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Original Article

Application value of ADC in the diagnosis of lipid-containing small hepatocellular carcinoma with different histopathologic grades

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Abstract: This study aimed to explore the application value of ADC on DWI imaging in the diagnosis of lipid-containing small hepatocellular carcinoma (HCC) with different histopathologic grades and the correlation of ADC with histopathologic differentiation. Retrospective analysis included 78 cases of hepatocellular lesions of lipid-containing small HCC, which were confirmed by pathological examination, were retrospectively reviewed, and all patients underwent preoperative MR, including conventional scanning DWI sequence and dual-echo in-phrase and opposed-phrase sequence. Then they were divided into well-differentiated group, moderately differentiated group, and poorly differentiated group according to pathologic results after surgery, following measurement of the ADC values of preoperative lesions in the three groups respectively. Statistical analysis was performed by using SPSS 17.0. Quantitative data of single group with normal distribution and homogeneity of variance was performed by analysis of variance (ANOVA). Independent samples t-test was applied to pairwise comparisons, while Spearman rank correlation analysis was used to assess the correlation of ADC values with HCC differentiation. The results of ADC measurement revealed that the mean ADC value of lipid-containing small HCC in the poorly differentiated group, moderately differentiated group, and well-differentiated group was approximately (0.96±0.03)×10(-3) mm/s, (1.14±0.09)×10(-3) mm/s, (1.43±0.04)×10(-3) mm/s, respectively. There was significant difference between poorly differentiated group and moderately differentiated group, as well as between poorly differentiated group and well-differentiated group ($P<0.05$), while there was no significant difference between well-differentiated group and moderately differentiated group ($P>0.05$). Meanwhile, there was moderately positive correlation between ADC value and pathological grade of lipid-containing small HCC ($P=0.002$, $r=0.419$) and the relevant coefficient was 0.95. Taken together, ADC value can distinguish different pathological grades of lipid-containing small HCC, and there is moderately positive correlation between ADC value and pathological grade.

Keywords: Lipid-containing small HCC, apparent diffusion coefficient (ADC), diffusion weighted imaging (DWI), pathological grade

Introduction

Hepatocellular carcinoma (HCC) is a highly specific malignant tumor with different histological subtypes, even if liver cancer with the same histological subtypes will have different degrees of differentiated cell subsets. Due to differences in biological behavior, liver cancer with different pathological grades has a different prognosis [1]. Magnetic resonance diffusion weighted imaging (DWI) possesses moderately high diagnostic accuracy for the detection of lesions, and has been widely applied in the studies on histopathologic grade and prognosis of small HCC [2]. Lipid-containing small hepatocellular carcinoma (lipid-containing-small HCC), as a special type of small HCC, also can be diagnosed by DWI effectively [3]. However, the researches on quantitative DWI for assessing the pathological grade of lipid-containing small HCC are few. And this study was aimed to explore the application value of quantitative DWI-derived parameter, apparent diffusion coefficient (ADC), in the diagnosis of lipid-containing small HCC with different pathological grades and analyze the correlation of ADC with well-, moderately, and poorly differentiated pathological grade.

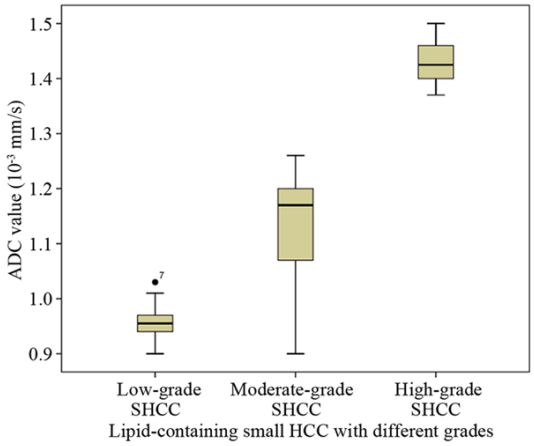

Figure 1. The distribution of ADC value of well-, moderately and poorly differentiated lipid-rich small HCC.

