Tumor Infiltrative Pattern Predicts Sites of Recurrence after Curative Gastrectomy for Stage II/III Gastric Cancer

Short title: Infiltration and recurrence of gastric cancer

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Synopsis

The tumor infiltrative pattern is useful for predicting sites of recurrence after patients with

stage II/III gastric cancer undergo surgery with curative intent.

ABSTRACT

Background. The tumor infiltrative pattern (INF) has been routinely evaluated by hematoxylin and eosin stained sections as a pathological characteristic of surgically resected specimens in East Asia.

Methods. Infiltrative pattern of gastric cancer (GC) has been histopathologically classified into INF types a, b, and c according to the Japanese Classification of Gastric Carcinoma. The prognostic value and characteristics of the pattern of disease recurrence for each INF type were assessed in 785 patients with various stages of GC, and also in 243 patients with stage II/III GC.

Results. Comparison of overall survival of patients independent of stage revealed that INF was significantly associated with prognosis. Specifically, peritoneal metastasis was present in 91% of stage IV patients in the INFc group, whereas hepatic metastasis was present in 39% of stage IV patients in the INFa/b. INF was not significantly associated with survival after curative gastrectomy of patients with stage II/III GC. Prevalence of peritoneal recurrence was significantly higher in the INFc group compared with that of the INFa/b group, whereas prevalence of hepatic recurrence was significantly higher in the INFa/b group compared with that of the INFc group. Multivariate analysis identified INFc as an independent risk factor for peritoneal recurrence after curative gastrectomy. The association of the INF type with the incidence of peritoneal recurrence was observed with all disease stages regardless of whether

the patient was given adjuvant chemotherapy.

Conclusions. Evaluation of the INF type shows promise as a predictor of postoperative sites

of recurrence in patients with GC.

Gastric cancer (GC) is the second leading cause of cancer related deaths worldwide.[1,2] Although the prevalence of the disease is gradually declining, it remains a major health problem.[3] Because the prognoses of patients with stage II/III GC are highly variable, management of their disease will likely benefit from accurate risk stratification.[4,5] For example, after complete curative resection, there is great variability among the outcomes of patients with stage II/III GC depending on distant recurrences.[6] Standardization of adjuvant chemotherapy such as S-1 monotherapy as well as capecitabine combined with oxaliplatin confers some, although insufficient, survival benefit.[7,8] Accordingly, prediction of sites of recurrence may be useful for postoperative monitoring, patient stratification, and selection of adjuvant therapy.

Treatment of GC has historically faced the challenge of combating recurrences. For example, after curative surgery, patients with advanced disease often develop recurrences to the peritoneum, liver, lymph nodes, or other organs, and peritoneal recurrence is the most frequent.[4,9-12] The macroscopic type (Borrmann classification), whether the tumor is intestinal or diffuse (Lauren classification), and serosal invasion are known as risk factors for peritoneal dissemination.[13,14] The tumor infiltrative pattern (INF) is defined in the Japanese Classification of Gastric Carcinoma, categorizing GC into expansive growth type, infiltrative growth type and intermediate type.[15] INF has been routinely evaluated as a pathological characteristic of surgically resected specimens in East Asia. Although INF can be easily

determined by hematoxylin and eosin stained sections and utilized without specialized

training, it has not gained widespread use in the clinic and there are few recent reports on the

predictive value of INF regarding outcome of GC.[16-18]

To address this issue, we evaluated the clinical significance of INF, particularly in patients

with stage II/III GC, to identify predictors of the sites of recurrence after curative

gastrectomy.

PATIENTS AND METHODS

Patients' characteristics

Between January 1999 and May 2015, 785 patients with GC were treated by surgery without

preoperative treatment at the Department of Gastroenterological Surgery, Nagoya University.

