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ORIGINAL ARTICLE

Tumor growth patterns on magnetic resonance imaging and treatment outcomes in patients with locally advanced cervical cancer treated with definitive radiotherapy

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Abstract

Background To evaluate the prognostic value of tumor growth patterns on magnetic resonance (MR) images in patients with locally advanced cervical cancer (LACC) treated with definitive radiotherapy or concurrent chemoradiotherapy (RT/CCRT).

Methods We retrospectively reviewed 102 patients with LACC who received definitive RT/CCRT and who underwent MR imaging before RT/CCRT. Growth patterns on pretreatment T2-weighted MR images were classified into expansive or infiltrative type according to tumor morphologic patterns in the myometrium and/or parametrial space.

Results The median age was 60 years (range 26–90 years). The median follow-up time was 47.7 months (range 5.7–123 months). The numbers of patients with stages IB, II, III, and IVA were 17, 39, 43, and 3, respectively. The 3-year overall survival (OS) rates for stages IB, II, III, and IV were 87%, 76%, 74%, and 67%, respectively. Regarding growth patterns on MR images, 31 were of expansive type and 71 were of infiltrative type. The infiltrative type was significantly associated with lower OS and locoregional recurrence-free survival (LRRFS) than the expansive type (3-year OS, 70% vs. 93%, $p=0.003$; 3-year LRRFS, 64% vs. 94%, $p=0.001$). On multivariate analysis, infiltrative tumor growth patterns were a significant independent factor for low OS (hazard ratio [HR], 3.81; 95% confidence interval [CI] 1.26–16.7; $p=0.015$) and low LRRFS (HR, 4.27; 95% CI 1.43–18.5; $p=0.007$).

Conclusion Tumor growth patterns on MR images could be an indicator of survival and locoregional control in patients with LACC treated with definitive RT/CCRT.

Keywords Cervical cancer · MRI · Radiotherapy

Introduction

Cervical cancer is one of the most common gynecologic cancers worldwide. It can be treated with radical hysterectomy plus pelvic lymphadenectomy, concurrent chemoradiotherapy (CCRT), or radiotherapy (RT) alone [1]. The clinical

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stages of cervical cancer have been classified using the International Federation of Gynecology and Obstetrics (FIGO) classification [2]. This classification is useful for predicting the prognosis of patients with cervical cancer and selecting appropriate treatment. The 5-year overall survival (OS) rates of FIGO I/II, III, and IVA cervical cancer patients treated with definitive RT have been reported to be 70%–90%, 60%, and 20%, respectively [3–5]. The FIGO classification is mainly based on physical examination and is not taken into account for lymph node metastasis and morphologic features of the primary tumor.

Recently, magnetic resonance (MR) images are being acquired routinely before treatment to evaluate tumor morphology, tumor size, parametrial/pelvic sidewall invasion, and lymph node metastasis [6–8]. In patients receiving RT for cervical cancer, MR images are useful for treatment planning of RT, evaluation of response to RT, and detection of recurrent disease. In addition, pretreatment MR images can potentially predict tumor response to RT in cervical cancer. A few recent studies have shown that tumor growth patterns in parametrial space on MR images were predictive of tumor response to RT. Yoshida et al. reported that FIGO IIB and IIIB cervical cancer of expansive type responded better to CCRT than those of infiltrative type [9]. Schmid et al. also reported that cervical cancer with predominantly expansive growth pattern had significantly better response to CCRT or RT alone during treatment than those with predominantly infiltrative growth pattern [10]. A good primary response to RT usually can be directly translated into an individual patient's outcome [11]. Although these studies have revealed good correlations between tumor growth patterns and primary response to RT [9, 10], the correlations between tumor growth patterns and patient prognosis have not been demonstrated.

This retrospective study thus aimed to evaluate the relationship between tumor growth patterns on pretreatment MR images and patient prognosis after CCRT or RT alone in patients with locally advanced cervical cancer.

Materials and methods

Patient selection

From April 2006 to March 2015, a total of 215 patients were pathologically diagnosed with FIGO IB-IVA cervical cancer and treated with definitive RT with or without concurrent chemotherapy in our institution. Of these, patients with the following characteristics were excluded from the study: (1) did not receive high dose rate (HDR) intracavitary brachytherapy ($n=39$); (2) had distant metastases other than paraaortic node (PAN) metastases at presentation ($n=11$); (3) were lost to follow-up within 12 months ($n=5$); (4) did not undergo MR imaging (MRI) before treatment ($n=45$); and (5) had primary tumors smaller than 2 cm on MR images ($n=13$). Patients with metastases only to the PANs were included in the study, because they received curative intent RT. Meanwhile, primary tumors smaller than 2 cm were too small to be evaluated for growth patterns correctly; hence, we excluded patients with such small primary tumors. Finally, we retrospectively evaluated the remaining 102 patients with FIGO IB-IVA cervical cancer treated with definitive RT. This retrospective study was approved by our institutional review board.

