Role of diffusion weighted MRI and ADC value in descrimination between low versus intermediate and high Gleason scores in peripheral zone prostate

Papel de la resonancia magnética ponderada por difusión y el valor del coeficiente de difusión aparente en la discriminación entre baja e intermedia

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Abstract

Prostate carcinoma is a major health issue affecting mainly aged males; Gleason Score (GS) obtained through histopathological study gives prediction about the biological behavior of the tumor as well as the management plan and prognosis of the patient. The aim of the study to correlate the apparent diffusion coefficient (ADC) values of prostate cancer with the Gleason score of tumor foci to assess the predictive capacity of ADC in discriminating between low grade (GS less than 7) forms higher grades (GS of 7 or more) tumor foci, aiding in the non-invasive assessment of prostate cancer aggressiveness. In this descriptive study, data of 35 patients with biopsy-proven prostate cancer localized to the peripheral zone obtained from the Urology Department including their biopsy and/or radical prostatectomy histopathological records. Subsequently, the MRI record system saved MRI Information retrospectively. The signal on the DWI image noted, corresponding ADC maps carefully examined, and ADC values of tumor foci recorded by two consultant radiologists. ADC values showed a significant negative correlation with tumor GS. ADC value of 0.75 × x 10^{3} mm^2/s was the greatest limit value to recognize cancer or prostate with 6 GS, with 93% sensitivity and specificity. Our results demonstrated that the tumor Gleason Score, and therefore, the biological aggressiveness of the tumor is likely to be inferred from the ADC values of the tumor. The present study suggests that DWI allows the non-invasive assessment of biological aggressiveness of prostate cancer, which may contribute to devising initial treatment planning strategies.

Keywords: Diffusion-Weighted MRI, ADC Value, Intermediate and High Gleason Scores, Zone Prostate Cancer.

Resumen

El carcinoma de próstata es un problema de salud importante que afecta principalmente a varones de edad avanzada; el puntaje de Gleason (GS) obtenido mediante estudio histopatológico permite predecir el comportamiento biológico del tumor, así como el plan de manejo y pronóstico del paciente. El objetivo del estudio fue correlacionar los valores de coeficiente de difusion aparente (CDA) del cáncer de próstata con la puntuación de Gleason de los focos tumorales para evaluar la capacidad predictiva del CDA para discriminar entre focos tumorales de bajo grado (GS menor que 7) y grados superiores (GS de 7 o más) que ayudan en la evaluación no invasiva de la agresividad del cáncer de próstata. En este estudio descriptivo, los datos de 35 pacientes con cáncer de próstata comprobado por biopsia localizado en la zona periférica obtenidos del Servicio De Urología incluyendo sus registros histopatológicos de biopsia y/o prostatectomía radical. Posteriormente, el sistema de registro de Imagen de Resonancia Magnética (IRM) guardó la información de IRM retrospectivamente. Se anotó la señal en la imagen DWI, se examinaron cuidadosamente los mapas CDA correspondientes y los valores CDA de los focos tumorales registrados por dos radiólogos consultores. Se observó una correlación negativa significativa entre los valores de CDA y la GS tumoral. El valor CDA de 0,75 x 10 x^{3} mm^2/s fue el mayor valor límite para reconocer el cáncer o la próstata con 6 GS, con una sensibilidad y especificidad del 93%. Nuestros resultados mostraron que la puntuación de Gleason del tumor y, por tanto, la agresividad biológica del tumor se puede inferir de los valores de CDA del tumor.

Palabras clave: Resonancia magnética ponderada por difusión, valor CDA, puntuaciones de Gleason intermedias y altas, cáncer de próstata de zona.