All resected specimen were histopathologically evaluated and classified according to the

Japanese Classification of Gastric Carcinoma which includes evaluation of the INF type. Of

these, 243 were diagnosed with stage II/III disease according to the TNM Classification of

Malignant Tumours, 7th Edition.[19] Data for clinicopathological characteristics and

postoperative course were retrieved from the prospective database. This study conforms to the

ethical guidelines of the World Medical Association Declaration of Helsinki–Ethical

Principles for Medical Research Involving Human Subjects. Written informed consent for

surgery and use of clinical data was obtained from all patients as required by the Review

Board of Nagoya University.

Pathological evaluation

Patients' histopathological features were determined by analyzing paraffin sections stained

with hematoxylin and eosin. Two expert pathologists reviewed the sections to confirm the

diagnosis. The INF type was determined strictly according to the Japanese Classification of

Gastric Carcinoma and classified as follows: INFa, expansive growth with a distinct border

with the surrounding tissues; INFb, intermediate between INFa and INFc; and INFc,

infiltrative growth without a distinct border with the surrounding tissues (Fig. 1).[15]

Clinical significance of INF

We first assessed the prognostic value of the INF type and distribution of the metastatic sites

for all disease stages. Next, we focused on patients with stage II/III GC and evaluated their

postoperative outcomes and recurrence patterns associated with the INF type. Further,

subgroup analyses were performed according to the TNM stage and whether the patients

received postoperative adjuvant chemotherapy.

Patient management

Patients with stage II/III GC underwent gastrectomy with $\geqq$ D2 lymphadenectomy according

to the Japanese Gastric Cancer Treatment Guidelines. Since 2007, adjuvant chemotherapy

with S-1 (an oral fluoropyrimidine derivative) was administered to all patients unless

contraindicated by a patient's condition.[7] The treating strategy after recurrence was decided at

the discretion of physicians. Patients received a postoperative follow-up that included a

physical examination, laboratory tests, and postcontrast computed tomography of the chest

and abdominal cavity at least once every 6 months for 5 years or until death.

Statistical analysis

The χ^2 and Mann–Whitney tests were used to compare two groups. Overall and disease-free

survival rates were calculated using the Kaplan–Meier method, and the difference between

survival curves was evaluated using the log-rank test. Risk factors for positive peritoneal

lavage cytology were evaluated using binomial logistic regression analysis. $P < 0.05$ was

considered statistically significant. All statistical analyses were performed using JMP 10

software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Clinical significance of INF in patients with stage I-IV GC

When we compared postoperative overall survival according to the INF type among all

patients, the INFc type was associated with the most unfavorable prognosis (Fig. 2a). The

distribution of the disease stages of each INF group is shown in Fig. 2b. Most patients with

INFa type had stage I GC whereas the INFc type was observed across all stages. The

incidence of peritoneal metastasis in Stage IV GC with the INFc type was 91% while hepatic

metastasis was observed only in 5%. In contrast, hepatic metastasis was observed in 39% of

stage IV patients with the INFa/b type (Fig. 2c).

Association between INF and recurrence patterns in Stage II/III GC

To evaluate the association of the INF type with postoperative recurrence patterns after

curative gastrectomy, we focused on patients with stage II/III GC and classified them

according to the Japanese Classification of Gastric Carcinoma as follows: INFa, $n = 10$; INFb,

$n = 134$; and INFc, $n = 99$. We next compared various clinicopathologic factors between

patients with the INFa/b type ($n = 144$) and those with the INFc type ($n = 99$). INFc was

significantly associated with younger age, female sex, Borrmann type 4/5, undifferentiated

phenotype, and less venous invasion (Table 1). Borrmann type 4/5 was relatively rare and

accounted for only 12% even in the INFc type. In contrast, undifferentiated tumors were

present in 89% of the INFc type. The INF type was not significantly associated with

disease-free or overall survival after curative gastrectomy (Supplementary Fig. 1a, b). The

overall recurrence rates of the INFa/b and INFc types were equivalent.

