Metastasis was detected in the para-aortic and station 3, 7, 8, and 9 lymph nodes before NIPS, and was replaced by foamy cells after NIPS. The incidence of lymph node negative (N0) disease was significantly higher in the NIPS group (137/107; 34.6% vs. 14/136; 10.3%) ($P<0.0001$) (Table 1). Table 2 shows the incidence of metastasis to each lymph node stations. The incidences of metastasis to all lymph node stations except stations 2, 10, and, 11 was significantly lower in the NIPS group.

Lymph node station	Non NIPS	NIPS	P values
No 1	45 (33.1%)	21(19.6%)	0.0192
No 2	26 (19.1%)	17 (18.9%)	NS
No 3	76 (55.9%)	39 (36.4%)	0.0025
No 4	94 (69.1%)	41 (41%)	<0.0001
No 5	38 (28.1%)	15 (14.0%)	0.0091
No 6	63 (45.3%)	27 (25.3%)	0.0007
No 7	52 (38.2%)	26 (24.2%)	0.0209
No 8	39 (28.7%)	14 (13.1%)	0.0188
No 9	31 22.8%)	23 (21.5%)	0.0075
No 10	25 (18.4%)	14 (13.1%)	NS
No 11	16 (11.8%)	11 (10.3%)	NS
No 12, 13, 14	25 (18.4%)	2 (1.9%)	<0.0001
No16	15 (11.0%)	3 (2.8%)	0.0239

Table 2: Lymph node metastasis according to the lymph node station number.

Figure 2 shows the survivals in both groups. Survival was significantly better after NIPS plus CRS than after CRS alone.

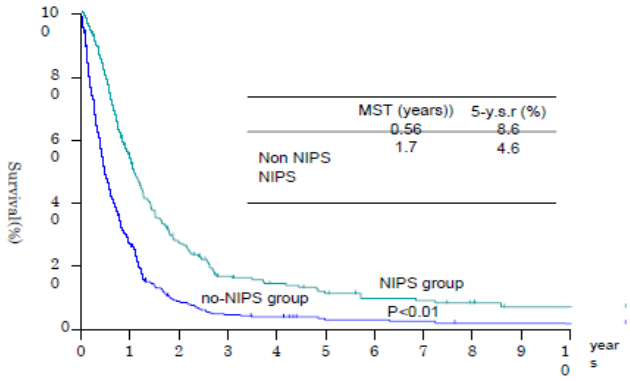

Figure 2: Survival curves of NIPS and non-NIPS group. Mean survival times of NIPS and non-NIPS group were 1.7 and 0.56 years, and the 5-year survival rates of patients in each group was 8.6% and 4.6%.

There was no significant difference in survival according to the pathologic grade of lymph node metastasis (Figure 3).

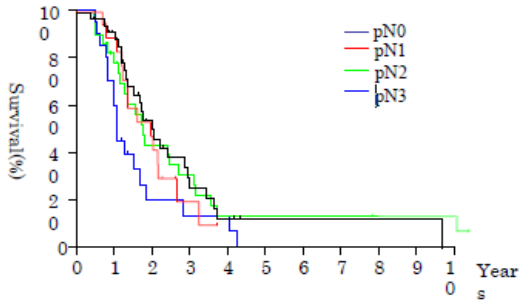

Figure 3: Survival curves of NIPS group according to the pathologic grade of lymph node metastasis.

Table 3 shows the median survival time and 5-year survival rates of patients with metastasis to each station.

Lymph node	Non NIPS		NIPS			P values
station	MST (years)	5-y.s.r (%)	MST (years)		5-y.s.r (%)	
No 1	0.92	5.3	1.27		11	NS
No 2	0.98	9.1	0.98		7.1	NS
No 3	0.98	8	1.37		7.6	NS
No 4	1.08	7.3	1.37		12.1	NS
No 5	0.93	7.6	1.27		14.5	NS
No 6	0.9	6.6	1.37		9.8	NS
No 7	0.9	6.8	2.42		12.7	0.007
No 8	0.93	8.5	1.08		NR	NS
No 9	0.82	nr	1.7		6.2	0.019
No 10	1.2	7	1.18		7.8	NS
No 11	0.62	NR	2.42		11.7	NS
No 12, 13, 14	0.78	4.3	0.56		0	NS
No16	1.12	0	1		0	NS

Table 3: MST and 5-year survival rates of patients with lymph node metastasis in non-NIPS and NIPS group according to the lymph node station number.

