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BLADDER AND INTESTINAL INJURIES FOLLOWING RADIATION THERAPY OF CARCINOMA OF THE UTERINE CERVIX

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Curative treatment of malignant tumours always implies a risk of serious complications from organs in their immediate vicinity. The bladder and the intestines are the organs most often affected by radiologic treatment of carcinoma of the cervix. The literature discussing the types and frequency of complications is extensive (GRAY & KOTTMEIER 1957, FLETCHER et coll. 1958, NOLAN 1962, HITTMAIR 1969, NIEMINEN et coll. 1970, STROCKBINE et coll. 1970, JOELSSON et coll. 1971, BORONOW & RUTLEDGE 1971, WEGHAUPT 1971, VAN DER WALL 1971, KOB et coll. 1972, MICKAL et coll. 1972, ROSWIT et coll. 1972, VILLASANTA 1972). The frequency of complications usually increases when a treatment technique is altered, and then slowly decreases as experience is gained (FLETCHER et coll., KOTTMEIER 1964).

The present report is an analysis of the types and frequency of complications arising in the bladder and intestines in connection with three different radiologic treatment techniques.

Material and Methods. The material consisted of invasive cervical carcinoma treated at different periods of time. The criteria for classifying the material as regards the stage of development have been uniform throughout the material (KOTTMEIER 1964), except that the border between stages I A and I B was established according to FRICK et coll. (1963) and used since the beginning of 1969. Only those complications in the

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urinary passages and the alimentary tract, caused by the primary treatment, and which required surgical measures, were recorded. Those cases where malignant tissue was found in the walls of fistulas and perforational openings were not included. Observation time was 2 years after completion of the radiologic treatment. The number of patients still alive 2 years following initial treatment was recorded for the different groups in the material.

Group I

This group consisted of 287 patients treated in the years 1952, 1953 and 1958 and were staged as follows: Stage I A 7 patients (2 %), stage I B 56 (20 %), stage II A 53 (18 %), stage II B 98 (34 %), stage III 56 (20 %) and stage IV 17 patients (6 %). Two years after the initial treatment 205 patients (71 %) were still alive.

Two intracavitary treatments were given at an interval of 3 weeks, using the Stockholm technique. The intrauterine and vaginal applicators were placed in the uterus and vagina, respectively, without being fixed to each other. The treatment time was standardized to 20 hours per session for both applicators (90 mg ^{226}Ra equivalent to 3.33 GBq in each applicator). No measurement of the dose in the bladder and rectum was performed.

External treatment was also administered to two lower abdominal fields and to two lower dorsal fields, directed towards the parametria and the pelvic wall. Irradiation parameters: 180 kV, HVL 1 mm Cu, SSD 60 cm, field-size 200 cm^2. One field treated each treatment day with an absorbed surface dose of approximately 5 Gy (500 rad) to a total of 15–20 Gy (1 500–2 000 rad) on each field. The abdominal fields were usually treated in connection with the first intracavitary treatment, and the dorsal fields at the time of the second treatment. Extraperitoneal lymphadenectomy was performed 4 months after completion of irradiation in 133 (46 %) patients (GORTON 1953).

Group II

This group consisted of 116 patients treated in 1969 and were staged as follows: Stage I A 20 patients (17 %), stage I B 38 (33 %), stage II A 19 (17 %), stage II B 20 (17 %), stage III 14 (12 %) and stage IV 5 patients (4 %). Two years after the initial treatment 87 patients (75 %) were still alive.

External treatment was given to the contents of the true pelvis without any central shielding using ^{60}Co or 33 MV photons, depending on the thickness of the patient. The absorbed dose varied with the extent of the tumour (Stages I or II), 33 Gy (3 300 rad) $\pm$ 10 %, or 44 Gy (4 400 rad) $\pm$ 10 %, respectively, given in 17–18 fractions or 23–24 fractions, respectively. Both of the opposing fields were treated daily five days a week. In some cases, where only external treatment was given, four-field technique was used with an absorbed dose in the primary tumour of 62–65 Gy (6 200–6 500 rad), split course, with a first series of 40 Gy, with 2 to 3 weeks intermission, and then 25 Gy.

The intracavitary treatment was given using combined applicators (JOHNSSON & NORDBERG 1973) consisting of an intrauterine applicator (Ø7 mm × 68 mm 90 mg ^{226}Ra equivalent to 3.33 GBq), attached to a vaginal applicator (5 mm × 44 mm × 44 mm 110 mg ^{226}Ra equivalent to 4.07 GBq), which gives well-defined geometry for the dose of irradiation around the radium.

