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ORIGINAL ARTICLE

Retrospective Study

Histological evaluation for chemotherapeutic responses of metastatic lymph nodes in gastric cancer

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Abstract

AIM: To investigate the effect of preoperative chemotherapy (pre-CTx) for metastatic lymph nodes (MLNs) of gastric cancer (GC).

METHODS: A retrospective cohort of patients with advanced GC, who underwent pre-CTx followed by gastrectomy, was reviewed. The histological tumor regression grade (TRG), which considered the percentage of residual cancer in the visible tumor bed, was applied to primary tumors and individual MLNs: G1a (complete response), G1b (< 10%), G2 (10%-50%) and G3 (> 50%). The clinical response to pre-CTx was retrospectively evaluated using only MLNs information, and we compared the histological and clinical evaluations of MLNs.

RESULTS: Twenty-eight patients were enrolled. A total of 438 MLNs were retrieved, and 22 (5%), 48 (11%), 63 (14%) and 305 (70%) LNs were assigned as G1a, G1b, G2 and G3, respectively. Stratification of the residual MLNs based on the TRGs was as follows: 28 G1b MLNs (9%), 48 G2 MLNs (15%), and 253 G3 MLNs (76%) in the D1 region; 20 (23%), 15 (17%), and 52 (60%) in the D2 region, respectively. However, no significant correlation was found between TRGs in MLNs and clinical response in the subgroup for which evaluation of clinical response was available.

CONCLUSION: Pre-CTx does not provide any outstanding histological benefit for MLNs, and an appropriate D2 lymphadenectomy should routinely be performed to offer the chance of curative resection.

Key words: Preoperative chemotherapy; Gastric cancer; Metastatic lymph node; Histological regression grade; Lymphadenectomy

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Core tip: Preoperative chemotherapy for gastric cancer does not provide any outstanding histological regression for regional metastatic lymph nodes, and residual metastatic lymph nodes were located irrespective of D1 and D2 region. In addition, no significant correlation was found between the clinical response of metastatic lymph nodes based on RECIST classification and histological response grading. Consequently, an appropriate D2 lymphadenectomy should routinely be performed in order to offer the chance of curative resection of advanced gastric cancer treated with preoperative chemotherapy.

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INTRODUCTION

Gastric cancer (GC) is one of most diagnosed cancers worldwide, and it is estimated to be the third most frequent cause of cancer-related deaths[1]. New incidences of GC have decreased worldwide during recent decades, but the cause-specific mortality remains considerable, even after surgery[2]. Several randomized trials in Western countries have demonstrated that preoperative chemotherapy (pre-CTx) markedly improves the survival rates of patients with resectable GC[3-5]; these results have led to an increasing use of pre-CTx in clinical practice around the world, including Asian countries[6-8].

The surgeon's main purposes in using pre-CTx as an intervention for advanced GC patients are an increased rate of tumor resectability and tumoricidal effects on possible lymph node metastasis[9]. Some retrospective studies have suggested that pre-CTx would improve rates of radical resection in locally advanced GC patients[10]; however, there is no detailed previous report concerning the effects of pre-CTx on lymph node metastasis in GC patients. In a meta-analysis of randomized controlled trials, Xu *et al*[11] reported that N0 status was more frequently achieved in GC patients treated with pre-CTx than those treated with surgery alone. This finding demonstrates the possible effectiveness of pre-CTx on micrometastasis. These findings prompted us to examine the effects of pre-CTx on the metastatic lymph nodes (MLNs) of GC patients. In the present study, we retrospectively examined the histological response to pre-CTx in primary tumors and the MLNs of advanced GC. We also compared the findings with clinical evaluations in order to determine whether limited lymph node dissection is possible for GC patients treated with pre-CTx.