Treatment

All 102 patients assessed in this study received RT, combining external beam radiotherapy (EBRT) and HDR intracavitary brachytherapy (microSelectron HDR; Nucletron, The Netherlands) with a 192-Ir source. CCRT with weekly cisplatin (30–40 ng/m^2), were administered when possible, and the gynecologists in our institution made a decision as to whether chemotherapy could be combined with RT or not. Sixty percent of patients (median age 56 years; range 26–76 years) received concurrent chemotherapy of ≥ 5 cycles, whereas 40% received RT alone (median age 77 years; range, 28–90 years) because of comorbidities and/or high age. EBRT was delivered using 10 MV X-ray from a linear accelerator (Clinac 21EX; Varian Medical Systems, CA, USA) to a total dose of 45–61 Gy (median 50.4 Gy) with a daily fraction size of 1.8–2 Gy to the pelvic region. In patients with PAN metastases, EBRT fields were extended to the PAN region and delivered to a total dose of 45–54 Gy (median, 50.4 Gy) to the PAN region. EBRT was mainly delivered using anterior and posterior parallel opposed portals ($n=61$) or the four-field technique ($n=39$). Intensity-modulated RT was used for two patients. Two patients with iliac node metastases received boost EBRT to iliac node metastases (6 Gy in 3 fractions), and one patient with remarkable parametrial invasion received boost EBRT to the parametrium (10 Gy in 5 fractions). After an initial whole pelvis dose of 19.8–50.4 Gy (median, 30.6 Gy), HDR intracavitary brachytherapy was started and the central shield (4 cm wide at the midline) was set in the whole pelvic field. HDR intracavitary treatment plans were prepared in compliance with International Commission on Radiation Units and Measurements-38 guidelines using the Oncentra brachytherapy planning system (Oncentra Brachy, V4.0-4.5; Nucletron, The Netherlands), and the dose was prescribed to point A. The dose at the point A was 4.5–6 Gy (median, 6 Gy) in each fraction. Each patient received 1–5 fractions (median, 4 fractions) of HDR intracavitary brachytherapy. Total doses of EBRT and HDR intracavitary brachytherapy at point A were calculated with equivalent dose at 2 Gy (EQD_2) values

using an α/β ratio of 10 for tumor. Median total EQD_2 at point A was 81.6 Gy (range 65.6–91.6 Gy).

Imaging evaluation

MR images were acquired using one of the three MRI units (Gyroscan Intera 1.5T Master, Achieva 1.5T Single Gradient, or Ingenia 3.0T; Philips, The Netherlands). Pretreatment T2-weighted MR images were independently reviewed by a radiation oncologist and a radiologist. Two observers were blinded to follow-up information and outcomes during evaluation of the images. They evaluated growth patterns of tumors in the surrounding tissues (myometrium or parametrial space). Growth patterns on the pretreatment MR images were classified as expansive or infiltrative type according to the modified criteria from Yoshida et al. [9]. Expansive growth patterns (type 1 or 2) were defined as expansive growing tumors with or without spiculae for surrounding tissues, and infiltrative growth patterns (type 3 or 4) were defined tumors with infiltrative parts (Fig. 1, Table 1). In case of difference in observations between the two reviewers, they discussed the results and arrived at a consensus. Meanwhile, tumor size was also measured on T2-weighted MR images by one observer.

