Evaluation of microscopic tumor extension in early-stage cervical cancer: quantifying subclinical uncertainties by pathological and magnetic resonance imaging findings

Naoko SANUKI[1,*], Shogo URABE[2], Hideo MATSUMOTO[3], Asami ONO[1], Eiji KOMATSU[1], Noritaka KAMEI[1] and Toru MAEDA[1]

[1]Department of Radiology, Oita Prefectural Hospital, 476, Bunyo, Oita-shi, Oita, 870-8511, Japan
[2]Department of Pathology, Oita Prefectural Hospital, 476, Bunyo, Oita-shi, Oita, 870-8511, Japan
[3]Department of Gynecology, Oita Prefectural Hospital, 476, Bunyo, Oita-shi, Oita, 870-8511, Japan
*Corresponding author. Tel: +81-97-546-7111; Fax: +81-97-546-0725; E-mail: nao5-tky@umin.org

We performed a detailed analysis of hysterectomy specimens of uterine cervical cancer to determine the appropriate length of uterine body to include within the clinical target volume. Between 2008 and 2011, 54 patients with uterine cervical carcinoma underwent hysterectomy. Those with quality pre-operative magnetic resonance imaging (MRI) data were included for analysis. Tumor sizes measured by MRI and microscopy were compared with regard to brachytherapy-oriented parameters. Detailed descriptive analysis focusing on the extent of tumor involvement was also performed. A total of 31 specimens were analyzed. The median maximal tumor length measured by MRI was slightly shorter than microscopic length (19 vs. 24 mm, respectively), while the maximal radius was almost identical. No tumors with a maximal size <2 cm by MRI ($n = 6$) extended to the uterine body ≥ 1/3. The majority of maximal tumor length underestimation on MRI was within 1 cm. Precise tumor delineation can be made by MRI. For patients with tumors <2 cm on MRI, treating the entire uterine body length may not be necessary. A 1-cm margin around an MRI-based gross tumor seems to be adequate to cover the actual tumor involvement.

Keywords: Brachytherapy; cervical cancer; clinical target volume; magnetic resonance imaging; radiotherapy; target volume definition

INTRODUCTION

Brachytherapy plays a major role in the treatment of patients with cervical cancer [1–3]. The rapid fall-off of dose distribution allows a very high dose to be delivered to the tumor. A sharp dose gradient helps to spare unnecessary exposure to surrounding normal organs. Standard brachytherapy for cervical cancer involves tandem source activation from the cervix to the fundus without knowing an actual range of tumor involvement. However, two-dimensional (2D) imaging-based treatment planning does not enable visualization of the precise anatomic boundaries for pelvic structures. Historically, not much attention has been paid to the accuracy of endometrial tumor extension because the proximal extension of the tumor to the uterine body has not been relevant to patients, especially those undergoing hysterectomy; indeed, the International Federation of Gynecology and Obstetrics (FIGO) staging system concentrates only on the factors that affect resectability with conventional surgical techniques.

Magnetic resonance imaging (MRI), with good soft-tissue contrast and multi-planar imaging capability, is now widely accepted as optimal for evaluation of gynecologic malignancies including uterine cervical cancer [4]. Moreover, systematic MRI image-guided brachytherapy (IGBT) has been introduced. Because of the superiority of MRI in identifying the target and organs at risk, the use of this technology is increasing in centers treating patients with gynecologic brachytherapy [5, 6]. Successful attempts to minimize possible variation in delineating tumor volumes have been made by the The Groupe Européen de Curiethérapie (GEC)—European Society for Therapeutic Radiology and Oncology (ESTRO) Working Group, which published recommendations for cervical cancer IGBT [7–9]. However, there is

limited information on the quantitative analysis of image-detected tumor spread despite the fact that significant uncertainties in MRI-based IGBT have been reported [10–12].

In this study, we performed a detailed, brachytherapy-oriented pathologic analysis of hysterectomy specimens from patients with early-stage uterine cervical carcinoma to understand the microscopic extension around the tumor. We particularly aimed to focus on the appropriate length of uterine body to include within the clinical target volume (CTV) to safely avoid activation of the entire length of the tandem source.

