Acta Medica et Biologica
Vol. 33, No. 1, 19-34, 1985

HISTOLOGIC ANALYSIS OF VENOUS INVASION IN COLORECTAL CARCINOMAS IN RELATION TO HEMATOGENOUS METASTASES

MUTSUO YAMAMOTO

Department of Surgery Niigata University
(Director: Professor Terukazu Muto)

(Received December 24, 1984)

INTRODUCTION

Hematogenous metastases have long been one of the most difficult problems in the treatment of colorectal carcinomas; it was reported that 18% of these carcinomas had liver metastases at the time of initial operation (Oxley et al., 1976)[1] and that 14.5% had metachronous pulmonary metastases (Schulten et al., 1976).[2] In a series of investigation conducted in Japan, 12.5% (735/5,890) of colorectal carcinomas had liver metastases at the time of initial operation and 4.2% (100/2,353) had pulmonary metastases according to the report by the Japanese Research Society for Cancer of Colon and Rectum (1982).[3] Welch et al. (1978)[4] reported that only 76.2% of 1,566 colorectal carcinomas had been curatively resected. Fortner et al. (1984)[5] reported that 50% of 120,000 colorectal carcinomas had generated recurrence and over 50% of such recurrence had been liver metastases. Tsuchiya (1982)[6] expressed that 80% of colorectal carcinomas with metachronous hepatic metastases already had microscopic hepatic metastases at the time of initial operation. At the present time, having achieved almost full development of surgical treatments, early diagnosis of primary lesions and prevention of recurrence are required most for the improvement of the prognosis of patients with colorectal carcinoma. The fact that the potential of hematogenous metastases was well correlated with venous invasion at primary sites has been accepted by many researchers. Venous invasion is only a factor in everything that seems to affect the mechanism of hematogenous metastases, and is demonstrated in specimens of colorectal carcinomas as "intravasation" and "intravenous embolization" reported by Nishi et al. (1962).[7] In the work of Brown and Warren (1938),[8] the incidence of venous invasion in 165 rectal carcinomas was 61%. Since this report, a considerable number of reports on venous

invasion have been published. The incidence of venous invasion has ranged between 20% (Seefeld et al., 1943) and 52% (Talbot et al., 1981).[9-13]

The fluctuation of this rate might be caused by the different methods for pathologic examination. In our previous studies, the incidence of venous invasion examined in three longitudinal sections with elastic tissue stain was 78.8%. This procedure was recommended by Konishi et al. (1982)[14] as a reliable method, but not adequate to predict hematogenous metastases because the incidence of venous invasion thus demonstrated is too high to evaluate. The purpose of this study is to evaluate the mechanism of hematogenous metastases on the basis of detailed analysis of venous invasion at the primary sites of colorectal carcinomas. It is expected that active adjuvant chemotherapy or other methods used on the high-risk patients will be effective in preventing hematogenous metastases.

Materials and Methods

One hundred and fifty-six patients with primary colorectal carcinoma (76 with rectal carcinoma and 80 with colonic carcinoma) with complete histologic examination and clinical follow-up were selected for the present analysis. These patients consisted of 87 (55.8%) males and 69 (44.2%) females, with age ranging from 25 to 83 years, 59.9 years in avarage (Table 1), and were divided into 3 groups: 102 patients (group A : metastasis-free group) living over 3 years after surgery without recurrence; 26 (group B) with metachronous hematogenous metastases; and 28 (group C) with synchronous hematogenous metastases. Patients with more than two primary lesions and those with indistinct or other principal patterns of recurrence were excluded from this study. For histologic analysis on specimens resected from 156 patients, 3 longitudinal sections from each lesion were examined by elastic tissue stain (Figs. 1 and 2). Each section of the lesions was divided into four subsections of proximal outer (PO), proximal inner (PI), distal inner (DI) and distal outer (DO) regions as indicated in Fig. 3. Each subsection was further divided into three layers (submucosa, muscular layer and subserosa). Location and size (the maximum length of the short axis of an elastic tissue ring being indicative of venous wall) of invaded veins were individually recorded (Fig. 2). Uncertain involvement of veins was judged as "negative".

Table 1. Sex and Average Age

Group	Total No. Cases	Male (%)	Female (%)	Average Age
A	102	53(52.0)	49(48.0)	59.9
B	26	19(73.1)	7(26.9)	59.3
C	28	15(53.6)	13(46.4)	60.7
Total	156	87(55.8)	69(44.2)	59.9

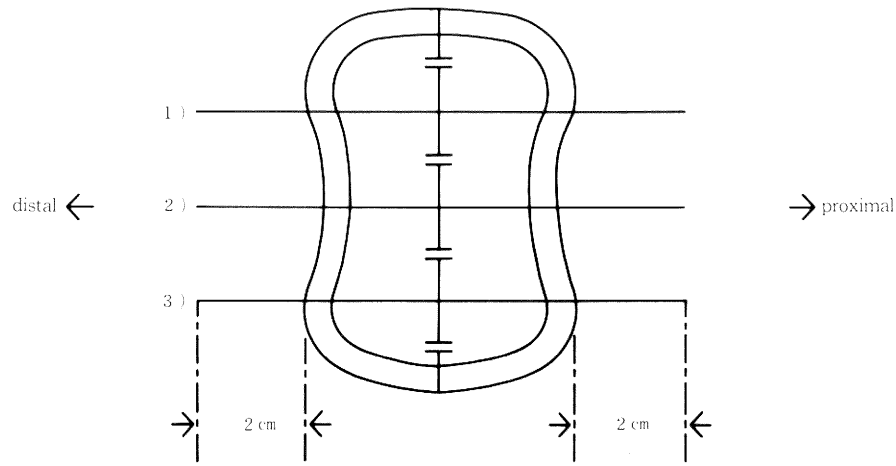

Fig. 1. Three longitudinal sections are taken from primary lesion, each including peripheral intact portions over 2 cm of length.

