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Yasuro Ninomiya · Akio Yanagisawa
Yo Kato · Tomoyuki Kitagawa
Sho Ishihara · Toshifusa Nakajima

Histological indications of a favorable prognosis with far-advanced gastric carcinomas after preoperative chemotherapy

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Abstract ***Purpose:*** Although preoperative chemotherapy for advanced gastric cancer is now commonly applied with favorable results, convincing evidence for life prolongation and predictive markers for a good prognosis are both lacking. We report here 5 cases that have shown a distinct positive effect of preoperative chemotherapy together with the results of a precise histological examination of materials indicating features predicting a favorable outcome. ***Patients and methods:*** A total of 18 patients with a far-advanced gastric carcinoma subjected to gastrectomy after FLEP (5-fluorouracil, leucovorin, etoposide, cisplatin) in the Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, could be divided into two distinct groups: 5 surviving over 5 years (group A) and 13 who died within 13 months (group B). Histological features (subtypes) of the carcinomas and chemotherapeutic effects were studied with reference to biopsy materials and resected stomachs and lymph nodes. ***Results:*** In group A, 3 of 5 patients had solid-type poorly differentiated adenocarcinomas. In contrast, in group B, 9 had tubular adenocarcinomas (well or moderately differentiated) and 3 non-solid or diffuse-type poorly differentiated adenocarcinomas and there was only one solid-type tumor. In group A, remarkable therapeutic effects were apparent histologically in 4 of the 5 patients with almost complete disappearance of cancer cells from metastases in lymph nodes, whereas no such changes were evident in group B. ***Conclusion:*** FLEP is distinctly beneficial for certain types of advanced gastric carcinoma, especially solid-type poorly differentiated adenocarcinomas, and favorable results can be predicted, to a certain extent, on the basis of findings for the material resected after chemotherapy.

Key words Histological evaluation · Preoperative chemotherapy · Long-term survival

Y. Ninomiya (✉) · A. Yanagisawa · Y. Kato · T. Kitagawa
Department of Pathology,
The Cancer Institute of the Japanese Foundation
for Cancer Research,
170-8455 Kami-Ikebukuro 1-37-1, Toshima-ku,
Tokyo, Japan
e-mail: cah66710@pop14.odn.ne.jp
Tel.: +81-3-5394-3865
Fax: +81-3-5394-3893

S. Ishihara · T. Nakajima
Department of Gastrointestinal Surgery,
The Cancer Institute Hospital of the Japanese Foundation
for Cancer Research,
Tokyo, Japan

Introduction

Since the introduction of the idea of preoperative chemotherapy (Frei et al. 1982), many patients with advanced and inoperable gastric cancer have been treated with various preoperative regimens in order to improve curability or to change an unresectable to a resectable tumor. However, while "favorable results" have been reported (Rougier et al. 1994; Ajani et al. 1995; Yonemura et al. 1993; Wilke et al. 1989; Stephens et al. 1986) and many doctors are aware that some gastric carcinomas are quite sensitive to chemotherapy, the degree of benefit remains controversial (Fink et al. 1995). Unfortunately, no clear-cut clinicopathological data showing a significant relationship between "favorable response" and life prolongation are presently available. One of the reasons for this lack is the relative rarity of conspicuously chemosensitive gastric carcinomas, so that positive outcomes may be obscured when series of cases are examined. It is, however, of great clinical importance to confirm the existence of distinct chemosensitivity as well as absolute resistance and clarify predictive features to encourage aggressive chemotherapy for cases with the former and avoid needless harm with the latter.

Reviewing 18 far-advanced gastric cancer cases undergoing preoperative chemotherapy in our Cancer Institute Hospital during 1989–l995, we realized that they

could be clearly divided into a group with a good prognosis (5 patients living over 58 months) and another with poor prognosis (13 patients who died within 13 months). This fact prompted us to make a precise comparative histological comparison of the two groups in terms of tumor histology and response to chemotherapeutics. The purpose of this paper is to document those cases showing distinct favorable results and histological indications that may predict a favorable outcome of preoperative chemotherapy.

