THE SPREAD OF CARCINOMA OF THE RECTUM: INVASION OF LYMPHATICS, VEINS AND NERVES*

PHILIP H. SEEFELD, M.D.

FELLOW IN SURGERY, MAYO FOUNDATION

AND

J. ARNOLD BARGEN, M.D.

DIVISION OF MEDICINE, MAYO CLINIC

ROCHESTER, MINN.

SINCE THE WORK OF HANDLEY,[15] in 1910, much attention has been given to the lymphatic route of spread of carcinoma of the rectum. Many extensive and painstaking studies have been made into this feature of rectal carcinoma in order to determine the prognostic implications of nodal involvement and the direction of spread of the carcinoma. The anatomic descriptions of the rectal lymphatic channels by Delamere, Poirier and Cuneo[9] paved the way for later studies. Early investigations by Miles,[22] Monsarrat and Williams,[24] Cole,[5] Cheatle,[4] Pennington,[29] and others, gave impetus to more exhaustive studies by McVay,[21] one of us (Bargen[2]) and Larsen, Gabriel, Dukes and Bussey,[12] Gilchrist and David,[13] Coller, and others,[6] and Grinnell.[14] These investigators, and the large numbers of cases studied by them, have emphasized the importance of the lymph nodes as prognostic indicators in rectal carcinoma, and around this pathologic feature of the disease have been centered the present methods of surgical treatment.

Venous invasion in rectal carcinoma has been observed for many years, Mayo,[19] McArthur,[20] Smith,[30] Monsarrat and Williams,[24] and Miles[23] noting this feature and commenting on it. During the past four years, increasing attention has been given to venous invasion of rectal carcinoma as its clinical and prognostic importance has been seen to grow. The frequent development of visceral metastatic lesions after radical resection of the rectum for carcinoma has stimulated interest in this phase of invasion by carcinoma.

Brown and Warren,[3] in one of the first reports during the present period of interest, expressed the opinion that the lymph nodes have been poor indicators of visceral metastatic lesions, which are often present independently of neoplastic nodes. They found that 31 per cent of patients without nodal involvement by carcinoma had visceral metastatic lesions, and they maintained that the spread of rectal carcinoma through the blood vessels is at least as important as by the lymphatic route, and that evidence of this spread is usually available in the primary growth. In the prediction of visceral metastatic lesions from the primary growth, the presence of intravascular invasion means as much from the prognostic standpoint as neoplastic nodes, and its absence means much more.

Dukes and Bussey found that in 16.6 per cent of 699 specimens of rectal carcinoma the veins were invaded and demonstrated small carcinomatous implants along the superior hemorrhoidal vessels.

Grinnell recently found veins involved in 36 per cent of 75 cases studied. In 90 per cent of 30 cases in which there were visceral metastatic lesions, venous invasion was demonstrated in the primary growth. Twenty-five per cent of the patients who had visceral metastatic lesions failed to show nodal involvement.

The first reported instance of neoplastic invasion of nerves was probably that of Cruveilhier,[8] in 1842, but this phenomenon has been encountered frequently since then, and almost all types of neoplasm have been observed to use the perineural spaces as a route of extension. Excluding reports of isolated instances of perineural invasion, no exhaustive investigation of invasion of nerves had been undertaken until 1936 when Warren, Harris and Graves[32] were struck with the frequency of its occurrence in prostatic carcinoma. Kahler,[16] in a later study, placed perineural invasion at the head of the list of criteria for the microscopic diagnosis of prostatic carcinoma.

As early as 1770, Cotugno[7] described spaces about the sciatic nerve which he demonstrated in the cadaver. Other investigators followed with studies to determine the anatomic nature of these spaces and the presence or absence of a definite communication with the spinal subarachnoid space. Key and Retzius,[17] Orr and Rows,[25-28] Weed,[33-36] Alford and Schwab,[1] and Sullivan and Mortensen[31] have contributed greatly through injection experiments on man and animals, to the knowledge of the nature of the neural spaces and of the direction of flow of the fluid therein.

The fact that these spaces exist about the nerves to their smallest ramifications, and that there is a circulating fluid medium within, gives rise to the contemplation of another possible mode of spread of neoplastic cells, and thus suggests a possible relation between recurrence and metastatic spread of a malignant growth and perineural invasion. This feature has been noted in rectal carcinoma but there has been little or no mention made in published reports of its possible relation to the recurrence and visceral spread of rectal carcinoma.

