Histological study on the extra-capsular cancer nests of regional lymph nodes in gastric cancer

by

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INTRODUCTION

Microscopic examination of lymph-nodal metastases in cancer often reveals examples of the growths of tumor cells infiltrating the extracapsular tissues of the metastatic lymph nodes. It is well known that, as described by WILLIS[48], secondary as well as primary tumors spread directly to the surrounding tissues by expansion or infiltration and produce further metastases by lymph stream or blood-stream. Most of secondary growths in regional lymph nodes arise initially from detached tumor emboli carried to the afferent lymphatics of lymph nodes which open into the peripheral sinuses.[10)16)48] Early metastatic deposits situated in the lymphatics grow into the peripheral sinuses and later the entire node is replaced by tumor tissues, which, however, may long remain confined within the distended capsule. In most cases, as admitted generally, secondary tumors in the nodes play a role of the source of further spread to the extra-nodal tissues or organs only in late stage of the growth.[49]

On the other hand, it has been noticed by some investigators[38)40] that even in early stage of cancer, small cancer nests exist occasionally in the extra-capsular tissues of regional lymph nodes. In gastric cancer these cancer cells, if left unremoved at radical operation, will be probably the source of recurrences after surgery. However there has been almost no detailed description which gives any available datum respecting the surrounding state of metastatic and non-metastatic regional nodes in gastric cancer.

In the present study, 71 specimens of gastric cancer surgically removed after radical method were used for examination, and close observation of these materials was done microspically in order that any cancer cells might be researched for either in lymph node itself or in the outside tissues.

From this examination it has become clear that, although some of the extra-nodal cancer cells resulted undoubtedly from the secondary tumors in the node by infiltration, others which seemed to have no relation to the intra-nodal tumors originated possibly from the primary source or other metastatic tumors. Besides, in several cases it was confirmed for cancer cells to situate in the extra-capsular tissues of non-metastatic lymph node.

The present paper reports in detail the findings respecting these extra-nodal cancer

nests or cancer cell groups with some pathological and clinical consideration concerning the subject.

MATERIALS AND METHODS

In the present study were used 945 lymph nodes from 71 cases of gastric cancer operated radically at our surgical clinics.

In order to examine the extra-nodal tissues, each lymph node was taken out carefully with abundance of these tissues after 10 per cent formaline fixation of the surgical specimens, from which were prepared paraffin sections in series and stained doubly with hematoxyline and eosin. In addition to the examination of the lymph nodes primary tumors and their surrounding tissues of the stomach were examined histologically as routine. As occasion demands, some sections from lymph nodes or stomach were examined by VAN GIESON's stain and PAP's technique for silver impregnation.

Almost all the lymph nodes belonging to a mass which was removed en bloc by gastrectomy including primary tumor were of suitable use for this purpose, but some of the other nodes which were separately excised for cleansing of lymph nodes were inadequate for this examination because of the absence or destruction of extra-nodal tissues.

Operative findings and gross and microscopic feature of tumors were graded chiefly according to the classification system settled by the Japanese Gastric Cancer Research Group[24] and the Committee of Histologic Classification of Gastric Cancer in the Japanese Pathologic Society.[46]

RESULTS

A. Metastasis to the regional lymph nodes in operable cases

1. Frequency of metastasis to the regional lymph nodes

In the present study on 71 cases, 61 (85.9 %) were taken with lymph-nodal metastases (Table 1). Degree of microscopic lymphatic metastases was classified into five groups according to the agreement in the Gastric Cancer Research Group[24]. These groups were termed n_{00} or n_0, n_1, n_2, n_3 and n_4. "n_{00} or n_0" represents the absence of metastasis, n_1 the presence of metastases only in nodes of the first lymphatic group adjacent to the primary tumors, and n_4 shows the farthest spread in lymphatic metastasis. Of the present 71 cases, 10 (14.1%) were group of n_{00} or n_0, 45 (63.4%) were n_1 and the other 16 (22.5%) belonged to n_2, n_3 and n_4.

Table 1 Lymph-nodal metastasis in 71 cases of gastric cancer

Lymph-nodal metastasis	No. of cases	Per cent
Negative (n_{00} or n_0)	10	11.1
Positive	61	85.9
n_1	45	63.4
n_2~n_4	16	22.5

n_{00} or n_0 shows the cases of gastric cancer which has no lymph-nodal metastasis, n_1 that which has metastasis to the first lymphatic group, n_2 to the second, n_3 to the third and n_4 the more wide-spread metastasis (according to the classification by the Gastric Cancer Research Group)[24].

2. Gross and microscopic feature of metastasizing and non-metastasizing lymph nodes

Of 945 lymph nodes persued, as shown in Table 2, 382 (40.6%) were metastasizing. Among these 382, macroscopic metastasis was proved in 203 nodes: their ratio to total nodes is 21.5 per cent, their ratio to all of metastasizing ones is 53.1 per cent. Namely, macroscopic confirmation of metastasis was impossible nearly in one half of metastasizing lymph nodes.

Table 2 Macroscopic and microscopic metastasis (945 lymph nodes)

Macroscopic metastasis	No. of nodes	No. of non-metastatic nodes (m_{00} or m_0)	No. of metastatic nodes	Degree of metastatic growth in nodes		
				m_1	m_2	m_3
Negative	717	555	162	81	64	17
Possibly positive	20	3	17	8	4	5
Positive	208	5	203	3	45	155
Total	945	563	382	92	113	177

m_{00} : no cancer cells to be proved in the node by the examination of sections in perfect series, m_0 : no cancer cells except m_{00} group, m_1 : cancer cells to be found exclusively in localized part of peripheral sinus, m_2 : metastatic tumors to be localized in peripheral sinus or partially in medullary one, m_3 : tumors spreading more widely than m_2 group.

As for the degree in size of lymph nodes and the metastasis, it was shown in Table 3 that the higher the degree, the more increased in frequency the metastatic lymph nodes, and that all of G_4 and G_5 groups had metastatic growths. It should be notable that, however, of 447 lymph nodes of G_1 group metastatic nodes numbered as many as 110 (24.6%).

Table 3 Size of lymph node and metastasis

Degree in size of lymph nodes	No. of nodes	No. of non-metastatic (m_{00} or m_0)	No. of metastatic nodes (per cent)	Degree of metastatic growth in nodes		
				m_1	m_2	m_3
G_1	447	337	110 (24.6)	42	38	30
G_2	350	193	157 (44.9)	39	56	62
G_3	125	33	92 (73.5)	11	18	63
G_4	21	0	21 (100)	0	1	20
G_5	2	0	2 (100)	0	0	2
Total	946		382 (40.6)			

G_1 : smaller than 5 mm in diameter, G_2 : smaller than 10 mm, G_3 : smaller than 20 mm, G_4 : smaller than 30 mm, G_5 : not smaller than 30 mm.

B. Extra-capsular cancer nests of regional lymph nodes

1. Frequency of extra-capsular cancer cells (Table 4)

As a result of careful examination of tumor spread in the omenta or in the other soft tissues as far as at least 3 mm distant from the capsule of a lymph node, following data were obtained.

Out of all the 945 lymph nodes in 71 cases of gastric cancer, cancer cells were seen

in the extra-capsular tissues of 116 nodes (12.3%) in 35 cases (50.3%). Of these 116 lymph nodes 101 (31 cases) were metastatic lymph nodes and 15 were non-metastatic ones. Most of these 116 were the nodes which belonged to "the first lymph-nodal group"[24] of the stomach; only 9 belonged to other lymph-nodal groups (nodes along a trunk of left gastric artery, coeliac nodes, pancreatico-lienal nodes and nodes along hepatic artery). Real extra-capsular cancer spread of the nodes which were excised separately might have been in more frequent degree than the results show, because the absence or destruction of the extra-nodal tissues was, as mentioned above, inevitable in some of these lymph nodes.