   The peritoneum was the most frequent site of recurrence in the INFc type and was

significantly more commonly observed in the INFc type than in the INFa/b types (Fig. 3a). In

contrast, hepatic recurrence was more frequent in the INFa/b types (Fig. 3a). Reflecting these

results, the cumulative peritoneal recurrence rate was significantly higher in the INFc type

compared with the INFa/b type (Fig. 3b). Univariate analysis identified tumors ≥50 mm,

Borrmann type 4/5 tumor, pT4, INFc, and TNM stage III as significant risk factors for

peritoneal recurrence. Multivariate analysis identified tumors ≥50 mm and INFc as

independent risk factors for peritoneal recurrence after curative gastrectomy (odds ratio, 2.31;

95% confidence interval, 1.02–5.39; $P = 0.045$) (Table 2). The INFa/b types were more likely

to develop hepatic recurrence compared with the INFc type (Fig. 3c).

Subgroup analyses according to TNM stage and adjuvant chemotherapy

We conducted subgroup analyses to explore further the clinical significance of the INF type in

patients with stage II/III GC. The associations of INF with the incidence of peritoneal

recurrences were similar for patients in stages II and III (Supplementary Fig. 2). There were

123 patients who received adjuvant chemotherapy with fluorouracil (5-FU) based drugs (S-1

for 111 patients, uracil-tegafur for 8 and 5-FU for 4). The peritoneal recurrence rate was

persistent exclusively in the INFc group, though the overall incidence of peritoneal

recurrences was decreased by adjuvant therapy (Supplementary Fig. 3). On the other hand,

adjuvant chemotherapy had little impact on hepatic recurrences regardless of the INF types

(Supplementary FIG. 4).

DISCUSSION

Since the initial report that the INFc type is associated with poor prognosis in patients with pT3 GC, INF has been devoted less attention in clinical practice.[16-18,20,21] One explanation is that the INF type is considered less important as a predictor of prognosis than the macroscopic type or the Lauren classification.[20,21] Our present findings are consistent with those of others, because although the INF type reflected prognosis among all patients, there was no difference in survival according to the INF type when stage-by-stage comparisons were made. In contrast, there was a distinct difference in metastatic sites between the INFa/b and INFc groups, indicated that the INF type is more useful in predicting sites of metastasis and recurrence.

To test our hypothesis, we focused on the correlation between the type of recurrence and the INF type in patients with stage II/III GC.[5,22,23] Although the survival curves for overall and disease-free survival of the INFa/b and INFc groups overlapped, the INF type was strikingly associated with recurrence patterns and were able to identify patients at risk for both peritoneal (INFc) and hepatic recurrence (INFa/b). Interestingly, INFc was identified as an independent predictive factor for peritoneal recurrences whereas macroscopic type, tumor differentiation, or tumor depth as were not. These findings emphasize the importance of INF

as a predictor of recurrence pattern. We suggest therefore that expansive tumor growth is associated with venous involvement and the release of cancer cells into the circulation (hematogenous metastasis), while GC with infiltrative growth pattern may allow cancer cells to penetrate through the gastric wall and to be shed into the abdominal cavity.

We suspected that the differences in the predictive value of INF for recurrence patterns may have been influenced by disease stage and adjuvant chemotherapy.[18,21,24] subgroup analyses in the current study revealed that the INFa/b type and the INFc type were associated with hepatic and peritoneal recurrence, respectively, even when patients were subdivided according to the TNM stage. We recently reported that several of the known prognostic factors lost clinical relevance and recurrence patterns changed significantly and peritoneal recurrence is decreased after administration of S-1 adjuvant therapy to patients with stage II/III GC.[25] In the current study, the peritoneal recurrence rate was persistent in the INFc group, whereas the incidence of peritoneal recurrences was decreased in the INFa/b by adjuvant therapy, indicating that the INF type may be useful for identification of patient with GC refractory to adjuvant chemotherapy with 5-FU based drugs.