This study concerns itself with the incidence of perineural invasion in a series of cases, along with that of venous invasion and nodal spread, and an attempt to correlate their presence with available clinical data.

METHODS AND MATERIALS

One hundred gross operative specimens of rectal carcinoma removed by the abdominoperineal or the abdominal route at the Mayo Clinic, during the year 1935 and the early part of 1936, were chosen for study in the order of their removal. Specimens removed during these particular years were chosen so that a sufficient interval for adequate follow-up study of the patients who had the growths might have elapsed.
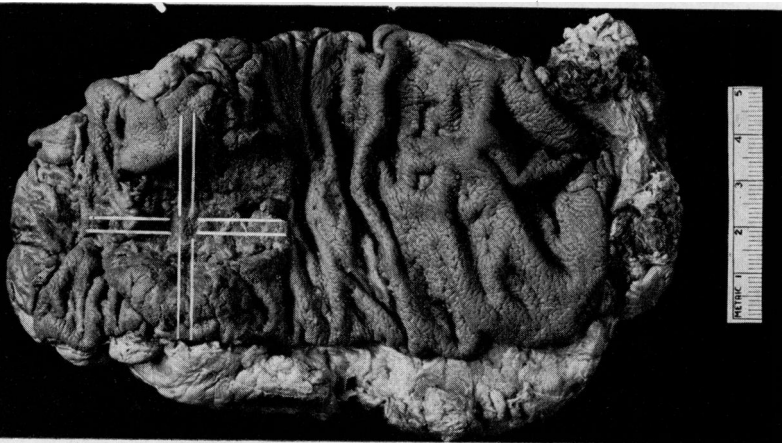
FIG. 3.—Posterior view showing cross-cuts and location of blocks removed in search of venous and perineural invasion. Blocks extend through the perirectal tissue to the intestinal wall.
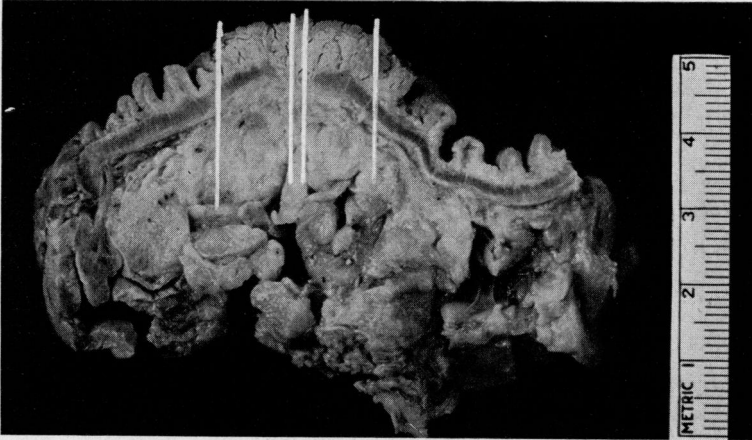

FIG. 2.—Cross-section showing depth of blocks from the four quadrants. Normal mucosa and perirectal tissue included in each block.
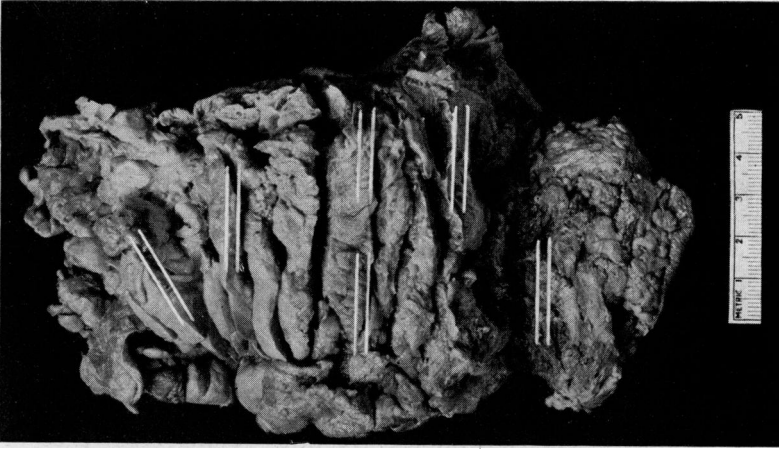

FIG. 1.—Surface view of lesion after bowel had been opened, showing location of blocks removed from each of four quadrants.