Patients and methods

Patients

From 1989 to 1995 in the Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, 30 of 42 patients with incurable gastric cancer (stage IV, M1 disease of the UICC TNM classification (Hermanek et al. 1997)) were entered into a combined-modality trial with intensive chemotherapy (5-fluorouracil, leucovorin, etoposide, cisplatin: FLEP regimen, Table 1) (Nakajima et al. 1997) and surgery. Entry criteria were as follows: (a) histologically proven adenocarcinoma of the stomach with no previous treatment; (b) patient age < 75 years, performance status ≤ 3, and normal liver, renal, and bone marrow functions; (c) unresectable disease due to wide local extension with intra- or extra-abdominal metastasis; (d) provision of informed consent. Patients who met all entry criteria were included in this study and 18 of them subsequently received surgical treatment. Of these 18, 12 (66.7%) had extensive node metastases, 2 had multiple liver metastases, 3 had both, and 1 had extensive lymph node metastasis and peritoneal dissemination. The local response to chemotherapy was evaluated by an upper-gastrointestinal series, endoscopy, computed tomography, and magnetic resonance imaging. The clinical criteria (WHO) for judging the local response to chemotherapy were complete response (CR), partial response (PR), no change (NC), and progressive disease (PD). To evaluate the total response to chemotherapy of patients with multilple lesions (primary and metastatic), the local response of each lesion was scored as follows: 4 points for CR, 3 for PR, 2 for NC, 1 for PD. The total response was rated as CR when the average score (AS) was atleast 3.5, PR when $3.5 > AS \geq 2.5$, NC when $2.5 > AS \geq 1.5$, PD when AS was less than 1.5 (Nakajima et al. 1997). After surgery, all the patients had a regular clinical follow-up and, retrospectively, they were classified into the long-term survivors (5 surviving over 58 months – group A) and those with poor prognosis (13 died within 13 months – group B).

Histological examination

The histological features of the carcinomas were studied using biopsy materials obtained before the FLEP therapy. They were classified principally according to the General Rules of the Japanese Research Society for Gastric Cancer (Japanese Research Society for Gastric Cancer 1995a) as listed in Table 2. It should be noted that, in this classification, poorly differentiated adenocarcinoma (por) is subclassified into solid type (por1) and non-solid type (por2). Por1 is characterized by an overall well-defined growth pattern, and histological evidence of medullary proliferation of cancer cells with scanty stroma and no tubular formation apparent. The por2 category is a kind of "waste basket" for most poorly differentiated adenocarcinomas other than por1 and signet-ring cell carcinoma (Kino 1991).

After formalin fixation, the resected stomachs were sectioned, in principle, along the lesser curvature as a reference line for other sections. In 5 cases, the whole stomach was sectioned at intervals of 8 mm or 4 mm. In 9 cases, the cancerous lesions were entirely sectioned parallel to the reference line. In the remaining 4 cases, only the area of the deepest invasion was sectioned parallel to the reference line with additional sections perpendicular to the lesser curvature. Two cut faces grossly showing the maximum extension of the carcinoma were cut into pieces of appropriate size and processed for histological examination. In the case of dissected lymph nodes, the planes with the largest diameter were sectioned. All dissected nodes were subjected to histological examination. The spread of the carcinoma in the stomach, including the depth of invasion, the effect of chemotherapy and the number of cancer-involved nodes before and after FLEP therapy, were determined by microscopical observation. The chemotherapeutic efficacy was classified into four major categories (0–3) according to the criteria of the Japanese Research Society for Gastric Cancer (1995b) (Table 3).

Table 1 Regimen of FLEP therapy

5-FU	370 mg/m^2 i.v. days 1–5
Leucovorin	30 mg i.v. days 1–5
Cisplatin	70 mg/m^2, intraaortic, days 6 and 20
Etoposide	70 mg/m^2, intraaortic, days 6 and 20

Table 2 Histological typing

Tubular adenocarcinoma (tub)
1. Well differentiated type (tub1)
2. Moderately differentiated type (tub2)

Poorly differentiated adenocarcinoma (por)
1. Solid type (por1)
2. Non-solid type (por2)

Signet-ring cell carcinoma (sig)
Mucinous adenocarcinoma (muc)

Table 3 Grading of histological changes

Grade 0. No change – neither necrosis nor cellular or structural change can be seen throughout the lesion

Grade 1. Slight change
- 1a. Necrosis or disappearance of the tumor is present in less than 1/3 of the whole lesion, or only cellular or structural changes are visible in various amounts
- 1b. Necrosis or disappearance of the tumor is present in no more than 2/3 of the whole lesion

Grade 2. Moderate change – necrosis or disappearance of the tumor is present in more than 2/3 of the whole lesion, but viable tumor cells remain

Grade 3. Marked change – the whole lesion falls into necrosis and/or is replaced by fibrosis, with or without granulomatous changes. No viable tumor cells are observed

Results

Clinical information, histological subtypes, data from clinical and histological evaluations of the effect of chemotherapy, the number of involved nodes, stages, survival time and the recurrence state are given in Table 4.

