

## Permanent interstitial re-irradiation with Au-198 seeds in patients with post-radiation locally recurrent uterine carcinoma

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This study sought to analyze the outcome of patients with post-treatment locally recurrent uterine carcinoma treated with Au-198 seed permanent interstitial re-irradiation (Au-198 IRI). A retrospective review of the data of 15 patients with post-treatment locally recurrent uterine carcinoma treated with Au-198 IRI between 1991 and 2009 was performed to evaluate the disease response, local control, overall survival and complication rates. All the patients had received definitive radiation therapy or surgery as the initial treatment. None were judged as being suitable candidates for surgical treatment, and were referred for Au-198 IRI. Au-198 IRI was performed for the vaginal wall in 8 patients, vaginal stump in 4 patients, vulva in 2 patients, and cervix in 1 patient. The median tumor volume was 1.3 cm<sup>3</sup> (range, 0.4–6.9), the median treated volume was 6.3 cm<sup>3</sup> (range, 1.8–11), and the median prescribed dose was 76 Gy (range, 68–90). At a median follow-up duration of 19 months (range, 4.3–146.9), 13 of 15 patients (87%) showed complete responses after Au-198 IRI, although 10 of these 13 patients (77%) developed repeat central recurrence again between 2.5 and 49.7 months after the Au-198 IRI (median, 12.5 months). The overall 2-year local control rate and 2-year overall survival rate in the 15 patients were 33% and 64%, respectively. Two (13%) of the 15 patients experienced late complications that were more severe than Grade III. As a result, Au-198 IRI is considered to be one of the salvage treatment modalities with tolerable complications for inoperable centrally recurrent uterine carcinoma.

**Keywords:** uterine carcinoma; brachytherapy; local recurrence; Au-198 seed permanent interstitial re-irradiation

### INTRODUCTION

Radiotherapy has been used as a useful treatment modality for uterine carcinoma. Combined treatment with external-beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) has been established as curative radiotherapy for Stage I, II and III/IV uterine cervical carcinoma, and the 5-year overall survival rates of patients with the aforementioned stages of the disease treated by curative radiotherapy have been reported to be 88–93.5, 69–77.0 and 10–60.3%, respectively [1–4].

In addition, EBRT with or without ICBT, or ICBT alone, has been used as adjuvant postoperative radiotherapy for cases of uterine cervical carcinoma and endometrial

carcinoma, and as a salvage treatment for relapse after surgery [5–8].

However, there is no consensus about salvage therapy for locally recurrent uterine carcinoma within previously irradiated areas. Although pelvic exenteration may be considered as a curative option for patients with central recurrence, the indications for this procedure are limited, and the procedure is associated with an elevated risk of critical complications according to the extent of treatment, and a reduced quality of life (QOL) [9–13]. For patients who are unwilling or medically unable to undergo salvage surgery, few potentially salvage treatment options remain.

At our institution, Au-198 IRI has been employed for salvage or supportive treatment of locally recurrent uterine

carcinoma after radiotherapy since 1979; there are about 30 patients each year who are referred for high-dose-rate (HDR) ICBT for primary cervical carcinoma or relapse after surgery. Only one or two of these 30 patients were included as candidates for Au-198 IRI. In this article, we present the results of evaluation of this treatment and of the post-treatment QOL.

## MATERIALS AND METHODS

### Patient characteristics

Between August 1991 and October 2009, 15 patients with post-treatment locally recurrent uterine carcinomas were treated with Au-198 IRI. The median age of the patients at the time of the Au-198 IRI was 65 years (range, 38–84). The primary tumor was carcinoma of the cervix in 12 patients and endometrial carcinoma in the remaining 3 patients. All of the recurrent tumors were local and located in the central region of the previously irradiated area, and were histopathologically proven to be squamous cell carcinoma in 11 patients and adenocarcinoma in 4 patients.

Distant metastasis was seen in 3 patients (in the lung in one patient, in the lung and thoracic vertebrae in another patient, and in the paraaortic lymph node in the third patient); the data for these patients were also included in this study, because it was considered that the distant metastases were not immediately interfering with the patients' lives, and that local control could be potentially expected to affect the QOL.

