Title: Radiomic features of cervical cancer on T2- and diffusion-weighted MRI: prognostic value in low-volume tumors suitable for trachelectomy


Article Type: Review Article

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Abstract: Background: Textural features extracted from MRI potentially provide prognostic information additional to volume for influencing surgical management of cervical cancer.
Purpose: To identify textural features that differ between cervical tumors above and below the volume threshold of eligibility for trachelectomy and determine their value in predicting recurrence in patients with low-volume tumors.
Methods: Of 378 patients with Stage1-2 cervical cancer imaged prospectively (3T, endovaginal coil), 125 had well-defined, histologically-confirmed squamous or adenocarcinomas with >100 voxels (>0.07cm3) suitable for radiomic analysis. Regions-of-interest outlined the whole tumor on T2-W images and apparent diffusion coefficient (ADC) maps. Textural features based on gray-level co-occurrence matrices were compared (Mann-Whitney test with Bonferroni correction) between tumors greater (n=46) or less (n=79) than 4.19cm3. Clustering eliminated correlated variables. Significantly different features were used to predict recurrence (regression modelling) in surgically-treated patients with low-volume tumors and compared with a model using clinico-pathological features.
Results: Textural features (Dissimilarity, Energy, ClusterProminence, ClusterShade, InverseVariance, Autocorrelation) in 6 of 10 clusters from T2-W and ADC data differed between high-volume (mean±SD 15.3±11.7cm3) and low-volume (mean±SD 1.3±1.2cm3) tumors. (p<0.02). In low-volume tumors, predicting recurrence was indicated by: Dissimilarity, Energy (ADC-radiomics, AUC=0.864); Dissimilarity, ClusterProminence, InverseVariance (T2-W-radiomics, AUC=0.808); Volume, Depth of Invasion, LymphoVascular Space Invasion (clinico-pathological features, AUC=0.794). Combining ADC-radiomic (but not T2-radiomic) and clinico-pathological features improved prediction of recurrence compared to the clinico-pathological model (AUC=0.916, p=0.006). Findings were supported by bootstrap re-sampling (n=1000).

Conclusion: Textural features from ADC maps and T2-W images differ between high- and low-volume tumors and potentially predict recurrence in low-volume tumors.

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**1. Cover Letter**

Pr. B Karlan
Editor in Chief,
Gynecologic Oncology

23 August 2019

Dear Professor Karlan,

Please find enclosed our manuscript entitled ***"Radiomic features of cervical cancer on T2- and diffusion-weighted MRI: prognostic value in low-volume tumors suitable for trachelectomy"*** for consideration for publication in Gynecologic Oncology.

Radiomic analyses, particularly in Magnetic Resonance Imaging are a burgeoning field of interest, and we feel we have brought a novel way of addressing feature selection by interrogating features that differ between high and low volume cervical tumors. Tumor volume is an established poor prognostic factor in this disease. We therefore sought to establish whether radiomic differences between high- and low-volume cervical cancers existed, and if so, whether the low-volume tumors that radiomically appeared like high-volume ones had a worse prognosis. We found that we could identify low-volume tumors at risk of recurrence using this method.

Cervical cancer is relatively rare now in countries with effective screening programmes, and tumors are often low-volume when detected. We feel this technique offers a means of flagging patients with low-volume tumors at risk of recurrence. This should enable a programme of more frequent monitoring in these often young women with potentially good life expectancy.

This was a prospective study done with IRB approval, and with written informed consent from all patients.

All authors contributed to this manuscript in one or more of the following ways: literature search, study planning, data acquisition, data analysis and manuscript drafting. In addition, all were involved in manuscript editing and final approval.

We are hopeful that you and your readers will find this work of major interest,

With kind regards,

**The Institute of Cancer Research**

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1      **Radiomic features of cervical cancer on T2- and diffusion-weighted MRI:**

2      **prognostic value in low-volume tumors suitable for trachelectomy**

3

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**Conflict of interest/disclosure statement*:***

All authors declare no potential conflicts of interest.

Abstract word count:      **250**

Manuscript word count:    **3707**

Number of Figures:        **2**

Number of Tables:         **4**

**Supplementary data:     2 Figures and 1 Table**

50

**Abbreviations**

51

52 ADC – Apparent diffusion co-efficient

53 ROI – Region of interest

54 AUC – Area under curve

55 DW – Diffusion weighted

56 GLCM – Grey Level co-occurrence matrix

57 ROC – Receiver operating curve

58 LLETZ – Large loop excision of transformation zone

59 LVSI – Lymphovascular space invasion

60 SNR – Signal to noise ratio

61

62

63

64   **Abstract**

65   **Background:** Textural features extracted from MRI potentially provide prognostic

66   information additional to volume for influencing surgical management of cervical

67   cancer.

68   **Purpose:** To identify textural features that differ between cervical tumors above and

69   below the volume threshold of eligibility for trachelectomy and determine their value

70   in predicting recurrence in patients with low-volume tumors.

71   **Methods:** Of 378 patients with Stage1-2 cervical cancer imaged prospectively (3T,

72   endovaginal coil), 125 had well-defined, histologically-confirmed squamous or

73   adenocarcinomas with >100 voxels (>0.07cm$^3$) suitable for radiomic analysis.

74   Regions-of-interest outlined the whole tumor on T2-W images and apparent diffusion

75   coefficient (ADC) maps. Textural features based on gray-level co-occurrence

76   matrices were compared (Mann-Whitney test with Bonferroni correction) between

77   tumors greater (n=46) or less (n=79) than 4.19cm$^3$. Clustering eliminated correlated

78   variables. Significantly different features were used to predict recurrence (regression

79   modelling) in surgically-treated patients with low-volume tumors and compared with

80   a model using clinico-pathological features.

81   **Results:** Textural features (Dissimilarity, Energy, ClusterProminence, ClusterShade,

82   InverseVariance, Autocorrelation) in 6 of 10 clusters from T2-W and ADC data

83   differed between high-volume (mean±SD 15.3±11.7cm$^3$) and low-volume (mean±SD

84   1.3±1.2cm$^3$) tumors. (p<0.02). In low-volume tumors, predicting recurrence was

85   indicated by: Dissimilarity, Energy (ADC-radiomics, AUC=0.864); Dissimilarity,

86   ClusterProminence, InverseVariance (T2-W-radiomics, AUC=0.808); Volume, Depth

87   of Invasion, LymphoVascular Space Invasion (clinico-pathological features,

4

AUC=0.794). Combining ADC-radiomic (but not T2-radiomic) and clinico-pathological

features improved prediction of recurrence compared to the clinico-pathological

model (AUC=0.916, p=0.006). Findings were supported by bootstrap re-sampling

(n=1000).

**Conclusion:** Textural features from ADC maps and T2-W images differ between

high- and low-volume tumors and potentially predict recurrence in low-volume

tumors.

## Introduction

Stage 1 cervical cancer is primarily treated with hysterectomy, although less radical surgical options (cone biopsy, trachelectomy) are considered where fertility preservation is desirable [1-4]. Decisions regarding the type and extent of surgery and the subsequent need for adjuvant therapy depend on tumor resectability and the risk of recurrence. Biomarkers that predict recurrence, therefore, are of paramount importance for selecting the most appropriate treatment options. In tumors >2cm in longest dimension, pre-operative tumor volume is a powerful adverse prognostic factor associated with reduced overall survival [5; 6]. Other prognostic factors, such as tumor type, grade, lymphovascular space invasion (LVSI) and depth of stromal invasion are derived from a biopsy [7-10], and therefore may not represent the tumor in its entirety. Prognostic biomarkers derived from imaging would be more representative of the whole tumor and would enable selection of the optimal surgical management at the outset in Stage 1 disease.

Magnetic Resonance imaging is routinely used to detect and stage cervical cancer, where T2-W and diffusion-weighted (DW) imaging form the mainstay of diagnostic sequences [11; 12]. Derivation of an apparent diffusion coefficient (ADC) from the DW images [13] and analysis of first order histogram distribution of ADC values has been shown to predict histological subtype [14; 15], staging [16], parametrial invasion [17], LVSI [18] the response to chemo-radiotherapy [19] and to aid surgical decision-making [20]. However, these first-order statistical quantitative imaging data remain limited in their prediction of likely recurrence [21]. It is possible to refine image analysis and convert the T2-W [22] and DW [23] imaging data into a high-dimensional feature space using algorithms to extract a more extensive set of statistical features within the data. This type of analysis, referred to as "radiomics",

123 requires that the data have a high signal-to-noise ratio to reduce error in the analysis

124 from image noise; this is achievable in cervical cancer using an endovaginal MRI

125 technique [24]. The purpose of this study was to identify radiomic features of cervical

126 cancers on endovaginal MRI that differed between tumors below and above the

127 volume threshold of eligibility for trachelectomy (less or greater than 4.19 cm$^3$,

128 equivalent to a 2cm diameter spherical tumor volume) and to determine their value in

129 predicting recurrence in patients in the low-volume tumor group.