Taken together, our findings indicate that the pathological evaluation of the INF type in surgically resected tissues is useful in the management of patients with stage II/III GC in that postoperative disease monitoring and therapeutic strategies could be focused to deal with the recurrence pattern predicted by the INF type. Limitation of the study is the retrospective

nature and relatively small number of patients evaluated. In addition, INF cannot be evaluated using biopsy specimens, and therefore cannot be used to select the strategy to be delivered preoperatively. In addition, immunohistochemical analysis of several molecules related with the biology of cancer could be included in future studies to gain a better understanding of the molecular mechanisms that generate the different phenotypes of each INF type as perceived by morphological examination with the conventional hematoxylin and eosin staining.[26,27] Nevertheless, evaluation of the INF type shows promise as a predictor of postoperative sites of recurrence in patients even when they had stage II/III GC and received postoperative adjuvant chemotherapy.

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Figure Legends

FIG. 1 Representative hematoxylin and eosin staining patterns of samples of each tumor

infiltrating growth (INF). (a) INFa, (b) INFb, and (c) INFc. Arrows indicated vessel invasion.

Magnification ×100.

FIG. 2 a Overall survival associated with the tumor infiltrative pattern (INF). **b** Distribution

of disease stages of each INF group. **c** Metastatic sites of stage-IV patients in the INFa/b and

INFc groups.

FIG. 3 a Frequencies of the sites of initial recurrence in the INFa/b and INFc groups. **b**

Cumulative incidence of peritoneal recurrence. **c** The INFa/b group tended to experience more

frequent hepatic recurrences compared with the INFc group. INF, tumor infiltrative pattern.

Supplementary FIG. 1 Survival analyses and recurrence patterns of 243 patients with stage

II/III gastric cancer. Patients in the INFa/b and INFc groups had similar **a** overall and **b**

disease-free survival after curative gastrectomy. INF, tumor infiltrative pattern.

Supplementary FIG. 2 Subgroup analysis of the impact of the tumor infiltrative pattern (INF) on the cumulative incidence of peritoneal recurrence according to TNM stage.

Supplementary FIG. 3 The cumulative incidence of peritoneal recurrence of subgroups categorized according to administration of adjuvant chemotherapy. INF, tumor infiltrative pattern.

Supplementary FIG. 4 The cumulative incidence of hepatic recurrence of subgroups categorized according to administration of adjuvant chemotherapy. INF, tumor infiltrative pattern.

TABLE 1. Association between infiltrative type growth and clinicopathological characteristics of 243 patients with stage II/III gastric cancer

Variables	INF a/b	INF c	*P* value
Age			
< 65 years	47	62	<0.001
≥ 65 years	97	37	
Sex			
Male	114	65	0.020
Female	30	34	
CEA (ng/ml)			
≤ 5	116	87	0.125
> 5	28	12	
CA19-9 (IU/ml)			
≤ 37	118	87	0.205
> 37	26	12	
Tumor location			
Entire	3	5	
Upper third	38	22	0.507
Middle third	51	39	
Lower third	52	33	
Tumor size (mm)			
< 50	72	41	0.126
≥ 50	68	58	
Macroscopic type			
Others	141	87	0.001
Borrmann type 4/5	3	12	
Multifocal lesions			
Absent	134	98	0.029
Present	10	1	
Tumor depth (UICC)			
pT1	12	3	
pT2	26	12	0.004
pT3	57	28	
pT4	49	56	
Differentiation			
Differentiated	77	11	<0.001
Undifferentiated	67	88	
Lymphatic involvement			0.696

ly 0	11	9	
ly 1	54	35	
ly 2	60	37	
ly 3	19	18	
Vessel invasion			
v 0	58	60	
v 1	55	31	0.005
v 2	27	7	
v 3	4	1	
Lymph node metastasis			
Absent	29	27	0.197
Present	115	72	
UICC stage			
II	75	46	0.389
III	69	53	

INF, tumor infiltrative pattern; CEA, carcinoembryonic antigen; CA19-9, carbohydrate
antigen 19-9; UICC, Union for International Cancer Control.