All of the patients had received some form of radiation therapy previously (Table 1); 9 of the 15 patients had received definitive radiotherapy (EBRT: 49.8–51.2 Gy/23–28 fractions; median, 50.4 Gy/26 fractions, and HDR-ICBT: 18–36 Gy/3–6 fractions; median, 24 Gy/4 fractions) with or without chemotherapy as initial treatment, and one of these patients had also undergone an additional surgery after definitive radiotherapy. As a result, 8 of the 9 patients were treated with Au-198 IRI for the first recurrence, and the remaining one underwent surgery for the first recurrence and Au-198 IRI for the second recurrence.

Of the 15 patients, 6 had undergone radical hysterectomy as the initial treatment. After surgery, 3 of these 6 patients had received postoperative EBRT, and the remaining 3 had undergone HDR-ICBT and/or EBRT. As a result, one of the 6 patients was treated with Au-198 IRI for the first recurrence, 4 received Au-198 IRI for the second recurrence, and the remaining 1 patient underwent Au-198 IRI for the third recurrence. Only 1 patient (No. 12 in Table 1) had received chemotherapy as salvage treatment for the second recurrence, and this patient was referred for Au-198 IRI for the rest of the recurrent tumor.

### Treatment

After a complete work-up for staging of the disease, including plain chest radiography and computed tomography

and/or magnetic resonance imaging of the abdomen and pelvis, Au-198 IRI was administered to all 15 patients. To evaluate the depth of the tumor, imaging methods such as ultrasound and/or computed tomography and/or magnetic resonance imaging were used.

Au-198 seeds are small granules measuring 0.8 mm in diameter and 2.5 mm in length, covered with platinum; the half-life is 2.7 days, and the gamma ray energy, 0.412 MeV. A seed dose of 80 Gy appears to be comparable to a radium implant dose of 70 Gy for 7 days, since in the case of seeds, the initial 7-day dose corresponds to 83% of the total nuclear decay.

The treatment volume with Au-198 IRI was set so as to have a margin of 2–5mm around the recurrent tumor, and the dosage was determined according to the dosage system described by Paterson-Parker. Au-198 seeds were implanted to a depth of  $\leq 7$ mm in the case of single plane implantations, and a depth of  $> 7$ mm in the case of spherical implantations, under local anesthesia. The total decay dose ranged from 68–90 Gy (median; 76 Gy).

### Follow-up and analysis

All patients were instructed about a regular follow-up schedule for the gynecologic physical examination and cytology. Local failure after Au-198 IRI was defined as histopathologically proven disease recurrence within or immediately adjacent to the treated area, based on biopsy. Survival analysis was performed using the Kaplan-Meier method, and the relationships between the survival rate and the clinical and treatment factors were compared using a log-rank test. A *P*-value of  $< 0.05$  was considered to indicate a statistically significant difference.

## RESULTS

Au-198 IRI was performed for disease in the vaginal wall in 8 patients, in the vaginal stump in 4 patients, in the vulva in 2 patients, and in the cervix in 1 patient. The median thickness of the tumor was 1 cm (range, 0.5–2), and the median tumor volume was 1.3 cm<sup>3</sup> (range, 0.4–6.9). A median of 11 Au-198 seeds (range, 8–18) with a median activity of 4.77 mCi/seed (range, 3.77–5.27) was implanted (Fig. 1), permanently, at a median prescription dose of 76 Gy (range, 68–90). Only 1 patient (No. 5 in Table 1) was administered EBRT (30 Gy/12 fractions) before the Au-198 IRI, as she had not received EBRT previously, the recurrent tumor was in the vulva, and the tumor volume was comparatively large. The median follow-up duration was 18.8 months (range, 4.3–146.9) from the date of implantation of the Au-198 seeds.

### Central recurrence-free survival (local control)

Of the 15 patients, 13 (87%) showed complete response to the Au-198 IRI, although 10 of these 13 patients (77%) developed local recurrence again between 2.5 and 49.7

