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ROLE OF RADIATION THERAPY IN THE MANAGEMENT OF PRIMARY CARCINOMA OF THE VAGINA

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Primary carcinoma of the vagina is an interesting disease, unique in its clinical behavior and response to the radiation treatment (CHAU 1963, FRICK et coll. 1968, HERBST et coll. 1970, BROWN et coll. 1971, PEREZ et coll. 1973, 1977, PREMPREE et coll. 1977, MARCUS et coll. 1978, PRIDE et coll. 1979, FLETCHER et coll. 1980). Recently, there has been a renewed interest in attempting to improve the management of this rare disease based on many years of experience from several centers (PEREZ et coll. 1973, 1977, PREMPREE et coll., MARCUS et coll., PIRTOLI & SANTONI 1980, NORI et coll. 1981, CHU & BEECHINOR 1981).

The concept of radiation management developed by CHAU, PEREZ et coll. and our group and others has brought about the improved survival rate in all stages of the disease and at the same time minimizing any serious complications (CHAU, PEREZ et coll. 1973, 1977, PREMPREE et coll.).

More importantly, the integration of external irradiation and extensive interstitial and intracavitary radium therapy coupled with highly individualized treatment planning has played an important role in managing more advanced cases effectively (PEREZ et coll. 1973, PREMPREE et coll., MARCUS et coll.). The presentation is intended to show the possibility of long-term control of the disease achieved by radiation treatment stage by stage with an excellent result and minimum complications.

Material and Methods

Eighty-eight patients with primary carcinoma of the vagina, treated between 1957 and 1975, were retrospectively analysed. All patients were followed for a minimum of 5 years. They were staged retrospectively following the classification adopted by the International Federation of Gynecology and Obstetrics (FIGO) with minor modification previously proposed for Stage II (KOTTMEIER 1963, PEREZ et coll. 1973, 1977; Table 1). The diagnosis of carcinoma of the vagina was microscopically confirmed in all patients. Of the 88 patients, 84 (95 %) were squamous cell carcinoma and 4 (5 %) adenocarcinoma.

The method of treatment was fully described previously (PREMPREE et coll.). The rationale for the treatment of primary carcinoma of the vagina was relatively straight forward following the policy that early carcinoma would only require local irradiation and that the advanced tumor would require both local and regional irradiation for control.

As previously stated, local irradiation consisted of either intracavitary radium therapy such as Bloedorn's vaginal application used in Stage 0 or interstitial radium therapy used in Stage I or II A. Regional external irradiation was given in the form of cobalt therapy or in some cases with 33 MeV photons

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produced by a 35 MeV Betatron until 1972. Lately, a 4 MeV linear accelerator has been used until the present time. Total pelvis irradiation was delivered through 16 cm × 16 cm a.p. and p.a. ports, and 16 cm × 10 cm lateral ports. Fraction size was usually 2 Gy per day up to 40 Gy/4 weeks. Parametrial boosts were given by parallel opposed 15 cm × 6 cm fields for one side and 15 cm × 15 cm fields with midline lead block for both sides.

Results

Survival

Carcinoma in situ (8 cases) was treated by intracavitary Bloedorn's applicator with excellent result (Table 2).

The absolute 5-year disease-free survival was 8/8 cases (100%) with no complication. The entire vaginal canal was irradiated with the surface dose of 70 to 80 Gy/4 days (Table 2).

Stage I. Of 9 patients with Stage I (Table 2), 5 patients were treated by interstitial brachytherapy utilizing radium needles implant to the entire vaginal canal with good results. The dose calculated was 55 Gy/4 days. Three cases were treated by combination of external irradiation and Bloedorn's vaginal applicator. Total tumor dose at 0.5 cm depth was 65 to 70 Gy. One case was treated by transvaginal cone.

The overall results showed an absolute 5-year disease-free survival of 7/9 (78%) with one local failure. Excluding death from other disease, the determinate 5-year disease-free survival was 7/8 (88%).

Stage IIA. The majority of cases was treated by the combination of external irradiation and radium. The dose of 40 Gy in 4 weeks was usually given with occasional parametrial boost of 10 Gy in one week. Volume implant using radium needles and Manchester ovoid was mostly performed immediately after external irradiation with additional tumor dose of 15 to 20 Gy in 30 to 40 hours. Bloedorn's vaginal applicator was sometimes used as well. The total tumor dose was 60 to 65 Gy. Of 23 cases treated, 14 (61%) survived more than 5 years without any tumor. Five patients died of conditions other than vaginal carcinoma, thus making a determinate 5-year disease-free survival of 14/18 (78%).

