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Embryonal Rhabdomyosarcoma of the Vagina in Children

Conservative Treatment with Curietherapy and Chemotherapy

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Abstract—*Eight cases of childhood rhabdomyosarcoma arising in the vagina are presented. All were treated with curietherapy, and 7 of 8 received chemotherapy in addition.*

With a median follow up of 4 yr, 6 of 7 had local control without surgery, 1 required colpohysterectomy for microscopic disease after curietherapy.

These techniques of curietherapy and chemotherapy for localized rhabdomyosarcoma of the vagina allow one to obtain the cure while avoiding mutilating surgery.

INTRODUCTION

VAGINAL rhabdomyosarcoma (RMS) is rare. There have been 12 vaginal lesions in our series of 380 cases of rhabdomyosarcoma (1954–1976) and this is in agreement with other published observations [1–2]. The first problem has been the local control of the primary tumor. It has been obtained in a number of cases with mutilating surgery such as complete exenteration or anterior exenteration [3–4]: more limited surgery e.g., colpohysterectomy has been advocated after primary chemotherapy, either alone [5], or combined with radiotherapy [6], and this approach represents a significant advance in treatment.

Our experience with local curietherapy in small subcutaneous sites (e.g., lip, nasolabial fold, perineum) has led us to adapt this technique to vaginal lesions. This local treatment was designed to obtain the control of the primary tumor without surgery. We report here the results obtained in eight children treated by this method.

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MATERIALS AND METHODS

The clinical features are summarized in Table 1. Seven patients were less than 2 yr old and 1 was 14 yr old. Five had tumor visible at the vulva either as a small polyp or a translucent grape-like swelling. In 2 cases the vaginal bleeding led to a vaginal examination.

The time from first symptom to the diagnosis was less than one month except for an African child (patient No. 6) who was seen for the first time in our department 4 months after onset of the disease.

Regional extension was appreciated by:

1. Clinical examination: 1 patient had a mass palpated by rectal examination (case 6) and another an abdominal mass extending up to the umbilicus (case 8). Six had no abnormal features;
2. Vaginal examination under general anesthesia: this was determined by the necessity to take a biopsy and appreciate the extension into the vaginal cavity, and the uterine cervix. Extension was difficult to ascertain when the tumor filled the cavity, and gross removal of grape-like tumor was necessary in 1 case (case 4). Appreciation of the involved area was easier after reduction of the gross tumor by 1 or 2 courses of chemotherapy (cases 6 and 8);

Table 1

	Case 1 MRV 70 0064Xt	Case 2 SR 71 01747LK	Case 3 IM 72 02280DB	Case 4 CC 74 0154KL	Case 5 PD 74 03782RN	Case 6 ID 74 02247KP	Case 7 SA 75 01456MZ	Case 8 de G. 76 06341TX
Age	14 yr	19 months	8 months	22 months	18 months	10 months	$2\frac{1}{2}$ yr	16 months
1st symptom	Problems with micturition and defaecation	Tumour visible at the vulva and haemorrhage	Tumour visible at the vulva	Haemorrhage	Tumour visible at the vulva	Tumour visible at the vulva	Tumour visible at the vulva	Haemorrhage abdominal mass
Extent of disease	One mass 6 cm, base $<\frac{1}{2}$ cm, on the lateral wall at 4 cm from the vulva	Left side wall and anteriorly concealing the cervix	Circumferential lower $\frac{1}{3}$ (level of the hymen)	Right cul de sac and right side of cervix	Lower $\frac{1}{4}$ of the anterior wall with 1.5 cm implantation	Whole vagina ? Cervix	Anterior wall urethral meatus, labia major, inguinal node	Whole vagina ? Cervix
Treatment before curietherapy	Ablation of the polyp with its base	1 course of MOP*	—	Laparotomy transposition of ovaries	1 course of VAC	—	2 courses of VAC	2 courses of VAC, laparotomy, transposition of ovaries
	Normal examination Biopsy negative	Cervix clear	—	—	Normal	—	Complete	Incomplete regression
Area of irradiation	Left vaginal wall	Whole vagina	Left posterior wall of the lower $\frac{1}{3}$ of vagina	Whole vagina + cervix	Anterior wall and urethral	Whole vagina	Lower $\frac{1}{3}$ of the anterior wall + urethral meatus	Whole vagina
	65 Gy 6 days	58 Gy 6 days	75 Gy 6 days 9 hr	58 Gy 2 days 22 hr	68 Gy 3 days 10 hr	58 Gy 5 days 20 hr	61 Gy 4 days 2 hr	50 Gy 4 days 1 hr
	none	Single agent alternating	Single agent alternating	VAC+ Procarbazine	VAC+ Procarbazine*	VAC (caused* septicaemia)	VAC-V-Ad*	VAC-V-AD* colpohysterectomy
	Alive NED 8 yr	Alive NED 7 yr	Alive NED 6 yr	Alive NED 4 yr 1 month	Alive NED 3 yr 9 months	Dead 1 month after diagnosis	Alive NED 3 yr	ALive NED 21 months

