Original Article

Diagnostic Accuracy of Calculated Tumor Volumes and Apparent Diffusion Coefficient Values in Predicting Endometrial Cancer Grade

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Abstract

Background: Magnetic resonance imaging (MRI) has been shown to be an accurate imaging technique for the preoperative assessment of local staging of endometrial cancer and for evaluating the depth of myometrial invasion. **Materials and Methods:** This was a single-center retrospective study performed on patients with histopathologically proven endometrial carcinoma who underwent an MRI examination of the pelvis between October 2017 and May 2020. **Results:** In the present analysis, mean apparent diffusion coefficient (ADC) values for each histologic grade were $0.72 \pm 0.13 \times 10^{-3}$ mm^2/s (G1), $0.76 \pm 0.17 \times 10^{-3}$ mm^2/s (G2), and $0.74 \pm 0.12 \times 10^{-3}$ mm^2/s (G3), respectively, showing no significant correlation between ADC values and tumor grade ($P = 0.73$). Overall, ADC minimum was significant in differentiating grades of endometrial carcinoma ($P = 0.02$) with the ability to differentiate Grade I and II lesions ($P = 0.01$). A mean tumor volume of 25.2 cc could differentiate low-grade tumors (Grade I and Grade II) from high-grade tumors (Grade III) with a sensitivity and specificity of 88% and specificity of 89%. The tumor volume/uterine volume ratio (TV/UV) differentiates high-grade tumors from low-grade tumors ($P < 0.001$), however, no significant difference in the ratio was observed among Grade I and II lesions ($P = 0.48$). The area under the curve of tumor volume was 0.875 (95% confidence interval 0.0–1.00) ($P = 0.001$), indicating that tumor volume was an effective tool for distinguishing high-grade and low-grade endometrioid adenocarcinomas. The corresponding sensitivity and specificity were 88.0% and 89.0%, respectively. **Conclusion:** Preoperative noninvasive radiological assessment for tumor volume, TV/ UV or tumor volume/uterine volume is important surrogate markers for preoperative prognostication of endometrial carcinoma.

Keywords: *Endometrial carcinoma, grade, magnetic resonance imaging, tumor volume*

Introduction

Endometrial cancer remains the most common gynecological malignancy in the developed world, with an upward trend observed in developing nations due to changing lifestyles, particularly related to an increase in obesity and life expectancy.[1,2] The prognosis of the disease depends on various factors such as the age of the patient, clinical stage, depth of myometrial invasion, grade of the tumor, lymphovascular invasion, and nodal metastases. These factors are pertinent for deciding the course of disease management, in particular, the need for retroperitoneal lymph nodal dissection. Magnetic resonance imaging (MRI) using the combination of diffusion, T2-weighted, and dynamic contrast-enhanced images is very useful for local staging of the disease, in particular, the myometrial and cervical invasion.[3-6]

Diffusion-weighted imaging is based on the principle of random water particle motion in space, with varying levels of contrast based on cellular density in the case of neoplastic lesions.[7] Using multiple B values, images can be acquired to generate signal intensity graphs; the log of these graphs gives the apparent diffusion coefficient (ADC), which forms a quantitative analysis of the diffusivity of the water particles in free space. ADC values depend on the degree of impedance to the motion of water molecules and are lowered in densely cellular tumors.[8] Diffusion-weighted imaging is now a part of a standard protocol for endometrial cancer as it delineates the tumor and normal tissue in a more discriminate manner.[5-6] Knowledge about the histological tumor grade in endometrial carcinoma is essential as it correlates with the aggressiveness of the tumor and the tendency for lymph nodal metastases. These issues are important to

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decide about the need for pelvic and retroperitoneal lymph nodal dissection along with total abdominal hysterectomy and bilateral salpingo-oophorectomy.[9-11]

The preoperative biopsy can underestimate tumor grade in a significant number of patients with a postoperative change of grade in the 25% patient population, this can significantly affect the management and long-term outcomes. Second, in a subset of patients with cervical stenosis or other local issues, preoperative sampling may not be possible or optimal.[12-13]

