Acta Medica et Biologica
Vol. 42, No. 3, 87-102, 1994

Carcinoid Tumors: A Statistical Analysis of a Japanese Series of 3,126 Reported and 1,180 Autopsy Cases

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Received June 24, 1994

Summary. **A series of carcinoid cases, 3,126 reported and 1,180 autopsied, were statistically analyzed from various clinicopathologic viewpoints of site(organ)-distribution of carcinoids with a comparative evaluation between Japanese and US/European series, age-distribution and sex preponderance of the patients, clinical manifestations including the carcinoid syndrome, and pathology consisting of histologic patterns, silver impregnations, immunocytochemistry and electron microscopy.**

It is considered that the concept, definition and diagnostic criteria of carcinoids, particularly of atypical varieties, and of related endocrinomas represent some controversial points that have to reach a general agreement. It is emphasized that the immunological techniques, consisting of amine/peptide hormone assays in the serum and tumor tissue extracts and histochemistry (immunocytochemistry) in the tissue preparations, that have been recently developed and popularized for practical use, will play an important role in elucidating the pathological entity of carcinoids as gut-endocrinomas.

Introduction

Since the nomenclature "carcinoid (karzinoide Tumoren)" and its concept were proposed in 1907,[1] gut-endocrinomas with this naming have become common findings on one hand, while the initial concept of such endocrinomas has been changed and revised to a certain extent over the past several decades on the other.[2,3] While the nomenclature "carcinoid" may be a misnomer,[2] this nomenclature has become too widely accepted to be converted to other expressions. To avoid confusion in the concept, definition and criteria of carcinoids, it is hoped that we might reach a world-wide agreement on these points. The purpose of this study is to analyze and evaluate the present status of carcinoids as has been reported at authorized medical congresses or meetings or in journals and recorded in the autopsy series, in order to contribute to the future development in investigation in this particular field of gut-endocrinological research.

Materials and Methods

A total of 3,126 clinically reported and 1,180 autopsy cases of carcinoids were collected from the Niigata Registry,[4] in which gut-endocrinomas (carcinoids) of both reported as Japanese at authorized medical congresses or meetings or in journals, and recorded in "Annual of Pathological Autopsy Cases in Japan"[5] were computerized in such a way as to avoid any duplication of individual cases on the basis of the age or sex of the patients, the authors or co-authors of the reports, clinical and laboratory data, or the source of materials such as institutes, universities or hospitals.

The data were statistically analyzed from various aspects of clinical and pathologic findings.

Observations and Considerations

1. Overall investigation (Tables 1A and 1B: Fig. 1)

1) Site(organ)-distribution of carcinoids: Fig. 1 reveals the chronological changes in the number of all reports regardless of the duplication of individual cases, related references and reports on carcinoid cases avoiding a duplication. All these show a rapid increase in the past 15 years (starting around 1980).

The site-distribution of 3,126 cases of the reported series and 1,180 cases of the autopsy series is shown in Table 1A. These are divided into two categories: digestive and extradigestive groups. The former

group comprises 69.0% (2,156/3,126) and 70.0% (826/1,180) of the entire series of carcinoids in reported and autopsy cases, respectively.

The reported series indicates a high incidence of site-distribution of carcinoids in the rectum, lung, stomach, and duodenum in this order, while the autopsy series exhibits such in the lung, rectum, stomach, small intestine and duodenum in a partly revised order.

2) Unusual sites of carcinoid origin: Table 1B shows unusual sites of carcinoid origin that are included in Table 1A. In most cases of primary hepatic carcinoids, other possible sites of origin are systemically searched with unsuccessful results: they are considered to have originated in the epithelium of the intrahepatic biliary tract. Carcinoids of the pancreas may belong to the category of "pancreatic endocrinoma", and the diagnostic criteria may be different depending on the pathologists in charge of the diagnosis.

Table 1A. Sites and distribution of carcinoids: Japanese series and US/European series.

Sites/organs	Japanese series 1994		Wedell[6]	Cheek[7]	Orloff[8]	Sanders[9]	Godwin[10] 1975	
	Reported[4]	Autopsy[5]	1969	1971	1971	1973	ERG	TNCS
Esophagus	38 (1.8)	14 (1.7)		1 (0.03)		1 (0.03)		
Stomach	589 (27.3)	177 (21.4)	89 (3.3)	93 (2.5)	(2.5)	98 (2.7)	42 (2.5)	19 (2.4)
Duodenum	321 (14.9)	113 (13.7)	64 (2.4)	135 (3.7)	(1.3)	80 (2.2)	33 (2.0)	22 (2.8)
Jejunum					(1.5)		19 (1.1)	19 (2.4)
Ileum	70 (3.2)	144 (17.4)	856 (31.9)	1,032 (28.0)	(27.5)	992 (27.3)	202 (12.2)	134 (16.8)
Small intestine							99 (6.0)	70 (8.8)
Meckel's diverculum	2 (0.09)	2 (0.02)	32 (1.2)	42 (1.1)	(1.0)	46 (1.27)		
Ileocecal region	24 (1.1)	11 (1.3)					14 (0.8)	0
Appendix*	142 (6.6)	21 (2.5)	1,241 (46.3)	1,686 (45.8)	(47.0)	1,609 (44.3)	820 (49.4)	340 (42.7)
Colon	69 (3.2)	54 (6.5)	72 (2.7)	91 (2.5)	(2.0)	94 (2.6)	122 (7.3)	65 (8.2)
Intestine							11 (0.7)	6 (0.8)
Rectum	781 (36.2)	179 (21.7)	319 (11.9)	592 (16.1)	(17.0)	706 (19.4)	296 (17.8)	121 (15.2)
Hepatobiliary tract**	97 (4.5)	56 (6.8)	7 (0.3)	12 (0.3)	(0.2)	7 (0.2)	2 (0.1)	0
Pancreas	23 (1.1)	55 (6.7)						
Subtotal	2,156 (100.0)	826 (100.0)	2,680 (100.0)	3,684 (100.0)	3,000 (100.0)	3,633 (100.0)	1,660 (99.9)	796 (100.1)
Lung/bronchus	602	247					191	137
Thymus/mediastinum	183	53						
Breast	27	5						
Ovary	54	4		34			0	3
Miscellaneous**	104	45	12				16	34
Subtotal	970	354	12	34			207	174
Total	3,126	1,180	2,692	3,718	3,000	3,633	1,867	970

ERG: End Results Group, TNCS: Third National Cancer Survey.
* Including 41 goblet cell type carcinoids. ** See Table 1B. ( ): %-Incidence.