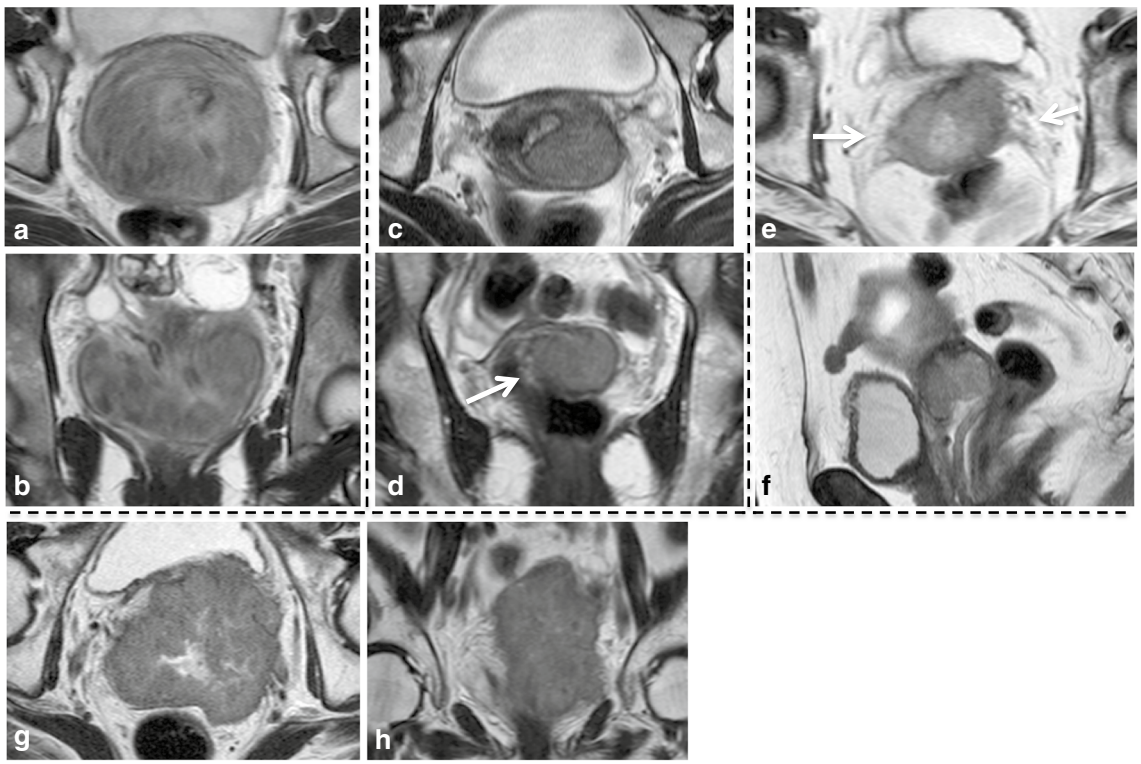


Fig. 1 Tumor growth patterns on pretreatment T2-weighted magnetic resonance images were classified into the expansive type or the infiltrative type. Expansive type 1 tumor on **a** axial and **b** coronal images. Small expansive type 2 tumor with spiculae (arrow) on **c** axial and **d** coronal images. Small infiltrative type 3 tumor with infiltrating parts (arrows) on **e** axial and **f** sagittal images. Infiltrative type 4 tumor on **g** axial and **h** coronal images

Table 1 Tumor growth patterns on pretreatment MR images were classified into four types

Growth pattern	Type	
Expansive	1	The expansive growing tumor with intact cervical stromal ring or well-circumscribed tumor for myometrium or parametrial space
	2	The expansive growing tumor with a focally disrupted stromal ring or tumor with spiculae for myometrium or parametrial space
Infiltrative	3	The expansive growing tumor with some infiltrating parts for myometrium or parametrial space
	4	The infiltrative growing tumor for myometrium or parametrial space

MR magnetic resonance

Statistical analysis

Characteristics of the two patient groups were compared using Fisher's exact test for categorical variables (such as FIGO classification) and the Mann–Whitney rank-sum test for continuous variables (such as tumor diameter). The generalized kappa statistic was used as a measure of interobserver agreement for growth patterns on MR images [12]. Survival time was calculated from the start of treatment for primary cervical cancer. Moreover, the Kaplan–Meier method was used to construct curves for OS, disease-free survival (DFS), locoregional recurrence-free survival (LRRFS), and distant metastasis recurrence-free survival (DMRFS). Statistical significance of the differences in survival rates was evaluated with the log-rank test. Univariate and multivariable analyses to identify significant predictive factors of OS, DFS, LRRFS, and DMRFS were performed using a Cox proportional hazards model. A two-sided p value of < 0.05 was considered statistically significant. Statistical analyses were performed with the JMP software (JMP version 12.2.0; SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Characteristics of the patients and tumors are listed in Table 2. Most patients (80%) had FIGO II or III cervical cancer. Most of them had good performance status (PS) (PS 0–1), while two patients had PS 3. Five patients had serious comorbidities: one with dermatomyositis, three with angina, and one with valvular disease that underwent surgery.