TABLE 2. Predictive factors of peritoneal recurrence of 243 patients with stage II/III gastric cancer

Variables		P-rec (-)	P-rec (+)	Univariate P value	Multivariate OR	95%CI	P value
Age	< 65 years	89	20	0.115			
	≥ 65 years	119	15				
Sex	Male	152	27	0.609			
	Female	56	8				
CEA	≤ 5 ng/ml	176	27	0.288			
	> 5 ng/ml	32	8				
CA19-9	≤ 37 IU/ml	176	29	0.793			
	> 37 IU/ml	32	6				
Tumor location	Lower third	74	11	0.632			
	Others	134	24				
Tumor size	< 50 mm	110	7	<0.001	2.91	1.20 - 7.83	0.017*
	≥ 50 mm	98	28				
Macroscopic type	Others	200	28	0.002	2.56	0.76 - 8.49	0.128
	Borrmann 4/5	8	7				
Multifocal lesions	Absent	198	34	0.587			
	Present	10	1				
Tumor depth	pT1-3	128	10	<0.001	1.95	0.80 - 4.93	0.143
	pT4	80	25				
Differentiation	Differentiated	130	25	0.302			
	Undifferentiated	78	10				
Lymphatic involvement	Absent	19	1	0.160			
	Present	189	34				
Vessel invasion	Absent	103	15	0.465			
	Present	105	20				
Infiltrative growth	INF a/b	132	12	0.001	2.31	1.02 - 5.39	0.045*
	INF c	76	23				
Lymph node metastasis	Absent	50	6	0.357			
	Present	158	29				
UICC stage	II	112	9	0.002	2.05	0.84 - 5.26	0.115
	III	96	26				
Adjuvant chemotherapy	Absent	101	19	0.531			
	Present	107	16				

*Statistically significant in multivariate analysis ($P < 0.05$). OR, odds ratio; CI, confidence

interval; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; INF, tumor infiltrative pattern; UICC, Union for International Cancer Control.
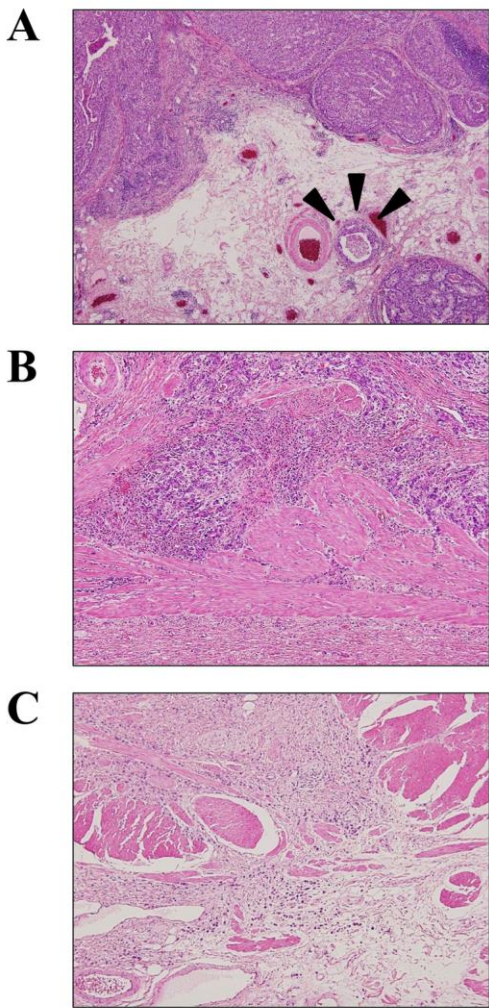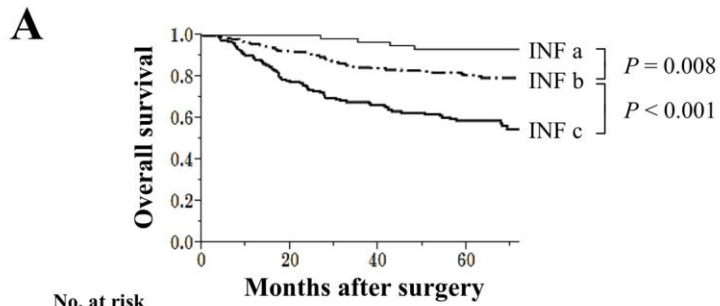
FIG 1