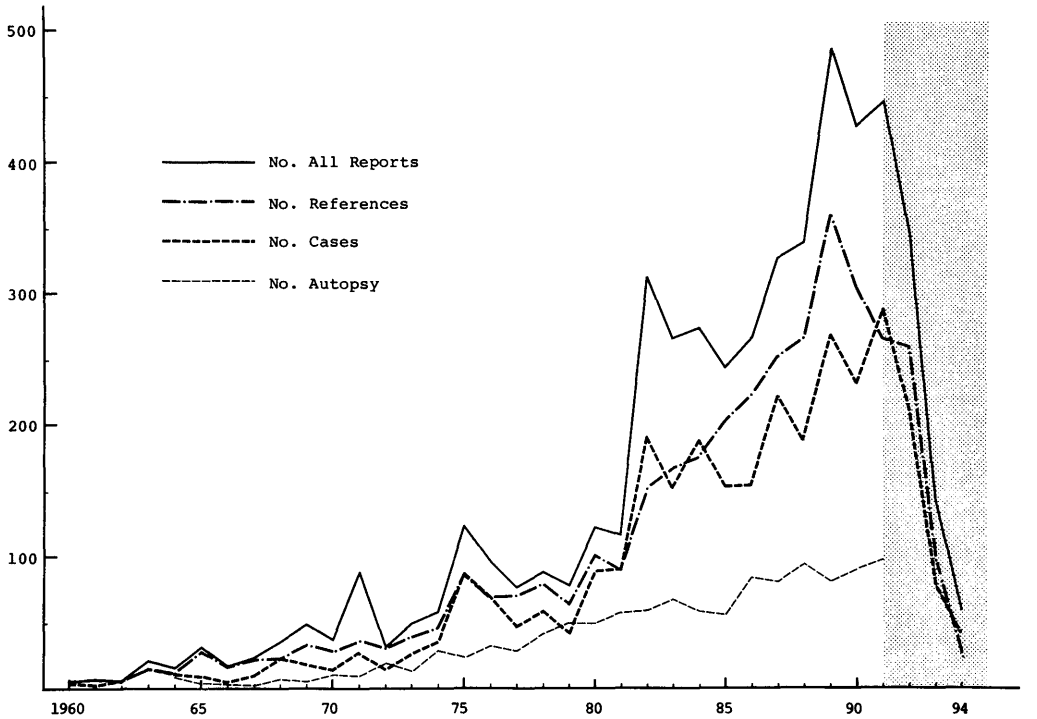

Fig. 1. Chronology of changes in research activity in carcinoids. Each line indicates respectively the number of all reports, references and reported cases excluding duplication, and autopsy cases.[4]

Table 1B. Unusual sites of carcinoid origin.

Sites	No. cases
Liver	31
Uterine cervix	28
Breast	27
Pancreas	23
Larynx	16
Testis	10
Middle ear	9
Urinary bladder	7
Kidney	5
Retroperitoneal region	5
Maxillary region	4
Others or not specified	20
Total	215

2. Comparison between the Japanese series and US/European series of reported cases (Table 1A: Fig. 2)

Table 1A and Fig. 2 indicate comparative information on the sites or organs and the distribution of carcinoids among both reported and autopsy cases of the Japanese series,[4,5] and authorized representative series of US/European cases.[6-10]

One of the most significant differences is found in the site-distribution of carcinoids in the digestive system. The US/European series exhibits an almost identical incidence in the site-distribution of carcinoids: a high incidence in the appendix (42.7-49.4%), small intestine (12.2-31.9%) and rectum (11.9-19.4%) in this order, while the present Japanese series shows a high incidence in the rectum (36.2%), stomach (27.3%) and duodenum (14.9%) in this order, and a relatively low incidence in the appendix (6.6%) and small intestine (3.3%). The incidence is also significantly different in the hepatobiliary-pancreatic system between the Japanese series and US/European series.

3. Autopsy series (Tables 1A and 2: Fig. 2)

1) The incidence in site-distribution: Tables 1A and 2 show the site-distribution of 1,180 carcinoids in the autopsy series collected from the "Annual of Pathological Autopsy Cases in Japan"[5] in a period for 28 years between 1964 and 1991.

A significant increase in the incidence of autopsy cases of carcinoids in comparison with reported cases is obvious in the small intestine (17.4% vs 3.3%: $P<0.01$), while a decrease is statistically significant ($P<$

