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INTRACAVITARY IRRADIATION OF CARCINOMA OF THE CERVIX STAGE I B AND II A

A clinical comparison between a remote high dose-rate afterloading system and a low dose-rate manual system

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Abstract

The clinical results of a remote high dose-rate afterloading technique with individual three-dimensional treatment planning were compared with those of a manual low dose-rate technique for intracavitary irradiation of cervical carcinoma stage I B and II A. The rates of residual tumour at operation, local recurrence and survival were comparable with the two techniques. The rate of treatment complications was lower with the high dose-rate technique even when external irradiation was added. Better central shielding for external pelvic irradiation is possible when intracavitary irradiation is performed with higher accuracy.

Distant afterloading techniques for intracavitary irradiation of cervical carcinoma provide an almost complete radiation protection for the staff and offer, with high dose-rate, short treatment times convenient to the patients (1, 8, 17).

In 1976 a system of this type was introduced at the department of gynecologic oncology in Gothenburg. A high dose-rate ^{60}Co technique with short treatment times was chosen. By combining this technique with individual computerised treatment planning and anatomically adapted applicators, not allowing risk organs in the treated volume, we hoped to improve local tumour control without an increased rate of side-effects. This would also improve the shielding accuracy when external irradiation was added (5).

The change from a low to a high dose-rate had to be considered. A larger number of fractions and a lower total dose had to be used to obtain a similar radiobiologic effect with the high dose-rate as with the low dose-rate technique (5).

The aim of the present analysis was to compare the clinical results of this remote high dose-rate regimen with those of the manual low dose-rate regimen in the same department.

Material and Methods

All women treated for carcinoma of the cervix stage I B and II A in our admission region from January 1970 until January 1981 were considered. Only non-pregnant women with an intact uterus who had not previously been treated for cancer or with pelvic irradiation were included in this retrospective analysis of intracavitary treatment regimens. Fifty-five of 659 patients were excluded by these criteria. Of the 604 remaining women, 108 were irradiated with the ^{60}Co afterloading technique. One woman had only palliative treatment and was excluded. These 107 patients, comprising the Co-group, were treated during the years 1976–1980.

The other 496 women were irradiated with man-

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Table 1

Distribution of background factors and their influence on crude survival

	Intracavitary irradiation		Distribution difference between the groups	Influence on crude survival
	Radium	Cobalt		
Age (years)	50 (SD=14)	41 (SD=12)	p<0.001	p<0.001
Stage (n)			p<0.001	p<0.001
I B	276 (57%)	84 (79%)		
II A	208 (43%)	23 (21%)		
Microscopy (n)			N.S.	
Epidermoid carcinoma				
High/mod.high diff.	170 (35%)	42 (39%)		
Low diff./undiff.	269 (56%)	49 (46%)		
Adenocarcinoma	45 (9%)	16 (15%)		
Size			N.S.	
Small	131 (27%)	18 (17%)		
Medium/uncertain	302 (62%)	80 (75%)		
Large	51 (11%)	9 (8%)		
Operation (n)	230 (48%)	92 (86%)	p<0.001	p<0.001

ually handled radium during the whole period. Twelve women had only palliative treatment because of age and intercurrent disease and were therefore excluded from the analysis. The remaining 484 women comprised the Ra-group. Radium-treated patients from a longer period of time were included as there was no change in survival during the period for these patients.

Staging was performed according to FIGO (10). Only routine microscopic examination was performed. The size of the primary tumour was retrospectively graded as small, medium or uncertain, or large from drawings and operation charts.

The selection of patients during 1976–1980 for intracavitary irradiation with ^{60}Co or ^{226}Ra was dependent on the doctor's familiarity with the two techniques. While some preferred one of the two techniques, some used the ^{60}Co technique only in cases where a suitable dosimetric plan was available.

In an attempt to compare results in the Co-group and the Ra-group, it was decided to analyse the following background factors: age, stage, microscopy, tumour size and operation. If the distribution of one of these factors differed between the two groups and the same background factor influenced on survival or recurrence in the total material, the influence of the different representation of this factor should be eliminated in the statistical comparison of survival or recurrence rates. Of the mentioned background factors only age, stage and operation showed both a significantly different distribution in the two groups and a significant association with survival and were therefore taken into account (Table 1).

Intracavitary irradiation. The high dose-rate ^{60}Co afterloading irradiation was performed with a modified Ralstron system. The minimum target dose was prescribed at points representing the surface of the target volume, according to CHASSAGNE & HORIOT (3). A total dose of 42.5 Gy was given in these points in 5 fractions within 29 days. The dose-rate in point A was 2 Gy/min. The individual system has been described earlier (5).