The anatomic reference for the prescribed dose was Point A, defined as a point lying 2 cm laterally and 2 cm cranially from the point of contact between the intrauterine applicator and the centre of the vaginal applicator (approximately external os.). The dose-rate in Point A = 2 Gy/h (200 rad/h).

The absorbed dose in Point A on each treatment occasion was 25–35 Gy (2 500–3 500 rad). Measurement in the bladder and the rectum was performed with a Siemens gammameter. The highest values measured were recorded. The total dose in the bladder and the intestines from external and intracavitary treatment was not allowed to exceed 65 Gy (6 500 rad). Neither the different biologic effects of external and intracavitary treatment nor the effect of the fractionation was considered when calculating dose.

Patients at the beginning of Stage I A received only two intracavitary treatments at an interval of 3 weeks. Stages I and II were given primary external irradiation of the contents of the true pelvis followed by one intracavitary treatment 3 weeks after the completion of external treatment.

External irradiation alone was given to cases in Stages III and IV, as well as to 18 patients in Stages I and II in whom the anatomy prevented the use of intracavitary treatment with radium.

Group III

This group consisted of 271 patients, treated in the years 1970, 1971 and 1972 and were staged as follows: Stage I A 39 patients (15 %), stage I B 78 (29 %), stage II A 77 (28 %), stage II B 33 (12 %), stage III 36 (13 %) and stage IV 8 patients (3 %). Two years after the initial treatment 198 patients (73 %) were still alive.

External treatment was given in the same manner as in Group II, although external treatment alone up to full absorbed dose was not used. Since 1972, mainly 8 MV photons from a linear accelerator were employed.

Intracavitary treatment was given using combined applicators as for Group II, but for patients in whom the uterus was 8 cm or less in size, estimated with a sound, a shorter intrauterine applicator was used (Ø7 mm × 46 mm 60 mg ^{226}Ra, equivalent to 2.22 GBq). The vaginal applicator used had the same size as for Group II, but its contents were reduced to 90 mg ^{226}Ra, equivalent to 3.33 GBq. Dose-rate in Point A was 1.8 Gy/h (180 rad/h). Apart from this, the geometry of the dose-distribution was the same as described.

In those patients, in whom the size and form of the vagina were such that it was not possible to insert the combined applicators, only a rod-like applicator measuring Ø7 mm × 68 mm was used, which had a spacer of plexiglass (Ø25 mm × 25 mm). The

Table

Carcinoma of the uterine cervix stages I–IV. Serious complications following radiation therapy. Observation period: Two years

	Group I (287 patients)	Group II (116 patients)	Group III (271 patients)
Bowel stenosis and necrosis	4 (1.5 %)	5 (4 %)	1 (0.5 %)
Recto-vaginal fistulas	6 (2 %)	0	1 (0.5 %)
Vesico-vaginal fistulas	4 (1.5 %)	0	0
Bladder necrosis	0	1 (1 %)	0
Total	14 (5 %)	6 (5 %)	2 (< 1 %)

applicator was placed in the cervix in such a way that 25 mm of its caudal part, which was capsuled in the centre of the plexiglass cylinder, lay in the upper part of the vagina. Point A was defined in the same way as for the combined applicators. The dose-rate in Point A was 1.6 Gy/h (160 rad/h).

The dose in Point A was 25–30 Gy (2 500–3 000 rad) for each treatment occasion. The total dosage in the bladder and intestines from both external and intracavitary treatment was not allowed to exceed 62 Gy (6 200 rad).

Early cases in Stage I were only given two intracavitary treatments. Stages I and II otherwise received the same external treatment as Group II, except that external treatment alone was not given up to full tumour dose. Stages III and IV were given 55 Gy (5 500 rad) external irradiation to the primary tumour.

All of the patients were given complementary treatment in the form of one intracavitary irradiation, administered 3 weeks after completion of external treatment.

Results

The complications recorded in the different patient groups included in the material appear in the Table.

Group I: Necrosis of the small bowel occurred in 2 of the 4 patients who had intestinal reactions. Both of these patients expired as a result of these complications. The others had a marked stenosis of the region between the sigmoid colon and the rectum. No patient had more than one of the recorded complications during the period of observation.