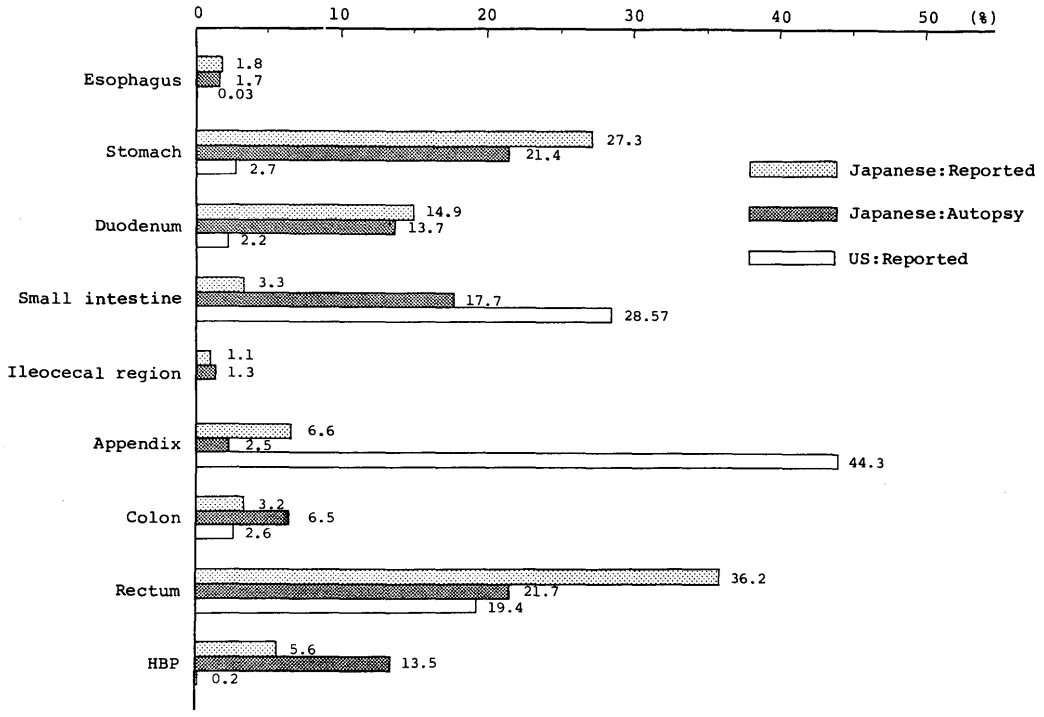

Fig. 2. A statistical comparison of site (organ)-distribution of digestive carcinoids between the Japanese[4] and US/European series.[9] HBP: Hepatobiliary-pancreatic system.

0.01) in the stomach (21.4% vs 27.3%), appendix (2.5% vs 6.6%) and rectum (21.7% vs 36.2%). In the Japanese autopsy series the incidence of carcinoids in the small intestine approximates the US/European series, while that in the appendix reveals a further decrease to only 2.5%.

It is remarkable that the incidence of carcinoids in the hepatobiliary-pancreatic system of autopsy cases shows a significant increase ($P<0.01$) within the Japanese series.

2) Chronological changes in the detection of carcinoids: Table 2 shows chronological incidence in the site-distribution of carcinoids. The detection rate of carcinoids in the first 5 years from 1964 to 1968 is 0.029% and that in the last 3 years from 1989 to 1991 is 0.239%, with a significant increase ($P<0.01$), suggesting that the attention to carcinoids has increased among physicians and pathologists in accordance with the recognition of more acceptable diagnostic criteria and concepts of endocrinomas of this type over the past several years.

4. Considerations on the comparative evaluation of incidence in the site-distribution of carcinoids

The comparative evaluation of incidence in the site-distribution of carcinoids in the present study is, however, not necessarily decisive with certain factors as indicated below: The analytical values of site-distribution of carcinoids may not reflect a faithful representation of the actual occurrence in the sites of carcinoid origin.

1) The different background in collecting individual carcinoid cases: The present study deals with carcinoid cases selected from the Niigata Registry:[4] cases individually identifiable on the basis of several factors such as the sex and age of patients and so on as mentioned above; cases without individual identification are excluded to avoid duplication. In the US/European series, massive collections of cases from an institute or hospital without individual identification are often included. In addition, it is not unusual to report multiple cases of appendiceal carcinoids in a group from single US/European institutes, but this is not likely in Japan where no single institute or hospital has a collection of multiple cases of carcinoids, for example, of the appendix and small intestine.

2) The different situations of postgraduate medical trainings, medical evaluation and diagnostic criteria: In our country physicians are urged to publish medical findings including case reports to fulfill the re-

Table 2. Chronological analysis of autopsy cases: Incidence in site-distribution of carcinoids.

Sites	1964-68	1969-73	1974-78	1979-83	1984-88	1989-91	Total
Esophagus		2	3	2	6	1	14
Stomach	1	7	31	53	48	37	177
Duodenum	1	5	20	25	33	29	113
Small intestine	4	12	17	31	47	35	146
Ileocecal region	2	2	4	1	2		11
Appendix*	1		4	5	6	5	21
Colon	3	4	9	10	18	10	54
Rectum	4	9	19	40	62	45	179
Hepatobiliary tract**	2		6	18	15	15	56
Pancreas	1	2	5	11	28	8	55
Subtotal	19	43	118	196	265	185	826
Lung/bronchus	5	14	25	63	80	60	247
Thymus/mediastinum		1	9	13	16	14	53
Breast			1	1	2	1	5
Ovary				2	1	1	4
Miscellaneous***	5	3	4	11	12	10	45
Subtotal	10	18	39	90	111	86	354
Total	29	61	157	286	376	271	1,180
No. Autopsy cases	99,998	113,833	126,285	186,801	199,103	113,293	839,313
% Carcinoids	0.029	0.054	0.124	0.153	0.189	0.239	0.141

Collected and calculated from "Annual of Pathological Autopsy Cases in Japan."[5]
* Including 3 goblet cell type carcinoids.
** Including 22 primary hepatic carcinoids.
*** Including 5 carcinoids of the prostate, 3 of the uterine cervix, 2 each of the urinary bladder and retroperitoneal region, and one each of the larynx, pharynx, testis, ureter, et al.

quirements for medical certificates of varying types. In such circumstances, they are always looking for clinical problems worth publishing that may be otherwise easily disregarded. For instance, carcinoids of the appendix and small intestine are, among others, still rare tumors in Japan and regarded as cases worthwhile to report individually. Diagnostic criteria of carcinoids may differ depending on the surgical pathologists in charge of diagnosis, and on the period when the diagnosis is made. So-called endocrine cell carcinomas[11-13] that are differentiated from typical or classical carcinoids, for instance, may be excluded from the regular carcinoid series, while they can be reasonably categorized in atypical carcinoids mostly with a type D pattern.[14]

3) The difference in the actual occurrence of carcinoids: It is also considered likely that the incidence of carcinoids in certain organs may represent the actual occurrence of these tumors, although this may be modified by several factors such as the background of case collection, and racial or genetic and social or circumstantial factors. Statistical significances of a high incidence of carcinoids in the rectum and stomach, and of a low incidence of carcinoids in the appendix and small intestine in the Japanese series are not adequately explained simply by differences in analytical methods or the background of case collection.

5. Male/female ratio (Table 3): **Average age and age-distribution** (Table 4)

The male preponderance of carcinoids is seen in the esophagus and thymus/mediastinum, while those for females dominate in the appendix and hepatobiliary-pancreatic system. The female preponderance in appendiceal carcinoids is explained as a frequent incidental pathologic finding following gynecologic surgery in the US/European series,[9] but most appendiceal carcinoids in the present Japanese series are

Table 3. Male/female ratio.

