Surg Today
Jpn J Surg (1997) 27:112–119

SURGERY TODAY


# Carcinoids of the Rectum: An Evaluation of 1271 Reported Cases

JUN SOGA

College of Biomedical Technology, Niigata University, 2-746 Asahimachi-dori, Niigata 951, Japan

**Abstract: The present study was conducted to evaluate the current status of rectal carcinoids from multiple systemic aspects, based on extensive information provided by 1271 cases cited in 465 international articles published since 1912. Each case report was carefully read, computerized, and analyzed by the gut-pancreatic endocrinoma analysis system (Niigata Registry). To avoid case duplication, cases without individual identification, such as the age and sex of the patient, and those with identical clinical and laboratory data and institutes of source, were excluded. Where appropriate, selected cases from an overall gastrointestinal (GI) series consisting of 4461 cases similarly documented in the same Registry were referred to for comparison. The representative characteristics of rectal carcinoids consisted of a male preponderance, small-sized tumors of 10 mm or less at detection, predominant submucosal invasion with a relatively high incidence of metastases, a high incidence of hematogenous spread, a predominant histology of the B-type growth pattern, a low rate of silver reactivity, the infrequent association of carcinoid syndrome, and a relatively high rate of mortality within 5 years after removal of the lesions.**

**Key Words:** rectal carcinoid, statistics, metastasis, immunohistochemistry, size distribution

## Introduction

Rectal carcinoids, a relatively rare malignancy in the U.S. and Western European countries,[1] are being found with increasing frequency in Japan.[2] The largest individual-case series of rectal carcinoids to date are those of the Mayo Clinic Groups[3,4] dealing with 147 and 133 cases, respectively, while the largest three collected-case series are represented by those listing 939, 706, and 592 cases,[5–7] respectively. These latter three series have dealt with several aspects and characteristics of rectal carcinoids. In view of the rapidly developing research activities in the field of recent endocrinoma investigations, the present study was conducted to evaluate and analyze the current status of rectal carcinoids from multiple systemic aspects based on extensive information obtained from a statistically reliable number of cases that until now have been unavailable.

Reprint requests to: J. Soga
(Received for publication on Jan. 17, 1996; accepted on July 4, 1996)

## Materials and Methods

The present study included 1271 cases of rectal carcinoids cited in 465 of a total 800 articles on rectal carcinoids individually collected as widely as possible from the international literature, covering approximately 30 countries and dating back to 1912[8] (Table 1). Each case was carefully read, computerized, and analyzed by the gut-pancreatic endocrinoma analysis system (Niigata Registry)[2]. To avoid case duplication, cases without individual identification, such as the age and sex of the patient, and those with identical clinical and laboratory data and institute of source, were excluded. Consequently, those reported in groups or as single cases without individual identification were excluded from the present series. Where appropriate, selected cases from the overall gastrointestinal (GI) series consisting of 4461 cases similarly documented in the Niigata Registry were referred to for comparative purposes. Statistical significance was calculated by the chi-squared test.

## Results

### *Chronological Changes in Case Reports*

The number of cases published in the last 15 years has increased twofold over those reported before 1980. This