Group II: One patient had necrosis of the small intestines. This patient succumbed as a result of these complications. The others had marked stenosis in the region between the rectum and the sigmoid colon. Necrosis of the bladder was localized to the fundus of the urinary bladder and was accompanied by leakage of urine into the abdominal cavity. It healed after surgical closure of the perforation. No patient had more than one of the complications recorded during the period of observation.

Group III: One of the patients developed a perforation in the sigmoid rectum which opened into the abdominal cavity. One patient had a recto-vaginal fistula. No case of death due to complications was recorded in this group during the observation period.

Discussion

Intracavitary treatment, which is the most common form of treatment used for cervical carcinoma, may cause complications first and foremost in the rectum and in the urinary bladder.

The classic Stockholm method has been used for treating the primary tumour since the 1950's. Extraperitoneal lymphadenectomy (GORTON) has not implied any increase of complications in the bladder or the intestines. The contribution to increased rates of complications from external treatment cannot be established with any degree of certainty, but ought to be rather small, if any.

Fistulas between the bladder and the vagina, and between the rectum and the vagina, were dominant. Their rate of occurrence was 1.5 and 2 %, respectively, i.e. close to the figures usually found in the literature.

The technique used may have permitted uncontrolled doses of irradiation to have been given to the bladder and intestines, as the intrauterine and vaginal applicators were not fixed in an ideal position (JOHNSSON & NORDBERG 1973, FRIBERG & JOHNSSON 1974). No measurements of the dose-rate in the bladder and the rectum after application of the intracavitary preparation were made. High dose-rates, which occur in these organs when the cervix is slender and thin even when correct applicator positions are used, therefore did not lead to the necessary reduction of the treatment time.

Complications in the sigmoid colon and the small intestines are caused by the intrauterine applicator and arise when it extends far up in the uterine fundus, and especially when the uterine wall is thin. The portions of the intestines lying in the true pelvis and mesenteric vessels may then receive quite high doses of irradiation (STROCKBINE et coll., FRIBERG & JOHNSSON).

Analysis of the treatment techniques and the curative results and complications obtained led to locking the intrauterine and vaginal applicators in a fixed treatment position, thus enabling a clearly defined radiation dose around them, and replacing external orthovoltage treatment and lymphadenectomy with external high-voltage irradiation. Dose measurements were carried out in connection with the intracavitary treatments. It was sometimes possible to adjust the position of the applicators in the true pelvis on the basis of these measurements. When high dose-rates were nevertheless found, the treatment time was reduced. External irradiation was always given primarily and without central shielding. External irradiation with central shielding following full tumour dose to the primary tumour from the intracavitary dose involves a risk of unpredictable underdosage to the cervix and parametrium or overdosage to the bladder and intestines (JOHNSSON & NORDBERG 1975). External ir-

radiation alone was given to all of the patients in Stages III and IV, and to those patients in whom it was not possible to apply satisfactorily the intracavitary applicators in the cervix and vagina.

No recto-vaginal or vesico-vaginal fistulas were observed in this material. This was probably due to locking the applicators to each other and also to the reduction of the intracavitary radiation treatment, which was replaced in part by external irradiation. The rate of complications was, however, the same as in the previous material, although organs higher up in the true pelvis were affected. Half of the recorded complications occurred in patients who had received only external irradiation. The risk for complications when tumour dose in the true pelvis is administered solely by external irradiation has been reported by KOECK & HILLSINGER (1971), who reported 3 to 15 per cent serious complications using that technique. CHAU et coll. (1962) and MARUYAMA et coll. (1974) have also reported an increase in complications in the intestines when the use of external high-voltage irradiation was increased. Particularly in slender patients intestinal complications occur, as in such patients large parts of the intestinal tract often lie in the true pelvis.

The size of the uterus is diminished by external irradiation; a size of 8 to 9 cm measured with probe before treatment is reduced to only 6 to 7 cm as a rule, 3 weeks after completion of treatment. It is probable that the thickness of the uterine wall has been reduced correspondingly. This implies that the same treatment time gives much higher doses outside the uterus than before the time of high-voltage irradiation. Women having scanty fatty tissue between the uterus and the intestines and bladder receive higher doses of irradiation to these organs. These factors probably contributed to necrosis of the bladder in one case and to colonic complications in 2 cases.

