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Vesicovaginal/rectovaginal fistula formation and outcome of Stage IVA carcinoma of the cervix treated with radiotherapy

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Summary

Purpose: To review the morbidity and mortality of Stage IVA cervical cancer, with a particular focus on the incidence of fistulae. *Materials and Methods:* The authors retrospectively analyzed 30 patients with Stage IVA cervical cancer, treated with whole pelvic-external beam radiotherapy (WP-EBRT) and high-dose-rate intracavitary brachytherapy (HDR-ICBT). *Results:* Seven patients presented with vesicovaginal fistula at the time of cancer diagnosis and six developed a fistula during or after radiotherapy (RT). Fistula was diagnosed 0–41 months after cancer diagnosis. The patients with fistulae had a median survival of 32 months. Six patients are alive, four of whom have no evidence of recurrence, while two have persistent disease. The five-year overall survival (OS) was 14.9% in the patients with fistula and was 39.4% in the total series. On multivariate analysis, RT without HDR-ICBT was an independent prognostic factor. *Conclusion:* High rates of vesicovaginal fistulae were observed in Stage IVA cervical cancer. Interventions for vesicovaginal fistula to improve quality of life are very important.

Key words: Cervical cancer; Stage IVA; Radiotherapy; Chemoradiotherapy; Vesicovaginal fistula; Rectovaginal fistula.

Introduction

International Federation of Obstetrics and Gynecology (FIGO) Stage IVA cervical cancer is defined as a disease in which the tumor invades the mucosa of the bladder or the rectum [1]. It is a relatively rare condition, accounting for < 3% of all cervical neoplasms. In Japan, 2.2–3.5% of cases of invasive cervical cancer are Stage IVA. Five-year survival rates for patients treated between 2001 and 2008 for this stage of cancer had a range of 18.7–41.2% (http://plaza.umin.ac.jp/~jsog-go/). Patients with Stage IVA cervical cancer are sometimes found to have vesicovaginal and/or rectovaginal fistulae. Some are diagnosed before commencing treatment, while there are also reports of fistulae developing during or after radiotherapy (RT) in 4–47.8% of patients [2-7]. Fistulae are more common in Stage IVA than in other cervical cancer stages, implying that tumor extension itself, as well as treatment modalities, are important influences on fistula formation.

This study aimed to review the morbidity and mortality of Stage IVA carcinoma of the cervix in the present institution, with a particular focus on the incidence of fistulae.

Materials and Methods

The authors retrospectively analyzed 30 patients with Stage IVA cervical cancer who were treated with concurrent chemoradiotherapy (CCRT) or RT between 1995 and 2014 at the University of the Ryukyus Hospital, Japan. Stage IVA cervical cancer was diagnosed at the time of examination, cystoscopy, and proctoscopy. None of the patients had received prior treatment. All treatments were performed by gynecologic oncologists in conjunction with radiation oncologists. All patients provided written informed consent. Patient charts were reviewed for clinicopathological data. This retrospective study was approved by the Institutional Review Board of the present university.

The eligibility criteria for patients were as follows: 1) an Eastern Cooperative Oncology Group (ECOG) performance status of 2, 2) age range 20–70 years, 3) adequate hematological (WBC count, 3000–10,000/μl, hemoglobin, ≥ 9.0 g/dl, platelet count, ≥ 100,000/μl), hepatic (bilirubin level, ≤ 1.5 mg/dl and aspartate aminotransferase and alanine aminotransferase levels, ≤ 2.5 × the upper limit of normal), renal (creatinine clearance, ≥ 60 ml/minute), and cardiac function (normal electrocardiographic findings). Pelvic lymph node enlargement was defined as enlargement over a short-axis diameter of one cm assessed by pretreatment computed tomography (CT) or magnetic resonance imaging (MRI).