To study the involvement of veins, blocks of tissue from all points of the lesion and rectal wall at which microscopic evidence of venous invasion could conceivably be present were removed. The lesion was divided into four quadrants and a block of tissue was taken from each quadrant. The block included the full-thickness of the lesion and the entire thickness of the rectal wall as well as a certain amount of perirectal tissue (Figs. 1 and 2). In addition, transverse cuts were made through the perirectal fatty tissue, exposing the larger vessels leading from the vicinity of the lesion (Fig. 3), and blocks were removed for microscopic study from regions which appeared suspicious, usually within a distance of four inches (10 cm.) above and below the growth.
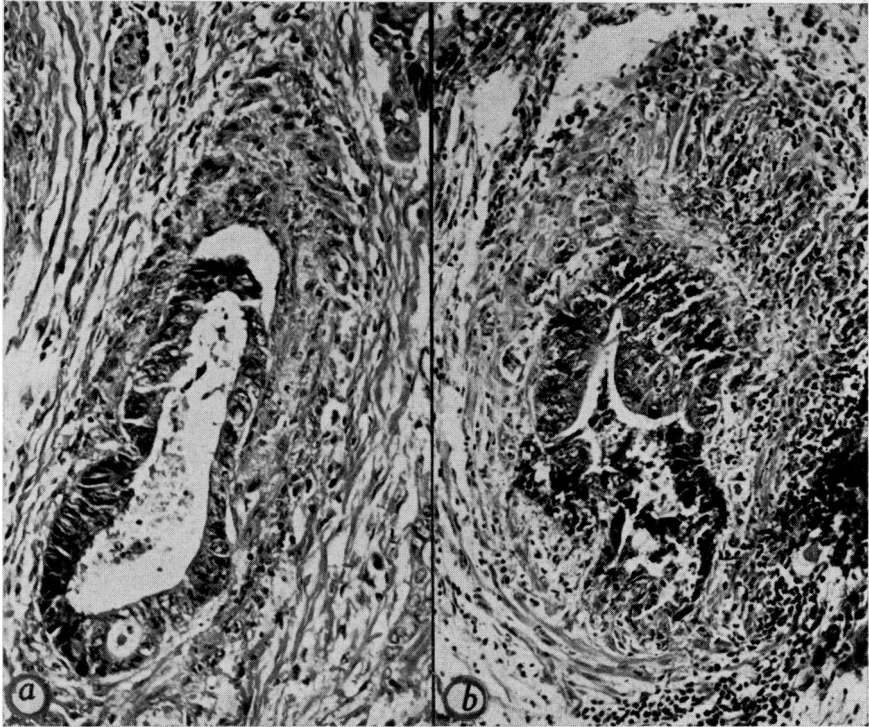

FIG. 4.—(a) Photomicrograph of small vein in the perirectal tissue; the lumen is lined by malignant cells (×185); (b) adenocarcinoma, Grade 4. (Broders' method), in the lumen of a small vein in the perirectal tissue (×140).

Preliminary microscopic examination of sections cut from the blocks, fast freezing technic being used, was facilitated by the use of an acid polychrome methylene blue stain, which is especially adaptable for tissues that have been long fixed in formalin. Of those tissues in which definite or presumptive evidence of venous or perineural invasion was found, permanent sections stained with hematoxylin and eosin were made and further study was carried out. We wish to thank Dr. MacCarty, in whose laboratory the study was made, and Dr. Dockerty, who reviewed the sections.

After examination of all sections was completed, results were tabulated and correlation with clinical data and follow-up records was attempted.