Stage IIB. All patients except one were treated by combination of external irradiation and radium therapy. Seven cases (7/17) were treated by intracavitary and interstitial radium therapy to parametrium, paracolpium, or both. A total tumor dose was

Table 1

Clinical staging (FIGO). Modified by Perez et coll. with the incorporation of subdivision of stage II into IIA and IIB

Carcinoma in situ	
Stage 0	Intraepithelial
Invasive carcinoma	
Stage I	Confined to vaginal mucosa
Stage II	Submucosal infiltration or into parametrium not extending out to pelvic wall
Stage IIA	Subvaginal infiltration, not into parametrium
Stage IIB	Parametrial infiltration, not extending to pelvic wall
Stage III	Tumor extending to pelvic wall
Stage IV	Tumor extension to bladder or rectum, or metastasis outside true pelvis

65 to 70 Gy.

An absolute or determinate 5-year disease-free survival was 7/14 (50%).

Stage III. Most of the patients received whole pelvis irradiation with a midline dose of 40 to 50 Gy/4 to 5 weeks and followed by radium therapy with an additional dose of 20 to 30 Gy in 45 to 48 hours. Radium therapy consisted of vaginal applicator and radium implant to parametrium or paracolpium.

Of 26 cases treated, 10 (39%) survived more than 5 years with no recurrence. Two patients died of disease other than vaginal carcinoma, therefore determinate 5-year disease-free survival was 10/24 (42%).

Stage IV. No long-term survival in this stage of disease.

Local control

Results obtained (Table 3) showed excellent local control in stage 0, I and IIA, ranging from 100 per cent for stage 0 to 87 per cent for stage IIA. Once there was evidence of parametrial or paracolpic involvement (stages IIB and III), the local control dropped to 64 and 54 per cent, respectively, in spite of extensive, and individualized radium therapy. No local control was recorded in stage IV, mainly due to extensive tumor and distant metastases (Table 3).

Failure

Local failure. No local failures occurred in *in situ* carcinoma (stage 0) and the failure rate increased

Table 2*Five-year survival*

Stage	No. of cases	Five-year survival	Died of carcinoma	Died of other disease	Determinate 5-year survival	
					No.	Per cent
0	8	8	0	0	8/8	100
I	9	7	1	1	7/8	87.5
II A	23	14	4	5	14/18	78
II B	14	7	7	0	7/14	50
III	26	10	14	2	10/24	42
IV	8	0	8	0	0/8	
Total	88	46	34	8	46/80	58

Table 3*Local control in vagina, parametrium and pelvis*

Stage	No. of cases	Local control
0	8	8/8
I	9	8/9
II A	23	20/23
II B	14	9/14
III	26	14/26
IV	8	0/8

Table 4*Failures*

Stage	No. of cases	Failures	
		Local	Distant
0	8	0	0
I	9	1	0
II A	23	3	1
II B	14	5	2
III	26	9	6*
IV	8	7	3*

* Some also have local failures.

proportionately with the increasing stage of the disease (Table 4). In stage III, the local failure was 35 per cent and in stage IV, the failure rate reached 88 per cent (Table 4).

Distant failure. No distant failure was recorded in stages 0 and I. Once again as expected, the distant

Table 5*Major complications*

Stage	No. of cases	Major complications		
		Recto-vaginal fistula	Vesico-vaginal fistula	Pelvic abscess
0	8	0	0	0
I	9	0	0	0
II A	23	1	0	1
II B	14	0	0	0
III	26	4	1	1
IV	8	1	0	0
Total	88	6	1	2

failure increased when the disease was advanced. In stage III and IV few patients with distant disease exhibited local failure as well (Table 4).

Major complications

The incidence of major complications was low (Table 5). No complications occurred in patients in early stages (stages 0 and I). In stage II A, serious complications occurred in 2 patients. One patient developed recto-vaginal fistula as a consequence of the irradiation and required colostomy as a corrective therapy. No tumor was found. The other patient developed pelvic abscess one year after the treatment and later died without evidence of recurrence of the tumor. No major complications occurred in stage II B.