Introduction

Prostate carcinoma is a major health issue affecting mainly aged males[1,2]. Cancer of the prostate is considered the third in cancer occurrence globally and sixth in cancer connected to high mortality[1]. Given the ongoing increase in the expected life span in the population, the relatively benign nature of the low-grade prostate cancer, and consequently the high 10-year survival rate of men with prostate cancer, the magnitude of the problem in the health sector is expected to increase dramatically[3]. Much debate is present in consideration of the prompt management of patients with prostate cancer. The therapeutic options are dependent on factors such as the age at diagnosis, stage, the histological grade of the tumor, and patient's medical conditions[4-7]. Most patients with prostate cancer have a disease that is limited to the prostate gland[8]. A well-known pathological grading system of Prostate tumors is the Gleason score (GS). Higher Gleason scores denote aggressive tumors[8,9]. Gleason scores classified as low score (≤6), intermediate score (7), or high score (>7)[1,10]. The Gleason score thus gives predictions about the biological behavior of the tumor as well as the prognosis of the patient. Samples for Gleason score were provided from the transrectal biopsy or radical prostatectomy specimen[11]. For a low score (GS <6) it is agreed that immediate treatment is not necessary, and it is reasonably safe to follow up with the patient. For intermediate-risk (Gleason score =7) the optimal line of management is monotherapy. In high-risk prostate cancer (Gleason score >7), the best treatment option, by agreement, is combination therapy[1,12]. For accurate localization of prostate cancer, it has been shown that Magnetic Resonance Imaging (MRI) is far more accurate than digital rectal examination (DRE) and more accurate than transrectal ultrasound (TRUS) biopsy[13]. Conventional T2-weighted MRI sequences have a crucial role in local staging of prostate cancer as it predicts the extracapsular spread of the tumor and detects tumor foci within the gland. Although T2-WI is sensitive for detection of tumor foci, it is not at all specific as the low T2 signal reported in cancer is also observed in many benign lesions, such as benign prostatic hyperplasia (BPH), hemorrhage, prostatitis, or treatment-related changes[4,14,15]. For this reason, conventional MRI has limited to local staging the known prostate cancer rather than primary detection of a suspected prostatic malignancy[14,16]. Recently, with the advent of multiparametric MRI combining conventional MRI, dynamic contrast-enhanced MRI (DCE-MRI), magnetic resonance spectroscopic imaging (MRSI), and diffusion-weighted MRI (DWI), the role of MRI started to extend to involve detection of cancer foci as well as localization and staging[15,17]. DWI is established to be useful in the recognition and location detection of tumor foci[18]. To differentiate between prostatic tumor, benign or malignant, DWI is very useful and plays an integral role in this differentiation[19-25]. Recently DWI was introduced as a potential predictor of tumor aggressiveness[11], possibly, replacing the need for invasive grading by Gleason score, which is so far the only possible tool to predict the tumor biological aggressiveness. Through this work, we aim to correlate the Apparent Diffusion Coefficient (ADC) values of prostate cancer with the Gleason score of these foci, to assess the predictive capacity of ADC in the noninvasive assessment of tumor grade.

Methods

This descriptive study was conducted at the Radiology and Uro Surgery Departments of Al Imamain Al Kadhimain Medical City, Irak, between December 2018 and September 2019. Data of 35 patients with biopsy-proven peripheral zone (PZ) prostate cancer were obtained from the Urology Department including their biopsy and/or radical prostatectomy histopathological records, subsequently, the MRI record system saved MRI Information retrospectively. Patients were excluded if they had experienced previous operation, radiotherapy, or hormonal treatment. The official ethical appraisal committee decided exception for patient's knowledgeable agreement because information retrospectively recovered. Entirely MRI scans were done with a 1.5 T device (Magnetom, Aera Siemens) by a pelvic phased-array coil. MRI pelvis procedure involved axial in addition to coronal turbo spin-echo T2-weighted pictures (TR: 4000-5000, TE 100-120, slice 3 mm, flip 130-150, FOV 180-230, gap 10%, NEX 2). Diffusion-weighted axial images (□-value 0, 500, 1000 s/mm^2) (TR: 4000-5000, TE 110, slice 4 mm, flip 130, FOV 200-250, gap 10%,NEX 10), with ADC maps and dynamic T1 flash 3D fat sat axial 1 pre-contrast and 10 post-contrast images (TR: 4-5, TE 2, slice 3 mm, flip 12, FOV 180-200). In all studies in our institution using contrast, patient verbal consent was obtained. Image Analysis and Reader Procedure: Two senior radiologists reviewed the images on the diagnostic workstation. The signal on the DWI image noted and corresponding ADC maps carefully examined. Circular regions of interest (ROIs) drawn on the ADC map display to obtain ADC value of foci of diffusion restriction. Only lesions with a confident anatomical correlation between the histopathology report of biopsy/surgical specimen and the MRI imaging localization were included in this study after the consensus decision of the two radiologists. Lesions with no confident correlation of location excluded from this study. The statistical analysis was performed using commercially available software SPSS (statistical package for social sciences) version 20.0. Mean of ADC values for each Gleason score calculated independently laterally with SD. Range similarly computed. For pairwise comparisons between ADC values in low Gleason score[6] and intermediate and higher scores (7 and more), the ROC (Receiver Operating Characteristics) curve was employed for sensitivity, specificity, and cut off value calculation. The diagnostic presentation was evaluated by computing the area below the curve and a $p<0.05$ was considered statistically significant.

