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FREQUENCY OF SEVERE COMPLICATIONS AFTER RADIATION THERAPY FOR CERVICAL CARCINOMA

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A determination of the frequency of late complications of primary radiation therapy for cervical carcinoma constitutes a complex problem; it may be difficult to distinguish early symptoms produced by a recurrence from those due to radiation injury. Moreover, the clinical picture may be confused by complications arising from additional irradiation or surgery for the recurrence. This report is a retrospective analysis of the frequency of severe complications following radiation therapy for cervical carcinoma in patients with and without recurrence manifested during a long follow-up period.

Material

The material comprised 321 patients treated at Radiumhemmet for cervical carcinoma during 1967 and followed up for 5 years. Of these, 38 were given combined irradiation and surgical treatment and were analysed separately. Fifteen patients receiving irradiation as the only primary treatment died from intercurrent disease within 5 years and 3 residing abroad were not followed up. Since the aim was to analyse the frequency of complications, rather than the cure or survival rate, the main analysis was performed on the remaining 265 patients with primary radiation

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Table 1

Distribution by clinical stage of patients with radiation therapy only

Clinical stage	No. of patients	5-year cure	
		No.	%
IA	35	35	100
IB	60	53	88
IIA	60	39	65
IIB	53	21	40
III	38	6	16
IV	19	2	(11)
Total	265	156	59

therapy and followed up for 5 years. The distribution by stage is presented in Table 1. Free of symptoms 5 years after the treatment were 156 patients (59 per cent) while 109 developed recurrence during the follow-up period.

Methods

Primary radiation therapy. The individualized Stockholm technique (KOTTMEIER 1964 a) was used for patients given irradiation only. The doses delivered by intracavitary irradiation were estimated by direct measurement in the bladder and rectum to reduce the frequency of complications (KOTTMEIER & GRAY 1961). In most cases the treatment was started with two intracavitary applications of radium at an interval of 3 weeks, the amount in the uterus as well as in the vagina varying between 45 and 100 mg and the treatment time between 20 and 27 hours for each course. The rectal dose was usually about 4 500 rad, sometimes below; the bladder dose was less than 5 000 rad. External irradiation was given to all patients except 35 in clinical stage IA to increase the dose to the lateral parametria and pelvic walls to 5 000 rad or 6 000 rad in more advanced cases. The total dose to the rectum did not exceed 5 000 rad, and that to the bladder not 6 000 rad. A few patients were first given external irradiation, followed by intracavitary applications of radium in the uterus and vagina; the total dose delivered and the dose distribution were the same.

The external irradiation was usually delivered by two opposing fields with central shielding blocks, and sometimes with 1 frontal and 2 lateral fields, using ^{60}Co as the radiation source; the weekly tumour dose was 800 rad, given in 5 daily fractions. The pelvic dose distribution with this technique has been reported by KOTTMEIER (1964 a), RANUDD (1966) and JOELSSON (1970).

The patients given combined therapy by radiation and surgery received 2 intracavitary applications of radium by the same technique and with the same dose as those treated by irradiation alone; this was followed by radical surgery by the Wertheim-Meig method. In 4 patients, where lymph node metastases were found during

Table 2

Frequency of severe complications in patients without and with recurrence within 5 years; primary radiation therapy only

Clinical stage	No recurrence			Recurrence		
	Total	Complications		Total	Complications	
		No.	%		No.	%
IA	35	1	2.8	0	—	—
IB	53	0	0	7	1	14
IIA	39	1	2.6	21	6	29
IIB	21	0	0	32	7	22
III	6	1	(17)	32	9	28
IVA	2	0	0	17	2	(11)
Total	156	3	1.9	109	25	23

operation, external radiation therapy was delivered, again with the same technique and dose as were used in the patients treated by irradiation only.

Follow-up. If no recurrence was indicated or the patients displayed no symptoms they were followed at intervals of 2 months during the first year after treatment, and then at increasing intervals of 3 to 6 months. Only 3 patients, residing abroad, were lost to follow-up. None of the 15 patients who died from intercurrent diseases during the follow-up had developed symptoms or signs of any severe complication.

Treatment of recurrences. Recurrence occurred in 109 patients after irradiation only; of these 17 were treated by electrosurgery, the unipolar fulguration technique (KOTTMEIER 1954) was used. In 15 cases supplementary external irradiation was delivered, usually unilaterally, as a palliative measure to alleviate symptoms from metastases on the lateral pelvic wall. The majority of the remaining 77 patients, as well as the 7 patients with recurrence after combined treatment, were given chemotherapy; some had no specific treatment aimed at influencing the tumour growth.

Definition of complications. It is always difficult, particularly in retrospect, to define and demarcate the more severe complications. Since the main purpose of the present analysis was to establish the relative frequency of such complications in different groups of patients, those complications were considered severe which required surgical intervention; this provided a well defined group. However, fairly severe manifestations, such as anorexia, loss of weight and intermittent diarrhoea, do not motivate surgery.

Results

Primary mortality. None of the patients died during the first 3 months after primary treatment.

Table 3

Severe complications in patients with recurrence. Distribution according to treatment

Treatment for recurrence	No. of patients	Severe complications	
		No.	%
Supplementary irradiation	15	5	(33)
Electrosurgery	17	4	(23)
Other treatment	77	12	14
Total	109	20	18

Irradiation only. Severe complications that motivated surgical intervention were observed within 5 years in 28 of the 265 patients, i.e. a frequency of 11 per cent. The distribution in relation to clinical stage is given in Table 2. Severe complications were found in only 3 of the 156 patients without recurrence (1.9 per cent). The remaining 25 were among the 109 with recurrence, i.e. a frequency of 23 per cent for this group (Table 2).

