

Association of Primary Neoplasms of the Small Intestine with Other Neoplastic Growths

J. WESLEY ALEXANDER,* M.D., Sc.D., W. A. ALTEMEIER, M.D.

*From the Department of Surgery of the University of Cincinnati, College of Medicine
and the Cincinnati General Hospital, Cincinnati, Ohio 45229*

THE COMPLICATIONS of primary tumors of the small intestine usually considered to be of surgical significance are related to their growth and metastasis. These include intestinal obstruction, intussusception, hemorrhage, and perforation. In addition, other complications may develop from the effects of metabolic products of certain tumors, particularly the carcinoids.

Recently another interesting characteristic of small bowel tumors has been noted, their association with an increased incidence of concurrent neoplasms in other parts of the body. To study this association, a review of all of the autopsy material at the Cincinnati General Hospital over a 15 year period has been made. This incidence of concurrent neoplastic growths was studied in patients with primary neoplasms of the small intestine and compared with that found in patients in the general autopsy population with allowances being made for age. The results of this study indicate that individuals with primary neoplasms of the small intestine are particularly prone to develop primary neoplasms elsewhere.

Materials and Methods

The records of 9,721 consecutive post-mortem examinations performed at the Cincinnati General Hospital during the 15-year period between January 1, 1950, and December 31, 1964, were individually examined for the presence of small bowel neoplasms. Only those tumors which were primary in the small intestine and truly neoplastic were included. Cysts, duplications, telangiectasias, hematomas, inflammatory polyps, aberrant pancreatic or other normal tissue, granulomas, metastatic tumors, ampullary tumors, and lymphomas which were not clearly primary in the small intestine were excluded from consideration. The remaining neoplasms were categorized into three major groups: malignant, carcinoid, and benign. Carcinoid tumors were placed in a separate category because of their peculiar nature and because of the difficulty in determining their malignant potential by gross and microscopic inspection.

In addition, records of 1,000 consecutive autopsies performed after January 1, 1955, were examined in detail to establish an incidence of all types of primary and concurrent neoplastic lesions in our autopsy population, these being categorized according to age. The records of patients with primary neoplasms of the small intestine were similarly reviewed to establish the incidence and occurrence of other neoplastic growths.

Reprint Address: Department of Surgery, University of Cincinnati, College of Medicine, Cincinnati, Ohio 45229.

* Advanced Clinical Fellow, American Cancer Society.

This work was supported, in part, by a grant from the American Cancer Society.

Epithelial tumors of the skin were excluded from consideration.

Results

Incidence of Primary Neoplasms of the Small Intestine and their Association with Concurrent Neoplasms. In the 9,721 consecutive autopsies, 112 subjects with primary neoplasms of the small intestine were encountered, representing 1.15% of the total autopsy population (Table 1). Malignant tumors were infrequent in this series, being present only seven times (0.07%). Ten per cent of the patients who had small bowel tumors had significant symptoms, the remainder having incidental lesions discovered at autopsy. Benign lesions occurred ten times as frequently as malignant lesions, but only three of the benign lesions produced clinical symptoms. Three of the 33 patients with carcinoid tumors has symptoms.

Of the 112 subjects with small bowel tumors, 83 (74%) had another independent neoplasm at the time of death. A wide variety of concurrent neoplasms was observed, not limited to a particular organ or tissue. It is of particular interest that 91% of those with carcinoid tumors had multiple tumors, and 52% of these had multiple carcinoid tumors. Even more striking was the finding that 70% of subjects with carcinoids had independent neoplasms not located in the small intestine. Tumors of vascular origin also tended to be multicentric in the small intestine (56%), and a strikingly high number (7 of 9 cases) had independent neoplasms not located in the small intestine. Fourteen per cent of all the benign neoplasms were multicentric in the small intestine. In only one instance were two types of benign tumor of the small intestine found in the same subject (a single lipoma and a single leiomyoma). In no instance was there an associated malignant lesion located in the small intestine.

To provide for an age adjusted comparison between the general autopsy series and

TABLE 1. Occurrence of Primary Neoplasms of the Small Intestine in 9,721 Consecutive Autopsies

Type	Total Number of Cases	Incidental Finding at Autopsy	Overall % Incidence
Malignant	7	2	0.07
Carcinoma	2	1	0.02
Sarcoma	1	0	0.01
Lymphoma	4	1	0.04
Carcinoid	33	30	0.34
Benign	72	69	0.74
Adenoma	19	18	0.20
Lipoma	17	16	0.17
Leiomyoma	16	15	0.16
Vascular origin	9	9	0.09
Neurogenic origin	6	6	0.06
Miscellaneous	5	5	0.05
Total	112	101	1.15

those having small intestinal lesions, all patients below 50 years of age were excluded in the tabulations given in Table 2. Since only 11 patients were removed from consideration, the figures are similar to those cited above.

