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COMPLICATIONS AT INTERSTITIAL RADIOTHERAPY OF GYNECOLOGICAL CARCINOMA

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Abstract – 36 patients with gynecological carcinoma, stages I-IV, were implanted. 18 of them had cervical carinoma, 5 endometrial, 6 vaginal and 7 ovarian carcinoma. Almost all patients had been intracavitarily and/or percutaneously irradiated on the pelvis to the tolerance dose on the point A 70 Gy. The implantation was indicated in cases of local recurrence *(20)*, regional metastases *(15)* and residual disease after primary treatment *(6)*, 5 patients had double indications.
Of 36 implantations, 16 were made by ^{198}Au grains and 20 were made by ^{192}wires. The reference dose at implanting was in the range of 26 to 120 Gy; the volume of the implanted area was from 3,9 to 70 cm^3.
Treatment-related complications were noted in 44% of patients. The mild complications were more frequent than the severe; there was a higher occurrence of acute complications.
The number of complications depended on the radiotherapeutic dose and on the volume of the implanted area. The statistical significance of these parameters, however, could not be evaluated.

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Introduction – For radiation therapy in patients with gynecological carcinoma we are mostly combining external beam irradiation and intracavitary irradiation. Both methods allow a high percentage of total disease control (1, 2) and a relatively low rate of post-therapeutic complications (3, 4). In spite of this, the post-treatment analyses in some cases report residual disease or recurrence in the primary tumour area, metastasis in lymph nodes, hematogene metastasis in the vicinity of the primary area, or even distant metastasis, which all need additional treatment. Another of the possible radiation therapies is brachytherapy with implantation of ^{198}Au grailns or radioactive ^{192}Ir wires into the very tumour or metastasis.

The interstitial treatment is a sole means of administering a cancericidal radiation dose in patients who have already received radical radiation therapy. Here, the bladder and rectal doses should be considered. In the vicinity of the tumour, the dose of radiation sources is rapidly lowered, which avoids the complications (5).

According to Fletcher, the indications for the interstitial gamma-ray therapy are carcinoma of the vagina, carcinoma of the uterine cervix extending into the lower third of the vagina, and carcinoma of the stump or recurrent carcinoma after surgery. For the advanced carcinoma of the anterior vaginal wall and base of the bladder, the suprapubic cystotomy for the insertion of implantation needles can be performed (6).

The interstitial brachytherapy is also very applicable and effective in the primary tratment of carcinomas of the uterine cervix – in conjunction with other methods of radiation treatment – especially in cases of inadequate radium dosage as a result of the extent of the tumour or of the local advance of disease (7, 8), as well as in cases where the distorted anatomy prohibits the intracavitary irradiation (9). The aim of our retrospective analysis is to evaluate interstitial radiation, taking into consideration the indications, local response and complications.

Material and methods – In the years 1979-1986 36 patients with gynecological carcinoma were implanted. The diagnosis, FIGO stages at the beginning of the therapy, and the indications for implantations, are presented in Table 1.

The patients were 26 to 77 years old; the average age was 31,5 years. Most patients were in stage III of the disease.

14 patients had been surgically treated; 34 patients had been treated with external beam

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Table 1 – The patient distribution by diagnosis, stage and indication for interstitial implants

Diagnosis	Stage					Total	Residue	Local recurrence	Regional metastases
	I	II	III	IV	X				
Cervical carcinoma	2	9	7			18	2	10	9
Endometrial carcinoma	1	1	3			5		2	3
Vaginal carcinoma	3	1	2			6	4	3	1
Ovarian carcinoma			5	1	1	7		5	2
Total	6	11	17	1	1	36	6	20	15*

(*5 patients with double indications)

Table 2: Technique of interstitial irradiation and local response

Diagnosis	^{198}Au grains	^{192}Ir wires	CR	PR	Progress
Cervical carcinoma	10	8	8	8	2
Endometrial carcinoma	1	4	2	2	1
Vaginal carcinoma	2	4	2	4	
Ovarian carcinoma	3	4	3	3	1
Total	16	20	15	17	4

CR – complete response
PR – partial response

irradiation (tumour dose 50-60 Gy); 15 patients had been additionally intracavitarily irradiated on the point A 70 Gy. In 14 patients residuum, local recurrence as well as regional metastases had also been additionally treated with external beam irradiation. We used 8 MeV X-rays from a linear accelerator.

Of 36 implantations, 16 were made by ^{198}Au grains and 20 by ^{192}Ir wires (Table 2).