MATERIALS AND METHODS

Patients

Of the patients with gastric cancer treated at Kyoto Prefectural University of Medicine between January 2001 and January 2013, those who had undergone pre-CTx followed by gastrectomy were enrolled in the retrospective study. All the pre-CTx protocols included the anticancer drug S-1 (TS-1, Taiho Pharmaceutical, Tokyo, Japan), an orally active combination of tegafur, gimeracil, and oteracil potassium, which were accepted as S-1 alone[12] (80 mg/m^2 orally every 28 d), S-1 plus cisplatin[13] (S-1: 80 mg/m^2 orally every 21 d; cisplatin: 60 mg/m^2 intravenously on days 8 and 15), or S-1 plus docetaxel[14] (S-1: 80 mg/m^2 every 21 d; docetaxel: 60 mg/m^2 intravenously on days 1, 6, and 15) were administered in two to four identical courses, and open distal or total gastrectomy with Japanese-style D2 lymphadenectomy[15] was performed afterward. Written informed consent was obtained from all of the patients prior to the initiation of this study.

In general, patients underwent a double-contrast barium examination, endoscopy, and multidetector-row computed tomography (MDCT). They were diagnosed preoperatively based on their results in our hospital. Staging laparoscopy was performed to determine whether peritoneal dissemination was present prior to pre-CTx, although this procedure was not mandatory in this study.

Evaluation of clinical response for MLNs

Based on the new Response Evaluation Criteria in Solid Tumors (RECIST) guidelines[16], the clinical

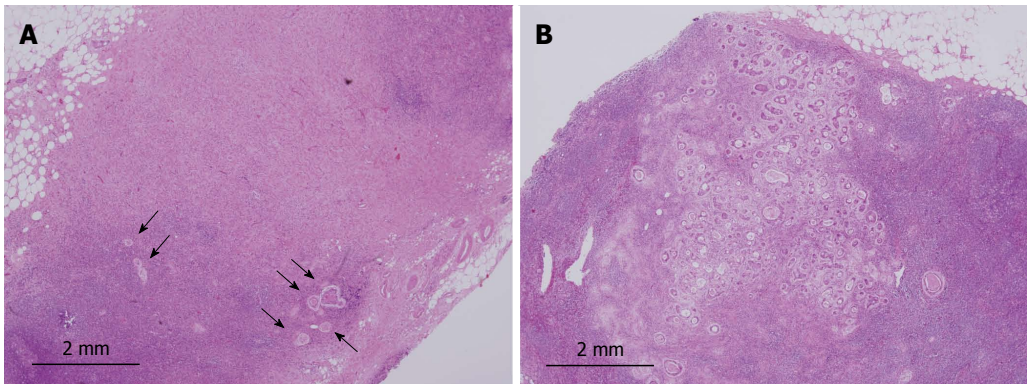

Figure 1 Representative slides of tumor regression grades in metastatic lymph nodes from the same primary tumor. A: G1b, slight residual cancer foci (arrows) are found in tumor bed; B: G3, residual cancer occupy > 50% of tumor bed. The scale bar indicates 2 mm.

response to pre-CTx was retrospectively evaluated by using only MLNs information according to the method reported by Schwartz *et al*[17]. In brief, a cine-mode display of contrast-enhanced MDCT images, which was performed two to four weeks after the completion of pre-CTx, was mainly used. The regional LNs were considered to show metastatic involvement if their longest diameter was ⩾ 15 mm, which is according to the RECIST guidelines. An experienced radiologist (Ichijo Y) who was blind to the patients' outcome reviewed the images and selected one or two of the most reproducible target MLNs per patient. Consequently, the MLNs were graded as "complete response" (CR), "partial response" (PR), "stable disease" (SD), and "progressive disease" (PD).

Histological evaluation

Immediately after resection, all the regional LNs were manually retrieved from the resected specimens. Following Japanese guidelines[15], the primary tumors were cut crosswise through the center of the tumor, and the retrieved LNs were cut longitudinally through the hilus. All slides were stained with hematoxylin and eosin in the routine fashion for use in histological evaluation.

The histological tumor regression grade (TRG) was evaluated using the grading system proposed by Becker *et al*[18,19]: G1a (complete response); G1b (< 10% residual tumor per tumor bed); G2 (10%-50% residual tumor per tumor bed); and G3 (> 50% residual tumor per tumor bed). We applied this grading system to the primary tumors and each individual's MLNs, comparing the patients' outcomes. Representative slides for TRG in the MLNs are shown in Figure 1. A pathologist specializing in gastrointestinal disorders (Kishimoto M and Yanagisawa A) who was blind to the patients' outcome reviewed the histology of all the slides.

