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Combination of Radiomics and Machine Learning with Diffusion-Weighted MR Imaging for Clinical Outcome Prognostication in Cervical Cancer

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Abstract: Objectives: To explore the potential of Radiomics alone and in combination with diffusion-weighted derived quantitative parameter namely apparent diffusion coefficient (ADC) using supervised classification algorithms in predicting outcomes and prognosis. Materials and Methods: Retrospective evaluation of the imaging was done for a study cohort of uterine cervical cancer, candidates for radical treatment with chemo radiation. ADC values were calculated from the darkest part of the tumor, both before (labeled preADC) and post treatment (labeled postADC) with chemo radiation. Post extraction of 851 Radiomics features and feature selection by taking the union of the features which had Pearson correlation >0.35 for recurrence, >0.49 for lymph node and >0.40 for metastasis, analysis was done to predict clinical outcomes. Results: The study enrolled 52 patients who presented with variable FIGO stages and age range 28–79 (Median = 53 years) with median follow-up of 26.5 months (range, 7–76 months). Disease recurrence occurred in 12 patients (23%). Metastasis occurred in 15 patients (28%). A model generated with 24 radiomics features and preADC using a monotone multi-layer perceptron neural network to predict the recurrence yields AUC of 0.80 and kappa value as 0.55 and shows that addition of radiomics features on ADC values improves the statistical metrics by 40% approximately for AUC and 223% approximately for Kappa. Similarly, neural network model for prediction of metastasis returns AUC of 0.84 and kappa value as 0.65 over performs by 25% for AUC and 140% for Kappa approximately. There was a significant input of GLSZM features (SALGLE and LGLZE) and GLDM features (SDLGLE and DE) correlation with clinical outcomes of recurrence and metastasis. Conclusions: The study is an effort to bridge the unmet need of translational predictive biomarkers in stratification of uterine cervical cancer patients based on prognosis.

Keywords: radiomics; diffusion-weighted; MRI; cervical cancer

1. Introduction

Uterine cervical cancer incidence ranks seventh of all cancers [1] and represents a significant burden in low and middle-income nations [2], while in developing nations accounts for leading mortality in women [3]. Radiation with concurrent chemotherapy forms the cornerstone of management for International Federation of Gynecology and Obstetrics (FIGO) stage IB2 to IVA uterine cervical cancer disease [4]. This treatment strategy used in neoadjuvant settings has gained popularity because of excellent response leading to debulking of these tumors, leading to shrinkage and possible resection [5–7]. Tumor size, histology, lymph node involvement, the infiltration of neighboring structures and the presence of distant metastases are steering the prognostication in cervical cancer [8], with a notable discrepancy in the prognosis among patients belonging to the same stage, which could not be attributed to the constellation of clinico-pathological features [9]. The determination of a few of these factors needs representative tumor tissue which warrants invasive procedures that adds to the risk and burden of existing disease.

Magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is vital for initial staging, therapeutic approach [10], and response assessment to treatment [11]. Studies in the past have explored the advanced functional imaging parameters obtained during MRI, namely, diffusion-weighted images (DWI) to identify tumors and further use the quantitative parameter apparent diffusion coefficient (ADC) from these DW images to assess response [12–16]. There is still a broad disparity regarding the selection of regions to measure ADC, as it argued that the selected part might not be representative of tumors exhibiting heterogeneity.

Radiomics is a growing arena of scientific research that uses imaging sets of high dimensional features, extracted from the normal acquired cross-sectional images and yields information that semantic analysis otherwise fails to acquire. The cystic and necrotic areas within the volume of the tumor that are representative of tumoral heterogeneity and behavior which mark aggressiveness and hence outcome, are captured by radiomics [17,18]. This branch of science exploits mathematical modeling to dig quantitative features from medical images to gain predictive models that provide insight into treatment prognosis and survival [19–21], with preliminary studies [22–28] expressing a multitude of clinical outcomes by exploring radiomics. The present study was endeavored to gain our existing knowledge regarding the role of functional imaging using diffusion-weighted derived quantitative parameter, namely apparent diffusion coefficient (ADC) and the augmented role of radiomics using supervised classification algorithms by machine learning in predicting clinical outcomes, namely the FIGO stage, lymph node status, metastasis, and development of recurrence in uterine cervical cancer patients.

