

# Hysterectomy for Recurrent/Residual Cervical Cancer Following Definitive Radiotherapy

TADAHARU NAKASONE, YUSUKE TAIRA, YUKO SHIMOJI, YOSHIHISA ARAKAKI,  
TOMOKO NAKAMOTO, TAKUMA OYAMA, WATARU KUDAKA, ITOMI KANESHIMA,  
KUMIKO NISHIHARA, KEIKO MEKARU and YOICHI AOKI

*Department of Obstetrics and Gynecology, Graduate School of Medicine,  
University of the Ryukyus, Okinawa, Japan*

**Abstract.** *Background/Aim:* Radical hysterectomy has been used for local recurrent or persistent (LR) cervical cancer after radiotherapy (RT), but the rate of serious complications is high and tolerance is low. This study determined the efficacy, safety, and prognostic factors of adjuvant simple hysterectomy in LR cervical cancer post-RT. *Patients and Methods:* A total of 21 patients who underwent hysterectomy for LR cervical cancer post-RT in our Department between May 2007 and September 2018 were included in the study. Primary, definitive RT was performed. Histological response by definitive RT in the extirpated uterus was classified on the basis of histological response criteria: effect (Ef) 0-3. *Results:* The 5-year overall survival (OS) and disease-free survival (DFS) rates were 51.9% and 50.1%, respectively. Ef 1 was significantly associated with poorer prognosis compared to Ef 2 or Ef 3. *Conclusion:* Adjuvant hysterectomy could be a treatment of choice for LR cervical cancer post-RT.

Radiotherapy (RT) is an effective treatment for cervical cancer, and concurrent chemoradiotherapy (CCRT) is the standard treatment for locally advanced cervical cancer. However, residual (1-4) or subsequent local recurrence is 10-30%, and these cases have poor prognosis. In Japan, best supportive care (BSC), chemotherapy for symptom relief, and pelvic exenteration or hysterectomy for central recurrence are the options for recurrence inside the radiation field of recurrence (5). Resection of local lesions alone might

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*Correspondence to:* Tadaharu Nakasone, Department of Obstetrics and Gynecology, Graduate School of Medicine, University of the Ryukyus, 207 Uehara Nishihara, Okinawa 903-0215, Japan. Tel: +81 988951177, Fax: +81 988951426, e-mail: miamiamia1229@gmail.com

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improve prognosis, but results are controversial. Radical hysterectomy has been used for local recurrent or residual (LR) cervical cancer post-RT, but the rate of serious complications is high and tolerance is low (6, 7). Several studies have reported the usefulness of salvage simple total hysterectomy, and efforts have been made to reduce complications (8, 9). These studies have shown a 5-year overall survival (OS) of 49%-72% (6-8) and a 5-year disease-free survival (DFS) of 90% (9), with the rate of complications being 42%-44% in radical hysterectomy (6, 7), and 0%-14% in simple hysterectomy (8, 9).

This study determined the efficacy, safety, and prognostic factors of adjuvant simple hysterectomy in LR cervical cancer post-RT.

## Patients and Methods

We included 21 patients who underwent hysterectomy for LR cervical cancer post-RT in our department between May 2007 and September 2018. We retrospectively reviewed their medical records for their background, clinicopathological factors, complications, and prognosis. Primary, definitive RT was performed as described previously (10). Briefly, a 50 Gy dose of whole-pelvic external beam RT was delivered in 25 fractions. A center shield 4 cm wide at the midline was used after delivery of a 40 Gy dose of RT. High-dose-rate intracavitary brachytherapy (HDR-ICBT) was delivered once per week at a fractional dose of 6 Gy one to three times at point A (total dose of 6-18 Gy). The cumulative linear quadratic equivalent dose (EQD2) was 62-65 Gy prescribed at point A (10). The CCRT regimen included 40 mg/m<sup>2</sup> of cisplatin per week for patients with squamous cell carcinoma (SCC) (10) and 50 mg/m<sup>2</sup> of cisplatin every 3 weeks and 50 mg/m<sup>2</sup> paclitaxel per week for patients with non-SCC (11).

Follow-up examinations were performed every month until 3 months post-RT or post-CCRT. LR cervical cancer was diagnosed on the basis of biopsies with pathological assessment and computed tomography (CT) scans, positron emission tomography (PET), or magnetic resonance imaging (MRI) 3 months post-RT. Patients with residual viable cancer in the cervix without distant metastasis or obvious lymph node metastasis underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node sampling. Ureteral stents were placed in all patients preoperatively.