In this method of study, as in others reported to date, there were a few cases in which it was extremely difficult to distinguish small submucosal lymphatic channels from venous channels, and in these cases van Gieson's stain was employed with some degree of success. The presence of erythrocytes within the lumen of a vessel may often aid in distinguishing the type of vessel, but it must be borne in mind that hyaline and necrotic
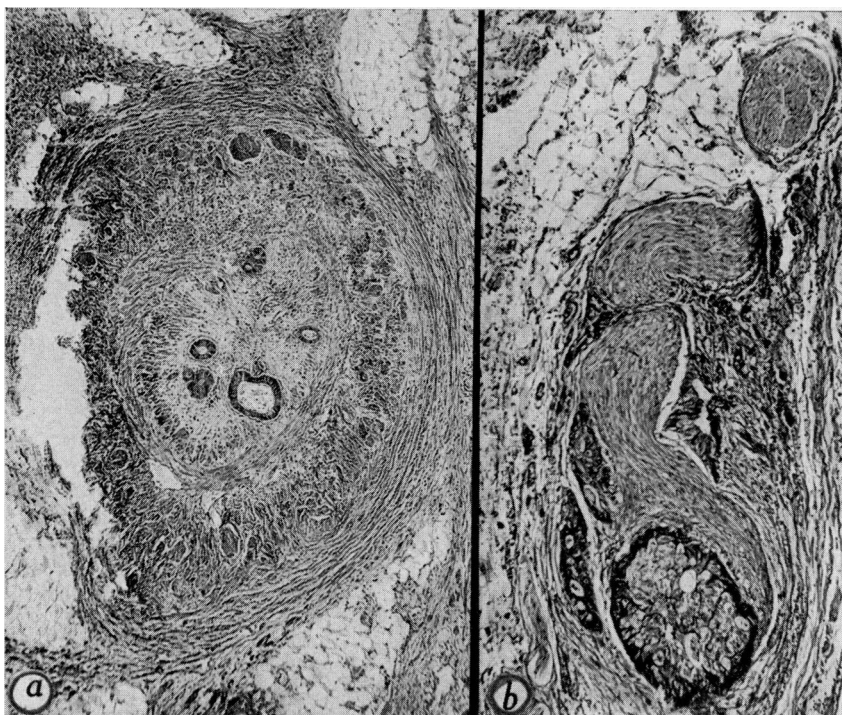

FIG. 5.—(a) Photomicrograph showing malignant canalization of a thrombus in a large vein in the perirectal tissue (× 35); (b) invasion of perineural spaces by colloid adenocarcinoma, Grade 2, showing formation of alveoli and secretion of mucus. Note uninvolved nerve nearby (× 6o).

material may closely resemble erythrocytes, and also that lymphatic channels may contain erythrocytes as a result of trauma or the surgeon's knife. The presence of smooth muscle, as demonstrated by van Gieson's stain, is of some help.

Most of the involved veins were found in the perirectal tissue near to the muscle wall or within the perirectal fat (Figs. 4 a and b and 5 a). There were no instances of invasion of an arterial lumen, a fact that emphasizes the oft-mentioned immunity of these vessels to carcinomatous invasion. Perivascular lymphatic vessels were seen to be involved, but there was no penetration of the arterial wall.

An interesting feature noted was the frequency of arterial thrombosis in cases in which the veins were involved. This occurred in a number of

instances, and when seen on preliminary examination was taken as an indicator of venous involvement.

In arriving at the final microscopic diagnosis, we considered only cases in which the involved vessels were definitely venous and eliminated all cases in which the observations were indefinite.

Perineural invasion is not as difficult to recognize as is involvement of venous channels. In most instances, involved nerves are abundant in the section, although by no means all of the nerves in one section are always involved. Many fields were examined in which a nerve was seen to be extensively involved whereas one or several nerves in the immediate vicinity were not involved (Fig. 5 *b*). Invasion of nerves was seen as far as four inches (10 cm.) from the site of the primary growth.
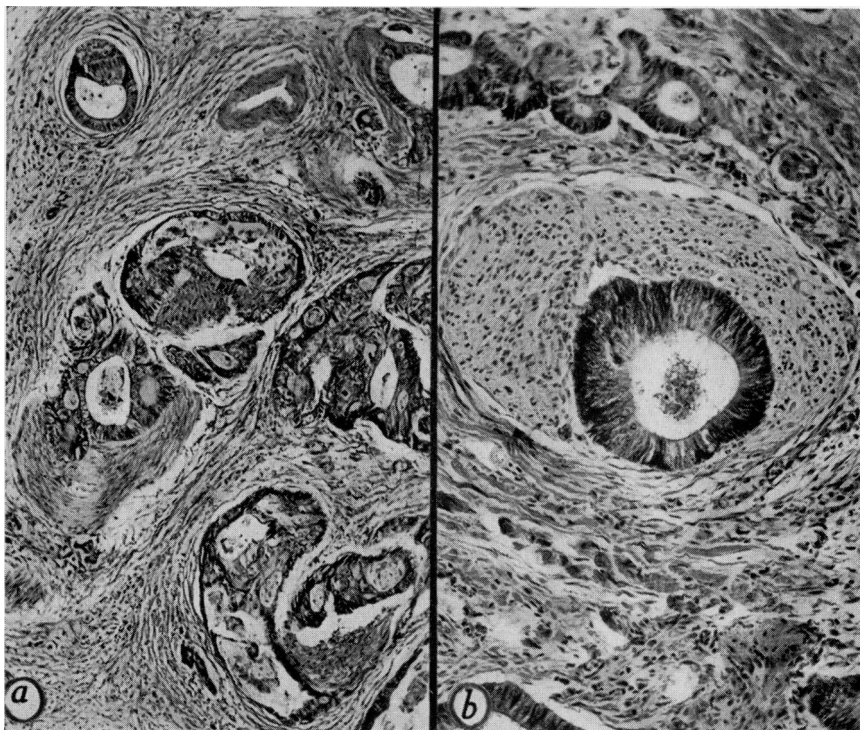
Fig. 6.—(*a*), Photomicrograph showing extensive invasion of nerves with marked distention of the neural spaces, and formation of alveoli (× 70); (*b*) showing alveolus in the endoneural space with compression of the surrounding nerve fiber, but without degeneration of the nerve (× 125).

