A predictor of tumor recurrence in patients with endometrial carcinoma after complete resection of the tumor: the role of pretreatment apparent diffusion coefficient

Objectives: To assess the prognostic and incremental value of pretreatment apparent diffusion coefficient

(ADC) values of tumors for the prediction of tumor recurrence after complete resection of the tumor in

patients with endometrial cancer.

Methods/Materials: This study enrolled 210 patients with stage IA to IIIC endometrial cancer who had

undergone complete resection of the tumor and pretreatment magnetic resonance imaging (MRI). The

minimum and mean ADC values (ADCmin, ADCmean) of tumors and normalized ADC (nADCmin,

nADCmean) were calculated from MRI. The primary outcome was recurrence free survival (RFS).

Receiver operating characteristic (ROC) analysis was performed to compare the diagnostic performance

of ADC values of four types. The Kaplan–Meier method, log-rank tests, and Cox regression were used to

explore associations between recurrence and the ADC values with adjustment for clinico-pathological

factors.

Results: In ROC analysis, the areas under the curve were significant for ADCmean and nADCmean

predicting tumor recurrence, but were not significant for ADCmin and nADCmin. Regarding univariate analysis, ADCmean and nADCmean were associated significantly with increased risk of recurrence. Multivariate analysis showed that ADCmean and nADCmean remained independently associated with shorter RFS. In the high risk group, the RFS of patients with lower ADC values (ADCmean and nADCmean) was significantly shorter than that of patients in the higher ADC value group.

Conclusions: Pretreatment tumor ADCmean and nADCmean were important imaging biomarkers for predicting recurrence in patients after complete resection of the tumor. They might improve existing risk stratification.

Key Words: endometrial cancer, prognostic factor, risk classification, apparent diffusion coefficient

Introduction

Endometrial carcinoma, the most common gynecologic malignancy in developed countries, has

markedly increased in the past few decades in Japan.[1,2] Most patients are diagnosed at an early stage as

International Federation of Gynecology and Obstetrics (FIGO) stage I or II, with a favorable prognosis.[1]

Still, 15–20% of patients develop recurrence after primary surgery[3,4] The 2009 FIGO is the most widely

used classification to standardize management and to predict outcomes.[1,5] Nevertheless, the existence of

other factors that affect overall outcome and recurrence such as age, histological subtype, and

lymphovascular space invasion (LVSI) are known not to be included in FIGO classification[6,7] During the

last decade, several risk stratification systems (RSS) that aggregate these prognostic factors were

formulated to identify patients at risk of recurrence more accurately: those who might benefit from

adjuvant therapy.[7–12] Among several new RSS, the European Society of Medical Oncology (ESMO), with

the support of the European Society for Radiotherapy & Oncology (ESTRO) and the European Society of

Gynaecological Oncology (ESGO), introduced a new risk classification based on clinical trial results.[13]

Although these RSS are used worldwide to guide clinical decision-making and clinical trial design

formulation, they are insufficient to stratify recurrence risk accurately.[14] Consequently, the need exists to

use novel biomarkers to improve recurrence risk assessment for individualized patient management.

Pelvic magnetic resonance imaging (MRI) has long been used for preoperative staging of

endometrial carcinoma as one-stop shopping.[15,16] Recent progress of hardware enables diffusion-weighted

imaging (DWI) to be used as an imaging biomarker in pelvic MRI.[17] Actually, DWI, a functional imaging

technique based on the random motion of water molecules, provides useful information to detect

malignant tumors because of its high conspicuity. It can also provide quantitative parameter: the apparent

diffusion coefficient (ADC).[17,18] The ADC value reflects the magnitude of diffusion of water molecule.

Therefore lower ADC value has been considered to correlate with higher cellular density, which act to

restrict water diffusion. Several reports have described correlation between ADC value and tumor

cellularity, aggressiveness, treatment response, and prognosis for cancers of different types.[19–22] For

endometrial carcinoma, only one report has described a correlation between pretreatment tumor ADC

values and prognosis in patients with FIGO IA–IVB.[23] However, no report of the literature describes

evaluation of the role of ADC value for predicting recurrence in patients with complete resection of the

tumor.

This study was conducted to evaluate the usefulness of ADC values for predicting recurrence in

patients with complete resection of the tumor and to assess the incremental value in recurrence risk

stratification.

Materials and Methods

This study was exempted from obtaining individual informed consent based on the Ethical Guidelines for

Medical and Health Research Involving Human Subjects by the Ministry of Education, Culture, Sports,

Science and Technology and Ministry of Health, Labour, and Welfare. The study protocol was approved

by the Ethics Committee, Kyoto University Graduate School and Faulty of Medicine.