2. Methods

2.1. Patient Cohort with Treatment Characteristics

After obtaining approval from the institutional review board, this retrospective study was carried out between January 2016 till January 2017 in our institute in patients referred to our hospital for a pelvic MR examination for the evaluation of histopathologically diagnosed uterine cervical cancer that fulfilled criteria for upfront treatment with chemoradiation and were not surgical candidates. Eighty-three patients with cervical cancer of variable stage (FIGO IB2-IVA) were enrolled, details of which are outlined in supplementary file. The CPRS (Computerized patient record system—hospital information system) was reviewed to evaluate the patient's age, presence of para-aortic lymph nodes, development of distant metastasis and recurrence. Nodal recurrences were documented as pelvic or para aortic. Metastasis was similarly recorded as to lung or other sites. The administration of radiotherapy may be delivered as external pelvic beam RT (EBRT), followed by brachytherapy or interstitial needle devices. The study

cohort included patients who were given upfront EBRT in a total dose of 45 Grays in 25 fractions. An MR examination after the conventional EBRT was done to know the status of any residual disease and facilitate the further decision for brachytherapy. As per the institutional protocol, CT-based image-guided brachytherapy was done. ICRT dose was 7.5 Grays in 3–5 fractions, and MUPIT was 20–25 Grays in 4–5 fractions.

2.2. Magnetic Resonance Imaging Technique

Standard non-contrast MRI of pelvis was done using Siemens Avanto Magnetom 1.5 T MR Scanner. All patients were imaged in supine position using pelvic body coil. Conventional and diffusion weighted (DW) MRI studies were done before the initiation and post completion of chemoradiation treatment. All of the patients underwent DWIs by using a multisection spin echo single shot echo planar imaging (EPI) sequence with b values of 0, 400, and 800 s/mm². An average of 15 sections was obtained in the axial plane covering the area of interest. Imaging parameters were: TR/TE of 10,000/108 ms, FOV of 40 × 40 cm, and acquisition matrix of 256 × 256 and section thickness of 5 mm with an intersection gap of 1–2 mm.

2.3. Conventional Image Analysis

A radiologist (XX), with more than six years of training in pelvic MR imaging, autonomously evaluated the Diffusion images and corresponding ADC maps, sentient to the fact that patients had cervical carcinoma but blinded to final clinical outcome. Under the supervision of a board-certified radiologist with 25 years of experience in treating genitourinary cancers, quantitative DWI analysis of the tumor was performed, based on a freehand-drawn region of interest (ROI) on the ADC map [29] that showed restricted diffusion (i.e., high signal on b800 DWI and low signal signal on the ADC map); mean ADCs were recorded. The labeling of ROI was independently checked by a senior radiation oncologist (XX) with more than 25 years of experience in treating genitourinary cancers. If any, the disagreement was resolved by a two senior radiologists (XX) with more than 40 years of experience. The ADC measured in initial baseline imaging was coded as ADC_{pre} and follow-up imaging post-treatment completion as ADC_{post}, with a separate calculation for change in referred as ADC_{change}. Regarding lymph nodes, a positive node was defined by a short-axis diameter >8 mm [30]. When in doubt positive cytology was considered the gold standard for diagnosis of malignancy, both for pelvic and distal recurrence and distant metastasis.

2.4. Image Segmentation and Feature Extraction

All segmentations of the tumor were performed by radiologist (XX) using Slicer software 3D Slicer [31] (<http://www.slicer.org/>). To minimize the errors cropping from the intra-operator and inter-operator variability arising from manual segmentation, a semi-automatic segmentation process was adopted [32]. This was further encouraged by the use of the Grow cut algorithm [33]. The task of 3D segmentation was aimed at culminating a volume of interest (VOI). The VOI consisted of regions of interest (ROIs) that were manually segmented along the tumor contour on each transverse section concerning T2 weighted images in the transverse axial planes. To remove any potential bias, the same radiologist re-segmented the VOIs, blinded to the previous task of segmentation about two months following the first segmentation process. Finally, all segmentations were validated by a senior radiologist (XXX) who has 40 years of experience. A representative ROI and VOI definition are shown in supplementary file. Post segmentation of images, using a semi-automated algorithm, 851 radiomics features were extracted using PyRadiomics [34], an open-source software. The details of radiomic features in concordance with previous literature [35–37] are provided in supplementary file as text.