130

131

**Methods**

*Study Design*

This single-institution, prospective, pilot cohort study included patients with

histologically confirmed cervical cancer, presumed Stage 1 or 2 (FIGO 2009 [25],

referred for endovaginal MRI between March 2011 and October 2018 and potentially

suitable for surgical management (trachelectomy or hysterectomy). This was part of

an on-going institutional review board (IRB) approved research study documenting

imaging features of cervical cancer indicative of poor outcome (NCT01937533). All

patients gave their written consent for use of their data.  All patients were treated

with curative intent with either surgery or chemoradiation following MRI and staging

investigations.  Surgical options included cold-knife cone, trachelectomy or

hysterectomy depending on their suitability for fertility preservation and their desire

for continued fertility.  A pelvic lymphadenectomy was performed in all cases.

Clinico-pathological metrics recorded in each case were tumor volume, type, grade,

LVSI, parametrial invasion, Depth of Invasion and lymph node metastasis. Patients

were followed up for median of 35 months (3-92). Median time to recurrence was 7

months (3-62 months).


*Study participant selection*

378 consecutive patients were imaged over the defined study period. In 98 cases,

tumor was not identified on MRI while in 127 cases tumor was poorly identified and

volume was <0.07 cm$^3$, (62 of these had negative histology). Of the remaining 153

patients, 10 had non-cervical origin tumours on histology, 12 had histology other

155 than squamous or adenocarcinoma (clear cell or neuroendocrine histology), 2 had

156 metastatic disease, in 3 the whole tumor was not within the imaged field-of-view, and

157 1 did not have a diffusion-weighted images (Supplementary data, **Figure S1**). These

158 28 exclusions resulted in 125 patients with histologically confirmed residual

159 squamous-or adeno carcinomas that could be defined on MRI and were therefore

160 eligible for analysis. No patients had to be excluded on the grounds of image artefact

161 degrading the data. In patients who underwent primary surgery, the post-operative

162 histological diagnosis was taken as the gold-standard. In those who received

163 chemoradiation therapy, their pre-treatment histological diagnosis was taken as the

164 gold-standard.  In assessing lymph node status, surgical pathology was the

165 reference gold-standard in those undergoing surgery, and imaging (MRI or PET-CT)

166 was the reference gold-standard in those treated with chemoradiation.

167

168 *MRI protocol*

169 All scans were performed on a 3.0 Tesla Philips Achieva (Best, The Netherlands)

170 with a dedicated in-house developed 37 mm ring-design solenoidal receiver coil that

171 has been previously described (20, 21, 24).  Cervical position was determined at

172 vaginal examination, after which the coil was inserted and placed around the cervix.

173 Image distortion from susceptibility artefacts were reduced by aspiration of vaginal

174 air via a 4 mm diameter tube (Ryles; Pennine Healthcare, London, England). The

175 administration of Hyoscine butyl bromide (Buscopan) 20 mg IM  decreased artefacts

176 from bowel peristalsis.

177 T2-W images were obtained in three planes orthogonal to the cervix: TR/TE 2750/80

178 ms (coronal and axial) and 2500/80 ms (sagittal); field of view (FOV) 100 mm x 100

179 mm; acquired voxel size 0.42 x 0.42 x 2 mm; reconstructed voxel size 0.35 x 0.35 x

180 2 mm; slice thickness 2 mm; slice gap 0.1 mm; 24 coronal and 22 sagittal slices;

181 number of signal averages (NSA) 2. Additionally, matched Zonal Oblique Multislice

182 (ZOOM) diffusion-weighted images (DWI) were acquired: TR/TE 6500/54 ms; b-

183 values 0, 100, 300, 500, 800 s/mm$^2$; FOV 100 x 100 mm; acquired voxel size 1.25 x

184 1.25 x 2 mm; reconstructed voxel size 0.45 x 0.45 x 2 mm; slice thickness 2 mm,

185 slice gap 0.1 mm; 24 slices, NSA 1. ADC maps were automatically generated by the

186 scanner software. These were compared with T2-W images to identify the presence

187 and extent of a tumor within the cervix. Mass-lesions disrupting the normal cervical

188 epithelial architecture that were intermediate signal-intensity on T2-W images with

189 corresponding restriction on the ADC maps were recognized as tumor.

190

191 _MRI analysis: extraction of texture features_

192 Scans were anonymised (DicomBrowser, Neuroinformatics Research Group,

193 Washington University, St Louis, MO) and transferred to an XNAT[26; 27] image

194 repository. Images were imported into OsiriX (Pixmeo SARL, Bernex, Switzerland)

195 and 2D regions-of-interest (ROI) were drawn by a radiologist, (25 years' experience)

196 on the coronal T2-W and ADC maps on every slice demonstrating tumor (**Figure 1**).

197 2D ROI contours were aggregated using a custom Python script, integrated into

198 OsiriX via pyOsirix [28] and exported as a single 3D volume (VOI) in DICOM RT-

199 STRUCT format, which was then uploaded to XNAT. Custom in-house software

200 (MATLAB, MathWorks, Natick, MA) was used to extract Grey Level Co-occurrence

201 Matrix (GLCM) features (Haralick texture analysis [29; 30]) from the both the T2-W

202 images and ADC maps.

*Statistical analysis*

204   Statistical analysis was performed with *R* (R Core Team (2019), Vienna, Austria.

205   http://www.R-project.org). Correlations between features indicated 10 distinct feature

206   clusters by creating a dissimilarity measure from a distance matrix (Supplementary

207   data, **Figure S2**). Several of the texture features were very highly correlated (r=0.97-

208   1) and were successfully clustered. The feature with the greatest dynamic range

209   from each cluster was selected for investigation (**Table S1**): these were Dissimilarity,

210   Contrast, Energy, Entropy, ClusterProminence, ClusterShade, InverseVariance,

211   Correlation, Autocorrelation and InformationalMeasureCorrelation2.  Contrast and

212   Entropy, although not clustered with Dissimilarity and Energy respectively, were

213   highly correlated (R>0.9), and were removed.

214   A Shapiro-Wilk test revealed that features did not have a normal distribution so non-

215   parametric tests were employed. A Mann-Whitney (*U*) test with Bonferroni correction

216   was applied to assess the differences in texture features between tumors greater

217   than or less than 4.19 cm$^3$ on T2-W imaging (volume threshold of eligibility for

218   trachelectomy, designated as high-volume and low-volume tumors). A p-value <0.05

219   was taken to be significant.  Stepwise logistic regression was used to determine

220   which combination of features from each category (ADC-radiomics, T2-W-radiomics

221   and clinico-pathological metrics) were indicative of recurrence. This was done in 2

222   scenarios i) in all patients with low-volume tumors using adjuvant therapy as a

223   feature in the model; ii) in only those patients who did not receive adjuvant therapy.

224   The logistic regression coefficients were used to combine the features identified from

225   each scenario to generate Receiver operating characteristic (ROC) curves for ADC-

226   radiomic features and for T2-W radiomic features predicting recurrence in low-

227   volume tumors. These were compared with the ROC curve of the clinico-pathological

228 features identified in both scenarios using the Akaike information criteria (AIC).

229 Further improvements in predicting recurrence were investigated by combining the

230 features identified in the ADC-radiomic and T2-W radiomic models with the clinico-

231 pathological features and evaluated with a Chi-square test.  A bootstrap resampling

232 (n=1000) procedure was performed to obtain estimates of optimism in the regression

233 models to provide a bias-corrected AUC value through a Somers' D rank correlation

234 metric whereby AUC = (1 + Somers D)/2. The rms: Regression Modelling Strategies

235 R package, version 5.1-0 was used.

236

237

**Results**

*Patient demographics and clinical characteristics*

Eligible patients were aged between 24-89 years (mean 38.4 years) at primary treatment. Initial diagnosis was made with biopsy in 77 patients and large loop excision of the transformation zone (LLETZ) in 48 patients. Biopsies confirming the presence of cancer were not large or deep enough to confirm tumor grade in 1 case or LVSI in 7.