Diffusion-weighted imaging has been used in the past to distinguish endometrial cancer from normal endometrium, and there have been attempts in predicting the histological grade of endometrial cancer, myometrial invasion, and lymph nodal metastases based on the ADC values.[14,15]

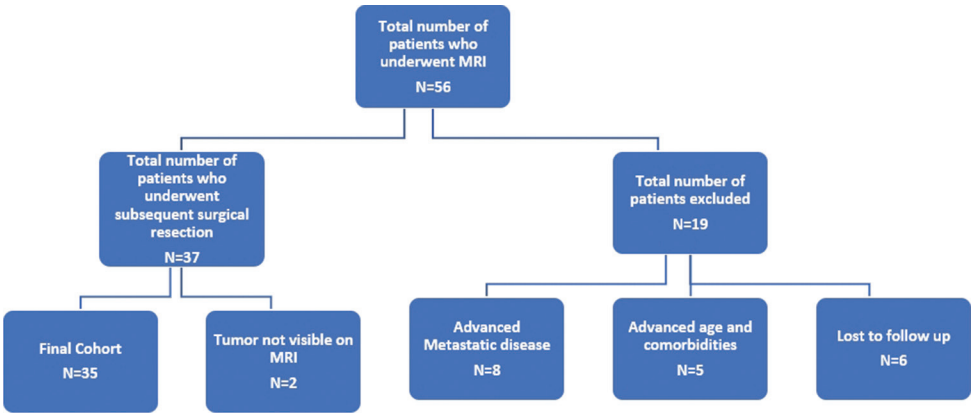
Tumor volumetry has been used as a prognostic tool in several malignancies, particularly rectal and cervical cancer of the pelvis.[16,17] Recent studies on the correlation between tumor volume and endometrial cancer grade have shown positive results.[18,19]

The current study aims to establish the correlation between the calculated tumor volumes and ADC values with the histological grade of endometrial cancer.

Materials and Methods

This was a single-center observational retrospective study performed on patients with histopathologically proven endometrial carcinoma who underwent between October 2017 and May 2020, an MRI examination of the pelvis, followed by total abdominal hysterectomy and bilateral salpingoopherectomy with pelvic lymph nodal dissection/sampling. The flow chart of patients enrolled in the study cohort is shown in Flow Chart 1. The study was approved by institutional ethics committee wide letter IEC: 2020/559.

All studies were performed on an 18-channel 3T MR unit (Skyra, Siemens Healthineers), using a phased array body coil. Patients were imaged in the supine position with partially distended bladder. Intramuscular buscopan (20 mg) was administered to decrease bowel peristalsis. The imaging sequences included axial T1-weighted turbo spin echo (TSE), standard T2 sagittal, large-field-of-view (FOV) T2-weighted images in straight axial plane followed by small FOV T2-weighted TSE and diffusion-weighted images along the endometrial axis in axial oblique plane. B - values of 50, 400, and 800 were used with high B-values of 1400–1600 for better tumor visibility reconstructed using extrapolation with an inbuilt software in the MRI system. All patients underwent postcontrast dynamic imaging in the sagittal plane followed by delayed axial and sagittal planes.