2.5. Radiomic Feature Selection

Pearson correlation of radiomic features with clinical prognostications was used for selecting the features which was calculated using stats v3.5.1 package in R v3.5.1. Features passing through any of the following correlation cut-off criteria were selected for the model building: (i) Correlation coefficient with Recurrence > 0.35 [$\text{cor}(f_i, \text{Recurrence}) > 0.35$], (ii) Correlation coefficient with Stage > 0.35 [$\text{cor}(f_i, \text{Stage}) > 0.35$], (iii) Correlation coefficient with Lymph Node > 0.49 [$\text{cor}(f_i, \text{Lymph Node}) > 0.49$], (iv) Correlation coefficient with Metastasis > 0.40 [$\text{cor}(f_i, \text{Metastasis}) > 0.40$] (details of radiomics features are provided in supplementary file).

2.6. Model Building

After feature selection, we used multiple modeling algorithms to predict the following clinical outcomes: (i) recurrence, (ii) distant metastasis, (iii) lymph node metastasis, and (iv) FIGO stage. Various models with leave-out-one cross-validation and hyperparameter tuning were trained using different classification algorithms using the caret v6.0-86 package for the R statistical software package. Each model is trained using different sets of features as follows: (i) 24 Radiomics features, (ii) 24 Radiomics features, preADC, postADC and change ADC (postADC - preADC), (iii) 24 Radiomics features, and preADC (iv) 24 Radiomics features, and changeADC, (v) preADC, postADC2, and changeADC to find the significance of radiomics features with or without ADC values over ADC parameters.

2.7. Statistical Analysis

Cohen's Kappa and Area under the curve (AUC) were used as the statistical parameters to find model efficiency, which was calculated using pROC v1.16.2 and caret packages available in R. (Details in supplementary file)

3. Results

3.1. Patient Characteristics and Disease Outcome

The study enrolled 52 patients who presented with variable FIGO stages and age range 28–79 (Median = 53 years) with a median follow-up of 26.5 months (range, 7–76 months). Disease recurrence occurred in 12 patients (23%). Four patients (33%) had an isolated pelvic recurrence and 8 (67%) a distant recurrence (omentum = 1, peritoneum = 2, supra-clavicular node = 2, paraaortic node = 3), with median recurrence free survival of 19 months (range, 5–60 months). Metastasis occurred in 15 patients (28%). Ten patients had distant metastases to lung which were proven histopathologically on all and clinical follow up with symptoms ruled out development of a second primary of lung carcinoma. The remaining five patients showed metastasis to peritoneum (n = 3), spine (n = 1) and liver (n = 1). PreADC had a median of $0.615 \times 10^{-3} \text{ mm}^2/\text{s}$ (range, $0.615\text{--}1.400 \times 10^{-3} \text{ mm}^2/\text{s}$) with an arithmetic mean value of $0.889 \times 10^{-3} \text{ mm}^2/\text{s}$ and postADC had a median of $1.760 \times 10^{-3} \text{ mm}^2/\text{s}$ (range, $0.656\text{--}1.620 \times 10^{-3} \text{ mm}^2/\text{s}$ with an arithmetic mean value of $1.469 \times 10^{-3} \text{ mm}^2/\text{s}$). The details of clinical characteristics are depicted in a table 1. Range of the selected 24 radiomics features and the average values have been mentioned in the supplementary file.

Table 1. Clinical characteristics of patients included in study.

| Clinical Parameters | Total N = 52 (%) |
|-------------------------------------|---------------------------|
| Age range | 28–79 (Median = 53 years) |
| FIGO Stage | |
| IB2 | 3 (5.7%) |
| IIA | 8(15.5%) |
| IIB | 16(30.7%) |
| IIIA | 16(30.7%) |
| IIIB | 4(7.7%) |
| IVA | 3(5.7%) |
| Clinical Outcomes/Variables | |
| Recurrence/ No recurrence | 12/40 (23% / 77%) |
| Distant Metastatic / Non metastatic | 15/37 (28% / 72%) |
| Metastasis to Lung / Other sites | 5/10 (9% / 19%) |
| Lymph node Present /Absent | 15/37 (28% / 72%) |
| Paraaortic lymph node/ Pelvic node | 2 /13 (3.8% / 25%) |
| Mean follow up | 29.9 months |
| Median follow up | 28.5 months |
| Mean recurrence interval | 18.5 months |