Table I. *Histological response classification.*

Effect	Histological findings
0	No morphological change such as degeneration or necrosis is observed in cancer cells and cancer tissue
1	1/3 or more of cancer cells survive
2	Less than 1/3 cancer cells survive
3	Cancer cells are not recognized or unable to survive even if they remain

Table II. *Patient characteristics.*

Variables	
Median age (range)	53 (31-84) years
Histological subtype	
Squamous cell carcinoma	14
Adenocarcinoma	7
FIGO stage	
IB2	11
IIB	8
IIIB	2
Persistence or recurrence	
Persistence	17
Recurrence	4
Median tumor diameter at hysterectomy (range)	10 (0-51) mm
Primary treatment	
P-CCRT	10
TP-CCRT	6
TP-NAC, TP-EFCCRT	2
Others	3

FIGO: The International Federation of Gynecology and Obstetrics; P-CCRT: concurrent chemoradiotherapy with cisplatin; TP-CCRT: concurrent chemoradiotherapy with paclitaxel and cisplatin; TP-NAC: neoadjuvant chemotherapy with paclitaxel and cisplatin; TP-EFCCRT: extended field concurrent chemoradiotherapy with paclitaxel and cisplatin.

Histological response by definitive RT in the extirpated uterus was classified on the basis of histological response criteria, as follows: effect (Ef) 0: no morphological changes, such as degeneration and necrosis, observed in cancer cells and cancer tissues; Ef 1: cancer cells that can survive in  $\geq 1/3$  of cancers; Ef 2: cancer cells that can survive in  $< 1/3$  of cancers; Ef 3: cancer cells not recognized or thought to be unable to survive, even if present (Table I) (12).

All statistical analyses were performed using JMP software version 15.0 (SAS Institute, Cary, NC, USA). The Kaplan-Meier method and the log-rank test were used to assess the survival rate.  $p < 0.05$  was considered statistically significant.

All the patients provided their written informed consent regarding the treatment. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or

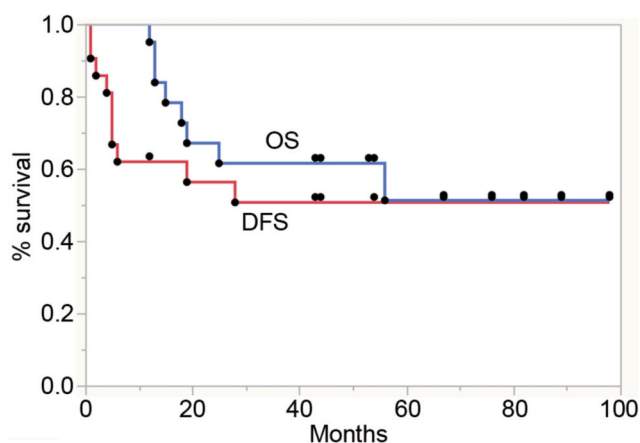


Figure 1. *Kaplan-Meier curves for OS and DFS in the study population (N=21). The 5-year OS and DFS rates were 51.9% and 50.1%, respectively. OS: Overall survival; DFS: disease-free survival.*

comparable ethical standards. This retrospective study was approved by the Institutional Review Board of our university (#1375 in Dec 10, 2018).

## Results

Table II shows the patients' characteristics. The patients' median age was 55 years (range=31-84 years). The International Federation of Gynecology and Obstetrics (FIGO) stage distribution was as follows: 11 patients in stage IB2, 8 in stage IIB, and 2 in stage IIIB. In addition, 14 patients had SCC and 7 had adenocarcinoma. Persistent lesion was observed in 17 patients and recurrence in 4 patients. The median tumor diameter at hysterectomy was 10 mm (range=0-51 mm). Serum SCC antigen was re-elevated in 5 patients (23.8%) at hysterectomy. The median total surgery time was 182 min (range=121-333 min), and the median total blood loss was 308 mL (range=62-685 ml). Perioperative complications included intraoperative bladder injury and postoperative pelvic abscess in 1 patient each (9.5%). Postoperative adjuvant chemotherapy was administered to 3 patients (14.2%) who had positive lymph nodes and close margins. Lymph node resection was performed in 5 patients with enlarged pelvic lymph nodes, revealing positive metastasis; 4 of these patients died of the disease.