Sites	No. cases	Male	Female	M/F ratio
Esophagus	38	29	9	3.2
Stomach	572	345	227	1.5
Duodenum	316	192	124	1.5
Small intestine	71	42	29	1.4
Ileocecal region	23	11	12	0.9
Appendix	140	58	82	0.7
Colon	67	40	27	1.5
Rectum	764	490	274	1.8
HBP*	119	48	71	0.7
Subtotal	2,110	1,255	855	1.5
Lung/bronchus	597	331	266	1.2
Thymus/mediastinum	182	136	46	3.0
Breast	25	4	21	0.2
Ovary	54		54	0.0
Miscellaneous	103	52	51	1.0
Subtotal	961	523	438	1.2
Total	3,071	1,778	1,293	1.4

* HBP : hepatobiliary-pancreatic system.

Table 4. Age-distributions and ranges.

Sites	Mean age			Ranges
	Male	Female	Overall	
Esophagus	62.1(29)	58.1(9)	61.2(38)	26 - 77
Stomach	57.7(345)	54.9(227)	56.6(572)	13 - 84
Duodenum	57.5(192)	58.0(124)	57.7(316)	9 - 87
Small intestine	55.4(42)	53.9(29)	54.8(71)	3 - 86
Ileocecal region	53.8(11)	70.3(12)	62.4(23)	36 - 85
Appendix	42.6(58)	37.5(81)	39.6(139)	9 - 92
Colon	53.7(40)	62.8(27)	57.3(67)	18 - 87
Rectum	51.2(490)	51.4(274)	51.3(764)	13 - 85
Hepatobiliary tract	61.9(39)	60.3(57)	61.0(96)	28 - 88
Pancreas	49.4(9)	43.8(14)	46.0(23)	12 - 77
Subtotal	54.4(1,255)	53.2(854)	53.9(2,109)	3 - 92
Lung/bronchus	50.1(331)	49.2(266)	49.7(597)	8 - 85
Thymus/mediastinum	49.0(136)	52.2(46)	49.8(182)	10 -101
Breast	73.5(4)	61.3(21)	63.3(25)	34 - 83
Ovary		48.9(54)	48.9(54)	16 - 83
Miscellaneous	57.3(52)	48.9(51)	53.1(103)	16 - 89
Subtotal	50.7(523)	50.0(438)	50.4(961)	8 -101
Total	53.3(1,778)	52.1(1,292)	52.8(3,070)	3 -101

( ) : No. cases examined.

incidentally found in the appendix resected because of acute appendicitis.

The age-distribution (Table 4) indicates the youngest age group to be females with appendiceal carcinoids showing an average of 37.5 years, and the oldest age group again is females with carcinoids in the ileocecal region exhibiting an average of 70.3 years, as compared with an overall average of 52.8 years.

6. Clinical manifestations (Table 5)

Table 5 shows predominant clinical manifestations of carcinoids represented mainly by the signs and symptoms and sites of carcinoids in order of the incidence of the clinical manifestations. Most cases of digestive carcinoids are accompanied by abdominal pain. In addition, carcinoids are characterized by dysphagia in the esophagus, by jaundice in the duodenum and in the hepatobiliary-pancreatic system, by an abdominal tumor and diarrhea in the colon, by melena in the rectum, by cough and bloody sputum in the lung, and by an abdominal tumor in the ovary. While appendiceal carcinoids in the Japanese series are most frequently accompanied by abdominal pain, the situation is quite different in the US/European series in that more than half of appendiceal carcinoids in the latter series are incidentally diagnosed in the asymptomatic appendix surgically removed in association with other surgery.[9]

7. Size-distribution (Table 6)

Size-distribution of carcinoids is shown in Table 6. Small-sized carcinoids less than 10 mm in diameter are frequently detected in the stomach and rectum by endoscopic observation among asymptomatic clients in mass survey or individual check-ups, particularly by systemic check-ups through AMHTS (Automated Multiphasic Health Testing and Services) that is now expanding worldwide.

8. Metastases and malignant nature (Table 7A, 7B and 7C)

1) Metastases and malignancy: The rate of metastases

Table 5. Clinical manifestations.

Signs and symptoms	Sites	%-Incidence
Abdominal pain	1. Appendix	93.2
	2. Colon	65.0
	3. Small intestine	57.1
	4. Hepatobiliary tract	48.2
Diarrhea	1. Ileocecal region	34.8
	2. Small intestine	28.6
	3. Colon	26.7
Dysphagia	1. Esophagus	40.0
Icterus	1. HBP	27.6
	2. Duodenum	15.4
Ileus/invagination	1. Small intestine	36.5
Melena	1. Rectum	21.9
	2. Ileocecal region	17.4
Palpable tumor	1. Ovary	60.4
	2. Colon	40.0
	3. Ileocecal region	34.8
	4. Small intestine	27.0
Cough/bloody sputum/hemaptysis	1. Lung/bronchus	65.3
Chest/back pain	1. Thymus/mediastinum	27.9
	2. Lung/bronchus	16.2

Table 6. Size-distribution of carcinoids.

Sites	No. cases	Size (mm)							
		-10	-20	-30	-40	-50	-70	-100	101-
Esophagus	26	23.1	7.7	15.4	19.2	7.7	11.5	11.5	3.8
Stomach	457	32.6	22.1	10.5	9.0	5.3	9.8	7.0	3.7
Duodenum	262	49.2	25.2	10.7	8.4	3.8	1.1	1.5	
Small intestine	43	14.0	32.6	9.3	16.3	9.3	9.3	7.0	2.3
Ileocecal region	17		11.8	11.8	17.6	23.5	17.6	5.9	11.8
Appendix	95	60.0	20.0	3.2	4.2	3.2	5.3	3.2	1.1
Colon	60	8.3	5.0	3.3	8.3	11.7	13.3	31.7	18.3
Rectum	718	71.2	17.4	5.2	1.7	2.4	1.0	1.0	0.2
Hepatobiliary tract	72	12.5	27.8	13.9	9.7	5.6	6.9	6.9	16.6
Pancreas	16		6.3	12.5	6.3	25.0	25.0	6.3	18.8
Subtotal	1,766	49.4	20.0	7.9	6.1	4.5	4.9	4.4	2.8
Lung/bronchus	340	13.2	27.4	18.5	16.2	10.0	8.2	4.1	2.4
Thymus/mediastinum	108	1.9	0.9	0.9	0.9	13.0	24.1	23.1	35.2
Breast	20		15.0	45.0	15.0	5.0	10.0	10.0	
Ovary	39	12.8	10.3		7.7	7.7	12.8	20.5	28.2
Miscellaneous	59	20.3	8.5	16.9	18.6	3.4	11.9	13.6	6.8
Subtotal	566	11.3	18.7	14.7	12.9	9.5	12.0	10.1	10.8
Total	2,332	40.1	19.7	9.6	7.7	5.7	6.6	5.8	4.8

All figures under the columns of size-distribution indicate %-incidence to the number of cases of each organ as the site of origin.

