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Downstaging of lymph node metastasis after neoadjuvant intraperitoneal and systemic chemotherapy in gastric carcinoma with peritoneal metastasis

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ABSTRACT

Purpose: The aim of the present study was to evaluate the clinical features and prognosis of lymph node metastasis (LNM) in gastric cancer patients with peritoneal metastasis (PM) after neoadjuvant intraperitoneal and systemic chemotherapy.

Methods: A total of 69 gastric cancer patients with PM and LNM who received neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) of intraperitoneal docetaxel (DXT) and cisplatin (CDDP); intravenous chemotherapy of DXT and CDDP and oral S-1in Kishiwada Tokushukai Hospital between January 2008 and February 2017. After surgical resection, the response of LNMs was studied to confirm the effect of NIPS on LNMs.

Results: After NIPS, 197 lymph nodes (LNs) (42.5%) were graded as G3, the progression in LNMs were significantly better than in the primary tumors. Until the last follow-up, 1-year overall survival rate was 82.6%, and the median survival period was 22.0 ± 3.7 months. In the group of patients who had achieved a more than 50% G3 grade of the response of LNMs, the median survival period is 38 months; in the less than 50% G3 grade group, it is 14 months, that is a significantly different result. Multivariate analyses showed that the factors PCI, Post-therapeutic N status and response of the LNMs were found to be as independent prognostic factors.

Conclusion: Downstaging of LNMs were achieved in patients of gastric cancer with PM who received NIPS. Downstaging of LNMs after NIPS is related with the prognosis of gastric cancer and should be valued in subsequent surgery for gastric cancer with peritoneal and lymph nodes metastasis.

Introduction

Gastric cancer is one of the most common leading causes of cancer related deaths in the world [1]. Peritoneal metastasis (PM) is a frequent mode of metastasis in patients with gastric cancer [2]. Most patients with PM of gastric cancer have lymph node metastasis (LNM) at the same time [3]. An increasing number of patients are being treated with preoperative chemotherapy before surgery [4–7]. In patients with PM, systemic chemotherapy alone has limited and non-curative effect [8–13]. The neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) could reduce the peritoneal cancer index (PCI) and improve the possibility to obtain a complete cytoreductive surgery [14–17]. However, there are only few reports for response of the LNM after NIPS.

Assessment of change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics. Histopathological regression may have an important prognostic impact. In addition to the UICC-TNM classification system, Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 provides an effective image assessment method [18]. It recommends that nodes with a short axis of 15 mm are considered measurable and assessable as target lesions. However, postoperative pathological examination is more

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accurate. Histological evaluation criteria of LNM response after preoperative therapy is a more accurate method. The Japanese Gastric Cancer Association (JGCA) developed an original method to evaluate the response of the primary gastric lesion to chemotherapy or radiotherapy [19]. This study adopts JGCA criterion to evaluate the response of lymph node metastases after gastric cancer surgery.

Patients and methods

Patient selection and treatment

This study included gastric cancer patients who received NIPS followed by surgical resection between January 2008 and February 2017 at Peritoneal Dissemination Center, Kishiwada Tokushukai Hospital. The histological response of primary tumors and the LNMs were examined. Every patient was confirmed by laparoscopy or surgery for diagnosis of PM and LNM of gastric cancer. The ECOG performance status of all patients was $\leq$2 grade.

The patients were treated by NIPS and laparoscopic hyperthermic intraperitoneal chemotherapy (LHIPEC) before the resection surgery. The treatment of NIPS was as follows: S1 80 mg/day was given orally for 2 weeks, and 1 week to rest. Simultaneously, for intraperitoneal chemotherapy, 30 mg/m^2 of docetaxel and 30 mg/m^2 of CDDP were introduced in 500 ml of saline on the first day. On the 8th day 30 mg/m^2 of docetaxel and 30 mg/m^2 of CDDP were infused via a central vein port. One course of treatment lasted for three weeks and repeated until observation of unacceptable toxicity, disease progression or response in which PM or peritoneal lavage cytology (CY) had down stage. LHIPEC was performed at 42 °C–43 °C for 60 min adding 3–5 L of the saline solution including 40 mg of docetaxel and 40 mg of cisplatin. Cytoreductive surgery (CRS) include peritonectomy, gastrectomy and LN dissection was performed after NIPS. Some patients also received hyperthermic intraperitoneal chemotherapy (HIPEC) during the surgery. Based on the patients' consent to LHIPEC and HIPEC treatment, it was decided whether to plus LHIPEC and HIPEC treatment or not.