The median OS and DFS were 43 months (range=9-98 months) and 19 months (range=1-98 months), respectively. The 5-year OS and DFS rates were 51.9% and 50.1%, respectively (Figure 1). With regard to prognostic factors, Ef 1 was significantly associated with poorer prognosis compared to Ef 2 or Ef 3. The 5-year OS was 88.9% in patients with Ef 2 or Ef 3 and 22.5% in patients with Ef 1 ( $p=0.0129$ ), while the 5-year DFS was 78.8% in patients with Ef 2 or Ef 3 and 24.2% in patients with Ef 1 ( $p=0.0172$ ) (Figure 2). Lymphovascular

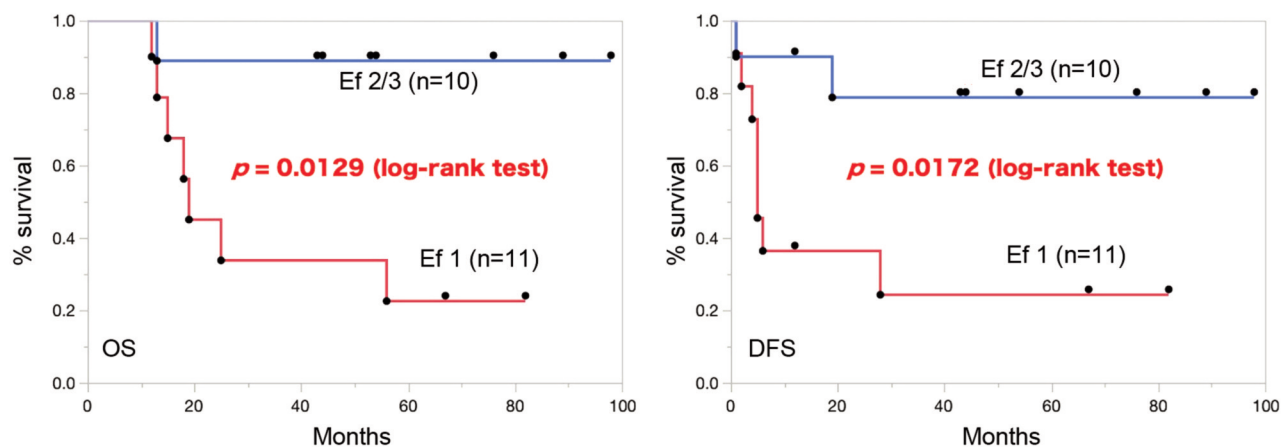


Figure 2. Kaplan-Meier curves for OS and DFS according to histological response (Ef 1 vs. Ef 2 or Ef 3). The 5-year OS was 88.9% in Ef 2 or Ef 3 patients and 22.5% in Ef 1 patients. The 5-year DFS was 78.8% in Ef 2 or Ef 3 patients and 24.2% in Ef 1 patients.

Table III. Univariate analyses for overall survival and disease-free survival.

Variables	No.	5-y overall survival (%)	p-Value	5-y disease-free survival (%)	p-Value
Age (years)			0.0876		0.483
≥56	10	77.8		60.0	
<56	11	22.2		40.9	
Histological subtype			0.591		0.693
Squamous cell carcinoma	14	63.6		55.1	
Adenocarcinoma	7	38.1		42.9	
FIGO stage			0.918		0.931
IB2	11	62.5		51.0	
IIB	8	50.0		50.0	
IIIB	2	0		50.0	
Recurrence or persistence			0.542		0.778
Recurrence	4	66.7		50.0	
Persistence	17	52.1		51.8	
Tumor diameter at surgery			0.884		0.928
≥20 mm	8	46.9		50.0	
<20 mm	13	61.1		51.3	
LVSI			0.0368		0.0570
Yes	10	26.7		30.0	
No	11	90.0		70.1	
Parametrial extension			0.565		0.721
Yes	3	66.7		66.7	
No	18	45.4		47.5	
LN metastasis			0.195		0.0836
Yes	5	20.0		20.0	
No	16	70.0		61.1	
Surgical margin			0.414		0.283
Positive	1	0		0	
Negative	20	54.3		53.2	
Histological response			0.0129		0.0172
Ef 1	11	22.5		24.2	
Ef 2/3	10	88.9		78.8	
Serum SCC			0.0717		0.113
Elevated	5	0		0	
Normal	16	66.7		61.9	