Table 4 Extra-capsular cancer cells of lymph nodes

Extra-capsular cancer cells	No. of nodes	No. of non-metastatic (m_{00} or m_0)	No. of metastatic lymph nodes			
				m_1	m_2	m_3
Positive	116	15	101	20	33	48
Negative	829	548	281			
Total	945					

2. Relation between extra-nodal cancer cells and metastatic growths in their lymph nodes

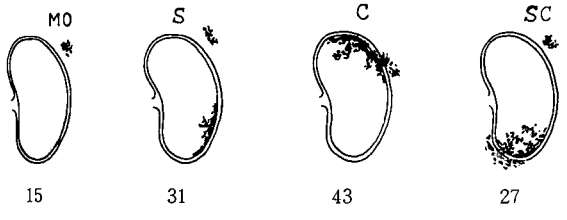

Fig. 1. Relation between the cancer cells in extra-nodal tissues adjacent to node and the metastatic tumors in the node.

As cancer cells occasionally located in the extra-capsular tissues of non-metastasizing lymph nodes, not every extra-nodal cancer nest was a part of the lymph-nodal metastatic tumors. Therefore, the extranodal cancer cell groups were divided into three types as follows.

MO: the extra-nodal cancer cell group without metastasis in the contiguous lymph node

S: the extra-nodal cancer cell group located separately from the intra-nodal metastatic tumors

C: the extra-nodal cancer cell group spreading continuously from the intra-nodal metastatic tumors

Co-existence of S and C is marked as SC (Fig. 1.).

The cancer cells of C and SC type would be sure appearance of continuous cancer spread from the intra-nodal tumor tissues to the outside by infiltration. These nodes numbered 70. The part of capsule where cancer cells went out to spread was generally the part where the afferent lymphatics opened into the peripheral sinuses. In this part of the capsule tumor spread to the outside was observed to occur even in early stage of growth of the metastatic tumors. Most of pathways in this part were perivascular tissue interspaces and in some cases the afferent lymphatics (retrograde lymphatic permeation). On the other hand, it was observed that at hilum side of the capsules infiltration of the

tumors proceeded to pass through the capsule to the outside only in advanced growth of the metastasis.

As for 31 lymph nodes of S and 27 of SC-type, some of the extracapsular cancer cells had undoubtedly arisen as the result of spread of either the primary tumor or the secondary ones excluding that of the node contiguous to these cancer cells. Good examples of these findings are MO-type of 15 nodes. Some of the other extra-capsular cancer cells of S and SC were thought to have originated from the tumor tissues of the contiguous lymph node.

3. Histological findings of the extra-nodal cancer nests

Most of them were small cancer-nests or cancer cell groups consisting of primitive and undifferentiated cancer without any macroscopical extension. They were classified into four types according to their location (Table 5) ; ly. represents that the cancer cells situate chiefly in lymphatics forming tumor cell emboli or infiltrating by lymphatic permeation, v. represents the cancer cells in veins, pv. the cancer cells in perivascular tissue interspaces and ad. in the fatty tissues often found along capillaries. The cancer nests spreading more were described with, for example, the mark of ly. pv. ad., which meant the cancer cells spreading in lymphatics, perivascular and fatty tissues. Number of lymph nodes of each type were shown in Table 5.

Table 5 Location of the extra-nodal cancer cells

Types			No. of nodes
Small cancer-cell groups	ly.	Tumor-cell emboli or permeation of lymphatics	58
	v.	Tumor-cell emboli or permeation of veins	8
	pv.	perivascular infiltration	75
	ad.	Infiltration in fatty tissues	75
Further growth by infiltration	ly. pv. ad. etc.	Mixed of these types	68

Cly., Cly. pv. or Cly. pv. ad. meant that tumor emboli in afferent lymphatics grew and permeated both into the peripheral sinuses and retrogradely along the lymphatics to outside of capsules. These tumor cells were occasionally seen to have penetrated the wall of lymphatics to invade perivascular tissue interspaces. It was suggested that the detached tumor emboli in the afferent lymphatics of lymph nodes might happen to extend retrogradely to the extra-nodal tissues, before or soon after the growths into sinuses started.

4. Relation between extra-nodal cancer cells and behavior of primary tumors

a) Microscopic structure of primary tumors (Table 6, 7)

Structural variants of carcinomas of the stomach were referred to the classification by the Committee of Histological Classification of Gastric Cancer in Jap. Path. Society[46] (Table 6).

As shown in Table 7, variants of grandular differentiation of the primary tumor showed nearly equal frequency of extra-nodal cancer appearance. Among the variants, the extra-nodal cancer cells of carcinoma solidum simplex situated more frequently in fatty

Table 6 Classification of microscopic structure of gastric cancer (by the Gastric Cancer Research Group[46])

Elementary type		Modificatory sub-type		Stroma
Elementary histologic form	Cellular atypism CAT I II III	Histoid manifestation	Functional manifestation	
Adenocarcinoma		tubulare papillare acinosum	muconodulare mucocellulare	medullare scirrhosum
Carcinoma solidum simplex	Structural atypism SAT 1 2 3	macro- meso- micro- alveolare	mucocellulare	medullare scirrhosum
Carcinoma epidermoides	Infiltration INF α β γ	macro- meso- micro- alveolare	keratosum	medullare scirrhosum
Adenoacanthoma				
Micellaneous carcinoma				

tissues than in lymphatics, while those of adenocarcinoma papillare were the reverse. MO was predominant next to C in group of adenocarcinoma papillare, most of which were isolated tumor cell emboli in lymphatics. Many of extra-nodal infiltration in fatty tissues observed in group of carcinoma solidum simplex were of S-type, and they were seen to have relation not to the contiguous nodes but to the primary growths in most cases. Group of carcinoma solidum simplex scirrhosum and adenocarcinoma tubulare muconodulare et mucocellulare showed high percentage of extra-capsular cancer cell with their own characteristics; ad. was prominent in carcinoma solidum simplex scirrhosum, while ly. in adenocarcinoma tubulare muconodulare et mucocellulare. The extra-nodal cancer cells of carcinoma solidum simplex scirrhosum had the main course of spreading by direct infiltration and adenocarcinoma tubulare muconodulare et mucocellulare through lymphatics.

Table 7 Microscopic structure of primary tumors and the extranodal cancer cells

Type	No. of nodes (cases) with extra-nodal cancer cells	Per cent of the nodes (cases) to total	Their contents, per cent to no. of nodes				
			C	S	MO	ly.	ad.
Adenocarcinoma papillare	14 (5)	17.0 (63.0)	50.0	21.4	35.7	50.0	42.8
Adenocarcinoma tubulare	64 (19)	12.2 (47.5)	46.8	56.2	17.1	46.8	57.8
Carcinoma solidum simplex	42 (11)	15.3 (52.5)	52.3	92.8	0	38.0	71.4
Adenocar. tubul. muconodulare (mucocellulare)	24 (6)	24.8 (78.2)	50.0	33.3	16.6	62.9	50.0
Ca. solidum simplex scirrhosum	31 (9)	21.7 (81.5)	54.8	61.2	0	29.0	74.1

b) Cellular and structural atypism of primary tumors (Table 8)

Cellular atypism (abbreviated as CAT) and structural atypism (SAT) of cancer were graded into three classes (according to the classification by the Committee of Histological Classification of Gastric Cancer in J. P. S.[46]). Frequency of extra-nodal cancer cells increased in higher classes of atypism. In CAT-I and SAT-1, ly. was predominant and ad. was rare. The reverse result was obtained in CAT-III and SAT-3. Ratio of C to S was higher in CAT-III or SAT-3 than in CAT-I or SAT-1.