Of 125 patients, 79 were low-volume (range 0.26 – 4.17 cm$^3$, mean 1.3 ± 1.2 cm$^3$); 70 were treated surgically and 9 with chemoradiation. Forty-six were high-volume (range 4.2-56.1 cm$^3$, mean 15.3 ± 11.7 cm$^3$); 7 were treated surgically and 39 with chemoradiation. Of the 70 patients with low-volume tumors treated surgically, 2 patients did not have follow-up data, so that prediction of recurrence was modelled on 68 patients (**Figure S1**). Patient and tumor characteristics in those with high- and low-volume tumors are detailed in **Table 1**.

Fifty-four of 68 patients in the low-volume group did not receive adjuvant therapy. Fourteen patients in the low-volume group received adjuvant therapy following surgery because of adverse features: 5 had unexpected lymph node metastases, 3 had unexpected extension of tumor to the parametrium, 1 had a 0.5 mm margin to the parametrium at surgical histology, 1 had spread to the vaginal cuff and 4 met 2 of the Sedlis criteria (LVSI) and deep stromal invasion). There were 7 recurrences overall: 5 in 54 patients who had not and 2 in14 in patients who had received adjuvant therapy.

261 *Differences in texture features based on tumor volume and clinico-pathological*

262 *metrics*

263 Number of voxels in the T2-W images ranged from 17441-209892 in the high-volume

264 tumors (median 38597) to 107-17324 in the low-volume tumors (median 2750).

265 Number of voxels in the ADC maps ranged from 10497-140650 in the high-volume

266 tumors (median 26812) to 75-13294 in the low-volume tumors (median 1927).

267 From heat-maps of correlated texture features (Supplementary data, **Figure S2**), ten

268 texture feature clusters were identified (Supplementary data, **Table S1**). After

269 Bonferroni correction, 6 texture features on both ADC maps and T2-W images

270 (**Table 2**) remained significantly different between the high- and low-volume tumors,

271 namely Dissimilarity, Energy, ClusterProminence, InverseVariance and

272 Autocorrelation. An additional feature on T2-W imaging (Correlation) differed

273 between groups (**Table 3**).

274 In low-volume tumors, Dissimilarity and Energy differed in patients without and with

275 LVSI. (Supplementary data, **Table S2)**. However, none of the Haralick features from

276 ADC maps or T2-W images differed between adeno- and squamous cancers, low

277 and high-grade tumors, or those with negative vs. positive lymph node status.

278

279 *Clinico-pathological features as predictors of recurrence*

280 AUCs and 95% CI for individual clinico-pathological features for predicting

281 recurrence in all low-volume tumors (n=68) regardless of adjuvant therapy were:

282 (tumor type (0.548 [0.340-0.756]), grade (0.501 [0.294-0.709]), LVSI (0.537 [0.347-

283 0.728]) , Depth of Invasion (0.553 [0.291-0.814]), lymph node metastasis (0.530

284 [0.386-0.675]) and T2-W tumor volume (0.691 [0.448-0.934]). Adjuvant treatment

285 had an AUC of 0.544 [0.357-0.732]. When patients receiving adjuvant therapy were

286 excluded (n=54), the AUCs were: tumor type (0.555 [0.305-0.805]), grade (0.504

287 [0.254-0.754]), LVSI (0.633 [0.570-0.695]), Depth of Invasion (0.510 [0.214-0.807]),

288 lymph node metastasis (0.510 [0.490-0.530]) and T2-W tumor volume (0.629 [0.327-

289 0.931]). Regression modelling which included adjuvant therapy as a confounding

290 feature indicated that volume and Depth of Invasion were indicative of recurrence

291 (AUC=0.766 CI 0.562-0.970), but that when patients who received adjuvant therapy

292 were excluded, LVSI alone was predictive of recurrence (AUC= 0.633 95% CI 0.570-

293 0.695).

294 Combining T2-W volume, Depth of Invasion and LVSI predicted recurrence in all 68

295 low-volume tumors with an AUC 0.794 (95% CI 0.617- 0.971) and AIC of 45.684.

296

297 *Texture features from ADC maps as predictors of recurrence*

298 When considering all 68 patients with low-volume disease, the texture features

299 Dissimilarity, Energy, InverseVariance, ClusterProminence, ClusterShade,

300 Autocorrelation and volume derived from ADC maps had an AUC of 0.775, 0.635,

301 0.674, 0.646, 0.508, 0.665 and 0.672, respectively for predicting recurrence. (**Figure**

302 **2, Table 3**). A regression model indicated that when combined, Dissimilarity and

303 Energy were contributory to prediction of recurrence (AUC=0.864, 95% CI =0.772-

304 0.956, AIC 41.044). However, when patients who had adjuvant therapy were

305 excluded, only Dissimilarity was predictive of recurrence (AUC=0.853, 95%

306 CI=0.725-0.981).

Combining metrics predictive of recurrence from ADC-radiomic and clinico-pathological models (Dissimilarity and Energy with T2-W volume+Depth of Invasion+LVSI ) significantly improved prediction of recurrence in all 68 low-volume tumors   (AUC=0.916, 95% CI 0.837-0.994, with 100% sensitivity, 77% specificity, p=0.006, AIC=39.638, **Table 4**) compared to the combined clinico-pathological model of T2-W volume+Depth of Invasion+LVSI.

 Examples of tumors with high Dissimilarity, and low Energy vs. low Dissimilarity and high Energy respectively are illustrated **in Figure 1**.


*Texture features from T2-W imaging as prognostic biomarkers*

When considering patients with low-volume disease, the texture features Dissimilarity, Energy, InverseVariance, ClusterProminence, ClusterShade, Autocorrelation, Correlation and Volume derived from T2-W images individually had an area under the curve (AUC) of 0.609, 0.604,0.671, 0.607, 0.628, 0.536, 0.511 and 0.691 respectively for predicting recurrence (**Table 4**).   When all low-volume tumors were considered, a regression model indicated that no combination of features improved prediction of recurrence. When patients who had adjuvant therapy were excluded, Dissimilarity, Clusterprominence and InverseVariance together were predictive of recurrence (AUC=0.837, 95% CI=0.698-0.976). These features applied to all 68 patients gave an AUC of 0.808 (95% CI=0.690-0.926, AIC=49.193).

Combining metrics predictive of recurrence from T2-W-radiomic and clinico-pathological models (Dissimilarity, ClusterProminence and InverseVariance with LVSI+Depth of Invasion+T2-W volume) did not significantly improve prediction of

330     recurrence in low-volume tumors (AUC=0.906, 95% CI 0.822-0.991, p= 0.09,

331     AIC=45.128, **Table 4**) compared to the combined clinico-pathological model of T2-W

332     volume+Depth of Invasion+LVSI.

333

334     *Validation of logistic regression models*

335     Bias-corrected AUCs generated through a bootstrap resampling process showed

336     reductions in AUC from 0.864 to 0.824 for the ADC-radiomic model (Dissimilarity and

337     Energy), from 0.808 to 0.716 for the T2-W radiomic model (Dissimilarity,

338     InverseVariance and ClusterProminence) and from 0.794 to 0.718 for clinico-

339     pathological model (T2-W volume, Depth of Invasion and LVSI). The combined

340     radiomic and clinico-pathological models were corrected from 0.916 to 0.84 (ADC-

341     radiomic and clinico-pathological features) and from 0.906 to 0.822 (T2-W-radiomic

342     and clinico-pathological features).

**Discussion**

Our data has identified the radiomic features from ADC maps and T2-W images that differ between high- and low-volume cervical tumors and shown that these features individually and in combination are useful for predicting recurrence in low-volume tumors. Patients in the high- and low--volume tumor groups were well matched by age, and although the low-volume tumors were by definition lower stage, there were more adenocarcinomas and LVSI in this group, both of which adversely affect outcome. Radiomic differences between high and low-volume tumors were largely similar for both the ADC and T2-W data although regression models identified different combinations of features as being contributory to prediction of recurrence in each case. Moreover, although radiomic features differed between tumors with and without LVSI, they did not differ between other histological parameters of poor prognosis (type, grade, Depth of Invasion, LN metastasis), indicating that they are likely to be independent.