MATERIALS AND METHODS

Patients and treatments

From August 2008 to February 2011, 54 patients with uterine cervical carcinoma underwent radical or modified radical hysterectomy for uterine cancer. Of these, 23 patients were excluded from the analysis: 12 patients had undergone pre-operative chemotherapy, and the other 11 patients did not have quality pre-operative MRI data. The remaining 31 patients comprised the study population. All patients provided written informed consent. The initial evaluation consisted of a complete history and physical examination as well as MRI. All patients underwent either cytology or needle core biopsy and were staged clinically by gynecologists based on the FIGO staging system (FIGO, 1995).

MRI studies and analysis

All patients underwent surgery within 3 weeks after MRI. MRI was performed with a 1.5-Tesla scanner (MAGNETOM Symphony; Siemens, Germany) and a pelvic coil.

T2-weighted scans were performed through the pelvis in the sagittal, transverse and coronal planes, and T1-weighted transverse images were obtained with or without contrast enhancement (gadopentetate dimeglumine, Magnevist; Bayer Schering Pharma, Japan). Axial diffusion-weighted images ($b = 800$ s/mm^2) were also obtained. T2-weighted images were used to determine the size of the primary tumor. All MRI data were analyzed with respect to brachytherapy-oriented parameters, such as the following: *maximal tumor length on MRI*, defined as a longer longitudinal tumor size along with an assumed tandem applicator in either the coronal or sagittal plane (Fig. 1, a and a') and *maximal tumor radius on MRI*, defined as the longest tumor radius measured around an assumed tandem applicator in the axial, coronal or sagittal plane (Fig. 1, b, b' and b''), both of which were evaluated on T2-weighted images. They were aimed to measure the distance to irradiate by a brachytherapy source and evaluated.

Correlation between pathologic findings and MRI findings

All hysterectomy specimen slides were reviewed by one pathologist (S.U.). The cervix was excised and sectioned, and examined with respect to the largest sagittal and radial size of the lesion. Sections were embedded with paraffin for routine histologic examination (hematoxylin-eosin staining). The findings were then correlated with the corresponding MRI findings. The pathological assessment was also focused on brachytherapy-oriented parameters, which corresponded to MRI parameters as follows: *maximal tumor length on microscopy*, defined as the maximal longitudinal tumor extension from the cervix to the uterine body (including lymphovascular invasion or direct
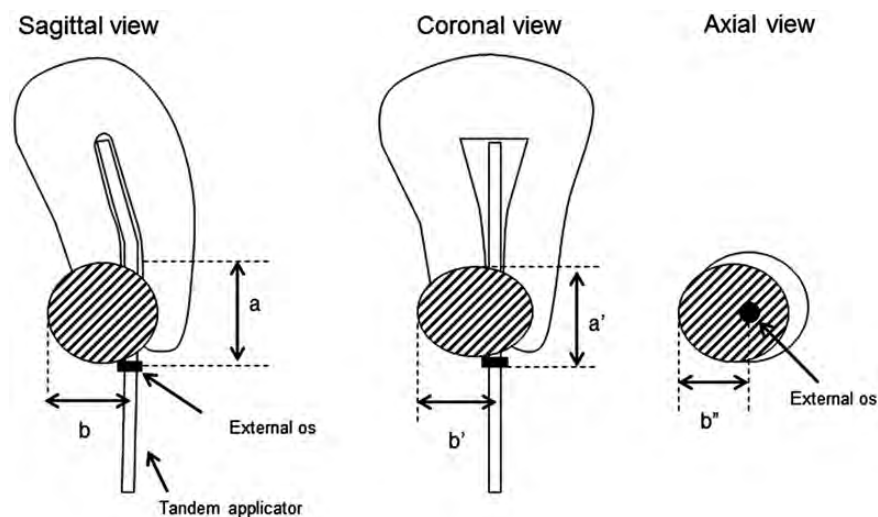

Fig. 1. Schema of measurements on MRI. (a or a') *Maximal tumor length* along with an assumed tandem applicator. The longer length is chosen either in the a (sagittal) or a' (coronal) plane. (b, b' or b'') The *maximal tumor radius* around tandem applicator. The longer length is chosen either in the b (sagittal), b' (coronal) or b'' (axial) plane.

microinvasion), and *maximal tumor thickness on microscopy*, defined as the maximal horizontal tumor extension (including parametrial invasion) (Fig. 2). These measurements were performed with regard to how far radiation from a brachytherapy source needed to extend to cover the actual tumor extension. The following additional information and pathologic features were also recorded for each specimen: status of frontline involvement (extension toward the endometrium or the vagina) such as *in situ* form, direct stromal invasion or lymphovascular invasion; endophytic or exophytic nature of the tumor; and status of the parametrial, vaginal and lymph node involvement.