Table 2. Tabulated content of recurrence with relevant classifier algorithm and corresponding AUC with kappa values.

| Output | Features | Model | Metric | AUC | Kappa |
|------------|--------------------------------------|--|-------------|------|-------|
| Recurrence | Radiomics | pcaNNet (Neural Networks with Feature Extraction) | Kappa + AUC | 0.77 | 0.53 |
| | Radiomics + ADC1 + ADC2 + Change ADC | svmLinearWeights (Linear Support Vector Machines with Class Weights) | Kappa + AUC | 0.76 | 0.49 |
| | Radiomics + ADC1 | Monmlp (Monotone Multi-Layer Perceptron Neural Network) | Kappa + AUC | 0.8 | 0.55 |
| | Radiomics + change ADC | RRFglobal (Regularized Random Forest) | Kappa | 0.74 | 0.5 |
| | Radiomics + change ADC | svmLinearWeights (Linear Support Vector Machines with Class Weights) | AUC | 0.77 | 0.48 |
| | ADC | FRBCS.W (Fuzzy Rules with Weight Factor) | Kappa + AUC | 0.57 | 0.17 |

Table 3. Tabulated content of Metastasis with relevant classifier algorithm and corresponding AUC with kappa values.

| Output | Features | Model | Metric | AUC | Kappa |
|------------|--------------------------------------|--|-------------|------|-------|
| Metastasis | Radiomics | svmLinearWeights (Linear Support Vector Machines with Class Weights) | Kappa + AUC | 0.76 | 0.5 |
| | Radiomics + ADC1 + ADC2 + Change ADC | pcaNNet(Neural Networks with Feature Extraction) | Kappa + AUC | 0.84 | 0.65 |
| | Radiomics + ADC1 | pcaNNet(Neural Networks with Feature Extraction) | Kappa + AUC | 0.79 | 0.59 |
| | Radiomics + change ADC | pcaNNet(Neural Networks with Feature Extraction) | Kappa + AUC | 0.73 | 0.46 |
| | ADC | Rocc (ROC-Based Classifier) | Kappa | 0.63 | 0.3 |
| | ADC | svmLinearWeights (Linear Support Vector Machines with Class Weights) | AUC | 0.67 | 0.27 |

Table 4. Tabulated content of Stage with relevant classifier algorithm and corresponding AUC with kappa values.

| Output | Features | Model | Metric | AUC | Kappa |
|--------|--------------------------------------|---|--------|------|-------|
| Stage | Radiomics | RRFglobal (Regularized Random Forest) | Kappa | 0.51 | 0.31 |
| | Radiomics | Knn (k-Nearest Neighbors) | AUC | 0.71 | 0.25 |
| | Radiomics + ADC1 + ADC2 + Change ADC | Earth (Multivariate Adaptive Regression Spline) | Kappa | 0.64 | 0.3 |
| | Radiomics + ADC1 + ADC2 + Change ADC | knn(k-Nearest Neighbors) | AUC | 0.71 | 0.25 |

| | | | | |
|------------------------|---|-------|------|------|
| Radiomics + ADC1 | evtree(Tree Models from Genetic Algorithms) | Kappa | 0.63 | 0.33 |
| Radiomics + ADC1 | knn(k-Nearest Neighbors) | AUC | 0.71 | 0.25 |
| Radiomics + change ADC | Earth (Multivariate Adaptive Regression Spline) | Kappa | 0.64 | 0.31 |
| Radiomics + change ADC | knn(k-Nearest Neighbors) | AUC | 0.71 | 0.25 |
| ADC | RRFglobal (Regularized Random Forest) | Kappa | 0.57 | 0.19 |
| ADC | LogitBoost | AUC | 0.66 | 0.06 |

Table 5. Tabulated content of Lymph Node with relevant classifier algorithm and corresponding AUC with kappa values.

