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RADIATION TREATMENT OF PRIMARY CARCINOMA OF THE VAGINA

Patterns of failures after definitive therapy

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Abstract

Patterns of failures after definitive radiation therapy were analyzed in 88 patients with primary carcinoma of the vagina treated between 1957 and 1975. The majority of the local failures in early stages of the disease (I, II and a few III) were due to inadequate treatment either by external beam therapy or brachytherapy. In some cases the inadequate treatments were unavoidable (previous radiation treatment) and in a few they were due to poor brachytherapy technique. Distant failures are still a problem and need to be given further attention.

Even though primary carcinoma of the vagina is rare, numerous reports have appeared suggesting appropriate treatment to improve the result (3, 4, 6, 7, 10, 12, 13, 15, 16, 18–20). Experience in managing primary carcinoma of the vagina is increasing steadily especially in major centers (5, 9, 11, 15–17). Today the consensus opinion regarding the method of treatment is radiation treatment for all stages of the disease, probably with the exception of carcinoma in situ in which wide local excision may be occasionally used, and stage IV A for which a combination of irradiation and surgery is indicated (9, 11–13, 15, 16).

The results from various centers seem to suggest that the prognosis for primary carcinoma of the vagina is about the same as the prognosis for carcinoma of the cervix, especially in the early stage of the disease (11–16). This appears to be true if the management of this disease is well individualized and integrated in the planning. The present report represents a continuation of the previous investigations on the management of primary carcinoma of the vagina.

Material and Method

This is a retrospective study of 88 patients with primary carcinoma of the vagina who were treated primarily by irradiation in the department of Radiation Oncology, University of Maryland Hospital, between 1957 and 1975.

All patients were staged using the FIGO classification (8) with the Perez modification as a guideline (Table 1). Their ages ranged from 26 to 87 years with a median and mean age of 60 years. The majority of the tumors (95%) were squamous cell carcinomas and only 5 per cent were adenocarcinomas.

The details of the method for radiation treatment have been described elsewhere (15, 16). The treatment policy has been that for early malignancy, only brachytherapy is used; for more advanced cases, both local and regional irradiation are used in order to achieve a better control rate.

Stage 0. Intracavitary radium therapy in the form of a Bloedorn vaginal applicator was used with a surface dose of 80 to 100 Gy in 5 to 6 days. The

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intention was to irradiate the entire vagina with a surface dose of 70 to 80 Gy and the vaginal cuff area with around 80 to 100 Gy.

Stage I. Interstitial brachytherapy alone was usually given utilizing long radium needles (4.5 cm active length) implanted into the vaginal canal and its subvaginal substance. ^{192}Ir was sometimes used when more than 4.5 cm in depth of implant was required. The tumor dose of the volume implant was usually 55 to 60 Gy for 4 days. A Bloedorn vaginal applicator was occasionally used in cases with a superficial lesion (<0.5 cm) and the surface dose was the same as that given in stage 0.

Stages II, III and IV. When the disease had reached stage II and beyond, a combined approach was usually attempted. External beam therapy whole pelvis irradiation with a dose of 40 Gy for 4 weeks was given with an appropriate parametrial boost of 10 to 15 Gy for 1 to 1.5 weeks, depending on the clinical situation (16).

Following the completion of external beam therapy, brachytherapy was given with an additional dose of 25 to 35 Gy for 2 to 3.5 days, depending on the clinical situation. The radium therapy was highly individualized with an attempt to obtain an optimal dose to the vaginal canal and the paracolpic and parametrial region if involved by cancer. The details of the technique and dosimetry have been published elsewhere (15, 16).

Results

Five-year survival

The absolute five-year disease-free survival for various stages of the disease is shown in the Figure. As can be seen, failures occurred mostly within two years and no failures at all occurred after three years.

The determinate five-year disease-free survival is also of interest since most of the patients were relatively old with a mean age of 60 years; many of them had died after treatment from various intercurrent diseases with no evidence of malignancy at the time of their death. The determinate five-year disease-free survival for each stage of the disease is shown in Table 2.