Results

Our study included 35 males with a mean age of 68±7 years old, these patients were under radical prostatectomy and/or transrectal prostate biopsy with histopathological diagnosis of prostate carcinoma. In the peripheral zone of the prostate,

all places of tumor found on histopathology. Figure 1 and 2 shows the T2- weighted MRI, diffusion image, and ADC value and measurement of two patients with prostate cancer examined at our institution.

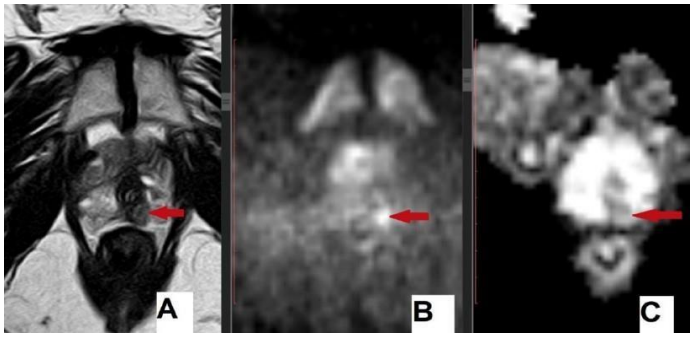


Figure 1 (A): T2-weighted MRI of a 63-year-old prostate cancer patient and (B) corresponding DWI and (C) ADC map with cancer demonstrated as a small nodule of low T2 and corresponding high DWI and low ADC signal involving the peripheral zones on the left at the apex of the gland.

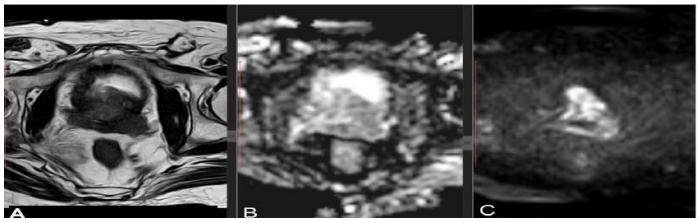


Figure 2: (A): T2-weighted MRI of a 79-year old prostate cancer patient with GS of 8 and (B) corresponding ADC map and (C) DWI images showing invasion of the bladder base and extension beyond the prostate capsule on the left base PZ.

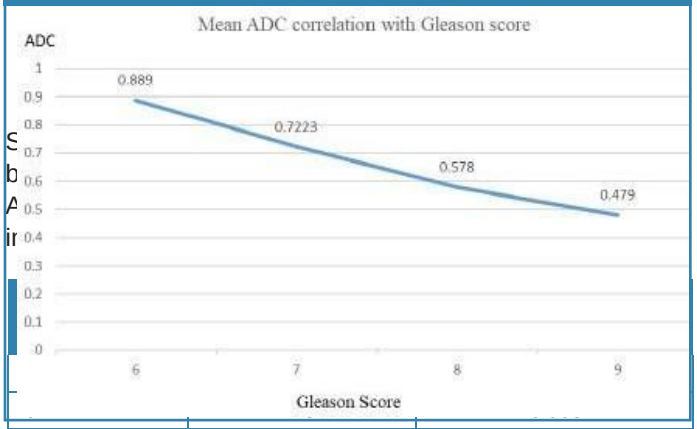
The mean ADC values of different Gleason scores of tumors are given in Table 1.