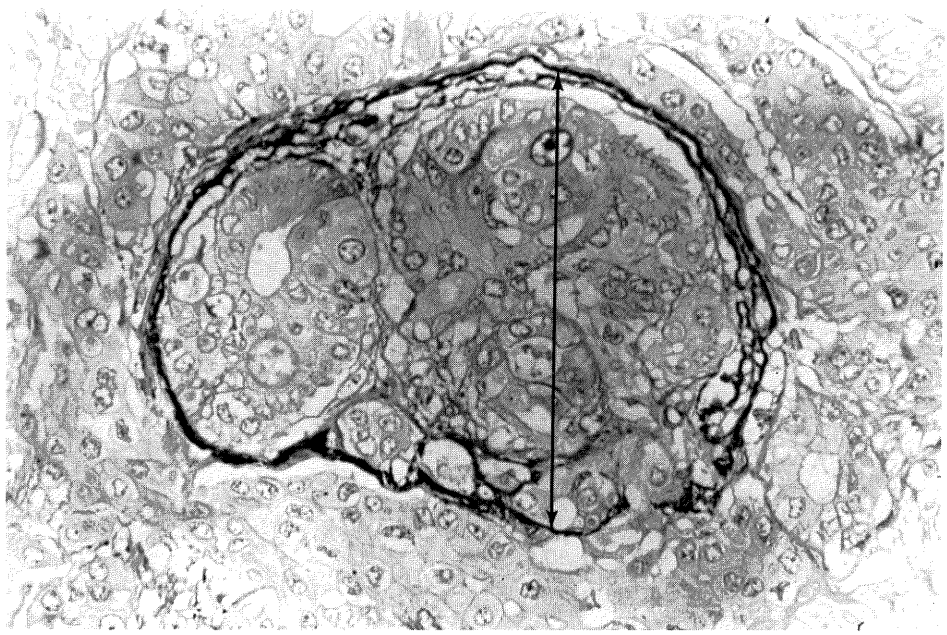

Fig. 2. Venous invasion is well indicated by elastic tissue stain (Van Gieson); the venule involved is otherwise not demonstrated. The arrow shows the maximum length of short axis of the venule as representing the size of invaded vein. × 400.

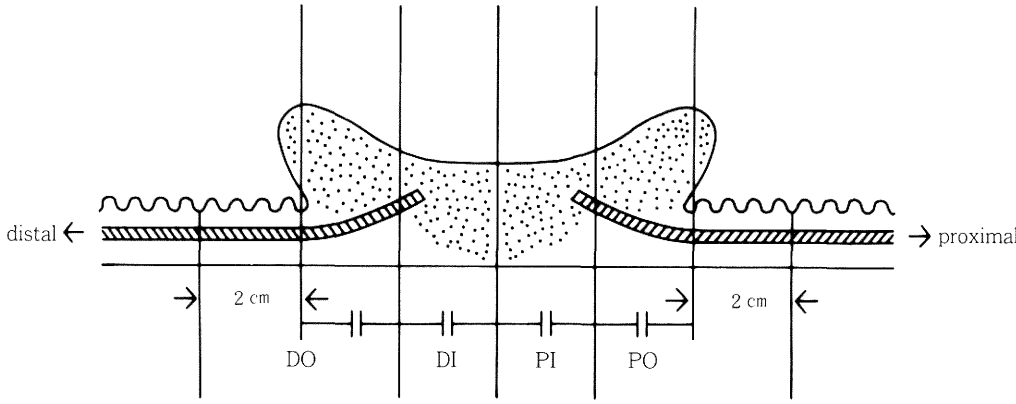

Fig. 3. Each longitudinal section is divided into four subsections (PO, PI, DI and DO), outer subsections including peripheral intact portions over 2 cm of length.

RESULTS

1. Basic Observation (Tables 2, 3, 4 and 5):

The depth of carcinomatous invasion shown in Table 2 was progressive with development of hematogenous metastases and no case with intramural invasion was seen in group C. There was little difference among the distribution of histologic types in the three groups and well-differentiated adenocarcinoma dominated in each group (Table 3). Each lesion was classified by Dukes' Classification and advanced carcinomas were increased parallel with the development of hematogenous metastases. The incidence of lesions in the Dukes' C Class was as follows; 37.3% in group A, 69.2% in B and 78.6% in C (Table 4).

Table 5 shows principal organs with hematogenous metastases in groups B and C. Liver metastases had a prominent incidence in both groups, 69.2% and 89.3%, respectively.

2. Incidence of Venous Invasion (Table 6):

Venous invasion was found in 72 patients (70.6%) in group A, 25 (96.2%) in B and 28 (100%) in C, totalling 125 (80.1%) out of 156. Only one (1.9%) of 54 patients with hematogenous metastases had no recognizable venous invasion. Subserosal invaded veins (ss-v_s) were found in 32 patients (31.4%) in group A, as compared with a high incidence of 21 (80.8%) in B and 25 (89.3%) in C.