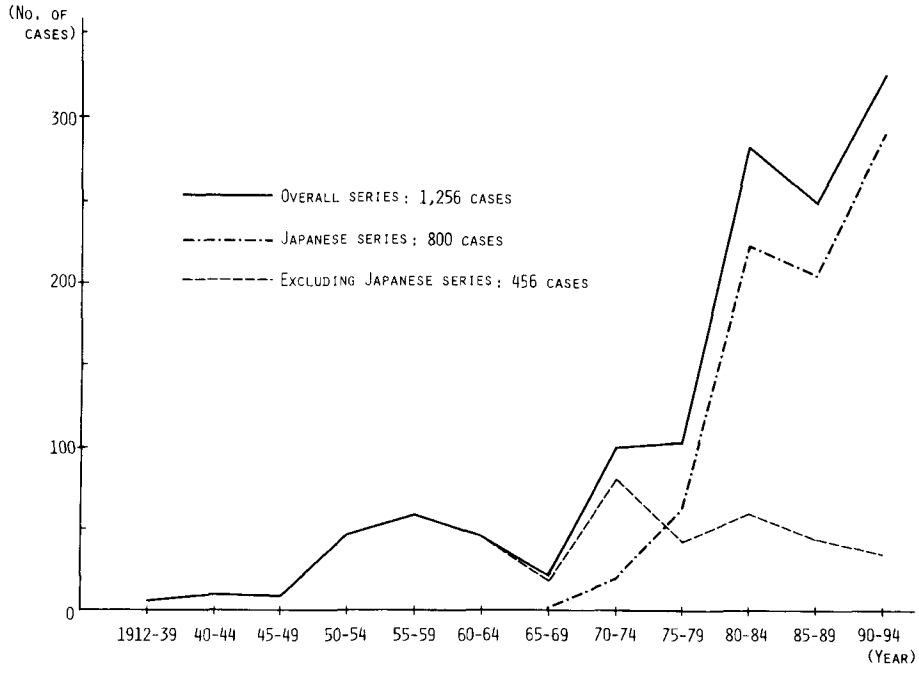


**Fig. 1.** The chronological changes in the number of reported cases of rectal carcinoids indicate that the recent rapid increase in the entire series is in parallel to the Japanese series. Fifteen cases reported in 1995 were excluded

**Table 1.** Cases of rectal carcinoids collected from the world literature

| Areas/countries | No. of cases |
|---|---|
| No. of cases | 1271* |
| Japan | 815 |
| U.S./Western European countries | 405 |
| Eastern European countries | 10 |
| Asian and African countries | 41 |
| After 1980 | 871 |
| Before 1980 | 400 |

* Cited in 465 articles

**Table 2.** Male to female ratio and age distribution ($n$ = 1271)

| | | |
|---|---|---|
| Male to female ratio | 1.6:790/481 | $P < 0.01$ |
| Overall GI carcinoids | 1.3:2484/1977 | |
| Age distribution | 10–85 | |
| Average age: overall | 51.3 | |
| Male | 51.4 | |
| Female | 51.1 | |

GI, gastrointestinal

is shown in Fig. 1, which demonstrates an abrupt, rapid chronological increase in the number of reported cases of rectal carcinoids during the last 15 years. This increase can almost exclusively be attributed to the increase in the Japanese series.

*Male to Female Ratio* (Table 2)

A significant difference in the male to female ratio was evident between the rectal carcinoid series and the overall GI series ($P < 0.01$). In the reported large series, the male to female ratio showed a wide range between 0.7 and 2.7[9,10] with an overall male preponderance.[2]

*Age Distribution* (Table 2)

In the present study, the age distribution ranged between 10 and 82 years, with an average age of 51.3, showing no statistically significant difference. Most large series of rectal carcinoids indicated an average age ranging between 46 and 52 years[2,10,11] while the series reported by Bates revealed an apparent difference in sex in the peak age decade, being the 6th for men and the 5th for women.[12,13]

*Clinical Manifestations* (Table 3)

Melena and anal bleeding were the representative clinical manifestations as reported in other series, with varying incidences.[2] Anal bleeding was recorded in 116

**Table 3.** Clinical manifestations ($n$ = 1271)

| | No. of cases | Per cent |
|---|---|---|
| Not recorded | 396 | 31.2 |
| Recorded | 875 | 68.8 |
| Asymptomatic | 145 | 16.6 |
| Symptomatic | 730 | 83.4 |
| Melena/anal bleeding | 288 | 39.5 |
| Abdominal pain | 139 | 19.0 |
| Constipation | 125 | 17.1 |
| Diarrhea | 85 | 11.6 |
| Weight loss | 50 | 6.8 |