Failures

The failures were divided into loco-regional and distant failures with some patients in stages III and IV who later developed local and distant failures

Table 1

Clinical staging (FIGO) of primary vaginal carcinoma

Carcinoma in situ	
Stage 0	Intra-epithelial
Invasive carcinoma	
Stage I	Confined to vaginal mucosa
Stage II*	Submucosal infiltration or into parametrium not extending out to pelvic wall
Stage II A	Subvaginal infiltration, not into paremetrium
Stage II B	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

* Modified by PEREZ et coll. (13) with the incorporation of subdivision of stage II into II A and II B.

Table 2

Determinate 5-year survival in 88 patients with carcinoma of the vagina

Stage	Total No. of cases	Disease-free 5-year survival	Failure	Died of other causes	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	14/23	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	0
Total	88	46 (52%)	34 (39%)	8 (9%)	46/80	58

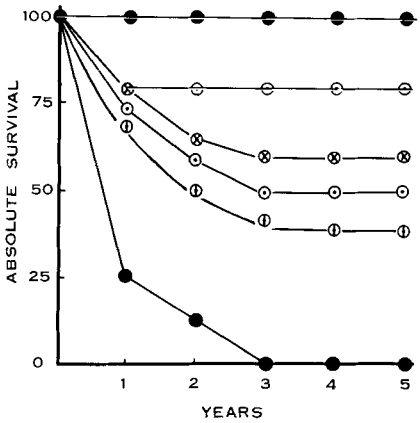
Table 3

Treatment failures in 88 patients with carcinoma of the vagina (percentage in parentheses)

Stage	Total No. of cases	Cases with failures	Failures	
			Local	Distant
0	8	0	0	0
I	9	1	1 (11)	0
II A	23	4	3 (13)	1 (4)
II B	14	7	5 (36)	2 (14)
III	26	14	9 (35)	6 (23)*
IV	8	8	7 (88)	3 (38)**

* One case had local failure as well.

** All had local failures.



Absolute 5-year survival (in per cent) in 88 patients with primary carcinoma of the vagina by stage. From top to bottom: Stage 0 (n=8), stage I (n=9), stage II A (n=23), stage II B (n=14), stage III (n=26), stage IV (n=8).

concomitantly (Table 3). The local failure rate increased with advancing stage of the disease. Distant failures occurred mostly in the advanced stage.

Local failures—Stage I. Only one local failure occurred (Table 4). This patient was a good example of not giving adequate radiation treatment to the entire vaginal canal even though the lesion was located in the upper one-third of the vagina. The recurrence was seen in the vaginal canal just below the area treated, in less than one year after completion of the treatment. Whether this was a clinical presentation of multicentric carcinoma of the vagina or whether the tumor was primarily understaged was not clearly known.

Stage II. Three cases of local failures (13%) occurred in stage II A (Table 4). All had received whole pelvis irradiation by small field rotational therapy because of previous radiation treatment by stationary field to the whole pelvis some ten years previously for other malignant diseases. One of these cases (aged 54) had received a radon seed implant following the rotational external radiation therapy while the other two had received a radium implant, volume type, with adequate doses to the vagina. The total dose to the vagina was adequate (65–70 Gy) but the dose to the parametrium and pelvic wall was low (30–40 Gy) due to the limited external radiation treatment. It is considered that all three failures in stage II A had inadequate external beam therapy and perhaps in the first case inadequate brachytherapy as well.

Stage IIB. Five cases of stage II B developed a local recurrence (35%). They all appeared to have had adequate external beam therapy with an appropriate pelvic side wall boost. Four cases could be identified as having had inadequate brachytherapy for variuos reasons. The first case had received inadequate brachytherapy because of poor choice of radium needles used in the implant and the dose to the vagina and paravaginal tissue was not adequate to control the malignancy. Recurrence occurred within three years after the treatment. The second case had been treated by ^{192}Ir implant with a total dose of 45 Gy in 58 hours while the external beam therapy was given some two years earlier. Inadequate brachytherapy was suggested. The third and fourth recurrences had not even received brachytherapy, due to some medical conditions; these two patients had been given additional external beam therapy in the form of rotation to substitute the brachytherapy. The last patient in stage II B appeared to have received both external beam and brachytherapy in a timely fashion with adequate dosage to both vagina and parametrium, but failed locally without any obvious reason. The films of the radium implant and the dosimetric analyses were adequate.