3. Number and Rate of Invaded Veins in Each Layer (Table 7):

In this study, 950 invaded veins were analysed, 330 in group A, 177 in B and 443 in C. Table 7 shows the number of invaded veins in the submucosa, muscular layer and subserosa in each group. In group A, 207 (62.7%) invaded veins were found in the submucosa (sm-v_s : submucosal invaded veins) and 102 (30.9%) in the subserosa. The rate of sm-v_s was twice as much as that of ss-v_s in group A. In group C, 151 (31.4%) invaded veins were found in the submucosa and 273 (61.6%) in the subserosa. Inversely,

Table 2. Depth of Invasion

Depth of Invasion	Groups			Total
	A	B	C	
sm	1	0	0	1
pm	15	1	0	16
ss a_1	52	5	10	67
s a_2	33	20	16	69
si ai	1	0	2	3
Total	102	26	28	156

Table 3. Histologic Type

Histologic Type	Groups			No. Cases
	A	B	C	
Well-differentiated adenocarcinoma	89	22	25	136(87.2)
Moderately differentiated adenocarcinoma	8	2	1	11(7.0)
Poorly differentiated adenocarcinoma	2	0	1	3(1.9)
Others	3	2	1	6(3.8)
Total	102	26	28	156

Table 4. Dukes' Classification

Classification	Groups (%)			Total
	A	B	C	
Dukes' A	11(10.8)	0(0)	0(0)	11(7.1)
Dukes' B	53(52.0)	8(30.8)	6(21.4)	67(42.9)
Dukes' C	38(37.3)	18(69.2)	22(78.6)	87(50.0)

Table 5. Organs with Hematogenous Metastases

Lesion	Groups (%)		Total (%)
	B	C	
Liver	18(69.2)	22(89.3)	43(79.6)
Lung	5(19.2)	3(10.7)	8(14.8)
Bone	2(7.7)	0(0)	2(3.7)
Others	1(3.8)	0(0)	1(1.9)
Total	26	28	54

Table 6. Incidence Rate of Venous Invasion

Group	Positive/Total No. Cases (%)	ss-v_s Positive/Total No. Cases (%)
A	72/102(70.6)	32/102(31.4)
B	25/ 26(96.2)	21/ 26(80.8)
C	28/ 28(100)	25/ 28(89.3)

the rate of ss-v_s was twice as much as that of sm-v_s in group C. In group B, sm-v_s and ss-v_s were exactly same in number (84) and rate (47.5%). Only 21 (6.4%) invaded veins were found in the muscular layer in group A, and the rate was almost identical to that in the other groups.

4. Average Number of Invaded Veins (Table 8):

Table 8 shows the average number of invaded veins in each layer. The overall average number of invaded veins was 3.24 in group A, 6.81 in B and 15.82 in C. The increase in the average number of ss-v_s was particularly remarkable with an increased incidence of hematogenous metastases. The average number of ss-v_s was as follows; 1.00 in group A, 3.23 in B and 9.75 in C.

5. Location of Venous Invasion (Tables 9 and 10):

In group A, 86 (26.1%) invaded veins were demonstrated in DO, 80 (24.2%) in DI, 76 (23.0%) in PI and 88 (26.7%) in PO (Table 9). The rates of venous invasion for the four subsections were almost equal in all the layers. This equivalence was also seen in groups B and C. The distribution of sm-v_s and ss-v_s is indicated in Table 10. In group A, sm-v_s were frequently seen in the outer part (DO+PO) of the tumor (70.1%), and ss-v_s in the inner part (DI+PI) (79.4%). The distribution of sm-v_s was almost identical in groups B and C, but the rate of sm-v_s in the outer part was slightly greater in group B (73.8%) and C (75.5%). Although high in incidence, the rates of ss-v_s in the inner part were obviously lower in group B (66.7%) and in C (58.6%). Conversely, the rates of ss-v_s in the outer part were higher in group B (33.3%) and C (41.4%) as compared with A (20.6%). In each group, sm-v_s were slightly predominant in the distal half (DO+DI) of the tumor, and ss-v_s in the proximal half (PO+PI).

6. Average Number and Rate of Increase of Venous Invasions (Fig. 4 and Table 11):

The average numbers of invaded veins in each subsection are shown in Fig. 4. The inner part of the subserosa and the outer part of the submucosa showed high averages. The rates of increase of venous invasions are shown in Table 11, and are divided into two groups: one in the outer part (OP) of the tumor and the other in the inner part (IP). The outer part of the subserosa had the highest rate of increase of venous invasions (5.14 in group B and 19.24 in C), and the inner part of the subserosa, which had the highest average, showed the second highest rate of increase of venous invasions.

7. Size of Invaded Veins (Table 12):

The sizes of 950 invaded veins were analysed, and are shown in Table 12. The average size of invaded veins for the three groups combined was 356 μ, 342 μ in group A, 314 μ in B and 383 μ in C. In each group, over 70% of all invaded veins showed a size of under 400 μ. In groups with hematogenous metastases, large invaded veins of over 400 μ were slightly increased in incidence. The distribution of size of invaded veins was almost identical among the three groups, and 5.2% of invaded veins in group A were unexpectedly over 1,000 μ.