Table 2 Patient and treatment characteristics

Characteristic	Total ($n=102$)	Expansive ($n=31$)	Infiltrative ($n=71$)	p
Age (years)				
Median (range)	60 (26–90)	57 (38–84)	61 (26–90)	
<60	48 (47%)	17 (55%)	31 (44%)	0.39
≥60	54 (53%)	14 (45%)	40 (56%)	
FIGO stage				
IB	17 (17%)	14 (45%)	3 (4%)	<0.001
II	39 (38%)	13 (42%)	26 (37%)	
III	43 (42%)	4 (13%)	39 (55%)	
IVA	3 (3%)	0	3 (4%)	
Histology				
SCC	84 (82%)	21 (68%)	63 (89%)	0.021
AC or ASC	18 (18%)	10 (32%)	8 (11%)	
Pelvic node involvement				
Negative	55 (54%)	22 (71%)	33 (46%)	0.031
Positive	47 (46%)	9 (29%)	38 (54%)	
Para-aortic node involvement				
Negative	91 (89%)	28 (90%)	63 (89%)	0.81
Positive	11 (11%)	3 (10%)	8 (11%)	
Tumor diameter (mm)				
Median (range)	51 (21–101)	38 (21–99)	54 (26–101)	<0.001
≤40	32 (31%)	18 (58%)	14 (20%)	<0.001
>40	70 (69%)	13 (42%)	57 (80%)	
Pretreatment hemoglobin (g/L)				
Median (range)	12.6 (6.4–14.9)	12.2 (7.2–14.9)	12.6 (6.4–14.7)	
<12	43 (42%)	15 (48%)	28 (39%)	0.51
≥12	59 (58%)	16 (52%)	43 (61%)	
Treatment				
CCRT	59 (58%)	16 (52%)	43 (61%)	0.51
RT alone	43 (42%)	15 (48%)	28 (39%)	

FIGO International Federation of Gynecology and Obstetrics, *SCC* squamous cell carcinoma, *AC* adenocarcinoma, *ASC* adenosquamous carcinoma, *CCRT* concurrent chemoradiotherapy, *RT* radiotherapy

MR images' evaluation

In six cases, the observation of tumor growth patterns was different between the two observers. However, agreement in growth pattern score between the two observers was substantial ($\kappa = 0.77$). There were no cases, where a consensus was not obtained. After consensus between the two observers for all observations, 31 patients were classified as having expansive type tumors and 71 as having infiltrative type tumors. Characteristics of the patients, tumors, and treatments according to tumor growth patterns are shown in Table 2. The infiltrative type had significantly higher incidence of advanced FIGO stage and large tumors than the expansive type ($p < 0.001$ and $p < 0.001$, respectively).

Clinical outcomes

The median follow-up time was 47.7 months (range 5.7–123 months). A total of 39 patients (38%) showed relapse post-definitive CCRT or RT alone: 12, intrapelvic failure only (local and/or regional); 6, developed extra-regional lymph node metastasis only (PAN, supraclavicular lymph node, mediastinal lymph node); 3, developed pelvic and extra-regional lymph node metastasis; and 18, distant metastasis. The median time from cancer diagnosis to recurrence was 9.0 months (range, 1.9–70.7 months).

Survival analysis

The (a) 3-year OS rates and (b) 3-year DFS rates for FIGO IB, II, III, and IVA cervical cancer were (a) 87%, 76%, 74%, and 67% and (b) 82%, 61%, 56%, and 67%, respectively. The Kaplan–Meier curves for OS, DFS, LRRFS, and DMFS according to growth patterns are shown in Fig. 2. The OS rate of patients with infiltrative type was significantly lower than that of patients with expansive type (70% vs. 93% at 3-year; $p = 0.003$). The difference in DFS, LRRFS, and DMFS between the expansive and infiltrative types was also statistically significant (Fig. 2).

The influence of tumor growth patterns on OS, DFS, LRRFS, and DMRFS was analyzed by the Cox proportional hazards model (Table 3). On univariate analysis, pelvic node involvement, larger tumor size, infiltrative tumor growth patterns, and treatment with RT alone were significantly associated with low OS and LRRFS. In addition, on univariate analysis, pelvic and PAN involvement, larger tumor size, infiltrative tumor growth patterns, and treatment with RT alone were significantly associated with low DFS and DMRFS. On the other hand, FIGO stage, histology, and pretreatment hemoglobin level were not significantly associated with OS, DFS, LRRFS, and DMRFS. On multivariate Cox regression analysis, infiltrative tumor growth patterns were the significant independent tumor-related factor for low OS (hazard ratio [HR], 3.81; 95% confidence interval [CI] 1.26–16.7; $p = 0.015$) and low LRRFS (HR, 4.27; 95% CI 1.43–18.5; $p = 0.007$). Furthermore, treatment with RT alone was the only significant treatment-related factor for lower OS, DFS, LRRFS, and DMFS (Table 3).