The activity of the ^{198}Au grains was estimated by 'dimension averaging', a method suggested by Cevc and Henschke (10), whereupon the dose was computer-calculated. On the basis of the computer data presentation a reference isodose was determined, considering the biological correction according to Ellis (11). The ^{198}Au grains were mostly utilized where tumours were not accessible enough to permit easy removal of souces. The ^{198}Au grains were applied by means of a special gun-applicator (Fig. 1 and Fig. 2), and remained permanent interstitial implants.

The dose of ^{192}Ir was determined by the isodose curve involving the whole tumour. The application was done by fork steel guide (Fig. 3). The ^{192}Ir wires were removable implants. The rectal dose was measured and the bladder dose calculated according to the distance determined by X-rays.

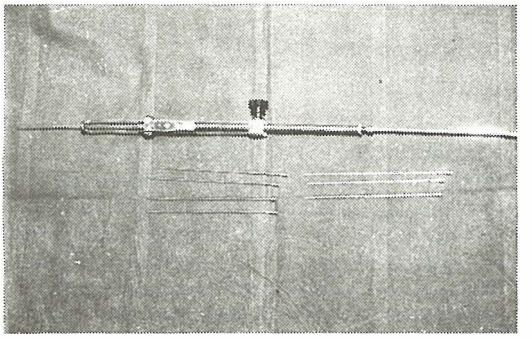

Fig. 1 – Gun-applicator for ^{198}Au grains

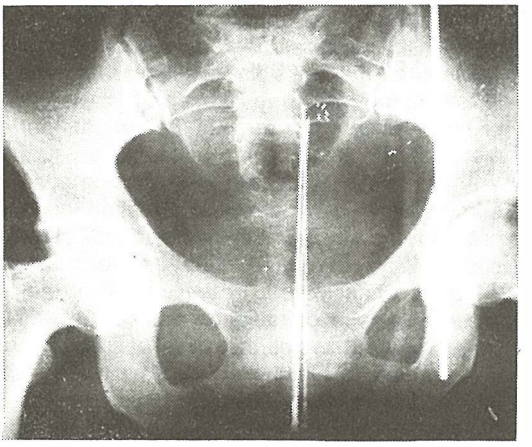

Fig. 2 – Application of ^{198}Au grains

Table 3 – Treatment-related complications

Complication	Acute			Late			Total	
Severity	1	2	3	1	2	3		
Cistitis	3	1		4	3		11	
Hydronephrosis			1				1	
Proctitis				1	1		2	
Paracolpitis		1					1	
colpitis	1						1	
Vaginal bleeding	1	1					2	
Phlebothrombosis		1					1	
Vesicovaginal fistula			2			1	3	
Rectovaginal fistula			1				1	
Total	4/36 11,1%	4/36 11,1%	4/36 11,1%	5/36 13,8%	4/36 11,1%	1/36 2,7%	23*/36	(16/36) (44,4%)

*Five patients had 2 post-therapeutic complications; one patient had 3 complications, whic lowered the total number of patients with complication to 16.

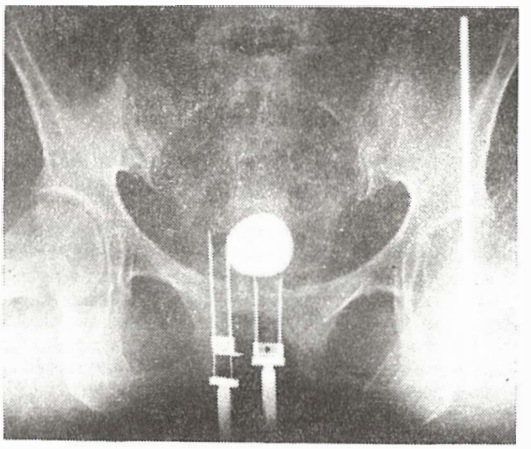

Fig. 3 – Application of ^{192}Ir wires by menas of fork steel guide

The reference dose at implanting was in the range of 20 to 120 Gy (average 45 Gy) and the volume of the implanted area was from 0,3 to 70 cm^3 (average 16.3 cm^3).

The severity of complications was graded as 1, 2 or 3. Grade 1 referred to minor symptoms which were self-limited or responded to outpatient management; grade 2 referred to major symptoms with repeated occurrences and requiring hospitalization for diagnosis and management; grade 3 required major surgery for correction.

