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Vaginal Applicators (ovoids) for Local Control and Alleviation of Rectal Complications of Cervical Cancers Treated by Brachytherapy

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Purpose: To assess the effects of vaginal applicators (ovoids) on dose distribution, local control and rectal complications in cervical cancers treated by brachytherapy. Methods: From 1984 to 1992, 41 patients (15 stages I+II; 26 stages III+IV) were treated by high-dose-rate brachytherapy (20 Gy in 4 fractions) after external beam irradiation (36-56 Gy). Twenty-three patients were treated by standard application of both intrauterine tandem and ovoids, and 18 patients were treated by non-standard application. Results: The five-year, local-relapse-free rates by standard application and tandem alone were 69 and 65% overall; 83 and 100% for stages I+II; and 62 and 49% for stages III+IV. Local control was related to tumor response following the external beam irradiation and initial tumor size by multivariate analysis. Rectal complications seen in patients followed for more than 1 year were 33% after standard application and 22% for tandem use alone. The rectal doses given for standard application (24 Gy) and tandem use (16 Gy) were significantly different. Conclusions: The ovoid sources did not always contribute to local control, and occasionally led to rectal complications. The optimization of brachytherapy was dependent on patients' anatomy, tumor size, and tumor response.

Key Words : Vaginal applicators, Local control, Rectal complications, Brachytherapy, Cervical cancer

INTRODUCTION

Carcinoma of the uterine cervix can be effectively treated by combining intracavitary brachytherapy with external beam irradiation [1-6]. In standard brachytherapy, intrauterine applicators (tandem) and vaginal applicators (ovoids or colpostats) are commonly used [7]. However, vaginal applicators can not always be inserted into a narrow vagina, especially in elderly patients [8]. Mini-colpostats have been developed to overcome this problem [9, 10]. However, when used, the rate of complications was higher than from regular colpostats [11]. The small separation of ovoid sources induces a decreasing parametrial dose and an increasing rectal dose, which may lead to local failure and rectal complications. Patients with a small vagina have sometimes been treated with a cylinder applicator (a linear source arrangement) instead of the ovoids [12-14], because of easy application and constant position for low-dose-rate (LDR) brachytherapy. The survival rate seems to be compatible to that achieved by standard application, but rectal complications increase when large volumes are irradiated in patients with vaginal involvement [10]. For high-dose-rate (HDR) brachytherapy, there is little in the literature concerning the effects of oviods on local control and rectal complications. Matsuoka et al. [15] have reported that results from HDR brachytherapy with a linear source arrangement are comparable to the results obtained after treatment using a standard application. We used tandem sources alone with small protrusion to vagina instead of ovoids for patients with a small vagina.

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In this study, the contributions of ovoid sources to dose distribution, local control, and rectal complications were retrospectively assessed by comparing the results of treatment with and without ovoids.

MATERIALS AND METHODS

Patient and tumor characteristics

From 1984 to 1992, 41 patients with squamous cell carcinoma of the uterine cervix were treated by radiotherapy. The average age was 67, and ranged from 38 to 86. The patients with stage I and II carcinomas were scheduled for radiotherapy because surgery was contraindicated due to age or medical condition. Seventeen patients had complications such as diabetes mellitus, cardiac problems, pulmonary problems, etc. There were 5 stage I, 10 stage II, 22 stage III, and 4 stage IV patients according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. Eleven patients had pelvic lymph node metastases.