After resection, all suspected LNMs were sorted out. The slides were stained with hematoxylin and eosin in the routine way for histological evaluation. Histological examination and classification of primary tumors and LNMs was performed according to Japanese classification of gastric carcinoma.

Histological evaluation criteria of primary tumors and MLNs response after preoperative therapy was the same as the grading system of Japanese classification of gastric carcinoma. It was evaluated in the section where the tumor was thought to have been located at the pretreatment assessment and in the sections where tumor cells are likely to remain. Viable tumor cells are defined as cells which are judged to be capable of proliferation.

The pathological changes of all lymph nodes after operation were observed by two professional pathologists. The basic pathological changes are the degeneration of tumor cells, that is nuclear concentration and cytoplasmic vacuolation. In this way, the no viable tumor cells and the no metastasis can be judged. The grade 0 is no evidence of effect; grade 1a is that viable tumor cells occupy more than 2/3 of the tumorous area; grade 1b is viable tumor cells remain in more than 1/3, less than 2/3 of the tumorous area; grade 2 is viable tumor cells remain in less than 1/3 of the tumorous area and grade 3 is no viable tumor cells remain (Fig. 1).

The differences between the groups were analyzed using Chi-square test. Differences were considered to be statistically significant at the $p < 0.05$ level. Overall survival (OS) rate was calculated from the date of laparoscopy or surgery diagnosis of peritoneal and lymph node metastases in gastric cancer. Kaplan-Meier method was used to estimate 1-year OS rate. Survival factors were analyzed by univariate and multivariate analysis with Cox proportional hazard model. All statistical analyses were performed with the Statistical Package for Social Sciences, version 17.0 (IBM, Armonk, NY, USA), and $P < 0.05$ was considered to be statistically significant.

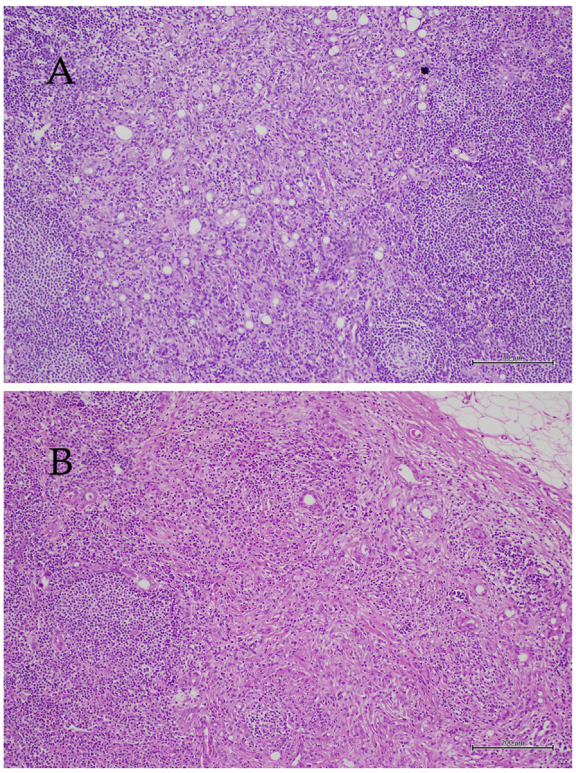

Fig. 1. Histological response of the MLNs. A is grade 1b, viable tumor cells remain in more than 1/3, less than 2/3 of the tumorous area. B is grade 3, no viable tumor cells remain.

Results

In the present study, 69 cases of gastric cancer patients were collected, including 31 females and 38 males, and clinical features were analyzed. The age of patients was from 23 to 74 years old, the average 51.0 ± 13.6 years old. They received 2 to 9 times of NIPS, at an average of 4.78 ± 2.05. The mean BMI was 17.7 ± 13.6 kg/m^2. Additionally, 11 cases (15.9%) received LHIPEC before they were treated by NIPS, and 24 cases (34.8%) had received HIPEC during the operation. Patients' characteristics are listed in Table 1.

After NIPS, 3 cases (4.3%) had the complete relief of primary tumors(G3), 12 cases (17.4%) were graded as G2, 29 cases (42.0%) as G1b, 23 cases (33.3%) as G1a, 2 cases (2.95) had no evidence of effect to NIPS that be as G0.