Complications which appeared 0-6 months from implantation were considered acute and those after six months were considered late; the former occurred slightly more frequently.

Results – In 15 patients we received a complete response, in 17 patients a partial response, and in 2 patients we were unable to control the progress of disease (Table 2).

The median measured cumulative rectal dose was 70 Gy and the median calculated cumulative bladder dose was 68 Gy.

Table 3 lists therapy-related complications.

Five out of 36 (13,8%) patients experienced grade 3 complilcations. The total incidence of complications was 23 out of 36, with 5 patients having 2 complications and one patient having 3 complications, which lowered the total number of complicatilons to 16 (44%).

The frequency of complications was higher in those patients who at implantation received tumour doses over 45 Gy (52,6%), than in patients with tumour doses under 45 Gy (35,3%). The Chi-square test did not reveal a statistically significant difference ($p > 0,5$).

The incidence of complications in patients with the treated volume over or under 16 cm^3 did not vary. The frequency varied at the tumour volume 8 cm^3. The implantation of tumour volume under 8 cm^3 gave 12,5% sequelae, at larger tumour volumes the sequelae were 55,6%. The Chi-square test (with Yates correction), shows $p > 0,05$, which is also not statistically significant.

Discussion – Although the analysis included irradiated patients with a high cumulative irradiation dose, we were astonished at the relatively high rate of complications (44%). It should be pointed out, though, that some authors, reporting

low incidence of adverse irradiation side effects, counted as complication from treatment only those injuries where there was no trace of malignant lesion and the injury was of a severe character (1, 9). Others, reporting high incidence of complications, scored as a complication of treatment also milder injuries such as cystitis and proctitis – damages recorded by Ulmer and Frischbier (12) in the majority of irradiated patients.

Similar to the external beam irradiation of gynecological cancer, where subacute fibroses and complications of the urinary tract occurred as the most frequent post-irridation complications (2), the implantation gave the highest number of cistitis.

Hydronephrosis is a frequent complication in gynecological oncology (13). However, only a single case of hydronephrosis as a consequence of the ureteral damage was recorded, since the implantations involved only the distal regions of the genitary tract.

Rectal complications were substantially avoided due to the measurement of rectal dose (4, 14). The recommended maximal cumulative rectal dose on the anterior surface of the rectum should not exceed 60 Gy. Accordingly, the rectal doses already delivered with the external beam and intracavitary irradiation should be considered in dosimetric measurements in imlantation. Montana and Wesley report a significantly higher occurrence of proctitis in the group of patients with the mean rectal dose higher than 69 Gy, whereas the mean bladder dose for the group of patients with cystitis exceeded 66,6 Gy (15).

We intentionally risked a higher cumulative measured rectal dose and calculated bladder in order to attain the cancericidal dose, this being the only possible therapy for the observed patients. Nevertheless we concluded that 4 severe post-therapeutic complications (3 vesicovaginal fistulas, 1 rectovaginal fistula) were a consequence of the large tumour volume rather than of the exceeded tolerance dose. According to Fletcher, at least 90% of fistulas are developed at the invasion of carcinoma into vagina, or due to the bulky tumour lesion, respectively (6).

In our case, the incidence of complications was conditioned by the radiation dose at implantation and the tumour volume. However, this correlation was not statistically significant. This could be explailned *(a)* by the small number of patients, *(b)* by the strong relationship between rectal and bladder doses and the distance between the implant and both organs and *(c)* the fact that the sequelae of treatment observed on rectum and bladder also depend on the previous dose rate and previous surgical treatment.

Manual application of the implants highly increased the exposure to irradiation of the professional staff over that of the machine technique of after-loading the interstitial implant. Although the department staff at our institute is exposed to 5-20 times lower equivalent dose of the yearly recommended dose limit for professional staff, we wish to lower this dose to a minimum with the introduction of the after-loading technique.

In our gynecological patients, the implantation is a rather rarely applied therapy. We have a smaller number of patients with residual tumour, a larger number with regional metastasis and the largest number with local recurrence.

We estimate that in the future the trend will be for the application of the implantation technique at the completion of radiation therapy. Similar assessments have been reached by other authors as well (6, 7, 8, 9, 16, 17, 18).