FIGO: The International Federation of Gynecology and Obstetrics; RT: radiotherapy; LVSI: lymphovascular involvement; LN: lymph node.

space invasion (LVSI) was significantly associated with poor OS ( $p=0.0368$ ). In addition, age, FIGO stage, histological subtype, recurrence or persistence at hysterectomy, tumor size at hysterectomy, parametrial extension, lymph node metastasis, positive surgical margin, and elevated serum SCC were not significant prognostic factors (Table III). Although multivariate analysis showed no independent prognostic factor, univariate analysis showed that only histological response was significant in both OS and DFS.

Posthysterectomy, 10 patients had recurrence between 1 and 28 months, of which 8 had recurrence within 6 months. Locoregional recurrence occurred in 5 patients (pelvic lymph nodes, ureters, vaginal stumps), local and distant recurrence in 1 patient, and distant recurrence in 4 patients (Table IV). One patient showed lung metastasis 19 months post-hysterectomy and underwent video-assisted thoracic surgery (VATS), with no evidence of disease (NED).

## Discussion

Hysterectomy for LR cervical cancer post-RT or post-CCRT seems effective and tolerable. By 3 months post-RT, local residuals should be fully evaluated and hysterectomy considered. Previous studies have reported a 5-year OS of 49%-72% (6-8), which is consistent with our study. In addition, complications have been reported to develop in 42%-44% of patients who underwent radical hysterectomy (6, 7) but only in 0%-14% of patients who underwent simple hysterectomy (8, 9). Urinary tract injuries, fistulas, and bladder dysfunction are reported most as complications due to radical hysterectomy. Because the prognosis of patients treated with radical hysterectomy and simple hysterectomy is comparable, simple hysterectomy seems better because of reduced complications. Therefore, adjuvant hysterectomy post-RT is considered a treatment of choice.

Histological response could be a good indicator for prognosis. There are no reports on histological response criteria in gynecological cancers. In pancreatic cancer, the prognostic importance of histological response has been demonstrated (12). A pathological complete response and <10% tumor remnants have been reported to have favorable prognosis in a neoadjuvant chemotherapy setting (12). Breast cancer guidelines also describe the therapeutic effects of neoadjuvant chemotherapy (13), and histological therapeutic effects are significantly related to prognosis. However, there are many different criteria, and methodological problems still remain (14-16). In cervical cancer, the residual tumor diameter (<2 cm) has been shown to be a significant prognostic factor for LR cervical cancer post-RT (6). In addition, Ota *et al.* have reported that the size of the persistent tumor at hysterectomy is important but the prognostic difference is not statistically significant (8). However, these two studies did not mention histological response. Many viable cancer cells would still

Table IV. Site of recurrence.

	Locoregional	Locoregional+distant	Distant
No.	5	1	4
Time to recurrence (months)	2, 4, 5, 6, 28	1	1, 5, 5, 19

remain in larger residual or recurrent tumors, which would be equivalent to Ef 1 in our study. Histological response shows significance for OS and DFS and seems to be important for prediction of prognosis.

Five patients with enlarged pelvic lymph nodes underwent removal of the lymph nodes, revealing positive nodes. Although positive node was not an independent prognostic factor in our study population, 4 of these patients died of the disease. Previous studies have demonstrated poor prognosis in patients with positive lymph nodes in residual disease post-RT (6-8), suggesting pelvic lymphadenectomy is not always necessary and rarely results in improved survival.

The significance of this study was that we analyzed patients who underwent hysterectomy for LR cervical cancer post-RT at a single institution. However, one of the limitations of this study was its retrospective nature, with a relatively small sample and selection bias. While we made all attempts to acquire complete and accurate data, recall bias and difficulty in data abstraction can affect retrospective chart reviews.

## Conclusion

Adjuvant hysterectomy could be a treatment of choice for LR cervical cancer post-RT. Histological response of cervical cancer is a good indicator that could help select patients who are most likely to benefit from adjuvant hysterectomy.

## Conflicts of Interest

The Authors declare that there are no conflicts of interest regarding the publication of this paper.

## Authors' Contributions

The work presented here was carried out in collaboration among all authors. TN and YA designed the methods, analyzed the data, interpreted the results, and wrote the manuscript. All Authors have read the manuscript, and approved this submission.

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