The manual low dose-rate radium irradiation was given in 3 fractions within 29 days. About 3000 mgh was used for the uterus and 3500 mgh for the upper vagina. The treatment time was decided by measurements in the bladder and rectum. A maximum dose of 50 Gy was allowed in the bladder and 45 Gy in the rectum. The dose-rate was about 0.025 Gy/min at point A (9). Eighty-three out of 484 women in the Ra-group received less than 3 fractions in the uterus and/or the vagina because of high doses in

the bladder or rectum, a narrow vagina or other technical difficulties. These women were either operated upon after the intracavitary irradiation or received their external irradiation without a central block in more fractions. As these patients had no significant influence on the survival of the total Ra-group, they were not excluded.

Operation. Three to four weeks after completion of intracavitary irradiation, a Wertheim-Meigs operation was performed in altogether 322 cases if there were no contraindications. All microscopically observed carcinoma tissue in the operation specimen was registered as tumour remnants and no attempt was made to evaluate the biologic viability of these remnants. Postoperative external irradiation was added for 35 patients with positive nodes at operation and for another 5 with tumour in the paracervical or paracolpic tissue.

External irradiation. Operation was not performed in 269 women. In these patients external irradiation was started 0 to 2 weeks after completion of the intracavitary treatment. This was a negatively selected group from a prognostic point of view. ^{60}Co or 5 MV photons, with SSD 80 to 100 cm, were used, depending on the thickness of the patient. Two opposite fields measuring 16 to 18 cm × 16 to 20 cm were used. A midline dose of 40 to 50 Gy in 17 to 23 fractions in 4 to 6 weeks was given.

For the radium-treated patients, a central block reducing the midline dose to 3 to 6 per cent was used for shielding. A total dose of 60 Gy was allowed in the bladder and rectum from the intracavitary and external irradiation. The irradiation without shielding was individualized with regard to measured doses in the bladder and rectum from the intracavitary treatment.

For the ^{60}Co-treated patients, a wedge filter giving a midline dose of 25 per cent was used. The small dose per fraction under this filter did not essentially contribute to the biologic effect of the radiation in the bladder and rectum in the midline region. A dose of 0 to 10 Gy was given without the wedge filter.

Follow-up and endpoints. After completion of treatment, the women were seen every second to third month during the first year and later at longer intervals. Clinical examination, vaginal cytology and nephrography or urography were performed regularly.

Local recurrence was defined as cancer recurring in the uterus or the upper two-thirds of the vagina.

Pelvic recurrence was defined as recurrence in the true pelvis or the lower third of the vagina.

Distant metastases were defined as cancer in distant nodes, lung, bone or other organs outside the true pelvis.

Recurrence and metastases were confirmed by biopsy or fine-needle aspiration if possible. Only the first manifestations of relapse were evaluated. Patients were regarded as having died of cancer if they died with recurrent disease or metastases, if the cause of death was uncertain or if death was due to a treatment complication.

In patients with recurrent disease or metastases, it is often uncertain whether a complication is due to cancer or to previous treatment. It was therefore decided to study the treatment complications until relapse. Complications in the colon-rectum and the bladder were registered according to KOTTMEIER & GRAY (11). Complications in the small bowel and elsewhere were registered separately.

Only two patients were lost to follow-up, both having moved to other countries. They were lost after 9 and 24 months of observation.

Statistical analysis. To enable comparison of the two treatment groups, elimination of the influence of unequal distribution of some background variables of prognostic significance was performed. By using non-parametric tests, false statistical assumptions were avoided in order to receive more reliable p-values. Two-tailed testing was performed.

Distribution of background variables as age, stage, etc. in the two treatment groups was compared with Pitman's correlation test (2). For calculating rates of survival, recurrence and metastases life-table technique was used (4).

Testing of the influence on survival of unequally distributed variables as age, stage, etc. was performed with a special test (13). The variables were either discrete (as stage I B and II A) or continuous (as age).

Analysis of survival, recurrence and metastases for the two treatment groups with elimination of the influence of relevant background factors was performed with the same special test (13).

Results for the two treatment groups were divided into homogeneous subgroups with regard to relevant background variables and then pooled for the test.

Mantel's test (12) was used for evaluation of complication rates and of tumour remnants in the operated specimen.

Results

Survival. The crude 5-year survival for the Ra-group was 77 per cent and for the Co-group 88 per cent (Table 2). There was no significant difference in survival after elimination of influencing differences in age, stage and operation.

Recurrences and metastases. The rate of local recurrence within 5 years seemed to be less in the Co-group (Table 2) but after elimination of the influence of unequal distribution of age, stage and operation, there was no significant difference.