| Output | Features | Model | Metric | AUC | Kappa |
|------------|--------------------------------------|--|-------------|------|-------|
| Lymph Node | Radiomics | Evtree (Tree Models from Genetic Algorithms) | Kappa + AUC | 0.75 | 0.6 |
| | Radiomics + ADC1 + ADC2 + Change ADC | evtree(Tree Models from Genetic Algorithms) | Kappa + AUC | 0.75 | 0.6 |
| | Radiomics + ADC1 | evtree(Tree Models from Genetic Algorithms) | Kappa + AUC | 0.75 | 0.6 |
| | Radiomics + change ADC | evtree(Tree Models from Genetic Algorithms) | Kappa + AUC | 0.75 | 0.6 |
| | ADC | evtree(Tree Models from Genetic Algorithms) | Kappa + AUC | 0.64 | 0.32 |

3.2. Application of Machine Learning Classifiers Algorithms to Predict Clinical Outcomes

A monotone multi-layer perceptron neural network model generated with 24 radiomics features and preADC predicted recurrence with an AUC of 0.80 and kappa value as 0.55, outperforming other combinations of radiomics features, preADC, postADC and changeADC. AUC and Kappa generated by using only ADC features (preADC, postADC, and changeADC) are 0.57 and 0.17 respectively, using fuzzy rules with weight factor which shows that addition of radiomics features on ADC values improves results. Using the same set of radiomic features for prediction of metastasis combined with preADC, postADC and changeADC using a neural network with feature extraction to predict the distant metastasis returns AUC of 0.84 and kappa value as 0.65 which over performs on other possible combinations of radiomics features, preADC, postADC and changeADC. AUC and Kappa generated by using only ADC features (preADC, postADC, and changeADC) are 0.67 and 0.27 respectively using fuzzy rules with weight factor.

For the prediction of Stage with 24 radiomics features, preADC, postADC and changeADC using k-nearest neighbors (KNN) algorithm yields AUC of 0.71 and kappa value as 0.25 which over performs on other possible combinations of radiomics features, preADC, postADC and changeADC. The use of Regularized Random Forest (method = RRFglobal) for the same had a drop in AUC to 0.51 but improved kappa value to 0.31. AUC and Kappa generated by using only ADC features (preADC, postADC, and changeADC) is 0.71 and 0.25 respectively using k-nearest neighbors (KNN) algorithm with weight factor. This result is out of line with our previous results of recurrence and metastasis, and we did not achieve any marginal increment in our AUC or kappa with integration of radiomics into functional MR parameters for prediction of stage. Lastly for prediction of Nodal metastasis by using 24 radiomics features, preADC, postADC and changeADC using Evolutionary Learning of Globally Optimal Trees (evtree) with feature extraction returns AUC of 0.75 and kappa value as 0.60, while the combination of ADC parameters using evtree provides us an AUC of 0.64 and kappa of 0.32.

The figures 1, 2, 3 and 4 depicts the correlation between different radiomics and ADC features with the two classes of Lymph Node (Absent and Present), Metastasis (Absent and Present), recurrence and clinical outcomes respectively. The details of interpretation of these heat maps are provided in supplementary file.

ing to treatment failure despite good rates of local control in cervical cancer post chemo radiation, and has an incidence as high as twenty percent [38]. Recurrence is seen in a third of the patients and occurs shortly after treatment completion [39]. Up to forty percent of the patients with a positive para-aortic node has distant metastasis [40]. In our study among three patients with paraaortic nodes distant lung metastasis was seen in one patient.

A previous study of MU w et al. found a statistically significant difference with an AUC of 0.8, between the early and advanced stages combining texture features derived from FDG-PET CT and SUV parameters using SVM algorithm [41]. We achieved an AUC (0.71) using more number of patients with multiple classifiers to predict differences in stages, with the best AUC obtained with k-nearest neighbors (KNN) algorithm. Due to differences in the acquisition and considering our granular approach by staggering out model output into four stages, rather than clubbing into early and advanced stages, however, a direct comparison of the study of Mu W et al. with our study is only hardly possible. The majority of determinants of pelvic LN metastasis are assessed only in a post-operative setting, like depth of stromal invasion and lymphovascular invasion [42]. So, a robust parameter that could help in pre-treatment prediction of LN metastasis would be desirable, as LN involvement is an independent prognostic marker for recurrence and overall survival [27,43,44]. While this study had an AUC of 0.864 for the prediction of LN involvement, we were able to achieve comparable levels with another study [45] (AUC = 0.75). Some radiomics features exhibited an escalating trend analogous to patients who developed either distant metastasis or recurrence versus patients with lack of such events. Previous studies have shown an AUC of 0.747–0.85 to discriminate nodal metastasis by using radiomic features on functional ADC maps in cervical cancer [46,47]. We attained similar AUC (0.75) by using evTree classifier on almost similar number of patients. Furthermore, our study could also demonstrate, that the combination of radiomic features with ADC parameters did not show any better performance than radiomics alone in LN assessment. This is in contrast to a study of Kan Y et al. with focused solely on the prediction of nodal metastatic stage (AUC 0.75), with integration of seven distinct clinical characteristics into the equation [48].