Incidence of Primary and Concurrent Neoplasms in 1,000 Consecutive Autopsies. The occurrence of benign and malignant neoplasms in the autopsy population according to age is shown in Table 3. These figures do not necessarily represent the overall incidence of neoplasms in the general population nor do they represent the cause of death from neoplasms since a number of malignant neoplasms and the majority of benign neoplasms were incidental findings at the time of postmortem examination. Malignant tumors were discovered in 204 of the 1,000 subjects, and benign neoplasms were found in 180. The most valuable figures for comparison with the group with neoplasms of the small intestine were obtained by comparing the incidence of neoplasms only in patients over the age of 50. Within this category, 295 of the 478 subjects (51%) were found to have primary benign or malignant neoplasms (see Table 4). One hundred eighty-

TABLE 2. *Concurrent Neoplasms in 101 Patients Over the Age of 50 with Primary Neoplasms of the Small Intestine*

Type	Total Number of Cases	Number with More than One Neoplasm of Any Kind	Multiple Neoplasms of Same Type in Small Bowel	Associated Neoplasms Not in Small Bowel	Associated Malignancy Not in Small Bowel	Associated Benign Neoplasm Not in Small Bowel
Malignant	7	2(29%)	0	2(29%)	1(14%)	1(14%)
Carcinoma	2	0	0	0	0	0
Sarcoma	1	0	0	0	0	0
Lymphoma	4	2(50%)	0	2(50%)	1(25%)	1(25%)
Carcinoid	29	26(90%)	13(45%)	22(76%)	13(45%)	15(52%)
Benign	65	49(75%)	9(14%)	45(69%)	15(23%)	37(57%)
Adenoma	18	14(78%)	2(11%)	13(72%)	5(28%)	9(50%)
Lipoma	17	12(71%)	1(6%)	11(65%)	4(24%)	9(53%)
Leiomyoma	13	8(62%)	0	8(61%)	2(14%)	8(61%)
Vascular origin	8	8(100%)	4(50%)	7(88%)	3(38%)	5(63%)
Neurogenic origin	6	5(83%)	1(17%)	4(67%)	0	4(67%)
Miscellaneous	3	2(67%)	1(33%)	2(67%)	1(33%)	2(67%)
Total	101	77(76%)	22(22%)	69(68%)	29(29%)	52(63%)

five (32%) had malignant tumors, and 167 (29%) had benign tumors. Multiple primary cancers were found in 22 (3.8%), whereas multiple tumors of all kinds were found in 92 (16%). Of those having cancer, 57 (31%) had concurrent benign neoplastic growths. The incidence of cancer in subjects over age 50 with benign tumors was 34%, and the incidence of any other neoplasm, benign or malignant in association with benign tumors, was 46%. Of the 295 subjects over the age of 50 with primary neoplasms, whether benign or malignant, 72 (24%) had a second lesion which was malignant and 77 (26%) had a second lesion which was benign. Thirty-one per cent of those over age 50 who had any type of neoplasm had another independent neoplastic growth.

Comparison of the Incidence of Associated Neoplasms in the General Autopsy Series and in Patients with Primary Neoplasms of the Small Intestine. Since the incidence of neoplastic disease was strikingly less before the age of 50, only those subjects over 50 years of age were considered for purposes of this comparison (Table 4). Concurrent neoplasms were found over twice as frequently in those with small bowel tumors. To provide for

two types of comparison, concurrent neoplasms arising in the same organ or type of tissue were not excluded from the autopsy series in the last two lines of Table 4, but were excluded from the group with small bowel tumors. Therefore, any increase in the incidence of concurrent neoplasms in those with small bowel tumors over those in the general autopsy subjects will be greater than is apparent from the figures. In the general autopsy series, 12% of those with one malignant lesion had an independently arising cancer at the time of autopsy, and 31% had a benign neoplasm. Malignant lesions of the small bowel were too few for adequate comparison. Of those having benign small bowel tumors, 23% were associated with an independently arising malignant lesion not located in the small intestine. This figure is not significantly different from the incidence of 34% of those with benign tumors of all origins when allowance is made for the inclusion of multiple benign tumors of the same type in the second group (23% compared to 28%). Fifty-seven per cent of subjects with benign small bowel tumors also had benign neoplasms arising outside of the small intestine, compared to 19% who had multiple benign neoplasms in the autopsy popu-