**Table 4.** Preoperative diagnoses and surgical procedures ($n$ = 1271)

| | No. of cases | Per cent | |
|---|---|---|---|
| Preoperative diagnosis | | | |
| Correct/suspicious | 674 | 53.0 | |
| Before 1980 | 183/400 | 45.8 | $P < 0.01$ |
| After 1980 | 491/871 | 56.4 | |
| Surgical procedures | | | |
| Not recorded | 73 | 5.7 | |
| No surgical procedures | 41 | 3.2 | |
| Laparotomy without removal of lesions | 62 | 4.9 | |
| Lesions removed* | 1095 | 86.2 | |
| Abdominoperineal(Miles) | 130 | 11.9 | |
| Abdominal/(low-) anterior | 55 | 5.0 | |
| Local | 365 | 33.3 | |
| Transanal | 131 | 35.9 | |
| Transsacral | 15 | 4.1 | |
| Not specified | 219 | 60.0 | |
| Polypectomy/identical proc. | 379 | 34.6 | |
| Without further proc. | 335 | 88.4 | |
| Proc. not specified | 271 | 24.7 | |

Proc., surgical procedures
* Procedures were duplicated in a small number of cases

**Table 5.** Sites of the lesions, size distribution, and depth of invasion

| | No. of cases | Per cent | |
|---|---|---|---|
| Sites of the lesions ($n$ = 1271) | | | |
| Distance* evaluated | 667 | 52.5 | |
| Anorectal region | 18 | 2.7 | $P < 0.01$ |
| –40 mm | 93 | 13.9 | $P < 0.01$ |
| –80 | 415 | 62.2 | $P < 0.01$ |
| –120 | 120 | 18.0 | $P < 0.01$ |
| 121– | 21 | 3.1 | |
| Size distribution ($n$ = 1075) | | | |
| Tumor size | Incidence | | |
| –10 mm | 710 | 66.0 | $P < 0.01$ |
| 11–20 | 200 | 18.0 | $P < 0.01$ |
| 21–30 | 70 | 6.5 | |
| 31–50 | 49 | 4.6 | |
| 51–70 | 31 | 2.9 | |
| 71–100 | 8 | 0.7 | |
| 101– | 7 | 0.7 | |
| Depth of invasion ($n$ = 776) | | | |
| Depth | Incidence | | |
| Intramucosal | 16 | 2.1 | $P < 0.01$ |
| Submucosal | 592 | 76.3 | $P < 0.01$ |
| To muscular layer | 79 | 10.2 | |
| Transmural | 51 | 6.6 | |
| Invasive to neighboring structures | 38 | 4.9 | |

* Distance (mm) from anorectal line

patients; however, in 25 with hemorrhoids it was difficult to decide whether the anal bleeding was definitely related to the carcinoids, only to the hemorrhoids, or to both. As a matter of fact, asymptomatic carcinoids were incidentally found in 97 patients with hemorrhoids. Intestinal obstruction was encountered in 10 patients who suffered abdominal pain and constipation.

*Preoperative Diagnosis* (Table 4)

The preoperative diagnosis of carcinoids was confirmed in most cases by histological examination of the biopsy or polypectomy specimens. Thus, over half the cases in the series were diagnosed preoperatively. In a few cases, experienced endoscopists were almost completely confi-

dent of the diagnosis based on the color and configuration of the lesions imitating a submucosal tumor. It is apparent that in the years since 1980, the diagnostic accuracy of carcinoids has improved in accordance with the popularization of endoscopic examinations.

*Surgical Procedures* (Table 4)

For small submucosal lesions of 10 mm or less, endoscopic polypectomy or an identical endoscopic procedure was often carried out without the need for further surgery.

*Sites of Lesions* (Table 5)

The site where rectal carcinoids were most frequently detected ($P < 0.01$) was in the middle portion of the rectum between 4 and 8 cm from the anorectal junction.