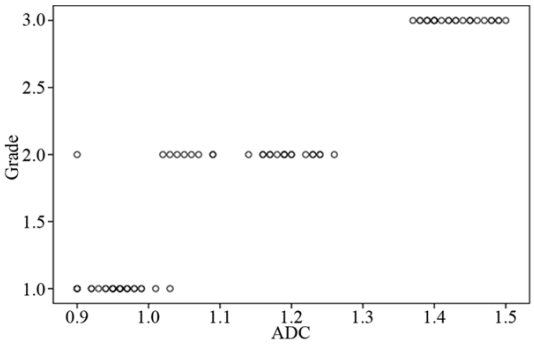

Figure 2. The relevance of ADC value of lipid-containing small HCC and different degrees of differentiation, and the relevant coefficient was 0.95.

Subjects and methods

Clinical data

76 HCC cases (a total of 78 lesions) with pathological confirmation, including 40 males and 36 females, aged 52-76 years, the median age of 68 years, were enrolled in this study from January 2012 to January 2014 (Supplementary Table 1). Inclusion criteria: (1) All patients undergoing preoperative MRI examinations; (2) The diameter of single lesion ≤ 3 cm or the sum diameter of two lesions ≤ 3 cm; (3) Confirmation of the lesions as lipid-containing HCC components by two diagnosticians with middle technical title; (4) First discovery and no anti-tumor therapy for the tumor. This study was conducted in accordance with the declaration of Helsinki, the seventh revision in 2013. This study was conducted with approval from the

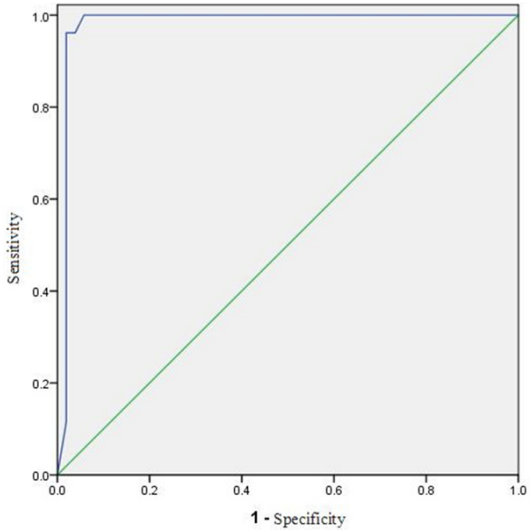

Figure 3. The ROC curve of ADC value in diagnosing different differentiated lipid-containing small HCC.

Ethics Committee of 302 Military Hospital of China. Written informed consent was obtained from all participants.

MRI examination

This study applied GE signa HDxt 3.0T 8-channel MR scanner (UAS) to receive signal, and scanning sequences included conventional axial T1WI and T2WI, coronal T2WI, axial dual-echo in-phase and opposed-phase sequence and dynamic enhanced sequence. DWI sequence parameters: TR 1500 ms, TE 47 ms, b= 0.800 s/mm^2; Slice thickness was 2.0 mm with the interval of 1.0 mm, and the longest time for breath was limited to 24 s for completion of liver DWI signal acquisition during each scanning. The whole liver was scanned for 4-6 times. ADC maps were generated by Futool software on the post-processing workstation. Horizontal surface respiration trigger fat-suppressed fast spin-echo sequence was applied on T2WI (TR 7000 ms, TE 85 ms), while T1WI (TR 160 ms, TE 4.5 ms) used breath-hold dual-echo spoiled gradient sequence Horizontal and coronal1iver acquisition with volume acceleration flexible (LAVA Flex) parameters: TE 1.7 ms, TR 3.7 ms, matrix 260×224, FOV 36 cm×36 cm-40 cm×40 cm, thickness 5.0 mm, scanning with no interval. Contrast agent Gd. DTPA was injected using high-pressure syringe by hand vein at 2.5 ml/s flow rate, with a dose of 0.2 ml/kg, on enhanced scan, and 20 ml saline was

Table 1. Blood supply and corresponding ADC values of lesions in lipid-containing small HCC

Pathological differentiation	Cases	Cases presenting rich blood supply	ADC value (mm/s)
Poorly differentiation	26	9	(0.96±0.03)×10(-3)
Moderately differentiation	26	12	(1.14±0.09)×10(-3)

then injected for washing pipe. Then arterial and portal venous phase images were obtained by scanning after contrast agent injection 17, 56 s, and venous phase images were obtained by scanning coronal surface at 1 min 40 s, and the late-stage phase images were obtained by scanning axial surface at 3 min.