Considering that tumor growth patterns were correlated with tumor size or FIGO stage, we performed the following subgroup analyses on prognosis. OS curves stratified by tumor size and growth patterns are shown in Fig. 3. Moreover, in patients with tumor size > 4 cm ($n = 70$) and those with FIGO II disease ($n = 39$), the Cox proportional hazards model was used to analyze the influence of tumor growth patterns on OS, DFS, LRRFS, and DMRFS. In patients with tumor size > 4 cm, infiltrative tumor growth patterns were significantly associated with low LRRFS (HR 3.55; 95% CI 1.06–22.1; $p = 0.038$) on univariate analysis (Table 4). The infiltrative type was associated with worse 3-year LRRFS, compared to the expansive type (61% vs. 92%; $p = 0.065$). In FIGO II patients, infiltrative tumor growth patterns were significantly associated with low OS (HR, 3.71; 95% CI 1.02–23.8; $p = 0.045$) and LRRFS (HR, 4.17; 95% CI 1.17–26.7; $p = 0.026$) on univariate analysis (Supplementary table).

Discussion

In this study, FIGO IB-IVA cervical cancer was classified into expansive and infiltrative types according to tumor growth patterns on pretreatment MR images. The infiltrative type showed worse prognosis than the expansive type, and such growth patterns were significant independent factors for OS and LRRFS based on multivariate analysis.

Various prognostic factors, including FIGO stage, tumor size, tumor histology, lymph node status, parametrial involvement, uterine corpus invasion, age, and hemoglobin level, have been identified in patients receiving RT for cervical cancer [13–21]. In addition, tumor morphology or growth pattern of a bulky primary tumor has been reported to be a prognostic factor in patients treated with RT or surgery [22, 23]. Eifel et al. reported the influence of tumor size and dominant morphology on disease control in FIGO IB cervical cancer patients treated with RT [22]. They classified tumors sized ≥ 4 cm into two groups, exophytic and endocervical, based on the dominant morphology. Patients with exophytic tumors sized 5–7.9 cm had significantly better 5-year central tumor control (97% vs. 91%; $p = 0.03$) and 5-year disease-specific survival (76% vs. 66%; $p = 0.03$) than patients with endocervical tumors of similar size. Trimbos et al. examined the relationship between morphologic type of primary tumors and survival time in patients who were treated with surgery [23]. In that study, patients who underwent surgery and postoperative RT for cervical cancer (85%