One of the wavelet features, HLH_GLSZM_small_area_low_grade_level_emphasis was reported in an earlier study done on T2WI, for prediction of Disease-free survival (DFS) in uterine cervical cancer [49], using 18 radiomic features and lymphovascular space invasion (LVI) with contrast MRI to obtain a Rad score for prediction of the DFS. Another wavelet feature LLL_grlm_Gray_Level_NonUniformity_Normalized was also found to be significant in the prediction of recurrence in uterine cervical cancer [50] and 5-year survival [51]. In concordance with the previous studies where GLCM Entropy is reported as a feature to predict Disease free survival [52], we found significance Entropy in our results in the GLDM, GLRLM and GLSZM. Unlike GLCM which characterizes the local information of gray levels between pairs of voxels, GLRLM captures the coarseness and GLSZM quantifies the clusters of homogeneous intensity regions within the tumor. The feature energy has been reported to predict recurrence with an AUC of 0.885, when derived from ADC maps in a study [53]. We found both first order and wavelet derivatives of Energy to be useful in building our radiomics model, and in combination with functional quantitative parameter yielded an AUC of 0.84 in our study for prediction of distant metastasis. A worse clinical outcome was associated with elevated values of these parameters, asserting the fact that a poor prognosis is exhibited by more heterogeneous tumors.

Most studies performed in past have focused on the standardized uptake value (SUV) derived from PET CT imaging, with few exploring ADC maps on MR imaging, as a predictor for treatment response overall survival and lymph node involvement [54] and proved the superiority of radiomic features in comparison to SUV, in the assessment of clinical outcome and as a descriptor of tumor heterogeneity [55]. Changes in ADC have been reported to be a promising imaging biomarker for early radiation response in prostate cancer [56]. Few studies have revealed the role of ADC as a predictor of recur-

rence [14,57]. In our study, pretreatment ADC (preADC) values did not show considerable performance as compared to radiomics features. One likely explanation for the above observation could be attributable to wide differences in methodology, where a certain ROI was drawn manually on ADC maps excluding the areas of necrosis. On the same hand the radiomics features were VOI achieved in a semi-automatic fashion by use of grow cut feature that encompassed the whole volume of the tumor. This potentially captures the tumor heterogeneity, including the areas of necrosis, which is believed to steer clinical outcome and response, even in uterine cervical cancer. The analysis of conventional method of tumor assessment by using diffusion sequences and ADC maps was prone to errors because ADC values were consequential from manually drawn ROIs. There are always chances of human errors while measuring the same and it also suffers from a certain degree of inter observer variability. Further restricted efficacy exists in assessment of mean ADC change within the ROI of the tumor on a single ADC map image, post treatment response pertaining tumor heterogeneity [58]. Few studies show the jarring results concerning the prognostic value of ADC in cervical cancer, some documenting poorer prognosis with a lower ADC value [59]. The VOI delineated on the T2W image could have been extrapolated on the ADC maps, to extract the radiomic features on ADC images as done in previous studies [60], but the additional normalization and binning done was beyond the scope of this study. Undeniably, a better understanding of the core spatial heterogeneity could be offered by VOI delineation and analysis of ADC imaging; however, the above factors with resource and time constrains prevented us from exploring this particular aspect, thus limiting the usefulness into routine clinical practice [61]. Further ADC values show heterogeneity between various MR scanners [62] which would be an obstacle in standardization.