Table 4 Clinical and histological information obtained before and after FLEP therapy. Histological typing defined in Table 2. Clinical evaluation (WHO classification): *CR* complete response, *PR* partial response, *NC* no change, *PD* progressive disease. *TNM* International Union Against Cancer classification of cancer (UICC): *T* primary tumor, *N* regional lymph nodes, *M* distant metastasis. *No. of involved nodes* the number of involved nodes/the total number of nodes examined: *pre* estimated number of involved nodes before FLEP therapy, *post* actual number of involved nodes. *LYM* lymph nodes, *HEP* hepatic, *PER* peritoneum: Metastases (*M*): *pre* estimated distant metastasis before FLEP therapy, *post* actual distant metastasis. *Stage* stage grouping according to UICC: *pre* estimated stage grouping before FLEP therapy, *post* actual stage grouping

Group	No.	Age (years)	Sex	Histological type	Clinical evaluation	No. of involved nodes pre → post	M pre → post	Histological evaluation (grade)	Stage pre → post	Survival time (months)	Recurrence
A	1	57	F	Por1	PR	5/54(M1) → 4/54(N1)	LYM → 0	2	IV → II	49 (alive)	−
	2	73	M	Por1	PR	4/58(M1) → 1/58(N1)	LYM → 0	2	IV → II	64 (alive)	−
	3	42	M	Por1	PR	32/79(M1) → 1/79(N1)	LYM → 0	2	IV → II	67 (alive)	−
	4	58	M	Tub1, Por1	PR	12/50(M1) → 12/50(M1)	LYM → LYM	1a	IV → IV	68 (alive)	+
	5	72	M	Tub1	PR	16/49(M1) → 0/49(N0)	LYM → 0	2	IV → IA	91 (alive)	−
B	6	55	M	Por1, Tub1	PD	21/22(M1) → 21/22(M1)	LYM → LYM	0	IV → IV	0	
	7	26	F	Sig	PR	76/85(M1) → 76/85(M1)	LYM → LYM	1a	IV → IV	2	
	8	57	M	Tub2	PR	3/21(N2) → 3/21(N2)	HEP → HEP	1b	IV → IV	2	
	9	49	F	Sig	PR	60/71(M1) → 60/71(M1)	LYM → LYM	0	IV → IV	3	
	10	64	M	Tub1	NC	7/61(M1) → 7/61(M1)	LYM, HEP → LYM, HEP	1a	IV → IV	3	
	11	53	M	Sig, Tub2	PR	13/99(M1) → 13/99(M1)	LYM → LYM	1a	IV → IV	5	
	12	61	F	Tub1	PR	7/24(N2) → 7/24(N2)	HEP → HEP	0	IV → IV	7	
	13	70	M	Tub1, Small	PR	14/25(M1) → 14/25(M1)	LYM, HEP → LYM, HEP	1a	IV → IV	7	
	14	51	F	Tub2	NC	22/103(M1) → 22/103(M1)	LYM → LYM	1a	IV → IV	8	
	15	38	F	Sig	PR	38/45(M1) → 38/45(M1)	LYM → LYM	1a	IV → IV	8	
	16	72	M	Tub1	PR	15/145(M1) → 15/145(M1)	LYM, HEP → LYM, HEP	0	IV → IV	10	
	17	67	M	Tub1	PR	12/35(M1) → 12/35(M1)	LYM → LYM	0	IV → IV	12	
	18	43	F	Por1	PR	32/62(M1) → 32/62(M1)	LYM, PER → LYM, PER	1b	IV → IV	13	

Age and sex

The ages of the patients in group A ranged from 42 years to 73 years (mean 60.4), while in group B they were aged 26–72 years (mean 54.3). The female-male ratio was 4:1 in group A, and 6:7 in group B.

Histological features (subtypes) of carcinomas in biopsy material before FLEP therapy

In group A, 3 out of 5 (60%) were por1 (Fig. 1), the remaining 2 being por1 partly with tubular formation (Fig. 2) and well differentiated (Fig. 3). In contrast, in group B, 6 out of 13 (46%) were well (tub1) or moderately (tub2) differentiated, the others being 3 signet-ring cell carcinomas (sig), 1 sig + tub2, 1 por1 + tub1, 1 tub1 + small-cell carcinoma, and one por1.