Statistical analysis

All the analyses were implemented using the R statistical software program (The R Foundation for Statistical Computing, Vienna, Austria). The differences between the groups were analyzed using a χ^2 test. Differences were considered to be statistically significant at the $P < 0.05$ level.

RESULTS

Clinical evaluation and effects in primary tumors

A total of 28 patients were enrolled in the study. Based on the TNM classification from the Union for International Cancer Control, 15 patients (54%) were clinically diagnosed as Stage Ⅲ; 13 (46%) were diagnosed as Stage Ⅳ. Of the 28 patients, 27 received a postoperative chemotherapy regimen including S-1. As for TRGs in primary tumors, two cases (7%) were graded as G1b, six (21%) as G2, and 20 (71%) as G3. However, no cases were found with a complete tumor regression (G1a).

Evaluation for clinical response to pre-CTx was performed based on MLN findings in 11 patients (43%), whose pre- and post-therapeutic MDCT images were both available. Of these, two cases were graded as CR, four cases as PR, and two cases as SD, while no applicable target MLNs were found in three cases. The details of the other patient characteristics are listed in Table 1.

MLNs

A total of 1044 regional LNs (mean: 37.3 in each patient; range: 8-71) were retrieved from the 28 patients. Of those, 438 were diagnosed as positive for lymph node metastasis; 22 (5%), 48 (11%), 63 (14%), and 305 (70%) LNs were assigned to G1a, G1b, G2, and G3, respectively. As summarized in Table 2 and Figure 2, the TRGs of the primary tumors were significantly associated with those of the MLNs ($P < 0.0001$, χ^2 test). As for pathological complete response LN graded G1a ($n = 22$), 13 LNs belonged to the peri-gastric region (D1) and nine LNs belonged to regions along the named vessels of the celiac axis (D2). On the other hand, stratification of the residual MLNs based on the TRGs was as follows: 28 G1b MLNs (9%),

Table 1 Patients' characteristics (*n* = 28) *n* (%)

Variables	
Age (yr) [mean ± SD, (range)]	60 ± 10.7, (28-81)
Sex	
Male	16 (57)
Female	12 (43)
Tumor location	
Upper	9 (32)
Middle	15 (54)
Lower	4 (14)
Histological type	
Differentiated	10 (36)
Undifferentiated	18 (64)
Pre-therapeutic staging	
cStage Ⅲ	15 (54)
cStage Ⅳ	13 (46)
Clinical response	
CR	0 (0)
PR	10 (36)
SD	16 (57)
PD	2 (7)
Post-therapeutic T status	
ypT2	1 (4)
ypT3	11 (39)
ypT4	16 (57)
Post-therapeutic N status	
ypN0	1 (4)
ypN1	1 (4)
ypN2	4 (14)
ypN3	22 (79)
Post-therapeutic M status	
ypM0	9 (32)
ypM1	19 (68)
Post-therapeutic staging	
ypStage Ⅱ	2 (7)
ypStage Ⅲ	7 (25)
ypStage Ⅳ	19 (68)
TRG in primary tumors	
G1a	0 (0)
G1b	2 (7)
G2	6 (21)
G3	20 (71)
Preoperative chemotherapy	
S-1 alone	5 (18)
S-1 plus cisplatin	16 (57)
S-1 plus docetaxel	7 (25)
Operative procedure	
Distal gastrectomy	7 (25)
Total gastrectomy	21 (68)
Postoperative chemotherapy	
With	27 (96)
Without	1 (4)

CR: Complete response; PR: Partial response; SD: Stable disease; PD: progressive disease.

48 G2 MLNs (15%), and 253 G3 MLNs (76%) in the D1 region; 20 (23%), 15 (17%), and 52 (60%) in the D2 region, respectively.