* See Table 2.

3. Radiological examination: cystography, vaginography and rectography together were done in all patients to visualize the anterior and posterior walls.

Lymphography was performed when it was possible (case 7);

4. Aspiration cytology of palpable lymph-nodes: in one patient (case 7);

5. Exploratory laparotomy: in two patients, one before any treatment (case 4), the other after two courses of chemotherapy (case 8) for transposition of ovaries.

Results are summarized in Table 1. Investigations for metastases included chest X-ray, skeletal survey and bone marrow aspiration in all patients. None had evidence of distant metastases.

Histology

The diagnosis of embryonal RMS "loose-type" (botryoïd) in all cases (Fig. 1) was confirmed by biopsy.

Radiation therapy technique

Plesiotherapy and interstitial implantation were the two techniques of curietherapy used, either alone or together [7, 8].

Vaginal plesiotherapy [9]: the first stage of the procedure was to take an impression or mould of the vaginal cavity under general anesthesia, if necessary, after gross removal of tumor masses. This impression allowed precise determination of areas of tumor implantation and was then used to make a negative plaster cast. From this cast the definitive plastic vaginal applicator was made to correspond exactly with the child's vagina and the areas of tumor implantation. Plastic tubes were fixed within the applicator according to the position of the tumor and then Iridium^{192} wires of the required length were inserted into these tubes when the applicator was in place. The same technique was extended, if necessary, to the endocervix by means of a plastic uterine probe, loaded with Iridium^{192} wire.

Interstitial implantation was achieved by Ir^{192} hairpins, (Pierquin's technique), or by plastic tubes placed in the mucosa or cutaneous or subcutaneous region to be irradiated, following the classical technique of Henschke [10].

The volume irradiated was the initial tumor volume, taking into account areas of tumor implantation on the vaginal wall and any possible extension to the cervix or vulva.

The dose planned for the target volume was limited by the doses to neighbouring critical organs.

A rectal probe with lead markers was introduced for radiographic films of the application to calculate the dose to the rectum. In the same way, the bladder dose was calculated at the posterior part of a catheter cuff which was filled with radio-opaque material. The dose to the ovaries could only be calculated accurately if they had been clipped during transposition to the iliac crests. Otherwise the dose could only be roughly estimated.

All these doses were calculated by the computer, in addition to isodose curves, in different preselected planes [7, 11]. The minimum dose was difficult to compare to fractioned cobalt irradiation in terms of radiobiologic efficiency.

Treatment

This can be considered in three stages:

1. Primary chemotherapy to reduce the tumor volume and facilitate curietherapy;
2. Curietherapy;
3. Maintenance chemotherapy to eradicate micrometastases.

This scheme was modified for some of the earlier patients, or because of intercurrent complications (e.g., varicella).