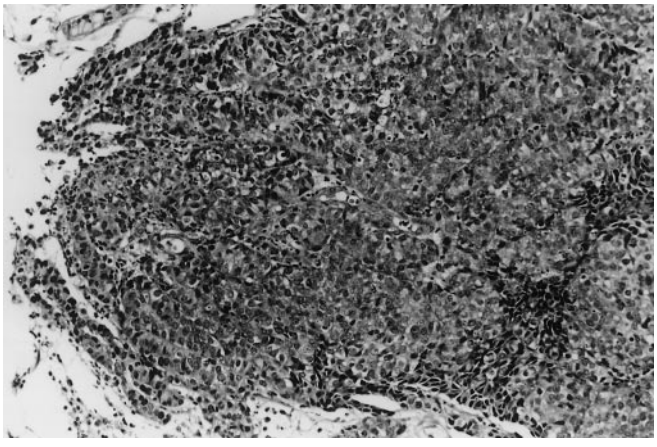

Fig. 1 Histology of case 1 showing solid-type poorly differentiated adenocarcinoma (por1), composed of medullary proliferation of carcinoma cells with no apparent tubular formation and scanty stroma (hematoxylin and eosin, H&E, × 200: biopsy material)

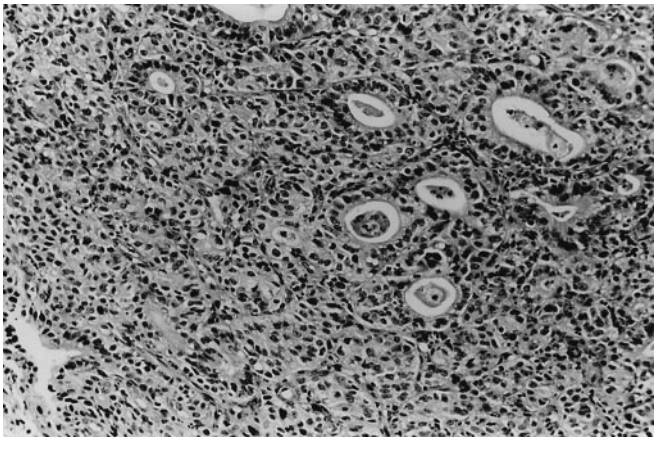

Fig. 2 Histology of case 4 showing por1 with partial tubular formation (H&E, × 200: biopsy material)

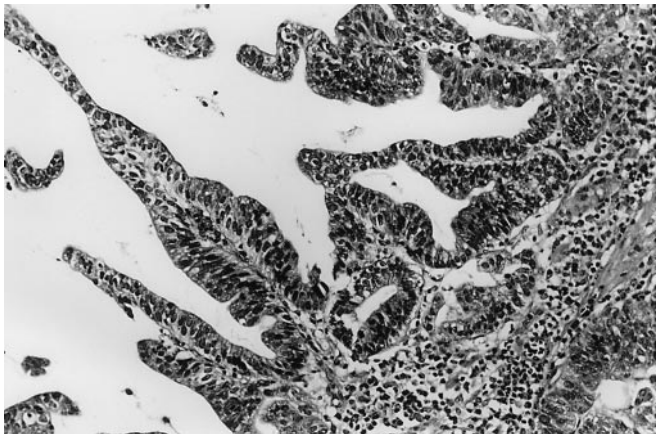

Fig. 3 Histology of case 5 showing well-differentiated adenocarcinoma (tub1) with a tendency toward stratification and micropapillary formation (H&E, × 200: biopsy material)

Clinical evaluation

In group A all the 5 patients were clinically evaluated as showing PR, whereas the 13 in group B comprised 10 PR, 2 NC and 1 PD. Out of the 15 PR patients (5 group A, and 4 group B), 9 were subjected to macroscopically curative gastrectomy with resection of involved organs and extended lymph node dissection including paraaortic nodes. The remaining 9 PR, NC and PD patients in group B underwent palliative gastrectomy. These 9 patients had atleast one unresectable metastatic lesion in various sites such as the paraaorta, the liver or the peritoneum.