*Size Distribution* (Table 5)

Most rectal carcinoids belonged to the category of small lesions of 20 mm or less. Smaller lesions of 10 mm or less comprised about two-thirds of the series.

*Depth of Invasion* (Table 5)

Approximately 76% of the cases had a depth of invasion extending into the submucosal layer, with a statistically significant difference from the other groups ($P < 0.01$). It has been proven in animal experiments[14] that gastric carcinoids originate in the lower portion of the glands and spread out into the neighboring stroma of the lower mucosal layer. The muscularis mucosae is quite rapidly invaded down into the submucosal layer where a nodule larger than the original site in the mucosa is formed, imitating a submucosal tumor in

**Table 6.** Metastases

| | No. of cases | Per cent | |
|---|---|---|---|
| Overall evaluation ($n$ = 1271) | | | |
| Metastases | 287/1271 | 22.6 | $P < 0.01$ |
| Overall GI series | 1385/4461 | 31.0 | |
| Site of involvement ($n$ = 287) | | | |
| Lymph nodes | 173 | 60.3 | NS |
| Liver | 167 | 58.2 | |
| Bone | 27 | 9.4 | |
| Mesentery/omentum/peritoneum | 24 | 8.4 | |
| Lung | 23 | 8.0 | |
| Tumor-size and metastases ($n$ = 1075) | | | |
| Tumor-size | Metastases | | |
| −10 mm | 391/710 | 5.5 | $P < 0.01$ |
| 11–20 | 60/200 | 30.0 | $P < 0.01$ |
| 21–30 | 49/70 | 70.0 | |
| 31–50 | 40/49 | 81.6 | |
| 51– | 38/46 | 82.6 | |
| Total | 226/1075 | 21.6 | |
| Depth of invasion and metastases ($n$ = 776) | | | |
| Depth of invasion | Metastases | | |
| Intramucosal | 0/16 | 0 | $P < 0.01$ |
| Submucosal | 69/592 | 11.7 | $P < 0.01$ |
| To muscular layer | 45/79 | 57.0 | $P < 0.01$ |
| Transmural | 37/51 | 72.5 | |
| Invasive to neighboring structures | 36/38 | 94.7 | |
| Total | 187/776 | 24.1 | |
| Lesions with submucosal invasion: size and metastases ($n$ = 519) | | | |
| Tumor-size | Metastases | | |
| −5 mm | 2/153 | 1.3 | $P < 0.01$ |
| 6–10 | 24/247 | 9.7 | $P < 0.05$ |
| 11–15 | 10/62 | 16.1 | $P < 0.05$ |
| 16–20 | 7/29 | 24.1 | |
| 21– | 15/28 | 53.6 | |

NS, no statistical significance demonstrated

endoscopic appearance. This is considered the typical invasion pattern of gastrointestinal carcinoids. In human specimens, such features are frequently encountered, particularly in serial sections of the lesion.

*Metastases* (Table 6)

The overall incidence of metastases from rectal carcinoids was 22.6%, which was significantly lower than that from overall GI carcinoids ($P < 0.01$). Hematogenous metastases, represented by those found in the liver, indicated a high value of 58.2%, which was almost identical to lymphogenous spread. Metastases in relation to tumor size and depth of invasion were particularly emphasized in the lesions of 20 mm or less and those with submucosal invasion. Small carcinoids with the most frequently detected sizes ranging between 6 and 10 mm and with the most predominant depth of submucosal invasion showed an unexpectedly high incidence of metastases of approximately 10%.