In stage III, 4 cases developed recto-vaginal fistula and one case developed vesico-vaginal fistula, all

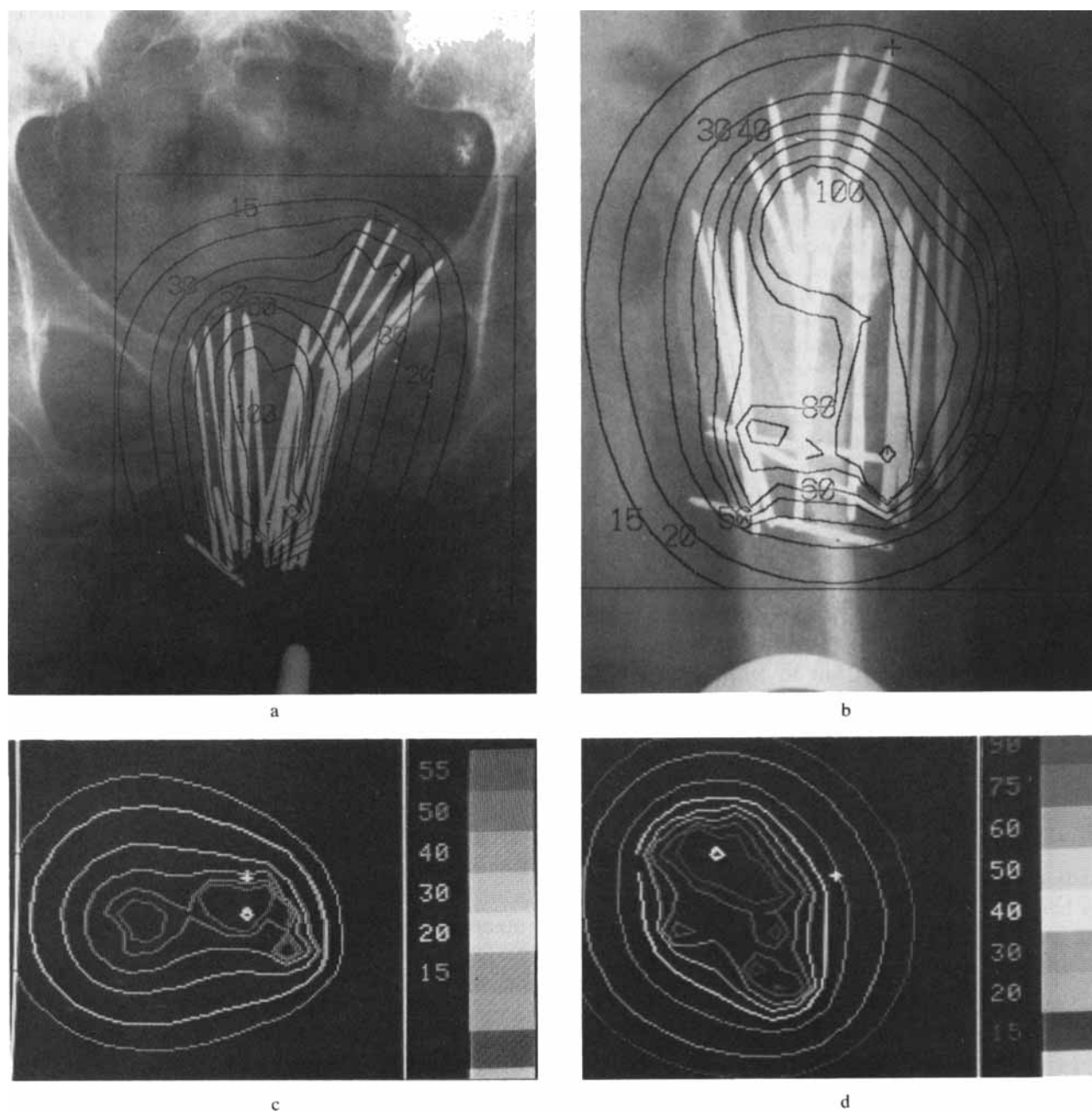


Fig. 1. Advanced case of vaginal carcinoma with extensive involvement of paracolpium and parametrium. External irradiation was given with 50 Gy/5 weeks. Radium therapy consisted of volume implant of radium needles (1.5 mg of radium each) to both vagina, paracolpium and left parametrium (1.0 mg of radium

each). a) A.p. and b) lateral view. Radium dose to the vagina was calculated to be 24 Gy/48 h and to left parametrium 19.2 Gy/48 h. Dose distribution of the cross section of c) the parametrial implant and d) of the vaginal implant.

resulted from persistent tumor tissue despite full course of external irradiation and radium therapy. It is difficult to single out these complications as a consequence of irradiation alone because of positive repeat biopsy. They eventually died of their disease. One patient developed pelvic abscess which required only conservative treatment.