Stage III. Nine cases developed local recurrences (35%) after treatment of advanced malignancy (stage III), four being identified as having had inadequate brachytherapy by our dosimetric analysis. The other five cases of local failures were thought to have received adequate external beam therapy and brachytherapy.

Distant failures—Stage IIA. One case of distant failure was noted (4%) in a 26-year old patient who presented with clinical stage II A but during the course of radiation therapy was found to have inguinal, obturator, external iliac and common iliac lymph node metastases. External beam therapy with an appropriate parametrial boost plus adequate radium therapy (volume implant) was given with excellent loco-regional control.

Stage IIB. Two cases of distant failures were noted (14%). Both cases had been treated adequately by external beam whole pelvis irradiation and brachytherapy by radium needle implant to the vagina and paracolpic region. Dosimetric analysis of external beam and brachytherapy was satisfactory in both cases. The first patient developed a 6 cm × 6 cm metastasis in the left supraclavicular node three years later but still had local control. The second patient developed metastases in the right inguinal and para-aortic nodes about one year later but still had loco-regional control.

Table 4

Analysis of local failures

Stage	Age	Cell type	Treatment			Outcome
			External beam therapy	Brachytherapy	Total dose	
I	76	Squamous cell ca.	No	Manchester ovoid, 25 mg radium	Surface dose 100 Gy/ 120 h	Recurred 1 year just below the area treated
II A	54	Squamous cell ca.	Small field rotation 45 Gy/4 weeks	Radon seed implant 25 Gy	Vag. 70 Gy PW 40 Gy	Central recurrence in 4 months
	72	Adenocarcinoma	Small field rotation 40 Gy/4 weeks	Radium, vol. implant 25 Gy/2 days	Vag. 65 Gy PW 40 Gy	Pelvic wall, Ant. vagina } Recurrence in 2 years
	70	Squamous cell ca.	Small field rotation 40 Gy/7 weeks	Radium, vol. implant 25 Gy/2 days	Vag. 65 Gy PW 40 Gy	Parametrium, Pelvic wall } Recurrence in 2 years
II B	59	Squamous cell ca.	TP 40 Gy/4 weeks LPW 10 Gy/1 week	Short Ra needles + ovoid 25 Gy/2 days	Vag. 65 Gy PW 50 Gy	Central recurrence in 3 years
	55	Squamous cell ca.	TP 40 Gy/4 weeks PW:s 10 Gy/1 week (1964)	^{192}Ir vol. implant 45 Gy/58 h (1966)	?	Central, Parametrium } Recurrence in 1 year
	57	Squamous cell ca.	TP 40 Gy/4 weeks PW:s 10 Gy/1 week Rotation 20 Gy/1 week	No	Vag. 60 Gy PW:s 60 Gy	Central recurrence in 1 year
	57	Squamous cell ca.	TP 40 Gy/4 weeks PW:s 10 Gy/1 week	No	Vag. 70 Gy PW:s 65 Gy	Central recurrence in 1 year
	81	Squamous cell ca.	TP 40 Gy/4 weeks PW:s 10 Gy/1 week	Radium, vol. implant 30 Gy/2 days	Vag. 70 Gy PW:s 50 Gy	Central, Pelvic wall } Recurrence in 1 year

Stage III. Even with the aggressive therapy applied, it was hard to achieve local control of the tumor because of massive disease and the large tumor volume to be treated. Our local failures occurred at the rate of 35 per cent, while distant failures occurred at the rate of 23 per cent. Many organ metastases were noted in the late stage of the disease. Six patients developed such distant metastases, presumably at the time of the diagnosis since they all died of their metastatic disease within two years. Five patients developed distant failure while having their pelvic disease controlled by radiation. Only one patient had distant disease concomitantly with local failure.

