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STENOSIS OF THE SMALL BOWEL AS A COMPLICATION IN RADIATION THERAPY OF CARCINOMA OF THE UTERINE CERVIX

by

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The adverse influence of radiation on the intestinal mucosa had been recognized before roentgen and gamma rays were first utilized in the therapy of malignant diseases. WALSH (1897) described a self-limiting condition of diarrhea and cramp, ascribed at the time to thermal action. This could be prevented by placing metallic shields between the observer and the sources of radiation. As irradiation techniques became sophisticated and large doses of radiation were administered in each case, a certain frequency of intestinal reaction and damage became accepted as an inevitable consequence of the therapeutic modality. This applies especially to the treatment of carcinoma of the uterine cervix with the application of radioactive sources in the uterus and vagina; the most common site of reaction is the rectum but the sigmoid colon, urinary bladder, small bowel, neck of the femur, and the skin, are also liable to injury.

Compared with the frequency of 5 to 20 per cent for rectal complications induced during treatment of carcinoma of the uterine cervix (ANDERSON et coll. 1955, KOTTMEIER 1964 a, FRISCHBIER & LOHBECK 1970, JOELSSON 1970), the

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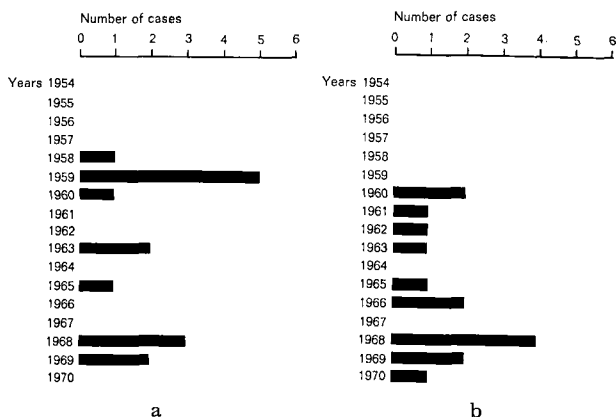


Fig. 1. Distribution of cases according to year of commencement of radiation treatment (a) and year of surgery because of intestinal obstruction (b).

rate for complications of the small bowel ranges only between 0.5 and 5 per cent (ASHBAUG & OWENS 1963, KAPLAN 1956, SHAMBLIN et coll. 1963, RUBIN & CASARETT 1968, GRAHAM & VILLALBA 1963).

The aim of the present paper is to report a series of cases, treated first by radiation therapy for carcinoma of the uterine cervix and later by surgery for verified radiation-induced stenosis of the small bowel.

Material and Methods. The cases in the series were selected in the following two ways: (1) A review was made of all cases treated for disease of the small bowel in any of the twelve departments of surgery in the Stockholm area during the period 1954—1968 inclusive. The investigation was organized to ensure that as far as possible, the total number of such cases was registered (RÄF 1967). The survey disclosed that during the 15-year period, approximately 3 000 cases had been operated upon for obstruction of the small bowel; non-specific inflammatory obstruction without the characteristics of regional enteritis occurred in 125 cases. Eighteen of these had a history of radiation treatment at Radiumhemmet for carcinoma of the uterine cervix. Cases in which surgical specimens had not been taken (2 cases) or in which carcinoma had been present at operation (1 case) were immediately excluded and the specimens of the remainder were re-examined by one of the authors (G. S.). Twelve cases fulfilled the criteria of having a history of radiation therapy and verification by microscopy of radiation-induced injury to the small bowel. (2) Three additional cases with radiation injury of the small bowel, operated upon during the period January 1969 to March 1970, were subsequently included in the present series; these were found in connection with a review of cases of carcinoma of the uterine cervix filed at Radiumhemmet.

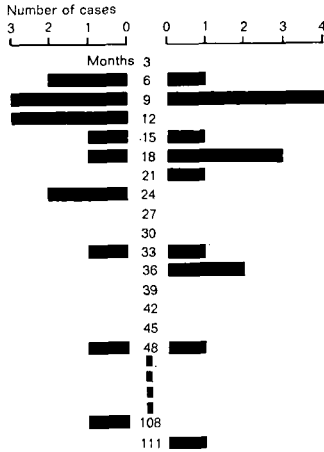


Fig. 2. Distribution of cases according to interval between radiation treatment and symptoms (left) and between radiation treatment and laparotomy because of ileus (right).