**Table 7.** Histologic, histochemical, immunohistochemical, and electron microscopic evaluations

| | No. of cases | Per cent | |
|---|---|---|---|
| Histologic types[15] ($n = 344$) | | | |
| A: nodular | 35 | 10.2 | |
| B: trabecular | 124 | 36.0 | |
| C: tubular/glandular | 12 | 3.5 | |
| D: poorly differentiated | 7 | 2.0 | |
| E: mixed | 166 | 48.3 | |
| Lesions ($n = 299$) including: | | | |
| A pattern | 118 | 39.5 | $P < 0.01$ |
| B pattern | 227 | 75.9 | $P < 0.01$ |
| C pattern | 69 | 23.1 | |
| D pattern | 18 | 6.0 | |
| Silver impregnations ($n = 676$) | | | |
| Recorded | 676/1271 | 53.3 | $P < 0.01$ |
| After 1980 | 532/871 | 61.1 | |
| Grimelius argyrophilia | 324/500 | 64.8 | $P < 0.01$ |
| Overall GI carcinoids | 1095/1365 | 80.2 | |
| Argentaffin cell type | 59/392 | 15.1 | $P < 0.05$ |
| Overall GI carcinoids | 177/892 | 19.8 | |
| Argyrophil cell type | 196/392 | 50.0 | $P < 0.05$ |
| Overall GI carcinoids | 508/892 | 57.0 | |
| Nonreactive cell type | 137/392 | 34.9 | $P < 0.01$ |
| Overall GI carcinoids | 207/892 | 23.2 | |
| Immunohistochemistry ($n = 209$) | | | |
| Recorded | 209/1271 | 16.4 | $P < 0.01$ |
| After 1980 | 209/871 | 24.0 | |

| | Rectal series | | Overall GI | | |
|---|---|---|---|---|---|
| NSE | 47/60 | 78.3 | 219/276 | 79.3 | NS |
| CEA | 18/27 | 66.7 | 92/144 | 63.9 | NS |
| PP | 66/106 | 62.3 | 89/312 | 28.5 | $P < 0.01$ |
| Chromogranin | 28/46 | 60.9 | 143/185 | 77.3 | $P < 0.05$ |
| Serotonin | 54/120 | 45.0 | 231/420 | 55.0 | NS |
| Glucagon | 48/111 | 43.2 | 78/399 | 19.5 | $P < 0.01$ |
| Somatostatin | 50/131 | 38.2 | 200/506 | 39.5 | NS |
| Multisecretors | | | | | |
| GI hormones | 68/209 | 32.5 | 184/870 | 21.1 | $P < 0.01$ |

| | | | |
|---|---|---|---|
| Electron microscopic evaluation ($n = 1271$) | | | |
| Observation attempted | 148/1271 | 11.6 | NS |
| After 1980 | 108/871 | 12.4 | |
| Endocrine granules ($n = 147$): | | | |
| Round | 87 | 59.2 | |
| Round and pleomorphic | 8 | 5.4 | |
| Pleomorphic | 18 | 12.2 | |
| No characteristics described | 34 | 23.1 | |

NSE, neuron-specific enolase; CEA, carcinoembryonic antigen; PP, pancreatic polypeptide

*Histologic Growth Patterns* (Table 7)

Histologic types A through E[15] representing the histologic growth patterns[16] were applied for this analysis. A significant predominance of the E type was evident, while the B pattern as a constituent component was found to be the most frequent of the other three patterns ($P < 0.01$).

*Silver Impregnations* (Table 7)

In rectal carcinoids the positivity of silver impregnations was generally low compared with the overall GI series. This might be reflected in the significantly lower value of Grimelius argyrophilia of 64.8% in rectal carcinoids ($P < 0.01$) than in the overall GI series. Consequently , a low incidence ($P < 0.05$) of two cell types, namely the argentaffin cell, and argyrophil cell varieties, and a relatively high incidence ($P < 0.01$) of the nonreactive cell variety, were shown to be characteristic of rectal carcinoids.[2]

*Immunohistochemistry* (Table 7)

All of the 209 cases in which immunohistochemical analysis was recorded had been published after 1980. In the present series of rectal carcinoids, pancreatic polypeptide (PP) and glucagon exhibited a positive incidence significantly higher ($P < 0.01$) than that in the overall GI series, while chromogranin was less frequently ($P < 0.05$) positive than in the overall GI series. Approximately one-third of the rectal carcinoids were found to secrete two or more types of GI hormones.