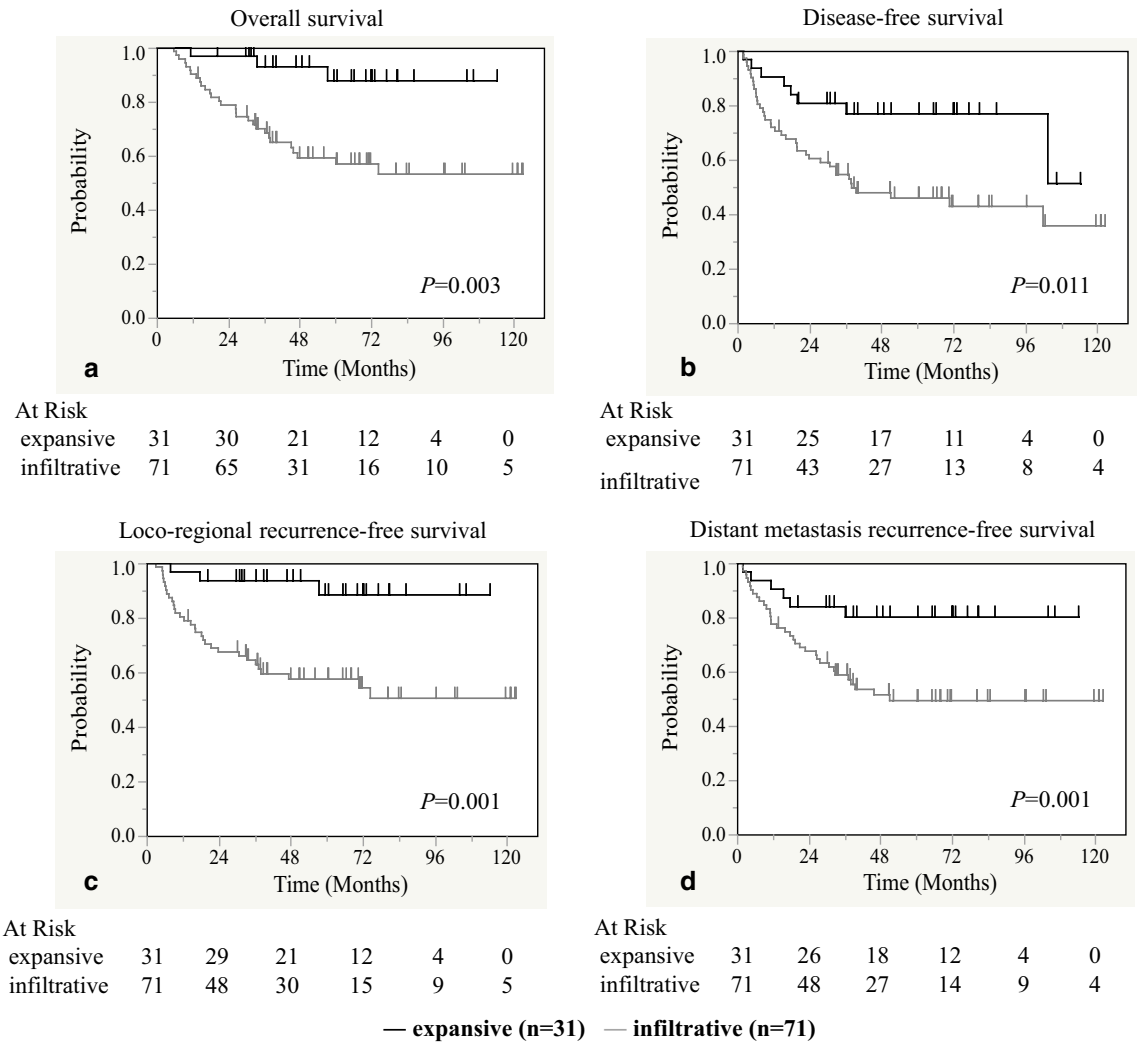


Fig. 2 Kaplan–Meier survival curve of **a** overall survival, **b** disease-free survival, **c** locoregional recurrence-free survival, and **d** distant metastasis recurrence-free survival according to tumor growth patterns. The difference in OS, DFS, LRRFS, and DMFS between the expansive and the infiltrative types was statistically significant

of cases were FIGO IB) were assessed. The OS and DFS rates were significantly worse in barrel-shaped bulky tumors (> 4 cm) than in exophytic bulky tumors (> 4 cm) and non-bulky tumors (< 4 cm), while exophytic bulky tumors (> 4 cm) had similar OS and DFS with non-bulky tumors. That study showed that tumor shape was likely a more significant prognostic factor for OS and DFS than tumor size in patients who underwent surgery and postoperative RT.

In these studies, tumor morphology or growth pattern was classified through pelvic examination [22] or pathological examination of surgical specimen [23]. Contrastingly, we used pretreatment MR images to define tumor growth patterns and evaluated the relationship between growth patterns and prognoses of cervical cancer patients. Tumor extent and growth patterns can be evaluated more objectively and more precisely by MRI than by physical examination. A few studies have reported a relationship between MRI-based tumor growth patterns of the primary tumor and tumor response during treatment in cervical cancer [9, 10]. Yoshida et al. performed a prospective study of 452 patients with FIGO IIB–IIIB cervical cancer and showed that tumor growth patterns in the parametrium were related to tumor response to CCRT [9]. With regard to tumor response during CCRT, the expansive type had a 10% higher rate of "good response" and 8% lower rate of "poor response" than the infiltrative type. In addition, Schmid et al. examined the relationship between tumor growth patterns on pretreatment MRI and tumor remnants in the parametrium detected on MR images obtained immediately before HDR intracavitary brachytherapy [10]. In their study, 85 patients with FIGO IIB and IIIB cervical cancer were classified as having predominantly infiltrative tumors and expansive tumors. Incidence

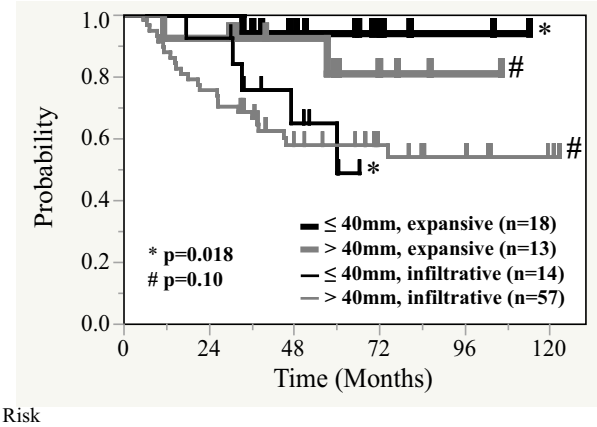
Table 3 Univariate and multivariate analyses for survivals in all patients