Table 7. Invaded Veins in Each Layer

Group	No. Invaded Veins (%)			Total
	sm	pm	ss	
A	207(62.7)	21(6.4)	102(30.9)	330
B	84(47.5)	9(5.1)	84(47.5)	177
C	151(31.4)	19(4.3)	273(61.6)	443
Total	442	49	459	950

Table 8. Average Number of Venous Invasion

Group	sm	pm	ss	Total
A	2.03	0.21	1.00	3.24
B	3.23	0.35	3.23	6.81
C	5.39	0.68	9.75	15.82

Table 9. Location of Venous Invasion

Group	No. Invaded Veins (%)			
	DO	DI	PI	PO
A	86(26.1)	80(24.2)	76(23.0)	88(26.7)
B	41(23.2)	45(25.4)	39(22.0)	52(29.4)
C	130(29.3)	110(24.8)	97(21.9)	106(23.9)

DO : distal outer region PO : proximal outer region
DI : distal inner region PI : proximal inner region

Table 10. Location of sm-v_s and ss-v_s

sm-v_s

Group	DO (%)	DI (%)	PI (%)	PO (%)
A	32.7	16.4	13.5	32.9
B	39.3	16.7	9.5	34.5
C	45.7	17.9	6.6	29.8

ss-v_s

Group	DO (%)	DI (%)	PI (%)	PO (%)
A	7.8	38.2	41.2	12.7
B	8.3	33.3	33.3	25.0
C	19.8	29.3	29.3	21.6

8. Size of sm-v_s and ss-v_s (Table 13):

Table 13 shows the numbers and rates of sm-v_s and ss-v_s in each size range. In each group, over 80% of sm-v_s were found in the range under 400 μ. The rate of large invaded veins of over 400 μ was 13.0% in group A, 19.0% in B and 19.9% in C, a rate slightly higher in groups B and C than in A. In group A, ss-v_s with a size of over 400 μ

had the highest rate (41.2%) in comparison with the other two ranges. In group B, ss-v_s of under 200 μ were most frequent (48.8%), while in group C, there was no difference in the rate of ss-v_s among the three size ranges.

Table 11. Rate of Increase of Venous Invasions in Each Part

Group	sm		ss	
	IP	OP	IP	OP
A	1.00	1.00	1.00	1.00
B	1.39	1.68	2.72	5.14
C	2.16	2.87	7.23	19.24

IP : inner part of tumor (PI+DI)
OP : outer part of tumor (PO+DO)

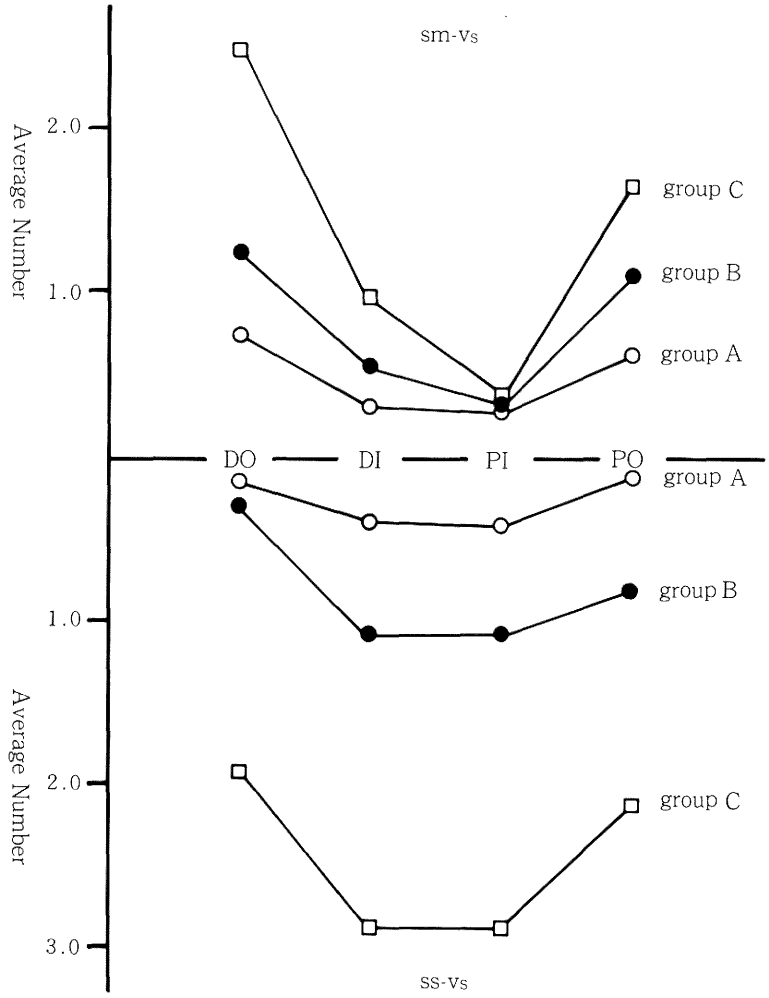

Fig. 4. Average numbers of invaded veins in each subsection in the submucosa and the subserosa. ○=group A; ●=group B; □=group C.

Table 12. Size of Invaded Veins

Size (μ)	No. Invaded Veins (%)		
	group A	group B	group C
~199	131(39.7)	82(46.3)	178(40.2)
200~399	129(39.1)	60(33.9)	141(31.8)
400~599	30(9.1)	14(7.9)	47(10.6)
600~999	23(7.0)	13(7.3)	46(10.4)
1000~	17(5.2)	8(4.5)	31(7.0)

Table 13. Size of sm-v_s

Size (μ)	No. Invaded Veins (%)		
	group A	group B	group C
~199	87(42.0)	40(47.6)	61(40.4)
200~399	93(44.9)	28(33.3)	60(39.7)
400~	27(13.0)	16(19.0)	30(19.9)

Size of ss-v_s

Size (μ)	No. Invaded Veins (%)		
	group A	group B	group C
~199	30(29.4)	41(48.8)	99(36.3)
200~399	30(29.4)	26(31.0)	81(29.7)
400~	42(41.2)	17(20.2)	93(34.1)