Flow Chart 1: Flow chart showing the study population

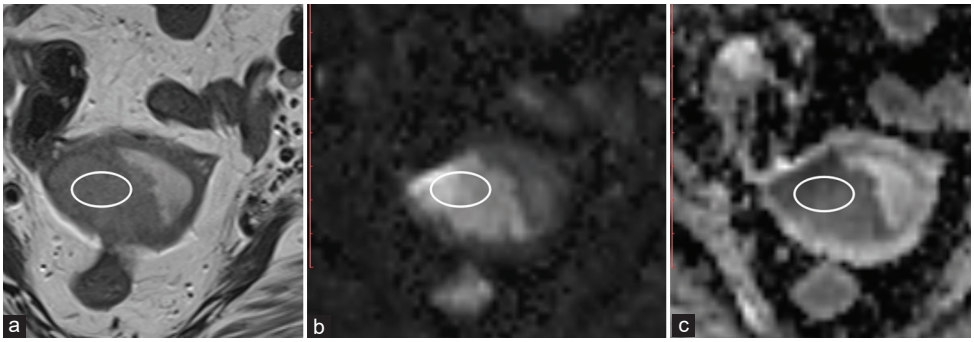


Figure 1: (a-c) 72-year-old female with Grade I endometroid adenocarcinoma: Axial T2 weighted image, High B-value (*b* = 1400/mm²) Diffusion-weighted imaging image and apparent diffusion coefficient map show the tumor. Region of interest precisely drawn using all three images to calculate apparent diffusion coefficient values

All images were reviewed by two radiologists with >5 years' experience in body MRI. Both radiologists were blinded to the final histopathological findings. The images were reviewed on the workstation using the Syngo platform from Siemens Healthcare in independent sessions. T2, postcontrast and diffusion-weighted images were used to identify and assess the tumor. The assessment included the size of the mass on T2, diffusion and postcontrast sequences, degree of myometrial invasion, and cervical invasion according to The International Federation of Gynecology and Obstetrics (FIGO) staging, adnexal, and lymph nodal involvement. For calculating ADC values, the freehand region of interest (ROI) was manually drawn to include the maximum volume of the tumor while taking care to avoid areas of necrosis and hemorrhage [Figure 1a-c]. Minimum and Mean ADC values were calculated by the software available within the workstation provided by Siemens Healthcare. For calculating the uterine volume (UV), T2 sagittal and axial oblique images were used [Figure 2a and b]. The tumor volumes were calculated using postcontrast delayed images at 3 min for craniocaudal dimensions and diffusion axial oblique images for transverse and anteroposterior dimensions considering the best tumor versus myometrium contrast on these images [Figure 2c and d]. T2 sagittal and axial oblique images were also used to calculate the tumor volume similarly [Figure 2a and b]; however, for the results, the volumes derived from postcontrast and diffusion images were used. The volume was calculated by the ellipsoidal formula craniocaudal × anteroposterior × transverse dimension multiplied by a factor of 0.52.

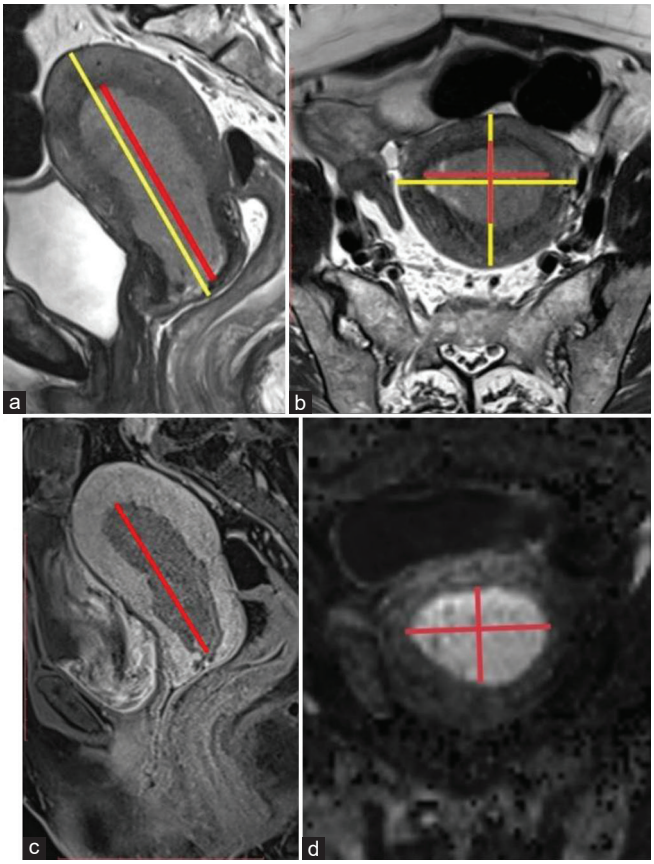


Figure 2: (a and b) 63-year-old female with Grade III endometrioid carcinoma: Axial oblique T2-weighted image images and T2 sagittal images used to assess uterine volume (yellow line) and tumor volume (red line) (c-d) 63-year-old female with Grade III endometrioid carcinoma: Postcontrast 3 min delayed sagittal image and Axial oblique high B value (b = 1400/mm^2) value diffusion images used for best tumor and myometrial contrast and measure tumor volume (red lines)