Table 7A. Metastases.

Sites	No. cases	Rates of metastases %
Esophagus	38	55.3
Stomach	589	35.3
Duodenum	321	23.4
Small intestine	72	55.6
Ileocecal region	24	66.7
Appendix	142	13.4
Colon	69	53.6
Rectum	781	17.5
Hepatobiliary tract	97	49.5
Pancreas	23	69.6
Subtotal	2,156	28.6
Lung/bronchus	602	19.9
Thymus/mediastinum	183	44.3
Breast	27	33.3
Ovary	54	9.3
Miscellaneous	104	38.5
Subtotal	970	26.3
Total	3,126	27.9

Table 7B. Primary sites of carcinoids and rates of metastases.

	Size (mm)								Subtotal	Unknown	Total
	-10	-20	-30	-40	-50	-70	-100	101-			
Site of metastases	936	459	223	180	133	155	135	111	2,332	794	3,126
Lymph node	3.8	17.9	27.8	29.4	34.6	36.1	51.1	27.9	18.7(435)	15.5(123)	17.8(558)
Liver	2.0	10.9	22.9	22.2	24.8	25.2	31.9	20.7	12.8(298)	16.5(130)	13.7(428)
Lung	0.4	1.7	4.9	4.4	7.5	10.3	9.6	12.6	3.6(84)	4.0(32)	3.7(116)
Bones	0.2	1.5	5.8	4.4	4.5	8.4	6.7	9.0	2.9(68)	5.2(41)	3.5(109)
Peritoneum	0.1	1.5	2.2	2.8	0.8	3.2	10.4	6.3	1.9(45)	2.6(21)	2.1(66)
Adrenal	0.2	0.2	2.2	2.2	3.8	2.6	5.9	4.5	1.4(32)	1.3(10)	1.3(42)
Pancreas	0.3	0.9	2.7	2.2	3.8	5.2	6.7	3.6	1.8(43)	3.3(26)	2.2(69)
Cases with metastases											
Overall No.	47	115	90	75	67	86	79	52	611	262	873
(%)	5.0	25.1	40.4	41.7	50.4	55.5	58.5	46.8	26.2	33.0	27.9
Stomach	10	28	22	22	17	33	25	9	166	42	208
(%)	6.7	27.7	45.8	53.7	70.8	73.3	78.1	52.9	36.3	31.8	35.3
Rectum	17	31	24	12	13	7	6	2	112	25	137
(%)	3.3	24.8	64.9	100.0	76.6	100.0	85.7	100.0	15.6	39.7	17.5
Lung/bronchus	1	11	12	9	11	14	5	5	68	52	120
(%)	2.2	11.8	19.0	16.4	32.4	50.0	35.7	62.5	20.0	19.8	19.8

All figures under the columns of size-distribution in the upper part of the table indicate %-incidence of metastases to each organ or tissue. ( ): No. cases examined.

Table 7C. Primary sites of carcinoids and sites of metastases.

Sites	No. cases with metastases	Lymph node	Liver	Lung	Bones	Peritoneum	Adrenal	Pancreas
Esophagus	21	76.2	61.9	33.3	38.1	14.3	14.3	4.8
Stomach	208	71.6	57.7	9.1	4.3	6.7	4.3	6.3
Duodenum	75	74.7	44.0	4.0	2.7	6.7		4.0
Small intestine	40	75.0	57.5	5.0	7.5	27.5	2.5	5.0
Ileocecal region	16	87.5	31.3	18.8	6.3	12.5		12.5
Appendix	19	57.9	5.3	5.3		63.2		10.5
Colon	37	64.9	54.1	13.5	5.4	10.8	2.7	5.4
Rectum	137	52.6	65.0	5.8	5.8	1.5	1.5	5.1
Hepatobiliary tract	48	54.2	77.1	12.5	12.5	6.3	4.2	14.6
Pancreas	16	62.5	75.0	37.5	6.3	12.5	18.8	12.5
Subtotal	617	66.1	57.2	9.7	6.5	9.4	3.4	6.6
Lung/bronchus	120	58.3	38.3	16.7	25.8		11.7	11.7
Thymus/mediastinum	81	59.3	8.6	30.9	33.3		4.9	8.6
Breast	9	77.8	11.1	11.1	11.1			11.1
Ovary	5	20.0	80.0	20.0	20.0	40.0		
Miscellaneous	40	60.0	42.5	22.5	22.5	15.0	7.5	15.0
Subtotal	255	58.8	29.4	22.0	27.1	3.1	8.2	11.0
Total	872	64.0	49.1	13.3	12.5	7.6	4.8	7.9

of carcinoids regardless of their size is shown in Table 7A. The true evaluation of malignancy should be carried out by histological examination on the invasive nature of individual cases. In this regard, a trial to scrutinize 125 cases of gastrointestinal carcinoids was performed, resulting in a decisive conclusion that this series exhibited a 100% maligancy rate including 18 cases of submucosal lesions with "possible malignancy."[15] Since, in the precise observation on early stage carcinoids or microcarcinoids of the stomach, the initiation of a carcinoid occurs in the basal region of the gastric glands,[16] it is worthy to consider that all submucosal lesions are one of the invasive patterns of neoplasms of this type, even if they are well-circumscribed and regularly-arranged or cytologically non-aggressive. It is well known that cytologically non-aggressive carcinoids often metastasize through hematogenous routes.

2) Size-distribution of carcinoids and sites of metastases: Table 7B shows the correlation between the size of carcinoids and sites of metastases, revealing a high incidence of the hematogenous spread of these tumors. Attention should be drawn to the relatively high incidence of metastases noted in small-carcinoid groups with a size of 10 mm or less, exhibiting 5.0% (47/936) for the overall incidence rate, and 6.7% (10/149) for the rate in the gastric carcinoid group.