Histological effects on involved nodes

In 4 out of 5 cases of group A, complete disappearance of cancer cells from almost all the nodes was observed. In case 3 as illustrated in Fig. 4, for example, 32 out of 79 resected lymph nodes featured remarkable liquefaction necrosis, irregular fibrosis or xanthogranulomatous lesions with a microscopic cancer nest remaining only in 1. No such changes were encountered in the remaining 47 lymph nodes of case 3, which were generally small in size and retained normal structure, therefore being considered metastasis-free from the beginning. A representative low-power microscopical view of a node estimated to have been involved before chemotherapy and a node considered to be cancer-free from the beginning is shown in Fig. 5.

Histological evaluation of chemotherapeutic effects on the primary stomach lesion

Histological changes were far more remarkable in group A cases than in group B, with marked tumor shrinkage and grade 2 histological changes being observed in 4 (80%). A representative histological section of a stom-

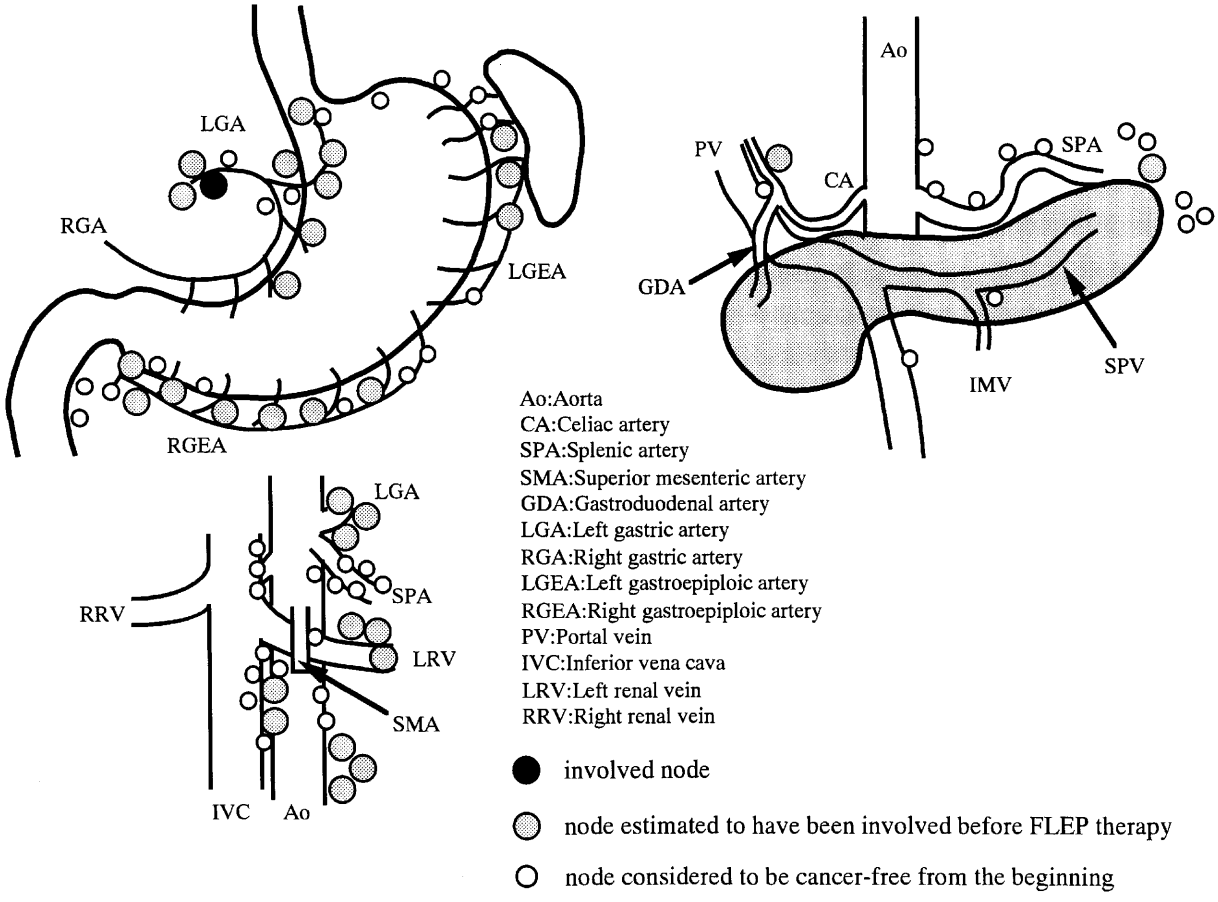

Fig. 4 The distribution of resected nodes in case 3: 32 out of 79 nodes featured histological changes after chemotherapy (◎), with a microscopical cancer nest remaining in one of them (●). No such changes were encountered in the remaining 47 nodes (○)

ach (case 2) is shown in Fig. 6a–c in which residual cancer cells are scarce and present only in the proper muscle layer with stromal fibrosis and xantho-granulomatous changes seen all through the layers.