Table 8 Cellular and structural atypism of primary tumors and the extra-nodal cancer cells

Atypism	No. of nodes (cases) with extra-nodal cancer cells	Per cent of the nodes (cases) to total	Their contents, per cent to no. of nodes				
			C	S	MO	ly.	ad.
Cellular atypism I	4 (3)	4.8 (37.5)	25.0	50.0	25.0	75.0	25.0
II	49 (15)	10.7 (42.8)	51.0	49.0	24.5	51.0	53.0
III	63 (17)	15.4 (60.7)	52.5	69.8	3.2	46.0	70.0
Structural atypism 1	4 (3)	6.6 (50.0)	25.0	50.0	25.0	75.0	25.0
2	38 (12)	9.5 (38.7)	44.8	36.9	34.2	44.8	50.0
3	74 (20)	15.2 (58.8)	55.4	73.0	2.7	50.0	69.0

c) Infiltration tendency of primary tumors (Table 9)

Its grade was represented by three classes of α, β and γ; γ is the highest degree of infiltration. No notable difference was obtained concerning the behavior of extra-nodal cancer cells in this factor of cancer spread.

Table 9 Infiltration tendency of primary tumors and the extra-nodal cancer cells

Infiltration	No. of nodes (cases) with extra-nodal cancer cells	Per cent of the nodes (cases) to total	Their contents, per cent to no. of nodes				
			C	S	MO	ly.	ad.
INF α	18 (8)	7.4 (40.0)	16.7	38.9	50.0	22.2	66.7
β	34 (10)	11.3 (43.5)	53.0	50.0	11.8	64.7	44.2
γ	64 (17)	16.0 (60.7)	59.5	72.0	3.1	48.5	68.8

d) Invasion to depth of the stomach wall (Table 10)

To what layer of the stomach the cancer infiltration has reached was represented by the mark of m, sm, pm, ss and s, according to the classification of the G. C. R. G.[24][46] "m" shows the tumor being localized in the mucosa, "sm" the tumor invading the submucosa, "pm" the muscularis, ss and s the subserosa and serosa. In ss and s group 62 per cent of cases of gastric cancer and 15 per cent of lymph nodes of these cases had extra-nodal cancer cells. In group of m, sm and pm 19 per cent of cases and 4 per cent of lymph nodes had extra-nodal cancer cells. Namely, the deeper the primary tumors invaded the wall of the stomach, the more frequent appearance of extra-nodal cancer cells was recognized. While, the extra-nodal cancer cells were seen even in early stage of gastric cancer in which the invasion was confined to the mucosa and submucosa. To

author's interest, most of such extra-nodal cancer cells in early gastric cancer were unexpected ad. or ly. type of S and MO groups. This fact, as will be mentioned below, suggested that gastric cancer can spread to the soft part of extra-gastric tissues by producing direct metastases from primary source via lymph vessels or blood-vessels and probably through the extra-vascular fluid pathways by KIHARA[26] as well as by continuous infiltration from the primary tumors or the secondary ones.

Table 10 Invasion to depth of the stomach wall[43] and the extra-nodal cancer cells

Invasion to depth	No. of nodes (cases) with extra-nodal cancer cells	Per cent of the nodes (cases) to total	Their contents, per cent to no. of nodes				
			C	S	MO	ly.	ad.
m, sm, pm	9 (4)	3.9 (19.0)	11.1	44.5	44.5	22.2	66.6
ss, s	107 (31)	15.0 (62.0)	54.2	61.6	10.3	51.4	60.7

m : mucosa, sm : submucosa, pm : muscularis, ss : subserosa, s : serosa.

e) Lymphatic and vein invasion of primary tumors (Table 11)

They were graded from 0 to 3, each being represented by ly_{00} or ly_0, ly_1, ly_2, ly_3, and v_{00} or v_0, v_1, v_2, v_3 (by the G. C. R. G.[24][46]). Cases in which the lymphatic invasion was predominant showed extra-nodal cancer cells in high frequency and those without lymphatic invasion in low frequency. The cases with high grade of lymphatic invasion accompanied many ly-type of extra-nodal cancer cells. The similar relation was observed between vein invasion and extra-nodal cancer cells. So far as the vascular invasion was concerned, the behavior of extra-nodal cancer cells reflected closely that of the primary tumors.

Table 11 Lymphatic and vein invasion of primary tumor[46][20] and the extra-nodal cancer cells

Intravascular invasion	No. of nodes (cases) with extra-nodal cancer cells	Per cent of the nodes (cases) to total	Their contents, per cent to no. of nodes				
			C	S	MO	ly.	ad.
Lymphatic invasion ly_0	5 (5)	2.1 (25.0)	40.0	40.0	20.0	20.0	60.0
ly_{1-3}	111 (31)	15.6 (60.8)	51.3	61.3	12.6	50.0	61.3
Vein invasion v_0	28 (11)	7.2 (35.5)	43.0	57.2	3.6	3.6	43.0
v_{1-3}	88 (24)	16.6 (60.0)	53.5	61.4	15.9	7.9	67.0
						v.	

5. Relation between extra-nodal cancer cells and the stromal reactions of primary tumors (Table 12)

CPL-classification[20] and the degree of lymphocytic reaction around the primary tumors [47] were adopted here. As for CPL-classification, comparison of two groups of C and PL was projected; C is cirrhotic from in which the preceding part of tumors is surrounded perfectly by proliferated connective tissue, and PL is progressive form or lymphatic and blood-vessel permeation from in which it is not surrounded by connective tissue. Result

was that far more frequently appeared the extra-nodal cancer cells in PL-form than in C-form, and no notable difference in their contents was seen between the two forms (Table 12).

Table 12 Stromal reactions of primary tumors[20)47)] and the extra-nodal cancer cells

		No. of nodes (cases) with extra-nodal cancer cells	Per cent of the nodes (cases) to total	Their contents, per cent to no. of nodes				
				C	S	MO	ly.	ad.
CPL-classification	C	22 (8)	6.6 (33.3)	36.4	50.0	22.7	40.9	54.5
	PL	94 (27)	15.6 (57.5)	54.2	62.8	10.6	51.0	62.8
Lymphocytic infiltration	LR-I	9 (5)	10.2 (62.5)	66.7	22.2	11.1	77.8	33.3
	LR-II	101 (26)	14.1 (48.2)	49.5	63.4	13.9	49.5	62.4
	LR-III	6 (4)	4.3 (44.4)	50.0	66.7	0	0	83.3

Intensity of lymphocytic infiltration around the primary tumors was graded from I to III; LR-I shows slight infiltration, LR-III shows the tumors perfectly surrounded by the infiltration and LR-II the intermediate cases. LR-III showed the least appearance of extra-nodal cancer cells.

These stromal reactions, which were regarded as factors to influence the survival rate after surgery by many reporters,[20)30)33)35)47)] were suggested to restrict the spread of tumors to the extra-nodal tissues.

6. Relation between extra-nodal cancer cells and the degree of lymphatic metastasis

The degree of lymphatic metastasis of gastric cancer was divided into three groups, i.e. n_{00}, n_1 and n_2-n_4, and the extra-nodal cancer cells in each group were examined (Table 13). The exta-nodal cancer cells appeared proportional to the degree of lymphatic metastasis. Both primary tumors in 2 cases of n_{00}-group, each having one lymph node infiltrated with cancer cells around its capsule, showed microscopic structure of adenocarcinoma tubulare, and the slight infiltration to gastric serosa was positive in both cases.