Table 1. Mean ADC values of different Gleason Scores

Gleason score	Number of patients	Mean ADC x 10^3 mm^2/s	SD	Range
6	13	0.998	0.195	0.456-1.3
7	9	0.722	0.1	0.5-0.88
8	9	0.578	0.0875	0.45-0.698
9	4	0.479	0.06	0.345-0.5
TOTAL	**35**	**0.691**	**0.11**	**0.345-1.3**

GS of (6) in 13 patients, ADC value was (0.99± 0.19) x 10^3 mm^2/s). In 9 patients with GS 7, the (mean ± SD) ADC value was (0.7 ± 0.1) x 10^3 mm^2/s). GS of (8) in 9 patients, ADC value was (0.58 ± 0.088) x 10^3 mm^2/s), GS of (9) in 4 patients, ADC value was (0.48 ± 0.06) x 10^3 mm^2/s). There was a negative significant association between ADC values in PZ cancer and tumor Gleason score (Figure 3).

Figure 3. Demonstrates the inverse relationship between ADC values and Gleason score.



7 or more	23	0.593

However, among the groups, the radiologist has detected ADC value difference and overlap as seen in Figure 4.

Figure 4. The association between ADC values in carcinoma of prostate and Gleason scores.

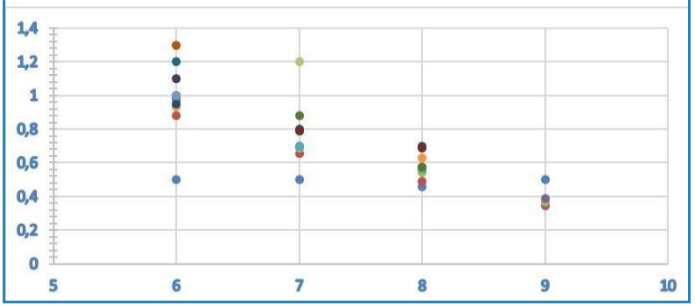


Figure 5 shows the receiver operating characteristics (ROC) curve we used for the correlation between low vs intermediate and high GS and ADC values, the area under the curve (AUC) of the ROC curve was 0.946 (95% confidence interval 0.897–0.919) indicating excellent correlation. Also, an ADC of 0.75 x 10^3 mm^2/s considered the best cutoff point for determining prostatic malignancy with a (6) GS, with 93% sensitivity and specificity, meaning that values of less than 0.75x x 10^3 mm^2/s are strongly associated with GS of 7 or more.

Figure 5. Evaluation of cutoff (ADC) value to calculate Gleason 6 disease. The area below the curve=0.946

Cut off value	Specificity	Sensitivity	Area under curve	P-value
0.75	93%	93%	0.946	<0.0001

Discussion

The appearance of prostate cancer on DWI as foci of diffusion limit in with matching low signal on ADC recording is fit recognized by numerous studies[4,19,20,21,24]. The basis for this appearance on DWI and ADC is increased water proton in the fast-dividing tumor cells, dense tumor cellularity giving restricted movements of water in the space outside the cells, therefore, decrease ADC values in comparison to the healthy prostatic tissue[18]. Likewise, it is possible that decreased ADC values in the higher GS group were the result of restricted motion of water molecules due to increased tumor cellularity. However, for possible correlation between tumor aggressiveness and ADC value of tumor foci, few prior studies were conducted to prove such association and to our knowledge, no similar study was done in our community. Our study showed that there is a strong negative association between the peripheral zone prostate cancer ADC value of and GS of the cancer foci, this result was reliable with previous studies stated that ADC values may be useful in differentiating patients with high, intermediate from patients with a low risk of prostatic carcinoma[1,8,16,26-29]. Other studies, reveal the results like to current study, the ADC values: patients with high GS (4+3) ADC lower than patients with high GS (3+3 and 3+4), but no future cut off point to distinguish low from high or intermediate Gleason scores[8]. Doo et al., and Yasushi et al.[30], also agreed with our study and reported that ADC values could provide a mean of differentiating lesions with a GS of 6 with mean ADC values of (0.875 × 10-3 mm2/s) from those with a GS of at least 7 with mean ADC of (0.779 × 10-3 mm2/s)[26]. Our results showed that lesions with a Gleason score of 6 had mean ADC of (0.998× 10-3 mm2/s) and those with GS at least 7 had mean ADC of (0.593× 10-3 mm2/s) which is different from those obtained in the Doo et al. in their study, possibly due to the difference in the studied population, study design as our study is retrospective, while Doo et al. is a prospective study. Hambrock et al. evaluated prostate cancer aggressiveness using a 3.0-T MRI with DWI, concluding that ADC values can be very effective in the differentiation of low- vs intermediate and high-grade prostate cancer foci. The median ADC values are given in their results for low, intermediate, and high-grade tumors were 1.30×10(-3) mm (2)/sec, 1.07×10(-3) mm (2)/sec, and 0.94×10(-3) mm (2)/sec respectively. Their ROC curve established a strong correlation between lowering ADC and higher Gleason Scores, but they measured median rather than mean ADC, and they used 3T MRI as opposed to 1.5 T MRI scanner used in our study[28]. Kim et al., also concluded the presence of a negative correlation between ADC values and the GS in prostatic carcinoma, that it was probable to distinguish GS[6] illness (meaning low grade with good prognosis) form intermediate and high GS (7 and more) according to ADC values, in their study, however, they have proposed cut off value of differentiation between Gleason score of 6 and higher scores was (0.830×10-3 mm2/s) were lower ADC values were mentioned to be significantly associated with intermediate and high-risk prostate cancer (GS 7 or higher disease)[29]. The absolute measured ADC values are noted to vary among different centers, possibly attributed to causes such as the project and form of MRI scanner, its field strength, the adapted imaging sequence, use of endorectal as opposed to pelvic array coils, and the diffusion b-values adapted in the diffusion protocol.