A monocentric and retrospective nature of study were the limitations which are repeated in most of radiomics studies in uterine cervical cancers. Despite the use of cross-validation, a clear limitation is the fact that there was no validation dataset (Study cohort included only 52 patients overall and hence a split would not have made statistical sense). But being monocentric, the study erases problems arising due to variations in acquisition and image reconstruction parameters, which negatively affected analysis [63]. The study cohort though small included a large number of features (more than 800), but training and testing was performed using Pearson correlation, and statistical significance was corrected for multiple testing by application of leave one out cross validation and hyper parameter tuning in order to avoid both over fitting and false-discovery. As has been pointed out previously, most radiomics studies encompass higher number of features than patients, probably culminating in high risk of false-positive rate [64]. Since the clinical variables are rather outcomes were dichotomized, the supervised analysis conducted aimed towards creation of good union with help of statistical learning models. In pursuit of this we chalked out the most efficient radiomic features that could predict clinical outcomes.

5. Conclusions

Devising a robust noninvasive strategy to assess tumor heterogeneity, preceding treatment, might have an insightful impact on the management of individual cancer patients by early prediction of treatment outcome with the prospect to modify therapy as part of the precision medicine exemplar. We tried to devise a machine learning prediction method for clinical outcomes exploiting multi classifier system. We further aim to validate our findings in larger cohorts, both within our centre and multi-institutional centers. Our results revealed an incremental role of radiomics over functional MR imaging deploying ADC values for prediction of recurrence and distant metastasis. The model will be greatly helpful for low to middle income nations which have an increasing incidence of cervical cancer as our study does not incorporate use of FDG PET CT and Contrast MR imaging, the availability and interpretation of both are limited in constrained low resource nations.

Abbreviations

- MRI: Magnetic resonance imaging.
- 18-FDG PET CT: 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography
- FIGO: International Federation of Gynecology and Obstetrics
- ADC: Apparent diffusion coefficient
- ICRT: Intracavitary brachytherapy
- FNAC: Fine needle aspiration cytology
- RFS: Recurrence-free survival
- VOI: Volumes of interest
- ROI: Region of interest
- GLCM: Gray level co-occurrence matrix
- GLRLM: Gray level run length matrix
- GLSZM: Gray level size zone matrix
- GLDM: Gray-Level Dependence Matrix

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: Heat map showing correlation between different radiomics and ADC features with Stages, Figure S2: (A–D) Line plot is used to represent the variation in the efficiency metrics of the model using different sets of features and modeling algorithms. The above figure shows our various classifiers used to predict clinical outcomes with kappa plotted on a scale 0–1, Figure S3: (A–D) Line plot is used to represent the variation in the efficiency metrics of the model using different sets of features and modeling algorithms. The above figure shows our various classifiers used to predict clinical outcomes with AUC plotted on a scale 0–1, Figure S4: T2 WI and diffusion imaging showing representative method of ADC calculation, Figure S5: Segmentation process using Slicer-3d software and VOI delineation for radiomics feature extraction, Table S1: Using Pearson coefficient method of cut-off, the final set of features has 24 radiomics features listed are: Two first-order features; Two GLDM gldm features; Two GLSZM features & 18 wavelet features ((i) Six first-order features; (ii) Two GLDM features; (iii) Seven GLSZM features; (iv) One GLCM feature; (v) Two GLRLM feature), Table S2: Showing the baseline and follow up ADC values in the various groups with percentage change in ADC. There is an obvious change in ADC in the recurrence and metastatic groups. The nodal positive and negative groups didn't show much of change.

Author Contributions: Conceptualization, A.J., H.P., M.M., A.M., S.Pu. and A.C.; Data curation, A.J., A.G., S.M. and S.Pa.; Investigation, A.J., A.G., H.P., M.M., S.M. and S.Pa.; Methodology, A.J. and A.G.; Project administration, M.M., S.M., S.Pa., A.M., S.Pu. and A.C.; Resources, H.P. and S.M.; Software, A.G. and A.M.; Supervision, A.M., S.Pu. and A.C.; Validation, A.J., A.G. and A.M.; Visualization, S.Pa.; Writing—original draft, A.J.; Writing—review & editing, H.P. and M.M.

Data Availability Statement: All data generated and analyzed during this study are included in this published article (and its supplementary information files).

Institutional Review Board Statement: IRB (ethical) approval was taken. Nos.RGCIRC/IRB-BHR/22/2020

Conflicts of Interest: The authors declare no conflict of interest.

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