Apparent Diffusion Coefficient in MRI Scan and Cervix Squamous Cell Carcinoma Histopathologic Grade: A Correlational Study

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Abstract

Background: Currently, MRI examination is the main radiological diagnostic examination option for determining cervical cancer staging. Apparent diffusion coefficient (ADC) predicts changes in cell density due to water quantity and diffusion. This study aims to determine the correlation between ADC value and cervix SCC. **Methods**: This is a correlation study with retrospective design that was conducted at Radiology Installation of Dr. Soetomo General Hospital, Surabaya, Indonesia for 2 years. Sample of this study was all cervix cancer patients at Dr. Soetomo General Hospital, Surabaya who met inclusion criteria. Histopathologic grades were collected from histopathologic archives and ADC values were collected through DWI sequence in MRI. Descriptive analysis was carried out to obtain sample characteristics then continued with ROC analysis to obtain ADC cut off value and non-parametric Spearman's rho correlation test was conducted to determine the correlation between ADC values in cervix cancer which was categorized according to their histopathologic grade. **Results:** Sample distribution based on cervix cancer histopathologic grade from 48 samples showed that 27 patients (56.3%) had grade I SCC, eight patients (16.7%) had grade II, and 13 patients (27.1%) had grade III. Apparent diffusion coefficient cut-off value for grade I cervix cancer was 0.90 ± 0.18 x 10^{-3}mm^2/s, grade II was 0.83 ± 0.14 x 10^{-3}mm^2/s, and grade III was 0.82 ± 0.12 x 10^{-3}mm^2/s. Spearman's rho correlation test result was -0.169 and p = 0.250 (p>0.05). **Conclusion:** There was a very weak negative and non-significant correlation between ADC value and cervix squamous cell carcinoma histopathologic grade.

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Keywords: Apparent diffusion coefficient, MRI, cervix cancer, squamous cell carcinoma, histopathologic grade

1. Introduction

Cervix cancer is the second most common cancer in women. In 2018, there were 32,469 new cases which compromised 17.2% of all cancers in Indonesian women, with an annual mortality rate of 13.9 per 100 000 women per year (The Global Cancer Observatory: Indonesia, 2020). Diagnosis of cervical cancer is determined through history taking, physical, radiology and histopathologic examinations. Accurate diagnosis is very important to achieve optimal management (Bourgioti C et al., 2016).

Squamous cell carcinoma (SCC) is a subtype of cervical cervix that is commonly found (two thirds of all cervical cancer cases). Squamous histology might provide prognosis for cervical cancer. Keratin is part of SCC classification that is associated with success rate of treatment. Keratin is an important element in SCC grading. Tumor characteristics are determined through tumor grade. Women with grade 1 tumor were more likely to have stage I tumor than those with grade II and III tumor (58.7% vs. 36.2%–43.3%). In contrast, grade III patients have a higher chance of stage IV tumor than grade I and II patients (15.2% vs 7.0% –10.1%), indicating that high grade tumors have worse prognosis (Matsuo K et al., 2018).

Currently, MRI examination is the main radiological diagnostic examination option for determining cervical cancer staging before and after therapy because of its high-level resolution in assessing soft tissue and its multiplanar technique. Final diffusion weighted imaging (DWI) is often used as cervical cancer staging protocol (Kundu S et al., 2012). Apparent diffusion coefficient (ADC) predicts changes in cell density due to water quantity and diffusion. It is a quantitative assessment from DWI (Keriakos NN et al., 2018). Apparent diffusion coefficient value in malignant tumors is often lower compared to ADC values in benign tumors or normal tissue due to increased cellularity, therefore ADCs are systematically evaluated in cervical cancer (Kundu S et al., 2012). There is an increase of cellularity in tumor tissues without restriction of intercellular water transfer, providing an increased DWI signal that is correlated with low ADC value (Atram S et al., 2016 and Demirbas T et al., 2014).

Several studies reported ADC correlation with tumor grade. Liu et al found that there were significant differences in each grade with mean grade I ADC value of 1.09 $x10^{-3}mm^2/s$, grade II=$0.86x10^{-3}mm^2/s$, and grade III=$0.71x10^{-3}mm^2/s$. However, in studies conducted by Demirbas et al and Dashottar et al found no significant difference in the ADC value compared to each grade.

