A Predictor of Tumor Recurrence in Patients With Endometrial Carcinoma After Complete Resection of the Tumor

The Role of Pretreatment Apparent Diffusion Coefficient

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Objectives: The aim of this study was 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: This study enrolled 210 patients with stages IA to IIIC endometrial cancer who had undergone complete resection of the tumor and pretreatment magnetic resonance imaging. The minimum and mean ADC values (ADCmin, ADCmean) of tumors and normalized ADC (nADCmin, nADCmean) were calculated from magnetic resonance imaging. The primary outcome was recurrence-free survival (RFS). Receiver operating characteristic analysis was performed to compare the diagnostic performance of ADC values of 4 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 clinicopathological factors.

Results: In receiver operating characteristic curve 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 significantly associated 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: Apparent diffusion coefficient, Endometrial cancer, Prognostic factor, Risk classification

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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% to 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) is known not to be included in FIGO classification6,7. During the last decade, several risk stratification systems (RSSs) that aggregate these prognostic factors were formulated to more accurately identify patients at risk of recurrence: those who might benefit from adjuvant therapy.7–12 Among several new RSSs, the European Society of Medical Oncology (ESMO), with the support of the European Society for Radiotherapy and Oncology (ESTRO) and the European Society of Gynaecological Oncology (ESGO), introduced a new risk classification based on clinical trial results.13 Although these RSSs are used worldwide to guide clinical decision making and clinical trial design formulation, they are insufficient to accurately stratify recurrence risk.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 a 1-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 acts 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 1 report has described a correlation between pretreatment tumor ADC values and prognosis in patients with FIGO stages IA to IVA.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 Faculty of Medicine.

Patients

Between July 2005 and March 2015, we retrospectively identified and analyzed 295 consecutive patients with stages IA to 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-risk 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 CA-125 level, tumor histology to World Health Organization classification, depth of myometrial invasion, LVSI, cervical stromal invasion, T3 factor (ie, serosal/adnexal/vaginal involvement), peritoneal cytology, synchronous ovarian carcinoma, FIGO stage, and the type of treatment. We used the FIGO 2009 staging system and Union Internationale Contre Le Cancer seventh TNM classification24 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 IIA or IB, grade 1 or 2 endometrioid carcinoma with LVSI, and stage IA, grade 3 endometrioid 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 nonendometrioid carcinoma (see Table, Supplemental Digital Content 1, http://links.lww.com/IGC/A712, which summarizes the risk classification).

Treatment and Follow-up

All patients underwent total hysterectomy and bilateral salpingo-oophorectomy and/or partial omentectomy with or without pelvic and/or para-aortic lymphadenectomy. Twenty-three patients with low risk of recurrence underwent total hysterectomy and bilateral salpingo-oophorectomy alone. Among 32 patients with cervical stromal invasion, 17 patients underwent radical hysterectomy, and the 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 6 cycles. No patient enrolled in this study received radiotherapy.

Patients were generally followed up every 3 months for the first 2 years, every 6 months during the third to fifth years, and every 12 months from the sixth year on. Follow-up
**TABLE 1. Patients and tumor characteristics**

| Age, median (range), y | 58 (28–85) |
|------------------------|------------|
| FIGO stage, n (%)      |            |
| IA                     | 108 (51)   |
| IB                     | 37 (18)    |
| II                     | 19 (9)     |
| IIIA                   | 6 (3)      |
| IIIC1                  | 15 (7)     |
| IIIC2                  | 25 (12)    |
| Histology, n (%)       |            |
| Endometrioid carcinoma grade 1 | 103 (49) |
| Endometrioid carcinoma grade 2 | 42 (20)  |
| Endometrioid carcinoma grade 3 | 31 (15)  |
| Serous carcinoma        | 17 (8)     |
| Clear cell carcinoma    | 3 (1)      |
| Carcinosarcoma          | 4 (2)      |
| Others                  | 10 (5)     |
| Risk classification, n (%) |      |
| Low                     | 80 (38)    |
| Low-intermediate        | 12 (6)     |
| High-intermediate       | 25 (12)    |
| High                    | 93 (44)    |