For local recurrence within the intracavitary target there was still a difference between the groups after elimination of the influencing age and stage distributions ($p<0.05$). After elimination of the influencing different represtation of operated patients there was no significant difference ($p>0.05$). There were only 15 non-operated patients in the Co-group.

The rate of pelvic recurrence and distant metastasis showed no difference between the Ra- and Co-groups (Table 2).

Tumour remnants in the operation specimen. Thirty-four out of 228 patients (15%) had tumour remnants in the operation specimen in the Ra-group and 17 out of 92 (18%) in the Co-group. There was no significant difference in this respect between the two groups.

Complications. The treatment complications in the Ra- and Co-groups are listed in Table 3. Only three bladder reactions grade 1 and one rectal reaction grade 1 occurred in the Co-group. The percentage of patients with major or minor complications was less in this group than in the Ra-group, 4 and 16 per cent, respectively ($p<0.001$). No complications indicating surgery occurred in the Co-group, while 3 per cent of the patients in the Ra-group had complications indicating surgery ($p=0.10$). When external irradiation was added, the complication rates were 7 per cent for 30 patients in the Co-group and 22 per cent for 259 patients in the Ra-group ($p=0.07$).

Table 2

Cumulative rates of survival, recurrence and metastasis after 5 years of observation (per cent). Life table technique was used. The effective sample size (n) after 5 years of observation is given in parentheses. No differences in these rates were found between the two treatment groups ($p>0.05$)

	Intracavitary irradiation	
	Radium (initially 484 patients)	Cobalt (initially 107 patients)
Crude survival	77 (479)	88 (50)
No evidence of disease	79 (469)	87 (92)
Local recurrence		
Total	10 (457)	2 (98)
Within the target	9 (464)	1 (110)
Pelvic recurrence	11 (441)	8 (81)
Distant metastases	8 (438)	4 (101)

Table 3

Major and minor treatment complications (n) within 5 years in the total material

	Intracavitary irradiation	
	Radium	Cobalt
Bladder, total	34 (7%)	3 (3%)
Grade 1	16	3
Grade 2	15	0
Grade 3	3	0
Colon/rectum, total	35 (7%)	1 (1%)
Grade 1	21	1
Grade 2	8	0
Grade 3	3	0
Grade 4	3	0
Vaginal fistula	9	0
Small intestine	8	0
Ureter	9	0
Surgery indicated by complication	15 (3%)	0 (0%)
No. of patients with complication/ No. of patients treated	77/484 (16%)	4/107 (4%)

Discussion

Remote high dose-rate afterloading techniques offer great practical advantages in the treatment of cervical carcinoma, as excellent radiation protection for the surroundings and convenient treatment times for the patients. Nevertheless the most essential question is how the clinical results compare with those of other techniques.

Several factors may cause differences in the results of the two compared treatment regimens. One is the high dose-rate, giving different early and late radiobiologic effects compared with the low dose-rate. Other factors are dose distribution and physical and anatomic accuracy of the treatment. Concerning the high dose-rate, possible radiobiologic disadvantages can be overcome by using a larger number of fractions (6). A fractionated regimen might even have some biologic advantages com-

pared with a continuous protracted treatment as reoxygenation of hypoxic cells can take place between fractions (7). A treatment system with fixed source positions and individual computerized dose-planning in combination with the short treatment times also provides good possibilities for obtaining suitable dose distribution and high accuracy of the treatment (5).

In the present comparison between a distant afterloading high dose-rate ^{60}Co technique and a manually handled low dose-rate radium technique, survival rates were the same with the two techniques. This is in agreement with the literature (16). A prospective randomized study between high and low dose-rate afterloading techniques with long term follow-up, is at present not available, however.

The incidence of tumour remnants in the operation specimen and of local recurrence was the same with the two techniques. A higher incidence might have been expected for the ^{60}Co technique as the CRE (cumulative radiation effect) for early effects at point A was somewhat lower with this technique than with the ^{226}Ra technique (21 and 24, respectively), while the CRE for late effects was the same with the two techniques (5). This was, however, probably compensated for by the greater dosimetric accuracy of the ^{60}Co technique.

SHIGEMATSU et coll. (14) reported a higher local control rate but also more complications with high dose-rates than with low dose-rates. TAINA (15) also reports a somewhat higher rate of complications with his high dose-rate technique. In this investigation, the high dose-rate technique resulted in less complications from the surrounding normal tissues. For the few patients receiving external irradiation with central shielding this difference was not statistically significant, however. The low complication rate after ^{60}Co irradiation was probably the result of accurate individual dosimetry, the use of anatomically well-adapted applicators and a radiobiologically adequate treatment schedule.

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