The pathological analysis included tumor histologic subtype (endometroid or nonendometroid) and Grade (I, II, or III), presence of deep myometrial invasion, cervical stromal, and adnexal invasion; metastasis in the sampled lymph nodes was confirmed microscopically.

The data were described in terms of range; mean ± standard deviation (±), median frequencies (number of cases), and relative frequency (percentages) as appropriate. Comparison of quantitative variables between the groups was made using analysis of variance and Mann–Whitney *U*-test Receiver operator characteristics (ROC) curve was done, and criterion value was estimated depending on the specificity and sensitivity. Area under the curve was measured. A probability value ($P < 0.05$) was considered statistically significant. All statistical calculations were done using (Statistical Package for the Social Science) SPSS 21 version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

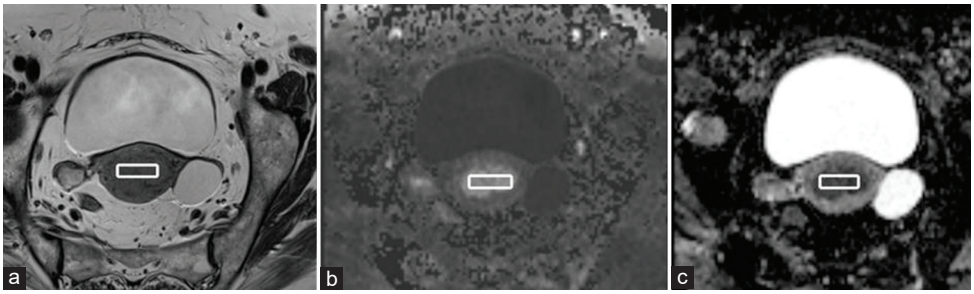


Figure 3: (a-c) 64-year-old female with Grade I endometrial carcinoma: Axial oblique T2-weighted images, axial oblique high B value (B = 1400/mm^2) and apparent diffusion coefficient map reveals endometrial mass. The mean and minimum apparent diffusion coefficient value of 0.52 × 10^{-3} mm^2/s and 0.38 × 10^{-3} mm^2/s

Results

The mean age of the patients in our cohort was 59.4 ± 5.8 years (45–72 years) and the predominant symptom was postmenopausal bleeding or menorrhagia.

On histopathology, majority of the tumors were endometrioid (29/35), followed by carcinosarcoma (4/35), and two cases of high-grade serous neoplasia (2/35). The histological grades in various groups were: I in 12/35, II in 15/35, and III in 8/35. According to the final histopathology, myometrial invasion of <50% was observed in 23 (66%) and more than 50% in 12 (34%) cases. The cervical stromal invasion was observed in 3 (8.5%) cases, adnexal invasion in 3 (8.5%) cases, and lymph nodal metastases in 6 (17%) patients.