There were a total of 1496 regional LNs (mean: 21.7 ± 9.4 in each patient; range: 8–54) were retrieved from the 69 cases, of which 464 LNs metastases were noted. After NIPS, 197 LNs (42.5%) were graded as G3, 107 LNs (23.1%) as G2, 58 LNs (12.5%) as G1b, 48 LNs (10.3%) as G1a, 54 LNs (11.6%) as G0.

To compare the difference in the response rate of NIPS between primary gastric cancer tumor and LNMs, we applied a Chi-square test. Table 2 shows that the response of NLMs were significantly better than in the primary tumors ($p < 0.0001$, χ [2] = 85.94).

In all patients, 36 cases (52.2%) achieved a G3 grade response in LNMs ratio that is more than 50%. We choose it to be as an assessment criterion for the treatment effect of NIPS. The response

Table 1
Patients' (n = 69) and tumor characteristics.

Variables	n = 69, n (%)
Age (yr) [mean ± SD, (range)]	51.0 ± 13.6 (23–74)
Gender	
Male	31 (44.9)
Female	38 (55.1)
BMI (kg/m^2) [mean ± SD, (range)]	17.7 ± 3.8 (11.0–30.3)
Last PCI [mean ± SD, (range)]	10.5 ± 9.6 (0–31)
Tumor location	
Upper	12 (17.4)
Middle	42 (60.9)
Lower	15 (21.7)
Borrmann type	
II	9 (13.0)
III	16 (23.2)
IV	44 (63.8)
Post-therapeutic T status	
ypT0	3 (4.3)
ypT1a	1 (1.4)
ypT1b	1 (1.4)
ypT2	6 (8.7)
ypT3	16 (23.2)
ypT4a	23 (33.3)
ypT4b	19 (27.5)
Post-therapeutic N status	
ypN0	23 (33.30)
ypN1	15 (21.7)
ypN2	16 (23.2)
ypN3a	13 (18.8)
ypN3b	2 (2.9)
LHIPEC	
With	11 (15.9)
Without	58 (84.1)
NIPS times [mean ± SD, (range)]	4.78 ± 2.05 (2–9)
HIPEC in operation	
With	24 (34.8)
Without	45 (65.2)
Operative procedure	
Distal gastrectomy	7 (11.1)
Total gastrectomy	62 (89.9)

BMI: body mass index, PCI: peritoneal cancer index, LHIPEC: laparoscopic hyperthermic intraperitoneal chemotherapy, NIPS: neoadjuvant intraperitoneal and systemic chemotherapy, HIPEC: hyperthermic intraperitoneal chemotherapy.

Table 2
Comparison of response between primary tumors and MLNs.

	G0 n (%)	G1a n (%)	G1b n (%)	G2 n (%)	G3 n (%)
Primary tumors	2 (2.9)	23 (33.3)	29 (42.0)	12 (17.4)	3 (4.3)
MLNs	54 (11.6)	48 (10.3)	58 (12.5)	107 (23.1)	197 (42.5)

Pearson χ 2 = 85.94 p < 0.001, MLNs: lymph node metastasis.

of LNMs in different characteristics of the patients were compared by Chi-square test (Table 3). There is no significant difference between two groups of treatment by NIPS with LHIPEC and without LHIPEC (p > 0.05, χ [2] = 0.029).

All patients received imaging and CY examination during NIPS treatment. When the peritoneal cytology was negative for carcinoma cells and response in imaging, CRS will be performed. Some patients who could not tolerant NIPS or in those which, even when the CY was not negative, but there was a significant improvement in imaging performance, CRS was performed. We compared the two groups of treatment by less than or equal to three times of NIPS and more than 3 times, and there was no significant difference in the results (p > 0.05, χ [2] = 0.047).

To assess the effect of peritoneal metastasis on LNMs treated with NIPS, we divided patients into two groups based on preoperative PCI, the group with PCI≤15 and PCI>15. In the group with PCI≤15, 32(72.7%) cases had a G3 grade of the response in LNMs ratio; while in the group with PCI>15, there were only 4(16.0%) cases. The result was significantly different (p < 0.05, Pearson χ [2] = 20.56).

Chi-square study was conducted for the influence of ascites, on the efficacy of LNMs. According to the amount of ascites the patients were divided into three groups. In the first group, the amount of ascites<100 ml; in the second group, the amount of ascites 100–500 ml; the third group, the amount of ascites >500 ml. According to statistical analysis, the therapeutic effect of LNMs in groups with more ascites was poorer than that in less ascites. There was a significant difference between the groups (p < 0.05, Pearson χ [2] = 13.31).