Patients

Between July 2005 and March 2015, we retrospectively identified and analyzed 295

consecutive patients with stage IA–IIIC endometrial carcinoma who had undergone surgical treatment

and pretreatment MRI with DWI at our institution. Of these, patients were excluded based on the

following criteria: poor quality of DWI because of severe motion artifact (n=3), no measurable lesion on

DWI because of small tumor size (n=55), patient with residual disease (n=2), incomplete staging surgery

at high-intermediate to high risk patients (n=15), and patients with neoadjuvant chemotherapy (n=10).

Finally, 210 patients were enrolled in this study. Clinical and pathological data were taken from clinical

records, including patient age, serum CA125 level, tumor histology to World Health Organization

classification (WHO), depth of myometrial invasion, LVSI, cervical stromal invasion, T3 factor (i.e.,,

serosal/adnexal/vaginal involvement), peritoneal cytology, synchronous ovarian carcinoma, FIGO stage,

and the type of treatment. We used a FIGO 2009 staging system and Union Internationale Contre Le

Cancer (UICC) Seventh TNM classification[24] for staging. Risk classification was determined based on

ESMO-ESGO-ESTRO classification. Each risk group was determined as follows: Low risk group was

classified as stage IA, grade 1 or 2 endometrioid carcinoma without LVSI. Low-intermediate risk was classified as stage IB, grade 1 or 2 endometrioid carcinoma without LVSI. High-intermediate risk was classified as stage IA or IB, grade 1 or 2 endometrioid carcinoma with LVSI, and stage IA, grade 3 endmetrioid carcinoma. High risk was classified as stage IB, grade 3 endometrioid carcinoma, stage II, with any histological subtype, stage III, endometrioid carcinoma with no residual disease and non-endometrioid carcinoma (see Table, Supplemental Digital Content 1, which summarizes the risk classification).

Treatment and Follow up

All patients underwent total hysterectomy and bilateral salpingo-oophorectomy (TH + BSO) and/or partial omentectomy with or without pelvic and/or para-aortic lymphadenectomy. Twenty-three patients with low risk for recurrence underwent TH + BSO alone. Among 32 patients with cervical stromal invasion, 17 patients underwent radical hysterectomy and remaining 15 patients underwent standard total abdominal hysterectomy. Additional adjuvant chemotherapy was determined based on FIGO stage, tumor histology, patient preference, and physician discretion. Adjuvant chemotherapy was performed for 117 patients and not for 83 patients. Among those 83 patients, 17 patients with high-intermediate to high risk had not received adjuvant chemotherapy. The standard regimen in our institution was paclitaxel and carboplatin, or adriamycin and cisplatin for six cycles. No patient enrolled in this study received radiotherapy.

Patients were generally followed up every three months for the first two years, every six months during the third to fifth years, and every 12 months from the sixth year on. Follow-up examination included a combination of a physical and pelvic examination, vaginal cytology, tumor marker

measurements, transvaginal ultrasonography, and optional CT scanning. The observation period was over 18 months from the final enrollment

The primary outcome was recurrence-free survival (RFS), defined as the time from the date of primary surgery to the date of recurrence. Patients who died without disease recurrence (n=4) were censored at the date of last follow-up.

MRI technique

For this study, MRI was performed using a 1.5-T unit (Symphony and Avanto; Siemens Health Care, Erlangen, Germany) or a 3.0-T unit (Trio and Skyra; Siemens Health Care, Erlangen, Germany). Before examinations, 20 mg of butyl scopolamine (Buscopan®; Nippon Boehringer Ingelheim Co. Ltd., Tokyo, Japan) was administered to reduce bowel motion, unless contraindicated. Sagittal DWIs were obtained in all patients along with basic sequence evaluations for primary lesion, Sagittal T1 and T2-WI, axial T2WI, oblique axial T2WI for uterine corpus and/without dynamic contrast enhanced T1W I. The parameters for DWI were the following: repetition time (TR)/echo time (TE) = 4800-5300/59-75 ms at 3.0 T, TR/TE = 2300-3000/70-79 ms at 1.5 T; field of view (FOV) = 260 × 195-260 mm at 3.0T and 1.5 T; slice thickness/ intersection gap = 4 mm/1 mm at 3.0 T and 1.5 T; matrix size: 128 × 128 at 3.0T, 128 × 90 at 1.5 T; fat suppression technique: spectral adiabatic inversion recovery (SPAIR) at 3.0T and chemical shift selective (CHESS) at 1.5 T. The b-values were 0, 500, and 1000 s/mm^2 until Mar. 2009 and 0, 100, 500, and 1000 s/mm^2 from July 2009. ADC maps were generated automatically using a mono-exponential decay model including all three or four b-values.