There was almost perfect agreement on image interpretation between the two radiologists (C. K., K. G., κ 0.821, P = 0.04). The overall accuracy of MRI in staging the disease based on myometrial infiltration in our study was 82.9% for reader 1 and 77.5% in reader 2. The results of reader 1 were used for the final analysis and discussion. Mean ADC values for each histologic grade were 0.72 ± 0.13 × 10^{-3} mm^2/s for G1, 0.76 ± 0.17 × 10^{-3} mm^2/s for G2 and 0.74 ± 0.12 × 10^{-3} mm^2/s for G3, respectively; accordingly, no significant correlation between ADC values and tumor grade was found (P = 0.73) [Figures 3a-c and 4a-c]. Minimum ADC values for each histological grade were 0.48 ± 0.08 × 10^{-3} mm^2/s for G1, 0.6 ± 0.01 × 10^{-3} mm^2/s for G2 and 0.5 ± 0.08 × 10^{-3} mm^2/s for G3. Overall, ADC minimum values were significant in differentiating Grade I and II lesions (P = 0.01); no statistical significance was found between Grade I and Grade III lesions (P = 0.55) and Grade II and III lesions (P = 0.08). Comparing the mean ADC value of 14 patients with 50% or more myometrial tumor invasion (0.73 ± 0.12 × 10^{-3} mm^2/s) with the mean ADC value of 21 patients with <50% invasion (0.76 ± 0.15 × 10^{-3} mm^2/s), the difference was not statistically significant (P = 0.66). No statistically significant difference was also observed between the minimum ADC (0.55 ± 0.1 × 10^{-3} mm^2/s) values of tumors with more than 50% myometrial infiltration and minimum ADC values (0.54 ± 0.13 × 10^{-3} mm^2/s) of tumors with <50% myometrial invasion (P = 0.76).

Mean tumor volume was 52.7 cc, with Grade III tumors having the highest mean tumor volume (161.7 cc ± 174.22) and Grade I/II lesions showing mild volumetric variation (22.14 ± 21.34 cc vs. 19.05 ± 24.92 cc) [Figure 4a and b]. The relationship of high tumor volume with tumor grade was statistically significant (P < 0.001), whereas low-grade tumor volume (P = 0.92) did not correlate [Figure 5]. A mean tumor volume of 25.2 cc could differentiate low-grade tumors (I and II) from high-grade tumors (III), with a sensitivity and specificity of 88% and specificity of 89% [Figure 6]. The mean tumor volume ratio of Grade III endometrial cancers was 0.46 ± 0.24, for Grade II tumors 0.15 ± 0.08, and for Grade I lesions 0.18 ± 0.1. The tumor volume/ratio (TV/UV) differentiates high-grade tumors from low-grade tumors (P < 0.001); however, no significant difference in the ratio was observed among Grade I and II lesions (P = 0.48). Combining the low-grade endometrial carcinoma (Grades I and II), it was observed that a ratio of 0.19 could differentiate between low-grade and high-grade endometrial carcinoma with a sensitivity of 88% and specificity of 67% [Figure 7].

Discussion

In the present analysis, the correlation between the calculated tumor volumes and ADC values with the histological grade of endometrial cancer was tested.

In our analysis, both ADC mean and minimum were not found to be useful tools in differentiating low-grade and high-grade endometrial cancers. While, ADC min values were found to be useful in differentiating Grade I and Grade II lesions, this is not very useful clinically as the management of these lesions is not different. The results of ADC values with tumor grade have been discordant in the past with variable observations.[11,14,15,17-24] Lack of correlation between mean ADC values with final tumor grade is in agreement with several prior studies.[14,15,18-21] Tamai *et al*.[23] and Yan *et al*.[24] found ADC mean values

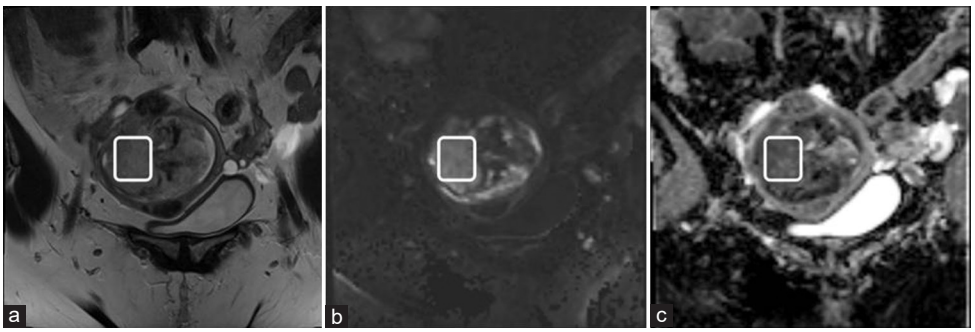


Figure 4: (a-c) 64-year-old female with Grade III endometrial carcinoma: Axial oblique T2 weighted images, axial oblique high B value (*B* = 1400/mm^2) and apparent diffusion coefficient map reveals endometrial mass. The mean and minimum apparent diffusion coefficient value of 0.95 × 10^{-3} mm^2/s and 0.67 × 10^{-3} mm^2/s