This data highlights the potential of texture feature analysis for predicting recurrence with potential to influence the surgical management of patients with early stage, low-volume cervical cancer. It means that surgical management can be altered, or appropriate patient counselling provided at the outset because the use of adjuvant therapy can be anticipated. The utility of such information would be particularly valuable in a young patient population seeking to retain fertility and minimize therapy. For instance, to avoid the toxicity of lymphadenectomy followed by adjuvant chemoradiation, patients with "good" radiomic features may elect to have sentinel node biopsy prior to curative treatment (surgery or chemoradiation). Additionally, patients could be counselled as to the need for adjuvant therapy at the outset. In larger tumors, where volume is a strong predictive factor of recurrence [31] and

18

368    survival [32] , the utility of additional radiomic analyses in altering management

369    remains to be established.

370    The greater tendency to decreased Dissimilarity in larger tumors, indicates that grey

371    levels in adjacent pixels were similar in larger tumors. Energy, which is a measure of

372    textural uniformity, and is highest when grey level distribution has either a constant

373    or a periodic form, also was higher in larger tumors. A previous prospective study

374    has confirmed the reproducibility of these features and their lack of dependence on

375    regional ROI selection within the tumor [33], nevertheless we used whole tumor

376    analysis in our study. A study by Hao et al has shown that radiomic analysis of the

377    tumor periphery is informative in differentiating those likely to recur from those that

378    do not [34], but the tumor volume in their cohort was high and patients were treated

379    with chemoradiation. Our data interrogates the differences in features between high-

380    vs. low-volume tumors across the entire tumor volume and uses these features to

381    recognize low- volume tumors with potentially poor prognosis. It confirms for the first

382    time using radiomic analysis, that as cervical tumors grow, they tend to become

383    texturally less dissimilar and more homogenous. This may well reflect the transition

384    from a morphology where tumor elements are interspersed with normal cervical

385    glandular elements and stroma in smaller tumors to more homogenous sheets of

386    malignant cells as tumors increase in size and de-differentiate. The T2W-radiomic

387    features, however, were less good than the ADC-radiomic features for predicting

388    recurrence. They did not offer significant improvements for prediction of recurrence

389    when combined with clinico-pathological features as the model over-fitted the data.

390    T2-W data also was affected by signal-intensity variations across the image,

391    particularly in the presence of an endovaginal coil, which was not an issue with the

392    quantified ADC from diffusion-weighted images.

393     Other retrospective studies have reported radiomic features derived from MRI and

394     [18]FDG-positron emission tomography (PET) scans of locally advanced cervical

395     cancer treated with chemoradiotherapy. Radiomics features such as entropy from

396     ADC maps and grey level non-uniformity from PET, respectively, have been shown

397     to be independent predictors of recurrence and loco-regional control in these larger

398     volume tumors with significantly higher prognostic power than usual clinical

399     parameters [35] .This supports our findings where these features are shown to differ

400     between high- and low-volume tumors and to be predictive of recurrence in the low-

401     volume tumor group.

402     A strength of this study was the derivation of the data using an endovaginal receiver

403     coil, particularly in small volume tumors where it was possible to obtain a minimum of

404     100 voxels. This provided a substantial boost in SNR [24]  and was invaluable for the

405     assessment of the ADC data where external array imaging in the low-volume tumors

406     would have limited the voxel numbers and precluded meaningful ADC feature

407     analysis.

408     The application of adjuvant therapy as a confounding factor represented an analysis

409     dilemma: removal of patients with low-volume tumours on MRI who went on to

410     receive adjuvant chemotherapy would have biased the sample and made it

411     unrepresentative of the final application. On the other hand, retaining these patients

412     in the analysis, potentially weakened the model because patients with MRI radiomics

413     features indicative of a recurrence after surgery will have that recurrence prevented

414     by the adjuvant treatment. Our solution here was to perform both sets of analyses.

415     As predicted, when the patients who received adjuvant therapy were removed, the

416     AUC of the model increased, but at the cost of a smaller sample size.

417 Like many current studies in tumor radiomics, our work has several limitations. First

418 it is a single site study with a relatively small sample size, albeit from a quaternary

419 referral gynaecological oncology centre which sees and treats a high volume of

420 patients. Second, the recurrence rate was low (~10%) but is in keeping with

421 expectations in this early stage, potentially curable disease. Even with a larger

422 sample size, it would not have been possible to avoid such an imbalance between

423 the recurrence and no-recurrence classes. Taken together, these factors lead to a

424 model based on a small number of recurrences and the consequent risk of overfitting

425 from the combined model, with a possibly over-optimistic value for the combined-

426 model AUC. However, we show that for *single-feature* models *any one* of the ADC

427 radiomic features Dissimilarity, Energy, InverseVariance, ClusterProminence,

428 Autocorrelation or ADC volume performed better than the highest-scoring "clinico-

429 pathological" features (T2-W volume and LVSI). Furthermore, when considering

430 models based on just *two* features, the radiomic model (ADC Dissimilarity and

431 Energy, AUC=0.864) compared well with the clinical model (T2-W volume and Depth

432 of invasion, AUC=0.766).Third, patients were often diagnosed following a LLETZ

433 biopsy which may remove a significant volume of disease, thus affecting the

434 assessment at their staging MRI and confounding our results; this was the case in 1

435 patient in our study group. Nevertheless, in a clinical setting a LLETZ or cone biopsy

436 is performed as part of the normal clinical pathway prior to MRI and imaging prior to

437 a diagnostic LLETZ or cone biopsy is unlikely, making our results more applicable in

438 a clinical workflow. In future, when determining the utility of radiomic features

439 combined with other clinical and histologic assessments, use of MRI plus LLETZ

440 volume is desirable.  Finally, the current poor availability of endovaginal MRI limits

441 radiomic assessments of low-volume tumors more widely. However, if further

442     accumulation of cases confirms the predictive power of this model and that high SNR

443     enables its implementation, this will provide a justification for more widespread use

444     of this MRI technique at specialist centres offering trachelectomy. Alternatively,

445     improvements of SNR in non-endovaginal MRI may be required.

446     In conclusion, in patients with low-volume tumors, ADC-radiomic texture analysis is

447     potentially a useful predictor of tumor recurrence. This can substantially impact the

448     treatment planning and counselling of patients with low-volume tumors seeking

449     fertility preservation.

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**Conflict of interest/disclosure statement**

"The authors declare no potential conflicts of interest."

**Author Contributions**

**Ben Wormald:** Conceptualization, Methodology, Data curation, Analysis, Writing-Original draft preparation. **Simon Doran**: Methodology, Data curation, Analysis Supervision. **Thomas Ind: Data Curation, Patient Management. James Petts:** Software, Analysis. **James D'Arcy:** Software, Analysis. **Nandita deSouza**: Conceptualization, Writing-Reviewing and Editing, Supervision.

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561      chemoradiotherapy. Eur J Nucl Med Mol Imaging 45:768-786

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564 **TABLES:**

565 **Table 1:** Patient characteristics for all tumors and for low- and high-volume tumor

566 sub-groups (*1 treated with chemoradiotherapy)*

567

568 **Table 2:** Texture features derived from ADC maps and T2-W images showing

569 differences between low- and high- volume tumors

570

571 **Table 3:** Texture features derived from ADC maps and T2-W images in 68 low-

572 volume tumors for prediction of recurrence

573

574 **Table 4:** Regression models in prediction of recurrence with bootstrap corrected

575 AUC and Chi-Square test of model differences. The reduction in AIC when ADC-

576 radiomic and clinico-pathological features are combined compared to clinico-

577 pathological features alone is indicative of the improvement of the combined model.

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**FIGURE LEGENDS**

581 **Figure 1:** T2-W (a) and ADC map (b) in a 33- year old patient with a 0.8 cm$^3$ volume

582 tumor that had high dissimilarity (0.808). Regions-of-interest delineate the tumor.

583 The intermediate signal-intensity tumor on the T2-W imaging (arrow) is restricted in

584 diffusion on the ADC maps (arrow). Tumor was confined to the cervix, and the

585 patient remains disease-free following trachelectomy. T2-W (c) and ADC map (d) in

586 a 26 year old patient with a 0.9 cm$^3$ volume tumor that had low dissimilarity (0.489).

587 The intermediate signal-intensity tumor on the T2-W imaging (c) is restricted in

588 diffusion on the ADC maps (d). Regions-of-interest delineate the tumor. Tumor was

589 confined to the cervix, but despite negative nodes on surgical histology, the patient

590 recurred centrally after 9 months.