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). 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-weighted imaging, axial T2-weighted imaging, oblique axial T2-weighted imaging for uterine corpus, and without dynamic contrast-enhanced T1-weighted imaging. The parameters for DWI were the following: repetition time/echo time = 4800 to 5300/59 to 75 milliseconds at 3.0 T, repetition time/echo time = 2300 to 3000/70 to 79 milliseconds at 1.5 T; field of view = 260 × 195 to 260 mm at 3.0 and 1.5 T; slice thickness/intersection gap = 4 mm/1 mm at 3.0 and 1.5 T; matrix size 128 × 128 at 3.0 T, 128 × 90 at 1.5 T; and fat suppression technique: spectral adiabatic inversion recovery at 3.0 T and chemical shift selective at 1.5 T. The b values were 0, 500, and 1000 s/mm² until March 2009 and 0, 100, 500, and 1000 s/mm² from July 2009. Apparent diffusion coefficient maps were generated automatically using a monoexponential decay model including all 3 or 4 b values.

Image Analysis

For measurements of the ADC values of the tumor, a round/oval 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 1 radiologist with 6 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. 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 are shown on Supplemental Digital Content 2, http://links.lww.com/IGC/A713.

**Statistical Analysis**

Statistical analyses were conducted using a commercially available software package (MedCalc version 12.3.0; MedCalc Software bvba, Ostend, Belgium). Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of ADC values of 4 types for predicting recurrence: nADCmean, nADCmin, ADCmean, and ADCmin. Receiver operating characteristic curve analysis was also applied to determine an optimal cutoff 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 clinicopathological factors: patient age, serum CA-125 level, tumor histology, depth of myometrial invasion, L VSI, cervical stromal invasion, T3 factor, peritoneal cytology, synchronous ovarian carcinoma, FIGO stage, risk classification, and adjuvant chemotherapy. We used 2 multivariate Cox regression models with different variable selection methods. The first model included statistically significant variables in the univariate analyses. The FIGO stage and risk classification were eliminated from the model to avoid

| AUC    | SE    | 95% CI       | P     |
|--------|-------|--------------|-------|
| ADCmean| 0.653 | 0.0645       | 0.526–0.779 | 0.0180* |
| ADCmin | 0.603 | 0.0699       | 0.472–0.734 | 0.1246  |
| nADCmean| 0.650 | 0.0598       | 0.533–0.768 | 0.0120* |
| nADCmin| 0.623 | 0.0634       | 0.498–0.747 | 0.0531  |

*P < 0.05.

AUC, Area under the curve; CI, confidence interval.
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 2-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 years (range, 28–85 years). According to the risk classification (Supplement Table http://links.lww.com/IGC/A712), 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 supradiaphragmatic lymph nodes, and 1 (4\%) at peritoneum.

ROC Curve Analysis

Receiver operating characteristic curve analysis showed that the AUC for ADCmean, ADCmin, nADCmean, and