Assessment of specimens resected from small HCC

HCC surgical specimens were conventionally fixed, embedded, sectioned and stained. Above samples were observed and confirmed by two pathologists with middle technical title and above to determine the pathological grade, and they were divided into well-differentiated, moderately differentiated and poorly differentiated group according to the pathological results.

Image analysis

Two radiologists (5-8 years liver diagnosis experience) reviewed the images together. The area of small HCC lesions was determined with specimens resected from liver cancer as reference. Combined with T2WI and dynamic enhanced MR lesion area, ROI was placed on DWI map with b=800 s/mm^2, and the ADC value were calculated. OI placement was in line with the following principles: (1) ROI placement on the central dimension of suspected lesion in order to minimize the impact of artifacts; (2) Coverage of the suspected lesion using ROI as far as possible; (3) Avoidance of the edge of the lesion, hemorrhage, necrosis, cystic degeneration and blood vessels. The area of each ROI and ADC values were recorded, with three repetitions, and the average was calculated as the final ADC value. ROI area was 0.21~1.32 cm^2, with the average of 0.61 cm^2. ADC values of 78 lesions were measured respectively, and meanwhile ADC values in poorly differentiated, moderately differentiated and well-differentiated group were measured according to the pathological grade.

Statistical analysis

All data were performed by using SPSS 17.0 statistical software (SPSS Inc, Chicago, IL, USA). Quantitative data of single group with normal distribution and homogeneity of variance was performed by analysis of variance (ANOVA). Independent sample t-test was applied to pairwise comparisons, while Spearman rank correlation analysis was used to assess the correlation of ADC values with HCC differentiation. P<0.05 was considered statistically significant.

Results

The correlation of ADC with small HCC

Among 78 lesions, ADC value on quantitative DWI of well- (n=26), moderately (n=26) and poorly differentiated group (n=26) was (0.96±0.03)×10(-3) mm/s, (1.14±0.09)×10(-3) mm/s and (1.43±0.04)×10(-3) mm/s respectively. There was significant difference between poorly differentiated group and moderately differentiated group, as well as between poorly differentiated group and well-differentiated group (P<0.05), while there was no significant difference between well-differentiated group and moderately differentiated group (P>0.05, **Figure 1**). Meanwhile, there was moderately positive correlation between ADC value and pathological grade of lipid-containing small HCC (P=0.002, r=0.419) and the relevant coefficient was 0.95 (**Figure 2**). The ROC curve of ADC value in diagnosing different differentiated lipid-containing small HCC showed that the area under the ROC curve was 0.981, the sensitivity was 96.2%, the specificity was 98.1% (**Figure 3**).

The results of image analysis

The tumor diameter of 78 lesions ranged 0.8~2.9 cm, and the median was 1.6 mm. Enhanced dynamic scanning showed that rich blood supply of small HCC was in 9 cases, less blood supply in 17 cases in poorly differentiated group; Rich blood supply was in 12 cases, less blood supply in 14 cases in moderately differentiated group; And rich blood supply was in 13 cases, less blood supply in 13 cases in well-