591

592 **Figure 2:** Receiver Operating Curves showing sensitivity and specificity for

593 prediction of recurrence by texture and clinic-pathological features (a) in 68 patients

594 with low-volume tumors where use of adjuvant therapy is included in the model; (b)

595 in 54 patients who did not receive adjuvant therapy; and (c) in all 68 patients using

596 features identified in both a and b (Dissimilarity, Energy for ADC-radiomics;

597 Dissimilarity, ClusterProminence, InverseVariance for T2-W-radiomics; and Volume,

598 Depth of Invasion, LymphoVascular Space Invasion for clinico-pathological

599 features). In a, no combination of T2-W features was significantly superior to

600 individual features. In b, of the clinico-pathological features, LVSI alone was

601 predictive of recurrence, In c, the optimal prediction of recurrence is shown by a

602 combination of ADC-radiomic an clinico-pathological features.

603

**Table 1:** Patient characteristics for all tumors and for low- and high-volume tumor sub-groups (**1 treated with chemoradiotherapy*)

| | All tumors | High volume >4.19cm$^3$ | Low volume <4.19cm$^3$ |
|---|---|---|---|
| **Age, mean (range)** | 38.4 (65.0) | 43.0 (64.0) | 35.6 (38.0) |
| **BMI, mean (range)** | 25.7 (36.3) | 26.2 (36.3) | 25.4 (32.9) |
| **FIGO stage, n** | | | |
| 1 | 74 | 69 | 5 |
| 2 | 51 | 10 | 41 |
| **Histological subtype, % patients (n)** | | | |
| Squamous | 61.6 (77) | 78.3 (36) | 51.9 (41) |
| Adenocarcinoma | 38.4 (48) | 21.7 (10) | 48.1 (38) |
| **Grade % patients (n)** | | | |
| 1 or 2 | 55.2 (69) | 52.2 (24) | 57.0 (45) |
| 3 | 43.2 (54) | 43.5 (20) | 43.0 (34) |
| Unknown | 1.6 (2) | 4.3 (2) | 0 |
| **LVSI, % patients (n)** | | | |
| Positive | 27.2 (34) | 15.2 (7) | 34.2 (27) |
| Negative | 65.6 (82) | 67.4 (31) | 64.6 (51) |
| Unknown | 7.2 (9) | 17.4 (8) | 1.2 (1) |
| **Depth of Invasion, mean (range)** | 7.1 (20.4) | 6.0 (19.0) | 7.4 (20.4) |
| **Parametrial invasion % patients (n)** | | | |
| Positive | 32.8 (41) | 76.1 (35) | 7.6 (6) |
| Negative | 67.2 (84) | 23.9 (11) | 92.4 (73) |
| **Lymph node metastasis, % patients (n)** | | | |
| Positive | 31.2 (39) | 58.7 (27) | 15.2 (12) |
| Negative | 68.8 (86) | 41.3 (19) | 84.8 (67) |
| **Treatment, % patients (n)** | | | |
| Surgery | 61.6 (77) | 15.2 (7) | 88.6 (70) |
| Chemoradiation | 38.4 (48) | 84.8 (39) | 11.4 (9) |
| **Surgery, % patients (n)** | | | |
| Cold Knife Cone CKC | 0 | 0 | 0 |
| Trachelectomy | 48.1 (37) | 14.3 (1) | 51.4 (36) |
| Hysterectomy | 51.9 (40) | 85.7 (6) | 48.6 (34) |
| **Adjuvant treatment after surgery % patients (n)** | | | |
| Yes | 23.4 (18) | 28.6 (2) | 22.9 (16) |
| **Recurrence, % patients (n)** | | | |
| Yes | 16.0 (20) | 26.1 (12) | 10.1 (8)* |
| No | 78.4 (98) | 65.2 (30) | 86.1 (68) |
| Unknown | 5.6 (7) | 8.7 (4) | 3.8 (3) |

25

**Table 2:** Texture features derived from ADC maps and T2-W images showing differences between low- and high- volume tumors

| | | Median low volume N=79 | IQR low volume N=79 | Median high volume N=46 | IQR high volume N=46 | Adjusted p-value |
|---|---|---|---|---|---|---|
| **Dissimilarity** | ADC | 0.64 | 0.28 | 0.35 | 0.17 | 1.22E-11 |
| | T2W | 0.49 | 0.32 | 0.25 | 0.12 | 4.31E-14 |
| **Energy** | ADC | 0.15 | 0.11 | 0.30 | 0.21 | 3.76E-09 |
| | T2W | 0.20 | 0.13 | 0.34 | 0.2 | 7.55E-10 |
| **InverseVariance** | ADC | 0.41 | 0.08 | 0.29 | 0.13 | 2.84E-11 |
| | T2W | 0.38 | 0.12 | 0.23 | 0.10 | 9.61E-13 |
| **ClusterProminence** | ADC | 29.33 | 40.77 | 10.52 | 10.11 | 5.95E-08 |
| | T2W | 22.66 | 24.14 | 8.03 | 6.50 | 1.49E-09 |
| **ClusterShade** | ADC | 2.82 | 3.62 | 1.26 | 1.42 | 3.84E-03 |
| | T2W | 2.29 | 2.28 | 1.18 | 1.30 | 0.02 |
| **Autocorrelation** | ADC | 11.41 | 5.68 | 9.13 | 4.64 | 0.02 |
| | T2W | 11.65 | 8.69 | 6.08 | 3.64 | 8.22E-09 |
| **InformationalMeasure Correlation2** | ADC | 0.63 | 0.21 | 0.54 | 0.07 | 0.08 |
| | T2W | 0.67 | 0.16 | 0.68 | 0.22 | 1 |
| **Correlation** | ADC | 0.44 | 0.18 | 0.47 | 0.07 | 0.89 |
| | T2W | 0.55 | 0.23 | 0.62 | 0.26 | 0.03 |

**Table 3:** Texture features derived from ADC maps and T2-W images in 68 low-volume tumors for prediction of recurrence

| Texture feature | From | AUC (CI) | Threshold | Sensitivity | Specificity |
|---|---|---|---|---|---|
| **Dissimilarity** | ADC map | 0.775 (0.646-0.904) | 0.635 | 100 | 61 |
| | T2-W image | 0.609 (0.334-0.883) | 0.318 | 43 | 89 |
| **Energy** | ADC map | 0.635 (0.432-0.838) | 0.178 | 71 | 61 |
| | T2-W image | 0.604 (0.373-0.835) | 0.235 | 71 | 67 |
| **Cluster prominence** | ADC map | 0.646 (0.425-0.868) | 53.789 | 100 | 33 |
| | T2-W image | 0.607 (0.364-0.849) | 12.113 | 43 | 85 |
| **Inverse variance** | ADC map | 0.674 (0.496-0.853) | 0.443 | 100 | 38 |
| | T2-W image | 0.665 (0.444-0.886) | 0.349 | 71 | 66 |
| **Auto-correlation** | ADC map | 0.665 (0.497-0.833) | 11.978 | 100 | 41 |
| | T2-W image | 0.628 (0.463-0.793) | 8.921 | 100 | 38 |
| **Correlation** | ADC map | - | - | - | - |
| | T2-W image | 0.536 (0.326-0.746) | 0.524 | 71 | 57 |
| **ClusterShade** | ADC map | 0.508 (0.292-0.724) | 5.75 | 100 | 23 |
| | T2-W image | 0.511 (0.274-0.747) | 3.474 | 86 | 26 |
| **InformationMeasureCorrelation2** | ADC map | - | - | - | - |
| | T2-W image | - | - | - | - |
| **Volume** | ADC map | 0.672 (0.426-0.919) | 1292.136 | 71 | 64 |
| | T2-W image | 0.691 (0.448-0.936) | 1248.191 | 71 | 64 |

**Table 4:** Regression models in prediction of recurrence with bootstrap corrected AUC and Chi-Square test of model differences. The reduction in AIC when ADC-radiomic and clinico-pathological features are combined compared to clinico-pathological features alone is indicative of the improvement of the combined model.

| | AUC | CI | Corrected AUC | AIC | Resid. Df | Resid. Dev | Df | Deviance | p Value* |
|---|---|---|---|---|---|---|---|---|---|
| **Clinico-pathological** | 0.794 | 0.617-0.971 | 0.708 | 45.684 | 64 | 37.684 | - | - | - |
| **ADC-Radiomic** | 0.864 | 0.772-0.956 | 0.824 | 41.044 | 65 | - | - | - | - |
| **T2W-Radiomic** | 0.808 | 0.690-0.926 | 0.716 | 49.193 | 65 | - | - | - | - |
| **ADC-Radiomic +Clinico-pathological** | 0.916 | 0.837-0.994 | 0.840 | 39.638 | 63 | 27.638 | 2 | 10.046 | 0.006 |
| **T2W-Radiomic +Clinico-pathological** | 0.906 | 0.822-0.991 | 0.822 | 45.128 | 61 | 31.128 | 3 | 6.556 | 0.086 |