Conclusion

Based on our study, the tumor Gleason Score, and thus the biological aggressiveness of the tumor may be inferred from the ADC values of the tumor. A probable cut off ADC value of 0.75x10^{3} mm^{2}/s may discriminate between GS of 6 representing low-grade good prognosis tumor (demanding only watchful waiting) vs higher grade tumors with GS of 7 or more (requiring active management plan). Thus, these result may assist in guiding treatment and giving insight into patient's prognosis.

References

1. Shayan S.M et al. "Assessment of Apparent Diffusion Coefficient Values as Predictor of Aggressiveness in Peripheral Zone Prostate Cancer: Comparison with Gleason Score." *ISRN Radiology* 2014 (2014):1–7.
2. NIH national cancer institution. [Online].; 2017 [cited 2017. Available from: https://www.cancer.gov/types/prostate.
3. Bjurlin MA, Taneja SS, Rosenkrantz AB. Introduction to Prostate Cancer: Clinical Considerations. In Rosenkrantz AB. MRI of the Prostate, A practical approach. New York: Thieme; 2017. p. 1.
4. Filip G. Claus MP, Hedvig Hricak MP, Robert R. Hattery. Pretreatment Evaluation of Prostate Cancer: Role of MRI imaging and 1HMR Spectroscopy1. Radiographic. 2004 May; 24(S167–S180).
5. Johansson, J.E et al. "Fifteen-Year Survival in Prostate Cancer: A Prospective, Population-Based Study in Sweden." *Journal of the American Medical Association* 277.6 (1997): 467–471.
6. Lu-Yao, Grace L., and Siu Long Yao. "Population-Based Study of Long-Term Survival in Patients with Clinically Localised Prostate Cancer." *Lancet* 349.9056 (1997): 906–910.
7. Holmberg, L et al. "A Randomized Trial Comparing Radical Prostatectomy with Watchful Waiting in Early Prostate Cancer." *New England Journal of Medicine* 347.11 (2002): 781–789.
8. Nagarajan, R. et al. "Correlation of Gleason scores with diffusion-weighted imaging findings of prostate cancer." *Advances in urology* vol. 2012 (2012):374805.
9. Albertsen, P.C. et al. "Competing Risk Analysis of Men Aged 55 to 74 Years at Diagnosis Managed Conservatively for Clinically Localized Prostate Cancer." *Journal of the American Medical Association* 280.11 (1998): 975–980.
10. Bianco, F.J. et al. "Ten-Year Survival after Radical Prostatectomy: Specimen Gleason Score Is the Predictor in Organ-Confined Prostate Cancer." *Clinical Prostate Cancer* 1.4 (2003):242–247.
11. Padhani, Anwar R. et al. "Diffusion-Weighted Magnetic Resonance Imaging as a Cancer Biomarker: Consensus and Recommendations." *Neoplasia*. Vol. 11. Elsevier B.V., 2009. 102–125.
12. Shipitsin, M. et al. "Identification of Proteomic Biomarkers Predicting Prostate Cancer Aggressiveness and Lethality despite Biopsy-

Sampling Error." *British journal of cancer* 111.6 (2014):1201–1212.