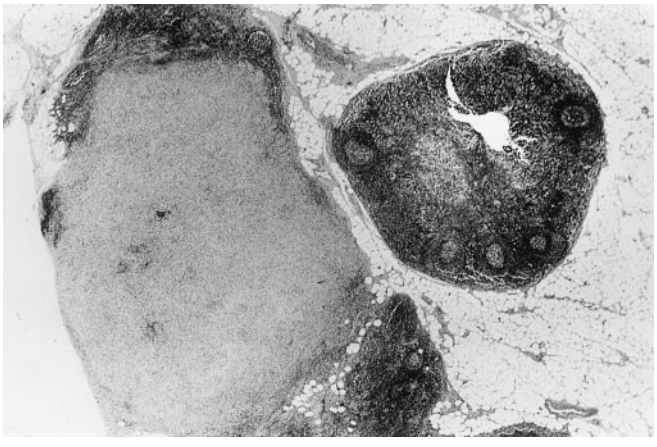

Fig. 5 A low-power microscopical view of a node estimated to have been involved before chemotherapy (*left*) and a node considered to be cancer-free from the beginning (*right*) (H&E, × 20)

Figure 7 shows the estimated extent of the carcinoma before chemotherapy and the distribution of the residual cancer in case 2. In group B, histological changes in all patients were classified as grade 0–1b.

Stage improvement after the chemotherapy

The estimated disease stages before chemotherapy were IV in all the patients subjected to this study. A remarkable stage improvement was seen in 4 out of 5 group A patients: IV → II in 3 and IV → IA in 1. These 4 patients have survived without recurrence for more than 58 months so far. In 1 patient in group A, who showed no improvement (case 4), a recurrence was observed in the Virchow lymph node and the liver 5 years after the treatment. In sharp contrast, no improvement in stage was observed in any group B patients.

Discussion

The present investigation showed that preoperative chemotherapy is distinctly beneficial for certain types of far-advanced gastric carcinomas and that a favorable prognosis can be predicted from the histological appearance of resected material after treatment. To the best of our knowledge, this is the first report docu-