*Electron Microscopic Evaluation* (Table 7)

Surprisingly, an electron microscopic search for carcinoid granules in neoplastic cells showed only a slight increase in frequency after 1980, compared with the entire period of carcinoid research. It seemed likely that despite the significant increase in rectal carcinoid cases over recent years, most were too small to be submitted for electron microscopic analysis. Granules of an endocrine type were detected in 147 cases, among which pleomorphic granules with possible serotonin content were described in 17.7%, exhibiting an almost identical value of argentaffin cell type in 15.1%.

*Carcinoid Syndrome* (Table 8)

It has been well established that the carcinoid syndrome is rarely encountered in rectal carcinoids compared with carcinoids of most other organs. In fact, only 9 (0.7%) cases of carcinoid syndrome were recorded in the present rectal carcinoid series. In the representative collective series[2,6,7] the incidence of carcinoid syndrome ranged between 0.2% and 0.5%, being even lower than in the present series.

*Elevated Serotonin Activity* (Table 8)

It has been pointed out that serotonin activity, represented by serotonin in the blood and its product 5-hydroxyindolacetic acid in the urine, in the presence of carcinoids was low in the general population but significantly high in a series of cases of carcinoid syndrome.[2] This was not proven in the present series due to the lack of a statistically sufficient number of cases of carcinoid syndrome.

*Association of Synchronous Malignancies* (Table 9)

Of a total 108 cases of patients with associated synchronous malignancies, 34 had rectal carcinomas, revealing a significantly high incidence compared to colon carcinomas ($P < 0.05$) and gastric carcinomas ($P < 0.01$).

*Postoperative Outcomes* (Table 10, Fig. 2)

Of 158 patients effectively followed up for 5 years or more, excluding those who died within 30 days of surgery and those who reportedly died from causes other than carcinoids, there were 105 5-year survivors, comprising 66.5%, with the remaining 33.5% representing those who died within 5 years. Figure 2 shows an overall 5-year survival rate of 81.5% (A) and a comparative evaluation of 5-year survival rates between two groups of patients without (B) and with (C) metastases. Although the postoperative survival of patients with

**Table 8.** Cases of carcinoid syndrome

| | No. of cases | Per cent | |
|---|---|---|---|
| Carcinoid syndrome ($n$ = 1271) | 9/1271 | 0.7 | $P < 0.01$ |
| Overall GI carcinoids | 242/4461 | 5.4 | |
| Elevated serotonin activity ($n$ = 261) | | | |
| Overall rectal carcinoids | 32/261 | 12.3 | |
| With the carcinoid syndrome | 4/6 | 66.7 | |

**Table 9.** Association of synchronous malignancies ($n$ = 1271)

| | No. of cases | Per cent |
|---|---|---|
| Synchronous malignancies | 102 | 8.0 |
| Lesions | 107* | |
| Rectal carcinoma | 34 | 33.3 |
| Early | 4 | 11.8 |
| Colon carcinoma | 17 | 16.7 |
| Early | 1 | 5.9 |
| Gastric carcinoma | 15 | 14.7 |
| Early | 5 | 33.3 |
| Uterine carcinoma | 6 | 5.9 |
| Perianal skin carcinoma | 5 | 4.9 |
| Pancreatic carcinoma | 3 | 2.9 |
| Others | 27 | 26.5 |

*Triple malignancies were found in five patients

**Table 10.** Postoperative outcome ($n$ = 488)

| | No. of patients | Per cent |
|---|---|---|
| Alive but followed up <5 years | 330 | 67.6 |
| Able to be effectively analyzed | 158 | 32.4 |
| 5-year survivors | 105 | 66.5 |
| Died within 5 years* | 53 | 33.5 |

*Excluding patients who died within 30 days following removal of lesions and those who died from causes reportedly other than carcinoids

carcinoids may in general be influenced by various factors including histologic growth patterns,[15,16] as with other malignancies, it seemed apparent that precise information was difficult to obtain because most of the patients with minute lesions were not followed up for a sufficient period of time.