Treatment Methods

Except for one stage Ia, all patients received whole pelvis external beam irradiation, to a total dosage of 30 to 56 Gy, in daily doses of 1.8 to 2 Gy. Within one week after termination of the external beam irradiation, planning of intracavitary irradiation was initiated using computed tomography (CT) and a computer planning system (Tosplan, Toshiba, Tokyo). The intracavitary dose was delivered at high-dose-rate (HDR) by a ^{60}Co remote afterloading system (RALS) with a total dose of 20 Gy at point A in 4 fractions, during a 2-weeks period. TAO applicators were used [16]. The size of the smallest ovoid was 14 mm in width and 21 mm in height. Twenty-three patients were treated with both tandem and ovoids (Group I). Six patients were treated with tandem and ovoids, but occasionally with tandem alone (group II). Twelve patients were treated with tandem alone, because the vaginal cavity was too small to insert ovoids (Group III). The tandem source was protruded about 1 cm from the external cervical orifice into the vagina instead of ovoid sources. The doses at various points were determined as follows: point A (cervical dose), 2 cm lateral from the center of the cervical canal at the level of 2 cm cephalic from the external cervical orifice; point P (parameterial dose), 2 cm lateral from the center of the cervical canal at the level of the external cervical orifice; point R (rectal dose), 2 cm dorsal from the center of

Table 1 Patient characteristics.

Factors	Class	Group I Tandem & Ovoids	Group III Tandem alone	
Age	<70:≧70	16:7	5:7	NS
KI	<80:≧80	4:19	6:6	NS
Medical problems	-:+	13:10	7:5	NS
Hb (g/dl)	<12:≧12	15:8	8:4	NS
Keratinization	+:-	4:13	4:8	NS
Tumor size (cm)	<5:≧5	15:8	6:6	NS
Stage	<3:≧3	9:14	4:8	NS

KI: Karnofsky index
NS: not significant

Table 2 Stage distribution and application methods for carcinoma of the cervix.

Group Appli-cators	I Tandem & Ovoids	II Tandem ± Ovoids	III Tandem alone	Number of patients
Stage I	3	1	1	5
II	6	1	3	10
III	11	4	7	22
IV	3	0	1	4
Total (%)	23 (56)	6 (15)	12 (29)	41

the cervical canal at the level of the external cervical orifice. The separation between ovoid sources, and the distance between orifice and ovoid sources, were measured by A-P and lateral X-ray films.

The differences in characteristics of patients and tumors among groups are shown in Table 1. Mean age was 72 for group III and 64 for group I patients (p=0.110). Karnofsky performance status for group III was marginally lower (p=0.053) than that of group I. The distribution of FIGO stages was not statistically different among groups (Table 2). Chemotherapy was carried out before radiotherapy in 15 patients. An operation for paraaortic or pelvic lymph adenectomy was performed in 14 patients, but no primary lesion was resected. The lymph nodes of 13 patients were irradiated intraoperatively.

Observations

The tumor response was determined 5 weeks after the beginning of external irradiation by palpation: partial response (PR), ≧ 50% reduction in tumor volume; no change (NC), < 50% reduction. Late complications and tumor recurrence were observed after radiotherapy with a median of 45 months, ranging up to 136 months. Local relapse meant recurrence at the primary and parametrial sites. Late complications were assessed for patients followed for more than 1 year, and were graded as follows: grade 1, transitional minimum symptoms; grade 2, slight symptoms continuing over 6 months without medical care; grade 3, symptoms necessitating medical care, grade 4, symptoms necessitating surgical intervention.

Analysis

The data were analyzed using the Chi-square method or Fisher's direct method, Student's t test, correlation factors, and logistic regression model. Survival and relapse-free survivals were estimated by the Kaplan-Meier method. Computer soft ware program of SPSS for Windows 95 (SPSS Japan, Tokyo) was used. Probability values under 0.05 were considered significant.

RESULTS

Evaluation of dose distributions

Table 3 shows the differences in radiation doses at various points between groups I and III. Doses at point A were not different, but doses at point P and R were significantly lower in group III than in group I. There

Table 3 Doses at various points according to ovoid application.