Table 8. 5-HT activity.

Sites	No. cases	Positive	%
Esophagus	5	1	20.0
Stomach	163	33	20.2
Duodenum	90	12	13.3
Small intestine	21	15	71.4
Ileocecal region	7	2	28.6
Appendix	7	3	42.9
Colon	14	5	35.7
Rectum	199	19	9.5
Hepatobiliary tract	13	6	46.2
Pancreas	9	9	100.0
Subtotal	528	105	19.9
Lung/bronchus	140	59	42.1
Thymus/mediastinum	26	2	7.7
Breast	1	0	0.0
Ovary	4	1	25.0
Miscellaneous	20	9	45.0
Subtotal	191	71	37.2
Total	719	176	24.5

3) Primary sites of carcinoids and sites of metastases: A significantly high incidence of hematogenous metastases represented by hepatic involvement exceeding that of lymphogenous metastases is apparent particularly in the rectum, hepatobiliary-pancreatic system and ovary (Table 7C).

9. 5-HT (5-hydroxytryptamine: serotonin) activity (Table 8)

High 5-HT activity is estimated by plasma levels of 5HT and urinary 5-HIAA (5-hydroxyindole acetic acid) calculated in patients with carcinoids and summarized in Table 8. Approximately one fourth (24.5%) of the cases recorded are accompanied by the abnormally high activity of 5-HT metabolism.

10. The carcinoid syndrome (Table 9A)

The incidence of the associated carcinoid syndrome in relation with primary sites of carcinoids is shown in Table 9A, indicating 2.6% in the digestive series and 4.5% in the extradigestive series with an overall average of 3.2%. In the representative US series,[7,9] the incidence of the associated carcinoid syndrome ranges from 1.7 to 3.2% in the digestive series. The carcinoid syndrome dominates in patients with carcinoids of the hepatobiliary-pancreatic system, small intestine and ileocecal region.

11. Symptomatology of the carcinoid syndrome (Table 9B)

Signs and symptoms included in the carcinoid syndrom are listed in Table 9B in the order of high incidence. Skin flush shows the highest incidence of all, and is apparently most specific to patients with carcinoids. High 5-HT activity measured in 101 patients with the carcinoid syndrome shows a significantly high incidence of 78.8% as compared to that in the general population of carcinoids (24.5%: Table 8). This fact indicates a possibility that a high 5-HT activity is, in most occasions, closely related to the carcinoid syndrome.

12. Histologic classification (Table 10)

Histologic classification of the 5 principal types based on the structural growth patterns of carcinoids[14] has been often employed in categorizing carcinoids and analyzing the prognosis of patients with carcinoids.[17]

Carcinoid growth pattern incidence rates are analyzed in relation to the primary sites of carcinoid

Table 9A. Incidence of the carcinoid syndrome.

Sites	Japanese series (1994)		US series	
	Incidence	Suspicious cases	Cheek (1971)[7]	Sanders (1973)[9]
Esophagus	0.0(0/ 38)	1	0.0(0/ 1)	0.0(0/ 1)
Stomach	3.2(19/ 589)	8	8.6(8/ 93)	7.1(7/ 98)
Duodenum	3.4(11/ 321)	1	3.9(4/ 135)	1.3(1/ 80)
Small intestine	11.1(8/ 72)	3	8.8(94/1,034)	4.3(45/1,038)
Ileocecal region	8.3(2/ 24)	1	———	———
Appendix	0.0(0/ 142)	2	0.4(6/1,686)	0.1(2/1,609)
Colon	5.8(4/ 69)	0	5.5(5/ 91)	3.2(3/ 94)
Rectum	0.5(4/ 781)	1	0.2(1/ 592)	0.3(2/ 706)
Hepatobiliary tract	5.2(5/ 97)	0	]	]
Pancreas	17.4(4/ 23)	0	]8.3(1/ 12)	]0.0(0/ 7)
Subtotal	2.6(57/2,156)	17	3.2(119/3,684)	1.7(60/3,633)
Lung/bronchus	5.8(35/ 602)	1		
Thymus/mediastinum	1.6(3/ 183)	1		
Breast	0.0(0/ 27)	0		
Ovary	5.6(3/ 54)	0	50.0(17/ 34)	
Miscellaneous	2.9(3/ 104)	0		
Subtotal	4.5(44/ 970)	2	50.0(17/ 34)	
Total	3.2(101/3,126)	19	3.7(136/3,718)	1.7(60/3,633)

origin (Table 10). The growth pattern in the present series is described in 606 cases and the rate of metastases is significantly high ($P<0.01$-0.05) in the type D group as compared to the other groups, suggesting a poor prognosis that is in accordance with the report published by one of the largest Oncology Groups organized in the United States.[17]

13. Depth of invasion and metastases (Table 11)

Table 11 shows the correlation between the depth of invasion and rates of metastases in 1,348 gastrointes-

Table 9B. Symptomatology of the carcinoid syndrome.

[n=104]	No. cases	%-Incidence
Flush	67	66.3
Diarrhea	43	42.6
Hepatomegaly	16	15.8
Cardiac disorder	12	11.9
Carcinoid heart	9	8.9
Asthma-like episodes	5	4.6
5-HT activity	52/66	78.8

Table 10. Histologic types and metastases.[14]

Sites of metastases	A	B	C	D	E	Total
Rates of metastases in cases (n=146) with metastases:						
Lymph node	76.5	65.2	70.0	77.2	75.7	74.0
Liver	52.9	47.8		59.1	47.3	46.6
Lung	11.8		10.0	13.6	12.2	10.3
Peritoneum	17.6	8.7	20.0	9.1	4.1	8.2
All over positive %	24.6	13.5	22.7	46.8*	26.9	24.1
(n)	(17/ 69)	(23/171)	(10/ 44)	(22/ 47)	(74/275)	(146/606)

*-Significantly high ($p<0.01$-0.05) as compared with remaining groups.

Table 11. Depth of invasion and metastases.