1. *Primary chemotherapy.* Four children (cases 2, 5, 7 and 8) had primary chemotherapy (one received one course of "MOP", 3 had one or two courses of "VAC") (Table 2). Results of the primary chemotherapy are shown in Table 1.

2. *Curietherapy.* Case 1 had an interstitial implant alone in the upper part of the left vaginal wall.

The other 7 children were treated with vaginal plesiotherapy after chemotherapy or gross removal of tumor: 5 had plesiotherapy alone (cases 2, 3, 4, 6 and 8): in case 4, plesiotherapy was given to the cervix and uterus because of obvious cervical involvement. Two children received a combination of plesiotherapy and interstitial implants: in case 7 to cover the tumor extension to the urethral meatus and the anterior part of the labia major, in case 5 because the tumor was implanted low in the vagina and an extension to the urethral meatus was suspected although the biopsy of this area was negative.

The doses received by the vagina are shown in Table 1: the highest dose was given in a small volume to the left half of the lower third of the vagina of case 3. Rectal and bladder doses also varied greatly; for example,

Table 2. Chemotherapy

"VAC"	Vincristine 2 mg/m^2/D_1 and D_{14}* IV Actinomycin D 15γ/kg D_1 to D_5 IV Cyclophosphamide 200–300 mg/m^2 D_1 to D_5† IV
"V-AD"	Vincristine 2 mg/m^2/injection IV Adriamycin 60 mg/m^2/injection‡ IV
Procarbazine 200 mg/m2/day during 10 days *per os*.	
"MOP"	Vincristine 1.4 mg/m^2 D_1 and D_8 IV Nitrogen mustard 6 mg/m^2 D_1 and D_8 IV Procarbazine 100 mg/m^2 *per os* D_1 to D_{10}

*1.5 mg/m^2 after 8 injections.
†7 days instead of five days for the 1st cure.
‡maximum 450 mg/m^2.

dose to the bladder varied between 13.7 Gy (case 3) and 23 Gy (case 4).

In the only case where the ovaries were transposed and also clipped, the right ovary received 0.5 Gy and the left 0.7 Gy (case 8).

Tolerance of curietherapy was good. One child (case 3) had a recrudescence of radiation reactions during subsequent courses of actinomycin D giving rise to rectal and vaginal haemorrhages.

3. *Maintenance chemotherapy.* Additional treatment was given to sterilize micrometastases except in case 1 which was treated in 1970. Cases 2 and 3 received alternating intermittent courses of actinomycin, cyclophosphamide and vincristine, each agent being given separately. Two of the 5 subsequent cases received courses of "VAC" alternating with procarbazine and the 3 others, courses of "VAC" and "V-AD" (Table 2). The course of treatment was 15–18 months, except for case 1 who had no chemotherapy. Tolerance of single agent therapy was good. For the multiple drug schedules, the problems were the same as those encountered in treating RMS at other sites (leucopenia, thrombocytopenia, viral and bacterial infections).

RESULTS

1. *Local sterilization*

This was achieved in seven cases, but the technique failed in case 8 where the RMS was implanted among the whole vaginal wall and obstructed the cervix. A two stage curietherapy was planned because it was impossible to catheterize the cervix at the first application. 50 Gy was given in this first application to the vagina (the lowest dose in this series). A second application was planned, but after 1 course of "VAC" and 1 of "V-AD" (3 months after the first application), biopsies taken from the irradiated area were positive and she therefore underwent colpohysterectomy. The tumor arose from the uterine isthmus and was localized to the uterus and vagina. Surgical excision was complete with clear histological margins, and the child is in complete remission on chemotherapy 12 months after operation.

2. *Survival*

Seven of the 8 children are alive and well with a follow-up of 21 months–8 yr (median 4 yr).

One died of chemotherapy complications (septicemia and interstitial pneumonitis) after eradication of primary tumor.