Group Applicators Dose (Gy)	I Tandem + Ovoids	III Tandem alone	p
External dose	46.7 ± 11.2	49.6 ± 5.4	NS
Point A by RALS	19.9 ± 4.9	19.7 ± 4.2	NS
Point A (total)	66.6 ± 9.1	69.4 ± 6.7	NS
Point P by RALS	44.9 ± 29.1	16.5 ± 3.6	0.002
Point P (total)	91.6 ± 20.2	66.2 ± 6.9	0.0001
Point R by RALS	24.4 ± 7.3	16.1 ± 3.4	0.001
Point R (total)	71.3 ± 10.1	66.0 ± 6.8	NS

NS: not significant

Table 4 Local control achieved with applicators.

	Number of patients			
Group Applicators Stage	I Tandem & Ovoids	II Tandem ± Ovoids	III Tandem alone	All (%)
I+II	8/9	2/2	4/4	14/15 (93)
III+IV	9/14	3/4	5/8	17/26 (65)
Total	17/23	5/6	9/12	31/41 (76)
(%)	(74)	(83)	(75)	

was a strong negative correlation between ovoid-sources separation and ovoid-orifice distance (Fig. 1). The limitation of ovoid insertion was considered to be 19 mm in inter-sources separation, and 12 mm in ovoid-orifice distance.

Survival and local control

The five-year survival was 57% overall; 65% for stages I+II, and 53% for stages III+IV. Stages I+II cases showed poor survival because of their medical problems. The five-year relapse-free rate was 66% overall; 92% for stages I+II, and 55% for stages III+IV. The five-year local-relapse-free rates for group I (standard application) and group III (tandem alone) were 69 and 65% overall; 83 and 100% for stages I+II, and 62 and 49% for stages III+IV, by the Kaplan-Meier method (Fig. 2 and Table 4). The local control rates

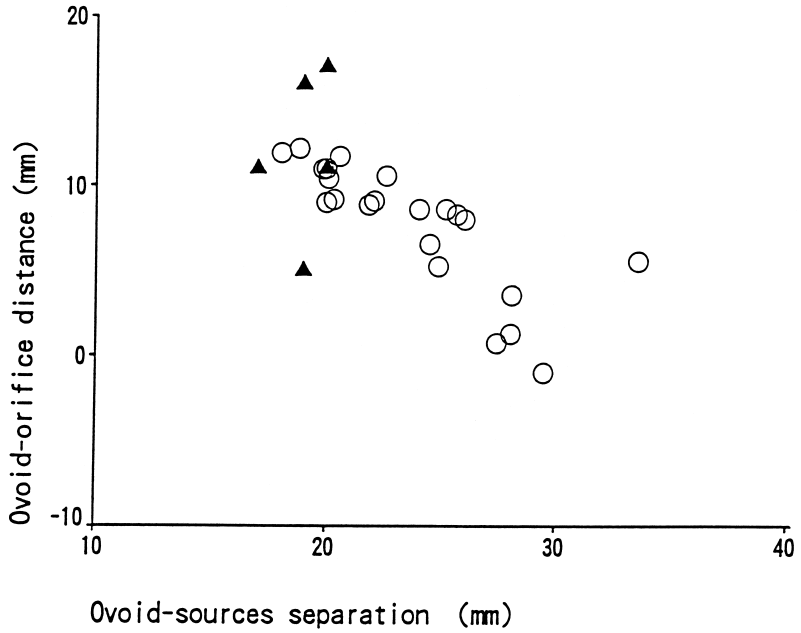

Fig. 1 The relationship between inter-ovoid separation and ovoid-orifice distance.