Many cases were rejected because of "secondary" involvement of nerves. This was usually present in nerves close to the lesion. The nerve was completely surrounded by extensive carcinomatous infiltration but the perineural space remained intact and did not contain carcinoma cells within its confines, indicating that the nerve was merely isolated by surrounding carcinoma and not actually invaded.

Involvement of the perineural space varied in architecture. In some instances a few malignant cells were seen lying within the space without

any apparent conformation, while in other cases the cells were arranged in alveoli and even distended the space with their mucous secretion (Fig. 6 a).

There was little or no degeneration of nerve fibers to be seen in the nerves involved, apparently because of the distensibility of the walls of the perineural spaces, which were seen to be extremely distorted in places (Fig. 6 b).

In no cases were the plexuses of Meissner and Auerbach seen to be involved, although nerve fibers both proximal and distal to these structures might be invaded.

RESULTS

Lymphatic Involvement.—Involvement of the lymph nodes was found to be present in 47 per cent of the 100 cases. In previous investigations based, in total, on more than 500 specimens, the proportion of cases in which lymph nodes were involved varied from 36 to 68 per cent (Table I). We found,

TABLE I

NODAL INVOLVEMENT FOUND IN PREVIOUS STUDIES

Author	Total No. of Cases	Percentage Involved
McVay	100	47
Wood and Wilkie[37]	100	51
Gabriel, Dukes and Bussey	100	62
Gilchrist and David	25	68
Coller, Kay and MacIntyre	53	64
Grinnell (1916-1932)	107	36
Grinnell (1938-1941)	75	55

as others before us, that the higher the grade of malignancy (Broders' method) the higher the incidence of nodal involvement (Table II).

TABLE II

INCIDENCE OF NODAL, PERINEURAL AND VENOUS INVASION ACCORDING TO GRADE OF MALIGNANCY (BRODERS)

Grade	Total Cases	Nodal Involvement		Perineural Involvement		Venous Involvement	
		Cases	Percentage	Cases	Percentage	Cases	Percentage
1	14	3	21.4	2	14.3	1	7.1
2	54	20	37.0	16	29.6	7	13.0
3	24	18	75.0	9	37.5	7	29.2
4	8	6	75.0	3	37.5	5	62.5
Totals	100	47		30		20	

Dukes[10] expressed the opinion that metastatic growths in lymph nodes are more frequently found among women than among men, a feature which is not borne out in this study, 46.1 per cent of women and 47.5 per cent of men having nodal involvement.

Dukes has stated that the highest incidence of nodal involvement occurs among young patients, while the tendency is less frequent among the older patients. This fact was also noted in this series (Table III).

Most investigators, notably Mayo and Schlicke,[18] have found the highest

incidence of nodal invasion in the upper part of the rectum and in the recto-sigmoid. In this series a slightly higher proportion of nodal involvement was found in the middle third of the rectum than in the other segments, 50 per cent in the middle third, and 48.8 and 40.2 per cent in the upper and lower thirds, respectively.

Of the series of patients who had nodal metastatic lesions, ten patients survived for three years while only two survived for five years.

Perineural Invasion.—Involvement of the perineural and endoneural spaces was demonstrated in 30 of the 100 cases, the average age of the patients who had perineural involvement being 51 years, almost exactly the average age in the entire series. Eighteen of the 30 patients were men (60 per cent), and 12 were women (40 per cent).