RT was performed as previously described in a study [8]. All patients were treated with anterior–posterior and posterior–anterior parallel–opposed ports or a four-field technique of whole pelvic-external beam radiotherapy (WP-EBRT). A 50-Gy dose of WP-EBRT was delivered in 25 fractions. A center shield (four-cm wide at the midline) was used in some patients after delivery of 40 Gy. High-dose-rate intracavitary brachytherapy (HDR-ICBT) was delivered once per week at a fractional dose of six Gy given one to three times at point A for total doses of six to 18 Gy. Boost EBRT of 6–20 Gy in one to four fractions was applied to the pelvic walls and/or nodal metastases (≥ ten mm in a short-axis diameter) for patients with nodular parametrial involvement. The concurrent chemoradiotherapy (CCRT) regimen consisted of cisplatin, 20 mg/m^2 for five days every three weeks [9] or 40 mg/m^2

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Table 1. — *Patient characteristics (n = 30).*

Characteristics	
Age (years), median (range)	60 (32-82)
Performance status	
0	12 (40%)
1	7 (23%)
2	11 (37%)
Body mass index (kg/m^2) , median (range)	21 (15-26)
Smoking	4 (13%)
Tumor size (mm), median (range)	70 (50-110)
Histological type	
Squamous cell carcinoma	27 (90%)
Adenocarcinoma/adenosquamous carcinoma	3 (10%)
Lymph node swelling	15 (50%)
Hydronephrosis	18 (60%)
Vaginal involvement	30 (100%)
Pelvic wall infiltration	29 (97%)
Bladder involvement	28 (93%)
Rectal involvement	6 (20%)
Serum SCC antigen (ng/ml), median (range)	61 (1.3-326)
Follow-up (Mo), median	25.5 (1-232)

Table 2. — *Treatment and fistula formation (n = 30).*

WP-EBRT alone, n	8
Median total dose, Gy (range)	50 (30-50)
WP-EBRT + ICBT, n	22
Median central pelvic dose, Gy (range)	50 (40-60)
Median pelvic side wall dose, Gy (range)	56 (50-70)
Median ICBT dose, Gy (range)	18 (6-18)
Center shield, n	9
CCRT	
No	13 (43%)
Yes	17 (57%)
Fistula formation	
VVF	10 (33%)
RVF	2 (7%)
VVF and RVF	1 (3%)

WP-EBRT: whole pelvic-external beam radiotherapy, ICBT: intracavitary brachytherapy, CCRT: concurrent chemoradiotherapy, VVF: vesicovaginal fistula, RVF: rectovaginal fistula.

weekly [10], administered concomitantly with RT. Follow-up examinations were conducted every month for the first year, every two months for the second year, and subsequently every three to six months thereafter.

Overall survival (OS) curves were estimated using the Kaplan–Meier method, and differences were tested by the log-rank test. The Cox proportional hazard model was used to perform multivariate analysis. A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics are presented in Table 1. The median age was 60 (range, 32–82) years, and the median follow-up period was 25.5 (range, 1–232) months. Squamous cell carcinoma was diagnosed in 27 patients and adenocarcinoma/adenosquamous carcinoma in the remaining three. Median tumor size was 70 (range, 50–110) mm. Twenty-eight patients (93%) had tumor extension into the bladder, four of whom had extension into the rectum as well. Three patients (10%) had only rectal involvement. Involvement of the pelvic side wall was present in 29 patients (97%). In 15 patients (50%), imaging showed enlarged lymph nodes. Seventeen patients (57%) were treated by CCRT, while 13 (43%) were treated with RT alone (Table 2). Of the latter,

Table 3. — *List of patients with vesicovaginal and/or rectovaginal fistulae (n = 13).*