	Univariate							
	OS		DFS		LRRFS		DMRFS	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)								
< 60 vs. ≥ 60	0.95 (0.47–1.91)	0.88	0.78 (0.42–1.37)	0.37	0.84 (0.42–1.66)	0.62	0.93 (0.49–1.74)	0.83
FIGO								
I/II vs. III/IV	0.91 (0.45–1.84)	0.79	0.65 (0.36–1.16)	0.14	0.91 (0.46–1.80)	0.78	0.70 (0.37–1.30)	0.26
Histology								
SCC vs. AC/ASC	0.56 (0.26–1.33)	0.18	0.58 (0.30–1.19)	0.13	0.64 (0.30–1.52)	0.30	0.50 (0.25–1.07)	0.072
Lymph node involvement								
Pelvic								
Positive vs. negative	2.25 (1.10–4.83)	0.025	2.07 (1.16–3.78)	0.013	2.20 (1.11–4.59)	0.028	2.50 (1.33–4.92)	0.004
Para-aortic								
Positive vs. negative	2.24 (0.83–5.12)	0.10	2.71 (1.17–5.55)	0.022	2.17 (0.81–4.94)	0.12	2.90 (1.24–6.00)	0.016
Tumor diameter (mm)								
≤ 40 vs. > 40	0.45 (0.17–1.03)	0.060	0.51 (0.24–0.98)	0.043	0.42 (0.16–0.94)	0.034	0.39 (0.16–0.83)	0.013
Tumor growth pattern								
Infiltrative vs. expansive	5.07 (1.80–21.2)	< 0.001	2.59 (1.28–5.98)	0.007	5.57 (1.99–23.2)	0.005	2.91 (1.31–7.71)	0.007
Pretreatment hemoglobin (g/L)								
< 12 vs. ≥ 12	1.24 (0.61–2.49)	0.54	1.38 (0.77–2.46)	0.28	1.42 (0.72–2.80)	0.31	1.33 (0.71–2.49)	0.37
Treatment								
CCRT vs. RT alone	0.42 (0.20–0.86)	0.017	0.45 (0.25–0.80)	0.007	0.45 (0.22–0.90)	0.023	0.48 (025–0.90)	0.022
	Multivariate							
	OS		DFS		LRRFS		DMRFS	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Lymph node involvement								
Pelvic								
Positive vs. negative	1.90 (0.90–4.22)	0.091	1.76 (0.89–3.53)	0.10	1.78 (0.87–3.81)	0.15	1.97 (0.94–4.26)	0.073
Para-aortic								
Positive vs. negative			1.84 (0.75–4.09)	0.17			1.95 (0.79–4.37)	0.14
Tumor diameter (mm)								
≤ 40 vs. > 40	0.54 (0.19–1.34)	0.19	0.56 (0.24–1.18)	0.13	0.52 (0.18–1.26)	0.15	0.44 (0.17–1.05)	0.065
Tumor growth pattern								
Infiltrative vs. expansive	3.81 (1.26–16.7)	0.015	1.98 (0.90–4.87)	0.093	4.27 (1.43–18.5)	0.007	1.85 (0.77–5.23)	0.18
Treatment								
CCRT vs. RT alone	0.28 (0.13–0.60)	0.001	0.31 (0.16–0.57)	< 0.001	0.30 (0.14–0.62)	0.001	0.31 (0.16–0.61)	< 0.001

OS overall survival, *DFS* disease-free survival, *LRRFS* locoregional recurrence-free survival, *DMRFS* distant metastasis recurrence-free survival, *HR* hazard ratio, *CI* confident interval, *FIGO* International Federation of Gynecology and Obstetrics, *SCC* squamous cell carcinoma, *AC* adenocarcinoma, *ASC* adenosquamous carcinoma, *CCRT* concurrent chemoradiotherapy, *RT* radiotherapy

of tumor remnants in the parametrium immediately before HDR intracavitary brachytherapy was significantly higher in the predominantly infiltrative tumors (88% vs. 43%, $p < 0.01$). These authors reported a significant relationship between growth patterns of primary tumors of cervical cancer and early response to RT, but the relationship with the long-term prognosis was not shown.

In our study, multivariate analysis revealed that infiltrative type tumors, but not tumor size, were a significant independent factor for OS and LRRFS (Table 3). However, it is possible that tumor size, FIGO stage, lymph node metastases, and tumor growth patterns were confounding each other, and therefore, the reliability of multivariate analysis was uncertain, and we performed subgroup analysis in patients with similar tumor sizes and FIGO stages (Table 4, Supplementary table). Tumor size is considered one of the significant prognostic factors in patients who had cervical cancer treated with RT [21, 24, 25]. In our study, frequency of the



At Risk						
≤40mm, exp	18	18	13	8	3	0
>40mm, exp	13	13	9	5	2	0
≤40mm, inf	14	13	7	0	0	0
>40mm, inf	57	44	25	16	10	5

Fig. 3 Overall survival according to tumor size and growth patterns. The 3-year overall survival of the expansive tumors ≤ 4 cm, the expansive tumors > 4 cm, the infiltrative tumors ≤ 4 cm and the infiltrative tumors > 4 cm were 94%, 92%, 76% and 68%, respectively

infiltrative type tended to increase as tumor size increased. For each growth pattern, tumor size was not associated with OS (Fig. 3). Furthermore, subgroup analysis showed that infiltrative type in patients with tumor size > 4 cm was significantly associated with low LRRFS (Table 4). Moreover, FIGO stage is also considered a prognostic factor in cervical cancer patients who were treated with RT [5]. In our study, the proportion of advanced FIGO III tumors was significantly higher with the infiltrative type than with the expansive type (Table 2). We assessed the relationship between morphologic type and prognosis only in patients with FIGO II cervical cancer and found that infiltrative type was significantly associated with low OS and LRRFS (Supplementary table). These results suggest that tumor growth patterns could be a good prognostic factor for OS and locoregional control.