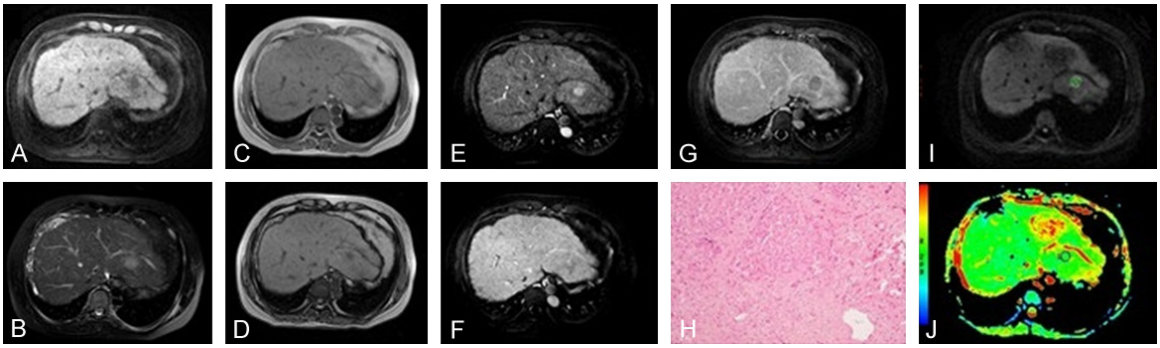

Figure 4. The manifestation of hepatic left lateral lobe in moderately differentiated lipid-containing small HCC on plan scanning images and dynamic contrast-enhanced MRI images: Longer T1 and longer T2 signal for lesions; Significantly enhanced arterial phase on enhanced scanning, presentation of slightly faded signal of contrast agent at portal venous stage images, low signal at later stage and visibility of enhanced fake capsule; Significant low signal on dual-echo opposed-phrase images; Slightly higher signal on DWI images. A: T1WI; B: T2WI; C: Dual-echo in-phrase image; D: Dual-echo opposed-phrase image; E: DCE-MRI arterial phase; F: DCE-MRI portal phase image: G: DCE-MRI later-stage phrase image; H: Differentiated lipid-containing small HCC, HE staining (10*40); I: DWI image; J: ADC pseudocolor (ribbon range $1.00e^{-0.4}$-0.00250).

differentiated group (**Table 1**). Lesions on MR presented clear boundary or blurred longer T1 and longer T2 signal, and DWI showed high signal or slightly higher signal (**Figure 4**).

Discussion

Small HCC refers to the maximum diameter of a single nodule ≤ 3 cm, and the number of lesion ≤ 2 with the sum of the maximum diameter <3 cm. Because of its small size and easy removal, this kind of cancer has aroused more and more attention worldwide [4]. The pathological differentiation of small HCC is closely related to prognosis and long-term survival. Meanwhile, poor prognosis of high-grade liver cancer has been the challenge that domestic and foreign clinicians must face, because its five-year survival rate is less than 70% [1, 5]. Preoperative biopsy puncture for clear pathological grade helps predictive treatment, but invasive puncture and transferring needle are the shortcomings. DWI, with no-invasion and higher sensitivity for lesions, has been widely used in the pathological grade and prognosis of small HCC [6]. Part of small hepatocellular cancer with lipid-rich ingredients becomes a special type, and some studies from domestic and foreign scholars found that DWI high signal sequence combined with conventional sequences and dynamic enhanced MR could accelerate the diagnostic rate [7-9]. However, the researches on quantitative DWI for assessing the pathological grade of lipid-containing small HCC are few. In this study, after DWI qualitative analysis, we explored the pathological grades of lipid-containing HCC using quantitative ADC to provide significant guidance for choosing a better clinical treatment and prognosis [10].

HCC pathological grade of differentiation is divided according to the specificity, packing density, trabecular, false glandular structure, infiltration and microvascular density of liver cancer cell [11]. Compared with poorly differentiated HCC, well-differentiated cancer presents lower cell density, larger extracellular space, and less degree of diffusion of water molecules, so the restricted degree of diffusion for ADC is not significant, resulting that its ADC measurement is slightly higher than that of poorly differentiated HCC [2, 3], and this is the basis of DWI for the diagnosis of liver cancer. This study showed that ADC value on quantitative DWI of well-, moderately and poorly differentiated group was (0.96±0.03)×10(-3) mm/s, (1.14±0.09)×10(-3) mm/s and (1.43±0.04)×10(-3) mm/s, respectively. And there was significant difference between poorly differentiated group and moderately differentiated group, as well as between poorly differentiated group and well-differentiated group ($P<0.05$), which suggested that the diffusion of extracellular water molecules was restricted. Moreover, this study indicated that capillary network in liver cancer with high grade was an independent factor, and in other words, blood supply could affect the differentiation of HCC cells [12]. In the present study, patients with less blood supply in the poorly differentiated group accounted