The average preoperative duration of symptoms among those patients who had involvement of nerves was 9.4 months, as compared with 9.7 months in the entire series. Pain was a prominent symptom, volunteered by the patient, in 24 cases; it was not mentioned in the history of three cases; and was stated

TABLE III

INCIDENCE OF NODAL, PERINEURAL AND VENOUS INVOLVEMENT ACCORD:NG TO AGE

Age, Years	Total Series	Nodal Involvement		Perineural Involvement		Venous Involvement	
		Cases	Percentage	Cases	Percentage	Cases	Percentage
20-39..........	11	7	63.6	3	27.3	4	36.4
40-59..........	68	34	50.0	21	30.9	13	19.1
60-79...:......	21	6	28.6	6	28.5	3	14.3
Totals.........	100	47		30		20	

to be absent in three cases. Thus, in 89 per cent of the cases in which information on this point was available, pain was a prominent symptom. In the evaluation of pain in this study, only cases in which the history indicated that the pain might be directly neurogenic and not just discomfort vaguely noted by most patients with rectal carcinoma, were recorded. Terms such as "aching," "boring," "gnawing," "constant" or "steady" were considered to be indicative of pain due to involvement of nerves, while tenesmus, cramps, a feeling of fullness and the desire to defecate were not so considered. Of the 70 cases in which the nerves were not involved pain was found to be a primary symptom in only 25. Pain was not mentioned in the history of 20 cases, and in 25 cases, when the patient was questioned, he stated that it was definitely absent or was present in one form or another but not localized to the rectum. The incidence, then, of pain for cases without perineural involvement in which information was available was 50 per cent.

Of the 30 cases in which there was involvement of the nerves, the lymph nodes were also involved in 20 (67 per cent).

When involvement of nerves was considered in the light of grading, both by cellular differentiation (Broders) and by mural penetration (Dukes), it was seen that the higher the degree of malignancy, the more frequently was perineural involvement present (Tables II and IV).

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TABLE IV

INCIDENCE OF PERINEURAL AND VENOUS INVASION ACCORDING TO DEGREE OF MURAL PENETRATION (DUKES)

Class	Perineural Involvement		Venous Involvement	
	No. of Cases	Percentage of Involved Cases	No. of Cases	Percentage of Involved Cases
A...	0		0	
B...	10	33.3	3	15
C...	20	66.7	17	85
Totals.......................................	30	100.0	20	100

There is no apparent relation between the size of the carcinoma and the presence of perineural invasion.

In considering the presence of perineural invasion in relation to the location of the growth, it seemed feasible to divide the rectum into lower, middle and upper thirds, including lesions of the rectosigmoid in the latter group. It was found that lesions exhibiting involvement of the nerves occurred equally in the three locations (ten cases in each third), so that the presence of perineural invasion is apparently not related to the location of the lesion. This result contrasts with involvement of lymph nodes, which, in this series, was more frequent in the middle and upper thirds of the rectum than in the lower third, and vascular invasion, which seems to increase with the height of the lesion in the rectum.

No relation could be observed between the location of the lesions (anterior, posterior or lateral wall) and the presence of involvement of nerves. Sixteen (50.3 per cent) of the lesions in which nerves were involved were annular in type and the rest were located at different points on the rectal wall. In the entire series, 30 lesions (43 per cent) were annular.

TABLE V

RELATION OF PERINEURAL INVASION TO LOCAL RECURRENCES

	Nerves Involved		Nerves Uninvolved	
	Cases	Percentage	Cases	Percentage
Definite local recurrence..........................	13	81.2	14	30.4
Definitely no local recurrence.....................	3	18.8	32	69.6
Totals................................	16	100.0	46	100.0
Questionable and inadequate follow-up, and post-operative complications.........................	14		24	
Grand Totals..........................	30		70	

The striking feature of perineural involvement of rectal carcinoma is its relation to local recurrences (Table V). Only recurrences in the scar or site of anastomosis were considered. Metastasis to nearby viscera, such as the bladder, vagina, prostate, perineal nodes, etc., was eliminated because of the probability of its being due to lymphatic or venous spread rather than to invasion of nerves. Definite local recurrences were found in 81.2 per cent of traceable cases in which there was perineural invasion, whereas, in those without perineural invasion, recurrences occurred in only 30.4 per cent. Cases in which there were definitely no local recurrences comprised only 18.8 per cent of those in which nerves were involved, whereas, in cases

without involvement of nerves there were definitely no recurrences in 69.6 per cent. It was necessary to eliminate certain cases from each group in comparing these results. These were considered to have been followed-up inadequately because of early deaths from unrelated causes, such as post-operative peritonitis or pulmonary embolism, and unconfirmed causes of death. All cases in which there was a question as to local recurrence, but no reliable evidence was found to substantiate its presence, were placed in the latter group.