Five-year survival rates of patients with positive lymph node metastasis in the 1st echelon station 1, 2, 3, 4, 5, 6 were 11.0, 7.1, 7.6, 12,1 14.5, and 9.8%, respectively. Those in the 2nd echelon station 7, 9, 10, and 11 were 12.7, 6.2, 7.8, and 11.7%, respectively. All patients with metastasis to station 12, 13, 14 or No16 (para-aortic lymph nodes) died of recurrence.

Discussion

NIPS is considered a potentially powerful neoajuvant chemotherapy to reduce the extent of PM from GC as measure by PCI [6,10,11]. Coccolini et al. reported a significantly better prognosis after CRS in patients with PCI ≤12 than in those with PCI≥13 [3]. Before NIPS, PCI was ≥13 in about 70% of all GC with PM but after 3 cycles of NIPS, it had decreased to ≤12 in 60% of patients [6]. Fujiwara et al. reported that PM disappeared after NIPS in 16 (83%) of 18 GC patients with PM [10] Additionally, positive peritoneal cytology became negative in 60-78% of patients treated with NIPS [6,10,11]. These results may indicate that NIPS eradicates micrometastases extent on the peritoneal surface before CRS [6]. The present study comparing patients treated and not treated with NIPS demonstrated that NIPS significantly improved the survival of GC patients with PM.

Accordingly, NIPS is essential for improving the survival of patients with PM after CRS.

However, few studies have been reported about the effects of NIPS on lymph node metastasis. In contrast, Neoadjuvant Systemic Chemotherapy (NSC) is widely used for advanced GC, and is effective against not only the primary tumor but also lymph node metastasis. The rates of response to NSC for lymph node metastasis were reported to range from 23% to 59% [12,13,14,15]. Noble et al. reported lymph node downstaging in 26.4% (259/981) of patients after NSC [14]. Ito et al. also reported that chemotherapy with docetaxel and cisplatin resulted in lymph node metastasis showed lymph node downstaging from pN3a/pN3b to pN0, pN1, pN2 in 59% (27/46) of patients with extensive lymph node metastasis [16]. In contrast to this, no report has described changes in lymph node metastasis in GC-patients with PM after NIPS.

Schwartz proposed using computed tomography to evaluate the effect of lymph node metastasis after chemotherapy [15]. In gastric cancer, a malignant lymph node diagnosed by CT scan is one that measures more than 1cm in diameter and tends to be round [17]. Sensitivities and specificities for the diagnosis of lymph node metastasis by CT ranged from 55 to 94% [18,19]. Most of the histologic type of GC with PM are poorly differentiated carcinoma, and the size of lymph nodes with metastasis from poorly differentiated carcinoma tend to be smaller than 1 cm in diameter [17]. Additionally, micrometastases less than 2 mm in diameter cannot be detected by CT, and nodes may only be swollen because they are inflamed. From the evidences, we concluded that CT cannot be used to evaluate the effects of lymph node metastasis and compare the effects of NIPS on lymph node metastasis.

In the present study, lymph node status was compared between the non-NIPS and NIPS group. Yamamoto reported the presence of lymph node metastasis in 85% of GC patients with PM [20,21]. In the present study, lymph node metastasis was found in 89.7% (122/136) of non-NIPS group, and was similar for those after systemic chemotherapy [15,22]. In contrast, NIPS group, when compared to the non-NIPS group, had significantly higher incidence of pN0, lower incidence of pN3 (26.2%, 28/107, vs. 63.2%, 86/136), TNMN (4.6, vs.14.8), and lower incidence of lymph node metastasis at station 1, 3, 4, 5, 6, 7, 8, 9, 12-14, and 16. Intraperitoneal concentration of docetaxel after intraperitoneal administration of 40 mg of docetaxel in 500 ml of saline, was found to reach 80 μg/ml, and remain at higher level for longer than 24 hours after administration [23]. Docetaxel and cisplatin are absorbed through omental milky spots, and the efferent lymphatic fluid containing high concentration of the drugs drains into the regional lymph nodes of the stomach [22,24]. As a result, lymph node metastases are exposed to much higher concentrations of docetaxel and cisplatin than can be achieved with systemic chemotherapy. This special lymphatic circulation through the omental milky spots is considered the basis for the very strong effects of intraperitoneal chemotherapy on lymph node metastasis.

In GC-patients with no peritoneal metastasis, nodal status is an independent prognostic factor. However, the present study showed that the prognosis after NIPS and CRS is unrelated to the degree of lymph node metastasis in GC patients with PM. In patients with PM, the degree of PM is a more important prognosticator than lymph node metastasis. However, patients with lymph node metastasis at station 7, 8, 9, 10, 11 had 5-year survival rate of 6.2% to 12.7% after NIPS and CRS. Accordingly, after NIPS, D2 dissection is recommended for the survival improvement.

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