Results

A total of 6 154 cases of carcinoma of the cervix were examined at Radiumhemmet during the period 1954—1969 with a view to treatment; 3 075 of these were living in the Stockholm area. The rate of small bowel stenosis as a function of radiation therapy of carcinoma of the uterine cervix was accordingly 0.49 per cent, a figure that is a non-corrected and overall one.

Five cases underwent radiation therapy in 1959 but the rest were evenly spread over the period 1958—1969 (Fig. 1 a). Four of the cases were operated upon for radiation stenosis in 1968, the rest being distributed over the eleven-year period 1960—1970 (Fig. 1 b). The interval between commencement of radiation therapy and laparotomy for ileus varied between 5 and 111 months (Fig. 2), the mean value being 25 months. The duration between the commencement of symptoms and surgery was 0 to 7 months.

The presence of adhesions before radiation therapy has been suggested as a cause of radiation damage to the small intestine. In the present series laparotomy before radiation treatment had been carried out in 10 of the 15 cases. Salpingo-oophorectomy had been performed in 5 cases (Table). Previous inflammatory disease in the pelvis or abdomen had occurred in 6 out of the 15 cases. Two of them had a history of gonorrhoea, one of non-specific acute salpingitis, two of appendicitis and one of cholecystitis (Table).

Radiation technique. Data for the details of the intracavitary and the external treatment were obtained for 14 cases; the 15th case was in stage I and may have had intracavitary irradiation as the only and definitive mode of therapy. Two additional cases in stage I received no external irradiation.

Table*Proportion of cases with previous inflammatory disease or previous laparotomy*

Previous inflammatory disease				Previous laparotomy			
Appen- dicitis	Chole- cystitis	Gonorrhea	Salpingitis	Appen- dectomy	Cholecystec- tomy	Salpingo- oophorectomy	Tubal ligation
2/15	1/15	2/15	1/15	2/15	1/15	5/15	2/15

The *intracavitary* part of the treatment was in 11 cases given according to the principles of the modified, individualized Stockholm technique. Regard was paid to the elasticity of the vagina, the type of the lesion, the extent of the growth and the position of the uterus. In cases of endocervical growth as well as in those in which the neoplasm had extended paracervically, the amount of radium in the intrauterine irradiator was increased (KOTTMEIER 1964 b). This was exemplified in 5 cases. From 43 to 150 mg radium were used in the uterus, and 60 to 144 mg of radium in the vagina. The treatment time varied between 20 and 25 hours per treatment course with two courses, 3 weeks apart.

The *intracavitary* irradiation was given in 4 cases with a remote afterloading technique that utilized applicators fixed to the patient by means of a corset. These carried activities 3.5 to 4 times larger than those in the modified, conventional Stockholm technique (WALSTAM 1965, JOELSSON & BÄCKSTRÖM 1970). From 159 to 209 mg of radium and 600 mCi cesium were used in the uterus and 600 mCi cesium in the vagina, respectively. The treatment times varied between 5 and 11 hours per course with two courses 3 weeks apart. The amount of irradiation was always indicated by the statement of dose of clinical significance, measured at the base of the bladder and the anterior wall of the rectum (GRAY & KOTTMEIER 1957, KOTTMEIER & GRAY 1961, JOELSSON & BÄCKSTRÖM 1969). The rectal dose from the *intracavitary* irradiation was below or about 4 000 rad, varying between 2 500 and 3 800 rad in 12 of the 15 cases; in the rest it was 4 100 and 5 000 rad. The bladder dose was below 6 000 rad, varying between 2 650 and 5 800 rad in 13 of the cases; in one case it was 7 150 rad.

External beam therapy was administered in 10 cases with a medium energy roentgen technique with two abdominal and two gluteal fields or two opposing fields with central shielding blocks. The field areas ranged between 125 and 250 cm², FSD 50 to 75 cm, tube potential 170 to 200 kV and the filtration 0.5 mm Cu + 1 mm Al (HVL 1 mm Cu) or 0.44 mm Sn + 0.25 mm Cu + 1 mm Al (HVL 2 mm Cu) (THORAEUS 1932). A total of 6 × 400 R (in one case 10 × 300 R) over 4 to 6 weeks gave a parametrial dose of 1 200 to 2 600

rad and a contribution to the bladder base and the anterior wall of the rectum of 600 to 1 300 rad. The pelvic dose distribution as a function of this technique has been reported by RANUDD (1966).

The external irradiation was in one case administered with ^{60}Co by two opposed beams with absorbers in both the anterior and the posterior beam to protect the central tissue volumes; the size of the fields was 250 cm^2 with SSD 60 cm. A parametrial dose of 4 500 rad was delivered in fractions of 300 rad (reference dose) six days per week, so that the contribution to the bladder base and to the anterior wall of the rectum was 1 500 rad.