In present day, there is still no correlation study between ADC value in cervix SCC and histopathologic grading results at our hospital. This study aims to determine the correlation between ADC value and cervix SCC. This data will be important in the future for radiologists to evaluate cervix cancer through MRI examination, therefore giving more accurate cervix cancer diagnosis for the benefit of treatment and treatment evaluation.

2. Methods

2.1 Study design and setting

This is a correlation study with retrospective design. This study was conducted at Radiology Installation of Dr. Soetomo General Hospital, Surabaya, Indonesia from January 1 2017 to December 31 2019.

2.2 Study population and sampling strategy

Population of this study was all cervix cancer patients at Dr. Soetomo General Hospital, Surabaya. We used consecutive sampling method by including all patients who met inclusion criteria as followed: cervical uteri cancer patients with squamous cell carcinoma (SCC) in their biopsy, patients who were conducted histopathologic grading, and had not received any treatment (surgical, chemotherapy, or radiotherapy), had undergone pelvic MRI with DWI examinations and their ADC value obtained.

2.3 Data collection

Histopathologic grades were collected from histopathologic archives. The grades were determined through tissue evaluation using four modified multifactorial grading system (MGS) parameters: structure, differentiation of cell type, nuclear pleomorphism, and mitosis. Afterwards, the total scores were divided into four grades: grade I (score = 4-6), grade II (score = 7-9), and grade III (10-12). This evaluation was conducted by a blinded pathologist.

Apparent Diffusion Coefficient value was obtained through DWI sequence in MRI. It is defined as water molecule diffusion magnitude in tissues. This value was determined by using 10-50 mm^2 round/oval-shaped region of interests (ROI) that was placed above three solid areas that had signal intensity changes on DWI. This was conducted by a blinded radiologist from female imaging division. Type of MRI machine that was used was 3 Tesla Siemens Magnetom Skyra and 1.5 Tesla GE MR360, with b value 50, $\geq$ 500 and $\leq$ 1000 s/mm^2. Apparent Diffusion Coefficient value was expressed in mm^2/second.

Parameter	Points 1	2	3
Tumour-cell population			
1. Structure	Exophytic, papillary and solid	Small cords and groups of cells	Marked dissociation
2. Differentiation in to cell type	Large cell no keratin	Large cell keratinisation	Small cell
3. Nuclear pleomorphism	>75% mature nuclei, few enlarged nuclei	75-25% mature nuclei moderate number of enlarged nuclei	<25% mature nuclei numerous irregular or anaplastic enlarged nuclei.
4. Mitosis	Single (0-1)	Moderate number (2-5)	Numerous (>5)
Tumour-host relationship			
5. Mode of invasion	Well-defined borderline	Cords, less marked borderline	Groups of cells or diffuse growth
6. Stage of invasion	Minimal stroma invasion or microcarcinoma	Nodular into submucosa and connective tissue	Massive, amongst muscle and vessels
7. Vascular invasion	None	Possible	Well-established within lumina of lymph or blood vessels
8. Cellular response (lymphoplasmocytic)	Marked (continuous rim)	Moderate (several large patches)	Slight or none (few small patches or no cells)

Figure 1. Parameters in multifactorial grading point (MGS)

2.4 Data analysis

MRI examination data for cervix cancer which consists of DWI sequence and ADC value as well as histopathologic results were arranged in tabular form. Descriptive analysis was carried out to obtain sample characteristics then continued with ROC analysis to obtain ADC cut off value and non-parametric Spearman's rho correlation test was conducted to determine the correlation between ADC values in cervix cancer which was categorized according to their histopathologic grade.

3. Results

Sample characteristics distribution based on this study results from 48 samples, according to Table 1, showed that the youngest patient was 28 years and the oldest patient was 68 years. Mean age of patients was 52.23 ± 9.54 years. Sample distributions when grouped based on age group were as followed: 20—40 years, 40—60 years, and > 60 years. The results showed that 10.4% (five patients) were in 20-40 years group, 29.3% (14 patients) in 40-60 years group, and 60.4% (29 people) were in >60 years.