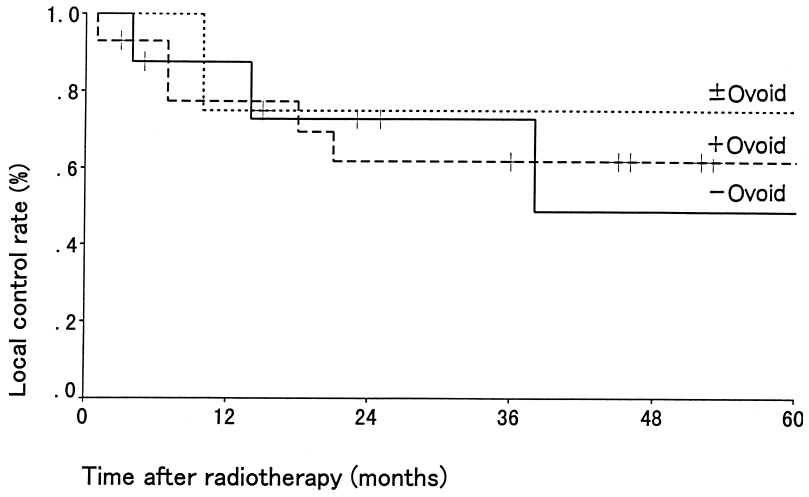

Fig. 2 Local control rates in each group for stages III+IV cervical carcino-

of group III were not significantly different from group I.

Prognostic factors

For stages III+IV, the prognostic factors for local control were the tumor response after external beam irradiation (p=0.0011) and initial tumor size (p=0.056), by the Cox hazard proportional method (Table 5). Although the routine parametrial doses did not influence local control, a parametrial dose greater than 90 Gy by ovoid application achieved local control in the three patients with poorly responding tumors (Fig. 3). For tumors that responded well, good local control was obtained whether ovoids were applied or not.

Rectal complications

Among the 34 patients followed-up for more than 1 year after radiotherapy, 11 (32%), 5 (15%), 2(6%) and 1 (3%) developed rectal complications of grades $\geqq 1$, $\geqq 2$, $\geqq 3$, and 4, respectively (Table 6). Rectal complications of grade $\geqq 1$ occurred in 2/7 (22%) of group III patients with grades 1 and 2, and in 6/18 (33%) of group I including, 2 patients with grades 3 and 4.

DISCUSSION

There are many patients in whom insertion of ovoids is difficult: almost half of our patients exhibited this problem. Vaginal width in the Japanese female is narrow (about 40 mm), with inter-sources separation of 20-30 mm in this study. The limitation in ovoid application was under 20 mm in inter-sources separation. When ovoids were inserted in patients with a narrow vagina, the ovoids slipped out and the ovoid-orifice distance increased. This causes the parametrial dose to decrease and the rectal dose to increase. The application of ovoids did not significantly contribute to local control, but increased rectal injury. For stages I+II, or tumor sizes smaller than 5 cm, the application of ovoids may not be necessary, because the parametrial dose can be sufficient from tandem sources. For stages III+IV, a parametrial dose derived only from tandem sources cannot suffice, and it did not significantly relate to local control under the same dose at point A. In this study, the factors related to local control were tumor size and response after external beam irradiation. It has been reported that radiosensitivity, or response to radiation, is the most important variable [17-19]. For good responding tumors even with the large tumor size of stages III+IV, the application of ovoids did not significantly contribute to local control. The dosage from ovoid sources could be decreased, so that rectal complications would be reduced. For poorly responding large-sized tumors, the incremental increase in parametrial doses might be necessary (Fig. 3). The patients with local control received a greater than 90 Gy parametrial dose with the standard application. Point P, as the parametrial dose in this study, corresponds to the width (d_w) of the maximum dimension perpendicular to the intrauterine source in the International Commission on Radiation Unit and Measurements (ICRU) Report 38 [20]. It is unknown whether higher doses at para-