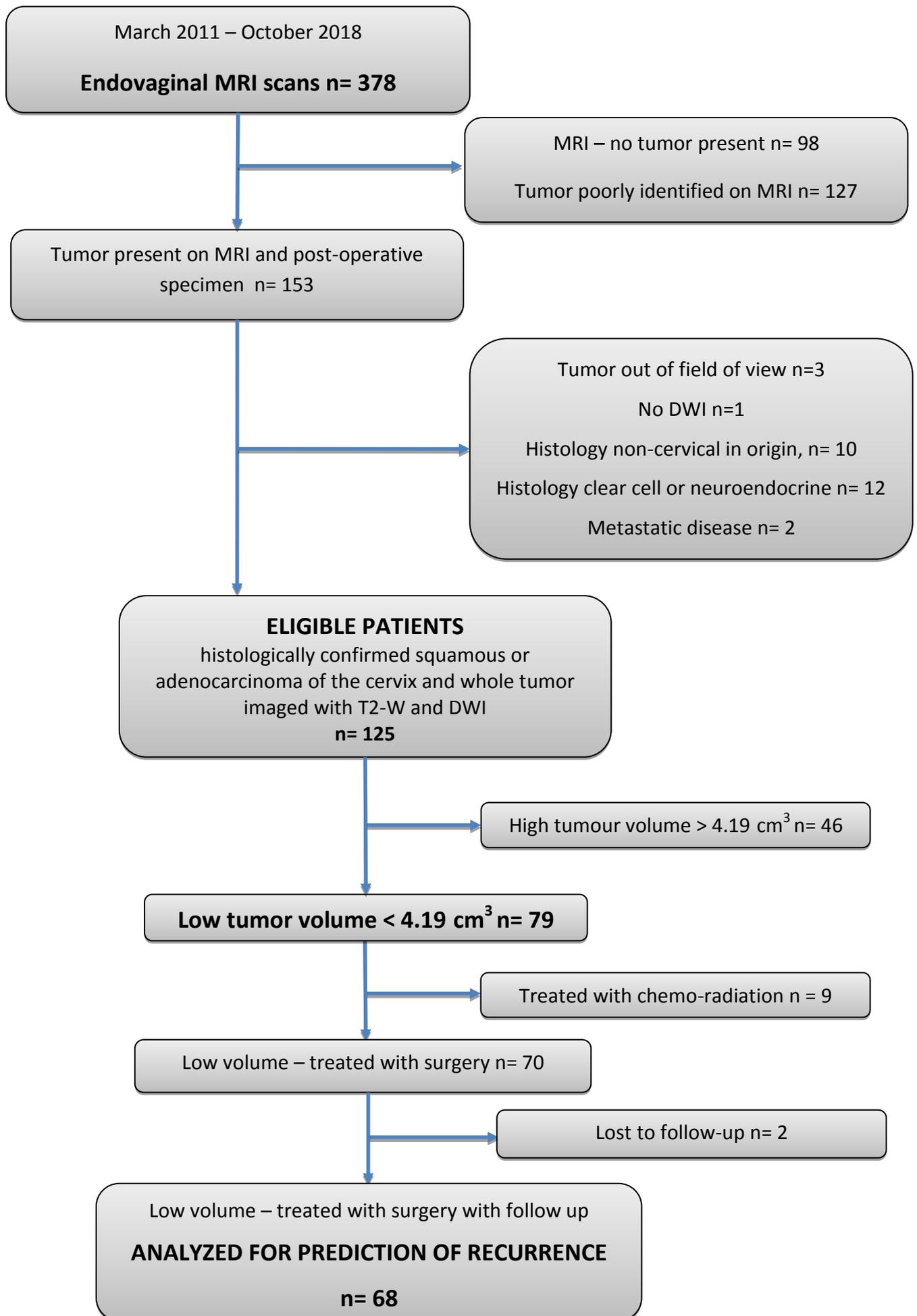*p- value of nested model compared to clinico-pathological model.
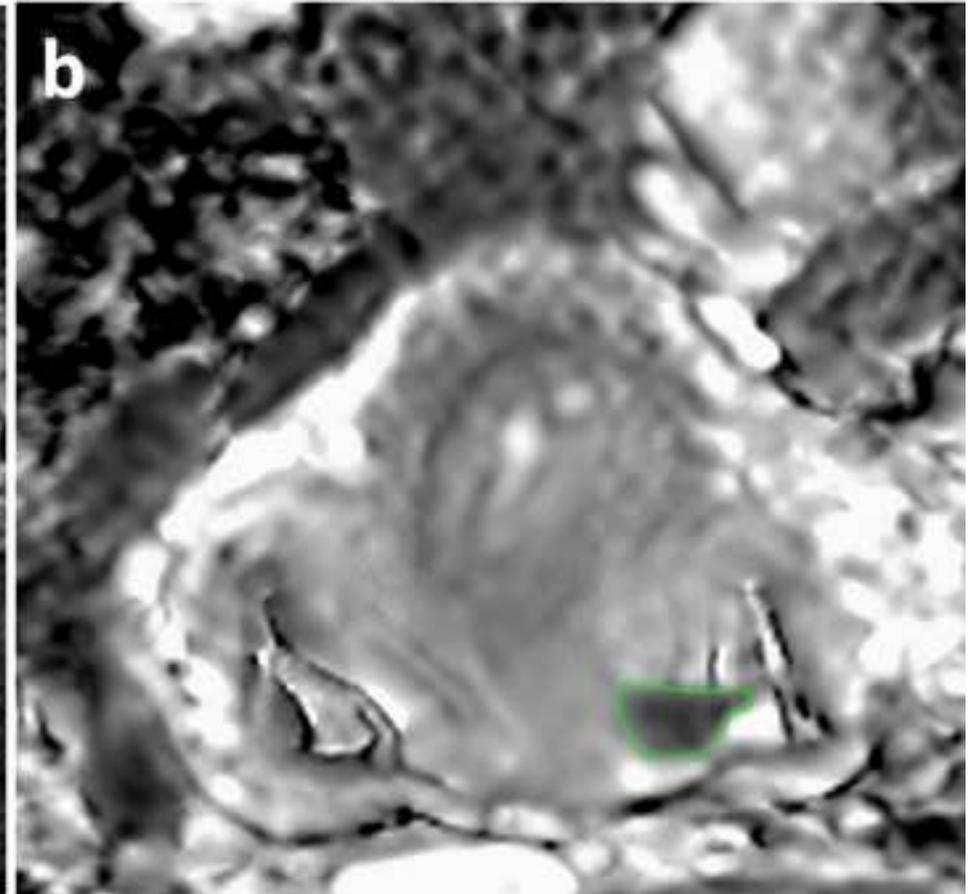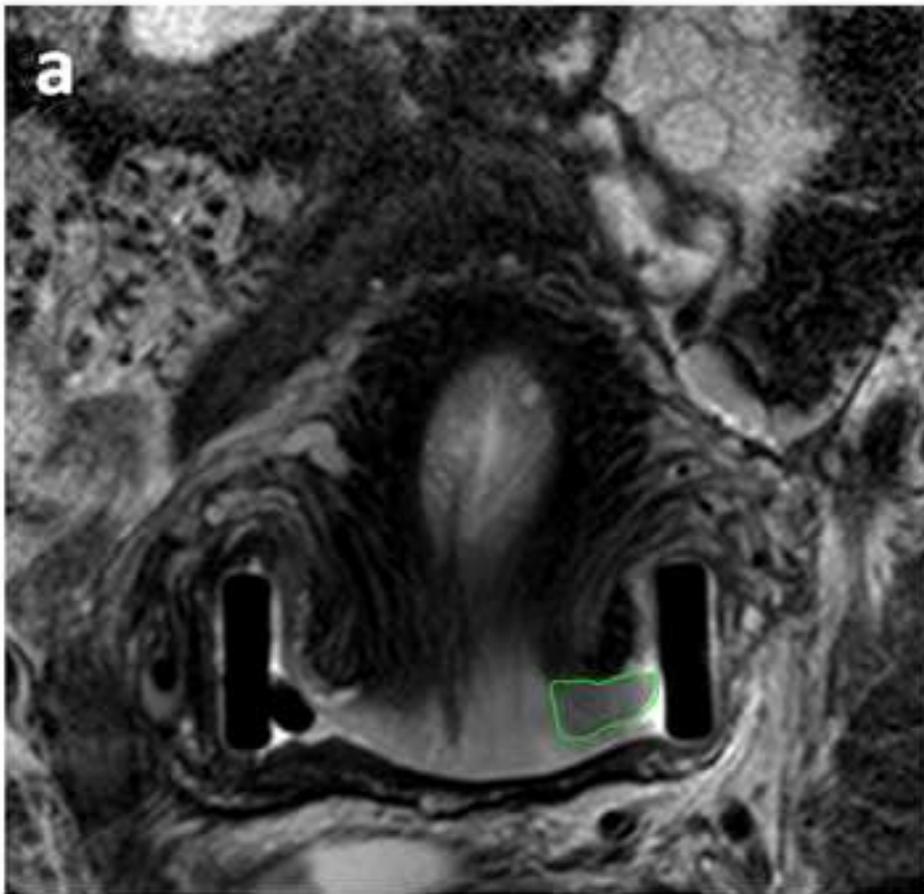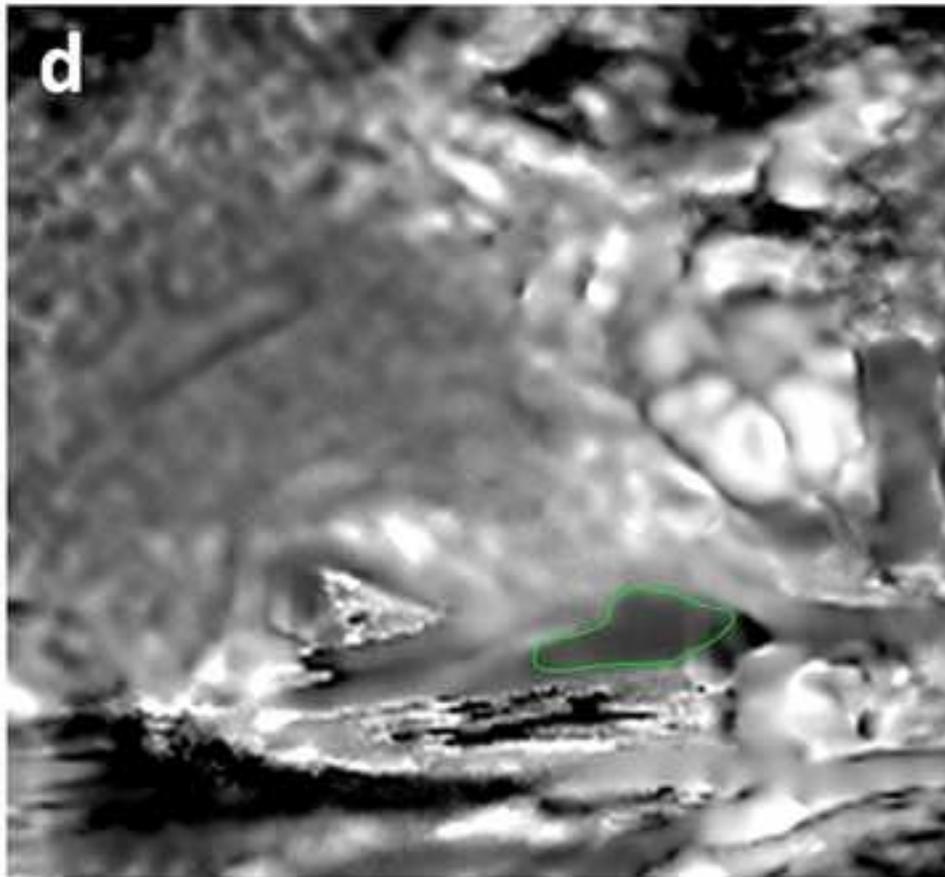