A shorter intrauterine applicator has been used since 1970 and, in addition, external irradiation up to full tumour dose has not been given. Patients with a narrow vagina have been given intracavitary treatment only using a rod-like applicator. STROCKBINE et coll. reported an increase of rectal complications from the use of such an applicator. Use of a spacer in the present material, however, gave a well-defined dose to the upper part of the vagina, and reduced the rectal dose to acceptable values. No complications due to this applicator were found. The intracavitary radiation dose was reduced by about 10 per cent in this material. The recto-vaginal fistula developed in a patient who had received two intracavitary treatments with combined applicators. Due to advanced multiple sclerosis her general condition was poor; she had ankylosed hip joints and reduced intestinal function. The application was technically difficult, and the applicators were probably not placed correctly.

The patient with a perforation of the sigmoid colon had been given external and intracavitary treatment. The uterine fundus was apparently pressed against the sigmoid colon, resulting in high doses in that area. No roentgen control of the position of the applicators was possible; the dose was measured in the rectum but not higher up in the colon.

Fixation of the intrauterine and vaginal applicators to each other, so that they remain in a precise position during the treatment, yields a well-defined and reproducible radiation dose around them. This implies that together with the measurement of the dose in the bladder and rectum, high doses of irradiation can be avoided or reduced. Since introducing this technique, the frequency of recto-vaginal fistulas has been reduced from 2 to less than 0.5 per cent, and no vesico-vaginal fistulas have been recorded. This is partly due to the reduction of the intracavitary radiation dose, which has been partially replaced with external high-voltage irradiation.

External high-voltage irradiation caused an increase of complications higher up in the true pelvis at the beginning, probably due to the fact that large parts of the intestine got high doses, and that the intrauterine applicators used were too long in a small uterus. When these factors were considered, the complications in the colon and small intestines decreased from 4 to less than 0.5 per cent.

A detailed analysis of the effects of the treatment techniques on the primary tumour and the regional lymph nodes must be available before a correct evaluation of the rate of complications can be made. Such analyses will be presented in reports to be published in the future. In the present report only figures on two-year-survival are presented.

Conclusion

The number of complications was reduced on the basis of the analysis made of different techniques of treatment. The groups of patients are, however, from different periods of time and are not, therefore, strictly comparable. Even though these results are not conclusive, the following statements can be made about the factors affecting the rate of complications.

External high-voltage irradiation giving full tumour dose to tumours in the true pelvis ought to be avoided, especially in thin patients. However, doses around 40 Gy (4 000 rad) with 'usual' fractionation seldom appear to cause intestinal complications. After initial external irradiation without shielding, the intrauterine applicator must be adjusted to the reduced length of the uterus (due to the effects of treatment), and it must not be allowed to extend up into the fundus. The dose to the bladder and rectum should be measured in connection with the intracavitary applicators to permit correction of the dose.

The intracavitary applicators ought to be designed in such a way as to give a well-defined and reproducible dose-geometry when they are in position.

SUMMARY

The frequency of serious complications in the bladder and intestines in 674 patients irradiated for carcinoma of the cervix using three different techniques is reported. The first technique was the Stockholm technique, which gave 5% severe complications. In the other two, the patients received primarily external irradiation without central shielding, comple-

mented with intracavitary treatment. Difficulties in the Stockholm technique and in techniques combining external high-voltage and intracavitary treatment were taken into account, and the frequency of serious complications decreased to less than 1 %.

ZUSAMMENFASSUNG

Die Häufigkeit ernster Komplikationen der Blase und des Darms bei 674 Patienten, die wegen eines Zervixkarzinoms unter Verwendung von drei verschiedenen Methoden behandelt worden waren wird, berichtet. Die erste ist die Stockholm-Technik, die bei 5 % zu schweren Komplikationen führte. Bei den anderen zwei Methoden erhielten die Patienten primär eine externe Bestrahlung ohne eine zentrale Abschirmung, die durch eine intrakavitäre Behandlung ergänzt worden war. Die Schwierigkeiten der Stockholm-Technik und der Methoden der mit der intrakavitären Behandlung kombinierten externen Hochvolt-Therapie wurden berücksichtigt, wobei die Frequenz schwerer Komplikationen weniger als 1 % war.

RÉSUMÉ

L'auteur présente la fréquence des complications vésicales et intestinales graves chez 674 malades irradiées pour cancer du col par 3 techniques différentes. La première technique est la technique de Stockholm qui donne 5 % de complications graves. Dans les deux autres techniques les malades recevaient en premier lieu une irradiation externe sans protection centrale, complétée par un traitement intracavitaire. Les difficultés de la technique de Stockholm et des techniques qui associent un traitement externe de haute énergie et un traitement intracavitaire ont été prises en considération et la fréquence des complications graves s'est abaissée à moins de 1 %.

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