Table 14. Location and Size of sm-v_s

sm-v_s under 400 μ

Group	DO (%)	DI (%)	PI (%)	PO (%)
A	37.2	17.8	13.9	31.1
B	38.2	16.2	11.8	33.8
C	47.1	17.4	7.4	28.1

sm-v_s over 400 μ

Group	DO (%)	DI (%)	PI (%)	PO (%)
A	37.0	7.4	11.1	44.4
B	43.8	18.6	0	37.5
C	40.0	20.0	3.3	36.7

9. Location and Size of sm-v_s and ss-v_s (Table 14 and 15):

All sm-v_s in each group were divided into two categories; one with sizes of under 400 μ and the other with sizes of over 400 μ (Table 14). Each group showed little difference between the distribution of all sm-v_s and sm-v_s of under 400 μ. The rate of sm-v_s of over 400 μ was slightly increased in the outer part of the tumor in each group as

Table 15. Location and Size of ss-v_s

ss-v_s under 400 μ

Group	DO (%)	DI (%)	PI (%)	PO (%)
A	5.0	31.7	46.7	16.7
B	9.0	31.3	35.8	23.9
C	11.7	33.9	36.1	18.3

ss-v_s over 400 μ

Group	DO (%)	DI (%)	PI (%)	PO (%)
A	11.9	47.6	33.3	7.1
B	5.9	41.2	23.5	29.4
C	35.5	20.4	16.1	28.0

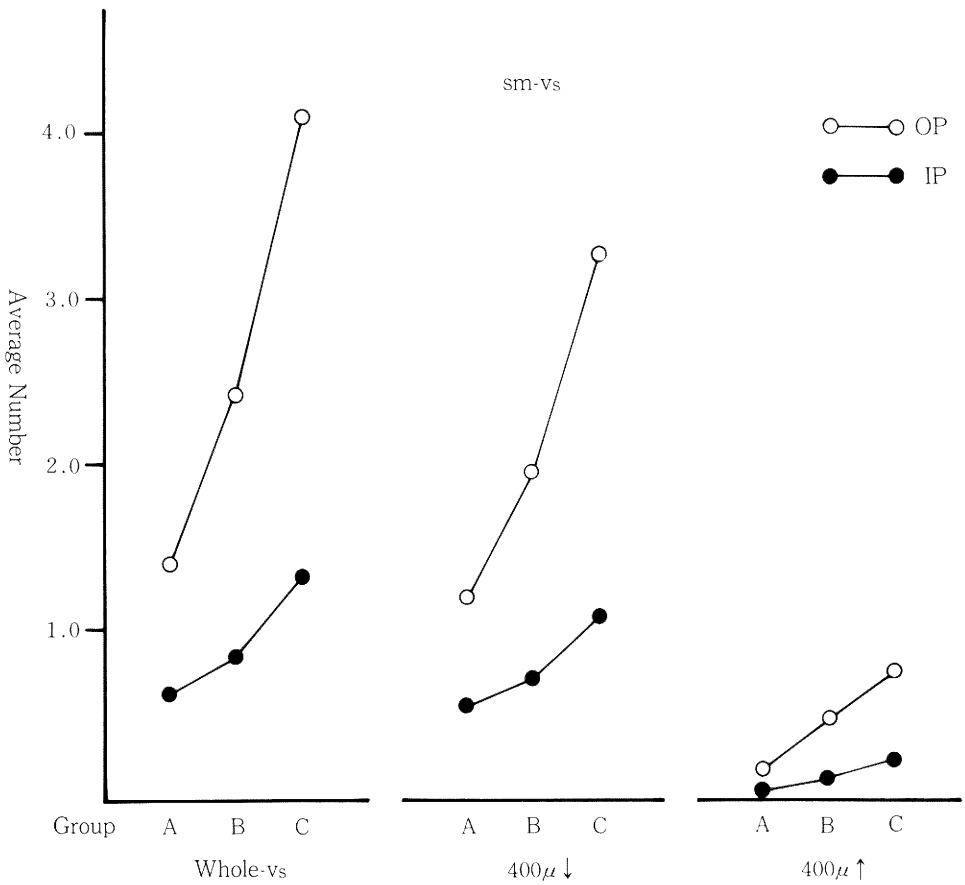

Fig. 5. Average numbers of sm-v_s in each size range. ○=outer part (OP); ●=inner part (IP).

compared with the rate of all the sm-v_s. All ss-v_s were similarly distributed (Table 15), as each group exhibited no significant difference in the distribution between all ss-v_s and ss-v_s of under 400 μ. In the outer part of the tumor, the rate of ss-v_s of over 400 μ was 19.0% in group A, 35.3% in B and 63.5% in C. This rate increase was remarkable, especially in group C, as ss-v_s of over 400 μ in the outer part comprised the majority of incidences as opposed to the inner part. The number of invaded veins of over 400 μ was not large enough to make significant influence upon the distribution of all sm-v_s and ss-v_s.