Table 13 Degree of lymphatic metastasis and the extra-nodal cancer cells

Degree of metastasis	No. of nodes (cases) with extra-nodal cancer cells	Per cent of the nodes (cases) to total	Their contents, per cent to no. of nodes				
			C	S	MO	ly.	ad.
n_{00}	2 (2)	2.3 (20.0)	0	0	100.0	50.0	50.0
n_1	59 (20)	10.4 (41.5)	44.1	66.2	18.7	47.5	64.5
n_{2-4}	55 (13)	18.8 (81.3)	60.0	56.4	3.6	51.0	58.2

DISCUSSION

High percentage of lymphatic metastases of more or less than 80 per cent of operated gastric cancer cases, as shown by many recent reports,[7)21)23)25)43)44)] should be a reason for importance of the cleansing of lymph nodes at surgical treatment of the disease. These metastases are often seen not only in the lymph nodes far distant from the primary tumor but in the nodes situating in the reverse direction against normal lymph flow as well.[7)9)13)]

[33][36][39] On the other hand SATO[40] reported, under the detailed microscopic examination of the greater and lesser omenta of operable cases of gastric cancer, 81.4 per cent of the whole cases had had the disseminated cancer nests in the omenta, showing far more frequency than in other reports.[18][19][27][42] Moreover, difficulty in cancer surgery lies also in the fact that the preceding part of tumor spread is usually of microscopic extent. Grossly visible metastases were, in the present study,existed only in approximately one half of all the metastatic lymph nodes as the results obtained by AONUMA[1]. And the metastases were seen in 24.6 per cent of non-swelling lymph nodes smaller than 5 mm in diameter. CHISAKA[7] observed the metastases in 24.9 per cent of lymph nodes smaller than a red bean.

In the case of dissemination to the omenta, microscopic examination reveals the spread of tumors to far more extent than it may be predicted macrospically[40]. Thus the necessity of extirpation of the omenta at gastrectomy has been emphasized.[11][14][17][35] The present author examined carefully these grossly unvisible spread of tumors in the omenta or in the other soft tissues as far as at least 3 mm distant from the capsule of a lymph node.

Most of these extra-capsular tumors, seen in 50.3 per cent of 71 cases of operable gastric cancer and in 12.3 per cent of 945 lymph nodes, were small cancer nests or small cancer cell groups which located in lymphatics and veins as emboli or permeating tumors, or in tissue interspaces as infiltrating tumors. Emboli or permeating tumors in vessels often penetrated the wall to spread to the extra-vascular tissues. These extra-capsular cancer cells were occasionally seen even in the lymph nodes distant from the stomach: coeliac nodes, pancreatico-lienal nodes, nodes along hepatic artery.

Original tumors from which the extra-capsular cancer cells have developed and their pathways may be classified as follows.

1) Continuous infiltration from the advanced growths of the metastatic tumors in the contiguous lymph node through the capsule

2) Permeation from the metastasis in the peripheral sinus of the contiguous node retrogradely through the afferent lymphatics

3) Emboli probably brought from the advanced metastatic tumors in the contiguous nodes through lymphatics or veins

4) Direct spread from the primary tumor by infiltration of tissue interspaces

5) Disseminated metastatic growth of detached fragments from the primary tumors through the abdominal cavity

6) Emboli from the primary tumor by way of lymphatics or veins

7) Lymphatic or vein permeation from the primary tumor

8) Non-continuous spread from the primary or secondary tumors possibly through the extra-vascular fluid pathways by KIHARA[26]

The findings of 1) which had been described by WILLIS[49] and SATO[40] were observed mostly in advanced cases of metastatic nodes. The findings of 2) were observed even in early stage of the secondary growth. Solitary detached tumor emboli were seen relatively in many cases, though, whether they belonged to 3) or 6) was not clear except few cases. Both ways may exist. There were observed the findings that some growths of these emboli had spread to the extra-vascular tissues by infltration. 4) was often seen in cases of scirrhus. Even in a few of these cases where infiltration of tumors had sur-

rounded the neighboring tissues of lymph nodes, not always could be recognized metastases in the contiguous nodes. OTA[36] pointed out that he could observe cancer cells not in lymph nodes but in the outside tissues even in early gastric cancer especially in scirrhus. According to JINNAI[23] the scirrhotic type tumors metastasize to the regional lymph nodes in lower frequency than the other variants of gastric cancer. It will be surely asserted that, although large nodular metastatic growths in the lymph nodes of scirrhotic type are scarcely observed, those lymph nodes have commonly metastatic cancer cells in their sinuses. 5) may be also common findings in advanced stage of gastric cancer. It was attempted by ISOHASHI[22] and YAMAMOTO[50] to explore how tumors spread to the extra-vascular fluid pathways.[26] Some of the extra-nodal cancer cells which separately infiltrated fatty tissue interspaces, chiefly along the capillaries, were thought to include the mode of spread by way of 8).

Many factors in the prognosis of cancer of the stomach have been advocated, i.e. gross classification by BORRMANN,[4] microscopic grading of malignancy by BRODERS,[6] stromal reactions and regional lymph-nodal reactions by MACCARTY,[30][31] TAKIZAWA,[45] LARMI[28] and BLACK[3], CPL-classification by IMAI[20] etc. And these factors were investigated by many others, some reports showing close relation to the post-operative survival rate[2][8][15][29][33] and the others no significant relation.[5][41][42] MUTO's detailed description presents significant relations of the following factors to survival : 1) CPL-classification, 2) Invasion to depth,[12][37][38] 3) Presence or absence of lymphatic metastasis and degree of its spread and 4) Peritoneal dissemination (P. C.-classification by MUTO).[34][35] Broders' grading may be added to these factors. MAKI[32] attached importance to these factors respecting the prognosis of gastric cancer in comparison with that of carcinoma of the colon. The extra-nodal cancer cells with respect to the behavior of primary tumors, to the stromal reactions in primary tumors and to the lymphatic metastasis, close and interesting relations were observed. Namely, frequency of extra-nodal cancer appearance increased in the higher classes of cellular and structural atypism or of infiltration tendency in the primary tumors. Similar results were obtained respecting the invasion to depth of the stomach wall. In cases of scirrhus extra-nodal cancer cells infiltrated the tissue interspaces, and in mucoid adenocarcinoma they were predominant in lymphtics. When there were invasions to lymphatics or veins in primary tumors, the extra-nodal cancer cells were also predominant in lymphatics or veins. Thus, the behavior of the extra-nodal cancer cells reflects closely that of the primary tumors. Degree of lymphatic metastasis went parallel with frequency of extra-nodal cancer cell appearance. C-type in CPL-classification and predominant lymphocytic infiltration around the primary tumors were observed to have cancer cells in extra-nodal tissues in lower frequency than the other types. It is thought that one of the reasons for these factors to influence the prognosis after surgery lies in the difference of extra-nodal cancer spread according to these factors.

The extra-nodal cancer cells are thought to produce significant problems in surgery of gastric cancer. The intra-capsular removal of metastatic lymph nodes will leave the extra-nodal cancer cells, so that we cannot expect so much in such a cleansing technic. Bloc dissection must be intended even in early stage of gastric cancer, because the extra-nodal cancer cells may exist.

SUMMARY

The spread of tumors to regional lymph nodes and to their surrounding tissues were studied in 71 cases of gastric cancer operated radically at our surgical clinics. Of 71 cases 61 (85.9 per cent) had lymphatic metastasis, and of 945 lymph nodes 382 (40.6 per cent) were metastatic ones. Approximately in one half of metastatic nodes the metastases could not be observed macrospically. All lymph nodes not smaller than 20 mm in diameter had metastases, but microscopic metastases were seen in 24.6 per cent of lymph nodes smaller than 5 mm in diameter. Tumors often spread to the surrounding tissues of regional nodes in microscopic extent. The behavior of these extra-nodal cancer nests and their histopathological findings and their significance in surgical aspects were summerized as follows.