No.	Age (years)	Primary treatment	Tumor diameter (mm)	Radiotherapy EBRT (Gy)	Radiotherapy ICBT (Gy)	CS	Type of fistula	Treatment	Time of diagnosis of the fistula (Mo)	Prognosis (Mo)
1	44	CCRT	70	56	18	No	VVF RVF	Catheterization No treatment	8 11	11AWD
2	70	CCRT	77	56	0	Yes	RVF	Colostomy	2	22NED
3	72	CCRT	88	50	18	No	RVF	Colostomy	8	14 DOD
4	52	RT	74	50.4	12	No	VVF	Nephrostomy	1	14 NED
5	81	RT	60	49.6	12	Yes	VVF	Catheterization	24	32 DOD
6	82	RT	100	50.4	0	No	VVF	No treatment	41	48 DOD
7	56	CCRT	54	60	6	No	VVF	Catheterization	0	47 DOD
8	47	CCRT	75	50	18	No	VVF	Catheterization	0	90 NED
9	40	CCRT	75	50	0	No	VVF	Catheterization	0	18 DOD
10	66	CCRT	80	50	12	No	VVF	Catheterization	0	12 DOD
11	67	RT	50	30	0	No	VVF	Catheterization	0	5 NED
12	74	RT	70	50	18	Yes	VVF	Nephrostomy	0	17 AWD
13	44	RT	60	50	12	Yes	VVF	Catheterization	0	6 DOD

EBRT: external beam radiotherapy, ICBT: intracavitary brachytherapy, CS: center shield, CCRT: concurrent chemoradiotherapy, RT: radiotherapy, VVF: vesicovaginal fistula, RVF: rectovaginal fistula, AWD: alive with disease, NED: no evidence of disease, DOD: dead of disease.

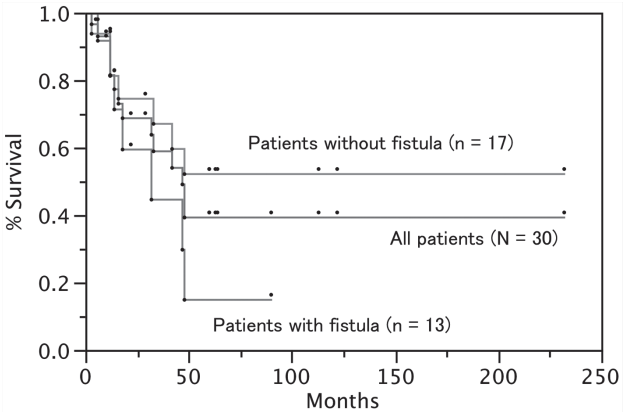

Figure 1. — The five-year overall survival was 14.9% in the patients with fistula, 52.1% in the patients without fistula ($p = 0.148$, log-rank test) and 39.4% in the total series.

seven received WP-EBRT with HDR-ICBT, while six received WP-EBRT alone. A center shield was not used in eight patients and set in five patients after delivery of 40 Gy. The radiation for patients treated with CCRT included WP-EBRT with no brachytherapy in three and HDR-ICBT in 14 patients. A center shield was used in four patients after delivery of 40 Gy and not set in 13 patients. Interstitial implants were not used.

Thirteen (43.3%) patients were diagnosed with one or more fistulae; seven presented with vesicovaginal fistula at the time of cancer diagnosis and six developed a fistula during or after RT. Table 3 summarizes the characteristics of the 13 patients with fistulae. Fistula was diagnosed 0–41 months after cancer diagnosis. The types of fistula were as follows: vesicovaginal in ten patients, vesicovaginal and rectovaginal in one, and rectovaginal in two. Two patients with a rectovaginal fistula had a colostomy; two patients underwent nephrostomy. Nine patients with a vesicovaginal fistula had catheterization into the urinary bladder. Only one patient was a current smoker. There was no significant difference in the incidence of fistula between patients treated with RT alone and those treated with CCRT. The patients with fistulae had a median survival of 32 (range, 6–90) months. Six patients are alive with median follow-up of 12 (range, 5–90) months, four of whom have no evidence of recurrence, while two have persistent disease. The five-year OS of the patients with fistula was 14.9% (Figure 1). In the total series of 30 patients, the five-year OS was 39.4% (Figure 1). Sixteen patients are alive with a median follow-up of 44.5 months (range, 1–232) months, 14 with no evidence of disease, and two with persistent or recurrent disease. No significant correlation between OS and any clinicopathological variables was found by log-rank analysis (Table 4). On Cox proportional regression analysis, RT without HDR-ICBT was a factor that significantly correlated with a poor OS ($p = 0.0324$) (Table 5).