One case received ^{60}Co external beam therapy with one 250 cm^2 anterior beam with a central shield and two opposed 125 cm^2 lateral beams with wedge filters; SSD 60 cm. The parametrial dose was 4 000 rad with a weekly tumor dose of 800 rad and treatment fractions on 5 days per week. This irradiation contributed 2 000 rad to the bladder base and 2 800 rad to the anterior wall of the rectum. (Characteristics of the pelvic dose distribution of the respective ^{60}Co techniques were reported by KOTTMEIER 1964 b, RANUDD 1966 and JOELSSON 1970.)

Clinical course. The main symptom was usually intermittent attacks of abdominal colicky pain. A heavy meal seemed to induce an exacerbation so that the food intake was lowered and weight loss almost invariably reported as a consequence. Hemoglobin values below 10.8 g per cent were observed in one case and serum protein values below 6.8 per cent in 2 cases. The symptoms occurred directly following the completed course of radiation therapy in only 1 of the 15 cases, a free interval being present in the rest. Along with the aggravation of symptoms, the signs were always those of intestinal obstruction. Roentgen examinations were performed in 10 cases in an attempt to establish this diagnosis and in 8 of these evidence of mechanical obstruction was obtained.

Resection of the stenotic part of the small intestine with end-to-end enteroanastomosis was performed in all except 3 cases in which the distal part of the ileum was resected together with the proximal part of the ascending colon; the resected segments measured 5 to 65 cm with a mean length of 30 cm. The presence of adhesion to the injured bowel was specifically noted in the report of 12 cases; in at least 7 of these the stenotic part of the bowel was firmly bound to the uterus but in the rest of the cases to the pouch of Douglas or the uterine tubes. The report of the operation gave no information concerning adhesions in 2 of the remaining cases but in the last case it was stated that no adhesions were present in the abdomen or pelvis.

A single stenosis, 0.5 to 4 cm in length, was evident in 14 cases. Two stenotic parts of the ileum were interconnected by approximately 80 cm of macroscopically normal intestine in the remaining case. A perforation of the small

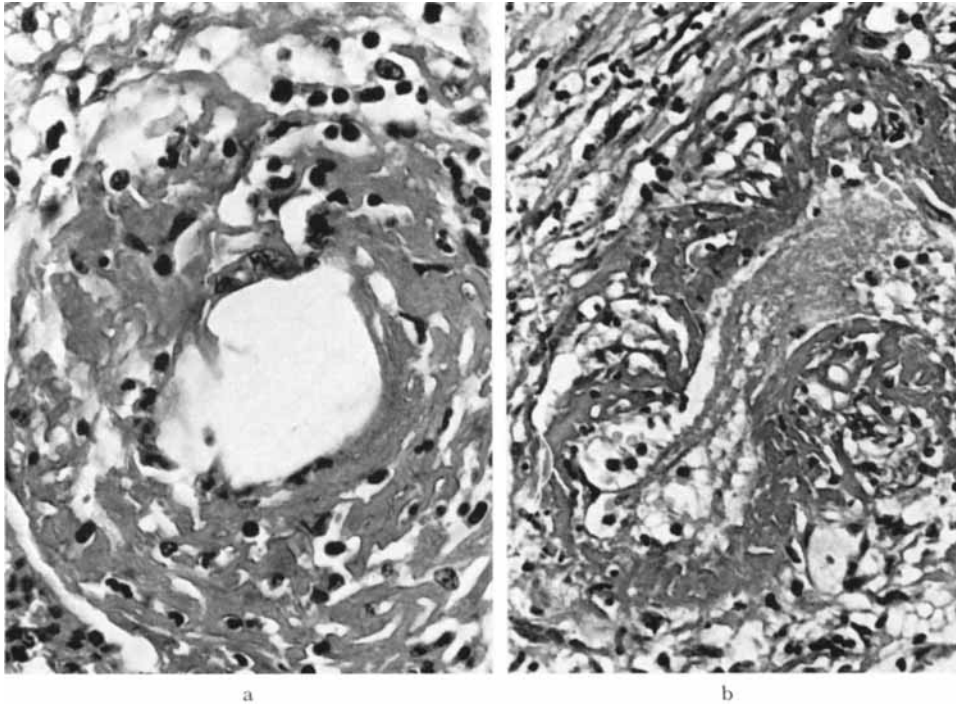


Fig. 3. Dilated, irregular capillary blood vessels with irradiation damage of fibrinoid type in the wall. a) $\times 400$. b) $\times 400$.

bowel proximal to the obstruction was either already present or was created in the dissection of adhesion in 3 cases; the bowel adjacent to the obstruction, especially proximally, was sometimes swollen and red but enlargement of mesenteric glands was only rarely evident. The stenosis usually lay in the distal part of the ileum; the length of bowel between the stenosis and the ileocecal valve exceeded 100 cm in only 2 cases.