10. Location and Average Number of sm-v_s and ss-v_s in Size Range (Figs. 5 and 6):

The average number of sm-v_s and ss-v_s in each size range is shown in Figs. 5 and 6. The distribution of all sm-v_s was closely corresponded with that of sm-v_s of under 400

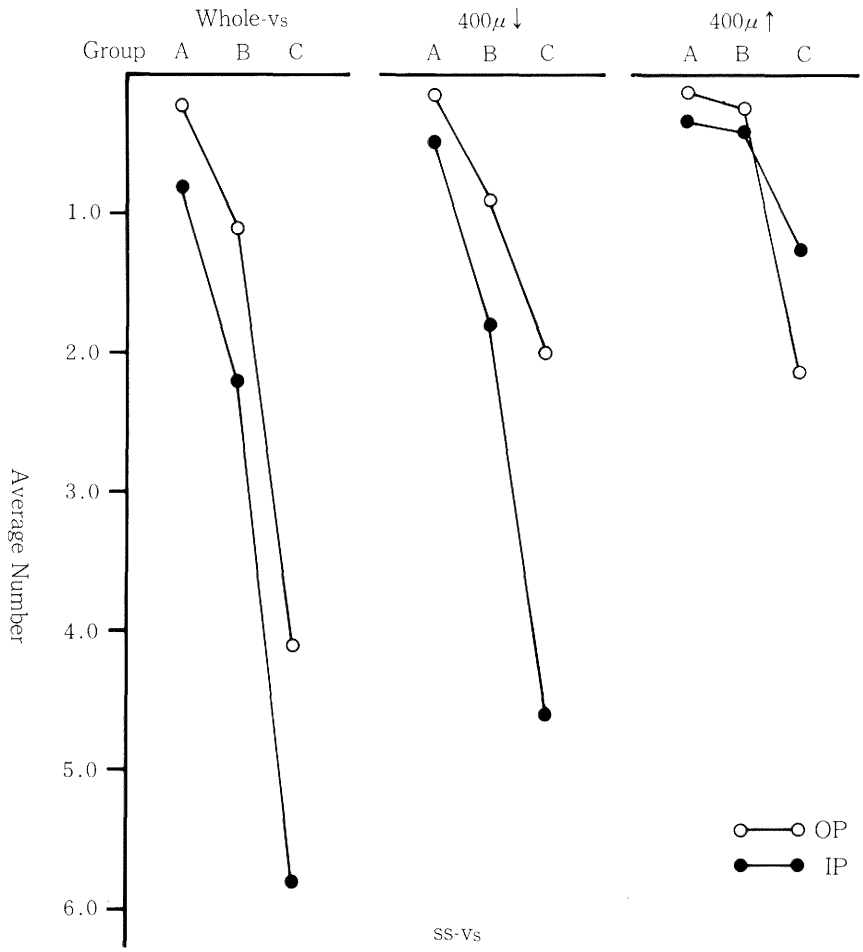

Fig. 6. Average numbers of ss-v_s in each size range.
○ = outer part (OP); ● = inner part (IP).

μ. Similarly, the distribution of all ss-v_s closely correlated to that of ss-v_s of under 400 μ, but the increased number of ss-v_s of over 400 μ in the outer part was remarkable, and the average number of ss-v_s of over 400 μ in the outer part exceeded that of the ss-v_s of over 400 μ in the inner part in group C.

11. Rate of Increase in Number of sm-v_s and ss-v_s in Size Range (Table 16):

Table 16. Rate of Increase in Each Size Range

sm-v_s

Group	All sm-v_s		under 400 μ		over 400 μ	
	IP	OP	IP	OP	IP	OP
A	1.00	1.00	1.00	1.00	1.00	1.00
B	1.39	1.68	1.30	1.55	2.40	2.09
C	2.16	2.87	1.91	2.69	5.00	3.73

ss-v_s

Group	All ss-v_s		under 400 μ		over 400 μ	
	IP	OP	IP	OP	IP	OP
A	1.00	1.00	1.00	1.00	1.00	1.00
B	2.72	5.14	3.76	6.54	1.27	2.88
C	7.23	19.24	9.78	14.85	3.67	26.38

IP : inner part of tumor
OP : outer part of tumor

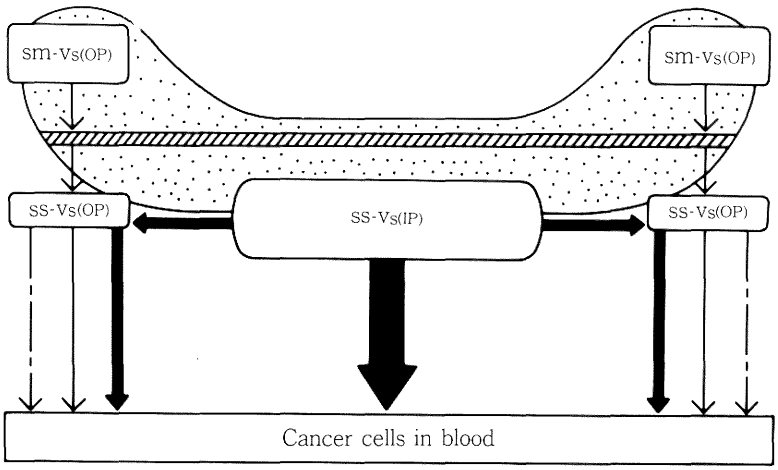

Fig. 7. Schematic diagram showing three routes of hematogenous metastases.

Table 16 shows rates of increase in number of invaded veins in each size range. The rate of increase in the number of all ss-v_s in the outer part was 5.14 in group B and 19.42 in C, indicating relatively high rates as compared with those in the inner part. Such high rates of increase were caused by the increase of ss-v_s of under 400 μ in group B and the increase of ss-v_s of over 400 μ in group C.