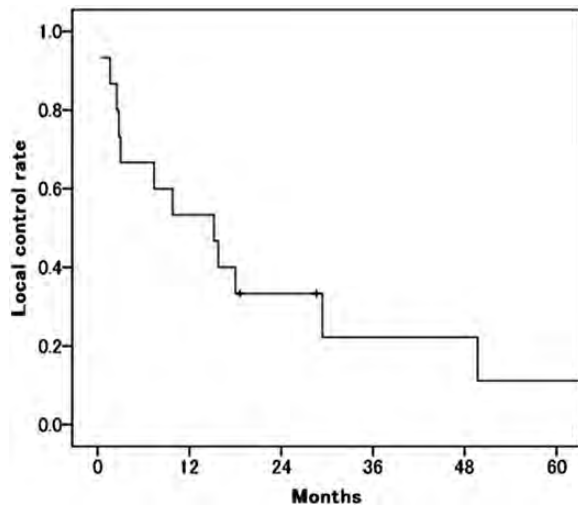
**Table 1.** Patient characteristics, prior radiotherapy, Au-198 IRI and treatment results

No.	Age	Primary site	Initial Stage	Pathology	Prior treatment (site of recurrence)	Au-198 IRI					Treatment results		
						Site of implantation	Interval (year)	Tumor volume (cm <sup>3</sup> )/Tumor thickness (cm)	Number of seeds	Treatment techniques	IRI dose (Gy)	Local control (months)	Late complications
1	42	Cervix	IIIb	Sq. cell	PS + EBRT → (Vaginal wall) → HDR-ICBT → (Vaginal wall) → HDR-ICBT	Vulva	0.14	6.9/2	18	Spherical	74.1	0.43	Mucositis (Grade II)
2	64	Cervix	IIIb	Sq. cell	EBRT + ICBT	Vaginal wall	0.53	0.5/1	12	Spherical	76	2.5	None
3	45	Cervix	IIIb	Sq. cell	EBRT + ICBT	Vaginal wall	1.55	0.5/1	10	Spherical	84	15.23	None
4	72	Cervix	IIIa	Sq. cell	EBRT + ICBT	Vaginal wall	0.04	0.4/0.5	10	Single plane	80	NR	Rectovaginal fistula (Grade IV)
5	70	Corpus	IIIc	Adeno	PS → (Vaginal stump) → HDR-ICBT	Vulva	2.92	2.9/1.6	12	Spherical	74	7.37	None
6	70	Cervix	Ib	Adeno	PS + ERBT + CT → (Vaginal stump) → HDR-ICBT	Vaginal stump	0.27	1/0.5	8	Single plane	78	49.7	Proctitis (Grade III), cystitis (Grade II)
7	77	Corpus	Iib	Adeno	PS + CT → (Vaginal stump) → HDR-ICBT	Vaginal stump	0.68	0.6/0.5	10	Single plane	74	29.4	None
8	54	Corpus	IVb	Sq. cell	EBRT + ICBT + CT + PS	Vaginal wall	0.2	2.1/1	11	Spherical	82	1.63	None
9	60	Cervix	IVa	Adeno	EBRT + ICBT + CT	Cervix	0.19	1.2/1	10	Spherical	81.5	18.03	None
10	67	Cervix	Ila	Sq. cell	EBRT + ICBT → (Cervix) → PS	Vaginal stump	2.91	1.8/1.5	15	Spherical	69	NR	None
11	70	Cervix	Iib	Sq. cell	EBRT + ICBT + CT	Vaginal wall	0.25	3.9/1	15	Spherical	68	15.77	None
12	44	Cervix	Iib	Sq. cell	PS → (Vaginal wall) → EBRT + CT	Vaginal wall	0.98	2.1/1	15	Spherical	72	9.8	None
13	65	Cervix	IIIb	Sq. cell	EBRT + ICBT + CT	Vaginal wall	0.75	2.1/0.5	16	Single plane	73	3	None
14	84	Cervix	IIIb	Sq. cell	EBRT + ICBT + CT	Vaginal wall	0.91	1/0.5	9	Single plane	90	NR	None
15	38	Cervix	IIIb	Sq. cell	PS + EBRT	Vaginal stump	0.32	1.3/0.5	11	Single plane	81	2.77	None

IRI = interstitial re-irradiation, Sq. cell = squamous cell carcinoma, Adeno = adenocarcinoma, PS = pelvic surgery, EBRT = external-beam radiotherapy, HDR-ICBT = high-dose-rate intra-cavitary brachytherapy, CT = chemotherapy, NR = no recurrence.