In the cases in which there was definite recurrence, there were nine (69.2 per cent) in which lymph nodes were involved in the group in which perineural invasion occurred, and there were seven (50 per cent) in which lymph nodes were involved in the group without perineural invasion. While these figures tend to indicate a somewhat greater degree of lymphatic spread in those cases of recurrence in which nerves are involved, they are not statistically significant, and, in any case, do not necessarily prove that re-currence is dependent on the lymphatic system rather than on the nerves. Nodal involvement in the entire series, in cases in which there was perineural involvement, was 66 per cent. Nodal involvement was 64.7 per cent (11 cases in 17) in those cases in which there was invasion of the nerves but no local recurrence.

There was a notable difference in the five-year survival rates of the patients who had, and those who did not have, perineural involvement. In the group of 29 traced cases in which there was perineural involvement, only two patients were living and well five years after the operation (6.9 per cent). Twenty-three were dead from cancer, either recurrent or metastatic, and of these, 19 were dead within two and one-half years. The average duration of life after operation of the 23 who died within five years, eliminating four patients who died because of postoperative complications, was 20 months.

In the group in which involvement of nerves was not found at operation, it was discovered that 18 of 51 patients who were traced, were living after five years (35.3 per cent). The average duration of life after operation in this group, of those who did not survive for five years was 25.7 months.

In the group in which there was perineural involvement, four patients, sooner or later, complained of a great deal of severe sciatic pain, which might be taken as a possible indication of further spread to greater distances, of the malignant cells within the perineural spaces. All four of these patients died within 15 months after operation of visceral metastatic lesions.

It has been mentioned earlier that perineural invasion can be traced for a considerable distance in some cases. Although measurements of this entire distance were not carried out in this study, perineural invasion did occur as far as four inches (10 cm.) from the site of the primary lesion. One might speculate that the invasion of the perineural spaces can take place to a distance above the line of operative resection and, at a later date, burst through the confines of the perineural space to give rise to a recurrent

lesion, perhaps at the line of anastamosis or at a higher level. Many sections showed a nerve surrounded by malignant cells. In these instances the perineural sheath appeared to be ruptured as though the cellular contents of the sheath had become too great for the distensibility of the membrane. In sections exhibiting 'secondary' nerve involvement, that is, isolation of a nerve by infiltrating carcinoma without penetration of the perineural membrane by the cells, the membrane was always intact, although completely surrounded by malignant cells.

Venous Invasion.—In 100 cases of rectal carcinoma studied in this series there was evidence of invasion of the veins in 20 cases. There may have been venous involvement in two others, but confirmation of its presence was impossible by the methods used.

The average age of the patients who had venous invasion was 47 years. The average duration of symptoms in cases in which there was invasion of the veins was 7.9 months. The duration of symptoms in these cases varied from three weeks to 30 months.

There were 13 men (65 per cent), and seven women (35 per cent) among the patients who had venous invasion.

The incidence of venous invasion in relation to histologic grading, according to cellular differentiation and to mural penetration (Tables II and IV) increased with the degree of malignancy. Only three of the 20 cases in which there was venous invasion fell into Dukes' Class B, while 17 cases fell into Class C. There were no cases in Class A.

Nodal involvement was present in all except three of the cases in which there was venous invasion (85 per cent). This would indicate that venous invasion rarely occurs before nodal involvement, but that it may do so.

In relating the frequency of venous invasion to the location of the lesion, we found that in lesions of the upper part of the rectum and rectosigmoid invasion was present more often than in lesions of the lower segments, the upper third in 55 per cent, and the middle and lower thirds in 15 and 30 per cent, respectively.

The postoperative survival of patients who had venous invasion was found to vary from four to 60 months, the average survival being 22 months. Three patients survived for three years, one patient for four years, and one for five years. The latter died exactly five years after operation, and, at necropsy, lesions were observed in the liver. Sixteen of the 20 patients finally succumbed to cancer.

In eight of these 20 cases venous invasion alone was observed, while in 12, perineural involvement was observed in addition to venous invasion. In 16 cases in the general series, involvement of nerves without venous invasion was observed.

In the total series of 100 cases, there were 27 local recurrences. In six of these, nerve invasion alone was observed (22.2 per cent); in three, venous involvement alone (11.1 per cent); in seven, involvement of nerves and veins together (25.9 per cent); and in 11, involvement of neither nerves

nor veins (40.7 per cent). In only four of the cases without involvement of nerves or veins was involvement of nodes observed. Therefore, in seven cases there was recurrence in spite of the fact that involvement of any of the three pathways of spread was not observed at operation.