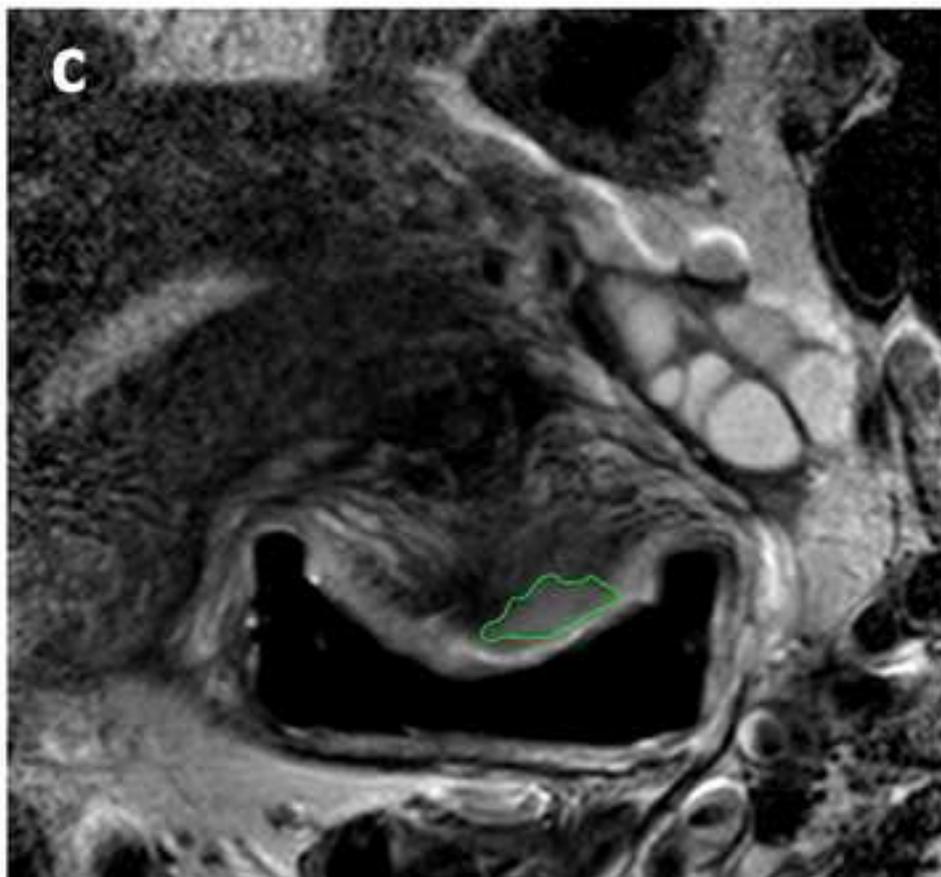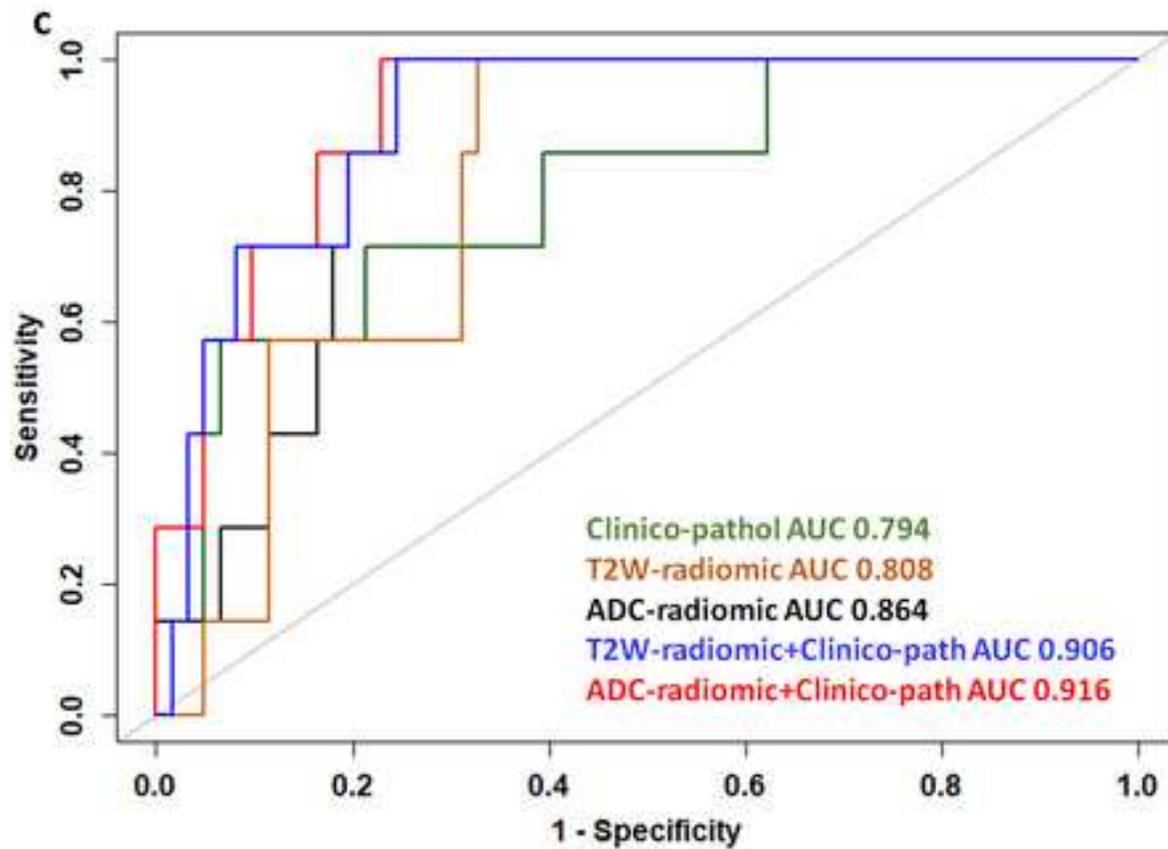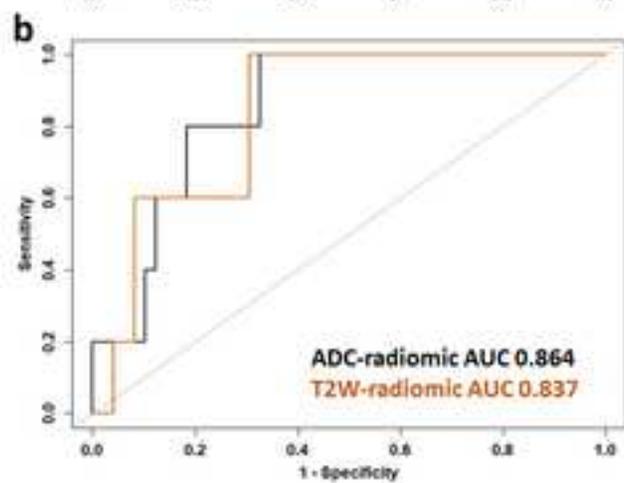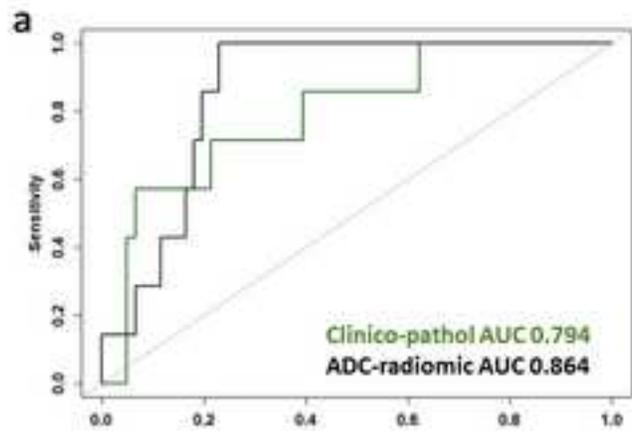
**6. Figure S1**
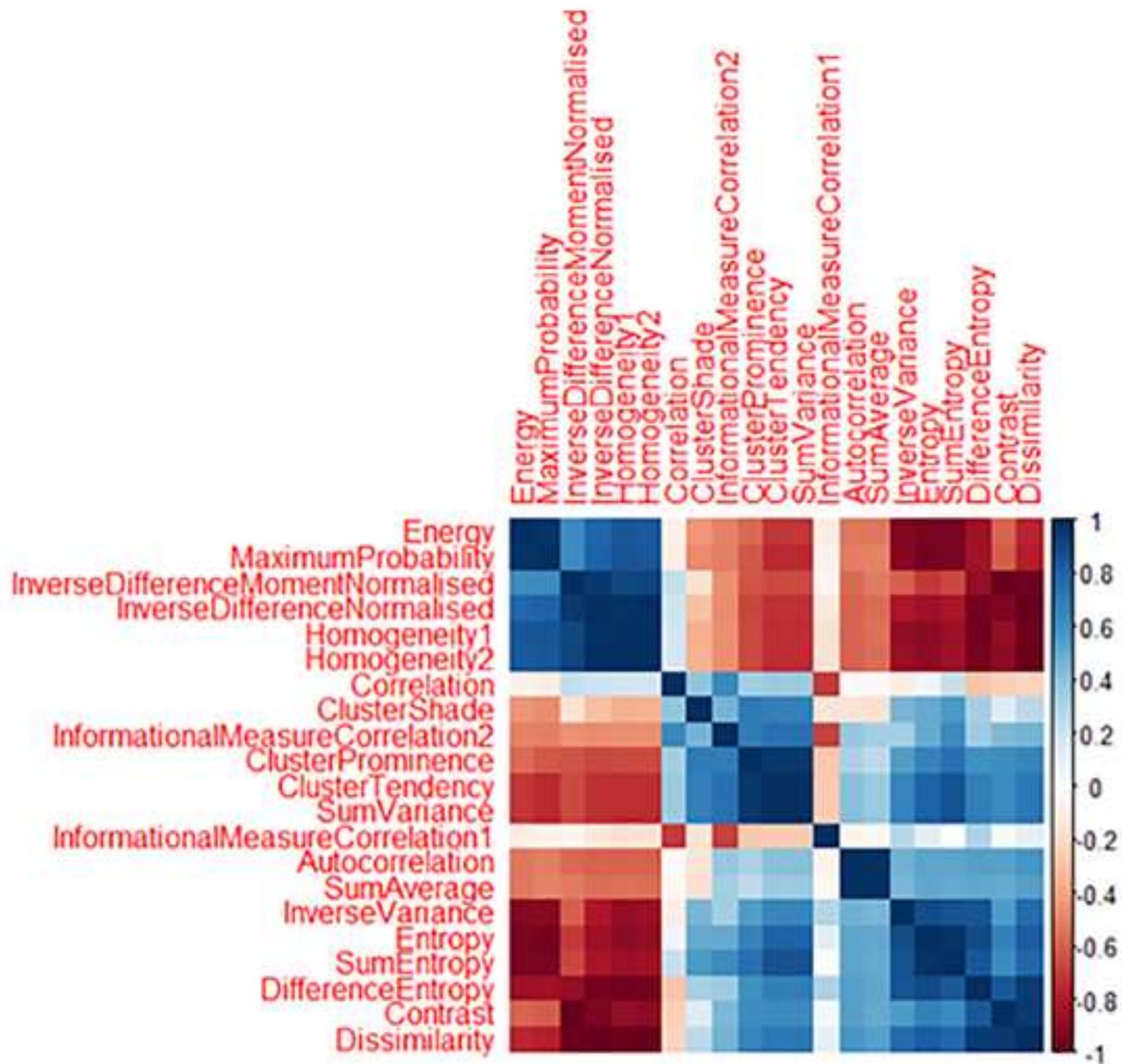
**Highlights**