Table 1. Sample distribution of cervix cancer based on age group

Age group	Patients (n)	Percentage (%)
20—40 years	5	10.4
40—60 years	14	29.2
>60 years	29	60.4
Total	48	100.0

Sample distribution based on cervix cancer histopathologic grade from 48 samples, according to Table 2, showed that 27 patients (56.3%) had grade I result, eight patients (16.7%) had grade II results, and 13 patients (27.1%) had grade III results.

Table 2. Sample distribution of cervix cancer based on cervix cancer histopathologic grade

Histopathologic grade	Patients (n)	Percentage (%)
Grade I	27	56.3
Grade II	8	16.7
Grade III	13	27.1
Total	48	100.0

According to Table 3, mean age of patients based on cervix cancer histopathologic grade was 54.18 ± 9.11 years in grade I group, the youngest was 28 years and the oldest was 68 years. Mean age of patients with grade II results was 51.75 ± 9.44 years, the youngest patient was 40 years and the oldest was 65 years. Furthermore, mean age of patients with grade III results was 48.46 ± 10.05 years, the youngest was 28 years and the oldest was 68 years.

Table 3. Age distribution based on cervix cancer histopathologic grade

Histopathologic grade	Mean age (years)	Standard Deviation (SD)
Grade I	54.18	9.11
Grade II	51.75	9.44
Grade III	48.46	10.05
All patients	52.23	9.54

Distributions of ADC value are shown in Table 4. The lowest ADC value was 0.63 x $10^{-3}mm^2/s$ and the highest was 1.42 x $10^{-3}mm^2/s$. Mean ADC value was 0.87±0.163 x $10^{-3}mm^2/s$. Cut-off value for each histopathologic grade was determined using mean ADC value for each cervix cancer histopathologic grade. Apparent diffusion coefficient value cut-off for grade I was 0.90 ± 0.18 x $10^{-3}mm^2/s$ with minimum ADC value of 0.73 x $10^{-3}mm^2/s$ and maximum value of 1.42 x $10^{-3}mm^2/s$. Apparent diffusion coefficient value cut-off for grade II was 0.83 ± 0.14 x $10^{-3}mm^2/s$ with minimum value of 0.65 x $10^{-3}mm^2/s$ and maximum value of 1.03 x $10^{-3}mm^2/s$. Apparent diffusion coefficient value cut-off for grade III was 0.82 ± 0.12 x $10^{-3}mm^2/s$ with minimum value of 0.63 x $10^{-3}mm^2/s$ and maximum value of 1.42 x $10^{-3}mm^2/s$.

Table 4. Distributions of ADC value based on cervix cancer histopathologic grade

Histopathologic grade	ADC value (x $10^{-3}mm^2/s$)	Standard Deviation (SD)
Grade I	0.90	0.18
Grade II	0.83	0.14
Grade III	0.82	0.12
All patients	0.87	0.16

Correlation between ADC value and Cervix Cancer Histopathologic Grade

The result for non-parametric Spearman's rho correlation test revealed spearman's rho value of -0.169, which means a very weak negative correlation, and p = 0.250 means that there was no significant correlation between ADC value and cervix cancer.