The recurrence was treated by electrosurgery in 17 patients, 4 developed severe complications; radiation therapy was administered to 15, 5 developed such complications, i.e. a frequency of about 28 per cent for those two groups combined. Of the 77 patients treated neither by electrosurgery nor by irradiation for the recurrence, 14 per cent developed symptoms or signs considered as a severe complication requiring surgical intervention (Table 3).

Three patients presented severe complications requiring surgery but had no known recurrence during the follow-up period. Rectovaginal fistula occurred in 2 and rectal stenosis in one, manifest from 7 months to 4 years after the primary treatment. Colostomy was performed in 2 of the patients; one fistula and the rectal stenosis healed spontaneously.

Combined therapy. Thirty-eight patients were subjected to intracavitary radium and radical surgery; severe complications occurred in 5; 3 being in the group of 31 cured patients and in 2 in the group of 7 patients with recurrences. All 4 patients with supplementary external irradiation for lymph node metastases were among the 5 patients with severe complications (Table 4). Only 1 of the 34 patients without this supplementary treatment developed such complications.

Discussion

A tendency for a higher frequency of severe complications existed in those patients with initially more advanced tumours as may be expected (Table 2); this may be due to the higher radiation doses and the larger treatment fields used in more advanced tumours. However, rectovaginal fistula developed in 1 of 35 patients in stage IA, who were given intracavitary applications of radium only.

Table 4

Frequency of severe complications in patients with combined treatment

Clinical stage	No. of patients	No recurrence			Recurrence		
		Total	Complications		Total	Complications	
			No.	%		No.	%
IA	1	1					
IB	15	13			2		
IIA	21	16	3*	18	5	2**	(40)
IIB	1	1					
Total	38	31			7		

* Two patients were given supplementary external irradiation postoperatively.
** Both patients were given supplementary external irradiation postoperatively.

The risk of complications in connection with radiation therapy may be reduced to some extent by careful dose planning and continuous observation of the patient during the irradiation. A certain frequency of complications must, however, be considered an inevitable consequence of curative irradiation for tumours of the pelvis. An increase in the radiation dose in cervical carcinoma has improved the survival rate, but has also produced a higher rate of severe late complications (KOTTMEIER 1961, 1964 b, JOELSSON et coll. 1971). The radiation dose and the size of the volume to be irradiated constitute a dilemma: a more agressive approach will result in a higher survival and cure rate, but involves a greater frequency of complications. Extensive personal experience including knowledge of the frequency of complications and their management are mandatory.

Eleven per cent severe complications requiring surgery might seem discouraging, but it should be noted that for the patients remaining free of recurrence the frequency was less than 2 per cent. The figure is much higher for patients treated by electrosurgery because of recurrence (more than 20 per cent) or by additional radiation therapy (more than 30 per cent in a small material, Table 3). It is doubtful whether these forms of supplementary treatment are at all justified. It is notable, however, that 10 out of 17 patients treated by electrocoagulation for histologically or cytologically verified residue of local recurrence still presented no sign of recurrence 3 to 4 years afterwards.

Cytostatic therapy would seem to offer an alternative to the supplementary radiation therapy given to alleviate symptoms in the case of recurrence or metastases on the pelvic wall (EINHORN 1967). In experienced hands this therapy involves a lower frequency of severe complications.

The greatest interest, however, attaches to those patients that received radiation

therapy as the only primary treatment and developed severe complications motivating surgery. In this group symptoms initially considered due to radiation complications in several of the patients were found in retrospect to be caused by recurrence of the tumour. In addition, in the 156 patients remaining free of recurrence during the 5-year follow-up period the frequency of severe complications requiring surgical intervention was 1.9 per cent only.

Complications after radiation therapy can occasionally be manifested after more than 5 years; even after more than 25 years (KOTTMEIER & GRAY 1961, YOUSSEF 1961). However, evidence of rectal injury usually appears 6 to 9 months after the initial irradiation, though the delay may be longer (KOTTMEIER 1964 b). Radiation injury to the colon and small bowel becomes manifest, on average, 13 months after treatment, but in about 4 per cent of cases with severe complications there is a lapse of 10 years or more (FABRIKANT et coll. 1959). Radiation complications from the bladder, although on average appearing after a somewhat greater lapse of time, are usually manifested within 5 years after the treatment (KOTTMEIER 1961, 1964 b, BUCHLER et coll. 1971). Thus, in the present series, severe complications may appear later on. It will, however, probably be only in a few cases, and the number of complications observed during the 5-year follow-up period is to be considered as quite close to the actual final rate of complications.

SUMMARY

An analysis of a material of 265 patients treated by radiation therapy for cervical carcinoma was performed with respect to severe complications. The complication rate in patients free of recurrence was 1.9 per cent and in those with recurrence 23 per cent, which indicates that severe complications are often caused by recurrence of the tumour.

ZUSAMMENFASSUNG

Es wurde eine Analyse eines Materials von 265 Patienten, die wegen eines Cervix Karzinoms Strahlentherapie unterzogen worden waren, hinsichtlich schwerer Komplikationen vorgenommen. Die Komplikationsfrequenz bei Patienten, die frei von einem Rezidiv waren, betrug 1,9% und bei denen mit einem Rezidiv 23%, was darauf hindeutet, dass schwere Komplikationen oft durch ein Rezidiv des Tumors verursacht werden.

RÉSUMÉ

L'auteur a analysé au point de vue des complications sévères une série de 265 malades traitées par les radiations pour un cancer du col de l'utérus. Le taux de complication chez les malades exemptes de récidive a été de 1,9% et de 23% chez les malades présentant une récidive, ce qui indique que les complications graves sont souvent causées par une récidive de la tumeur.

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