In the subgroup of 11 cases for which MDCT images were available, a total of 436 regional LNs were retrieved. Of these, 226 MLNs were available for histological evaluation; 6 (3%), 23 (10%), 28 (12%), and 169 (76%) LNs were assigned to G1a, G1b, G2, and G3, respectively. Table 3 shows a breakdown of TRG in MLNs according to clinical response based on RECIST classification; however, there was no significant correlation between the clinical and histological response.

Table 2 Comparison of tumor regression grade in primary tumors *n* (%)

Variables		TRG in primary tumors			*P* value
		G1b (*n* = 2)	G2 (*n* = 6)	G3 (*n* = 20)	
TRG in MLNs	G1a	9 (2)	6 (1)	7 (2)	< 0.0001
	G1b	2 (0)	22 (5)	24 (5)	
	G2	2 (0)	17 (4)	44 (10)	
	G3	7 (2)	45 (10)	253 (60)	

TRG: Tumor regression grade; MLNs: Metastatic lymph nodes.

Table 3 Correlation between clinical response and histological evaluation *n* (%)

Variables		Clinical response			
		CR (*n* = 2)	PR (*n* = 4)	SD (*n* = 2)	No applicable target LNs (*n* = 3)
TRG in MLNs	G1a	1 (0)	4 (2)	1 (0)	0 (0)
	G1b	0 (0)	23 (10)	0 (0)	0 (0)
	G2	2 (1)	20 (9)	6 (3)	0 (0)
	G3	15 (7)	79 (35)	51 (23)	24 (11)

CR: Complete response; PR: Partial response; SD: Stable disease; TRG: Tumor regression grade; MLNs: Metastatic lymph nodes.

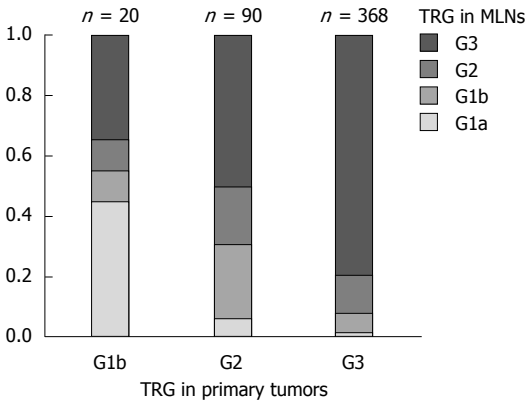

Figure 2 Breakdown of tumor regression grades in metastatic lymph nodes according to that in primary tumors. TRG: Tumor regression grade; MLNs: Metastatic lymph nodes.

DISCUSSION

In Asian countries, gastrectomy with D2 lymph node dissection has been generally regarded as the standard treatment for achieving a radical cure[15]. Recently, the D2 lymphadenectomy is increasingly recognized to be associated with lower locoregional recurrence and gastric cancer-related death rates than D1 lymphadenectomy in Western countries; therefore, it is the recommended surgical approach for patients with resectable gastric cancer[20]. On the other hand, pre-CTx has also been recognized as effective for latent

lymph node micrometastasis[21]. However, there is no detailed previous report concerning the effects of pre-CTx on MLNs in GC patients, and there is no consensus as to whether limited lymph node dissection is possible for GC patients treated by pre-CTx.

This study investigated histological effects in each individual's MLNs in 28 patients with advanced GC who were treated with pre-CTx, and to the best of our knowledge, this is the first report to address this issue. One of the most important findings in this study underlined that even MLNs clinically exhibiting favorable pre-CTx response showed an unsatisfactory histological response in practice. Kurokawa *et al*[22] also compared clinical and histological responses of GC to treatment with pre-CTx, focusing particularly on survival rates, and concluded that histological criteria showed higher response assessment validity than RECIST criteria and yielded the best surrogate endpoint for overall survival. Our results showed that histologically proven residual MLNs were located irrespective of D1 and D2 region. The residual tumor also existed in MLNs regardless of the degree of clinical response based on RECIST. Only 1 of 18 MLNs (5%) graded as clinically CR could achieve complete tumor regression (G1a,) and most MLNs had limited response. Taken together, appropriate D2 lymphadenectomy should be routinely performed in advanced GC patients who become candidates for curable surgical treatment by pre-CTx irrespective of the clinical response, as suggested by previous reports[23]. Some authors proposed that the clinical evaluation using MLNs information of GC patients treated with pre-CTx contributed to improving the complete resection rate by D2 lymphadenectomy[7]. However, Hayashi *et al*[24] called attention to the fact that D2 lymphadenectomy for GC patients, who had lower creatinine clearance treated with pre-CTx, caused greater surgical complications.