| Variable                        | Category     | n (%)     | HR     | 95% CI          | \( P \)  |
|---------------------------------|--------------|-----------|--------|-----------------|---------|
| **Age**                         |              |           |        |                 |         |
| <60 y                           | 117 (56)     | Reference |        |                 | 0.189   |
| \( \geq 60 \) y                  | 93 (44)      | 1.739     | 0.766–3.951 | 0.010   |
| **CA-125 (U/ml)**               |              |           |        |                 |         |
| <40                             | 152 (72)     | Reference |        |                 | 0.086   |
| \( \geq 40 \)                    | 58 (28)      | 2.060     | 0.907–4.678 | 0.010   |
| **Tumor histology**             |              |           |        |                 |         |
| Grades 1–2                      | 145 (69)     | Reference |        |                 | 0.002   |
| Grade 3 and nonEC               | 65 (31)      | 4.529     | 1.928–10.638 | 0.010   |
| **Myometrial invasion**         |              |           |        |                 |         |
| <1/2                            | 124 (59)     | Reference |        |                 | 0.001   |
| \( \geq 1/2 \)                   | 88 (41)      | 4.327     | 1.714–10.925 | 0.010   |
| **LVSI**                        |              |           |        |                 |         |
| Absent                          | 134 (64)     | Reference |        |                 | 0.037   |
| Present                         | 76 (36)      | 2.405     | 1.059–5.463 | 0.010   |
| **Cervical stromal invasion**   |              |           |        |                 |         |
| Absent                          | 178 (85)     | Reference |        |                 | 0.002   |
| Present                         | 32 (15)      | 3.864     | 1.679–8.894 | 0.010   |
| **Peritoneal cytology**         |              |           |        |                 |         |
| Absent                          | 188 (89)     | Reference |        |                 | 0.221   |
| Present                         | 24 (11)      | 1.859     | 0.692–4.990 | 0.010   |
| **Lymph node metastasis**       |              |           |        |                 |         |
| Absent                          | 170 (81)     | Reference |        |                 | 0.001   |
| Present                         | 40 (19)      | 4.420     | 1.957–9.986 | 0.010   |
| **T3 factor**                   |              |           |        |                 |         |
| Absent                          | 191 (91)     | Reference |        |                 | 0.001   |
| Present                         | 19 (9)       | 6.582     | 2.796–15.497 | 0.010   |
| **Synchronous ovarian ca.**     |              |           |        |                 |         |
| Absent                          | 201 (96)     | Reference |        |                 | 0.409   |
| Present                         | 9 (9)        | 1.843     | 0.435–7.813 | 0.010   |
| **FIGO stage**                  |              |           |        |                 |         |
| I                              | 145 (69)     | Reference |        |                 | 0.001   |
| II–III                          | 65 (31)      | 5.370     | 2.219–12.997 | 0.010   |
| **Risk classification**         |              |           |        |                 |         |
| Low-LI                          | 92 (44)      | Reference |        |                 | 0.004   |
| HI-high                         | 118 (56)     | 8.268     | 1.953–35.005 | 0.010   |
| **Adjuvant chemotherapy**       |              |           |        |                 |         |
| Absent                          | 93 (44)      | Reference |        |                 | 0.010   |
| Present                         | 117 (56)     | 4.900     | 1.464–16.399 | 0.010   |
| **ADCmean (10^{-6} \text{mm}^2/\text{s})** |         |           |        |                 |         |
| >702                            | 121 (58)     | Reference |        |                 | 0.004   |
| \( \leq 702 \)                   | 89 (42)      | 3.683     | 1.518–8.933 | 0.010   |
| **nADCmean**                    |              |           |        |                 |         |
| >0.2563                         | 129 (61)     | Reference |        |                 | 0.008   |
| \( \leq 0.2563 \)                | 81 (39)      | 3.190     | 1.358–7.493 | 0.008   |

*\( P < 0.05. \)

CI, confidence interval; HI, high-intermediate; HR, hazard ratio; LI, low-intermediate; nonEC, nonendometrioid carcinoma.
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 cutoff value of ADCmean and nADCmean were, respectively, 702 \times 10^{-6} \text{mm}^2/\text{s} and 0.2635.