1) The extra-capsular cancer cells were seen in 35 cases (50 3 per cent) out of 71 cases of gastric cancer and in 116 (12.3 per cent) out of 945 lymph nodes under the examination of sections in series prepared from each lymph node with its surrounding tissues intervening within a distance of at least 3 mm from the lymph-nodal capsule.

2) Most of these extra-nodal cancer cells did not developed to macroscopic extent. They were emboli and permeation in vessels or infiltration type in fatty tissue interspaces or in perivascular tissues.

3) The extra-nodal cancer cells were seen more frequently in cases of advanced stages of gastric cancer than in early stages, but they were also seen even in the cases without lymphatic metastasis or with invasion to depth limited to the submucosa or to the muscularis. Cancer cells were observed in the surrounding tissues not only of the lymph nodes in the omenta but of the other nodes, i e. coeliac nodes, hepatic nodes, pancreaticolienal nodes etc.

4) Original tumors from which the tumor cells spread to the extra-nodal tissues are divided into two; one is metastatic tumors in the contiguous lymph nodes and the other is primary tumors or other metastatic tumors. The spread of lymph-nodal metastatic tumors to the extra-capsular tissues was observed not only in the case of advanced growths of the metastatic tumors but in the case of early stadium of their growths. In the former, tumor cells were often seen to infiltrate through the hilar side of the capsule and in the latter they invaded chiefly along the afferent lymphatics. It was presumed that the emboli in lymphatics and veins originating from the lymph-nodal metastatic tumors could exist. The spread of primary tumors to the soft tissue interspaces adjacent to regional lymph nodes were frequently seen in case of scirrhus, while the emboli in lymphatics and veins from primary tumors were predominant in case of gelatinous carcinoma. Most of these emboli located in the afferent lymphatics of lymph nodes. The emboli seemed to spread either into the sinuses or retrogradely to extra-capsular region by permeation. Cancer cells in lymphatics or veins were occasionally observed to invade the wall. Vein permeation from the primary tumors was seen in only one case. The extra-vascular fluid pathways must possiblly play a role of the tumor spread.

5) Primary tumors with highly atypic cancer cells and highly atypic structure, with high infiltration tendency, with deep invasion to the gastric wall, or with high invasion to lymphatics or veins, showed high frequency of extra-nodal spread of tumors respectively. The primary tumors with the predominant invasion to lymphatics or veins had the same

invasion in the extra-nodal tissues. Thus the behavior of extra-nodal cancer cells reflected closely that of the primary tumors. C-type in CPL-classification and predominant lymphocytic infiltration around the primary tumors were observed to have less frequent appearance of cancer cells in the extra-nodal tissues than the other types. Therefore, extra-nodal cancer cells influence the prognosis after surgery without doubt.

6) In the surgical operation of gastric cancer, it will be of little value to add cleansing of lymph nodes that may leave the extra-nodal cancer cells unremoved. On the other hand the greatest possible bloc dissection is required in early stage of gastric cancer.

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REFERENCES

*1) Aonuma, T. : Studies on metastases to the regional lymph nodes in gastric cancer. Jour. Jap. Surg. Soc., **64** : 710-719, 1963.

2) Balfour, D.C. : Factors of significance in the prognosis of cancer of the stomach. Ann. Surg., **105** : 733-740, 1937.

3) Black, M. M. et al. : Microscopic structure of gastric carcinomas and their regional lymph nodes in relation to survival. S. G. O., **98** : 725-734, 1954.

4) Borrmann, R. : Geschwülste des Magens und Duodenums. Henke-Lubarsch, Hdb. d. spez. path. Anat. u. Hist., Bd. 4, Ht. 1, 855-1054, Berlin, 1926.

5) Borst, M. : Die histologische Erfassung der Bösartigkeit von Gewächsen. Z. Krebsf., **40** : 3-29, 1934.

6) Broders, A. C. : Carcinoma of the mouth; type and degrees of malignancy. Am. J. Roentgenology, **17** : 90-93, 1927.

*7) Chisaka, T. : Histopathological study on the regional lymphatic metastasis in gastric cancer with special references to relation of the metastasis to the end results after surgery. Jour. Jap. Surg. Soc., **57** : 387-395, 1956.

8) Douchat, G. R. and H. K. Gray : Carcinoma of the stomach; prognosis based on a combination of Dukes' and Broders' methods of grading. Am. J. clin. Path., **13** : 441-449, 1943.

9) Eker, R. : Carcinomas of the stomach ; investigation of the lymphatic spread from gastric carcinomas after total and partial gastrectomy. Acta Chir. Scand., **101** : 112-126, 1951.

10) Ewing, J. : Neoplastic Diseases. Philadelphia, 1940.

11) Finsterer, H. : Meine Erfahrungen bei 3020 Operationen wegen Magenkrebs. Arch. klin. Chir., **273** : 611-682, 1953.

12) Fischer, E. R. et al. : The practical value of histopathological classification of gastric carcinoma ; an appraisal based on 1000 consecutive cases. Cancer, **8** : 389-395, 1955.

13) Fly, A. O. et al. : Metastasis to the regional nodes of the splenic hirus from carcinoma of the stomach. S. G. O., **102** : 279-286, 1956.

14) Fohl, T. et al. : Netzexstirpation bei der Magenresektion wegen Karzinom. Dtsch. Z. Chir., **232** : 317-326, 1931.

15) Gatewood, G. : Carcinoma of the stomach an analytical survey. Ann. Surg., **96** : 588-594, 1932.

16) Gray, J. H. : The relation of lymphatic vessels to the spread of cancer. Brit. J. Surg., **26** : 462, 1939.

17) Groves, E. W. H. : The radical operation for cancer of the pylorus. Brit. med. J., **1** : 366-370, 1910.

18) Harvey, H. D. et al. : Gastric carcinoma, experience from 1961 to 1949 and present concepts. Cancer, **4** : 714-725, 1951.

*19) Hirao, K. : On the method of gastrectomy for the cleansing of tumors in gastric cancer. Rinsho to Kenkyu, **23** : 209-215, 1946.

*20) Imai, T. : The growth of human carcinoma, A morphological analysis. Fukuoka Acta Medica, **45** ; 72-