The follow-up of survival was performed at least 13 months after the first laparoscopy or surgery, nobody was lost, the max follow-up time was 97 months. Currently, 19 patients (27.5%) are still alive. The 1-year overall survival rate was 82.6%, and the median survival period was 22.0 ± 3.7 months.

The survival period between the treatment with LHIPEC and without LHIPEC was compared. For the LHIPEC group, the median survival period is 32 months; the median survival period is 21 months in the patients without LHIPEC group, there is no significant difference.

Fig. 2 shows that in the group of patients who had achieved a more than 50% G3 grade of response of LNMs, the median survival period is 38 months; in the less than 50% G3 grade group, it is 14 months, that is a significantly different result (p < 0.001).

A multivariate analysis with a Cox regression model was performed to determine independent predictors of improved OS after NIPS. By multivariate analysis, PCI, Post-therapeutic N status, and response of the LNMs were found to be correlated significantly with survival (P < 0.05).

Discussion

Recent multi-institutional trials of preoperative chemotherapy have showed acceptable safety and efficacy for gastric cancer with PM and LNMs [15,16,20]. In our study we found that most patients

Table 3
Comparison of response of MLNs in different characteristics of patients.

Variable	G3 MLNs ratio<50% n (%)	G3 MNLs ratio≥50% n (%)	Total	Pearson χ2	P value
Without LHIPEC	28 (48.3)	30 (51.7)	**58**	0.029	>0.05
With LHIPEC	5 (45.5)	6 (54.5)	11		
NIPS times ≤ 3	12 (46.2)	14 (53.8)	26	0.047	>0.05
NIPS times > 3	21 (48.8)	22(51.2)	43		
PCI ≤ 15	12(27.3)	32(72.7)	44	20.56	<0.001
PCI > 15	21(84.0)	4(16.0)	25		
Ascites group 1	7(31.8)	15(68.2)	22	13.31	<0.001
Ascites group 2	9(34.6)	17(65.4)	26		
Ascites group 3	17(81.3)	4(19.1)	21		

MLNs: lymph node metastasis, LHIPEC: laparoscopic hyperthermic intraperitoneal chemotherapy, NIPS: neoadjuvant intraperitoneal and systemic chemotherapy, PCI: peritoneal cancer index.

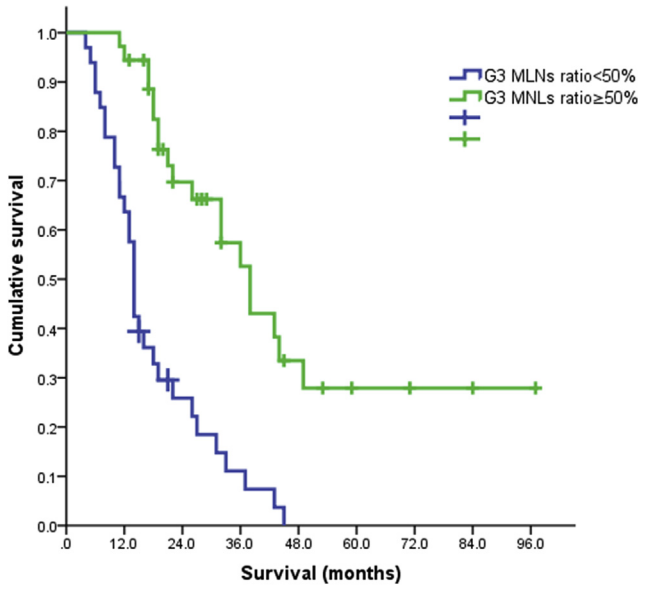

Fig. 2. KaplaneMeier survival curves of patients. The group with the response of MNLs >50% G3 grade, the median survival period is 38 months; the group with the response of MNLs<50% G3 grade, it is 14 months. There is significant difference between the groups ($p < 0.001$).

had benefited from NIPS and LHIPEC treatment to the primary tumors and LNMs. After NIPS, the response of LNMs was better than in primary tumors. In a retrospective study, Kinoshita reported that preoperative chemotherapy does not provide any outstanding histological benefit for LNMs [21]. In their study, they only used traditional oral and intravenous chemotherapy. Although similar chemotherapeutic agents and measurements were also performed, we have added the use of intraperitoneal chemotherapy to achieve better results in the improvement of LNMs.