Intra-cavitary length, defined as the distance from the external os (assuming a tandem ring placed at the external os) to the proximal fundus of the uterine body, was measured by gross measurement before fixation, which was assumed for tandem applicator length in brachytherapy. The apparent corresponding length on MRI was also recorded to determine the consistency between gross measurement and MRI measurement. Length of cancer involvement in the uterus was defined as microscopic tumor length from the edge of the cervical tumor (assuming a tandem ring placed at the external os) to that of endometrial involvement toward the direction of an applicator axis. Then, a proportion of the proximal extension was calculated as the length of cancer involvement in the uterus over the intra-cavitary length $\times$ 100.

Statistical analysis

Statistical analysis was performed with Dr. SPSS II version 11 (SPSS Inc., Chicago, IL, USA). Potential risk factors for overestimation and the association of characteristics with percentage of proximal extension were analyzed using a chi-square test and Fisher's exact test for categorical variables, and Student's *t*-test for continuous variables. A *P* value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

This study included 31 patients, ranging in age from 27 to 83 years (median 52 years), who underwent radical or modified radical hysterectomy for cervical carcinoma. Upon clinical and radiological examination, 23 patients had been classified pre-operatively as stage I (1 in T1a, 22 in T1b1, and 0 in T1b2), and 8 were as stage II (1 in T2a and 7 in T2b) before surgery. A pelvic lymph node dissection was performed in 29 patients (94%). Patient characteristics are summarized in Table 1.

The MRI findings were compared with the pathologic findings (Table 2). Underestimation of size in *maximal tumor length on MRI* was observed in 20 (65%) specimens (median 4 mm, range 1–17 mm), while underestimation of *maximal tumor radius on MRI* was observed in 11 (35%) specimens (median 3 mm, range 1–11 mm). Figure 3 shows the distribution of underestimation and overestimation of each case in order sorted by length. On univariate analysis, no potential risk factor for overestimation was identified in tumor size, tumor location, tumor type and lymphovascular invasion.

Tumor involvement was divided into two types: invasive extension (in direct or lymphovascular form) and *in situ* extension in either the endometrial or vaginal direction. Figures 4 and 5 show examples of patterns of tumor extension. Regarding the status of the frontline involvement, extension in *in situ* form toward the endometrium was observed in 10 (32%) specimens, and that toward the
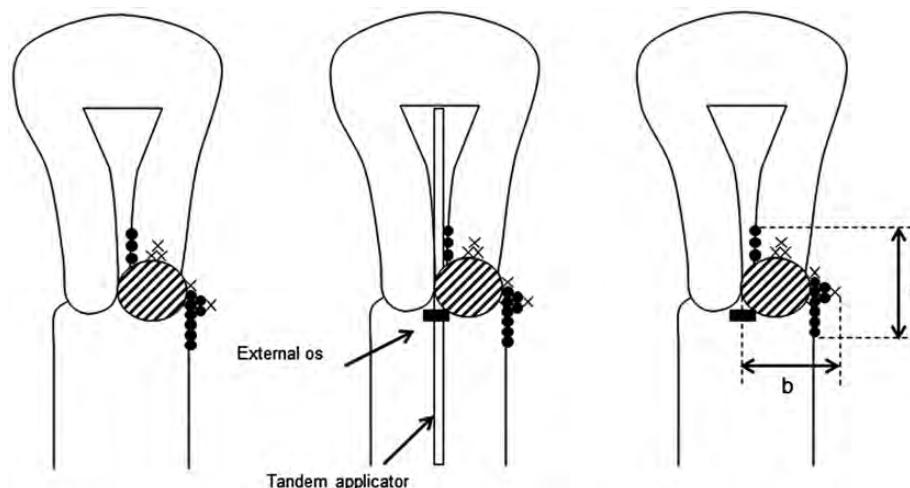

Fig. 2. Schema of patterns of tumor extension on microscopy. (a) *Maximal tumor length*; (b) *maximal tumor radius*. Crosses indicate stromal invasion in 'lymphovascular invasion' form; black circles indicate microscopic tumor extension.