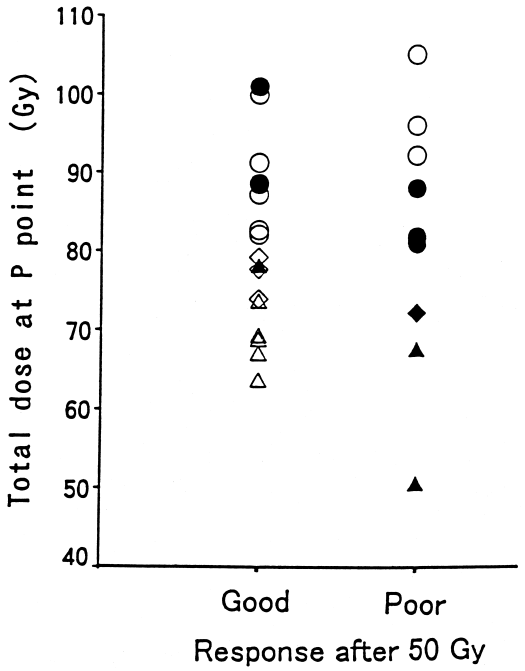

Fig. 3 Local control for stage III + IV by total parametrial dose and tumor response after the external irradiation dose of 50 Gy. Good and poor response indicate >50% and <50% reduction in tumor volume. Open and closed markers indicate local control and recurrence, respectively. Circles, diamonds, and triangles indicate application of brachytherapy by tandem+ovoids, tandem ± ovoids, and tandem alone.

metrium will improve local control or not. Montana et al. [21] have reported that cumulative paracentral doses greater than 85 Gy, in combination with external beam irradiation and low dose rate (LDR) brachytherapy, did not improve disease-free survival. Ito et al. [10] have reported that 30 Gy external doses plus 24-27 Gy/4-6 fractions at HDR brachytherapy is not enough for large tumors. It is necessary to try to deliver a high parametrial dose, or a high dose at point A, in HDR brachytherapy using ovoids.

An application of ovoids contributes to the rectal dose rather than point A dose, especially in patients with a narrow vagina. The rectal complication rate was high in group I patients, who received rectal doses of 71.3 Gy. Point R, as a rectal dose, would be available as an indicator of rectal injury. It has been reported that the rectal reference dose (ICRU 38), the maximum dose to the rectum on CT, and reference volume encompassing a given isodose of 60Gy, relate to late rectal complications [22-24]. When ovoids are applied in patients with a narrow vagina, it is necessary to reduce the rectal dose either by using ovoids with a rectal shield or by a reduction in external beam dose. Otherwise, an ovoid application is not indicated to reduce rectal complications from small sized, radiosensitive tumors after the external beam radiotherapy. Tumor response after external beam radiotherapy is valued for prediction of local control and planning of intracavitary irradiation. Computed tomography (CT) and magnetic resonance (MR) imaging are useful when planning brachytherapy [19,24,25].

In conclusion, brachytherapy without ovoids was performed on patients with a small vagina. The ovoids did not always contribute to local control, but led to rectal complications, especially for small-sized and/or well-responding tumors. The incremental

Table 5 Factors related to local control of stages III&IV cervical cancers.

Factors	Class	p value by Log-rank	p value by Cox hazard
Age	<65:≧65	NS	NS
KI	<80:≧80	NS	NS
Tumor size	<5cm:≧5	0.055	0.056
Adenopathy	-:+	0.057	NS
Ovoid applied	-:+	NS	NS
Chemotherapy	-:+	NS	NS
Dose at point P	<80Gy:≧80	NS	NS
Response	PR:NC	0.014	0.011

KI: Karnofsky index, PR: partial response, NC: no change
NS: not significant

Table 6 Rectal injury (grade≧1) according to applying applicators.

	Number of patients			
Group Applicators	I Tandem & Ovoids	II Tandem ± Ovoids	III Tandem alone	All (%)
Stages I+II	2/6	1/2	0/3	3/11 (27)
Stages III+IV	4/12	2/4	2/6	8/22 (36)
Total	6/18	3/6	2/9	11/33 (33)
(%)	(33)	(50)	(22)	
Grade 0	12	3	7	22 (67)
Grade 1	3	2	1	6 (18)
Grade 2	1	1	1	3 (9)
Grade 3	1	0	0	1 (3)
Grade 4	1	0	0	1 (3)

increase of the paramerial doses by ovoids might be indicated for patients with poor-responding large-sized tumors, but careful planning must be paid to the rectal dose. The optimization of brachytherapy was based on the patients' anatomy, tumor response, and tumor size.

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