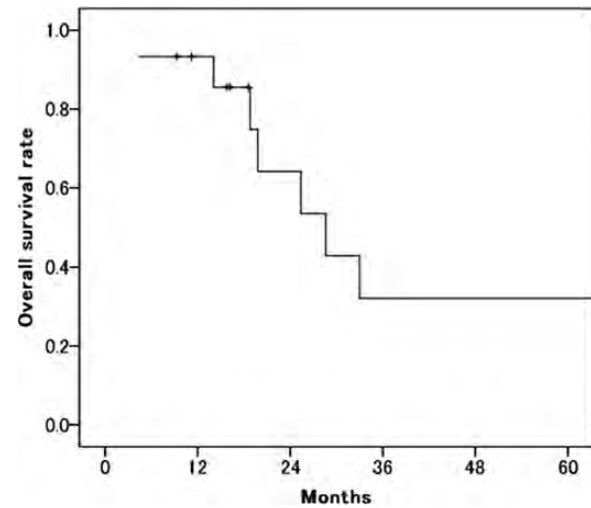
**Fig. 1.** Orthogonal radiograph obtained post- Au-198 seeds implantation to the vaginal wall.



**Fig. 2.** Kaplan-Meier plot of local control rate after Au-198 IRI.

months after the Au-198 IRI (median, 12.5 months). A poor response was observed in the remaining 2 patients (Patients No.1 and No.8 in Table 1). The 2-year central recurrence-free survival rate in the 15 patients was 33% (Fig. 2).

The central recurrence-free survival rate of the patients who were  $\geq 65$  years old was significantly better than that of the patients who were  $< 65$  years old (hazard ratio [HR] = 0.2,  $P = 0.006$ ). Moreover, the central recurrence-free survival rate of the patients with a tumor volume of  $< 2 \text{ cm}^3$  was significantly better than that of the patients with a tumor volume of  $\geq 2 \text{ cm}^3$  (HR = 0.2,  $P = 0.009$ ). No other factors (primary site, pathology, site of recurrence, interval from previous radiation therapy to Au-198 IRI, number of times of recurrence, previous irradiation dose [biological effective dose using an  $\alpha/\beta$  ratio of 10 {BED<sub>10</sub>}] to the central region, Au-198 IRI dose) had any significant influence on the central recurrence-free survival rate.



**Fig. 3.** Kaplan-Meier plot of overall survival rate after Au-198 IRI.

### Overall survival

The overall 2-year survival rate of the 15 patients was 64% (Fig. 3). Three patients had no local failure. Of these, one patient had a repeat central recurrence (vulva) and received additional Au-198 IRI, however, she died; one was alive with distant metastasis; the third patient died of a complication. The median survival time of these 3 patients was 65 months (range, 18.6–146.9).

Twelve patients experienced local recurrence or showed a poor response to Au-198 IRI; of these, 7 patients died of local recurrence and/or metastatic disease, and 5 patients remained alive with local recurrence and/or metastatic disease. The median recurrence-free period of the 10 patients who developed a local recurrence was 12.5 months (range, 2.5–49.7).

A significant relationship was observed between the overall survival rate and the site of recurrence, tumor volume, and local response to Au-198 IRI. The overall survival rates of the patients with recurrence in the vagina, tumor volume of  $< 2 \text{ cm}^3$ , or good local response to Au-198 IRI were significantly higher than those of the other patients; (HR = 0.1,  $P = 0.02$ , site of recurrence; HR = 0.2,  $P = 0.03$ , tumor volume; HR = 0.1,  $P = 0.02$ , local response to Au-198 IRI). Age, primary site, pathology, interval from previous radiation therapy to Au-198 IRI, number of times of recurrence, previous irradiation dose (BED<sub>10</sub>), Au-198 IRI dose, and M-stage had no significant influence on the overall survival.

### Complication

Rectovaginal fistula (Grade IV) occurred in one patient 14 months after the Au-198 IRI in the vaginal wall (Patient No. 4 in Table 1). She underwent surgery, but died of sepsis. Proctitis (Grade III) and cystitis (Grade II) occurred in another patient (Patient No. 6 in Table 1) 22 months

after the Au-198 IRI, and both were managed conservatively. None of the other patients developed any late complications that were more severe than Grade III.

## DISCUSSION

Management of uterine carcinoma often includes radiotherapy, either as primary or adjuvant treatment. However, recurrent carcinomas within previously irradiated areas present considerable management difficulties.