Table 1. Patient demographics and characteristics

	Numbers	%
Total	31	
Median age (years) (range)	52 (27–83)	
Clinical stage (FIGO)		
Ia	1	3
Ib1	22	71
Ib2	0	0
IIa	1	3
IIb	7	23
Tumor location		
Endocervix	17	55
Portio	14	45
Histology		
Squamous cell carcinoma	22	71
Adenocarcinoma	8	26
Adenosquamous cell carcionma	1	3
Type of tumor		
Endophytic	25	81
Exophytic	6	19

vagina was seen in 11 (35%) specimens. As for the lengths of *in situ* involvement for both directions toward the endometrium or the vagina, the median lengths were 6 mm (range 1–18 mm) and 3 mm (range 1–16 mm), respectively. Eighty-six percent (18/21) of the *in situ* extensions were within 10 mm. Extension in lymphovascular form at the tumor frontline toward the endometrium was observed in two patients.

Analysis of length and percentage of uterine involvement

The gross measurement of the intra-cavitary length before fixation was almost identical to the corresponding length on MRI; the median intra-cavitary length was 63 mm (range 46–82 mm) and 64 mm (range 45–85 mm), respectively. The MRI measurement was employed to calculate the percentage of uterine body involvement. As a result, the median length and percentage of uterine body involvement were 19 mm (range 5–44 mm) and 31% (range 7–72%), respectively. A massive uterine body involvement of 50% or more was observed in 6 (19%) patients, and that of 1/3 or more was observed in 17 (55%) patients. Among 25 patients with a *maximal tumor size on MRI* of 2 cm or more, 18 (72%) showed an extension of 1/3 or more toward the endometrium. In contrast, none of the tumors

Table 2. Relations between pathologic findings and MR staging

	MRI	(%)	Microscopy	(%)
Maximal tumor length				
Median (mm) (range)	19 (10–43)		24 (7–55)	
Maximal tumor radius				
Median (mm) (range)	14 (4–28)		13 (3–29)	
Maximal tumor diameter				
Median (mm) (range)	30 (10–43)		26 (7–55)	
Positive parametrial invasion	7	23%	4	13%
Positive lymph node metastases	1	3%	5[a]	17%
Positive vaginal invasion	2	6%	5	16%
Stage (FIGO)				
Ia	1	3%	2	6%
Ib1	22	71%	14	45%
Ib2	0	0%	9	29%
IIa	1	3%	3	10%
IIb	7	23%	3	10%