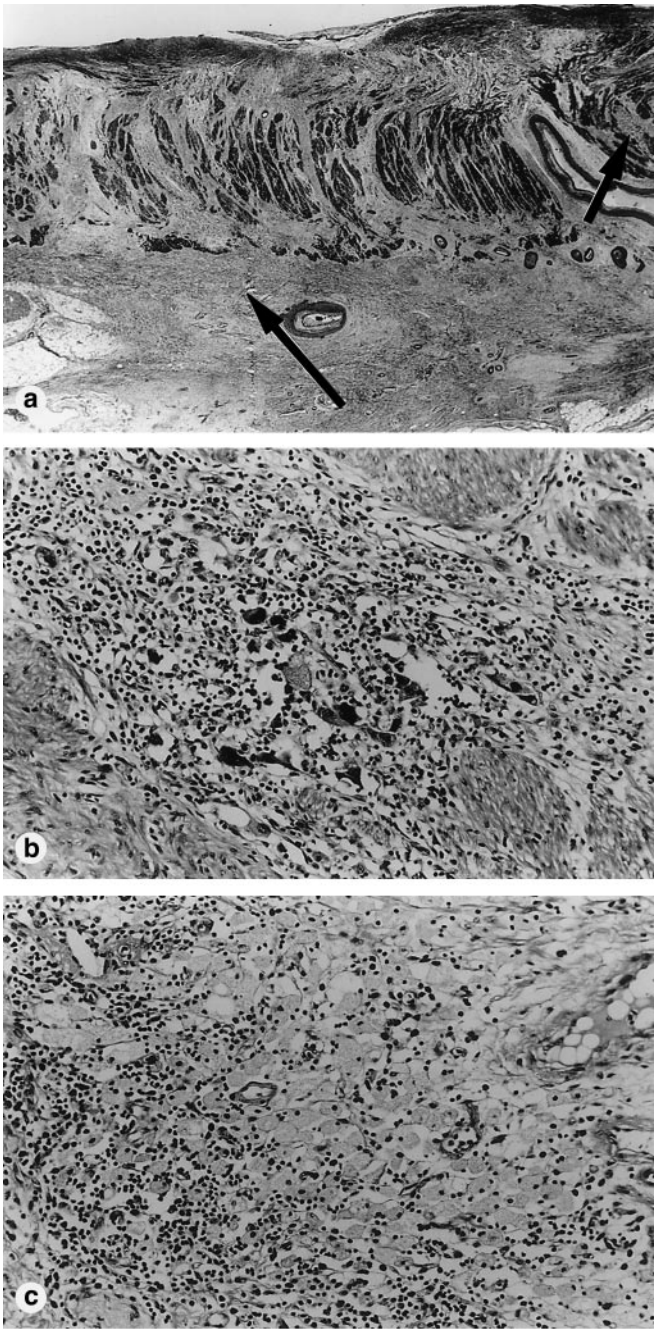

Fig. 6a–c A representative histological section of a gastric carcinoma showing a remarkable chemotherapeutic effect (case 2). **a** Fibrosis and xanthogranulomatous change are visible throughout the gastric wall, separating muscle bundle (stained dark in the photograph) (azan stain, × 12.5). **b** Residual cancer cells in the background of a granulomatous reaction (*short arrow* in **a**) with marked degeneration (H&E, × 100). **c** A portion showing only aggregates of foamy histiocytes observed through the gastric wall (*long arrow* in **a**) (H&E, × 100)

menting far-advanced gastric carcinoma cases with long-term survival probably cured by preoperative chemotherapy and surgery, with precise histological examination of the resected material to confirm the remarkable efficacy. Most previous studies on the usefulness of preoperative chemotherapy for far-advanced gastric carcinomas (Rougier et al. 1994; Ajani et al. 1995; Yonemura et al. 1993; Wilke et al. 1989; Stephens et al. 1986) were limited to efforts to correlate any clinically observed reduction of tumor burden or debulking with the prolongation of the survival period.

It is generally not a simple task to estimate the precise extent of a preexisting carcinoma after chemotherapy. According to the criteria of Japanese Research Society for Gastric Cancer, the xanthogranuloma, especially aggregation of foamy histiocytes, is the most convincing histological manifestation. In the present study, we confirmed this by observing degenerated cancer cells scattered in xanthogranulomatous lesions and the absence of such lesions in apparently cancer-free sites in the resected stomach or lymph nodes. Fibrosis was considered a positive indication only when it was irregular, in outline and orientation, and accompanied by disruption of the normal structures of the gastric wall, which is often observed in advanced gastric cancer but not in a benign ulcer. As pointed out before (Kiyabu et al. 1992), the histological changes should be distributed in a pattern similar to that of neoplastic infiltration into the gastric wall.

A similar quantitative study to ours was conducted on stage IV gastric cancers resected after chemotherapy (Yonemura et al. 1996). The study concluded that histological responders with grade 1a–3 histological changes survived significantly longer than non-responders with grade 0 effects. In our study, a grade 2 effect was needed for favorable prognosis and no significant prolongation of life was observed with grade 1a or 1b.

It is noteworthy that, in 4 patients belonging to group A, cancer cells almost completely disappeared from metastasized lymph nodes, leaving fibrosis and/or xanthogranulomatous changes. The remaining cancer cells were all degenerative and considered to be nonviable. In these patients, some metastasized lymph nodes along the celiac axis and abdominal aorta might not have been removed during the macroscopically curative operation and any cancer cells presumably also disappeared from these nodes left in the body, because these patients have survived cancer-free for 4–8 years so far. However, survival for several more years is required to confirm a complete cure because, as seen in case 4, cancer recurrence may occasionally occur after more than 5 years. Even if such a late recurrence happens, it would not detract from the remarkably favorable results of the preoperative chemotherapy seen in this study.

Concerning the histological subtype, 3 of 5 cancers in group A were por1 whereas only 1 por1 lesion was seen in the group B. Thus a patient with por1 may be a good candidate for chemotherapy. The only por1 case in group B (case 18) also showed a fairly good response, both clinically and histologically, attaining the longest survival time of 13 months for group B patients. This patient had peritoneal dissemination at the time of