Image analysis

For measurements of the ADC values of the tumor, a round/oval shaped region of interest

(ROI) was drawn manually on an ADC map in each patient. The ROIs were placed on the largest solid

portion of the tumor, avoiding any necrotic or cystic portion. The mean and minimum values (ADCmean,

ADCmin) of all pixels of the ROI were obtained. All ROIs were drawn by one radiologist with six years

of experience who specialized in gynecologic imaging. To reduce ADC variation across the mixed data

from various MRI equipment and different *b* values, we used urine in the bladder as an internal reference

for the normalization of ADC values, as described in earlier reports.[25–27] Normalized ADC (nADC) was

calculated as tumor ADC / urine ADCmean. Urine ADC value was obtained from the ROI placed in the

center of the bladder lumen. The methods of placing ROI both on bladder and tumor on ADC map were

shown on Supplemental Digital Content 2.

Statistical Analysis

Statistical analyses were conducted using a commercially available software package (Medcalc ver.

12.3.0; MedCalc Software bvba, Ostend, Belgium). Receiver operating characteristic (ROC) analysis was

performed to evaluate the diagnostic performance of ADC values of four types for predicting recurrence:

nADC mean, nADC min, ADC mean, and ADC min. ROC analysis was also applied to determine an

optimal cut-off value using the Youden index. The Kaplan–Meier method, log-rank tests, and Cox

regression were used to explore the associations between recurrence and the ADC values with adjustment for clinico-pathological factors: patient age, serum CA125 level, tumor histology, depth of myometrial invasion, LVSI, cervical stromal invasion, T3 factor, peritoneal cytology, synchronous ovarian carcinoma, FIGO stage, risk classification, and adjuvant chemotherapy. We used two multivariate Cox regression models with different variable selection methods. The first model included statistically significant variables in the univariate analyses. FIGO stage and risk classification were eliminated from the model to avoid multicollinearity with the depth of myometrial invasion, cervical stromal invasion, T3 factor, and lymph node metastasis. A second model was built with risk classification alone. The ADC values were added to each model separately to evaluate their associations with recurrence under different adjustment factors. All p-values were two-sided; results for which $p < 0.05$ were inferred as statistically significant.

Results

Patient Characteristics and Outcome

Patient and tumor characteristics are presented in Table 1. The median age was 58 (range, 28-85). According to the risk classification (Supplement table), 80 patients (38%) were classified as low risk, 12 (6%) as low-intermediate risk, 25 (12%) as high-intermediate risk, and 93 (44%) as high risk. At the median follow-up period of 54 months (range, 1–123 months), 23 of 210 patients developed recurrence after surgery. Of the 23 recurrences, 21 (91%) were high risk; 2 (9%) were of the low risk group. The recurrence sites were as follows: 7 (30%) at vaginal site, 7 (30%) at lung, 5 (23%) at pelvic or para-aortic lymph nodes, 3 (13%) at supra-diaphragmatic lymph nodes and 1 (4%) at peritoneum.

ROC curve analysis

ROC analysis showed that the AUC for ADCmean, ADCmin, nADCmean, and nADCmin were 0.653, 0.603, 0.650 and 0.623 respectively. The AUCs for ADCmean and nADCmean were significantly different from 0.5. On the contrary, the AUCs for ADCmin and nADCmin were not significant (Table 2). Therefore ADCmean and nADCmean were used for remaining analyses. The optimal cut-off value of ADCmean and nADCmean were, respectively, 702×10^{-6} mm^2/s and 0.2635.

Univariate and multivariate analyses

From univariate analysis, we found that tumor histology, depth of myometrial invasion, LVSI, cervical involvement, lymph node metastases, T3 factor, FIGO stage, risk classification, addition of adjuvant chemotherapy, ADCmean and nADCmean were associated significantly with increased risk of

recurrence (Table 3). Using stepwise variable selection, we found that tumor histology, cervical stromal invasion, and T3 factor were independently associated with shorter RFS. These three covariates formed the first model for testing the independent association of ADC values with RFS.

As the next step, ADCmean and nADCmean were added to the model separately (Table 4). As a result, both ADCmean and nADCmean remained independently significant factor. ADCmean and nADCmean were also associated independently with RFS when added to a second model that included the risk classification (Table 5).

Kaplan–Meier analysis was applied for patients with high risk because almost all patients with recurrence were in the high risk group (n=21/23). Patients with lower ADC values (ADCmean and nADCmean) showed significantly shorter RFS than patients in the higher ADC value group (Figure 1).

Discussion

Our results showed that pretreatment low ADC values of endometrial carcinoma correlate with decreased recurrence-free interval, independent of their relation with other prognostic factors and risk classification based on ESMO-ESGO-ESTRO classification. All factors included in risk classification (i.e., tumor histology, depth of myometrial invasion, LVSI, cervical involvement, lymph node metastases, T3 factor, FIGO stage) and risk classification itself were associated significantly with recurrence in univariate analysis. Both ADCmean and nADCmean were independent prognostic factors in multivariate analysis with prognostic factors and with risk classification. Furthermore, ADC values can improve risk classification in patients of the high risk group.