[a]Among those with lymph node dissection (*n* = 29).
Maximal tumor length, defined as the longitudinal tumor size along with an assumed tandem applicator
Maximal tumor radius, defined as the longest tumor radius measured around an assumed tandem applicator in the axial, coronal or sagittal plane.
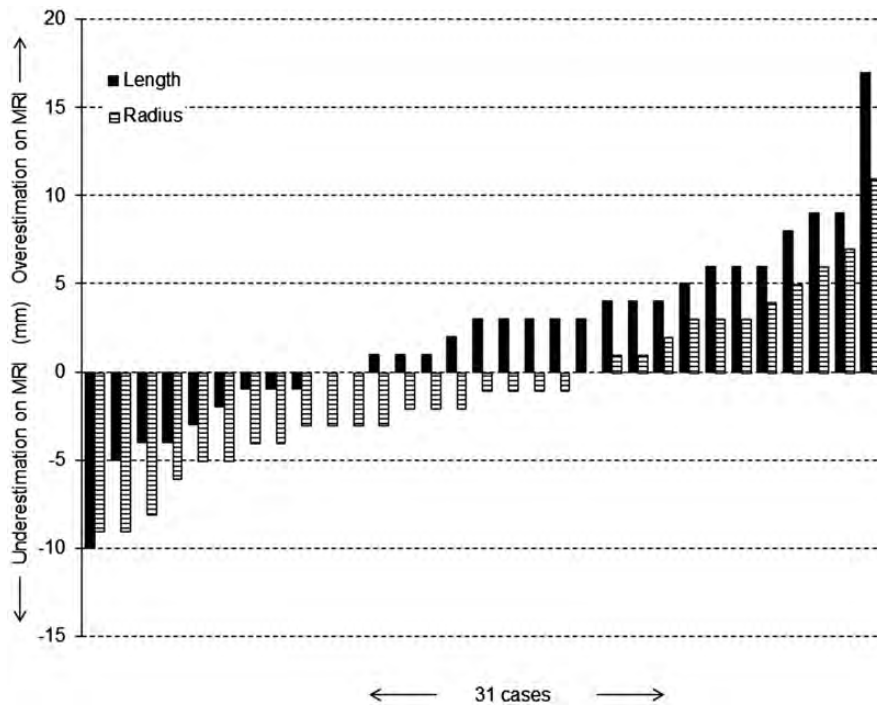
Fig. 3. Distribution of underestimation and overestimation of all cases in the order sorted by length.
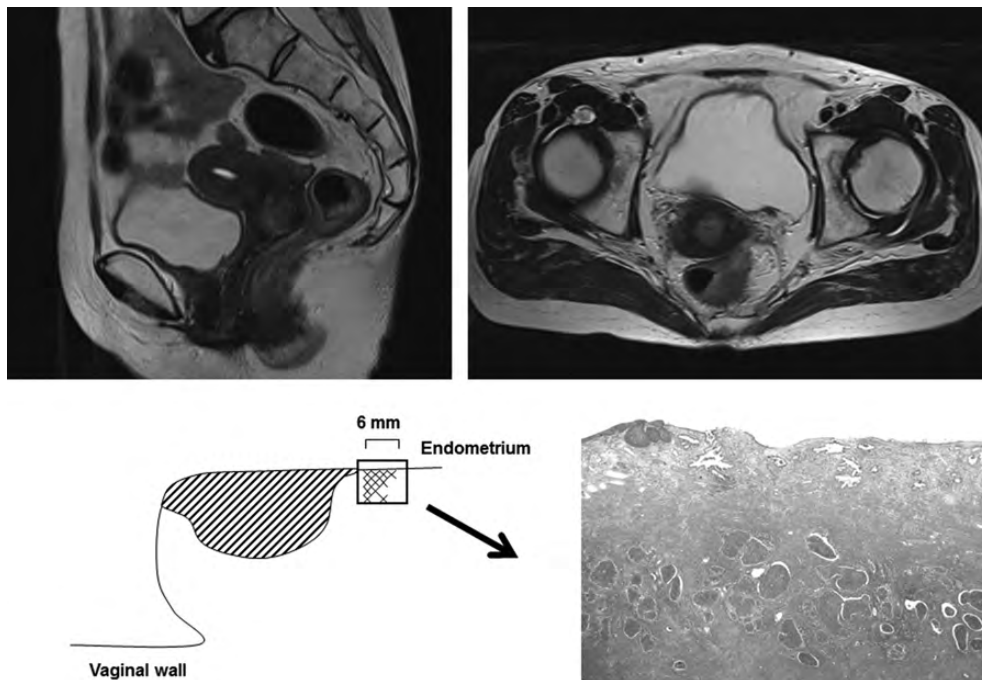