The changes in the intestinal wall were always verified by histologic sections through the altered tissues. Fibrosis of a more or less progressive type, with thick strands of insufficiently vascularized hyalinized connective tissue, replaced the muscularis to a lesser or greater extent; the sclerotic fibrous tissue caused obstruction in most cases by circular constriction of the lumen. Fibrinoid degeneration and necrosis, arising from damage to blood vessels, was often noted in the connective tissue. The blood vessels were dilated (teleangiectatic) and irregular with degenerated walls (Fig. 3). Deep fibrinoid necrosis with surrounding inflammatory reaction was present in 5 cases and perforation of the wall occur-

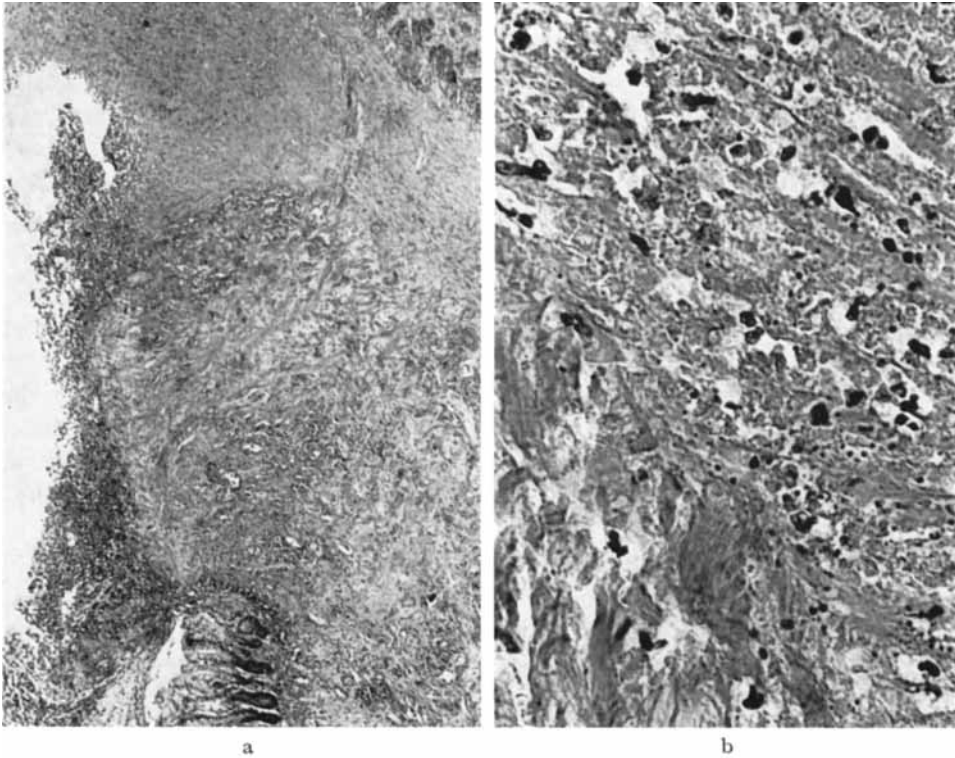


Fig. 4. Radiation injury of small intestine with fibrosis and deep fibrinoid necrosis under an ulcerated surface. a) $\times 40$. b) $\times 400$.

red in 3 cases (Fig. 4). Ulceration was seldom observed but changes in the epithelium secondary to previous ulceration and inflammation with regeneration were often apparent.

Inadequacy of the enteroanastomosis complicated the postoperative period in 4 cases. Ileocecal resection was performed in 2 of these cases and ileocolostomy without resection in 1 case. Resection with end-to-end enteroanastomosis was performed five weeks after the commencement of symptoms in the remaining case; the patient died of peritonitis, with no evidence of carcinoma at autopsy.

Symptoms and signs of intestinal obstruction were present postoperatively in 3 cases although these did not necessitate intervention. An abscess in the abdominal scar occurred in 4 cases. The mean duration of stay in hospital after operation was 25 days.