Stage IV. Distant disease occurred in three patients in whom local failures were detected concomitantly. All distant failures were pulmonary and liver metastases.

Major complications

Among 88 patients treated with curative intent nine (10%) developed major complications as a result of radiation treatment and concomitant persistent disease. No complications occurred in patients with stages 0, I and II B. In stage II A, one patient developed a recto-vaginal fistula as a consequence of radiation treatment and required colostomy. No malignancy was found. One patient developed a pelvic abscess and was treated successfully by conservative measures but died later of intercurrent disease without evidence of malignancy. In stage III, four patients developed recto-vaginal fistulae and one developed a vesico-vaginal fistula. All five cases who developed fistulae also had persistent disease proven by biopsy at the site of the fistula. They all died of their tumors. One patient developed a pelvic abscess which necessitated conservative treatment. In stage IV, one patient developed a recto-vaginal fistula as a result of massive disease and radiation. Excluding those patients whose serious complications developed in conjunction with persistent disease, such complications associated with radiation treatment occurred in only 5 per cent (4/88).

Discussion

Patients with stage 0, I and II lesions had excellent local control and survival rates, as shown in

Table 2, with a minimum of complications. This compares well with many series (9, 12, 15). For stage 0, the use of a Bloedorn vaginal applicator to irradiate the entire vaginal canal appears to yield excellent results with no failure in the present series. For stage I and some early stage II A lesions, the use of interstitial radium (or radioactive iridium) gives excellent results and minimal vaginal fibrosis, and is recommended by several authors (3, 4, 12, 15). Once the disease is beyond stage II A, and in some poorly differentiated stage I lesions, the use of external beam therapy to cover regional lymphatics in combination with the individualized brachytherapy is essential to achieve good results. A variety of brachytherapy techniques and examples of implants have been described previously by many authors (4, 9, 12, 16). These improved brachytherapy techniques (interstitial) have provided a better chance for tumor control without an excessive dose to the vaginal mucosa, bladder and rectum. The interstitial brachytherapy is a good complement to intracavitary brachytherapy, especially in advanced vaginal malignancy.

An aggressive approach is obviously needed in more advanced stages (II B, III and IV), in which local failures were reported to be high (35–88 %) in all series.

There may be four possible ways to improve the local control and survival in advanced malignancy.

1) An increase in the dose of external beam therapy has been suggested, which, however, may give a larger number of major bowel complications. Extreme care must therefore be taken to achieve an optimal dose with maximum benefit and tolerable complications, especially among old patients.

2) Integration of external beam therapy and brachytherapy with stress on individualization of brachytherapy to achieve an acceptable result, as shown in the present series, especially in stages II and III.

3) Integrated pre-operative irradiation and surgical resection, especially in those patients in whom a surgical intervention not completely radical is desirable. This approach has recently been investigated by BORONOW (1, 2), with good results. Obviously, this combined therapeutic approach deserves further clinical analysis.

4) The potential value of radiation sensitizers combined with an optimal dose of radiation for advanced loco-regional vaginal malignancy needs to be further explored.

These aggressive approaches will undoubtedly increase the risk of undesirable effects and complications. The risk of serious complications must be weighed against the benefits. Fortunately the second approach, integration of external beam therapy and brachytherapy and individualization of brachytherapy, as shown in this series, has a low overall complication rate. In this series it was only 10 per cent (9/88); excluding those who developed complications in conjunction with persistent disease, the rate of major complications as a result of radiation treatment was only 5 per cent (4/88).

The analysis of the failures in stages I, II A and II B shows that some of the pitfalls could be prevented within the frame of our treatment planning: It is essential to irradiate the entire vaginal canal even in a localized stage I disease in order to minimize the possibility of a geographic miss and to neutralize the tendency of multicentric behavior of the tumor; in a clinical situation when only a suboptimal dose of external beam therapy can be safely given, it is advisable to give an additional dose by brachytherapy whenever possible, to achieve a cancericidal dose and eventually a better control of the disease; conversely, in a clinical situation when brachytherapy cannot be given, or inadequate brachytherapy (a suboptimal or inhomogeneous tumor dose), a booster dose by external beam therapy should be given within the tolerance limit with small fields or rotational therapy.