Table 4. — *Univariate analysis for overall survival.*

Variables		n	5-year OS (%)	*p* value
Age (years)	> 60	17	19.7	0.066
	≤ 60	13	61.1	
Performance status	0.1	19	32.6	0.341
	2	11	58.3	
Tumor size (cm)	> 7	12	49.9	0.633
	≤ 7	18	32.6	
LN enlargement	Yes	18	30.1	
	No	12	56	
Hydronephrosis	Yes	26	37.1	0.626
	No	4	66.7	
Fistula formation	Yes	13	14.9	0.148
	No	17	52.1	
CCRT	Yes	17	48.9	0.287
	No	13	24.9	
WP-EBRT+ICBT	Yes	22	50.3	0.130
	No	8	14.6	

OS: overall survival, LN: lymph node, CCRT: concurrent chemoradiotherapy, WP-EBRT: whole pelvic-external radiotherapy, ICBT: intracavitary brachytherapy.

Table 5. — *Multivariate analysis for overall survival.*

Variables	HR	95%CI	*p* value
Age (years)	1.089	0.999-1.203	0.0512
Performance status	0.840	0.237-2.341	0.7559
Tumor size (mm)	1.001	0.945-1.065	0.9759
Lymph node swelling	6.676	0.683-151.6	0.1091
Hydronephrosis	0.551	0.034-14.53	0.6765
Fistula (VVF or RVF)	1.529	0.374-6.032	0.5409
CCRT	4.847	0.458-68.24	0.1926
No brachytherapy	6.710	1.168-53.14	0.0324

HR; hazard ratio, CI; confidence interval, VVF; vesicovaginal fistula, RVF; rectovaginal fistula, CCRT; concurrent chemoradiotherapy.

Discussion

For all patients, the three- and five-year OS were 58.9% and 39.4%, respectively; 14 patients are alive with no evidence of disease, while two patients are alive with persistent or recurrent disease over a median follow-up of 44.5 (range, 1–232) months. Although no statistically significant correlation between OS and clinicopathological variables (Table 4) was found in log-rank tests, the five-year OS in patients with age > 60 years, the presence of fistula, or EBRT without ICBT was rather low. When assessed by the Cox proportional regression analysis, only EBRT without ICBT was identified as an independent prognostic factor.

Before the CCRT era, superior survival for patients with Stage IVA cervix cancer was reported to be associated with two factors: minimal parametrial disease and radiation with combined EBRT and ICBT. Stage IVA disease is defined by a larger tumor size with more bilateral parametrial involvement than in lower stages. A Gynecologic Oncology

Group (GOG) study reported on 28 patients treated with brachytherapy and 22 received only external irradiation, with median survival of 24 and 13 months, respectively ($p = 0.07$) [3]. In that study, advanced tumors that did not shrink enough to initiate HDR-ICBT after whole-pelvic EBRT were treated only with EBRT with boost fields. Murakami *et al.* stressed that an adequate radiation dose to point A confers favorable local control and progression-free survival, indicating that efforts must be made to deliver as high a dose as possible [7].

The benefits of chemotherapy addition to RT in patients with Stage IVA disease have not been validated. The use of cisplatin-based chemotherapy had no impact on progression-free survival or OS in the GOG study, but that investigation was underpowered to address this particular question [6]. No impact of cisplatin-based chemotherapy on the outcome of the patients with Stage IVA disease was observed in another study because of small sample size [11]. Also, the present study cannot adequately answer this question, although CCRT did seem to result in better OS.

Although the number of patients in the present series was small, the study indicates that high rates of vesicovaginal and/or rectovaginal fistulae were observed when treating women with Stage IVA cervical cancer. Use of examination with cystoscopy and proctoscopy in the management of advanced cervical cancer may be helpful for prognostic identification of bladder and/or rectal involvement, and useful for treatment planning and for evaluation of future response in collaboration with radiation oncologists. Thirteen (43%) patients were diagnosed with one or more fistulae; among those, seven presented with vesicovaginal fistula at the time of cancer diagnosis and six developed a fistula during or after RT. Previous reports documented vesicovaginal and/or rectovaginal fistulae in 4% to 47.8% of women with Stage IVA cervical cancer [2-7]. Vesicovaginal fistulae are difficult to repair surgically after RT because of poor vascularity and healing. Some success has been reported with strategies, such as myocutaneous rectus abdominus muscle flaps, ileocystoplasty, and even conservative management with prolonged catheterization [12-15]. Regardless of the treatment chosen, fistula have a serious impact on quality of life.