In stage IV, one patient developed recto-vaginal fistula as a result of tumor and treatment.

Of 88 patients treated, 9/88 (10%) developed major complications. It should be pointed out that all 9 patients who developed major complications, were treated by both external beam therapy and brachytherapy.

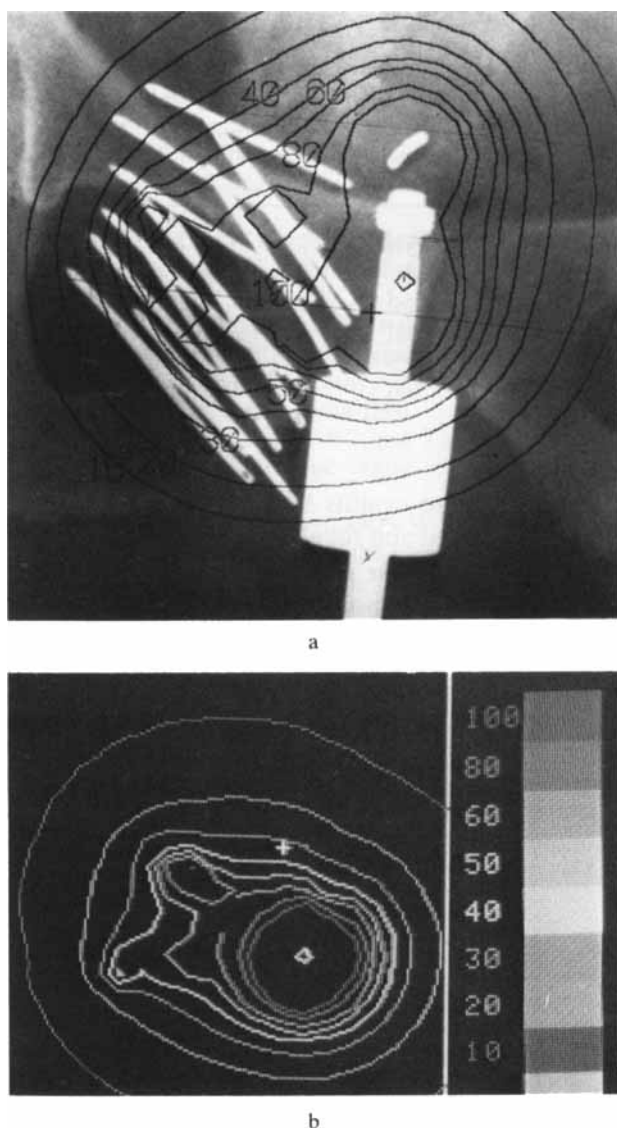


Fig. 2. Vaginal carcinoma stage III. Whole pelvis external irradiation was given with 50 Gy/5 weeks plus 5 Gy/2 days boost to the right parametrium and paracolpium. a) A.p. view of the pelvis. Combination of Bloedorn vaginal applicator and 1.5 mg radium needles inserted into right parametrium and paracolpium. The radium implant dose to right parametrium was 28.8 Gy/48 h. b) Dose distribution at the middle part of the implant.

Discussion

The management of patients with vaginal carcinoma presents a constant challenge as to the selection of the best possible approach to achieve a successful result and yet minimize all serious complications. This challenge is reflected in a continuing search for the best combination and integration of both external irradiation and brachytherapy, and some have already been published (PEREZ et coll. 1973, 1977, PREMPREE et coll.).

Integration of external irradiation and brachytherapy. The present data show excellent results in 5-year survival in stages 0 and I with no associated complication due to the treatment. All patients with stage 0 and most with stage I received only radium therapy, either in the form of intracavitary Bloedorn vaginal applicator or interstitial radium implant. Furthermore, the present results and those of others indicate that only local irradiation (best given by intracavitary or interstitial therapy) alone could control this type of tumor most of the time.

Treatment of patients with more advanced tumor than stage I should include external beam therapy as part of the overall plan in order to achieve good result. The rationale for including external beam therapy is obvious. In stage II and beyond, larger tumor volume is to be encountered and usually required a homogeneous dose distribution throughout the target volume. This dose distribution can only be achieved by external beam irradiation and not by brachytherapy. In stage II and beyond, not only are we dealing with a larger tumor volume, but also the potentials of having regional pelvic lymph node involvement. In most instances, when external beam therapy is integrated into the overall plan of the management, its objective is to cover the disease in the vagina, paravaginal structures, parametrium, as well as regional pelvic lymph node bearing area. The homogeneous dose distribution is obtained in both vaginal disease and pelvic lymph node disease. When brachytherapy, whether in the intracavitary or interstitial form was given, the dose contributing to the pelvic lymph node bearing area was not high enough to achieve tumoricidal dose as in the vagina or paracolpium. Modification of brachytherapy or addition of external beam therapy is usually required to obtain a respectable high dose level.