FIG 2

A

Overall survival

INF a
INF b   *P* = 0.008
INF c   *P* < 0.001

Months after surgery

No. at risk				
INF a	84	68	57	44
INF b	450	293	219	170
INF c	251	142	107	74

B

□ Stage I
▨ Stage II
▧ Stage III
■ Stage IV

INF a   INF b   INF c

C

INF a/b   INF c

□ P
■ P/H
▨ H
□ Others

FIG 3

Supplemental FIG 1

A

Overall survival

INF a/b

INF c

NS

Months after surgery

No. at risk

INF a/b	144	101	65	48
INF c	99	73	57	37

B

Disease-free survival

INF a/b

INF c

NS

Months after surgery

No. at risk

INF a/b	144	85	63	47
INF c	99	66	48	35
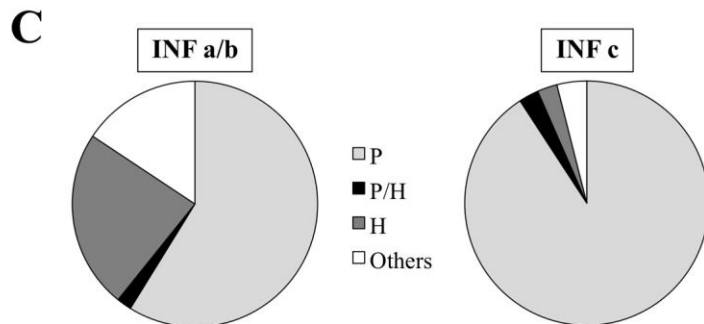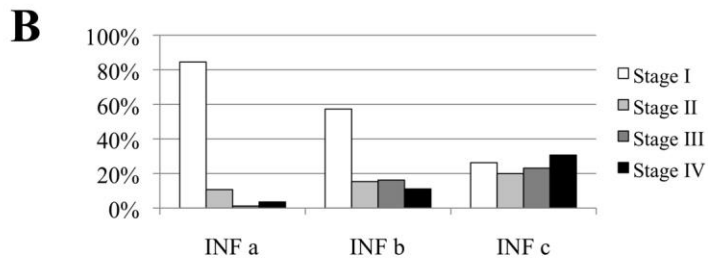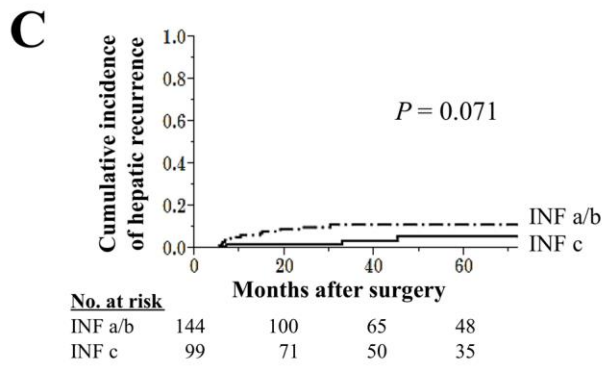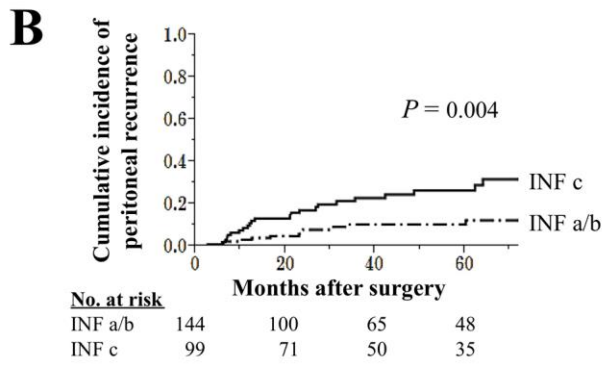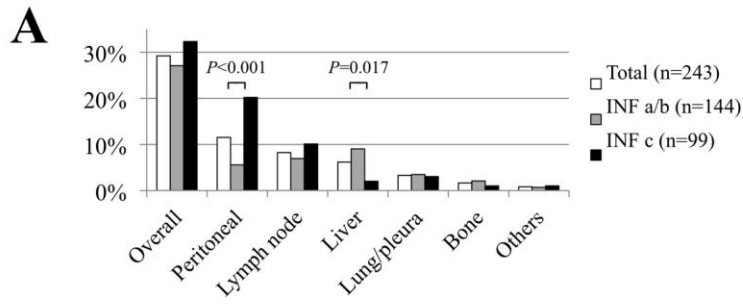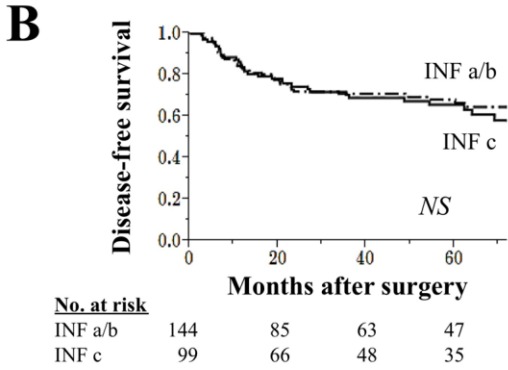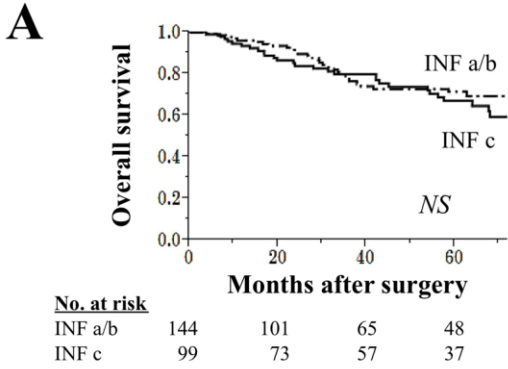
Supplemental FIG 2