The high incidence of distant disease often concomitant with local failure, in advanced malignancy, is of interest and gives cause for concern. These patients usually present initially with massive disease in the vagina, paracolpium and parametrium, and perhaps should be treated by a combined approach, radiation and chemotherapy concomitantly, or radiation, chemotherapy and surgery. Further investigations are needed.

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REFERENCES

1. BORONOW R. C.: Therapeutic alternative to primary exenteration for advanced vulvovaginal cancer. Gynecol. Oncol. 1 (1973), 233.
2. — Combined therapy as an alternative to exenteration for locally advanced vulvovaginal cancer. Cancer 49 (1982), 1085.

3. BROWN G. R., FLETCHER G. H. and RUTLEDGE F. N.: Irradiation of in situ and invasive squamous cell carcinomas of the vagina. Cancer 28 (1971), 1278.
4. CHAU P. M.: Radiotherapeutic management of malignant tumors of the vagina. Amer. J. Roentgenol. 89 (1963), 502.
5. FLETCHER F. H., DELCLOS L., WHARTON J. T. and RUTLEDGE F. N.: Tumors of the vagina and female urethra. *In:* Textbook of radiotherapy. Third edition, p. 813. Lea and Febiger, Philadelphia 1980.
6. FRICK H. C. II, JACOX H. W. and TAYLOR JR H. C.: Primary carcinoma of the vagina. Amer. J. Obstet. Gynecol. 101 (1968), 695.
7. HERBST A. L., GREEN JR T. H. and ULFELDER H.: Primary carcinoma of the vagina. An analysis of 68 cases. Amer. J. Obstet. Gynecol. 106 (1970), 210.
8. KOTTMEIER H. L.: The classification and clinical staging of carcinoma of the uterus and vagina. J. Int. Fed. Gynecol. Obstet. 1 (1963), 83.
9. MARCUS JR R. B., MILLION R. R. and DALY J. W.: Carcinoma of the vagina. Cancer 42 (1978), 2507.
10. MURPHY W. T. and BOZZINI M. A.: End results in the irradiation of primary carcinoma of the vagina. Radiology 80 (1963), 566.
11. PEREZ C. A.: Definitive radiotherapy for carcinoma of the vagina. Int. J. Radiat. Oncol. Biol. Phys. 7 (1981), 20.
12. — KORBA A. and SHARMA S.: Dosimetric considerations in irradiation of carcinoma of the vagina. Int. J. Radiat. Oncol. Biol. Phys. 2 (1977), 639.
13. — ARNESON A. N., GALAKTOS A. and SAMANTH H. K.: Malignant tumors of the vagina. Cancer 31 (1973), 36.
14. PIRTOLI L. and SANTONI R.: Radiation therapy of primary vaginal carcinoma. Acta radiol. Oncology 19 (1980), 353.
15. PREMPREE T.: Role of radiation therapy in the management of primary carcinoma of the vagina. Acta radiol. Oncology 21 (1982), 195.
16. — VIRAVATHANA T., SLAWSON R. G., WIZENBERG M. J. and CUCCIA C. A.: Radiation management of primary carcinoma of the vagina. Cancer 40 (1977), 109.
17. PRIDE G. L., SCHULTZ A. E., CHUPREVICH T. W. and BUCHLER D. A.: Primary invasive squamous carcinoma of the vagina. Obstet. and Gynecol. 53 (1979), 218.
18. RUTLEDGE F. N.: Carcinoma of the vagina. Amer. J. Obstet. Gynec. 97 (1967), 635.
19. UNDERWOOD P. B. and SMITH R. T.: Carcinoma of the vagina. J. Amer. med. Ass. 217 (1971), 46.
20. WHELTON J. and KOTTMEIER H. L.: Primary carcinoma of the vagina. Acta obstet. gynec. scand. 41 (1962), 22.