TABLE 3. Incidence of Primary Neoplasms in 1,000 Consecutive Autopsies by Age

	Over 80	70-79	60-69	50-59	40-49	30-39	20-29	10-19	NB-10	Newborn or Still-born
Number of patients	114	184	162	118	77	48	18	12	63	204
Single malignant lesion	20	39	38	16	8	3	1	3	0	0
Multiple malignancies	5	6	3	1	0	0	0	0	0	0
Multiple malignancies with benign neoplasms	2	4	1	0	0	0	0	0	0	0
Single malignancy with benign neoplasm	9	15	18	8	3	1	0	0	0	0
Multiple benign neoplasm	6	4	7	3	1	1	0	1	0	0
Single benign neoplasm	17	30	25	18	10	4	0	2	1	0
Total with malignant neoplasm	36(32%)	64(35%)	60(37%)	25(21%)	11(14%)	4(8%)	1(6%)	3(25%)	0(0%)	0(0%)
Total with benign neoplasm	34(30%)	53(29%)	51(31%)	29(25%)	14(18%)	5(10%)	0(0%)	3(25%)	1(2%)	0(0%)

lation (15% if those of identical cell types are excluded).

The most striking group was that with carcinoid tumors of the small intestine. Forty-five per cent had a malignant lesion arising outside the small intestine, and the carcinoid tumors were multicentric in origin in the same number of subjects. Fifty-two per cent were found to have benign neoplasms not located in the small intestine. It is interesting that none of the subjects with carcinoid had concurrent benign or malignant lesions of the small intestine of a different cellular type. A further breakdown of the group with carcinoid tumors is shown in Table 5. When these were divided according to the decade of life in which they died, it was found that multicentricity of the tumors tended to occur more frequently in younger patients with a decreasing incidence of multicentric tumors with age. The occurrence of associated malignant lesions, while greater than that in the general autopsy population, followed the same distribution pattern with the greatest number being seen between the ages of 50 and 60. Benign neoplasms associated with carcinoid tumors occurred slightly more frequently in the older age

group, following a pattern which is almost the opposite of that seen for the incidence of multiple carcinoid tumors of the small intestine.

None of six neurogenic tumors were associated with a malignant lesion whereas three of the eight tumors of vascular origin had an independently arising cancer. Of the benign small bowel tumors, those of vascular origin were associated most frequently with multicentricity followed by those of neurogenic origin and adenomas.

Discussion

A great deal of information has accumulated in the past few years concerning the incidence of multiple primary malignant neoplasms, and occasional papers have dealt with the simultaneous occurrence of benign and malignant neoplasms in an attempt to relate the two or to show a lack of correlation. Moertel⁴ stated that over 12,000 cases of multiple primary malignant lesions had been reported in the literature before 1964. In a review of 1,909 cases from the Mayo Clinic, he found that the rates of occurrence of multiple primary cancers were 10.6% at autopsy and 4.6% at operation. If only those arising in different or-

TABLE 4. Comparison of the Incidence of Associated Neoplasm in 295 Consecutive Autopsies on Patients with Neoplasms Over the Age of 50 and 101 Consecutive Autopsies on Patients with Primary Neoplasms of the Small Intestine Over the Age of 50

	Patients with Primary Small Bowel Tumors				Patients with Primary Neoplasm of Any Origin		
	Total	Malignant	Carcinoid	Benign	Total	Malignant	Benign
	(101 Cases)	(7 Cases)	(29 Cases)	(65 Cases)	(295 Cases)	(185 Cases)	(167 Cases)
Associated Independent Neoplastic Growth of Any Type	77 (76%)	2 (29%)	26 (90%)	49 (75%)	92 (31%)	72 (39%)	77 (46%)
Associated Independent Malignancy of Any Type	29 (29%)*	1 (14%)*	13 (45%)*	15 (23%)*	72 (24%)†	22 (12%)†	57 (34%)†
Associated Independent Benign Neoplasm of Any Type	53 (52%)*	1 (14%)*	15 (52%)*	37 (57%)*	77 (26%)†	57 (31%)†	32 (19%)†

* Excludes all other neoplasms arising in the small intestine.