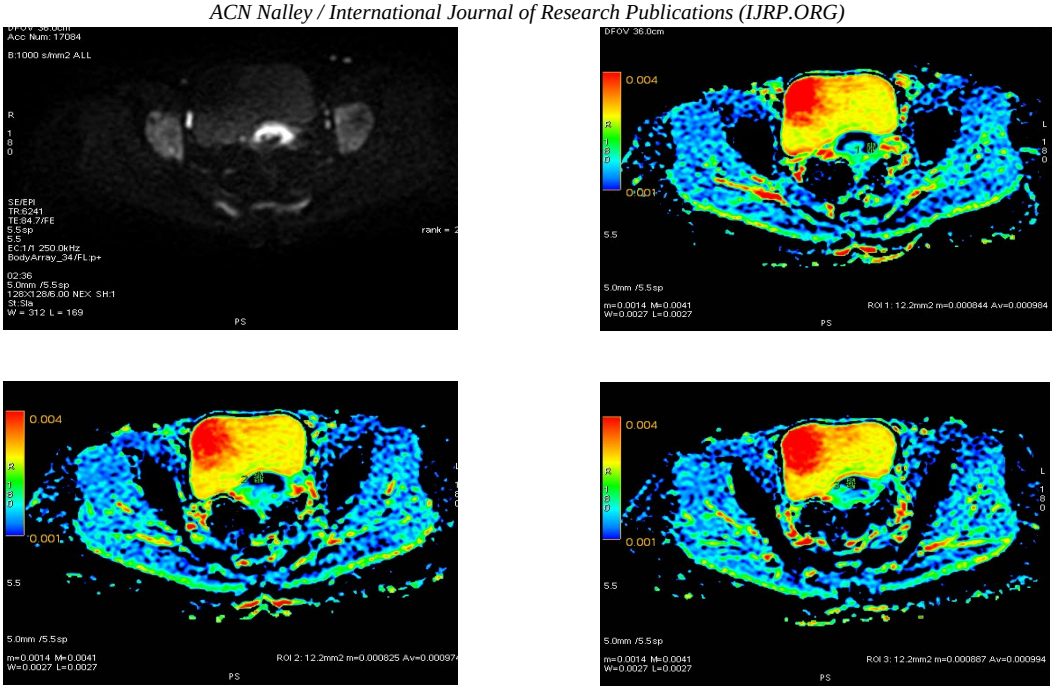

Figure 2. A 46 years woman with grade I cervix squamous cell carcinoma and mean ADC value of 0.984 x $10^{-3}$$mm^2$/s

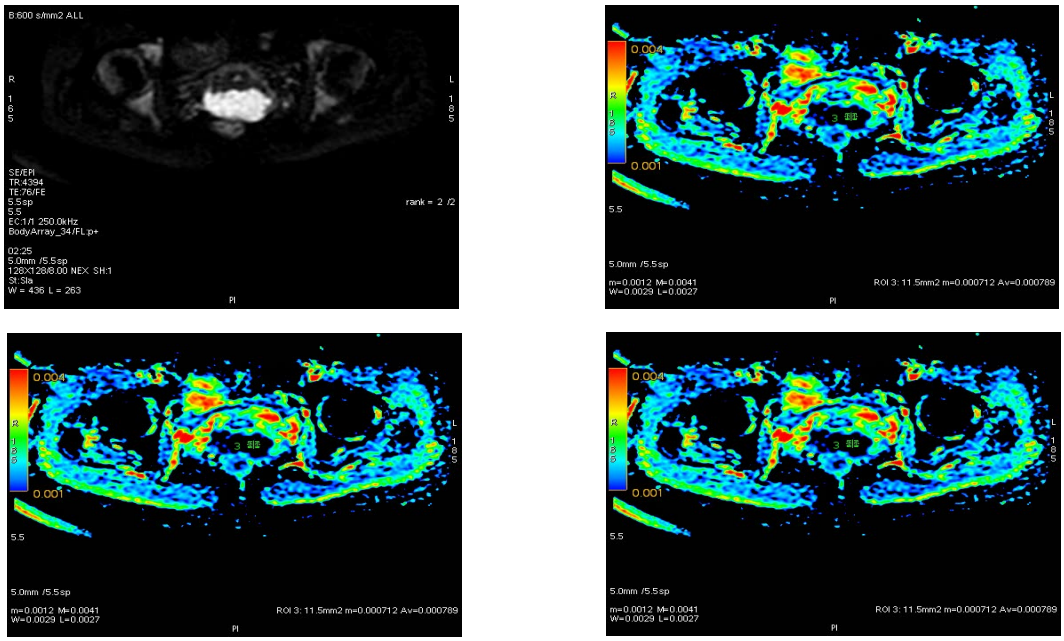

Figure 3. A 46 years woman with grade II cervix squamous cell carcinoma and mean ADC value of 0.801 x $10^{-3}$$mm^2$/s