### Univariate and Multivariate Analyses

From univariate analysis, we found that tumor histology, depth of myometrial invasion, LVS, cervical involvement, lymph node metastases, T3 factor, FIGO stage, risk classification, addition of adjuvant chemotherapy, ADCmean, and nADCmean were significantly associated 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 3 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 factors. The 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 compared with patients in the higher ADC value group (Fig. 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 (ie, tumor histology, depth of myometrial invasion, LVS, cervical involvement, lymph node metastases, T3 factor, FIGO stage) and risk classification itself were significantly associated 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 4 types (ADCmin, ADCmean, nADCmin, and nADCmean) and initially performed comparison of diagnostic values of each ADC value 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. However, continuous discussion has ensued as to which ADC parameter of ADCmin, ADCmean, and percentile ADC is better to use for evaluate relation with prognostic factors. Regarding the prediction of prognosis, only 1 report describes the role of ADC values. Nakamura et al showed that ADCmin is an independent predictor for disease-free survival in patients with FIGO stages IA to IVB but did 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. This discrepancy might be explained by the difference of study populations. Their population included patients with FIGO stage IV who had lower ADC values compared with patients with FIGO stage I. The difference in ROI method might be another cause of this discrepancy. We used singular round/oval 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 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, it

### TABLE 4. Results of multivariate Cox proportional hazard regression analyses for the risk of tumor recurrence with selected variables and ADC values

| Parameter | Attribute | HR | 95% CI | P  |
|-----------|-----------|----|--------|----|
| Model 1 alone | Grades 1–2 vs 3 and nonEC | 4.114 | 1.718–9.850 | 0.002 |
| | Cervical involvement | 3.595 | 1.528–8.461 | 0.004 |
| | T3 factor | 3.996 | 1.645–9.706 | 0.002 |
| Model 1 with ADCmean | Grades 1–2 vs 3 and nonEC | 3.562 | 1.486–8.539 | 0.005 |
| | Cervical involvement | 3.018 | 1.227–7.418 | 0.017 |
| | T3 factor | 4.607 | 1.780–11.925 | 0.002 |
| | ADCmean | 3.652 | 1.456–9.157 | 0.006 |
| Model 1 with nADCmean | Grades 1–2 vs 3 and nonEC | 3.170 | 1.291–7.781 | 0.012 |
| | Cervical involvement | 2.795 | 1.142–6.841 | 0.025 |
| | T3 factor | 5.080 | 1.959–13.176 | 0.001 |
| | nADCmean | 2.969 | 1.190–7.407 | 0.020 |

CI, Confidence interval; HR, hazard ratio; nonEC, non endometrioid carcinoma.
might be more influenced by the ROI method and magnetic resonance imaging signal artifact. Recently, volumetric histogram analysis has been applied for patients with cervical and endometrial carcinoma to reduce the influence of such artifacts and sampling biases. 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. Apparent diffusion coefficient 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. Therefore, our result indicates that ADC values might reflect independent biologic characteristics of tumor that cannot be evaluated by tumor grade, LVS1, or other means. Recently, some studies have investigated the correlation between ADC values and Ki-67 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. In endometrial carcinoma, Ki-67 is also an important biomarker for evaluation of tumor aggressiveness, prediction of prognosis, and improving target therapy. 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-risk to high-intermediate-risk group. Some risk arises because 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 $b = 0, 100, 500, 1000$). To reduce intrastudy variation of ADC values, we calculated nADC 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. 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 compared with endometrial carcinoma. Therefore, further

**TABLE 5.** Results of multivariate Cox proportional hazard regression analyses for the risk of tumor recurrence with risk classification and ADC values

| Parameter | Attribute | HR (95% CI) | P |
|-----------|-----------|-------------|---|
| Model 2 alone | Low/LI vs HI/high risk | 8.2678 (1.9527–35.0052) | 0.004 |
| Model 2 with ADCmean | Low/LI vs HI/high risk | 2.4428 (1.3837–4.3126) | 0.002 |
| | | 3.2489 (1.3364–7.8983) | 0.010 |
| Model 2 with nADCmean | Low/LI vs HI/high risk | 7.916 (1.8690–33.5271) | 0.005 |
| | | 3.0175 (1.2840–7.0918) | 0.012 |

CI, Confidence interval; HI, high-intermediate; HR, hazard ratio; LI, low-intermediate.
study is necessary to assess the prognostic impact on specific histologic subtypes such as carcinosarcoma.

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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