1. Texture features differed significantly between high- compared to low-volume cervical tumors (p<0.02).

2. In low-volume tumors, predicting recurrence from ADC-radiomics was superior to T2-W-radiomics or clinico-pathologic features.

3. Combining ADC-radiomic and clinico-pathologic features together improved recurrence prediction further.

**Statement of Translational Relevance:**

This data indicates that in small volume cervical cancers suitable for trachelectomy, a combination of radiomic features derived from ADC maps on MRI and clinico-pathological factors best predicts likelihood of recurrence.  These patients are currently selected for adjuvant therapy based on clinico-pathological features post-trachelectomy.  Although selection of patients for adjuvant therapy based on imaging radiomic features as predictors of recurrence requires further validation in a test set, the robustness of our data as indicated by bootstrap re-sampling technique, warrants close follow-up of individuals with tumors exhibiting poor radiomic features. We suggest that in patients with tumors <4 cm$^3$ treated surgically, where ADC-radiomics show that Dissimilarity is high and Energy low, introduction of more frequent vault smears and imaging in the first 3 years post-operatively would help identify recurrences early.

## CRediT author statement

**Ben Wormald:** Conceptualization, Methodology, Data curation, Analysis, Writing-Original draft preparation. **Simon Doran**: Methodology, Data curation, Analysis Supervision. **Thomas Ind:** Data Curation, Patient Management. **James Petts:** Software, Analysis. **James D'Arcy:** Software, Analysis. **Nandita deSouza**: Conceptualization, Writing-Reviewing and Editing, Supervision.