13. Mullerad, M. et al. "Comparison of endorectal magnetic resonance imaging-guided prostate biopsy and digital rectal examination in the preoperative anatomical localization of prostate cancer. Journal of Urology. 2005; 174(6):p.2158–2163.

14. Abdel Maboud N.H. The role of diffusion – Weighted MRI in evaluation of prostate cancer. The Egyptian Journal of Radiology and Nuclear Medicine. 2014 March; 45(1).

15. Mazaheri, Y. et al. "MRI of the Prostate: Clinical Relevance and Emerging Applications." *Journal of Magnetic Resonance Imaging* Feb. 2011: 258–274.

16. Woodfield CA, Tung GA, Grand DJ, Pezzullo JA, Machan JT, Renzul JF. Diffusion-weighted MRI of peripheral zone prostate cancer: comparison of tumor ADC with Gleason score and percentage of tumor on core biopsy. AJR. 2010 APRIL; 194: p. 316-322.

17. Cornud F. Diffusion-Weighted Imaging of the Prostate. In Andrew B. Rosenkrantz M. MRI of the Prostate a Practical Approach.; 2017. p. 41-60.

18. Ocak I. et al. Dynamic contrast-enhanced MRI of prostate cancer at 3 T: a study of pharmacokinetic parameters. AJR Am J Roentgenol. 2007 Oct;189(4):849. doi: 10.2214/AJR.06.1329. PMID: 17885055.

19. Kim CK, Park BK, Han JJ, Kang TW, Lee HM. Diffusion-weighted imaging of the prostate at 3 T for differentiation of malignant and benign tissue in transition and peripheral zones: preliminary results. Journal of Computer Assisted Tomography. 2007; 31(3):p.449–454.

20. Pickles MD, Gibbs P, Sreenivas M, Turnbull LW. Diffusion-weighted imaging of normal and malignant prostate tissue at 3.0 T. Journal of Magnetic Resonance Imaging. 2006.; 23(2): p. pp. 130–134.

21. Gibbs P, Pickles M.D, Turnbull LW. Diffusion imaging of the prostate at 3T. Investigative Radiology. 2006; 41(2): p. 185-188.

22. Zelhof, B. et al. Correlation of diffusion-weighted magnetic resonance data with cellularity in prostate cancer. BJU International. 2009.; 103(7): p. 883–888.

23. Tamada, T. et al. Apparent diffusion coefficient values in peripheral and transition zones of the prostate comparison between normal and malignant prostatic tissues and correlation with histologic grade. Journal of Magnetic Resonance Imaging. 2008; 28, no. 3, p. 720–726.

24. Kumar, V. et al. "Apparent diffusion coefficient of the prostate in men prior to biopsy: determination of a cut-off value to predict malignancy of the peripheral zone. NMR in Biomedicine. 2007; 20(5): p. pp. 505–511.

25. Issa B. In vivo measurement of the apparent diffusion coefficient in normal and malignant prostatic tissues using echoplanar imaging. Journal of Magnetic Resonance Imaging. 2002; 16(2): p. 196–200.

26. Doo K.W. Detectability of low- and intermediate- or high-risk prostate cancer with combined T2-weighted and diffusion-weighted MRI. Eur Radiol. 2012; 22(1812-9).

27. Caivano R RPLAea. Comparison between Gleason score and apparent diffusion coefficient obtained from diffusion-weighted imaging of prostate cancer patients. Cancer Invest. 2013; 31(625-9).

28. Hambrock, T. et al. Relationship between Apparent Diffusion Coefficients at 3.0-T MR Imaging and Gleason Grade in Peripheral Zone Prostate Cancer. Radiology. 2011 May; 259(2).

29. Kim, T.H, et al. Relationship between Gleason score and apparent diffusion coefficients of diffusion-weighted magnetic resonance imaging in prostate cancer patients. Can Urol Assoc J. 2016; 10(11-12).

30. Yasushi et al., (ADC) Clinical Utility of Apparent Diffusion Coefficient Values in Patients with Prostate Cancer: Can ADC Values Contribute to Assess the Aggressiveness of Prostate Cancer? J. Magn. Reson. Imaging 2011; 33:167–172.