The present authors believe that improved local control of Stage IVA cervical cancer seen with CCRT techniques comes at the expense of vesicovaginal and/or rectovaginal fistulae. Kramer *et al.* reported a 47.8% incidence of fistula, the highest documented so far, occur particularly among women who smoke. They found no significant difference in the incidence of fistula between patients treated with RT alone as compared with CCRT, which is consistent with the present findings [3]. Furthermore, evidence from several phase III trials showed no difference in genitourinary complications with the addition of chemotherapy to radiation therapy [16-18]. Twenty-two of the present patients were treated with HDR-ICBT, of whom four patients developed a fistula during or after radiotherapy. In the study by Kramer *et al.*, fistula developed in two of the five patients who received low dose rate (LDR)-BT and in nine of the 14 patients treated with HDR-BT [3]. Recent studies have not shown a statistically significant difference in complications between LDR-ICBT and HDR-ICBT [19-21]. However, patients with Stage IVA disease were generally excluded from those studies. The present authors could not identify by multivariate analysis any clinicopathological factors that might have predicted fistula formation in this series (data not shown), which is consistent with the findings of Biewenga *et al.* [5].

Strength of the present study is that Stage IVA cancer was diagnosed by examination, cystoscopy, and proctoscopy in all patients that is more accurate than the ability of CT or MRI assessment for bladder/rectum involvement. Limitation is that this analysis is retrospective in a small number of patients from one center over a relatively long period of time.

Compared with patients with earlier stage disease, those with Stage IVA cervical cancer have larger tumor size, more parametrial involvement, and poorer survival. High rates of vesicovaginal and/or rectovaginal fistulae can be expected in Stage IVA cervical cancer. Some patients are cured of the disease, but are left with a fistula as a consequence of the disease or its treatment. Interventions for vesicovaginal fistula to improve quality of life are very important. Multi-institutional studies of larger number of patients are necessary to clarify the incidence and optimal management of genitourinary fistulae associated with Stage IVA cervical cancer.

References

[1] Pecorelli S., Zigliani L., Odicino F.: "Revised FIGO staging for carcinoma of the cervix". *Int. J. Gynaecol. Obstet.*, 2009, *105*, 107.
[2] Million R.R., Rutledge F., Fletcher G.H.: "Stage IV carcinoma of the cervix with bladder invasion". *Am. J. Obstet. Gynecol*., 1972, *113*, 239.
[3] Kramer C., Peschel R.E., Goldberg N., Kohorn E.I., Chambers J.T., Chambers S.K., *et al.*: "Radiation treatment of FIGO stage IVA carcinoma of the cervix". *Gynecol. Oncol.*, 1989, *32*, 323.
[4] Moore K.N., Gold M.A., McMeekin D.S., Zorn K.K.: "Vesicovaginal fistula formation in patients with stage IVA cervical carcinoma". *Gynecol. Oncol.*, 2007, *106*, 498.
[5] Biewenga P., Mutsaerts M.A., Stalpers L.J., Buist M.R., Schilthuis M.S., van der Velden J.: "Can we predict vesicovaginal or rectovaginal fistula formation in patients with stage IVA cervical cancer?" *Int. J. Gynecol. Cancer*, 2010, *20*, 471.
[6] Rose P.G., Ali S., Whitney C.W., Lanciano R., Stehman F.B.: "Outcome of stage IVA cervical cancer patients with disease limited to the pelvis in the era of chemoradiation: a Gynecologic Oncology Group study". *Gynecol. Oncol.*, 2011, *121*, 542.
[7] Murakami N., Kasamatsu T., Morota M., Sumi M., Inama K., Ito Y., *et al.*: "Radiation therapy for stage IV cervical cancer". *Anticancer Res.*, 2013, *33*, 4989.
[8] Toita T., Moromizato H., Ogawa K., Kakinohana Y., Maehama T., Kanazawa K., *et al.*: "Concurrent chemoradiotherapy using high-dose-rate intracavitary brachytherapy for uterine cervical cancer". *Gynecol. Oncol.*, 2005, *96*, 665.
[9] Fields A.L., Anderson P.S., Goldberg G.L., Wadler S., Beitler J.,