102, 1954.
*21) Ishiyama, H. et al. : Reconsideration of surgical treatment of carcinoma of the stomach. Jour. Jap. Surg. Soc., **47** : 148-154, 1946.
*22) Isohashi, T. : Morphological study on intramural development of gastric cancer with special reference to the behavior of argentophil fibrils. Arch. Jap. Chir., **34** : 125-148, 1963.
*23) Jinnai, D. : On the metastases in cancer of the stomach. Geka, **21** : 1235-1241, 1959.
*24) Jinnai, D. et al. : Comments on "the agreements about the method of dealing with gastric cancer in surgical clinics". Shujutsu, **17** : 951-959, 1963.
*25) Kajitani, T. : On the prognosis of cancer of the stomach. Sogo-Igaku, **12** : 555-559, 1955.
*26) Kihara, T. : Distribution of capillaries and its relation to lymphatics and extravascular fluid pathways. Osaka Medical College J., Special number : 14, 1957.
27) Kitani, H. : Zur Kenntnis der Häufigkeit und der Lokalization von Krebsmetastasen mit besonderen Berücksichtigung ihres histologischen Bau. Virchow's Arch., **238** : 289-309, 1922.
28) Larmi, T. K. I. and L. Saxen : "Host reactions" in gastric cancer. Acta Chir. Scand., **125** : 144-146, 1963.
29) Lewin, E. : Gastric cancer — a clinical study with reference to total gastrectomy and microscopic grading. Acta chir. scand., **262** : 1-89, 1960.
30) MacCarty, W. et al. : Relation of differentiation and lymphocytic infiltration to postoperative longevity in gastric carcinoma. J. laborat. clin. Med., **6** : 311-337, 1921.
31) MacCarty, W. et al. : Factors which influence longevity in cancer. Ann. Surg., **76** : 9-12, 1922.
*32) Maki, T. et al. : Why the prognosis of cancer of the colon is more favorable than that of the stomach. Rinsho-Geka, **19** : 299-307, 1964.
*33) Matsuo, N. : Consideration on the cases having five year or more survival after gastrectomy in cancer of the stomach. Jour. Jap. Surg. Soc., **64** : 306-336, 1963.
*34) Muto, M. : Clinical significance of the dissemination to the omenta in gastric cancer. With special references to its relation to the end results after surgery. Jour. Jap. Surg. Soc., **59** : 884-885, 1958.
*35) Muto, M. : Gastric cancer in surgical aspects. Kanahara, Tokyo, 1963.
*36) Ota, K. : presented at the 3rd Meeting of the Gastric Cancer Research Group. Japanese Journal of Cancer Clinics, **10** : 64, 1964.
37) Ranson, H. K. : Cancer of the stomach. S. G. O., **96** : 275-287, 1953.
38) Re Mine, W.H. et al. : Some factors which influence prognosis in surgical treatment of gastric carcinoma. Ann. Surg. **138** : 311-319, 1953.
39) Sanderland, D. A. et al. : The lymphatic spread of gastric cancer. Cancer, **6** : 987-996, 1953.
*40) Sato, K. : Histopathologic studies on carcinomatous dissemination in the omentum in surgical cases of gastrectomy for gastric carcinoma, with special reference to the relation of the dissemination with the end results. Jour. Jap. Surg. Soc., **59** : 263-274, 1958.
41) Schindler, R. et al. : The classification of gastric carcinoma. S. G. O., **73** : 30-39, 1941.
42) Stout, A. P. : Pathology of carcinoma of the stomach. Arch. Surg., **46** : 807-822, 1943.
*43) Takeda, H. : Morphological study on the regional lymphatic metastasis in gastric cancer. Okayama Medical Journal, **64** : 1499-1520, 1952.
*44) Takizawa, T. : Histological study on the regional lymphatic metastasis in gastric cancer. Gann, **41** : 83-84, 1950.
*45) Takizawa, N. et al. : Degrees of malignancy of gastric cancer respecting the qualitative changes in cancer stroma. Proceedings of the Jap. Cancer Association, the 21st General Meeting, 250-251, 1962.
*46) Takizawa, N. : Comments on the histologic classification according to "the agreements about the method of dealing with gastric cancer in surgical clinics" Shujutsu, **18** : 457-460, 1964.
*47) Urabe, T. et al. : Extension and metastasis of the gastric carcinoma. Rinsho-Geka, **18** : 1341-1351, 1963.
48) Willis, R. A. : The spread of tumors in the human body. London, 1952.
49) Willis, R. A. : Pathology of tumors. Butterworths, London, 1960.
50) Yamamoto, M. et al. : Cancer spread via extra-vascular fluid path. Arch. Jap. Chir., **29** : 1456, 1960.

(* in Japanese)

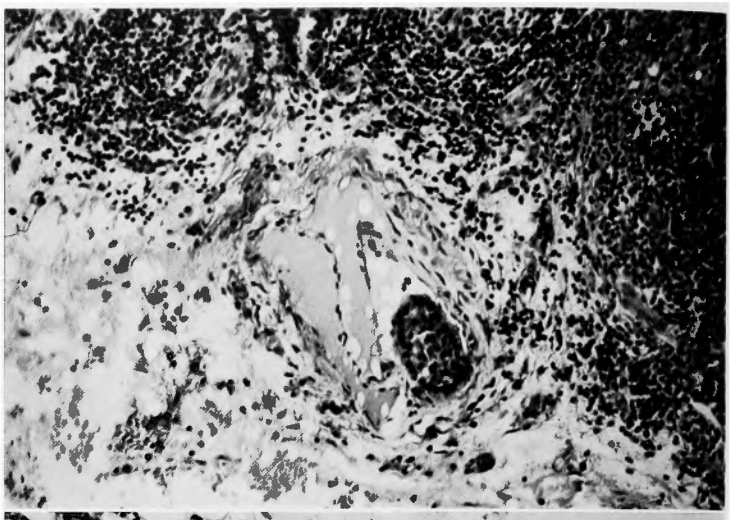

Fig. 2. Tumor cell embolus in the afferent lymphatic of regional lymph node with early metastasis.
H-E ×100

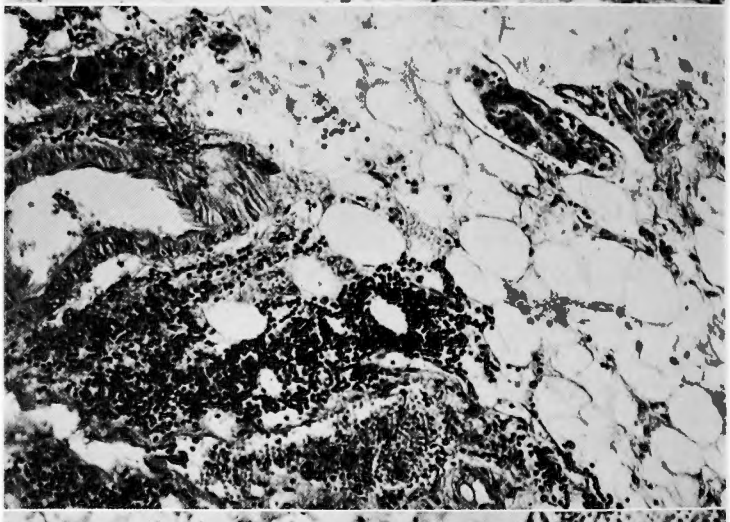

Fig. 3. MOly Emboli in the lymphatics in extra-nodal region with no metastasis in the contiguous node.
H-E ×100

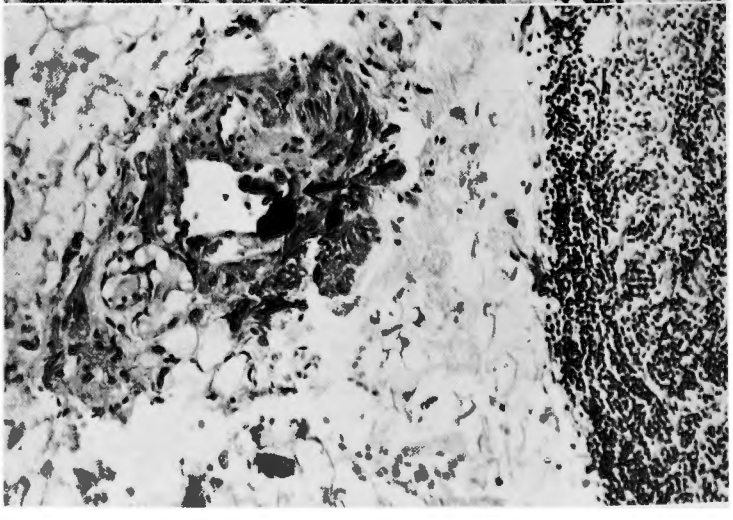

Fig. 4. Sv. Embolus in a vein in extra-nodal region. The contiguous node has metastatic tumors only in the localized part of the peripheral sinus.
H-E ×100