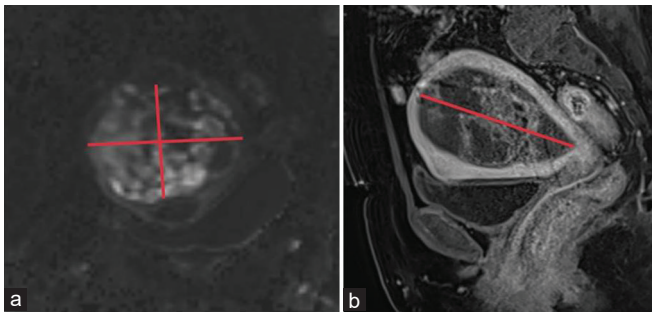


Figure 5: (a and b) 64-year-old female with Grade III endometrial carcinoma (Same patient as in Figure 4): Postcontrast T1 delayed and axial oblique high B value (*B* = 1400/mm²) image reveals the tumor outline. The mean tumor volume and tumor volume/uterine volume ratio were 289 cc and 0.63

helpful in differentiating low-grade and high-grade endometrioid carcinoma ($P = 0.0002$).[12,18] Nougaret *et al*.[17] found a significant correlation between the ADC min and tumor grade with lower ADC min observed in high-grade tumors. Of the various parameters, the tumor cellularity is the main determinant of the ADC values, which statistically results in lowering of the ADC values as the tumor grade increases. However, the correlation is not very linear between the ADC values and tumor grade. The variability of results in various studies can be explained based on other parameters such as nuclear atypia, tumor architecture, and tumor differentiation on histopathology, which determine the tumor grade rather than the cellularity alone.[15,19,21]

Tumor dimensions and volume have been conventionally associated with response and recurrence rates, which affected the overall survival of the patient in different tumors.[16,17] The mean tumor volume of Grade III tumors was significantly higher ($P = 0.001$) than low-grade (Grade I and II) tumors in our analysis. Correspondingly, TV/UV ratio of Grade III lesion was also found to be significant ($P = 0.000$) in differentiating these from low-grade lesions. Nougaret *et al*.[19] found a significant correlation between the total tumor volume ($P < 0.01$) and tumor volume/UV ratio of 25% ($P = 0.007$) in differentiating Grade I and II endometrial cancers from Grade III tumors. Bonatti *et al*.[18] found a significant correlation between the tumor volume and total UV ratio ($P = 0.002$), which is in agreement with our observations; however, in their observations, no significant correlation was found between the total tumor volume and grade (high-grade tumors of larger volume compared to the low-grade tumors (>0.05).

In our analysis, no significant correlation was observed between mean or minimum ADC values and degree of myometrial infiltration, which is similar to Rechichi *et al*.[15] Nakamura *et al*.[22] did not find a significant correlation between the mean ADC and degree of myometrial infiltration; however, they found a significant correlation between ADC minimum and degree of myometrial infiltration with lower ADC values associated with deeper myometrial infiltration.