Fig. 4. Patterns of tumor extension in a Stage T1b, 56-year-old cervical cancer patient with endometrial invasion in lymphovascular form. Sagittal and transverse T2-weighted images on MRI showed a 20-mm-length hyperintense tumor in the cervix with preserved low signal intense stroma. On microscopy, the maximal length was measured as 25 mm, with frontline involvement of 6 mm toward the endometrium (hematoxylin and eosin, ×10 magnification).
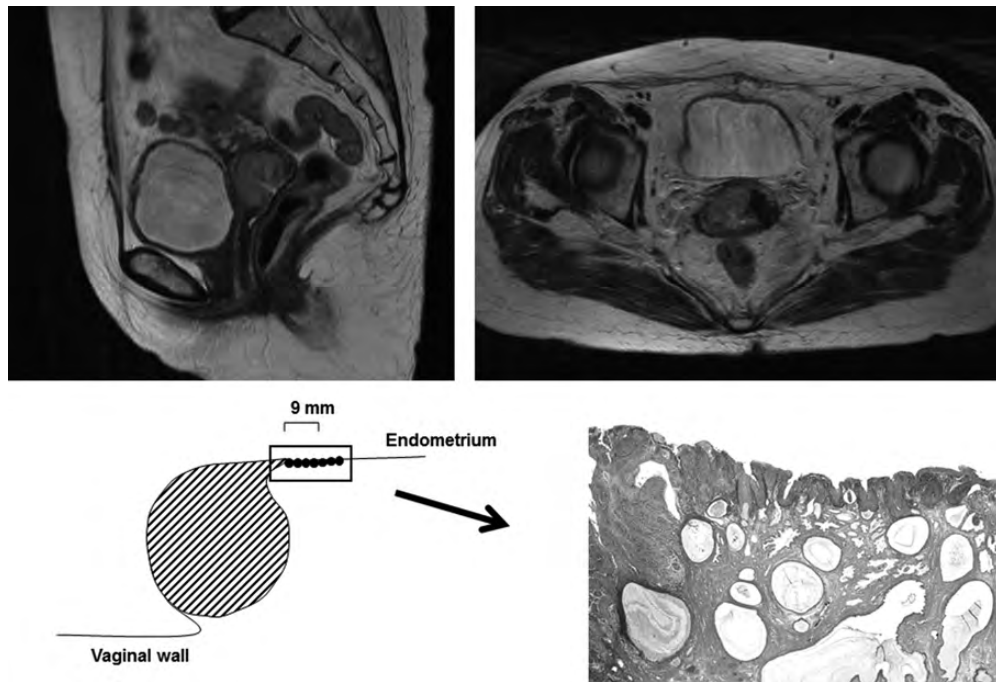
Fig. 5. T2-weighted MRI images of a 59-year-old patient demonstrated a hyperintense tumor in the right wall of the cervix with a maximal size and length of 31 and 24 mm, respectively. Although there was a part where low signal intense stroma looked to be interrupted, no clear evidence or parametrial invasion is indicated on MRI. On microscopy, the *maximal tumor length* was measured as 30 mm including an 8-mm lesion of *in situ* endometrial involvement (hematoxylin and eosin, ×10 magnification).

with a maximal size < 2 cm measured by MRI ($n = 6$) extended to the endometrium more than 1/3.

Factors that were associated with longer endometrial extension (for 1/3 or more extension vs. <1/3, respectively) included median maximal tumor size by MRI (30.9 vs. 23.2 mm, $P = 0.01$), squamous cell carcinoma histology ($n = 15/17$ (88%) vs. $n = 7/14$ (50%), $P = 0.02$) and lympho-vascular invasion ($n = 17/17$ (100%) vs. $n = 4/14$ (29%), $P < 0.01$). The range of extension was not affected by age, endophytic tumor type or clinical tumor stage.

DISCUSSION

When defining target volumes in radiotherapy, radiation oncologists routinely take the safety margin of arbitrary dimensions into account. An additional margin to account for a possible microscopic involvement is usually added around the tumor volume because a spherical extension of malignant cells is hypothesized. Landoni *et al.* reported that the tumors spread endocervically, equally in all directions, by investigating 230 operative specimens from radical hysterectomies of patients with clinical stage IB–IIA disease. According to their report, tumor extension to the anterior, posterior parametrium, and parametria was noted in 23%, 15% and 28–34% of cases, respectively [13]. However, they indicated only the presence of invasion in

each direction and did not provide information regarding the actual tumor extent. In fact, in our series, the tumor extension from the tumor periphery did not seem to be 'spherical' in each direction. Although there are several reports on radiological and pathological correlations of cervical cancer [14–18], information on topographic tumor extension especially on T2-weighted MRI, in respect to IGBT, remains limited. As it is important to understand microscopic extension around the tumor in gynecological IGBT, we tried to quantify the magnitude of uterine body involvement relative to MRI data. This information may add to the knowledge on tumor density around the gross tumor volume, which cannot be visualized by any available imaging modalities.