† Includes all other neoplasms arising in the same organ or type of tissue.

gans or tissues were considered, the rate was 2.8%. The incidence of occurrence of multiple primary malignant tumors in their autopsy population compares with the figure of 12% in this series over the age of 50. Spratt and Hoag¹⁰ recently compared the incidence of independent cancers arising in a large number of patients with colorectal carcinomas, mammary carcinomas, carcinomas of the cervix, chronic leukemia, and lymphomas with 1,000 persons who had no neoplasm when first examined, and also with the age specific incidence of cancers in Connecticut for the same period. They concluded that the incidence of newly arising malignant tumors per man year of risk was not significantly different from that which could be expected in the general population based on age specific incidence.

Nevertheless, there is evidence that certain types of neoplastic growths have an increased association with other tumors. Poke, Spratt, and Butcher⁸ noted that 2-3% of colonic carcinomas were multiple when first seen, and they felt that a new malignant lesion of either colonic or extra-colonic origin could be expected to develop in approximately one-third of the patients

surviving their initial colorectal carcinoma. Garlock *et al.*² reported that 22.1% of patients with carcinoma of the large intestine had polyps associated with the tumors. It is also recognized that individuals with familial polyposis develop malignant change, often before the age of 35. Lynch *et al.*³ reported that 20% of 109 consecutive patients with carcinoma of the prostate developed a second primary malignancy at another site. O'Brien and Brasfield⁶ reviewed 63 patients with Kaposi's Sarcoma between the period 1935 to 1963, and found that 31% of these patients subsequently died with a second primary malignant tumor.

Lack of attention to the association of primary small bowel neoplasms and other neoplastic growths has undoubtedly resulted from the small number of cases obtained from any given series. River, Silverstein and Tope⁹ in a collective review of 1,399 cases of benign neoplasms of the small intestine failed to mention such an association. The number of malignant lesions of the small intestine found in our series was insufficient for adequate comparison, but the association with concu-

TABLE 5. Association of Carcinoid Tumors of the Small Intestine with Other Neoplasms

	Age of Patient				
	50	50-59	60-69	70-79	80+
Number of patients	4	8	10	7	4
Multiple carcinoid tumors	4 (100%)	5 (63%)	5 (50%)	2 (29%)	0 (0%)
Malignant neoplasms not in small bowel	1 (25%)	4 (50%)	5 (50%)	3 (43%)	1 (25%)
Benign neoplasms not in small bowel	0 (0%)	3 (38%)	5 (50%)	5 (71%)	2 (50%)

rent neoplasms was striking for carcinoid tumors and significant for benign tumors.

The observation of an association of independent malignant tumors with carcinoid tumors is not original, having been reported several times previously. In 1949, Pearson and Fitzgerald⁷ reported that 8 of 31 patients with carcinoid tumors of the small bowel had primary malignant lesions outside the small intestine. Warren and Coyle¹¹ studied 31 cases of carcinoid tumors of the gastrointestinal tract and noted that 10 had associated independent malignant neoplasms. Thirteen of their 31 carcinoids were in the small intestine. Foreman¹ found that six of his 14 cases in which carcinoid tumors were located in the small intestine had associated malignant tumors. Moertel *et al.*⁵ published a report in 1961 of 209 cases of carcinoid tumors of the small intestine. Of these, 29% had second primary carcinomas. Of the 137 subjects in which the tumors were found only at the time of autopsy, 49 (36%) had second primary carcinomas while twelve of the 72 in their surgical group (17%) had second primary carcinomas.

The reason for the increased association of small bowel tumors with other neoplastic growths is not apparent, but the presence of a common etiologic factor is suggested. At least it seems that whatever serves as an etiologic factor for the development of carcinoid tumors also serves as an etiologic factor for neoplastic growths not arising in the small intestine.

Summary

Nine thousand seven hundred twenty one consecutive autopsy protocols during the 15-year period between January, 1950, and December, 1964, were reviewed to determine the incidence and types of primary neoplasms of the small intestine in this autopsy population. The records of 1,000 consecutive autopsies were reviewed for the incidence of both benign and malignant lesions for purposes of comparison with those having neoplasms of the small intestine. Only those with neoplastic growths over the age of 50 were used for this comparison. Associated independent neoplastic lesions occurred in 76% with small bowel tumors compared to 31% of those with primary neoplasms of all origins. The frequency of both concurrent malignant and concurrent benign tumors was greatest in the group with carcinoid tumors. These findings suggest that common etiological factors may exist for neoplastic growths arising in the small intestine, especially carcinoid tumors, and those arising elsewhere in the body. In subjects over 50 years of age with neoplasms of the small intestine, and particularly carcinoids, the importance of considering the presence or future development of other benign and malignant tumors elsewhere in the body is obvious.