Another interesting finding of this study was that pre-CTx response in MLNs was, to some extent, correlated to the response in the primary tumors. We made an unwarranted assumption that the pre-CTx response in regional MLNs would parallel that of primary tumors; however, there is limited histological data supporting this correlation. The extent to which MLNs would histologically benefit from pre-CTx is unclear. Our present study revealed that 45% of the MLNs had a limited response (G2 or G3), even with G1b primary tumors, and that only 5% of the total MLNs achieved complete tumor regression (G1a). Similar findings were previously described by Mandard *et al*[25] for esophageal cancer treated with pre-CTx. Some previously published circumstantial evidence has also revealed that the interaction of the tumor cell with the organ environment creates differences between the primary tumors and their metastatic lesions in terms of their histology as well as their gene or protein expression[26,27]. Taken together, these findings suggest that pre-CTx may have no outstanding benefit for regional MLNs, even when the primary could achieve a considerable therapeutic effect. However, cumulative evidence[3-8] showed that some patients benefited from pre-CTx, in this context, with more effective pre-CTx regimens. Patient selection might be required for further effect.

Our study had several limitations, the first of which is its small sample size: the total number of patients was 28, and the final number of cases available for clinical evaluation was only 11. Further investigations using larger sample sizes would therefore be needed to confirm our findings. Second is that this study cohort included many advanced cases and limited information concerning patients in earlier stages of GC. Staging laparoscopy was not mandatory for patients suspected to have peritoneal dissemination during this period, and subsequently, this study cohort included many advanced cases of GC. The advanced stage of cancer progression and the large amount of tumor potentially influence the therapeutic effects of pre-CTx on MLNs in this study.

In summary, pre-CTx for advanced GC does not provide any outstanding histological regression for regional MLNs, and residual MLNs were located irrespective of D1 and D2 region. Further, little correlation was found between TRGs in MLNs and their clinical evaluation. Consequently, an appropriate D2 lymphadenectomy should always be performed in order to offer the chance of curative resection of advanced GC treated with pre-CTx. However, this study was based on a small number of patients with advanced GC, and limited data was given concerning patients in earlier stages of GC. Thus, a well-selected larger cohort study would be required to confirm our findings.

COMMENTS

Background

To reduce the mortality from gastric cancer (GC), improvement of perioperative intervention is essential and is still challenging. Since several large, randomized trials have demonstrated that preoperative chemotherapy (pre-CTx) markedly improves the survival rates of patients with GC, therapeutic strategies including pre-CTx have gradually been introduced into clinical settings around the world.

Research frontiers

One important concern for surgeons relates to interventions for patients with GC who become surgical candidates after pre-CTx. However, despite the cumulative evidence for pre-CTx in GC, the extent to which metastatic lymph nodes (MLNs) would histologically benefit from pre-CTx is unclear, and there is no detailed previous report concerning this issue.

Innovations and breakthroughs

These results showed a histological pre-CTx effect on regional MLNs using tumor regression grade (TRG). The TRGs of MLNs were closely correlated with those of the primary tumors. Furthermore, in this study, the clinical response to pre-CTx, which was retrospectively evaluated using only MLNs information, was compared with the histological pre-CTx effect. However, there was no significant correlation between the clinical and histological response in regional MLNs.

Applications

Pre-CTx for advanced GC does not provide promising histological regression for regional MLNs; consequently, an appropriate D2 lymphadenectomy should always be performed in order to offer the chance of curative resection. However, this study was based on a small number of patients with advanced GC, and limited data concerning patients in earlier stages of GC was available. A well-selected larger cohort study is necessary to confirm our findings.

Peer-review

The manuscript draws potentially interesting conclusions, although based on a limited number of patients.

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