Significance of treating entire uterine body in brachytherapy

In the treatment of cervical cancer with brachytherapy, there is a trade-off between inclusion of the entire uterine fundus and inclusion of only the proximal portion of the uterus to avoid excessive doses to organs. It is important to know how much of a reduction in dwell time of the radio-active source in the uterine fundus is safe.

The significance of treating the entire uterine body has been questioned. Anker *et al.* reported the results of adaptive brachytherapy retracting the tandem source from the

uterine fundus according to clinical response in 45 patients with stage IB1–IVA cervical cancer [19]. At a median follow-up time of 24.5 months, their method yielded excellent local control rates (3-year overall survival of 67%, local control rate of 97%). It was also indicated that adaptive brachytherapy may be useful in decreasing late toxicities. Similar excellent results of MRI-based planning in cervical cancer brachytherapy have been reported to date [20–22].

In our series, in which the clinical stage of the majority (73%) was TIb1 or less, a massive uterine body involvement of 50% or more was observed in 6 (19%) patients, and that of 1/3 or more was observed in 17 (55%) patients. Further, the length of the longitudinal direction tended to be underestimated more often than that of the radial direction. These points may be helpful to keep in mind when delineating the CTVs. Another finding was that none of the tumors with a maximal size < 2 cm as measured by MRI extended toward the endometrium more than 1/3, suggesting that the entire uterine body does not always need to be treated. In contrast, larger tumors, squamous histology and lymphovascular invasion were related to an endometrial extension over 1/3 of the intracavitary length. Therefore, retracting the tandem source should be performed with caution especially for larger tumors > 2 cm.

The value of MRI in the assessment of tumor extension

In this study, we present a brachytherapy-oriented description of tumor extension. With regard to size measurement by MRI, a good correlation was observed. Sheu *et al.* reported that size measured by MRI underestimated pathological size, while there was a consistent correlation for tumors > 1 cm in diameter [17]. In our series, all but one tumor exceeded 1 cm in size, and the sizes obtained from both measurements were well correlated. However, one of the limitations of our study may be relevant to the uncertainties of size between microscopy and MRI. It is reported that surgical specimens usually shrink due to fixation for preparation. Such shrinkage is reported to be typically <10% in any dimension [23]. Considering the median underestimated length of 4 mm (range 1–17 mm) in our series, as well as tumor shrinkage due to fixation, a CTV margin of 1 cm around the tumor [7] seems to be adequate to cover the majority of potential tumor spread when focusing on only a high-intensity area in T2-weighted MRI. However, our result does not apply to more advanced disease, in which tumor size and appearance can be modified by proceeding with external beam radiation therapy.

Other limitations of our study include the small sample size as well as the unbalanced distribution of subjects with predominantly early-stage disease. We had to exclude patients whose tumors were difficult to identify due to their physiological and anatomical features, which were often influenced by age or coincident pregnancy. As our study subjects had resectable cervical cancers, our results apply only to early-stage patients in which target volumes are delineated on MRI, with less impact of preceding external beam radiation therapy. In addition, MRI in our study were only taken in routine transverse, sagittal, coronal planes although GEC-ESTRO required MRI acquisition in para-axial (orthogonal to the uterine axis), para-sagittal and para-coronal (parallel to the uterine axis) orientation [9]. In contrast, the strength of the study includes a detailed, brachytherapy-oriented analysis of the morphology of tumor extension and the magnitude of uterine body involvement. These findings would help careful delineation of the CTV and support to retract the tandem source from the uterine fundus in selected patients.

With modern imaging modalities, identification of the actual possibility of tumor existence within target volumes is still one of the most challenging tasks. In addition, the validity of retracting the tandem source from the uterine fundus should be tested in prospective trials.

CONCLUSION

A small underestimation of extension toward the endometrium occurred with MRI, suggesting that precise tumor delineation could be made by MRI. For patients with tumors < 2 cm, treatment of the entire uterine body length by activating the tandem source at the fundus may not be necessary. A 1-cm margin around MRI-based gross tumor volume seems to be adequate to cover the actual tumor involvement.

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