Stage II

Cumulative incidence of peritoneal recurrence

$P = 0.355$

INF c
INF a/b

Months after surgery
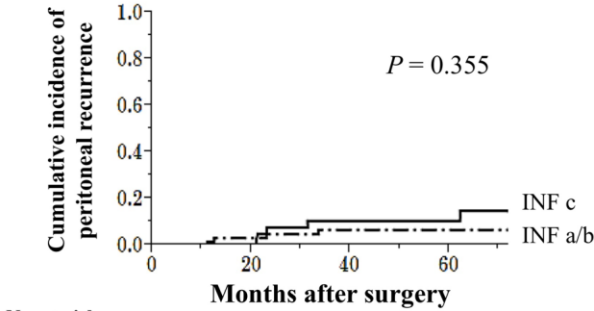
No. at risk
INF a/b   75   60   41   32
INF c   46   43   31   25

Stage III

Cumulative incidence of peritoneal recurrence

$P = 0.008$

INF c

INF a/b
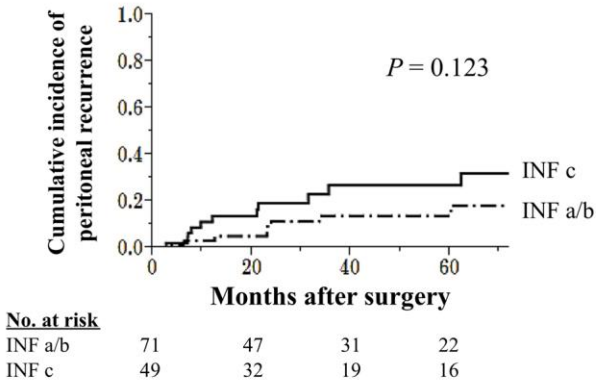
Months after surgery
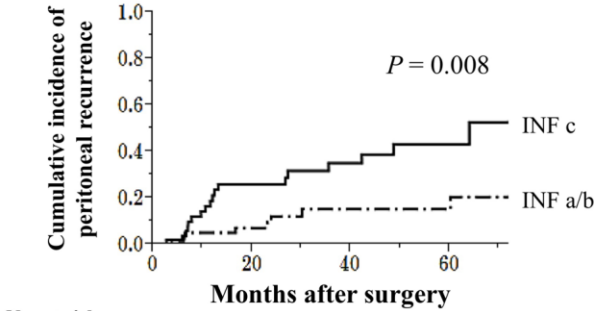
No. at risk
INF a/b   69   41   25   17
INF c   53   29   20   11

Supplemental FIG 3

Surgery alone

Cumulative incidence of peritoneal recurrence

$P = 0.123$

INF c

INF a/b

Months after surgery

No. at risk

INF a/b	71	47	31	22
INF c	49	32	19	16

Adjuvant chemotherapy

Cumulative incidence of peritoneal recurrence

$P = 0.008$

INF c

INF a/b

Months after surgery

No. at risk

INF a/b	73	45	35	27
INF c	50	40	32	20
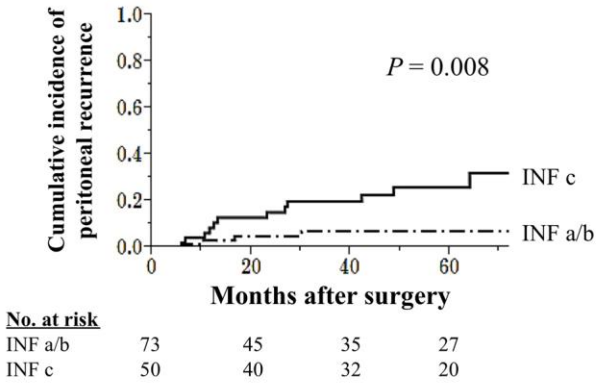
Supplemental FIG 4

Surgery alone

Cumulative incidence of hepatic recurrence vs. Months after surgery

$P = 0.227$
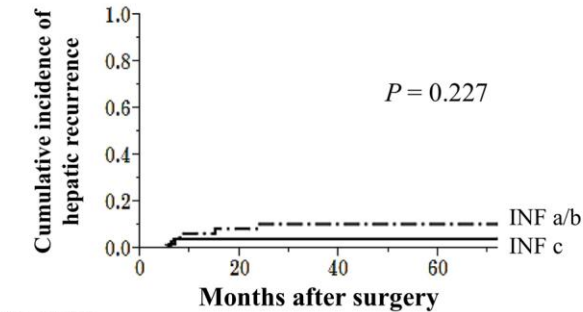
INF a/b
INF c

No. at risk

INF a/b	71	45	30	22
INF c	49	33	23	17

Adjuvant chemotherapy

Cumulative incidence of hepatic recurrence vs. Months after surgery

$P = 0.173$
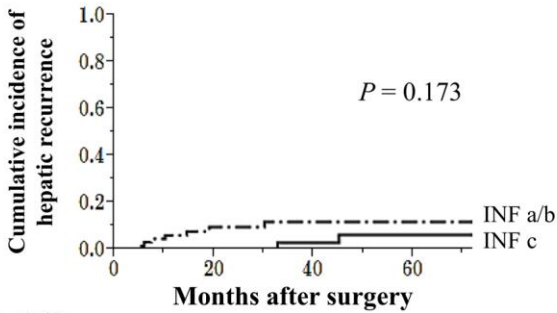
INF a/b
INF c

No. at risk

INF a/b	73	51	35	27
INF c	50	41	35	21