This study measured ADC parameters of four types (ADCmin, ADCmean, nADCmin, and nADCmean) and initially performed comparison of diagnostic values of each ADC values for the prediction of recurrence. In earlier articles, several studies investigate the relation between several types of ADC values and prognostic factors in endometrial carcinoma.[28–30] However, continuous discussion has ensued as to which ADC parameter of ADCmin, ADCmean, and percentileADC is better to use for evaluate relation with prognostic factors. Regarding the prediction of prognosis, only one report[23] describes the role of ADC values. Nakamura et al. showed that ADCmin is an independent predictor for disease-free survival in patients with FIGO stage IA to IVB, but do not evaluate ADC values of other types. In our results, neither ADCmin nor nADCmin showed a significant difference, in contrast to results described in an earlier report[23]. This discrepancy might be explained by the difference of study populations. Their population included patients with FIGO stage IV who had lower ADC values than

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patients with FIGO stage I. The difference in ROI method might be another cause of this discrepancy. We used singular round/oval shaped ROI, whereas Nakamura et al. used multiple small round ROIs to obtain ADC values. Regarding the effects of ROI method measuring ADC values, Inoue et al.[31] showed that ADCmin for multiple small ROIs was significantly higher than ADCmin for round ROI. Although ADCmin has been suggested to reflect the highest tumor cell density,[32,33] it might more influenced by the ROI method and MR signal artifact.[34] Recently, volumetric histogram analysis has been applied for patients with cervical and endometrial carcinoma to reduce the influence of such artifacts and sampling biases.[30] Although volumetric analysis was not used because it is time-consuming for clinical use and because it entails difficulty in delineating outlines and avoiding cystic portion in several cases.

Results showed that lower ADC values predict worse prognosis, independent of the histological grade. ADC values are expected to reflect the tumor cellularity, but controversy persists about the correlation between ADC values with tumor grade. Some earlier studies found significant differences among tumor grades, but others did not.[18,23,28–30,35–38] Therefore, our result indicates that ADC values might reflect independent biologic characteristics of tumor that cannot be evaluated by tumor grade, LVSI, or other means. Recently, some studies have investigated the correlation between ADC values and Ki67 proliferation index based on the hypothetical association between tumor cellularity and proliferative activity in brain tumors, breast cancer, and renal cell carcinoma, although it remains controversial.[39–42] In endometrial carcinoma, Ki67 is also an important biomarker for evaluation of tumor aggressiveness, prediction of prognosis, and improving target therapy.[43–45] Further analysis must be done to define those relations.

This study had several limitations. First, our study cohort was small, leading to a small number of recurrence cases. We used stepwise variable selection to reduce the risk of overfitting because the

number of recurrence events was too small compared with the number of predictors. The same reason also applied not to evaluate the additional power of ADC values for prediction of recurrence at low to high-intermediate risk group. Some risk arises of underestimation of some important combination of variables. Second, some variation of ADC values occurs with different MRI scanners (1.5 and 3.0 T) and different sets of b values (b= 0,,500, 1000 and 0, 100, 500, 1000). To reduce intra-study variation of ADC values, we calculated normalized ADC using urine in bladder as an internal reference. Results of earlier studies have shown that urine in the bladder is a superior internal reference to skeletal muscles in pelvic MRI.[25–27] Third, we did not consider the difference of ADC values between histologic subtypes. Carcinosarcoma was shown in an earlier study to exhibit higher ADC values than endometrial carcinoma.[46] Therefore, further study is necessary to assess the prognostic impact on specific histologic subtypes such as carcinosaroma.

In conclusion, pretreatment tumor ADCmean and nADCmean can be important imaging biomarkers for the prediction of recurrence in patients with complete resection of the tumor, independent of their relation with other prognostic factors and risk classification based on ESMO-ESGO-ESTRO classification. Moreover, ADC values might be able to improve existing risk stratification in a high-risk group.

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FIGURE 1. Kaplan–Meier curves for the RFS rates of 72 patients at high risk group, according to ADCmean (A) and nADCmean (B). Cut-off values were 702×10^{-6} mm^2/s and 0.2635 respectively. The p values were calculated using the log-rank test.

SUPPLEMENTAL FIGURE.

ADC measurements of tumor and urine in bladder. By referencing the sagittal T2-weighted images (A) and DWI, round or oval shaped ROIs were placed manually on the largest solid portion of the tumor and the center of the bladder lumen on the ADC map (B).

List of Supplemental Digital Content

Supplemental Digital Content 1.   Table which summarizes the risk classification.   doc

Supplemental Digital Content 2.   Figure which shows the methods of placing ROI both on bladder and tumor on ADC map.   tif