One patient died from complications in connection with the surgical procedure and one patient died 30 months after the laparotomy, the cause of death being

ileus. The latter had been free from signs of carcinoma at the last clinical examination, performed less than two months before death. All the remaining patients are alive. One of them has had diarrhea and occasional abdominal pain for 6 years after surgery. Three of the patients had diarrhea as the only symptom for 8 to 10 months after the laparotomy. One patient had sigmoid obstruction with abdominal distension and pain, which necessitated colostomy. The remainders have been free from symptoms.

Discussion

The pathogenesis of radiation enteritis has been described in detail by a great number of investigators (WARREN & FRIEDMAN 1942). The early radiation changes in the small bowel are edema and degeneration and necrosis of the epithelial cells of the mucosa. Repair may be complete after an interval of weeks. Edema and vascular damage with small hemorrhages occur in the submucosal and subserosal layers, and the lymphatic tissue in the injured part of the intestinal wall disappears.

Enderteritis and fibrinoid degeneration of dilated blood vessels are evident in all layers of the intestinal wall in chronic processes. Ulceration of the mucosa with deep necrosis sometimes develops and causes inflammation and fibrosis in the deeper layers. Irradiation, however, may also selectively affect the connective tissue of the submucosa and cause an extensive fibrosis with hyalinization; thus a ring-like band beneath an intact mucosa may contract centripetally and produce delayed intestinal obstruction.

Investigations have elucidated that the small bowel is more sensitive to radiation than the colon (DESJARDINS 1931, ANDERSON et coll. 1955). The fact that the frequency of complications of the small bowel despite this is low is generally ascribed to the motility of the small intestine. When a radiation-induced injury of the small bowel occurs, this part of the intestine has often been observed to be fixed to the uterus or its appendages by adhesions. Subsequently, adhesions due to previous laparotomy or previous inflammatory disease increase the risk of small bowel complication (FRIEDMAN 1955, GRAHAM & VILLALBA 1963, POWEL-SMITH 1965). In addition, the fact that in the present series the injured part of the small bowel was nearly always bound to the uterus and the adnexa makes it probable that the intracavitary rather than the external radiation treatment is incriminated as the cause of complication. This contention is supported by the fact that the external irradiation had been given with medium energy roentgen techniques in all but two cases, the midpelvic doses being below 1 300 rad.

The interval between the commencement of radiation therapy and start of symptoms varies considerably. FABRIKANT et coll. (1959) reported in a series

of 71 cases with radiation injuries to the colon and small bowel that this interval averaged 13 months, but that in 4 per cent there was a delay of more than 10 years. A few cases have also been reported with an equally long time lag between the therapy and clinical signs in a smaller series, including radiation stenosis only of the small intestine (FRANK & POHLE 1951, GARDNER & ANLYAN 1952). Figures similar to those observed in the material of Radiumhemmet seem to be widespread (WHILEY & SUGERBAKER 1950).

The overall rate of radiation induced obstruction of the small bowel was 0.5 per cent in the present material. The results indicate, however, that the incidence of this complication to radiation therapy was higher during the last five years of the investigation period, especially when allowance is made for the shorter observation time of cases from this latter period. Among 2 085 cases treated with radiation therapy during the period 1954—1964, 8 (0.3 per cent) developed radiation stenosis of the small bowel, while among those treated during 1965—1969, 7 out of 989 cases (0.7 per cent) had this sequela.

Pertinent to the influence of the intracavitary treatment, and especially the distribution of radium, is the observation by KOTTMEIER (1953) that 2 756 patients treated for carcinoma of the cervix at Radiumhemmet from 1936 to 1945 had no complications of the small bowel. The radium was applied at the time according to the principles of the old Stockholm method and the doses given were comparatively small. The 5-year apparent recovery rate was 42.5 per cent.

The Stockholm technique after 1945 was changed considerably in the direction of individualization (KOTTMEIER 1964a). Suffice it to say that among several factors, the extent of the tumor was especially considered. For example, in cases of endocervical malignant growth and in those with paracervical involvement, an increased amount of radium was introduced into the uterine cavity and the cervix. The observation had been made that the intrauterine radium was responsible for the larger proportion of the dose to the paracervical tissue and the area of the regional lymph nodes. After this change in the application technique, the 5-year apparent recovery rate has markedly increased; if cases of endocervical carcinoma are considered, the rate for stage I and IIa, which had been 57 per cent rose to 81 per cent after the introduction of the individualized treatment method.