3. *Local sequelae*

Six patients are living with local control after curietherapy and without ablative surgery. Two have no vaginal sequelae (cases 1, 7), the oldest has normal sexual relations; 2 have telangiectasia without symptoms (cases 3, 5) and 2 have adhesions of the vaginal walls in the upper 1/3.

Clinical examination and growth of these children are normal. In 5 children additional investigations have been undertaken to look for possible complications in critical organs: rectum, bladder, ureters and bone. One child

(case 4) at 3 yr 10 months of follow up has rectosigmoïdal stenosis and low bilateral ureteral strictures, with small hydronephrosis. Cystography and cystoscopy show a normal bladder. She was the only patient who had an intra-uterine source because of cervical involvement. She received 65 Gy to the rectum and 93 Gy to the bladder. Case 3 was a unilateral absence of part of the ischiopubic ramus due to sterilization of the growth cartilage plate. One child (case 1) was pubescent at the time of her illness and she now has normal periods and normal sexual relation. Ovarian function cannot be usefully investigated in the other patients as they are too young.

DISCUSSION

To our knowledge, there have been no publications concerning attempts to obtain local control of vaginal RMS with conservation of the genital tract, including the vagina. In 1970 Hilgers [1, 2] reported 10 cases from the Mayo Clinic and 51 from the literature: 10/61 were alive 10 yr after surgical excision which consisted of anything from colpohysterectomy to pelvic exenteration. One patient had also received curietherapy with radium and external radiation to an unspecified dose.

Other reports of cures have been published since 1970 using the same treatment methods: colpohysterectomy with pelvic and perineal radiotherapy [12] anterior pelvectomy [13], anterior pelvectomy, radiotherapy and chemotherapy [4], total exenteration with actinomycin D [3]. Rivard [5] proposed intensive chemotherapy and Kumar [6] chemotherapy and radiotherapy as primary treatment for RMS of the vagina, but both relied on hysterosalpingectomy and partial colpectomy for local control.

Three of the 4 patients treated before 1970 at the Institut Gustave-Roussy .died with local recurrence after limited surgical excision. One is alive 7 yr after anterior exenteration and total colpectomy followed by Cobalt irradiation to the pelvis and perineum (45 Gy in 5 weeks). She has suffered considerable toxicity and has an ileal loop bladder, hydronephrosis, and radiation changes in the rectum.

Of this present series of patients, 5 are free of disease at more than 3 yr without mutilating surgery and with fewer complications. The factors leading to the choice of curietherapy as the modality of radiotherapy were the following:

1. It gives a continuous irradiation to a defined tumor volume.

2. A high dose can be given to the tumor with a better chance of sparing neighbouring tissues than is possible with external beam therapy.

The technique itself can be adjusted so that the geometry of the application corresponds with the patients' anatomy and tumor, as the applicator is made from a direct vaginal impression. In 4 patients multiple chemotherapy was used before curietherapy to obtain intra-vaginal tumor regression so that its base, (the area requiring treatment) could be visualized and the applicator positioned correctly.

The indications of curietherapy for vaginal treatment must be well defined. It can only be used for localised RMS which does not deeply infiltrate the rectovaginal or vesicovaginal walls, and does not extend to the parametrium, bladder or abdomen. Implantation in, or extension to the cervix can be treated with an intra-uterine source of maximal length 3 cm.

The treatment volume for our 8 patients was the initial volume i.e., the area implantation of the mass on the vaginal mucosa (the actual size of the botryoïd part is irrelevant) even when tumor reduction was marked after chemotherapy. It has not been proved that RMS can be cured by chemotherapy followed by local treatment limited to residual tumor, although some observations suggest that this is the case [14]. A controlled therapeutic trial organised by the International Society of Pediatric Oncology and currently underway is trying to answer this question for RMS with loco-regional spread. Since the sequelae are minimal in the patients in our series, we think that in these localized forms of vaginal RMS, the whole initial volume should be treated.