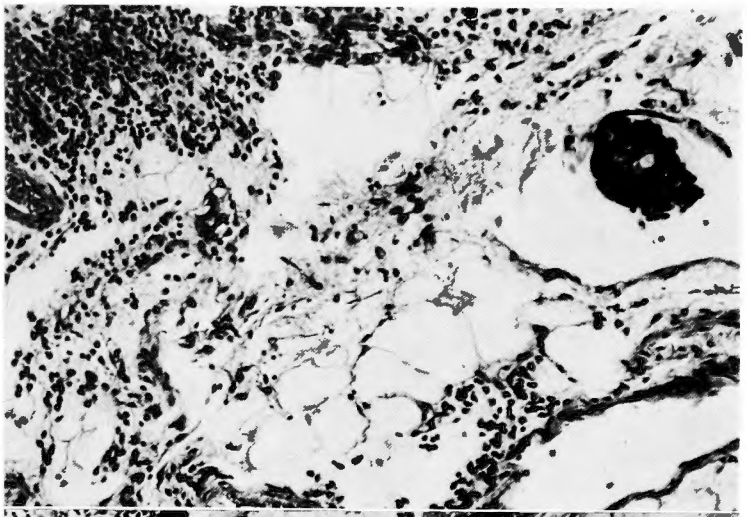

Fig. 5. Sly. Embolus in a lymphatic in extra-nodal region. The contiguous node has metastatic growth in the peripheral sinuses.
H-E ×100

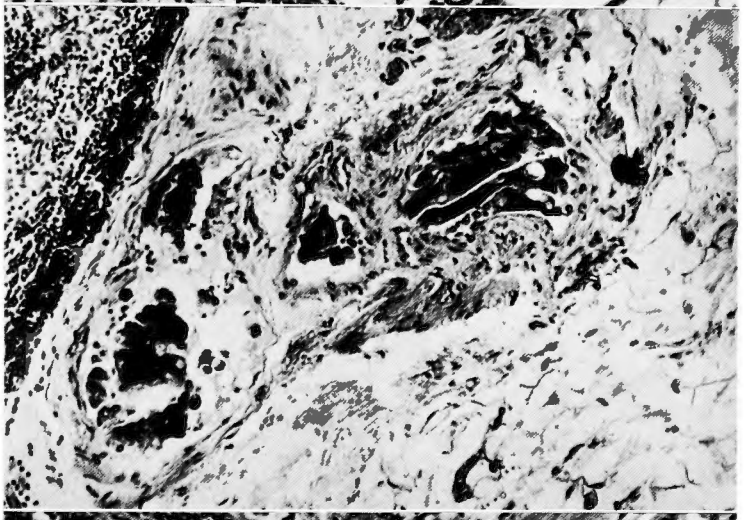

Fig. 6. Cly.v. Continuous spread of tumors to the extra-nodal tissues by lymphatic and vein permeation from the metastatic tumors in the node. Partially the cancer cells invade the wall to the extra-vascular tissues.
H-E ×100

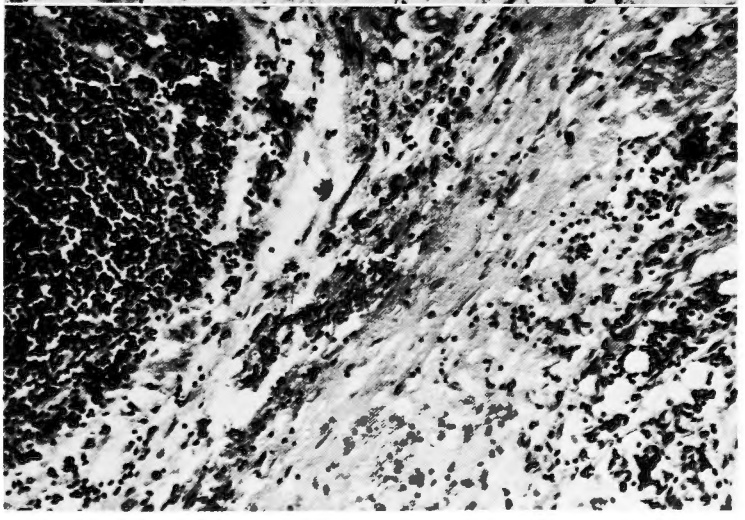

Fig. 7. Thickened capsule of the node with infiltration of cancer cells.
H-E ×100

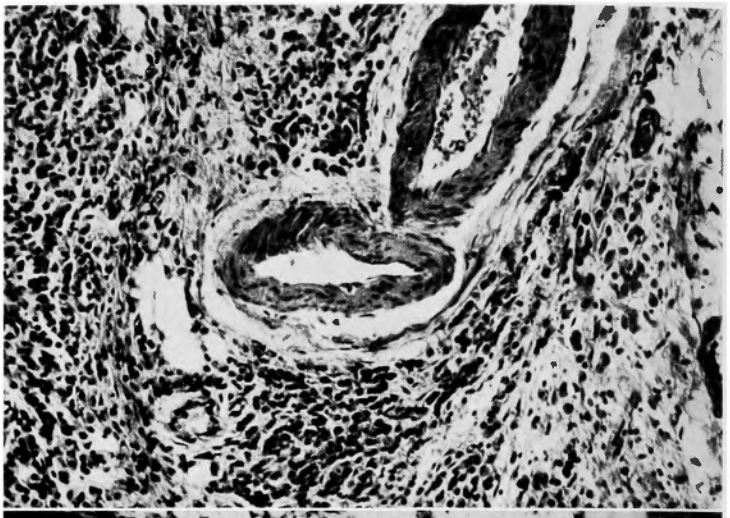

Fig. 8. Infiltration of undifferentiated cancer in the extra-nodal region, spreading chiefly along the vessels.
H-E ×100

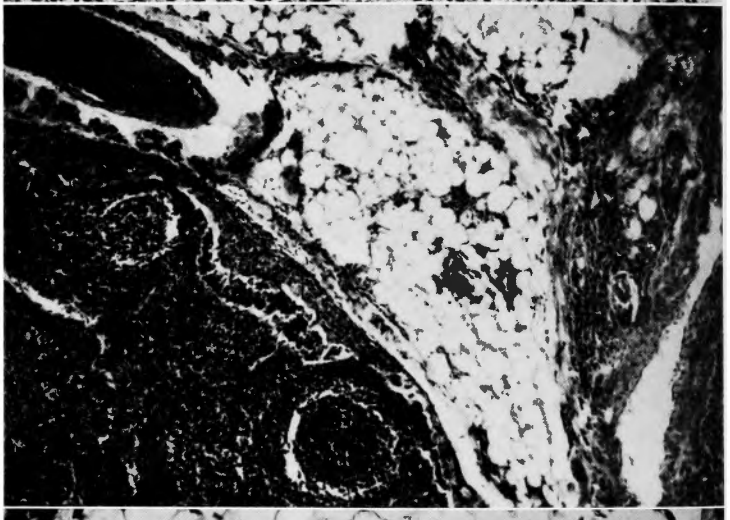

Fig. 9. SCpv.ad. Spread of undifferentiated cancer in the extra-nodal tissues, with scanty growth of tumors in the contiguous node.
H-E ×40