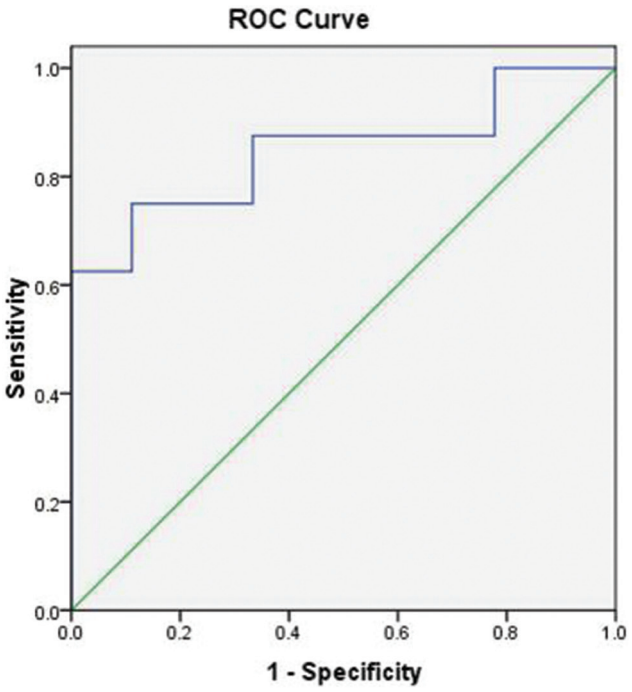


Figure 6: Receiver operator characteristics of tumor volume in differentiating high grade (Grade III) versus low-grade (Grade I and II) endometrial carcinoma: The area under the curve of tumor volume was 0.875 (95% confidence interval 0.0–1.00) (*P* = 0.001)

The study has several limitations, first the small size of the sample population. Aside from this, our assessment of ADC values is on single slice ROI, unlike other recent studies which did volumetric assessment of ADC values. This can reflect more realistic values of the complete internal architecture of the tumor. Similarly, our assessment of tumor volume is based on the ellipsoidal method similar to Bonatti *et al*.;[18] however, we agree with the authors regarding the ease of use of this model in clinical practice. Larger sample population with deriving from volume and ratio cut-offs can be helpful in predicting the grade of the tumor in future.

Conclusion

Histological tumor grade is a strong prognostic factor in endometrial cancer. The preoperative biopsy can underestimate the tumor grade in a significant number of patients. Preoperative noninvasive radiological assessment of endometrial carcinoma is an essential tool to plan appropriate management of a certain subsets of patients if analyzed by experienced radiologists. Additional features such as tumor volume and tumor volume/UV ratio are important surrogate markers for preoperative prognostication and can be helpful in predicting tumor grade.

Ethical clearance

Institutional ethics committee wide letter IEC: 2020/559.

Financial support and sponsorship

Nil.

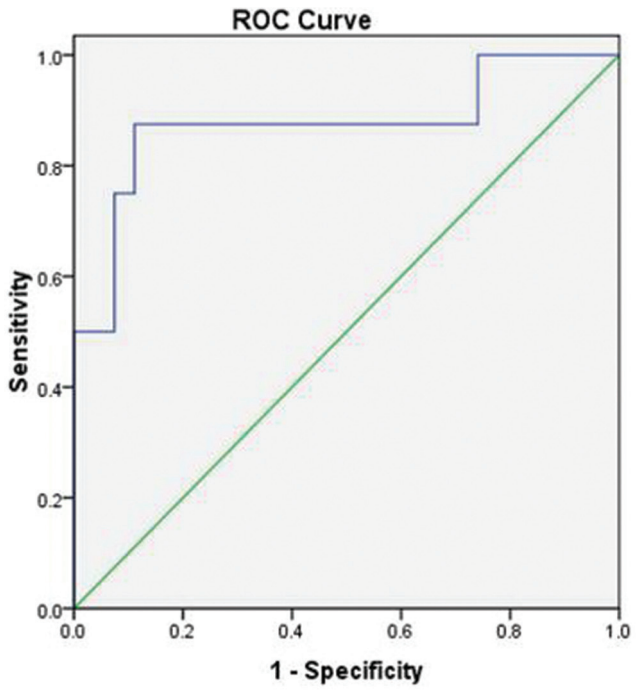


Figure 7: Receiver operator characteristics of tumor volume/uterine volume ratio in differentiating high-grade (Grade III) versus low-grade (Grade I and II) endometrial carcinoma: The area under the curve of tumor volume/uterine volume ratio was 0.847 (95% confidence interval 0.0–1.00) (*P* = 0.003)

Conflicts of interest

There are no conflicts of interest.

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