Individualization. In order to achieve the best possible result, the treatment has to be individualized, starting from adjusting the dose from external irradiation to brachytherapy. The result of individualization of radium therapy to accommodate the patient's disease is demonstrated in Figs 1 and 2. Radium needles implant was often used as part of the entire plan of the therapy after optimum dose of external irradiation. High dose to vagina, paracolpium and parametrium can be achieved without comprising the result and complications. Fig. 2 shows a combination of intracavitary (Bloedorn vaginal applicator) and interstitial brachytherapy. High dose to the right paracolpium and parametrium

Table 6

Comparison of absolute 5-year survival in patients with no evidence of neoplastic disease (per cent in parentheses)

Authors	No. of cases	Stage distribution and absolute 5-year survival				All stages
		I	II	III	IV	
BROWN et coll. (1971)	107	17/27 (63)	26/47 (55)	10/27 (37)	0/6	53/107 (50)
PEREZ et coll. (1977)	94	24/29 (82)	21/51 (41)	2/7 (28)	1/7 (14)	48/94 (51)
CHU & BEECHINOR (1981)	37	— (85)	— (50)	— (26)	—	— (50)
NORI et coll. (1981)	36	10/14 (71)	4/6 (66)	1/3 (33)	0/13	15/36 (42)
PEREZ (1981)	105	26/32 (81)	22/52 (42)	3/10 (30)	1/11 (9)	52/105 (50)
Present series	80	7/9 (78)	21/37 (57)	10/26 (39)	0/8	38/80 (48)

was achieved. The surface dose of the vagina was increased by a high dose from the applicator as well.

Survival. Absolute and determinate 5-year disease-free survival in stages 0 and I was comparable to the result in cervical carcinoma (Table 2). However, in stage II, the survival in substage IIB decreased compared with that in stage IIA (PEREZ et coll. 1973, 1977, PREMPREE et coll., PEREZ 1981) mainly due to parametrial and paracolpial infiltration. Careful and individualized therapy by external irradiation and modified radium implant should be secured to improve the result. Absolute and determinate survival (Table 2) in stage III was excellent as compared with other series mainly due to individualized radium therapy (Figs 1, 2; LIVINGSTONE 1950, WHELTON & KOTTMEIER 1962, MCGARRITY 1967, RUTLEDGE 1967, GRAY & CHRISTOPHERSON 1969, UNDERWOOD & SMITH 1971).

Local control and failures. With the present technique of treatment, it can be seen that local control of the tumor can be achieved with excellent results in early stages (Tables 3, 4). While local control decreased when clinical stage increased (stages III and IV), it reflected the need for the improvement of the treatment policy as well as seeking the new or additional modality for stages III and IV. Distant failures were also significantly high in these stages; therefore, it would seem appropriate to seek additional chemotherapy to local irradiation in order to improve the survival rate.

Complications. In spite of intensive external beam and brachytherapy given to most of the patients, very few major complications occurred in association with the treatment itself. For example, the overall recto-vaginal fistula occurred only in 6.8 per cent, vesico-vaginal fistula only in 1.1 per cent. Minor complications such as vaginal fibrosis, vagi-

nal stenosis and cystitis were infrequent and they were self-limited and required only supportive care.

Comparison of the present results with other series. Absolute 5-year disease-free survival from several pertinent series, stage by stage, are compared in Table 6. The series by BROWN et coll., PEREZ et coll. (1977) and PEREZ compared with the present data, demonstrate that the disease-free survival is similar. This is mainly due to individualization of the treatment as well as integration of external beam therapy with brachytherapy.

SUMMARY

A retrospective analysis of 88 patients with microscopically proven primary carcinoma of the vagina is presented. All patients were treated between 1957 and 1975 and have been followed for a minimum of 5 years. The technique of treatment, external, intracavitary and interstitial irradiation has been highly integrated and individualized. Several important features could be drawn from the current data: (1) The necessity for individualized radiation treatment to achieve the success, (2) the necessity to subdivide stage II into IIA and IIB is clearly shown by the 5-year survival data, (3) a relatively low complication rate from the use of high dose combined radiation modalities in higher stages is demonstrated.

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