Sood B., Runowicz C.D.: "Mature results of a phase II trial of concomitant cisplatin/pelvic radiotherapy for locally advanced squamous cell carcinoma of the cervix". *Gynecol. Oncol.*, 1996, *61*, 416-22.

[10] Toita T., Kitagawa R., Hamano T., Umayahara K., Hirashima Y., Aoki Y., *et al.*: "Cervical Cancer (Vulva Cancer) Committee of Japanese Gynecologic Oncology Group (JGOG).: "Phase II study of concurrent chemoradiotherapy with high-dose-rate intracavitary brachytherapy in patients with locally advanced uterine cervical cancer: efficacy and toxicity of a low cumulative radiation dose schedule". *Gynecol. Oncol.*, 2012, *126*, 211.

[11] Quinn M.A., Benedet J.L., Odicino F., Maisonneuve P., Beller U., Creasman W.T., *et al.*: "Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer". *Int. J. Gynaecol. Obstet.*, 2006, *95*, S43.

[12] Bipat S., Glas A.S., van der Velden J., Zwinderman A.H., Bossuyt P.M., Stoker J.: "Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: a systematic review". *Gynecol. Oncol.*, 2003, *91*, 59.

[13] Horch R.E., Gitsch G., Schultze-Seemann W.: "Bilateral pedicled myocutaneous vertical rectus abdominus muscle flaps to close vesicovaginal and pouch-vaginal fistulas with simultaneous vaginal and perineal reconstruction in irradiated pelvic wounds". *Urology*, 2002, *60*, 502.

[14] Tabakov I.D., Slavchev B.N.: "Large post-hysterectomy and post-radiation vesicovaginal fistulas: repair by ileocystoplasty". *J. Urol.*, 2004, *171*, 272.

[15] Madjar S, Gousse A.: "Postirradiation vesicovaginal fistula completely resolved with conservative treatment". *Int. Urogynecol. J. Pelvic Floor Dysfunct.*, 2001, *12*, 405.

[16] Morris M., Eifel P.J., Lu J., Grigsby P.W., Levenback C., Stevens R.E., *et al.*: "Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer". *N. Engl. J. Med.*, 1999, *340*, 1137.

[17] Keys H.M., Bundy B.N., Stehman F.B., Muderspach L.I., Chafe W.E., Suggs C.L. 3rd, *et al.*: "Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky Stage IB cervical carcinoma". *N. Engl. J. Med.*, 1999, *340*, 1154.

[18] Pearcey R., Brundage M., Drouin P., Jeffrey J., Johnston D., Lukka H., *et al.*: "Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix". *J. Clin. Oncol.*, 2002, *20*, 966.

[19] Teshima T., Inoue T., Ikeda H., Miyata Y., Nishiyama K., Inoue T., *et al.*: "High-dose rate and low-dose rate intracavitary therapy for carcinoma of the uterine cervix. Final results of Osaka University Hospital". *Cancer*, 1993, *72*, 2409.

[20] Hareyama M., Sakata K., Oouchi A., Nagakura H., Shido M., Someya M., *et al.*: "High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix". *Cancer*, 2002, *94*, 117.

[21] Lertsanguansinchai P., Lertbutsayanukul C., Shotelersuk K., Khorprasert C., Rojpornpradit P., Chottetanaprasith T., *et al.*: "Phase III randomized trial comparing LDR and HDR brachytherapy in treatment of cervical carcinoma". *Int. J. Radiat. Oncol. Biol. Phys.*, 2004, *59*, 1424.

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