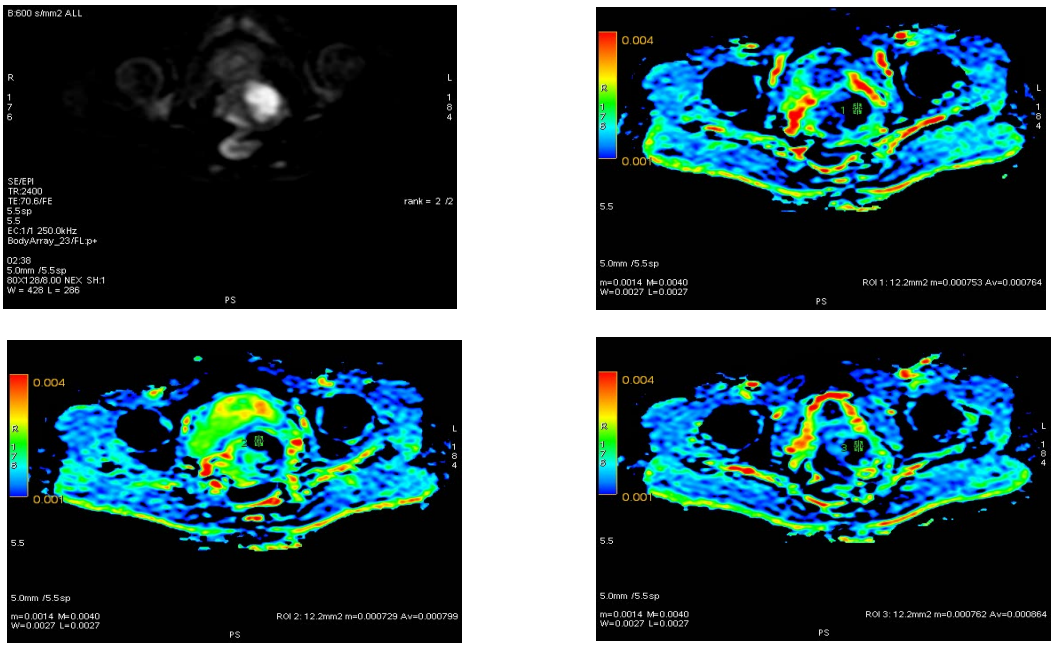

Figure 4. A 54 years woman with grade III cervix squamous cell carcinoma and mean ADC value of 0.809 x $10^{-3}mm^2/s$

4. Discussion

Our study found that the lowest ADC value was 0.63 x 10^{-3}mm-/s and the highest was 1.42 x $10^{-3}mm^2/s$. Mean ADC value in our study was 0.87 ± 0.163 x $10^{-3}mm^2/s$. These results were similar to previous studies by Liu et al, Atram et al, Dermibas et al, and Dashottar et al,where mean cut-off value for benign lesion in cervix was >1.3x$10^{-3}mm^2/s$ and for malignant lesion was <1.3x$10^{-3}mm^2/s$. This is in accordance to previous theory where ADC value is lower in cervix cancer compared to normal cervix because cervix cancer has denser cell and larger cell diameter, therefore water diffusion becomes limited (Dashottar S et al., 2019).

Based on histopathologic grading in our study, 27 (56.3%) samples were grade I, 8 (16.7%) samples were grade II, and 13 (27.1%) were grade III. Apparent diffusion coefficient cut-off value for grade I cervix cancer was 0.90 ± 0.18 x $10^{-3}mm^2/s$, cut-off for grade II was 0.83 ± 0.14 x $10^{-3}mm^2/s$, and cut-off value for grade III was 0.82 ± 0.12 x $10^{-3}mm^2/s$. Cut-off values for grade II/III were lower than cut-off value for grade I. These results were similar to previous studies by Liu et al, Payne et al, and Kuang et al, where higher cervix cancer grades had lower ADC values. This is in accordance to previous theory where higher cervix cancer grades have denser cells, therefore their ADC values become lower (Liu Y et al., 2009).

However, there was no significant difference found in ADC values between cervix squamous cell carcinomas grade II and III. This result is in accordance to previous studies by Dermibas et al and Dashottar et al.These inconsistencies might be caused by few patients in these study groups.

5. Conclusion

There was a very weak negative correlation (rho = -0.169) and non-significant correlation ($p = 0.250$, with $\alpha = 0.05$) between ADC value and cervix squamous cell carcinoma histopathologic grade. Further studies with larger population and longer period are needed to determine further the correlation between ADC value and cervix squamous cell carcinoma histopathologic grade. Furthermore, future studies are required to investigate modified MGS.

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