In chemotherapy for advanced gastric cancer, systemic administration is a routine method and is considered to be effective. But since large amounts of chemotherapy drugs cannot be transported and concentrated around the LNs area, conventional systemic administration like intravenous and oral may be not very efficient. Intraperitoneal-systemic chemotherapy adds another route of administration. Intraperitoneal (IP) provides sustained high local concentrations in the abdominal cavity.

Recklinghausen firstly reported the peritoneal lymphatic stomata, which are small openings of the subperitoneal lymphatic vessels in peritoneal cavity [22]. Subsequent researches suggested that the peritoneal cavity is an integral part of the lymphatic system with enormous absorption powers, functioning primarily by means of the subperitoneal lymphatics via the peritoneal lymphatic stomata [23–25]. Thus, it has important clinical implications, especially in ascites drainage. It has also been observed that solutions containing chemotherapeutic drugs such as taxanes are absorbed by the peritoneal lymphatic stomata [26]. Chemotherapy drugs entering the LNMs region through the subperitoneal lymphatic network may be more than through the vascular system and it was also important supplements. NIPS treatment perhaps aggregated the higher chemotherapeutic drug concentrations in the LNM region through both pathways. Consequently, we found a better improvement of LNMs in our study. In addition, the peritoneal cavity is an integral part of the lymphatic system, therefor LNMs achieved better results than primary tumors after NIPS treatment.

In the patients with higher PCI and larger volume of ascites, there is least improvement in LNMs. Patients with higher PCI have more metastasis of cancer on the peritoneum. These metastases of cancer may block peritoneal lymphatic stomata and prevent intraperitoneal chemotherapy drugs from entering the subperitoneal lymphatic system. At the same time, the peritoneal metastasis produces a large amount of ascites, which dilutes intraperitoneal chemotherapy drug concentration of NIPS. Therefore, it is difficult to accumulate high drug concentrations around LNMs.

There are retrospective studies which show that after LHIPEC plus NIPS, the PCI score was decreased in the gastric cancer patients with PM, and the average score was significantly reduced [27,28]. Some studies have reported that hyperthermia may increase drug absorption in the peritoneal cavity [29–31]. Chemotherapy drugs pass through the subperitoneal lymphatic vessels to increase the concentration of drug around the LNMs. In this study we have not found the patients who received LHIPEC treatment had better improvement in LNMs. This may be due to the small number of cases in the LHIPEC treatment group and only one-time LHIPEC treatment before the operation.

According to this study, increasing the cycle of NIPS did not lead to a better response for LNMs. More studies suggest that preoperative chemotherapy for advanced gastric cancer does not exceed 3 times [4–6,32,33]. Increase the number of the cycle of chemotherapy, there will be drug resistance of cancer cells and tumor progression, with better efficacy. In our study, there were indeed cases in which more than 6 cycles of NIPS were treated to obtain improvement in peritoneal metastasis. For NIPS treatment of peritoneal metastasis and LNM, each patient should be treated individually.

Despite with the development of many new systemic chemotherapy, systemic chemotherapy for peritoneal metastasis from gastric cancer remains poor [8–12]. Recently, intraperitoneal chemotherapy was proposed as an effective treatment to improve survival [14–16,34]. There have been few studies on the prognostic significance of gastric cancer with peritoneal metastasis and LNM after NIPS. According to our follow-up, the downstaging of LNMs is significantly related to survival. The progression of LNMs is similar to that of primary tumors and peritoneal metastasis and plays a key role in the prognosis of gastric cancer with peritoneal metastasis and LNM. Therefore, the downstaging of LNMs of gastric cancer after NIPS had a great significance on the prognosis of patients with PM from gastric cancer.

Patients treated with LHIPEC did not show prognostic advantages, although patients treated with LHIPEC has been observed to have a significant effect on the improvement of peritoneal metastasis in our other studies [28]. Peritoneal metastasis from GC is considered an independent prognostic factor for poor prognosis [35]. From the multivariate analysis, the PCI and response of the LNMs were independent predictors of improved OS after NIPS in the study. As the PCI, response of the LNMs after NIPS should be valued in subsequent surgery for gastric cancer with peritoneal and lymph nodes metastasis.

Conclusion

Downstaging of MLNs were achieved in patients of gastric cancer with PM who received NIPS. Downstaging of LNMs after NIPS is related with the improved prognosis of gastric cancer and should be valued in subsequent surgery for gastric cancer with peritoneal and lymph nodes metastasis.

Disclosure

Yuan Hao, Yang Liu, Haruaki Ishibashi, Satoshi Wakama, Eisei Nishino and Yutaka Yonemura there is no conflict of interest to disclose.

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