Discussion

In this study, venous invasion at primary sites was analysed in relation to its location and size. With the development of hematogenous metastases, both sm-v_s (submucosal invaded veins) and ss-v_s (subserosal invaded veins) increased in number as compared with the metastasis-free group (group A). The increase in the number of ss-v_s was especially notable, and subserosal venous invasion might be one of the reliable indicators for predicting hematogenous metastases.[15,16] The incidence of intramuscular venous invasion was almost constant (approximately 5%) in all groups. The majority of intramuscular invaded veins were found in the ulcer base of tumors, these veins being collapsed by dense cancer tissue and their metastatic potentials doubtful. The increase in the number of sm-v_s in the outer part of tumors and ss-v_s in the inner part was remarkable. Few ss-v_s were seen in the outer part in the metastasis-free group and the increase in the number of invaded veins in this part was not so notable although this part indicated the highest rate of increase in the number of invaded veins among the four parts.[17]

A variety of estimations for the metastatic potential of sm-v_s were described in previous reports.[16,18] Even at present, no difinite estimation has been settled upon. It is, however, a fact that venous invasion first occurs in the submucosa. It is thought that the high incidence of sm-v_s in the outer part is influenced by the following two factors: The active growth and invasion in the peripheral region of tumors in the submucosa; and the disappearance of the submucosal layer in the central region with the presence of ulceration of the tumor. In spite of a high incidence of sm-v_s in the outer part, few invaded veins were found in the outer part of the muscular layer and the subserosa in the metastasis-free group, and this fact suggests certain defensive mechanism to hematogenous metastases in the muscular layer.

The route of direct metastases from sm-v_s can not be ignored because 13.0% of the colorectal carcinomas with hematogenous metastases had no ss-v_s. On the other hand, the number of ss-v_s remarkably increased in the inner part, and it is conjectured that the subserosal cancer tissue may result in the greater part of the direct venous involvements, because few ss-v_s were demonstrated in the primary lesions with intramuscular carcinomatous invasion.

The result of this study suggests three routes of hematogenous metastases (Fig. 7). The first is the route of direct metastases from sm-v_s in the outer part. This route is regarded as a minor route because of the defensive mechanism of the muscular layer.

The second is the route from ss-v_s in the inner part and is regarded as a main route because it has the higest frequency of venous invasion among the four parts. The last route is from ss-v_s in the outer part. It is thought that the invaded veins found in this part originated in sm-v_s in the outer part, ss-v_s in the inner part and the cancer tissue itself in this part. The ss-v_s in this part may be considered to be caused largely by the inflow from ss-v_s in the inner part. Such speculation could be made on the basis of the defensive mechanism of the muscular layer and the remarkable increase in the number of ss-v_s in the outer part.

The following three factors predicting hematogenous metastases may be pointed out based on the present analysis:

1) Presence of more than six invaded veins in all layers.
2) Presence of more than three invaded veins in the extramuscular regions.
3) Presence of invaded veins in the peripheral part of the extramuscular regions.

The last factor is especially characteristic of groups with hematogenous metastases and may have a close relation to the metastatic potential of colorectal carcinomas.

Lesions with one of these characteristics should be treated at least by active adjuvant chemotherapy or other methods in an early postoperative period, and be obsearved by a close long-term follow-up. In recent reports,[5,19] resection of metastatic lesions from colorectal carcinomas had fairly satisfactory results and it is considered that this should be actively attempted, with the expectation that these efforts, that include adjuvant chemotherapy, will improve the prognosis of patients with colorectal carcinomas.

Changes in the size of the invaded veins in accordance with the development of hematogenous metastases were one of the interesting problems. Despite our prospection that larger invaded veins might be demonstrated more frequently in groups with hematogenous metastases (groups B and C) than in a metastasis-free group (group A), there was little difference in the distribution of sizes of invaded veins among the three groups. Considerably large invaded veins were also found in the metastasis-free group. The invaded veins were, therefore, divided into two groups; one with sizes of under 400 μ in the submucosa and subserosa (about 70% of all) and the other with sizes of over 400 μ. With hematogenous metastases, sm-v_s of over 400 μ increased in the outer part. It is thought that sm-v_s were present in the submucosa for a considerably long period until the occurrence of hematogenous metastases, and growing during all that time. On the other hand, ss-v_s of under 400 μ increased in both parts in the group with metachronous hematogenous metastases (group B), the increase in the outer part being especially remarkable. In the group with synchronous hematogenous metastases (group C), both ss-v_s of under 400 μ and ss-v_s of over 400 μ increased remarkably in the outer part.

These results suggest the process of venous invasion occurring at the primary sites with subsequent hematogenous metastases (the increase in the number of small ss-v_s in the inner part—inflow to the outer part with migration of cancer cells or masses into the initial venous flow—growth of ss-v_s in the outer part).

It is emphasized that detection of large ss-v_s in the outer part may indicate the possibility of early hematogenous metastases.

CONCLUSION AND SUMMARY

1. The purpose of this study is to evaluate the mechanism of hematogenous metastases on the basis of detailed analysis of venous invasion at primary sites of colorectal carcinomas.

2. One hundred and fifty-six patients with primary colorectal carcinomas histologically scrutinized (76 with rectal carcinoma and 80 with colonic carcinoma) were selected for the present investigation, and 950 invaded veins demonstrated at primary sites of their lesions were analysed in relation to the location and size.