Pelvic exenteration is known as the only potentially curative approach for patients with central recurrence with a history of having undergone radiotherapy. Kasamatsu *et al.* [14] reported that the 5-year survival rate after exenteration was 36% and that the procedure-related mortality was 6%. While acknowledging the usefulness of the procedure as the only means for saving the patient's life, they cautioned that patients should be selected after careful preoperative assessment, because pelvic exenteration is a highly traumatic operation. Therefore, for patients who are unwilling or medically unable to undergo salvage surgery, few potentially curative treatment options remain.

The response to chemotherapy using cisplatin, which has been considered the most active single agent for recurrent cervical cancer, is generally low, varying from 17% to 38% [15]. Mabuchi *et al.* [16] reviewed the data of patients that were treated with carboplatin and paclitaxel for recurrent cervical carcinoma after radiotherapy with curative intent and demonstrated that the paclitaxel-carboplatin regimen yielded superior progression-free survival compared to a platinum-based regimen. However, the median progression-free survival was only 7 months.

Success of re-irradiation for recurrent gynecologic cancer has also been shown to be limited by the significant morbidity, and only marginal success [17–19]. In stringently selected patients, however, a few studies have demonstrated some success with re-irradiation using permanent interstitial brachytherapy (ISBT) [20, 21]. Iodine-125, palladium-103, or Au-198 has been used for permanent ISBT, and iridium (Ir)-192 or cesium-137 for temporary ISBT. A list of the relevant articles is shown in Table 2. Badakh *et al.* [22] reported 22 patients with post-radiation recurrent cervical carcinomas treated by HDR-ISBT. The median survival was 9.2 months (range, 4.1–56.6). Four of the 22 patients (18%) developed Grade IV complications. Concerning the use of CT image-based Ir-192 HDR-ISBT for locally advanced uterine cervical carcinomas, Saitoh *et al.* [23] reported that the dose distribution of image-based ISBT was improved compared with that of typical ICBT, and that HDR-ISBT twice a day for 2 to 5 days was not as invasive. Both Ir-192 HDR-ISBT and Au-198 IRI can deliver tumor-icidal doses to small tumor volumes without giving substantial additional doses to uninvolved areas.

At our institution, Au-198 seeds have been used for re-irradiation in selected patients with locally recurrent uterine carcinoma, because the seeds can be implanted so as to obtain localization of the high-dose area on the tumor itself. Moreover, since Au-198 IRI is relatively simple to perform and is well-tolerated by patients, it can be considered even for patients in poor general condition. We usually selected Au-198 IRI for small, thin tumors, however, there were 3 patients in whom the tumor was more than 1.5 cm in thickness. All of these 3 patients had received HDR-ICBT previously. Reports from previous studies include local control rates of 46 and 63%, and survival rates of 53 and 62% [20, 21]. The local control rate in our study was a little lower than in these reports, and we suppose that the primary cause of treatment failure may be the insufficient diagnosis of the extent of the recurrent tumor. However, it may not be reasonable to compare the data from these reports with our results, because these earlier reports included second primary malignancies and various other gynecologic malignancies. Randall *et al.* [20] reported that the pathology, tumor volume, implant dose, and site of recurrence were significantly related to the local control rate in his study. While Puthawala *et al.* [17] treated only patients with recurrent tumors measuring <5 cm in diameter, Brabham *et al.* [21] treated patients with tumors <1 cm in thickness and median volume of 3.3 cm<sup>3</sup>.

In our study, the size of the recurrent tumor volume was significantly related to the local control rate and overall survival rate, and the initial local response also significantly affected the overall survival rate. Although the difference was not statistically significant, the local control rate in the patients with recurrence in the vagina was better than that in the patients with recurrence in other regions (HR = 0.4,  $P = 0.2$ ), and the overall survival rate of the former group of patients was significantly better than that of the latter patients. Thus, small recurrences in the vagina may be the most suitable condition for this treatment. Puthawala *et al.* [17] mentioned that the most significant prognostic factor relative to re-irradiation is the disease-free interval. In our results, however, the local control rate and the overall survival rate of the patients with an interval to recurrence of >1 year was similar to the values in the patients with interval to recurrence of <1 year (HR = 0.9,  $P = 0.8$ , local control; HR = 1.4,  $P = 0.7$ , overall survival).