The minimum dose required to sterilize the tumor locally is difficult to determine. A direct comparison cannot be made with the doses given by external beam therapy, since the irradiation is continuous and only experience will establish the necessary dose with more certainty. It should be noted however that the tumor which received a minimum dose of 50 Gy (case 8) was not sterilized and this dose is perhaps too low.

Curietherapy of vaginal RMS should be associated with combination chemotherapy which has been shown to be effective in RMS [15] in order to deal with possible

subclinical metastases. Chemotherapy has varied over the years for our patients, but now consists of repeated courses of multiple agents over a period of 18 months. Better knowledge of the optimum duration of chemotherapy in RMS at any site would enable us to shorten or prolong the treatment period and to use more efficacious combinations.

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REFERENCES

1. R. D. Hilgers, G. D. Malkasian and E. H. Soule, Embryonal rhabdomyosarcoma of the vagina. A clinicopathologic review. *Amer. J. Obstet. Gynec.* **107,** 484 (1970).
2. R. D. Hilgers, Pelvic exenteration for vaginal embryonal rhabdomyosarcoma. A review. *Obstet. Gynec.* **45,** 175 (1975).
3. F. Ghavimi, P. R. Exelby, G. J. D'Angio, W. F. Whitmore, P. H. Lieberman, J. L. Lewis, V. Mike and M. L. Murphy, Combination therapy of urogenital embryonal rhabdomyosarcoma in children. *Cancer (Philad.)* **32,** 1178 (1973).
4. J. L. Grosfeld, J. P. Smith and H. W. Clathworthy, Pelvic rhabdomyosarcoma in infants and children. *J. Urol.* **107,** 673 (1972).
5. G. Rivard, J. Ortega, R. Hittle, R. Nitschke and M. Karon, Intensive chemotherapy as primary treatment for rhabdomyosarcoma of the pelvis. *Cancer (Philad.)* **36,** 1593 (1975).
6. A. P. M. Kumar, E. L. Wrenn, I. D. Fleming, H. O. Hustu and C. B. Pratt, Combined therapy to prevent pelvic exenteration for rhabdomyosarcoma of the vagina or uterus. *Cancer (Philad.)* **37,** 118 (1976).
7. B. Pierquin, *Précis de Curiethérapie.* Masson, Paris (1964).
8. B. Pierquin, D. Chassagne, H. Chabazian and J. Wilson, *Brachytherapy.* Warren Green, St. Louis (1977).
9. D. Chassagne and B. Pierquin, La plésiothérapie des cancers du vagin par moulage plastique avec Ir^{192}. *J. Radiol. Electrol.* **47,** 89 (1966).
10. U. K. Henschke, B. S. Hilaris and G. D. Mahan, After loading in interstitial and intracavitary radiation therapy. *Amer. J. Roentgenol.* **90,** 386 (1963).
11. D. Chassagne, A. Gerbaulet, A. Dutreix and J. M. Cosset, Utilisation pratique de la dosimétrie par ordinateur en curiethérapie gynécologique. *J. Radiol. Electrol.* **58,** 387 (1977).
12. M. S. Piver, J. J. Barlow, J. J. Wang and N. K. Shah, Combined radical surgery, radiation therapy and chemotherapy in infants with vulvovaginal embryonal rhabdomyosarcoma. *Obstet. Gynec.* **42,** 522 (1973).
13. R. Underhill, Neoplasm of the vagina in infant. Two cases. *Proc. roy. Soc. Med.* **68,** 229 (1975).
14. R. A. Voute and A. Vos, Combination chemotherapy as primary treatment on children with rhabdomyosarcoma to avoid mutilating surgery or radiotherapy. *Proc. Amer. Ass. Cancer Res.* **18,** 327 (1977).
15. J. R. Wilbur, W. W. Sutow and M. P. Sullivan, Successful treatment of rhabdomyosarcoma with combination chemotherapy and radiotherapy. *Proc. Amer. Soc. clin. Oncol.* **7,** 56 (1971).