Povzetek

KOMPLIKACIJE PO INTERSTICIALNI RADIOTERAPIJI GINEKOLOŠKEGA KARCINOMA

36 bolnic z rakom na rodilih, stadij I-IV, smo implantirali. 18 se jih je zdravilo zaradi raka vratu maternice, 5 zaradi endometričnega raka, 6 zaradi raka v nožnici in 7 zaradi raka na jajčnikih. Pred implantacijo so bile operirane in/ali perkutano obsevane, skoraj polovico od njih pa je prejelo tudi intrakavitarno radioterapijo. Obsevane so bile do tolerančne doze 70 Gy na točko A.

Indikacije za implantacijo so bile: lokalni recidiv (*20*), regionalne metastaze (*15*) in reziduum tumorja po primarnem zdravljenju *(6)*. 5 bolnic je imelo dvojno indikacijo.

Od 36 inplantacij smo naredili 16 z ^{198}Au zrni in 20 z ^{192}Ir žicami. Referenčna doza pri takem obsevanju je bila od 26 do 120 Gy; volumen inplantiranega področja pa od 3,9 do 70 cm^3.

Komplikacije smo ugotovili pri 44% bolnic. Bolj pogoste so bile blage in akutne, kot pa težje in kasne.

Komplikacije so bile odvisne od višine tumorske doze in velikosti obsevanega volumna pri implantaciji, vendar povezava ni bila statistično signifikantna, ampak se je le nakazovala.

References

1. Comber PF, Daly NJ, Horiot JC et al. Results of radiotherapy alone in 581 patients with stage II carcinoma of the uterine cervix. Int J Radioat Oncol Biol Phys 1985; 11:463-71.

2. Kuhelj J, Kavčič M, Habič M et al. Naši pogledi na liječenje porcije vaginalis uteri. Radiol Iugosl 1975; 9:291-4.

3. Grigsby PW, Kuske RR, Perez CA et al. Medically inoperable stage I adeno-carcinoma of the endometrium treated with radiotherapy alone. Int J Radiat Oncol Biol Phys 1987; 13:483-8.

4. Kuhelj J, Kavčič M. Frequency of subacute complications in the high dose radiation therapy of cancer of the uterine cervix. Radiol Iugosl 1974; 8:21-7.

5. O'Sullivan B, Sutcliffe SB. The toxicity of radiotherapy. Clin Oncol 1985; 4:485-509.

6. Fletcher GH. Textbook of radiotherapy. 3. ed. Philadelphia: Lea & Fibeger, 1980.

7. Prempree T, Scott RM. Treatment of stage III B carcinoma of the cervix. Cancer 1978; 42:1105-13.

8. Prempree T. Parametrial implant in stage III B cancer of the cervix. Cancer 1983; 52:748-50.

9. Gaddis O Jr, Morrow CP, Klement V, Schlaerth LB, Nalick RH. Treatment of cervical carcinoma employing a template for transperineal interstitial Ir^{192} brachy-therapy. Int J Radiat Oncol Biol Phys 1983; 9:819-27.

10. Henschke UK, Cevc P. Dimension averaging a simple method for dosimetry of interstitial implants. Radiol Radiother 1968; 9:287-98.

11. The Ellis nominal single dose concept. Ottawa: Atomic Energy of Canada Limited Commercial Products, 1973.

12. Valente S, Onnis GL. Urologic complications and urodynamics in gynecological oncology. Eur J Gynaec oncol 1987; 7:174-6.

13. Ulmer HU, Frischbier HJ. Treatment of advanced cancer of the cervix uteri with external irradiation alone. Int J Radiat Oncol Biol Phys 1983; 9:809-12.

14. Pourquier H, Dubois JB, Delard R. Cancer of the uterine cervix: dosimetric guidelines for prevention of late rectal and rectosigmoid complications as a result of radiotherapeutic treatment. Int J Radiat Oncol Biol Phys 1982; 8:1887-95.

15. Montana GS, Fowler WC. Carcinoma of the cervix: analysis of bladder and rectal radiation dose and complications. Int J Radiat Oncol 19l89; 16:95-100.

16. Syed AMN, Feder BH. Technique of after-loading interstitial implants. Radiol Clin 1977; 46:458-75.

16. Syed AMN, Feder BH. Technique of after-loadilng interstitial implants. Radiol Clin 1977; 46:458-75.

17. Aristizabal SA, Woolfitt B, Valencia A et al. Interstitial parametrial implants in carcinoma of the cervix stage II B. Int J Radiat Oncol Biol Phys 1987; 13:445-50.

18. Sewchand W, Prempree T, Patanaphan V et al. Radium needles implant in the treatment of extensive vaginal involvment from cervical carcinoma. Acta Radiol Oncol 1984; 23:449-53.

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