for 65.3%, indicating that lower ADC value for poorly differentiated HCC was not only related to closely arranged cells, but also to less blood flow as a result of microcirculation vessels. And this result was inconsistent with Enomoto's facts that the proportion of rich blood supply for poorly differentiated HCC was higher [13], which needs to be further studies whether this is owing to our collected pathological specimens contained rich lipid. Meanwhile, this study found no statistical difference between the moderately differentiated and well-differentiated groups. In addition, well-differentiated and moderately differentiated lipid-containing small HCC presented higher extracellular water molecular diffusion when compared with poorly differentiated type, but there was no significant difference in water molecular diffusion restriction between moderately and well-differentiated small HCC. This study also showed there was positive correlation between pathological grade and ADC, and the relevant coefficient was 0.95. This also explained that the lower degree of differentiation lipid-containing small HCC presented, the lower the ADC value was, but the higher the extracellular water molecule diffusion was, and the more enhanced the signal was on DWI [14-16].

However, as a retrospective review, this study was lack of the comparison between pathological specimens of large slices from liver cancer lesions and the MR images, and during ROI placement, we used the position of cancer lesion in resection specimens as the reference, the ROI was placed on the most suspected position for cancer, which was confirmed by two experienced radiologists with middle technical title, to obtain ADC value. This was aimed to minimize errors caused in terms of match between them. Moreover, this study only enrolled patients with surgical resection of liver cancer, and excluded the patients who did not undergo radical surgery, which might lead to data selection bias. Finally, ADC value was vulnerable to a variety of factors, such as MR imager, values and so on, so it might cause the changes in ADC value measurement. Therefore, there were limitations for ADC value in assessing the degree of malignancy of hepatocellular carcinoma.

In conclusion, ADC value on quantitative DWI can be used to distinguish well-, moderately, and poorly differentiated lipid-containing small HCC. With the increase in the degree of differentiation, ADC value will increase, and there is a positive correlation between them, which plays an important role in choosing the therapeutic regimen and predicting the outcomes of lipid-containing small HCC.

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Disclosure of conflict of interest

None.

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References

[1] Cong WM, Wu MC. New ideas and clinical strategies for molecular pathological diagnosis of liver cancer. National Medical Journal of China 2014; 94: 1521-1523.

[2] Chen J, Wu M, Liu R, Li S, Gao R, Song B. Preoperative evaluation of the histological grade of hepatocellular carcinoma with diffusion-weighted imaging: a meta-analysis. PLoS One 2015; 10: e0117661.

[3] Liu Y, Qu NZ, Li ZY, Gao YJ, Chen M, Zhang DP. Contrast enhanced ultrasound features of hepatic tumors contained lipid: comparing with MRI findings. Chin J Med Ultrasound (Electronic Edition) 2014; 11: 29-32.

[4] Lu XY, Xi T, Lau WY, Dong H, Xian ZH, Yu H, Zhu Z, Shen F, Wu MC, Cong WM. Pathobiological features of small hepatocellular carcinoma: correlation between tumor size and biological behavior. J Cancer Res Clin Oncol 2011; 137: 567-575.

[5] Zhou L, Rui JA, Wang SB, Chen SG, Qu Q. Clinicopathological predictors of poor survival and recurrence after curative resection in hepatocellular carcinoma without portal vein tumor thrombosis. Pathol Oncol Res 2015; 21: 131-138.

[6] Nasu K, Kuroki Y, Tsukamoto T, Nakajima H, Mori K, Minami M. Diffusion-weighted imaging of surgically resected hepatocellular carcinoma: imaging characteristics and relationship among signal intensity, apparent diffusion coefficient, and histopathologic grade. AJR Am J Roentgenol 2009; 193: 438-444.