Recurrence of rectal carcinoma, in the light of these findings, is probably not concerned with only one of the three pathways of spread, but results from different ones in different cases, and may involve any of them. However, it may be said that local recurrences are more frequent in rectal carcinoma when nerves and veins are involved than when they are uninvolved, and that there are twice as many recurrences when nerves alone are involved as when veins alone are involved.

In studying the relation of the three pathways of spread of rectal carcinoma to the presence of visceral metastatic lesions occurring at operation and later, it was found that metastatic lesions were present or occurred later most frequently in the group that showed venous invasion (Table VI).

TABLE VI

OCCURRENCE OF VISCERAL METASTATIC LESIONS AT OPERATION, AND LATER, IN CASES IN WHICH THERE WAS NODAL, PERINEURAL OR VENOUS INVASION

	Entire Series		Nodal Involvement		Nerve Involvement		Vein Involvement	
	Cases	Percentage	Cases	Percentage	Cases	Percentage	Cases	Percentage
Metastatic lesions present at operation, or occurring later......	31	45.6	22	78.6	13	81.2	16	94.1
Metastatic lesions......	37	54.4	6	21.4	3	18.8	1	5.9
Totals...........:	68	100.0	28	100.0	16	100.0	17	100.0
Inadequate follow-up, and postoperative complications.......:	32		19		14		3	
Grand totals......	100		47		30		20	

In 94 per cent of the cases in which venous invasion was observed at operation and in which the follow-up was adequate, visceral metastatic lesions either were present at the time of operation or developed later, whereas, visceral metastatic lesions were less frequent in cases in which nerves or nodes were invaded. This fact would seem to indicate that venous invasion is important in regard to visceral metastasis while perineural invasion may be related to local recurrence.

In the entire series of 100 cases, visceral metastatic lesions were found at the time of operation in seven cases, and in six of these, venous invasion was present in the specimen removed (86 per cent). Lymph nodes were involved in five of these seven cases (71 per cent).

In only four of the 20 cases in which there was venous invasion were metastatic lesions observed in the liver at operation, and the surgeon made the diagnosis of malignancy by palpation correctly in three instances.

When one considers that one-fifth of the patients in this series of rectal

carcinoma had veins invaded by carcinoma, and that practically all (94 per cent) of these already presented, or later acquired, visceral metastatic lesions, the prognostic importance of the presence of venous invasion in the operative specimen is seen. The fact that four-fifths of the patients in the series of 100 cases failed to show invasion of the veins at operation and that visceral metastatic lesions occurred in only 18.7 per cent (15) of these patients emphasizes the prognostic significance of the absence of venous invasion, as has been mentioned by Brown and Warren.[3]

CONCLUSIONS

1. In 100 cases of rectal carcinoma, lymph nodes were involved in 47 per cent, nerves in 30 per cent, and veins in 20 per cent.

2. Invasion of lymph nodes, nerves and veins increases with the degree of malignancy of the carcinoma.

3. Invasion of lymph nodes occurred equally in the two sexes, while venous invasion and perineural invasion were more frequent among men than among women.

4. Venous and nodal invasion occurred more often among young than among old patients, while invasion of nerves was not related to age.

5. Invasion of nerves was not related to the location of the lesion, while venous invasion was most frequent in lesions of the upper part of the rectum, and nodal invasion was slightly more frequent in lesions of the middle segment of the rectum than in lesions of other segments.

6. Venous invasion occurred more frequently in cases in which there was involvement of nodes than in other cases, but it occurred in cases without involvement of nodes as well.

7. Nodal invasion was somewhat more frequent in cases in which there was involvement of nerves than in those in which the nerves were not involved.

8. Pain was a prominent symptom in 89 per cent of cases in which there was invasion of nerves.

9. Local recurrence was more than two and one-half times as frequent in cases in which invasion of nerves was observed as in cases in which it was not observed.

10. Visceral metastatic lesions at operation, or later, occurred in 94 per cent of patients who had venous invasion in the primary growth, and were five times as frequent as in patients without venous invasion in the primary growth.

11. Venous invasion in the primary growth does not always mean that hepatic metastatic lesions are present.

12. Eighty-six per cent of patients among whom visceral metastatic lesions were present at operation exhibited venous invasion in the primary growth, while 71 per cent exhibited nodal invasion.

13. Eighty per cent of patients who had venous invasion in the primary growth died from carcinoma, either recurrent or metastatic.

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