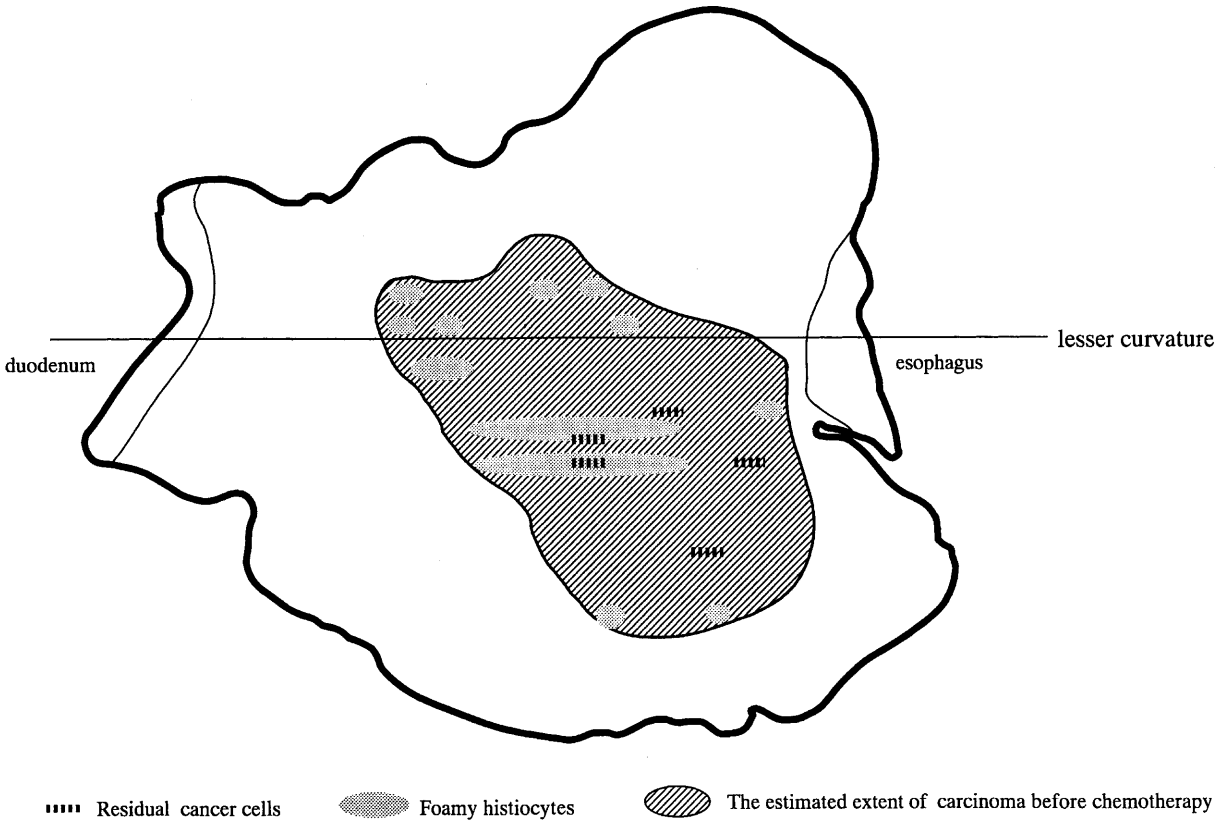

Fig. 7 Schematic illustration of the resected stomach in case 2 showing the estimated extent of the carcinoma and the distribution of residual cancer cells

operation, which appeared to be a factor indicating an unfavorable prognosis, as previously proposed by one of the present authors (Nakajima et al. 1997). On the other hand, we should not overlook the fact that one tub1 (case 5) of group A was also remarkably sensitive to chemotherapy and had a good prognosis. This tub1 carcinoma exhibited some unique morphological features including a tendency toward stratification and micropapillary formation in the lining of the tubular structures (Fig. 3). Apparently certain types of tubular carcinomas of the stomach are highly chemosensitive. In the future, we should be able to distinguish chemosensitive tub1 carcinomas clearly from their non-sensitive counterparts, by increasing use of genetic and biochemical information in combination with histopathological experience.

The establishment of predictive markers for chemosensitivity is not only important for encouraging aggressive chemotherapy but also to avoid needless harm to patients having chemoresistant tumors. Thus, if recurrence is noted in any of the 4 particularly sensitive cases in group A, another FLEP regimen might be considered as a second-line chemotherapy. Since the 3 signet-ring carcinomas in group B did not show any recognizable response, this type of gastric carcinoma may be distinctly chemoresistant, especially to the FLEP regimen, and such chemotherapy should be avoided.

Though our study was small, and further work is needed, it provided histological evidence of chemotherapeutic effects, and chemo-responders should be selected on the basis of such histological evidence, which must be obtained by detailed histological examination not only on the primary lesion but also on the metastatic site.

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