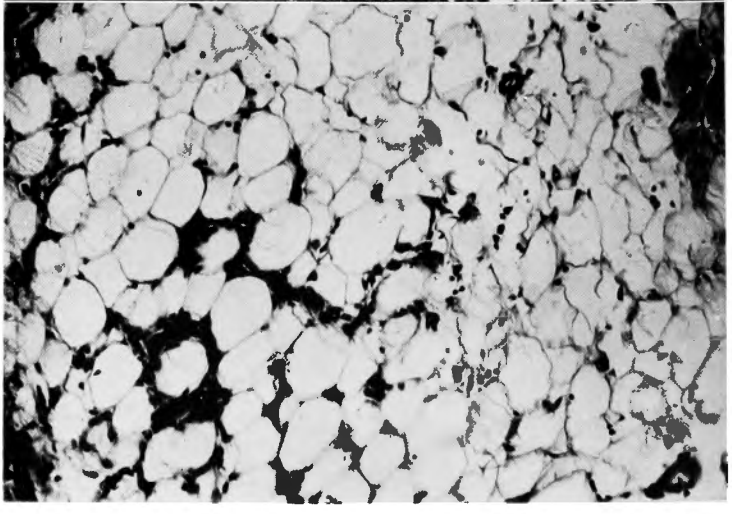

Fig. 10. Cancer cells in the intercellular interspaces of the extra nodal fatty tissue.
H-E ×100

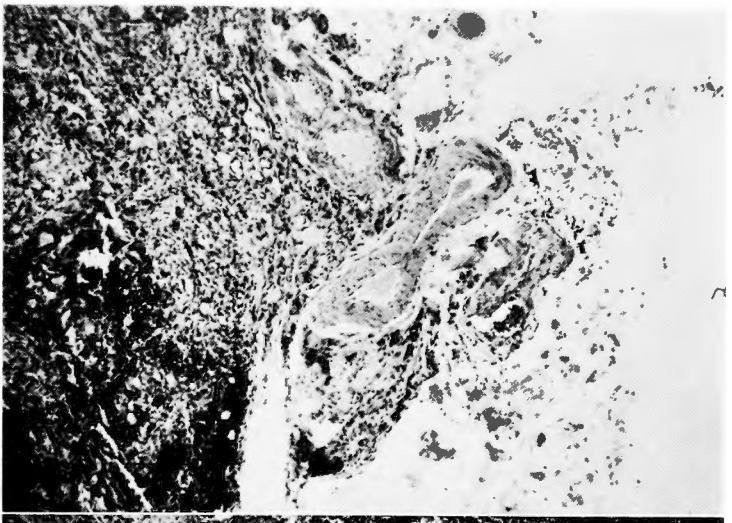

Fig. 11. Cly.pv.ad. Continuous infiltration from the lymphnodal metastasis to the extra-nodal tissues chiefly along the vessels at the part where the afferent lymphatics open into the sinuses.
H-E ×40

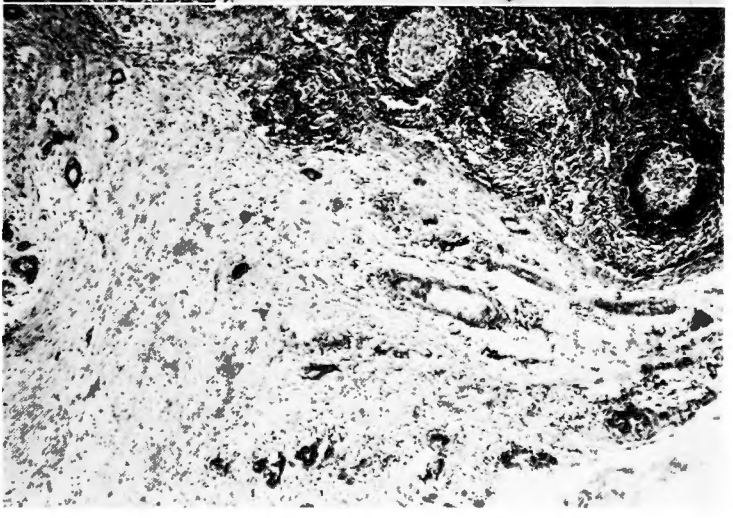

Fig. 12. The spread of cancer with glandular structure and proliferated stroma in the extra-nodal tissues from the primary tumor.
H-E ×40

和文抄録

胃癌における所属リンパ節の被膜外癌巣に関する組織学的研究

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胃癌根治手術例71例の新鮮材料を用い，特に胃癌の所属リンパ節の被膜外組織への癌進展状態を組織学的に検索した．手術標本は10%ホルマリン固定後にそれぞれのリンパ節を可及的に多くの周囲組織をつけたまま切り出し，連続切片によるヘマトキシリン・エオジン染色標本を作製観察した．同時に主腫瘍並びに他の転移巣についても詳細に検索し，胃癌研究会の規約に従つて分類した．また必要に応じ，Papの渡銀法またはvan Gieson染色標本を作製観察した．

検索症例71例中61例（85.9%）にリンパ節転移を認め，全リンパ節945個中382個（40.6%）が転移リンパ節であつた．このうち約半数は肉眼的に転移を証明できなかつた．また一般にリンパ節の大きさが大きい群ほど転移リンパ節が多く，長径20mm以上のリンパ節には全例に転移が認められたが，長径5mm未満のものにもその24.6%に転移を認め，これらの大部分は肉眼的に転移を証明できなかつた．これら945個のリンパ節について，その周囲組織を検索しそこに認められた癌巣または癌細胞群についてその組織学的所見と原発巣及び転移巣における癌進展状態との関係を考察し次の結論を得た．

1）胃癌71例のリンパ節945個中35例（50.3%），116個（12.3%）に被膜外癌巣が認められた．これら被膜外癌巣を伴つたリンパ節の大部分は第1群のリンパ節で，9個が第2群以上のリンパ節であつた．

2）これら被膜外癌巣と隣接リンパ節内の転移巣との関係から4型を区別した．隣接リンパ節内に転移を認めないもの（MO型）は15例，リンパ節内の転移巣から離れた部位に被膜外癌巣のあるもの（S型）は31例，リンパ節内の転移巣から連続的にリンパ節外へ進展しているもの（C型）43例，S型とC型の両者をもつもの（SC型）は27例であつた．

3）これら被膜外癌巣の殆どが，未分化な癌細胞よりなる癌細胞群乃至小癌巣であり，肉眼的に確認できるほどの発育を示すものは認められなかつた．これらは，リンパ管内または血管内の腫瘍栓塞または連続浸潤，旁脈管性の浸潤或は脂肪組織等の組織間隙における浸潤として認められた．これら癌細胞群には直接原発巣に由来するものと，隣接リンパ節内の転移巣から進展したものがあり，前者は組織間隙を介しての連続浸潤，リンパ管及び血管を介しての腫瘍栓塞または連続浸潤，腹腔を介しての播種の他に非連続性の組織間隙浸潤があり，脈管外通液路系による転移の可能性が思考された．後者に於てもリンパ節内転移巣が被膜を破つて連続性に浸潤するものの他にリンパ行性または血行性に連続的または非連続的に進展したと考えられる所見を認めまた，リンパ節転移巣は必ずしもその末期に至るまでリンパ節内での発育にとどまるとは限らず，むしろその初期に於てもリンパ節外へ小癌巣として進展する場合の多い事を知つた．

4）被膜外癌巣の出現頻度およびその進展状態は原発巣の組織像およびその進展様式をよく反映している点が注目された．特に胃癌手術の予後に影響を与えると考えられている原発巣の諸因子が被膜外癌巣と密接な関係を有することを認め，従つて，これら因子が一面では胃外軟部組織への癌進展の難易性に関連していると解釈し得よう．

5）また早期胃癌においても，胃外軟部組織内に癌巣の存在する可能性を常に考慮しなければならない．

6）以上の所見から，被膜外癌巣は胃癌手術後の再発に関連した重要な要因の一つと考えられる．またリンパ節廓清に際してはできるだけbloc dissectionの立場に立つべきことを強調したい．

（本論文の要旨は第24回日本癌学会総会に於て発表した）