3. With regard to hematogenous metastases, the following features were pointed out:

a. Venous invasion increased remarkably in number with metastatic potentials; the average number of invaded veins was 3.24 in metastasis-free group (group A), but was 6.81 in the group with metachronous hematogenous metastases (group B) and 15.82 in the group with synchronous hematogenous metastases (group C).

b. The increase in the number of sm-v_s (submucosal invaded veins) was marked in the outer part of the tumor as was the increase in the number of ss-v_s (subserosal invaded veins) in the inner part.

c. The rate of increase in venous invasion in the outer part of the subserosal region was the highest of those in the four parts.

d. The incidence of intramuscular venous invasion was almost constantly observed at the incidence of approximately 5%, suggesting a defensive mechanism of the muscular layer.

e. The distribution of the size of invaded veins showed no significant difference, but sm-v_s of over 400 μ increased in number in the outer part of groups B and C, ss-v_s of under 400 μ increased in both the outer and inner parts in group B, and both ss-v_s of under 400 μ and ss-v_s of over 400 μ increased in the outer part in group C.

4. The following three routes of hematogenous metastases were suggested:

a. Direct metastasis from sm-v_s.

b. From ss-v_s in the inner part.

c. From ss-v_s in the outer part.

5. The following three factors predicting hematogenous metastases were pointed out:

a. Presence of more than six invaded veins in all layers.

b. Presence of more than three invaded veins in the extramuscular region.

c. Presence of invaded veins in the peripheral part of the extramuscular region.

It is particularly emphasized that the presence of ss-v_s of over 400 μ in this region predict the possibility of early hematogenous metastases.

ACKNOWLEDGEMENT

The author is grateful to Dr. Jun Soga, Professor of Surgery, College of Biomedical Technology, Niigata University, for having kindly supplied him with helpful suggestion and advice during the investigation of the present work and the preparation of this manuscript. Thanks are also due to Dr. Shin Koyama, Associate Professor, Department of Surgery, Niigata University School of Medicine for his constant encouragement throughout this investigation, and to Mr. Takashi Hatano for his technical assistance in preparation of the histologic materials.

REFERENCES

1) Oxley, E. M. and Ellis, H.: Prognosis of carcinoma of the large bowel in the presence of liver metastases. *Brit. J. Surg.* **56**: 149-152, 1969.
2) Schulten, M. F., Heiskell, C. A. and Shields, T. W.: The incidence of solitary pulmonary metastasis from carcinoma of the large intestine. *Surg. Gynecol. Obstet.* **143**: 727-729, 1976.
3) Yasutomi, M., Matsuda, T. and Izumimoto, G.: Policy of treatment for colorectal carcinomas with metastases. *Surg. Diag. Treatm.* **24**: 149-156, 1982 (In Jpn).
4) Welch, J. P., and Donaldson, G. A.: Detection and treatment of recurrent cancer of the colon and rectum. *Amer. J. Surg.* **135**: 505-511, 1978.
5) Fortner, J. G. et al.: Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. *Ann. Surg.* **199**: 306-324, 1984.
6) Tsuchiya, S.: Recent advance in diagnosis and treatment for carcinomas of the large intestine. -Factors influencing prognosis-. *Herusu Publ. Co., Tokyo,* pp. 119-128, 1982 (In Jpn).
7) Nishi, M., Tamura, T. and Takatsuki, H.: Clinico-pathological study of gastric cancer with liver metastases. *Jpn. J. Cance clinics* **8**: 759-767, 1962 (In Jpn).
8) Brown, C. E. and Warren, S.: Visceral metastasis from rectal carcinoma. *Surg. Gynecol. Obstet.* **66**: 611-621, 1938.
9) Seefeld, P. H. and Bargen, J. A.: The spread of carcinoma of the rectum. Invasion of lymphatics, veins and nerves. *Ann. Surg.* **118**: 76-90, 1943.
10) Sunderland, D. A.: The significance of vein invasion by cancer of the rectum and sigmoid. A microscopic study of 210 cases. *Cancer* **2**: 429-437, 1949.
11) Knudsen, J. B. et al.: Venous and nerve invasion as prognostic factors in postoperative survival of patients with resectable cancer of the rectum. *Dis. Col. & Rect.* **26**: 613-617, 1983.
12) Grinnell, R. S.: The lymphatic and venous spread of carcinoma of the rectum. *Ann. Surg.* **116**: 200-216, 1942.
13) Talbot, I, C. et al.: The clinical significance of invasion of veins by rectal cancer. *Brit. J. Surg.* **67**: 439-442, 1980.
14) Konishi, F. et al.: On the methods of histologic analyses for venous invasion of carcinomas of the large intestine (Abst.). *J. Jpn. Soc. Colo-Proctol.* **33**: 69, 1980 (In Jpn).
15) Shida, H., Kubo, T., Sakamoto, M. and Oya, G.: Extramural venous invasion as a prognostic factor of postoperative liver metastasis in colorectal cancer. *J. Jpn. Surg. Soc.* **82**: 277-283, 1981.
16) Talbot, I. C. et al.: Spread of rectal cancer within veins. *Amer. J. Surg.* **141**: 15-17, 1981.
17) Kato, H., Sugano, H., Nakamura, K. and Takahashi, T.: The evaluation on venous invasion (v (+)) in resected specimens of carcinomas of the large intestine-with special emphasis on subserosal venous invasion- (Abst.). *J. Jpn. Soc. Colo-Proctol.* **32**: 73, 1979 (In Jpn).
18) Kam-Kei Lui, Enjoji, M. and Inokuchi, K.: Venous permeation of colorectal carcinoma. *Jpn. J. Surg.* **10**: 284-289, 1980.
19) Adson, M. A. and Van Heerden, J. A.: Major hepatic resections for metastatic colorectal cancer. *Ann. Surg.* **191**: 576-583, 1980.