Depth	Intramucosal	Submucosal	Muscular layer	Transmural	To neighboring structures	Total
	%	%	%	%	%	%
Overall	0.0(47)	13.5(793)	42.4(158)	58.8(267)	71.1(83)	28.9(1,348)
Stomach	0.0(24)	16.4(214)	57.1(42)	78.7(89)	70.8(24)	37.2(393)
Rectum	0.0(12)	9.4(395)	47.9(48)	75.0(36)	100.0(7)	18.9(498)

( ): No. cases examined

Table 12. Diagnostic significance of silver impregnations.

Sites	No. cases	G(−)F(−)	G(+)F(−)	G(+)F(+)	G(−)	G(+)	G(+)%
Esophagus	29	2	14		3	10	82.8
Stomach	276	14	121	17	4	120	93.5
Duodenum	146	19	39	8	10	70	80.1
Small intestine	16	2	3	7		4	87.5
Ileocecal region	7			4		3	100.0
Appendix	63	1	15	34	3	10	93.7
Colon	32	5	7	4	6	10	65.6
Rectum	385	114	158	34	31	48	62.3
Hepatobiliary tract	69	2	27	8		32	97.1
Pancreas	16		7	1	2	6	87.5
Subtotal	1,039	159	391	117	59	313	79.0
Lung/bronchus	199	5	45	11	6	132	94.5
Thymus/mediastinum	86	5	20	3	9	49	83.7
Breast	22	3	5	1		13	86.4
Ovary	46	5	17	12		12	89.1
Miscellaneous	76	1	30	8	4	33	93.4
Subtotal	429	19	117	35	19	239	91.1
Total	1,468	178	508	152	78	552	82.6

G: Grimelius' argyrophilia, F: Fontana-Masson argentaffinity. Argentaffin cell type 18.1% (152/838), Argyrophil cell type 60.6% (508/838), Non-reactive cell type 21.2% (178/838).

Table 13. Immunocytochemistry.

	HT	Gs	Sm	Vp	Gl	CT	AC	PP	In	CG
No. cases examined (n=676)	327	236	818	96	224	183	141	136	110	154
Positive (%)	53.2	28.0	34.9	11.5	22.3	21.3	29.1	36.0	2.7	74.7

HT: serotonin, Gs: gastrin, Sm: somatostatin, Vp: vasoactive intestinal polypeptide, Gl: glucagon, CT: calcitonin, AC: ACTH, PP: pancreatic polypeptide, In: insulin, CG: chromogranin.

tinal carcinoids and representative series of gastric and rectal carcinoids. The rate of metastases in the entire series of 1,348 carcinoids is calculated as 28.9%, and is significantly ($P<0.01$) higher (37.2%) in the gastric carcinoid group and lower (18.9%) in the rectal carcinoid group. The considerable high rates of metastases in the mid-advanced (with invasion to the muscular layer: overall 42.4%) and advanced (with transmural invasion: overall 58.8%) carcinoid series may draw the attention of surgeons. It is also shown that gastrointestinal carcinoids not infrequently metastasize even in the relatively early stage (with invasion to the submucosa: 16.4% in gastric carcinoid series).

14. Diagnostic significance of silver impregnations (Table 12)

The response of carcinoid tissue to silver impregnations is recently represented most often by Grimelius' argyrophilia or by Fontana-Masson's argentaffinity. The combination of these two enables us to make a classification of carcinoids depending on silver reactivity. Table 10 shows such a classification with 3 categories with a diagnostic value of Grimelius argyrophilia that is calculated as 82.6%.

15. Immunocytochemistry (Table 13)

It is widely known that gut-pancreatic endocrinomas in general often produce multiple brain-gut hormones or active substances of amine and peptide types (multisecretors). In the present series 676 cases are recorded for immunocytochemical analysis, all but 3 reported since 1980. Table 13 shows representative active substances and the incidence of a positive response of carcinoid tissue to each of these substances, indicating that the highest reactivity of 53.2% is shown by 5-HT.

Although immunocytochemical techniques have been recently popularized, most cases of gut-pancreatic endocrinomas reported prior to 1980 have no advantage of such detective methods. This means that the incidence of multisecretors is to increase in the future.

Table 14. Ultrastructure of carcinoid granules.

Electron microscopy performed	843 cases : 27.0%
Granular configurations described	634 cases
Pleomorphic granules contained	79 : 12.5%
Round granules only	555 : 87.5%
Size range	100-1100 nm

16. Electron microscopic evaluation (Table 14)

There are 843 cases (27.0%) of carcinoids in which electron microscopic observation is described. Of these the configuration of endocrine granules is described in 634 cases: round granule type is recorded in 555 (87.5%) and pleomorphic (EC) granule type in 79 (12.5%). A brief description of the presence of endocrine granules in neoplastic cells without explaining the configuration of the granules is made in 199 cases, and unsuccessful identification of granules in the remaining 10 cases. More than 2 types of endocrine cells are pointed out in at least 23 cases. The size of endocrine granules ranges between 100 and 1,100 nm.

17. Carcinoids of unusual histology

1) Goblet cell carcinoids: A total of 53 cases of goblet cell carcinoids and related neoplasias are recorded in the present series. Of these, 41 (77.4%) are included in the series of appendiceal carcinoids. Goblet cell carcinoids[18,19] are one of the composite tumor types represented by type C components.[14]

2) Composite tumors with carcinoid components: These are variously called adenocarcinoids, mucinous carcinoids, goblet cell carcinoids, and others. Composite tumors with endocrine elements, composite A, B and C tumors, may offer an important clue for clarifying the histogenesis of both endocrine and non-endocrine neoplasias.[20] In the present series there are 8 cases of mixed carcinoid/carcinomatous components with definite transitions between them (composite A). Furthermore, coexisting components

Table 15. Multiple gastric carcinoids with atrophic gastritis, achylia, hypergastrinemia complex.