The previously reported occurrence rate of serious complications is 5.3–35%, and our result was consistent with these reports. Russell *et al.* [18] found that patients with symptomatic radiation sequelae from their first course of irradiation developed major complications of retreatment more often. Sharma *et al.* [19] emphasized that there was no significant relationship between the tumor volume and the incidence of major complications, however in their study, the volume of the tumors in all the patients was large, >10 cm<sup>3</sup>, except in one case. We could not identify

**Table 2.** Review of articles

Author (Reference No.)	<i>n</i>	Disease ( <i>n</i> )	Previous treatment	Re-irradiation	Local control rate	Survival rate	Complications ( <i>n</i> )
Puthawala [17]	40	cervix (14), endometrium (5), vagina (5), ovaries (2), rectosigmoid colon (10), prostate (2), urinary bladder (2)	Surgery + EBRT	Interstitial BT (Ir-192, I-125) + exploratory laparotomy	67% at 2 years	33% at 2 years	soft tissue necrosis (2), rectovaginal fistula (1), vesicovaginal & rectovaginal fistula (1), enterovaginal fistula (1), rectal stricture (1)
Russell [18]	25	vagina (10), vulva (3), cervix (7), endometrium (5)	EBRT and/or BT + Surgery	EBRT + interstitial BT (Cs-137, Ir-192, I-125)	56%	44%	proctitis (2), cystitis (1), aseptic necrosis of femoral neck (2), small bowel obstruction requiring surgery (1), rectovaginal fistula (1)
Sharma [19]	20	cervix (11), endometrium(6), ovaries(1), vagina(1), vulva(1), uterine sarcoma (1)	EBRT and/or BT + Surgery	Interstitial BT (I-125)	75%	35%	vesicovaginal fistula (4), rectovaginal fistula (2), rectal fibrosis (1)
Randall [20]	13	cervix (4), endometrium (6), new primary: vagina (3)	EBRT and/or BT	Interstitial BT (Ir-192, Au-198, Pa-103)	46%	62%	rectovaginal fistula (1)
Brabham [21]	19	cervix (6), uterus (5), vagina (4), vulva (3), urethra (1)	EBRT and/or BT	Interstitial BT (Au-198)	63%	53%	vaginal mucositis (1)
Guckenberger [24]	19	cervix (12), endometrium (7)	Surgery ± BT and/ or EBRT + BT	SBRT + EBRT ± BT	81% at 3 years	34% at 3 years	sigmoidovaginal fistula (1), rectovaginal fistula (1), small bowel ileus (1)
Present study	15	cervix (12), endometrium (3)	EBRT + BT Surgery + EBRT	Interstitial BT (Au-198)	33% at 2 years	64% at 2 years	rectovaginal fistula (1), proctitis and cystitis (1)

EBRT = external beam radiotherapy, BT = brachytherapy, SBRT = stereotactic body radiotherapy

any factors that significantly influenced the risk of major complications in our present study.

Recently, there have been a few reports of stereotactic body radiotherapy (SBRT) for primary or recurrent gynecological cancer [24–26]. In the largest study, Guckenberger *et al.* [24] reported 19 patients with recurrent gynecologic carcinoma treated with SBRT and EBRT with or without brachytherapy (BT) (Table 2); the median size of the recurrent tumor was 4.5 cm (range, 1.5–6.5 cm). In that report, the 3-year local control rate was 81% with a median follow-up of 22 months. They concluded that SBRT may be appropriate, even for patients with a large recurrent tumor.

Our study was limited by its retrospective nature, and relatively small sample size from a single institution. There have been few reports of analysis of data for more than 20 patients. In addition, because the toxicities were retrospectively determined, it is not certain that all complications were captured. Further follow-up is needed to fully assess the long-term complications. Au-198 IRI is only applicable to a very limited subset of patients who cannot be treated by any other treatment modality. Combination with appropriate chemotherapy may be selected to improve the prognosis. Nonetheless, in our opinion, our study results indicate the feasibility of Au-198 IRI for patients with recurrent uterine carcinoma in the central region.

## CONCLUSION

In conclusion, Au-198 IRI is one of the less invasive salvage treatment modalities, with tolerable complications, for locally recurrent uterine carcinoma in patients in poor general condition with a previous history of various types of radiotherapy, and may be the most appropriate treatment for recurrent tumors of small size (tumor volume of <2 cm<sup>3</sup>) located in the vaginal wall or stump.

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