[7] An C, Park MS, Jeon HM, Kim YE, Chung WS, Chung YE, Kim MJ, Kim KW. Prediction of the

histopathological grade of hepatocellular carcinoma using qualitative diffusion-weighted, dynamic, and hepatobiliary phase MRI. Eur Radiol 2012; 22: 1701-1708.

[8] Choi JW, Lee JM, Kim SJ, Yoon JH, Baek JH, Han JK, Choi BI. Hepatocellular carcinoma: imaging patterns on gadoxetic acid-enhanced MR images and their value as an imaging biomarker. Radiology 2013; 267: 776-786.

[9] Chang WC, Chen RC, Chou CT, Lin CY, Yu CY, Liu CH, Chou JM, Hsu HH, Huang GS. Histological grade of hepatocellular carcinoma correlates with arterial enhancement on gadoxetic acid-enhanced and diffusion-weighted MR images. Abdom Imaging 2014; 39: 1202-1212.

[10] Oishi K, Itamoto T, Amano H, Fukuda S, Ohdan H, Tashiro H, Shimamoto F, Asahara T. Clinicopathologic features of poorly differentiated hepatocellular carcinoma. J Surg Oncol 2007; 95: 311-316.

[11] Chinese Society of Liver Cancer, Chinese Anti-Cancer Association; Chinese Society of Clinical Oncology, Chinese Anti-Cancer Association; Liver Cancer Study Group, Chinese Society of Hepatology, Chinese Medical Association; Chinese Pathological Group of Hepatobiliary Tumor and Liver Transplantation. Expert consensus on the scheme of pathological diagnosis of primary liver cancer. Zhonghua Gan Zang Bing Za Zhi 2011; 19: 254-256.

[12] Kim BK, Han KH, Park YN, Park MS, Kim KS, Choi JS, Moon BS, Chon CY, Moon YM, Ahn SH. Prediction of microvascular invasion before curative resection of hepatocellular carcinoma. J Surg Oncol 2008; 97: 246-252.

[13] Enomoto S, Tamai H, Shingaki N, Mori Y, Moribata K, Shiraki T, Deguchi H, Ueda K, Inoue I, Maekita T, Iguchi M, Yanaoka K, Oka M, Ichinose M. Assessment of hepatocellular carcinomas using conventional magneticresonance imaging correlated with histological differentiation and a serum marker of poor prognosis. Hepatol Int 2011; 5: 730-737.

[14] Muhi A, Ichikawa T, Motosugi U, Sano K, Matsuda M, Kitamura T, Nakazawa T, Araki T. High-b-value diffusion-weighted MR imaging of hepatocellular lesions: estimation of grade of malignancy of hepatocellular carcinoma. J Magn Reson Imaging 2009; 30: 1005-1011.

[15] Choi YS, Rhee H, Choi JY, Chung YE, Park YN, Kim KW, Kim MJ. Histological characteristics of small hepatocellular carcinomas showing atypical enhancement patterns on gadoxetic acid-enhanced MR imaging. J Magn Reson Imaging 2013; 37: 1384-1391.

[16] Kim I, Kim MJ. Histologic characteristics of hepatocellular carcinomas showing atypical enhancement patterns on 4-phase MDCT examination. Korean J Radiol 2012; 13: 586-593.

Supplementary Table 1. Basic information and clinic features for all included patients