The radium was evenly distributed in the cylindrical irradiator in the uterus from the beginning. When, however, attention was focussed on the dose contribution, not only to the rectum and urinary bladder but also to the sigmoid colon and small bowel that often lay in close proximity to the uterine body, the radium was redistributed in the intrauterine cylindrical irradiators with the administration of a lower dose to the fundus. When the remote afterloading

system was first employed in clinical routine (WALSTAM 1965), an intrauterine applicator loaded with 160 to 210 mg radium was used, a capsule of low activity being placed in the fundus. Later, when ^{137}Cs replaced radium, the loading of 600 mCi was divided among six sources of equal activity.

The present investigation elucidates that in 7 of 13 cases radium irradiators and in 2 cases cesium irradiators of high activity had been introduced into the uterus; other factors might have contributed to causing a high, local dose of radiation to an intestinal loop of limited length in the remaining cases. The radiation therapy had been immediately preceded by salpingo-oophorectomy in 2 cases and in one case by pelvic inflammation; a perforation of the uterus was moreover probable at the first radium treatment in one of these cases. Abundant pelvic adhesions were present at operation in the 3 cases. In one case local infection with discharge had occurred in between the radium applications as a sign of local infection, while in the last case no cause for the complication was apparent and the operation report recorded no pelvic adhesions.

Although acute radiation gastro-intestinal injury may be fulminant, it either spontaneously resolves or progresses only slowly to symptoms. Chronic radiation disease presents with anorexia, weight loss, diarrhea, vomiting and intermittent intestinal obstruction. The hematocrit and albumin levels are often both low and it is questionable whether the hypoalbuminemia is secondary to a lesion of the wall of the small intestine or is a function of the decreased food intake (VATISTAS & HORNSEY 1966). Such malnutrition is probably more common in intestinal damage due to external radiation therapy, where long segments of small bowel may be involved. Severe malnutrition resulting in hypoproteinemia was uncommon in this series of short intestinal stenoses.

Roentgenographic examination of the intestine may disclose puddling of barium in the terminal part of the ileum, with a bulbous appearance and segmental saw-tooth strictures. A rigid intestine with destruction of the mucosal folds, often similar to that in regional enteritis, may also be observed. A barium examination of the small bowel is necessary to localize stenosis but signs of obstruction are usually evident in conventional films. The roentgen examination had given the correct diagnosis in most cases of the present series.

It is recognized that the risk of postoperative complications is markedly increased after surgery in the irradiated region in patients with previous radiation therapy; a complication at the site of the intestinal anastomosis with fistula formation is therefore not unusual. This has also been the experience in the present series in which 4 of 15 cases had this sequela. Surgical removal of the damaged part of the intestine was however followed by the absence of further major signs in the rest of the series. It is suggested that the explanation of this good result of surgical intervention is the limited length of the damaged segment

of the intestine (0.5 to 4 cm). This made resection possible with the enteroanastomosis located in healthy tissue. Such a situation might be encountered more often when the intracavitary part of the treatment is incriminated, as in this series, rather than when high energy external irradiation is the cause of the lesion. The limited extent of injury of the intestine encountered in this series may also be an explanation for the good long term results after intestinal resection. Despite an observation period of several years, signs of serious obstruction have not developed.

SUMMARY

Radiation induced injury of the small bowel was observed in 15 of 3 075 cases from the Stockholm area, treated for carcinoma of the uterine cervix during the 16-year period 1954—1969. Factors that might increase the risk of this complication are discussed. Symptoms and signs of the intestinal complications are described and the results of surgical treatment presented.

ZUSAMMENFASSUNG

Strahleninduzierte Schäden des Dünndarms wurden bei 15 von 3 075 Fällen des Stockholmer Gebietes, die wegen eines Carcinoms des Cervix uteri während der 16-Jahres-Periode 1954—1969 behandelt worden waren, beobachtet. Faktoren, die das Risiko für diese Komplikationen steigern mögen, werden besprochen. Die Symptome und Zeichen der intestinalen Komplikationen werden beschrieben und die Resultate der chirurgischen Behandlung dargestellt.

RÉSUMÉ

Sur 3 075 cas de cancer du col utérin traités pendant une période de 16 ans, de 1954 à 1969, dans le district de Stockholm, les auteurs ont observé 15 cas de radiolésions de l'intestin grêle. Ils étudient les facteurs qui pourraient augmenter le risque de cette complication. Ils décrivent les signes fonctionnels et les signes physiques de ces complications intestinales et présentent les résultats du traitement chirurgical.

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