In our study, infiltrative tumor growth patterns were a statistically significant unfavorable factor for locoregional control but not for distant metastasis. Considering this, more aggressive locoregional treatment is likely to have potential to improve treatment outcomes of cervical cancer with infiltrative growth pattern. A study reported that intracavitary brachytherapy combined with computed tomography-guided interstitial brachytherapy was useful for bulky and/or irregularly shaped tumors [26]. This technique could lead to increased total dose for a high-risk clinical target volume

Table 4 Univariate analysis for survivals in patients with tumor size > 4 cm ($n = 70$)

	OS		DFS		LRRFS		DMRFS	
	HR (95% CI)	*p*	HR (95% CI)	*P*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)								
< 60 vs. ≥ 60	0.86 (0.39–1.88)	0.70	0.79 (0.41–1.52)	0.48	0.73 (0.34–1.54)	0.40	0.87 (0.43–1.73)	0.69
FIGO								
I/II vs. III/IV	1.34 (0.61–2.91)	0.46	0.90 (0.46–1.72)	0.75	1.38 (0.65–2.93)	0.39	0.96 (0.47–1.90)	0.90
Histology								
SCC vs. AC/ASC	0.45 (0.19–1.24)	0.11	0.53 (0.24–1.32)	0.16	0.57 (0.24–1.57)	0.26	0.47 (0.21–1.19)	0.10
Lymph node involvement								
Pelvic								
Positive vs. negative	1.30 (0.59–3.05)	0.53	1.43 (0.74–2.90)	0.29	1.25 (0.59–2.82)	0.56	1.51 (0.75–3.23)	0.26
Para-aortic								
Positive vs. negative	1.69 (0.49–4.46)	0.37	2.28 (0.85–5.14)	0.094	1.64 (0.48–4.32)	0.39	2.32 (0.86–5.26)	0.090
Tumor growth pattern								
Infiltrative ($n = 57$) vs. expansive ($n = 13$)	3.14 (0.93–19.6)	0.067	2.01 (0.80–6.73)	0.15	3.55 (1.06–22.1)	0.038	1.73 (0.68–5.82)	0.27
Pretreatment hemoglobin (g/L)								
< 12 vs. ≥ 12	1.19 (0.54–2.59)	0.66	1.39 (0.72–2.68)	0.32	1.35 (0.64–2.88)	0.43	1.34 (0.67–2.68)	0.40
Treatment								
CCRT vs. RT alone	0.38 (0.17–0.86)	0.021	0.34 (0.18–0.66)	0.002	0.40 (0.18–0.86)	0.020	0.37 (0.18–0.75)	0.006

OS overall survival, *DFS* disease-free survival, *LRRFS* locoregional recurrence-free survival, *DMRFS* distant metastasis recurrence-free survival, *HR* hazard ratio, *CI* confident interval, *FIGO* International Federation of Gynecology and Obstetrics, *SCC* squamous cell carcinoma, *AC* adenocarcinoma, *ASC* adenosquamous carcinoma, *CCRT* concurrent chemoradiotherapy, *RT* radiotherapy

(HR-CTV). A recent study by Dang et al. reported that intracavitary brachytherapy combined with interstitial brachytherapy resulted in increased D90 of HR-CTV and favorable treatment outcomes (the 5-year local control, DMFS, and OS rates were 89%, 82%, and 78%, respectively) [27]. This combined treatment is a new technique that can enhance local control; however, proper selection of patients suitable for this treatment is important, and tumor growth patterns could be one of the selection criteria.

This study has several limitations. First, it is a retrospective study conducted in a single Japanese institution. Second, it has a small sample size, especially with patients having an expansive type cervical cancer. Finally, there was bias in the FIGO stage and tumor size between the two growth patterns.

In conclusion, this study revealed that patients with cervical cancer with infiltrative growth patterns had a poor prognosis and tumor growth patterns on MR images could be an indicator for survival and locoregional control in patients with cervical cancer treated with definitive RT with or without concurrent chemotherapy. In addition, tumor growth patterns may be a potential indicator for selection of patients who need more aggressive locoregional treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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