References

1. Foreman, R. C.: Carcinoid Tumors: A Report of 38 Cases. *Ann. Surg.*, 136:838, 1952.
2. Garlock, J. H., Lerman, B., Klein, S. H., Lyons, A. S. and Kirschner, P. A.: Twenty-five Years

- Experience with Surgical Therapy of Cancer of the Colon and Rectum: An Analysis of 1,887 Cases. *Dis. Colon Rectum*, 5:247, 1967.
3. Lynch, H. T., Larsen, A. L., Magnuson, C. W. and Krush, A. J.: Prostate Carcinoma and Multiple Primary Malignancies: Study of a Family and 109 Consecutive Prostate Cancer Patients. *Cancer*, 19:1891, 1966.
 4. Moertel, C. G.: Incidence and Significance of Multiple Primary Malignant Neoplasms. *Ann. N. Y. Acad. Sci.*, 114:886, 1964.
 5. Moertel, C. G., Sauer, W. G., Dockerty, M. B. and Baggenstoss, A. H.: Life History of the Carcinoid Tumor of the Small Intestine. *Cancer*, 14:901, 1961.
 6. O'Brien, P. H. and Brasfield, R. D.: Kaposi's Sarcoma. *Cancer*, 19:1497, 1966.
 7. Pearson, C. M. and Fitzgerald, P. J.: Carcinoid Tumors—A Re-emphasis of Their Malignant Nature. *Cancer*, 2:1005, 1949.
 8. Polk, H. C., Spratt, J. S., Jr. and Butcher, H. R., Jr.: Frequency of Multiple Primary Malignant Neoplasms Associated with Colorectal Carcinoma. *Amer. J. Surg.*, 109:71, 1965.
 9. River, L., Silverstein, J. and Tope, J. W.: Benign Neoplasms of the Small Intestine: A Critical Comprehensive Review with Reports of 20 New Cases. *Surg. Gynec. Obstet.*, 102:1, 1956.
 10. Spratt, J. S. and Hoag, M. G.: Incidence of Multiple Primary Cancer Per Man-Year of Follow-up: 20-Year Review From the Ellis Fischel State Cancer Hospital. *Ann. Surg.*, 164:775, 1966.
 11. Warren, K. W. and Coyle, E. B.: Carcinoid Tumors of the Gastrointestinal Tract. *Amer. J. Surg.*, 82:372, 1951.

DISCUSSION

DR. ISIDORE COHN, JR. (New Orleans): Approximately a year and a half ago we reported a 15-year experience at Charity Hospital with histologically demonstrated small bowel tumors. During this period we found 60 small bowel tumors, exclusive of those of the ampullary and periampullary region. We were not at that time impressed with the importance of secondary tumors, but when I saw the program I went back and looked at this particular facet of our study.

Of the 60 patients, ten had tumors elsewhere than in the small bowel. Three of these were in the cervix, three in the prostate, and there were others scattered—the esophagus, the stomach, the lungs, the brain, the pancreas, et cetera. As a matter of fact, there were about 17 additional tumors found in ten patients so that there were two or three additional tumors in some patients.

I am not sure that we know the significance of these multiple tumors, but Dr. Altemeier has called attention to an interesting combination of tumors.

DR. J. WESLEY ALEXANDER (Closing): I would like to emphasize a few points which Dr. Altemeier did not have time to discuss. (Slide) One observation of particular interest to us was that multiple carcinoid tumors seemed to occur more frequently

in the younger age group than in the older. However, the association with malignant neoplasms not located in the small bowel, which occurred in 45% of these patients, had a pattern of distribution similar to that found in the patients with other small bowel tumors, with the greatest incidence between the ages of 50 and 80.

It is also significant that 57% of the patients with benign small bowel tumors had benign neoplasms located elsewhere. (Slide) It is significant, I believe, that this represents about three times the incidence of multiple benign neoplasms of different origins in the general autopsy population. There may be some variance in the incidence of concurrent neoplasms depending on the tissue type of tumor, such as those of neurogenic origin, in which there was no associated malignancy, and those, for instance, of vascular origin, in which 38% had a concurrent malignancy. However, in the group of adenomas there was a fairly high incidence of associated malignancy, not in the small bowel. The number of cases involved are too small to draw definite conclusions.

In closing I would like to say that it is of interest to note the similarity in the distribution of concurrent neoplasms in these patients with that which occurs in many experimental animal models where oncogenic viruses or chemical carcinogens have been administered.