ADC value	Histopathologic grade	Sex	Year	Arterial blood supply	Diameter of lesion
0.90	Poorly differentiated	Male	68	Y	0.80
0.92	Poorly differentiated	Male	68	N	1.00
0.95	Poorly differentiated	Male	67	Y	1.60
0.94	Poorly differentiated	Female	67	N	0.90
0.96	Poorly differentiated	Female	66	N	1.10
0.90	Poorly differentiated	Female	66	Y	1.60
1.03	Poorly differentiated	Female	67	N	0.90
0.95	Poorly differentiated	Male	67	Y	1.00
0.96	Poorly differentiated	Male	66	N	1.00
0.97	Poorly differentiated	Male	66	N	1.10
0.92	Poorly differentiated	Male	66	Y	1.60
0.95	Poorly differentiated	Female	67	N	2.20
0.96	Poorly differentiated	Male	69	N	2.30
0.97	Poorly differentiated	Female	69	N	1.20
0.98	Poorly differentiated	Female	70	Y	1.60
0.99	Poorly differentiated	Male	68	N	1.10
0.99	Poorly differentiated	Female	68	N	2.30
1.01	Poorly differentiated	Female	69	Y	1.50
0.95	Poorly differentiated	Female	52	N	1.20
0.96	Poorly differentiated	Male	70	Y	1.50
0.98	Poorly differentiated	Male	84	N	1.60
0.97	Poorly differentiated	Male	69	N	1.50
0.95	Poorly differentiated	Male	53	N	1.30
0.94	Poorly differentiated	Female	70	Y	1.50
0.90	Poorly differentiated	Female	69	N	1.40
0.93	Poorly differentiated	Female	71	N	1.40
1.16	Moderately differentiated	Female	70	N	1.60
1.07	Moderately differentiated	Male	65	N	1.40
1.23	Moderately differentiated	Male	70	N	1.40
1.20	Moderately differentiated	Female	60	Y	2.20
1.02	Moderately differentiated	Male	71	Y	1.90
0.90	Moderately differentiated	Male	64	N	2.20
1.09	Moderately differentiated	Female	83	N	2.40
1.26	Moderately differentiated	Female	62	Y	1.70
1.24	Moderately differentiated	Male	80	Y	1.50
1.24	Moderately differentiated	Male	72	Y	1.60
1.19	Moderately differentiated	Female	73	N	1.40
1.03	Moderately differentiated	Female	54	N	1.50
1.05	Moderately differentiated	Male	70	Y	1.70
1.17	Moderately differentiated	Male	76	N	1.80
1.06	Moderately differentiated	Male	66	N	1.70
1.23	Moderately differentiated	Female	56	Y	1.50
1.22	Moderately differentiated	Female	68	N	1.60
1.19	Moderately differentiated	Female	65	Y	2.00
1.04	Moderately differentiated	Male	76	N	1.60
1.09	Moderately differentiated	Female	68	N	1.80
1.16	Moderately differentiated	Male	80	Y	2.10
1.17	Moderately differentiated	Male	64	Y	2.00
1.18	Moderately differentiated	Male	60	Y	1.70
1.19	Moderately differentiated	Male	68	N	1.50

1.20	Moderately differentiated	Female	56	N	1.70
1.14	Moderately differentiated	Male	70	Y	1.60
1.41	Well-differentiated	Male	74	N	2.10
1.42	Well-differentiated	Female	64	N	2.10
1.49	Well-differentiated	Male	83	Y	1.70
1.48	Well-differentiated	Male	73	Y	1.60
1.38	Well-differentiated	Female	72	N	1.40
1.44	Well-differentiated	Female	65	N	1.60
1.48	Well-differentiated	Female	63	Y	1.80
1.39	Well-differentiated	Male	68	Y	1.60
1.45	Well-differentiated	Male	63	N	1.60
1.43	Well-differentiated	Male	65	Y	1.60
1.49	Well-differentiated	Male	64	N	2.20
1.40	Well-differentiated	Male	60	N	1.70
1.43	Well-differentiated	Female	74	N	1.00
1.40	Well-differentiated	Female	71	Y	1.80
1.40	Well-differentiated	Female	71	N	1.60
1.46	Well-differentiated	Male	68	Y	1.50
1.45	Well-differentiated	Male	71	N	1.80
1.42	Well-differentiated	Female	69	Y	1.60
1.39	Well-differentiated	Female	67	Y	1.80
1.45	Well-differentiated	Male	76	Y	2.20
1.39	Well-differentiated	Female	66	N	0.90
1.50	Well-differentiated	Female	72	N	1.40
1.47	Well-differentiated	Female	68	Y	2.30
1.38	Well-differentiated	Female	65	Y	1.80
1.37	Well-differentiated	Female	70	N	1.70
1.40	Well-differentiated	Female	62	Y	1.00