## Discussion

In accordance with the rapid popularization of endoscopic examination of the rectum, an increasing number of small lesions including carcinoids have been detected in their early states, and are being safely and effectively treated by minor surgical procedures such as endoscopic polypectomy. Such progress in detection and minor surgery has resulted in a decreasing number of advanced cases of carcinoids presenting with hormonal manifestations or the carcinoid syndrome. Thus, the status of carcinoids is changing dramatically in many aspects with progress in the research of carcinoids and related endocrinomas.

**Table 11.** Representative characteristic features of rectal carcinoids

| | |
|---|---|
| Male preponderance | 1.6 |
| Small lesions 10mm or less | 66.0% |
| Submucosal invasion | 76.3% |
| Submucosal invasion with metastases | 11.7% |
| Hematogenous (hepatic) spread | 58.2% of 287 metastases (13.1% of all 1271 cases) |
| B-type growth pattern | 75.9% |
| Low rate of silver reactivity (negative Grimelius argyrophilia) | 35.2% |
| Low incidence of the carcinoid syndrome | 0.7% |
| Deaths within 5 years after removal of lesions | 33.5% |

The representative characteristics of rectal carcinoids as demonstrated in the present study and summarized in Table 11, were: (a) a male preponderance, (b) small tumors of 10mm or less at detection, (c) predominant submucosal invasion with a relatively high incidence of metastases, (d) a high incidence of hematogenous spread, (e) a predominance of the B-type growth pattern, (f) a low rate of silver reactivity, (g) the infrequent association of carcinoid syndrome, and (h) a seemingly high rate of deaths within 5 years after removal of the lesions.

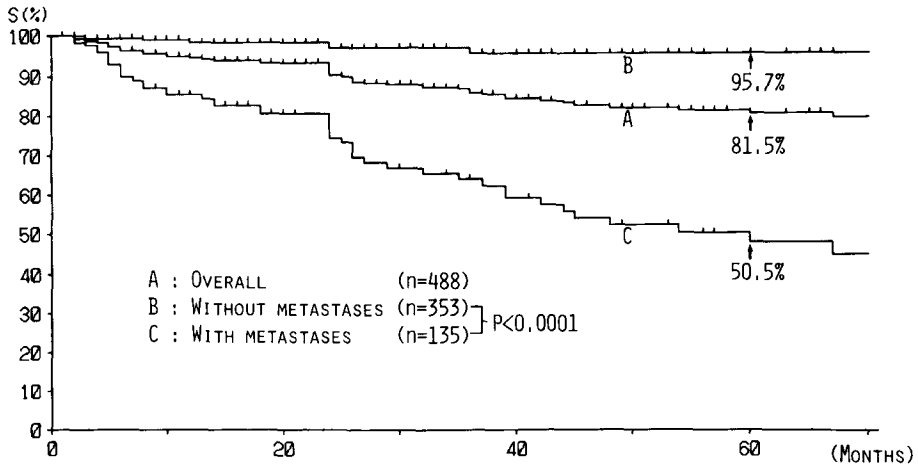


**Fig. 2.** Reported 5-year-survival rates in patients with rectal carcinoids, as calculated by the Kaplan-Meier method. The reported cases of rectal carcinoids able to be effectively analyzed ($A$; $n$ = 488) were divided into two groups: those without ($B$; $n$ = 353) and with ($C$; $n$ = 135) metastases. A statistically significant difference was evident between the latter two groups

*Acknowledgments.* The author expresses his gratitude to Ms. Y. Yakuwa for her help in the preparation of this manuscript. This work was supported in part by a Grant-in-Aid for Scientific Research (Nos. 01480322 and 07457268), from the Ministry of Education, Science, Sports and Culture of Japan.

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