No. of gastric carcinoids	589
Multiple	113
[A] Atrophic gastritis (A type)	67
[B] Achylia/Achlorhydria	34
[C] Hypergastrinemia	86
[D] Antral gastrinosis (G cell hyperplasia)	12
[E] ECLoma	5
[F] Pernicious anemia	9
[A+B+C]	21
[A+B+C+D]	7
[A+B+C+E]	2
[A+B+C+F]	1

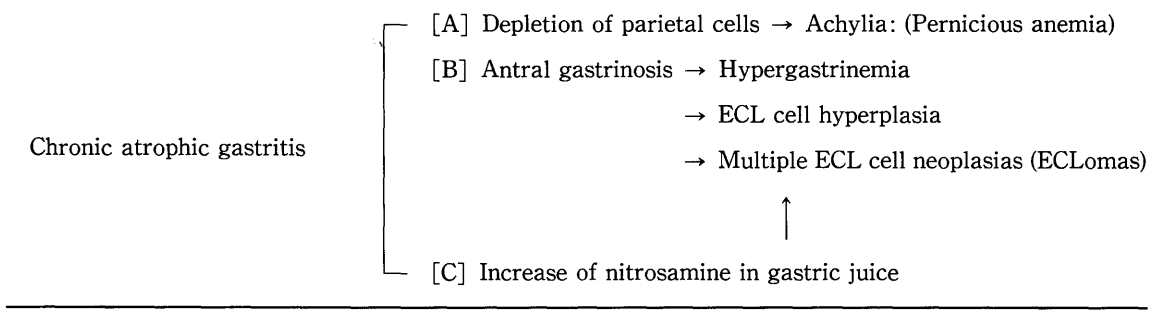

Fig. 3. Possible mechanism of clinicopathologic complex with chronic atrophic gastritis, hypergastrinemia, antral gastrinosis, ECL cell hyperplasia and multiple gastric carcinoids (ECLomas). (Modified from E. Wilander, 1981[24]).

of both tumors that may lead either to a composite A or simply to a collision tumor are also available in 64 cases. Goblet cell carcinoids and related neoplasias expressed under different nomenclatures such as argentaffin cell adenocarcinomas[21] are one of the typical examples of a composite B tumor.

18. Carcinoids of special attention (Table 15: Fig. 3)

Multiple gastric carcinoids with chronic atrophic gastritis, achylia, pernicious anemia, antral gastrinosis (gastrin (G) cell hyperplasia), hypergastrinemia and ECL cell hyperplasia are a well-known clinicopathologic complex[22-24] whose detailed mechanism is not sufficiently well understood.

At present Fig. 3[24] may suggest a possible mechanism for this particular complex.

Table 15 summarizes related information. Pernicious anemia is definitely rare in the Japanese as compared to the US/European series. Among 589 patients with gastric carcinoid, only 21 (3.6%) seem to fulfill the criteria of this complex consisting principally of triads of 1) atrophic gastritis, 2) achylia and 3) hypergastrinemia, accompanied by multiple gastric carcinoids.

Comments

A. Categorization of carcinoids

While the term "carcinoid" may be a misnomer,[2] there are many other expressions or synonyms given to neoplasias in this category as indicated below.

Synonyms: gut(urgut)-endocrinoma (malignant or benign), gut-endocrine carcinoma (in a broad sense), argentaffinoma, argyrophiloma, serotoninoma, enterochromaffinoma, ECLoma, carcinoid apudoma.

Since most carcinoids—particularly from the gastrointestinal tract—are nothing but carcinomas[2] in the sense of epithelial malignant tumors from the standpoint of histologic invasiveness in the submucosa or deeper in the underlying layers of the digestive canal,[15] the term gut-endocrine carcinoma may explain most types of carcinoids. In order to include a few histocytologically benign carcinoids with encapsulation in the extragastrointestinal regions such as lungs and pancreas, it seems that the term "gut-endocrinoma"[3] as a part of gut-pancreatic endocrinomas may offer a better understanding. We believe that the term "carcinoid", even though it may be a misnomer, should be preserved, albeit only with a complete understanding of its significance and entity, along with the vast amount of works performed under this nomenclature in the research field of gut-endocrinology by numbers of pioneers over many years past.

B. Classification of carcinoids

On any occasion the calssification should be simple and uncomplicated, or at least should not be confusing. It is preferable to divide carcinoids primarily into two groups, typical and atypical. The contents of the latter group are, however, inevitably complicated with many transitional and borderline neoplasias including composite varieties.[20]

1. Typical (classical, ordinary) carcinoids:
   Type A carcinoid: Insular type carcinoid
   Type B carcinoid: Trabecular type carcinoid
   Type E (mixed type) carcinoid
2. Atypical carcinoids:
   Type C carcinoid: Tubular (acinar) adenocarcinoid
   Type D carcinoid: Poorly to undifferentiated carcinoid
   Argentaffin cell adenocarcinoma
   Adenocarcinoid: Mucinous carcinoid

Goblet cell carcinoid
Endocrine cell carcinoma: Gut-endocrine carcinoma (in a narrow sense: mostly type D carcinoid)
Neuroendocrine carcinoma
Oat cell carcinoma of an endocrine type
Small cell carcinoma of an endocrine type
Composite A carcinoid
Composite B carcinoid
Composite C carcinoid

C. Concepts, definitions and diagnostic criteria of carcinoids

In the statistical series of carcinoids, there are certain controversial points in diagnostic criteria of carcinoids closely related to the concept and definition of these endocrinomas.[2,3] In the comparative statistical study of the organ-distribution of carcinoids between the Japanese and US/European series, it seems that the differences among the concept, definitions and diagnostic criteria may be attributed to the differences in incidence rates of carcinoids in the sites (organs) of carcinoid origin to a certain extent, although the reason may depend less on that of the difference of background in collecting cases as above-described.

On the basis of the concept that most carcinoids particularly from the gastrointestinal canal are considered carcinomas with varying degrees of malignancy,[15] carcinoids except for a few with a benign histocytology are endocrine (cell) carcinomas that are for such reasons included in the present series. Oat cell and small cell carcinomas with an evidence of endocrine origin are also thought to be one of the varieties of a type D carcinoid or an atypical carcinoid, and also included in the present series.

It has been found that unexpectedly large numbers of duodenal carcinoids produce somatostatin: Somatostatinomas are reported more often in the duodenum than in the pancreas,[25,26] and are rightfully called duodenopancreatic endocrinomas rather than pancreatic endocrinomas.[26] With an understanding of the concept of carcinoid somatostatinoma[25,27] meaning that an endocrinoma can be a carcinoid and simultaneously a somatostatinoma, most duodenal somatostatinomas are included in the carcinoid series.

In accordance with the advancement of research in this particular field of gut-endocrinomas, a general agreement concerning the concepts, definitions and diagnostic criteria must be reached to avoid unnecessary confusion.

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